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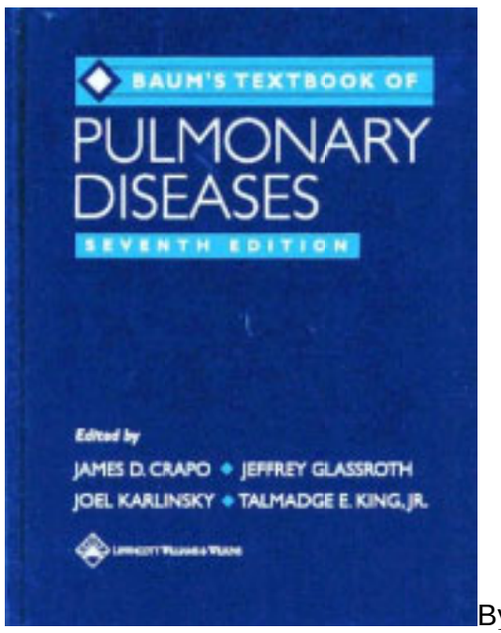

By OkDoKeY

Textbook of Pulmonary Diseases

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Introduction

The Sociopolitical Response to the Discovery of *Mycobacterium Tuberculosis*

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> "'Children and others, who work in the large cotton factories, are particularly disposed to be affected by contagion of fever, and when such infection is received it is rapidly propagated, not only amongst those who are crowded together in the same departments, but in the families and neighborhoods to which they belong.' However, the warning went unheeded. The passion for financial gains made acquisitive men blind to the fact that they were part of the same social body as the unfortunates who operated their machines. Tuberculosis was, in effect, the social disease of the nineteenth century, perhaps the first penalty that capitalistic society had to pay for the ruthless exploitation of labor."
>
> Rene and Jean Dubos, *The White Plague*

> "To combat consumption successfully requires the combined action of a wise government, well-trained physicians, and an intelligent people."
>
> A. S. Knopf, *Tuberculosis as a Disease of the Masses, and How to Combat It*

In the previous edition of this book, we discussed the historical development of tuberculosis, from Fracastoro's critical formulation of the germ theory during the Renaissance to Robert Koch's landmark discovery of *Mycobacterium tuberculosis* in 1882. Discovery of the bacterium, confirming the contagious nature of this epidemic disease, had broad implications that demanded a response from both the medical/scientific community and society as a whole. Because space is limited here, and the developments in medical treatment are already reasonably well-known, this chapter focuses on the closely interwoven social and political reactions to tuberculosis.

We are doing this in a general textbook on pulmonary diseases because tuberculosis—which infects one third of the world's population—is still the leading infectious killer of adults. It is responsible for 26% of avoidable deaths in developing industrial countries, which face health problems similar to those that confronted countries undergoing industrialization during the 19th century. And it is resurgent now in these same industrialized countries, as past problems—homelessness, overcrowding, inadequate health infrastructure, and disenfranchisement—re-emerge and the pool of patients with drug-resistant tuberculosis, particularly among disenfranchised groups, increases. To these problems must be added the epidemic of HIV infection; tuberculosis is becoming the leading cause of death among affected individuals. Worldwide, tuberculosis will kill 30 million people in this decade, according to the World Health Organization.

Our hope is that this chapter will be "useful to those who want to understand clearly the events which happened in the past and which—human nature being what it is—will, at some time or other and in much the same ways, be repeated in the future."[1]

PERCEPTION OF THE DISEASE

> "...Cleanse the slums, limit the pubs, stop the smoke, clear the air,
> And the water, of all the foul things that they bear,
> Give food to the needy and good clothing to wear,
> Shut up the wild lads who turn night into day,
> And succor the women who lead them astray,
> When your race is again strong, healthy and fair,
> Rely on my word, you'll not find us there,
> When struma, syphilis, cancer and gout,
> By cleaner living have been driven out,
> When lechery's over, carousing and riot,
> We'll gladly return to our guinea-pig diet ..."
> James Hurd Keeling (1831–1909), *The Song of the Squirt*

While the industrializing northern Europeans were still relegating tuberculosis contagion to the closet, the Italians and Spanish were returning to strong anticontagion public health legislation—modeled on Lucca's 1699 laws—to protect their citizenry. In Florence, the 1754 edict included the admonition "to take care that the patient does not empty his sputum except into vessels of glass or glazed earthenware, and that these utensils be frequently cleansed and boiled..." Naples built a tuberculosis hospital and passed the stringent laws of July 19, 1782, stipulating both precautions during illness and measures to be taken after death.[2] Although these laws were eventually revoked because of the financial burdens they placed on both families and the community, the common people in these regions continued to fear contagion throughout the 19th century.

In contrast, northern Europe and North America had adopted the notion that tuberculosis reflected an inherited constitutional vulnerability and was a disease capable of bestowing genius—the *spes phthisica*—on its victims. The ubiquitous nature of the disease and the long, lingering death it entrained may well have fueled the romantic movement in the arts, making languid consumptive pallor—exemplified by Marie Duplessis, the mistress of Alexandre Dumas *fils* and the model for Marguerite of *The Lady of the Camellias*—highly attractive. Lord Byron, for example, was overheard saying while looking into a mirror, "I look pale. I should like to die of consumption." When asked why, he answered, "Because the ladies would all say, 'Look at that poor Byron, how interesting he looks dying'" (Dubos and Dubos, 1987).

Although the longstanding notion of inheritability persisted throughout the 19th century, a changing perspective on the source of vulnerability began to surface—particularly in North America and England—in the latter part of the century. Vulnerability was now attached to class and morality. Tuberculosis was becoming a social disease, a "...diathesis ...built up with equal certainty by impure air, drunkenness, and want among the poor, and by dissipation and enervating luxuries among the rich ..." (Dubos and Dubos, 1987). Since one could now, in that current view, avoid tuberculosis by leading a "good life," it followed that contracting and dying of the disease documented one's inner weakness and intrinsic moral unfitness. Discovery of the tuberculosis bacterium clearly accelerated this trend in both Europe and the United States. A typical example was Dr. S. Adolphus Knopf, an American whose prize-winning tract—*Tuberculosis as a Disease of the Masses, and How to Combat It,* published in 1907—identified those most susceptible to the disease as either the personally depraved, whose alcoholism had temporarily or permanently enfeebled them, or the innocent victims of poverty.

Fertile Conditions for the Spread of Tuberculosis

As the population in Europe moved from rural to urban centers and immigrants inundated the eastern cities of the United States, greedy landlords on both sides of the Atlantic Ocean built dark, cramped living quarters—lacking adequate water, sewage, and ventilation—in the open yards behind apartment buildings. These “back tenements” and “dark rooms” created virulent seedbeds of tuberculosis (Fig. 1 and Fig. 2). Ernest Poole, a member of the antituberculosis committee of New York City's Charity Organization Society, described this typical scene in the “lung block” (Fig. 3) in the most crowded part of the city:

FIG. 1. Tenement house yard. Photograph by Jacob Riis (reproduced with permission of the Museum of the City of New York).

FIG. 2. There were 361,000 such “dark rooms” in New York City. Photograph by Jacob Riis (reproduced with permission of the Museum of the City of New York).

FIG. 3. Ground-plan of the “lung block.” The shaded sections are courts and air shafts. Each letter represents a new case of tuberculosis reported to the Health Department between 1894 and 1903 (e.g., *a* represents 1 case in 1894 and *b* represents 1 case in 1895). Because the records do not indicate whether a given case resided in the front or rear tenement, all have been assembled in the front building except at 144 Cherry Street, as there was not enough room. (Huber JB. *Consumption: Its Relation to Man and His Civilization; Its Prevention and Cure.* Philadelphia: JB Lippincott; 1906:147.)

> “In a rear tenement a young Roumanian Jew lay dying of consumption.... In this room, 10 feet square, six people lay on the floor.... The other room was only a closet six feet by seven, with a grated window high up opening on an air shaft 18 inches wide. And in that closet four more people were sleeping” (Huber, 1906).

Another typical house, called the “ink pot,” had front and rear tenements five floors high, with a small court between them. One hundred forty-five people, including 23 babies, lived in this building.

> “Up on the third floor, looking down into the court, is a room with two little closets behind it. In one of these a blind Scotchman slept and took the plague in 1894.... He died in the hospital. Only a few months later the plague fastened ...(on) his little daughter.... At last she, too, died. Then one year later, in October, a Jew rented this same room. He was taken, and died in the summer. The room was rented ...in the autumn by a German and his wife. She had the plague already, and died. Then an Irish family came in. The father was a hard, steady worker, and loved his children.... But six months later he took the plague. He died in 1901.... In the rear house is another plague room.... Here, in 1896, lived an old Irish hat maker with his wife, small daughter, his two sons.... He took the plague, worked a year or more there on his hats, then died. The cough came on his wife soon after. She suffered long, weary months, only to see at the end her young daughter begin the same suffering. The mother died. The home was shattered. The girl was taken by her aunt, and soon followed her mother. The two sons died of the same disease, spreading it out into other tenements.... When the next housekeeper came to this same room with his wife, both were strong and well. The man took the plague in 1899. He still fought for life when all knew he was hopeless ...; he ...could ...only lie alone in one of these closed bed rooms. (There are no fewer than 20 such rooms in this rear house—windowless, six feet by eight.) That winter of 1900 brought the memorable blizzard. While it was raging, a settlement visitor came to his room and found the water pipe burst, the room flooded. The plucky little wife had carried her husband upstairs on her back. A few days later his struggle was ended. The wife is still there” (Huber, 1906).

Responding to the Threat

Although laws with codes setting minimum ventilation and window areas for individual rooms had been on the books since 1890, greed, indifference, political corruption, inventiveness of landlords, plus the sheer numbers of immigrants, overwhelmed any attempt at enforcement or further reform. During that decade, however, a death rate of 776/100,000 and the knowledge that the “white plague” was reaching out beyond these impoverished neighborhoods added to the urgency for action.

One response to this threat was zealous reform. Progressive reformers such as Jacob A. Riis,[3] the author and photographer of *How the Other Half Lives,* brought the plight of the tenement-dwelling poor in New York City to public notice. One of the most effective of the tenement house reformers in New York, he advocated broad welfare programs to eliminate both poverty and illness and urged programs for remodeling tenement houses, abolishing sweatshops, reducing work hours, outlawing child labor, purifying water, and building parks and playgrounds.

The alternate response was fueled by the conviction that those living in such abominable circumstances found themselves there because they were morally unfit. The designation of “unfit” was applied to those who made the power structure anxious. In the United States, one saw an escalating xenophobia among Americans who feared being outnumbered by aliens who did not share their language, heritage, or democratic institutions. Europeans feared the revolutionary zeal of the anarchists and socialists among the poor. Throughout the industrial world, the germ of tuberculosis spread by immigrants and the poor became intertwined with the “germs” of radical political reform.

Governments attempted to meet both the social activists' reform agenda and the conservatives' demand for restraining the behavior of the poor, as the same means could be applied to satisfy both. The operative tenets were that the disease was preventable if patients could be removed from society, and that it was curable if patients could be persuaded (or helped) to live properly (or humanely). The first required a political reaction—the development of public health departments and policy, so that patients with tuberculosis could be identified and controlled. The second involved the development of treatment facilities, and accompanying efforts to return

these patients to society.

THE POLITICAL RESPONSE

The Local Department of Health

Politically, the results of the debate over the establishment of strong departments of health—which included compulsory identification of the tubercular patient—varied from place to place. But rather than present a superficial survey of these variations, we have opted to focus on New York City, where the establishment of a strong Department of Health and compulsory notification reflected the first clear victory for the group of physicians, politicians, and lay people who were convinced that only through strong administrative control could tuberculosis be contained.

In the United States, state health departments were first established in the mid-19th century. They employed sanitarians—engineers sent out to locate the causal elements in the transmission of disease (then believed to stem from foul-smelling or miasmic conditions). They were to establish uncontaminated water supply systems and uncontaminating sewage systems, and develop efficient and safe disposal for garbage and dead animals.

In the 1890s these sanitarians began to be replaced by public health physicians, whose mandate was broadened to the control of all transmittable diseases. For them, notification of contagious diseases was a necessary step in effective social policy to protect public health. Foremost among the proponents of this kind of social control was Hermann M. Biggs of New York (Fig. 4).

FIG. 4. Hermann M. Biggs, 1859–1923, established the New York City Board of Health Laboratory, set administrative controls for tuberculosis, and introduced diphtheria antitoxin and programs in child health.

Born in Trumansburg, a small village in the Finger Lakes region of New York State, Biggs took pride in the fact that he was descended from six American-born generations on his father's side and eight on his mother's. Convinced that one's station in life is partly a gift of inheritance, he grew up with a strong autocratic sense modulated by his father's passion for order. Early in his career, Biggs fastened onto the notion that cleanliness is next to godliness, turning his views on hygiene into a political credo in his baccalaureate thesis at Cornell in 1882 (coincidentally, the year of Koch's discovery of the tuberculosis bacillus): “Upon recognition and careful observance of hygienic laws depend the healthy physical condition, and so prosperity, not only of individuals and communities, but also of whole states and nations” (Winslow, 1929).

Biggs received his medical degree from the Bellevue Medical College in 1883, in the first medical class in the United States to take a formal pathology course, which was held in the country's first pathology laboratory.[4] William H. Welch, who founded the laboratory, remembered Biggs as the most active and interested student in the class, often staying late and working on special problems assigned him by Welch.

Biggs' choice of Bellevue was fortunate for other reasons as well. First, the faculty (including Edward Janeway and Francis Delafield as well as Welch), which had already begun to be involved in bacteriologic studies, espoused the highly unpopular hypothesis that all of tuberculosis was one disease, and readily accepted Koch's etiologic discovery of the tuberculosis bacterium. They countered the prevailing view of this microbe, as stated, for example, in the *Report of the Committee on Practical Medicine and Epidemics of the Illinois State Medical Society for 1882–83:* “...mere accompaniments of certain deteriorative changes in organic matter, and possessing no causative relations whatever.” Second, Bellevue's origin in 1816 as a prison, evolving into a hospital that embodied the notion of providing aid—sometimes forcibly—to the indigent population, provided an orientation that Biggs, probably because of his upbringing, supported unflinchingly. He clearly stated his position several years after entering medical practice, in an address to a meeting of the British Medical Association in Montreal:

> “The government of the United States is democratic, but the sanitary measures adopted are sometimes autocratic, and the functions performed by sanitary authorities paternal in character. We are prepared, when necessary, to introduce and enforce, and the people are ready to accept, measures which might seem radical and arbitrary, if they were not plainly designed for the public good, and evidently beneficent in their effect” (Winslow, 1929).

Biggs' first application of bacteriology to a Health Department problem occurred in 1887, when he and T. Mitchell Prudent (then professor of pathology at the College of Physicians and Surgeons, and Biggs' close friend) correctly identified the cholera spirillum in an Italian immigrant who had presented with a clinically doubtful case of cholera and died on board the steamship Britannia. The passengers had been quarantined on the ship, and Asiatic cholera later developed in a considerable number of them.

This incident helped convince Commissioner of Health Joseph D. Bryant of the need to establish a Division of Bacteriology and Disinfection within the Board of Health. In 1888, as a consequence of meetings on the cholera issue between the New York City Health Department and the New York Academy of Medicine, Biggs and Prudent, along with colleagues Drs. Janeway and Loomis, were appointed as consulting pathologists to the New York City Board of Health. In May 1889, Commissioner Bryant asked them to issue a position paper on tuberculosis for the Board.

This document asserted the validity of Koch's findings and declared that tuberculosis was preventable, was not directly inherited, and required direct transmission from sick to healthy individuals. As such, the position paper suggested the following measures: a system of rigid inspection of cattle to prevent public consumption of tainted meat and milk; public education regarding the dangers of pulmonary discharges from tubercular people; and disinfection of rooms and hospital wards occupied, or previously occupied, by tubercular patients. Their report was received coolly by the medical community, with the large majority indicating that no official action was called for.

The Push for Public Health Measures

Because Biggs, Prudden, Commissioner Bryant, and Board President Dr. C. C. Wilson were sufficiently politically astute to realize that any further legislative initiative would be fruitless without public support, they undertook a direct campaign of public education, handing out flyers—issued in several languages—prepared by the pathologists and signed by the Board of Health President and Secretary. (Cultivating a favorable political constituency by means of educational materials would become a hallmark of the campaign waged by Biggs and colleagues to control tuberculosis via a strong Board of Health and compulsory notification.) These flyers detailed the following preventive measures:

> “DO NOT—permit consumptive patients to spit on the floor; sleep in a room with a consumptive patient; fail to wash thoroughly the eating utensils of a consumptive patient as soon after eating as possible; mingle a patient's unwashed clothing with the clothing of others; fail to catch the bowel discharges of a consumptive patient with diarrhea in a vessel containing corrosive sublimates; fail to consult the family physician regarding the social relations (i.e., 'sexual relationships') of people suspected of having consumption; permit mothers suspected of having consumption to nurse; keep, but destroy, household pets suspected of having consumption; fail to cleanse thoroughly the floors, walls, and ceilings of the living and sleeping rooms of consumptive patients at least once in two weeks” (Winslow 1929).

On November 28, 1893, 41/2 years after the initial report, the Board again took up the cause of tuberculosis control by asking Dr. Biggs (now Chief Inspector of the Division of Pathology, Bacteriology, and Disinfection) for an updated recommendation. His report—curiously dated the same day as this request—presented seven measures:

> “(1) Educate the public via circulars and publications; (2) require notification by public institutions (e.g., asylums, social welfare facilities, hospitals) within 7 days of all persons suffering from pulmonary tuberculosis; (3) appoint special inspectors to ensure effective disinfection of contaminated premises; (4) separate tuberculosis patients from other patients; (5) establish a

> hospital exclusively for tuberculosis patients; (6) require the Board of Health Department to carry out a diagnostic bacteriologic sputum examination in every case of pulmonary disease of doubtful character; (7) insist that all physicians practicing in this city notify the Board of all pulmonary tuberculosis coming under their professional care (Winslow, 1929).”

This time around, the Board adopted Biggs' plan as “timely and well advised,” except for the notification clause addressed to individual physicians. They correctly sensed that the medical profession would not passively accept it. Biggs strategically retreated—temporarily—to “recommending” full notification and counterbalanced by recommending even more stringent treatment of infected dwellings. He required that “...the Medical Sanitary Inspectors visit all premises (vacated) ...by consumptive patients either by death or removal, and shall forward written recommendations as to the cleansing and renovation of the premises.... The Board (would) not allow the premises to be occupied by (new renters) ...until the (recommendations have) been complied with” (Winslow, 1929).

The Board found Biggs' slightly softened position acceptable. On February 15, 1894, the *Sun* newspaper wrote that “the Board of Health formally declared war upon consumption when it adopted Professor Hermann Biggs' plan of campaign.” However, the article, noting the parallel to the Naples law of 1792 (see footnote 2)—which had punished nonreporting physicians with 10 years of banishment and punished those who resisted the intervention of authority with 3 years in the galleys—stated that “...the Board *will not yet compel* (the authors' emphasis) physicians to report their consumptive patients. That will come later on” (Winslow, 1929).

Grumbling by the New York medical establishment—whose members saw the handwriting on the wall—was not yet followed by organized resistance. However, repercussions were felt elsewhere. Philadelphia's College of Physicians—over the objections of Dr. L. F. Flick, the compassionate pioneer of Pennsylvania's antituberculosis movement, and Dr. William Osler—met on January 12, 1894, and presented an antinotification edict to their municipal Board of Health, ostensibly because “the attempt to register consumptives and to treat them as the subjects of contagious disease would be ...stamping (these unfortunates) as the outcasts of society ...(and) not lead to any measures of real value not otherwise obtainable....” (Winslow, 1929).

Notification: Friends and Enemies

Overt hostility between the New York Board of Health and the medical establishment broke out in earnest the following year, but the Board held firm and eventually—on January 19, 1897—Biggs saw his vision become reality in an amendment to the sanitary code:

> “Section 225. That pulmonary tuberculosis is hereby declared to be an infectious and communicable disease, dangerous to the public health. It shall be the duty of every physician in this city to report to the Sanitary Bureau in writing the name, age, sex, occupation, and address of every person having such disease who has been attended or who has come under the observation of such physician for the first time within 1 week of such time....” (Winslow, 1929).

The medical profession's response to what they saw as a loss of authority and possible income was immediate. Dr. George Shrady's editorial in the influential *Medical Record* minced no words:

> “The real obnoxiousness of this amendment to the sanitary code is its offensively dictatorial and defiantly compulsory character.... The profession as a whole has watched with jealous eye the encroachments of the Board upon many of the previously well-recognized privileges of the medical attendant....” (Winslow, 1929).

And in a follow-up editorial he accused the Board of wanting “...to assume official control of the cases after they have been reported, thus not only ...directly interfering with the physician in the diagnosis and treatment of the patient, but ...possibly depriving him of one of the means of a legitimate livelihood” (Winslow, 1929). (Ironically, Shrady—as a consulting physician to the Board—had written an editorial in the 1983 *Medical Record* endorsing the original compulsory notification regulation for cases diagnosed in public institutions. Why he eventually changed sides is unclear, although he did voice the views of a considerable faction of physicians.)

This feared loss of income because of anticipated interference by the Board of Health was paramount in the resistance of the medical profession, both to the notification program and to the establishment of tuberculosis hospitals. Physicians felt that the eradication or limitation of this disease would dramatically shrink the income-producing population of tuberculosis patients, and that improved public health facilities would attract many of the remaining patients. They blamed elimination of the income assessment previously used to qualify patients for these facilities—now leaving it up to individual honesty—for “distributing the best care below market cost.”[5] The welfare cheat, who can afford to pay but pretends poverty (a recurrent image in the United States), was evoked: “Dispensary patients leave their carriages and servants around the nearby corner of a street” (Fox, 1974).

The issue came to a head in March 1897. The Medical Society of the County of New York unanimously protested the view of tuberculosis as infectious and communicable, and stated “that in the judgment of this society the recent edict of the Board of Health in relation to compulsory reporting of cases of tuberculosis is unnecessary, inexpedient and unwise” (Winslow, 1929).

The West Side German Dispensary resolved that the view of tuberculosis as a communicable disease “is not entirely correct, (and that) ...to grant the Health Board officials further powers ...in regard to the removal of those subjects of tuberculosis ...would be an interference that would be alike humiliating to the physician and intolerable to the patient and his family” (Winslow, 1929). The *Medical Record* asserted, “It would now appear that the time has come for the Health Board to rescind the obnoxious regulation, in order that it may, as formerly, work in harmony with the wishes of the profession.” Arthur M. Jacobus in his presidential address to the County Society accused the Health Department of “usurping the duties, rights, and privileges of the medical profession” (Fox, 1974).

Despite this bellicose posturing, Prudden described the opposition as the “little scattering of a gang of purps” [*sic*] who longed for the “good old times when a patient with tuberculosis could be lulled into a sense of security....” (Fox, 1974). Biggs attributed this medical opposition to “timidity, selfishness and ignorance.”

However, the local medical societies did not speak for all physicians in New York City. The Medical Association (the local branch of the American Medical Association, or AMA) was already competing for physician support in two other extremely sensitive areas: the right to consult with homeopaths, and the right to advertise and sell proprietary remedies. Both rights were favored by the local societies, but stringently opposed by the AMA's code of ethics. The split of the medical community on the notification issue fell along these predrawn organizational alliances.

The pro-notification group included members of the New York Academy of Medicine, the state's most prestigious group of physicians. The Academy contingent worked behind the scenes for a compromise. The Academy's Committee of Eight, with Biggs' friends Prudden and Janeway as spokesmen, suggested that the Board of Health “might wisely delay the enforcement of compulsory notification but should adopt more stringent measures for the care of all sputum.” The full Academy accepted this motion that the Board delay, but not rescind, enforcement of compulsory notification of tuberculosis patients. With Shrady leading the outraged physicians and Biggs leading the notification forces, an agreement was forged to leave the new but gently enforced regulation on the books in return for an official consulting board, chosen by the Academy, to advise the Board of Health. (This new board came into being in 1898.)

The medical societies, however, would not accept the Academy compromise. Both the New York County and Kings County Medical Societies tried to push bills through the state legislature calling to rescind that provision of the New York City charter empowering the municipal Board of Health to deal with tuberculosis as an infectious disease. They had gone to Albany believing that the Republican-dominated legislature would be eager to discredit the Board of Health as a means of diminishing the power of Tammany Hall.[6] But because the notification controversy had divided Republican physicians just as it had other physician subgroups, the legislators saw no clear gain in restricting New York City's Board of Health on this issue. Although a legislative committee was appointed for show, in actual fact the issue was quickly dropped. Thus, a strong, well-organized minority with access to sufficient patronage and publicity—like Biggs and his colleagues—was able to achieve its goals over the objections of a poorly organized majority.

The primacy of New York City's Board of Health in this realm can be attributed to public health innovators who—by need, inclination, or both—were intensely political and selectively partisan and had cultivated ties to the various power bases. Joseph Bryant had connections with the Democratic organization. Dr. Alvah H. Doty, Health Officer of the Port of New York, was close to the Republican organization. Prudden had ties to the anti-Tammany reformers, and Biggs himself had a warm relationship with C. F. Murphy, then Tammany district leader and subsequently county leader.

Once notification was finally the rule, Biggs, Prudden, and their allies were careful to develop a favorable constituency among their fellow physicians. This was done in part by increasing the Board's importance in the city's medical economy, which was particularly influential because of the economic depression afflicting the country during the century's final decade. The Board paid out approximately $250,000 yearly in part-time and full-time salaries. In 1897, for example, in a politically popular move, the Board hired 192 physicians as school inspectors, with each one receiving $30 per month to spend 40 minutes a day in neighborhood schools. (The move was practical as well as politically prudent. On the first day alone they examined 4225 children and found among them 14 cases of diphtheria, 3 of measles, and 55 of parasitic disease.)

The reformers also avoided antagonizing the general population. They separated the antidisease and antipoverty issues. Prudden, in an article in *Harper's Magazine* in March 1894 entitled “Tuberculosis and Its Prevention,” said that the tuberculosis bacilli lived in the “thick pile carpets” belonging to the rich and to those others who also accepted the “tyranny of things.” And they remained neutral in the controversy about society's responsibility to the poor, and in debates about heredity versus environment, self-help versus charity, fit versus unfit, and the movement against health abuses in the workplace.

They also gained the loyalty of that 80% of the New York City population who were either foreign-born or first-generation Americans by printing educational circulars in a variety of languages (initially German, Italian, and Yiddish, and eventually Bohemian, Finnish, Polish, Slovakian, Ruthenian, Swedish, Armenian, Spanish, and Chinese), and making sure that Board of Health personnel who visited the homes of tubercular patients either spoke their native language or were accompanied by an interpreter who did.

Furthermore, so as not to exacerbate the alienation of opposing physicians, the Board of Health's eventual enforcement was, as promised, cautious, selective, and politically wise. During the first decade of compulsory notification, only six “recalcitrant” physicians were fined.

In retrospect, the Board of Health's compulsory notification directive was successful. Reported cases of tuberculosis increased from 8559 in 1898 to 32,065 in 1910, and sputum examinations increased from 2920 to 40,000 during this same period.

The forum in which the antituberculosis public health crusaders had fought for compulsory notification was the political arena. As such, it required the resolution of political conflicts and use of the bargaining process to transform positions into legislated public policy and workable administrative arrangements. Although similar battles were fought in most industrialized communities, the successful achievement of compulsory notification in New York was unique. (For example, although Sir Robert Philip first pressed for compulsory notification in Britain as early as 1890, it took 20 years to be enacted into law.)

The medical profession in New York City could take pride in the international recognition they received for their success in identifying tubercular patients. In 1901 Robert Koch told Biggs, “I wish to cite the example of the American people, who of their own free will accepted the limitation of their liberties in the interest of public health,” and recommended the New York model to the “study and imitation of all municipal sanitary authorities” (Fox, 1974). This model, in fact, dominated medical and public debate so thoroughly that it helped bring about an international medical and public consensus about the communicability of tuberculosis and the importance of notification.

THE CRUSADE

National Organizations

The world's first international medical congress, which met in Paris in 1867, included presentations on tuberculosis, among them Jean-Antoine Villemin's classic work on its specificity and communicability. Afterward, international congresses devoted specifically to tuberculosis were held at regular intervals until the end of the century.

This latter period also saw the emergence of national organizations—made up of medical, lay, and government personnel—to battle the disease. The first of these national organizations, called “A Society for the Establishment of Sanatoria for the Consumptive Poor,” was established in Austria in 1890. Organizations in Denmark (“National League for the Campaign Against Tuberculosis”) and France (“French League Against Tuberculosis”) were established in 1891, and then Germany, Belgium, England, Portugal, Italy, and Canada rapidly followed suit.

A large, variegated country like the United States initially produced local antituberculosis organizations, with Philadelphia in the lead. On April 22, 1892, Dr. Lawrence F. Flick gathered 25 people, mostly lay persons, in his office, carefully excluding everyone who was inimical to the contagious theory of tuberculosis, to form the first American organization dedicated to combatting tuberculosis. With Flick as president, it became incorporated in 1895 as the Pennsylvania Society for the Prevention of Tuberculosis and set itself the following objectives: (1) to spread the gospel of contagiousness (still far from universally accepted) through public education; (2) to provide the poor with hospital treatment; (3) to visit poor patients and supply the necessary materials for protecting those they lived with; (4) to cooperate with the Board of Health's preventive measures; and (5) to lobby for appropriate public health laws. After the establishment of this unique antituberculosis group, another one finally followed in Ohio in 1901; then in quick succession associations were incorporated in six more states, including New York, and 11 local societies were formed.

The initial impetus to form a national association came not from the medical establishment, but from the Medico-Legal Society of the City of New York, a group of lawyers, scientists, and physicians who had organized a national meeting in 1900 to discuss state laws relating to the disease and its treatment. This meeting had heralded a shift in emphasis from treating individual patients to controlling the disease in society, a point of view that had been accepted a decade earlier in Canada and several European countries.

Between 1900 and 1903, Clark Bell (nonmedical president of the Medico-Legal Society) led an abortive attempt to parlay this meeting into a permanent, all-inclusive national organization. However, it failed because of territorial squabbles between physicians and lay persons. These often bitter conflicts arose between the AMA-supported organizations—representing practicing physicians' predominant emphasis (motivated by self-interest) on what they felt should be a purely medical approach to the disease—and organizations supported by public health officials and social workers dedicated to educational and legislative weapons for controlling the disease.

One of these conflicts erupted over an AMA-supported International Congress on Tuberculosis planned to be held Paris in 1904. On December 5, 1903, the *Journal of the American Medical Association* published a letter calling attention to the impropriety of proposed American congresses by “certain groups of little-known people who independently had been soliciting support, lay and political, for conflicting congresses.” The AMA called for the formation of the following:

> “...a committee with power to act to consider the conditions existing with regard to the proposed Tuberculosis Congress and other National Antituberculosis Associations in the United States; also to consider the formation of a National Committee to represent this country at the International Congress at Paris, and that the members of this conference will abide by the action of the Committee; also that the Committee had power to add to its membership ...” (Knopf, 1922).

The formative meeting took place, fittingly, in Philadelphia on March 28, 1904. Present on the medical side were the profession's foremost luminaries in the fight against tuberculosis: Edward Livingston Trudeau, S. A. Knopf, Henry Bowditch's son Vincent (founder of the first sanatorium in Massachusetts), Lawrence Flick, Sir William Osler, William Welch, and Hermann Biggs. Although physicians were heavily in the majority, all parties present resolved to coalesce into a national organization. Thus, the committee that was initially formed to head off anti-AMA competition became a stepping stone to the formation of an inclusive national organization. On June 6th, in Atlantic City, New Jersey, the United States Society for the Study and Prevention of Tuberculosis[7]—with Trudeau as its first president in recognition of his past achievements—was born; it comprised a broad alliance of health care workers, politicians, clergy, employers, and philanthropists.

The International Movement

At this same time, the international movement was materializing. The first step had been taken at the 1899 International Congress, held in Berlin, with the granting of official recognition to lay government and voluntary organizations as part of the expanding drive against tuberculosis. The Congress of 1902, again in Berlin, formalized acceptance of these organizations by creating the Central Bureau for the Prevention of Tuberculosis (soon renamed the International Antituberculosis Association). Headquartered in Berlin and composed of representatives appointed by national organizations and governments, the Association's work was interrupted by World War I, then resumed with 24 member nations. Renamed the International Union Against Tuberculosis (IUAT) and based in Paris, the IUAT—currently with 114 member countries—continues to organize international meetings and publishes the *Bulletin of the International Union Against Tuberculosis.* Its expanded mission eventually called for the following:

> “All countries wishing to eradicate tuberculosis to decide among themselves on the methods, to agree on the most effective weapons, and to forge and implement them jointly against the common enemy.... Antituberculosis measures must some day be standardized ..., but first it is necessary for the research workers to make a thorough investigation of the problem in order to provide governments with the necessary information. It is in this spirit and for these ends that we wish to create an International Union Against Tuberculosis” (Rouillon, 1982).

It was also at this meeting that the double red cross, as suggested by Dr. Gilbert Sersiron of the French national association, became the unofficial—and in 1928 the official—international symbol[8] of the voluntary movement to control tuberculosis. The cross, associated with the Christian Crusades, was the ideal symbol for what was viewed as an international “crusade” against this killer disease. Eradication was the common goal, although individual eradication campaigns reflected their national gestalt.

The Crusade in America

Because Americans typically viewed tuberculosis as a disease of the poor, the unfit, and the ethnically inferior, the campaign here took on an evangelical aura fed by the melding of three judgmental philosophies that stemmed, respectively, from the following: (1) the ascetic Protestant-capitalist tradition based on the Calvinistic doctrine of predestination[9]; (2) the converse view that individuals are responsible for their actions; and (3) a newly emerging corollary of Darwinian evolution whose precept was survival of the morally and physically fittest for the good of the human race—the biologic equivalent of the Calvinistic doctrine of predestination. Despite the obvious differences between these three social views, they all identified a subclass—the *same* subclass—as needing help.

Central to ascetic Protestantism (and those sects, such as Puritanism and Methodism, that derive from Calvinism) is the two-point doctrine of predestination: (1) God chooses before birth those to be saved and those destined for eternal damnation. (2) God's choice can only be guessed at by looking for signs of His grace. Although ascetic Protestants professed to disdain the pursuit of wealth as an end in itself, when it was attained as the fruit of one's labor, it was surely a sign of God's blessing. So the rich were confident that their wealth documented their place among the chosen, and they found the damned equally recognizable simply because of their poverty. Tuberculosis was easily woven into this fabric; the chosen did not fall ill, while those afflicted with tuberculosis were clearly among the damned.

A group opposing this deterministic view held that individuals could control where and how they lived. People who chose to live in filth, or were too unambitious or lazy to find work outside the crowded tenement districts, bore full responsibility if they contracted tuberculosis.

The third version—of the “defective” patient, the “Darwinian” point of view in relation to tuberculosis—was expressed in an article in the *Atlantic Monthly* by the noted Boston physician Henry Bowditch:

> “We must confess the sad and unwelcome truth that (some children) are doomed to an early death ...by the diseased condition of the parents, sometimes ...alas! due to their own or their ancestors' previous excesses.... 'For the sins of the fathers are visited upon the children unto the third and fourth generation.' Such children die early; **and this is exactly right. The race would constantly deteriorate were it otherwise** (*authors' emphasis*).... Only to strength and perfect health belongs the highest life, which alone has as its birthright the will and the power to contribute to the continuance of the human race” (Bowditch, 1869).

As all three viewpoints regarded the tubercular patient as inferior—whether damned by God, by his ancestors, or by his own actions—the National Association for the Study and Prevention of Tuberculosis found it easy to integrate them. The organization embarked on a campaign of propaganda, education, and aid dedicated not only to controlling tuberculosis, but also to developing a power base to control what was becoming a major industry. (By 1950, for example, the antituberculosis program in the United States approached $500 million.)

The *Confidential Bulletin,* the organization's internal newsletter, urged a concerted effort to recruit employers into the antituberculosis crusade because of their influence over their workers. Employers, selfishly motivated, were easily persuaded to join. On the one hand, the need to keep a healthy work force led these “captains of industry” to confront the “captain of all these men of death.” Some large corporations built “cure” facilities for their workers. The Standard Oil Company of New Jersey, for example, built such a pavilion at the Loomis Sanatorium in the Catskill Mountains of New York. (Ironically, during and after the industrial revolution it had been the blind drive for wealth—and thus evidence of God's grace—with its exclusive focus on profits and consequent disregard for humane working conditions, that had created an environment so favoring the spread of the disease.) And on the other hand, at a time when labor was becoming more restive and militant, this health crusade taught that passive obedience to employers was in the worker's best interest. Because the National Association viewed the city-dwelling poor as morally inadequate and thus in need of society's vigilance, they offered hygiene and morals in one basket. Lectures on tuberculosis, housing, and working conditions went hand in hand with such lectures as “The Amusement Problem: Snares of Amusements, Saloons, Dance Halls and Burlesque Theaters.” And the urban masses themselves were given the following admonitions:

Don't spit on the floor of your shop.
When you spit, spit in the gutters or spittoon.
Don't cough without holding a handkerchief or your hand over your mouth.
Don't drink whiskey, beer, or other intoxicating drinks.
Whatever thou take in hand, remember the end and thou shall never do amiss.
Whatever is worth doing is worth doing well.

Because health and personal conduct were now intertwined, coming down with tuberculosis became plainly unpatriotic: “Community health is essential to national preparedness. Now is the time to show that wasteful sickness can be prevented.”

Consistent with the prevailing capitalistic mentality, public participation in the fight against tuberculosis took the concrete form of donations to finance the different programs. The very first appeal for public funds was a small-scale effort mounted in Denmark, based on Einar Holboell's idea of selling special stamps or seals to raise money. In 1907, one of these seals reached the notice of photographer and social reformer Jacob A. Riis, whose ensuing article in an American magazine sparked the idea here. Emily P. Bissell of Wilmington, Delaware, who had read the article, commissioned the artist Howard Pyle to design a seal that she sold to raise $3000, financing construction of an eight-bed tuberculosis cabin. She then persuaded the American Red Cross to apply the idea nationwide, and they raised $135,000 in 1907 and $200,000 in 1908. For the next decade, the seal campaign was a joint Red Cross and National Tuberculosis Association effort. Then in 1919 the Red Cross gave full proprietorship and responsibility to the National Tuberculosis Association, which used the seal to raise $4 million that year. By 1950, the Christmas Seal program, as it came to be known, raised $20 million a year.

MEDICAL CARE

Compulsory notification and the social welfare movement were necessary, but not sufficient, weapons in the fight against tuberculosis. Once identified, tubercular patients needed treatment—whether they wanted it or not. The form that treatment took was tied to economic level, and patients were segregated by race. The wealthy were often treated at home by a private physician, to whom they paid a standard fee. Private funds were also required for sanatorium treatment, which promised a cure in return for subservient obedience. The majority of poor patients relied on public dispensaries combined with some sort of home care. The municipal hospitals cared for patients who were either terminally ill, noncompliant, or indigent.

The Sanatorium Movement

The history of the sanatorium movement has been well documented, if somewhat idealized, and the reader is referred to the ample literature on this subject for a detailed review. The summary here provides the outlines.

Sanatoria had sprung up in central Europe during the last half of the 19th century, then spread to coastal and riverside areas of Great Britain; after 1882 they crossed the Atlantic to America. Philosophically, sanatoria fell into two groups. One adhered to the motto of the Hotel/Sanatorium at Davos, Switzerland—*mox sani* (“the merry are soon well”)—illustrated in Thomas Mann's *The Magic Mountain.* The other upheld the motto of Brehmer's Sanatorium at Gobersdorf—*die Patienten kommen nicht um zich zu amusiren sondern um geheilt zu werden* (“patients do not come here to amuse themselves but to be cured”)—agonizingly portrayed in A. E. Ellis's *The Rack.*

The latter approach, incorporating the same Puritan ethic that permeated the National Association, better suited the American psyche. Patients entering sanatoria here implicitly agreed to a bargain: medical advice, treatment, and nursing care in exchange for complete submission to a rigorously demanding institutional authority. Although the sanatorium life was often romanticized in European literature, in reality it meant sacrificing dignity for the uncertain prospect of a cure. Patients typically entered an Orwellian society in which they became a number, divested of all sense of individuality via a combination of ideologic and psychologic assaults.

The experience was unchanged decades later when Marshall McClintock, who became a long-term resident of the Adirondack Cottage Sanatorium, described his arrival. On entering he was handed a rule book inscribed with his number (8027), which he was required to read and sign. He noted, “I felt worse than ever. Like a prisoner. And the book was full of rules, lots of rules” (McClintock, 1931).

Some patients viewed sanatoria as oases because they provided a refuge from sweat shops and squalid tenements. But the rigidly regimented life (not by accident reminiscent of monastic routine) often quickly became untenable, especially when it came to segregation of the sexes. Sex was believed to be both a major factor in the development of tuberculosis (“...girls with the tuberculosis diathesis do not have the same moral stamina that girls in robust health have.... This explains ...why so many prostitutes are tubercular” [Peters, 1909]), and a result of tuberculosis “toxemia,” which was regarded as “...effective in the direction of causing sexual irritability” (Fishberg, 1919). The harshness of sanatorium rules caused between 10% and 30% of these patients to leave within their first month.

Society replicated its inequalities and prejudices in the health care system in general, and in the sanatoria in particular. Blacks, for example, whose death rate from tuberculosis was twice that of whites, were completely barred from sanatorium treatment. When Lawrence F. Flick defended the initial nonsegregation policy at White Haven Sanatorium in Pennsylvania, the white patients there threatened to leave:

> “As there is nothing in your advertising literature sent to patients ...that they would be expected to associate with Negroes; we think it is an injustice to live in daily contact with them ...(and) we do not think it desirable for the White and Black Races to mix” (Bates, 1992).

Flick, to his credit, pitted his principles against the economic survival of the institution he had helped found. But the sanatorium board voted against him and issued a

new rule: “No Negroes will be admitted to the sanatorium.” In response, Flick resigned as medical director.

Patients who were poor and/or addicted to alcohol were also looked down on. These elitist attitudes are illustrated by the Otisville Sanatorium in New York, which had been built at Hermann Biggs' urging and embodied his autocratic notions. It was the first municipal sanatorium in the United States and, unlike most sanatoria, had a “work cure” to prevent “the cultivation of habits of idleness.” Biggs objected to the rest cure enforced at various other sanatoria on the grounds that their successful cases often consisted of “converting a sick tuberculosis individual into a fairly healthy loafer” (Winslow, 1929). (There was also a practical aspect, because inmates who were earning their keep to some degree reduced operating costs.)

Alcoholics were the most “worthless” patients of all. The rather terse notice sent to patients newly accepted at the Otisville Sanatorium included the following: “If under the influence of liquor, or smelling of the same, you will be rejected.” The antituberculosis movement was obsessed with alcohol, which in the United States was viewed as the prime nonbacterial factor contributing to the disease. (One can speculate as to the role of the antituberculosis movement in the development of Prohibition.)

Whether or not sanatorium treatment was effective in curing tuberculosis—it was never scientifically evaluated—in reality, the great majority of patients never had the opportunity to experience it. (By 1954, for example, when the incidence of tuberculosis was well on the wane, the 130,000 existing sanatorium beds could accommodate only half of the patients with active disease. Some of those unable to find space, or unwilling to submit to the demeaning regimen, went to the Colorado mountains or the southwestern desert, where large and desolate tent colonies—known as “bugsvilles” or “lunger's camps”—had been set up beyond town limits. The colony at Tucson, Arizona, for example, located 1 mile beyond the last bus stop and with no running water and only primitive sewage conditions, was a place of “lost souls and lingering death.” Those remaining in the city most often sought help via dispensaries and home care, and as a last resort entered a local municipal hospital.

The Dispensary

Antituberculosis dispensaries first appeared in Europe several years after the discovery, if not universal acceptance, of the communicability of the disease. The initial one was established in Edinburgh, Scotland, by Sir Robert Philip. In 1900, Ernest Malvov established the second dispensary in Liége, Belgium, with Albert Calmette doing the same in Lille, France, in 1901. The first American dispensary, the Henry Phipps Institute in Philadelphia, opened in 1903, and was followed soon after by Gouverneur and Bellevue Hospitals in New York City. The 1904 Bellevue Report described the dispensary as providing the following: (1) careful and thorough medical attention; (2) systematic investigation and supervision of the patient's home conditions; (3) education of both patient and family; and (4) evaluation of the social and economic conditions affecting the medical aspects of each case (Miller, 1904). Figure 5 shows the Bellevue Dispensary's first 5 months of activity.

FIG. 5. Expenses incurred by the Bellevue Hospital outpatient tuberculosis clinic during its first 5 months. (Miller JA. The tuberculosis clinic of the Bellevue Hospital outpatient department. In: Lambert A, Draper WK, Curtis BF, Woolsey G. *Medical and Surgical Report of Bellevue and Allied Hospitals in the City of New York,* 1904;1:204–205.)

Although all dispensaries shared these same basic aims, each institution had its individual perspective. At Bellevue, for example, “careful and thorough medical attention” involved collecting sputum for analysis by the Department of Health, making a probable diagnosis, and instructing the patient—both orally, and with written instructions for home use—as to nature of the disease and the needed precautions. Patient and family education was an ongoing responsibility of the physicians and nurses, and was supported with printed circulars. The 1904 Bellevue Report observed that each patient “is now a center of information in regard to the general principles of healthful living” (Miller, 1904). In contrast, the 1904 Gouverneur Report noted, “We have distributed very little literature. It has seemed to us that what patients know they will talk about, and that those with whom we work are usually more confused than helped by printed information” (Bradford and Seymour, 1904).

Both dispensaries prescribed a daily diet that started with a minimum of 2 quarts of milk and 4 raw eggs and increased to 3 quarts of milk and 10 eggs. (Very few patients were thought to benefit from more.) Patients were given a cuspidor and pocket sputum pouches free of charge. However, medication played a very minor role at Bellevue, whereas Gouverneur regularly used therapeutic agents such as strychnine, cod-liver oil, and ichthyol, and heroin was touted to control cough.

Patients at Bellevue were seen weekly, and their weight, temperature, pulse, and general condition were recorded. If needed, patients could be admitted to Bellevue's tent cottage (Fig. 6). The dispensary could also refer patients to an appropriate sanatorium and/or charitable organization. Investigation and supervision of the patient's home situation was done by home visits. In France, Calmette trained former tuberculosis patients for these visits, whereas the Phipps Institute and the New York City hospitals used visiting nurses. The year that the Phipps Institute dispensary opened, Dr. Lawrence L. Flick, soul of Philadelphia's antituberculosis movement, wrote, “Tactful, kind supervision by a well-trained woman soon brings the most ignorant consumptive under control” (Bates, 1992).

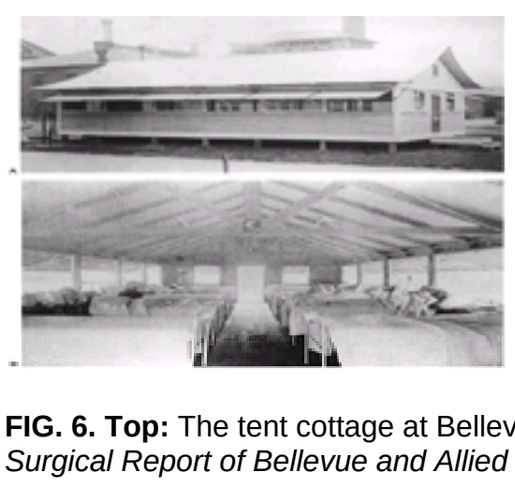

FIG. 6. Top: The tent cottage at Bellevue Hospital. **Bottom:** A tent interior, with gas light and steam heat. (Lambert A, Draper WK, Curtis BF, Woolsey G. *Medical and Surgical Report of Bellevue and Allied Hospitals in the City of New York,* 1904;1:204–205.)

As stated in the Bellevue Report, the aim of the visit was “to arrange the whole domestic economy to the best interest of the patient, and to provide against dangers of infection to his household and associates” (Miller, 1904). This included instructions for room ventilation, disinfection, expectoration, and general hygiene. Plans for taking the “rest cure” outdoors were made and, where possible, outdoor sleeping accommodations were constructed (Fig. 7 and Fig. 8). If a home was found to be completely unsuitable, the visiting nurse could insist that the patient be moved to a more healthful location.

FIG. 7. Fighting tuberculosis on the fire escape. (Lambert A, Draper WK, Curtis BF, Woolsey G. *Medical and Surgical Report of Bellevue and Allied Hospitals in the City of New York,* 1904;1:204–205.)

FIG. 8. Fighting tuberculosis on the roof. Photograph by Jacob Riis (reproduced with permission of the Museum of the City of New York).

As well-meaning as these health efforts were, patients did not always welcome them, as the following letter to Dr. Flick at the Phipps Institute indicates:

> “And doc, I now right to you to tell you, that you sent 2 nearses here to see Katie MiCarty and I would like to know, if you can tell who sent you a letter about my doarter.... I would like to tell your's nearses to pleas not bother a bout my business, for there is only one cure for my child and that is in heven” (Bates, 1992).

Just as it is today, patient compliance was of great concern to these public health pioneers. The 1904 Gouverneur Hospital Report notes the following:

> “The intelligence of these patients varies greatly.... Some at once sense the situation and work with us.... Among our most intelligent are the schoolchildren, who take kindly to the idea that they are in training as important as any athlete. On the other hand, there are those who come when they feel the need, and stay away at the slightest improvement.”

In the Phipps Institute's second annual report, Dr. Flick's earlier optimism that patients could easily be swayed to lead a “proper” life style with “tactful and kind supervision” had been replaced: “Considerable pressure is brought to bear on patients to induce them to practice preventive measures when they seem reluctant to do so.... When, ultimately, they are found to be intractable, they are discharged from the institute” (Bates, 1992).

The Municipal Hospital

For these disobedient patients, only the municipal institutions remained. As early as 1896, the AMA was urged to promote a network of state hospitals where “indigent consumptives who were careless in their hygienic habits could forcibly be confined.” The Rhode Island Commission, charged in 1911 with building such an institution there, listed “confinable” offenses as follows: being found a public nuisance; noncompliance; homelessness; friendlessness; dependency; dissolute behavior; dissipated and vicious behavior; residence in a lodging house or public institution with refusal to enter one's assigned hospital; living at home in unfavorable sanitary conditions, thus posing a danger to the family; and insisting on being discharged from a hospital against medical advice.

The New York Department of Health designated Riverside Hospital on North Island as the facility for involuntary confinement of all tubercular patients whose dissipated and vicious habits presented a danger to the community. But it failed both as a prison and as a hospital, as was typical of municipal efforts in the early 20th century. Riverside was often short of sputum cups, at the time a staple in the fight against contagion. It failed to give instruction in, or enforce, hygienic measures. Discipline was lax, bed rest was not enforced, and patients spent their days playing cards and wandering about.

In 1913, a report on 25 municipal facilities in five major cities (issued by the Committee on Hospitals for Advanced Cases of Tuberculosis of the National Association for the Study and Prevention of Tuberculosis) observed that, as in almshouses, patients would admit themselves as the weather grew cold and leave as soon as temperatures improved.[10] These institutions made no attempt to provide even rudimentary treatment or enforce the rules designed to prevent contagion. They were also cited for permitting patients to leave to visit friends and relatives. These municipal facilities, the Association concluded, served as “a place of last resort to the narrow group of cases in the extreme stages of physical and economic helplessness” (Rothman, 1993).

HOW EFFECTIVE WAS THE PUBLIC HEALTH INITIATIVE?

The death rate from tuberculosis between 1880 and 1920 decreased throughout the industrial world. In New York State, for example, it declined from almost 400/100,000 to just over 100/100,000, and in Wales and England from 200/100,000 to 100/100,000. The respective public health movements and national associations regarded this decline with pride and attributed it to their public health measures—that is, the education and isolation of an increasing proportion of patients.

This self-congratulatory attitude has been challenged on the grounds that these measures simply happened to coincide with a decline in tuberculosis deaths that reflected the larger cycles of the disease, a decline that was in reality not even accelerated by the public initiative. And a closer examination of death rates between 1800 (the start of reasonably accurate data) and 1950 (when effective antibacterial agents were first used) indicates that a constant decline in tuberculosis mortality had begun well before the interventions described above, and continued to fall at the same constant rate even after the health initiatives were put in place. Thomas McKeown and R. G. Record, among others, attribute this constant decline in tubercular deaths to a general improvement in social conditions during the period (improved housing, sanitation, and nutrition). Their position is based on two negative-inference arguments.

The first is that the slope of the mortality line did not grow steeper with each new public health initiative (Fig. 9, *top*), indicating that these initiatives apparently had no significant effect. The second argument is that the slope of the death rate remained nearly constant despite the increasing proportion of patients receiving treatment. Throughout most of this period, in any given decade the incidence of tuberculosis continuously decreased, while the number of patients isolated and treated remained fairly constant. (In New York, for example, it held steady at about 15,000 per decade.) Because this meant an increasingly greater proportion of patients were being treated, the death rate should have decreased more and more rapidly if the treatments were successful. But again the slope of the line appears constant, suggesting that these medical and social interventions were not having a significant impact.

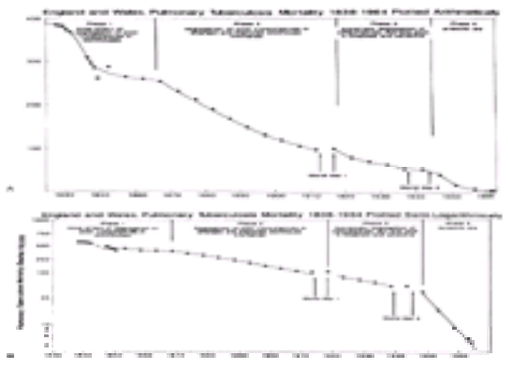

FIG. 9. Top: Arithmetic graph of tuberculosis mortality in England and Wales. **Bottom:** Semilogarithmic graph of the same data. (Wilson LG. The historical decline of tuberculosis in Europe and America: its causes and significance. *J Hist Med Allied Sci* 1990;45:390.)

In contrast, the public health and medical interventionists argue that their policies *did* accelerate the decrease in tuberculosis deaths. Leonard Wilson provides mathematical support for this view using the same data from England and Wales (Fig. 9, *bottom*). He argues that the decreasing mortality was not constant, but rather declined exponentially. And when the mortality data are plotted semilogarithmically, four distinct segments of increasing slope emerge. The discontinuity in the lines corresponds to the World Wars. The accelerated decrease in death rate, indicated by the steeper slope of each segment, coincides with better isolation of tubercular patients from the healthy population. A similar plot can be obtained from New York City data (Fig. 10), in which the steepest drop (1918–1922) immediately followed the opening of three large tuberculosis hospitals. Subsequently, the decline in deaths returned to approximately its previous steady exponential rate. (Those hypothesizing that the continued drop in tuberculosis deaths was a consequence of continuously improving social conditions could also view the two World Wars—during which the death rate soared in response to dramatically deteriorating social conditions—as perverse retrospective experiments favoring their hypothesis.)

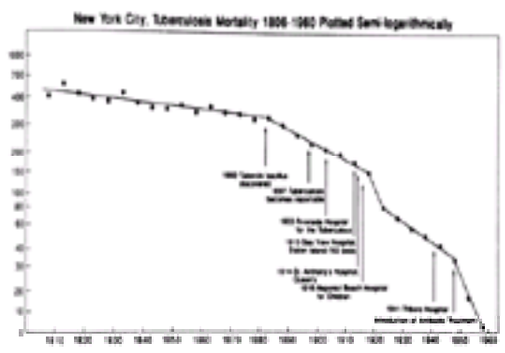

FIG. 10. Mortality in New York City between 1806 and 1960 plotted semilogarithmically. (Wilson LG. The historical decline of tuberculosis in Europe and America: its causes and significance. *J Hist Med Allied Sci* 1990;45:393.)

In our opinion, these conflicting observations actually illustrate two coincidental and superimposed mechanisms, one reflecting human interventions and the other reflecting the innate rhythms of the disease. On the one hand, a slow steady decline representing the effects of social improvements was interspersed with periods of accelerated decline consistent with the introduction of new antituberculosis initiatives. Disease epidemics, however, have their own natural and characteristic ebb and flow. For tuberculosis, these dynamics are dictated by the three types of postinfectious responses (Fig. 11). In most people who are infected, the disease does not develop further. Those remaining in the infectious pool separate into the relatively small group of “fast” (primary progressive) tuberculosis, and the larger group of “slow” (reactivation) tuberculosis. The early phase of an epidemic obviously represents the fast cases, and thus the death rate is high. As the epidemic progresses, the “slow” component becomes dominant and dictates a time unit of many decades, with the typical tuberculosis epidemic operating on a protracted time scale of 100 years or more. During this long-term phase, the death rate flattens substantially.

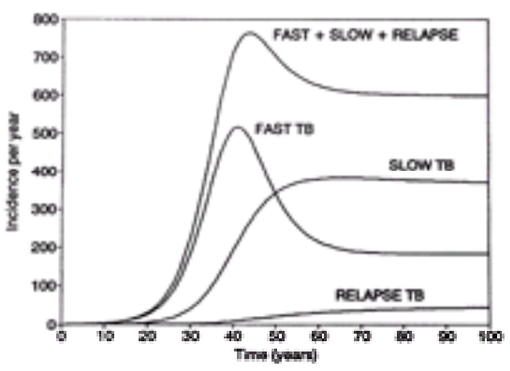

FIG. 11. A numerical simulation of a tuberculosis epidemic initiated by one infectious case at time zero in a disease-free, susceptible population of 200,000. The simulation illustrates the relative contributions of the three categories of tuberculosis (fast, slow, and relapse) to the incidence rate of this disease. A decline occurs in the absence of change in any parameter, and is simply the consequence of the intrinsic dynamics of transmission. (Blower SM, McLean AR, Porco TC, Small PM, et al. The intrinsic transmission dynamics of tuberculosis epidemics. *Nat Med* 1995;1:820.)

Current thought suggests that the rising phase of the ongoing epidemic in Europe and North America started when population densities exceeded transmission threshold levels. This coincided with the development of industrialization and the consequent vast migration from rural to industrial areas in both Europe and North America, and the inundation of North America by massive numbers of immigrants looking for a better life. After peaking in the early 19th century, deaths would have been expected to decrease as a consequence of the unique dynamics of a tuberculosis epidemic. Because the medical innovations and improved social conditions outlined here (with respect to hygiene and nutrition) happened to coincide with this declining phase, they were constrained to operate within—and thus appear muted by—the slow response time dictated by the intrinsic dynamics of the epidemic.

CONCLUSION

The discovery of *Mycobacterium tuberculosis* was essential for the development of an antituberculosis technology. The accumulation of new knowledge that followed precipitated an atmosphere of optimism, with the expectation that the means for detection and elimination of this single agent would ultimately achieve elimination of a feared and widespread disease. The irony is that altruism and charity played only a minor role in society's eventual attempts at controlling the tuberculosis epidemic. It was the often greedy fear of economic loss, combined with the anxiety of self-protection, that drove the campaign against this disease.

The leading edge of the current tuberculosis epidemic coincided with the initial phase of the Industrial Revolution, and its crest coincided with the subsequent apotheosis of unrestrained capitalism. The initial stimulus for the development of a societal antituberculosis initiative, therefore, came from the need to protect the investment and profits of the owning class. In the early phase, when large numbers of laborers migrated from farms to industrialized centers and the jobs there required little special training, workers were cheap and easily replaceable. In this kind of labor market, the health of individual workers was of little concern to employers. Eventually, however, the reserve of potential workers from rural areas shrank while the demand for skilled labor increased, so that employers had to spend significantly more to retain their workers. It became financially meaningful not to lose employees. (This cycle of an epidemic of tuberculosis coinciding with rapid industrialization, dense migration from rural to urban slum districts, and the exploitation of laborers, which characterized the Industrial Revolution in Western Europe and North America,

is recurring now in Latin America, Asia, and Africa.)

The second catalyst in the antituberculosis movement came from the gradual realization by physicians that the untreated and unsupervised poor were a real threat, not only to their fellow poor living alongside them in squalor, but to the middle and upper classes as well:

> “Then the poor servants of the well-to-do, if there be consumption in their own homes, are likely to bring infection into the families of their masters; as are also poor consumptive workmen who are employed upon repairs in the homes of the rich. There is in fact, no limit to the extent to which the disease may be disseminated from its primal base—the home of poor sufferers” (Huber, 1906).

The foot soldiers of the antituberculosis crusade—the compassionate nurses and physicians who dealt directly with patients—often participated for altruistic reasons, but the development of effective public health programs often had little to do with compassion and altruism and were, in fact, determined by hard economic concerns and fears. The antituberculosis program was enabled by scientific progress, brought to fruition through the deft amalgamation of public fears and self-interest, and facilitated by the skillful political manipulations of ambitious men to overcome what Castiglioni, in his 1933 *History of Tuberculosis,* called “...the short-sighted interests of a few who, in all times and every land, tried to sacrifice the public good to the selfish motive of the minority.”

The crusade achieved its success by playing on society's fears and bigotry. Because the poor were a ready target, the antituberculosis campaign purposefully emphasized and perpetuated the stereotype of the poor tenement dweller as an immoral drunkard who was sexually promiscuous and lazy, and reinforced the general notion that the tubercular patient was the cause, rather than the victim, of disease. This stereotype was a critical element in galvanizing and financing the public health campaign to eliminate tuberculosis. The dynamics of this campaign aptly illustrated Hermann Biggs' conviction: “Public health is purchasable and within natural limitations, any community can determine its own death rate” (Winslow, 1929).

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[1]Thucydides (circa 460–400 BC), *The History of the Peloponnesian War.*

[2]The law of July 19, 1782, from the Kingdom of Naples:

I. The physician shall report a consumptive patient, under penalty of 300 ducats for the first offense and 10 years' banishment for repetition of it.

II. The authorities ...shall inventory ...the clothing in the patient's room to be identified after his death...if any opposition ...be made, (if) the person doing so ...belongs to the lower class, (he) shall have 3 years in the galleys or in prison, and if of the nobility, 3 years in the castle and a penalty of 300 ducats.

III. Household goods not susceptible of contamination shall immediately be cleansed and that which are susceptible shall at once be burned and destroyed.

IV. The authorities ...shall tear out and replaster the house from cellar to garret, carry away and burn the wooden doors and windows and put in new ones.

V. Newly built houses shall not be inhabited for 1 year after ...completion or 6 months after plastering has been done and everything (else) ...has been finished.

VI. The poor sick shall at once be removed to a hospital.

VII. Hospital superintendents must keep clothing and linens for the use of consumptives in separate places.

[3]Ironically, although Jacob A. Riis is known as a social reformer who was instrumental in improving living conditions for poor tenement dwellers in New York City, his outrage over these living conditions was reserved for victims of German or Bohemian descent. Virulently anti-Semitic, he castigated Jews for their industriousness even though fully aware that this was exactly what would lift them out of their poverty. He also admonished the Italians, Irish, and Chinese for various perceived sins.

[4]The College of Physicians and Surgeons had offered W. H. Welch a faculty position, but refused to build a laboratory in which he could implement the histology and microbiology techniques he had learned in Germany. Bellevue Hospital gave him this laboratory, and he joined the faculty there as Professor of Pathological Anatomy and General Pathology. The College of Physicians and Surgeons, soon realizing its mistake, built a pathology laboratory under T. Mitchell Prudent.

[5]Feared loss of income by physicians was a recurrent concern. A 1904 report from the tuberculosis clinic at Gouverneur Hospital, in an attempt to counter this apprehension, noted: “We are sure that the medical profession is not being impoverished because people are treated free. Occasionally we have a well-dressed child, but the appearance of some other member of the family outweighs the first impression of competence.”

[6]Tammany Hall, led at that time by Richard Cocker, was the political oligarchy—associated with corruption and governmental mismanagement—that ruled New York City at the turn of the 20th century. The Board of Health evolved mainly during Tammany's control of City Hall.

[7]This organization was renamed the National Tuberculosis Association in 1904 and is with us still as the American Lung Association.

[8]This double cross symbolized Christian Jerusalem in the second century AD. Eventually appearing in Byzantium as a “Greek cross,” it entered the Hungarian coat of arms in 1074 when the Byzantine Emperor gave it to Hungary's King Geasa I. Then, in 1099, Godefroy de Bouillon, Prince of Lorraine, added it to his banner to commemorate his Crusaders' capture of Jerusalem. Almost a millennium later, this cross was adopted as an emblem by the Free French in World War II. Since it has become associated with the antituberculosis movement, some countries have replaced it with a culturally more meaningful symbol (double red crescent or red lion and sun).

[9]Even a cursory discussion is beyond the scope of this chapter. The interested reader is referred to Erich Fromm, *Escape From Freedom* (New York: Avon Books; 1965) and Max Weber, *The Protestant Ethic and the Spirit of Capitalism* (New York: Charles Scribner's Sons; 1958).

[10]I (F.H.) remember a spring day in my childhood (in the early 1950s) when I accompanied my father to his job as Director of the Pulmonary Rehabilitation Program at Bellevue Hospital. A panhandler approaching our car suddenly recognized my father and apologized. That winter I saw him again, this time in Bellevue. My father explained that every year, he would check into the hospital when the weather turned cold, stay for the winter, then leave in the spring.

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Introduction

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The respiratory system, perhaps more often than any other organ system, frequently bears the brunt of injury initiated by diseases that are primarily nonpulmonary in origin. Indeed, in many of these diseases, pulmonary manifestations are the first indication of a multisystem disease. Furthermore, the respiratory features or complications may persist as the most significant clinical aspects of the nonpulmonary diseases. The mechanisms by which such involvement occurs are almost as diverse as the diseases themselves.

The most common and best-documented mechanism of lung injury is the inhalation of pathogenetic substances including dusts, gases, smoke, microorganisms, and various types of antigens and chemicals. Injuries arising from these usually appear in the conducting airways or pulmonary parenchyma as infections, bronchitis, emphysema, asthma, bronchogenic carcinoma, malignant mesothelioma, or pneumoconioses. These entities are appropriately covered in other sections of this textbook.

Changes in the lung vasculature may accompany widespread disease of the systemic blood vessels or be caused by various pulmonary or extrapulmonary conditions. Leakage of protein or red blood cells from capillaries into the extravascular and alveolar spaces can occur by mechanisms that are not well understood. This is exemplified by the intraalveolar hemorrhage of Goodpasture's syndrome, in which circulating anti-basement-membrane antibody is present, and the alveolar bleeding is a dramatic indication of underlying glomerulonephritis. A second example is the nonhydrostatic pulmonary edema of the respiratory distress syndrome, which may result from a wide variety of insults ranging from the hypoperfusion of the shock state to amniotic fluid embolism and pancreatitis. In contrast, the intraalveolar hemorrhage of Wegener's granulomatosis, systemic lupus erythematosus, and hypersensitivity angiitis results from the necrotizing vasculitis of small vessels, which occurs in these diseases as part of the damage caused by deposition of circulating immune complexes. Auscultatory and roentgenographic changes caused by pulmonary arteriovenous fistulas may be early indications of hereditary hemorrhagic telangiectasia, and bleeding from the lesions can be severe enough to threaten life. Chemical mediators produced at a nonpulmonary site may enter the pulmonary circulation and cause respiratory problems, as exemplified by the bronchospasm noted in patients with extrapulmonary carcinoid that produces serotonin.

The lung interstitium is involved in a number of heritable diseases. Defective collagen synthesis is believed to be a significant factor in the abnormalities of the Marfan and Ehlers–Danlos syndromes, and in both disorders tissue fragility may predispose to spontaneous pneumothorax. In some cases of tuberous sclerosis, smooth muscle replaces normal alveolar interstitial tissue to such an extent that gas exchange is rendered ineffective, and irreversible respiratory failure is produced. Interstitial fibrosis observed in collagen disorders such as rheumatoid arthritis, scleroderma, and polymyositis may have underlying autoimmune mechanisms.

More commonly, the lung parenchyma is a site of pathologic changes that represent infiltration by acquired disease processes. Prominent among these are the lymphoproliferative disorders, characterized by multiplication and aberration of lymphocytes and histiocytes and their precursors and derivatives. Similar mechanisms are responsible for lung involvement in uncommon diseases such as Langerhans cell granuloma (histiocytosis X or eosinophilic granuloma) of the lung, Gaucher's disease, and plasma cell dyscrasia. Diffuse infiltrative changes, both microscopic and roentgenographic, occur in acute and chronic leukemias, whether lymphocytic or nonlymphocytic. More nodular changes are seen in the tumor masses of Hodgkin's and non-Hodgkin's lymphomas, but pulmonary involvement by myeloma or Waldenström's macroglobulinemia is distinctly rare. These conditions and Langerhans cell granuloma of the lung, whose generic designation covers several patterns of histiocytosis, lack specific roentgenographic features that would permit ready diagnosis in the absence of microscopic proof. In all of them, pulmonary involvement may be an early or late feature. These statements are also true of the noncaseous granulomas of sarcoidosis, which may be recognized first in lung parenchyma without the presence of the characteristic hilar and paratracheal adenopathy. In both of these diseases, deposition of collagen often follows the inflammatory changes in the lungs, which are themselves only one part of a more generalized process. A similar progression can occur from a hypersensitivity or dose-related lung reaction to certain drugs.

The respiratory system is the most common site of infection in immunosuppressed patients. Frequently, unusual or recurrent pulmonary infections alert the clinician to the possibility of immunosuppression. For instance, *Pneumocystis carinii* pneumonia, in patients with undiagnosed acquired immunodeficiency syndrome, may alert the clinician to the possibility of underlying disease. It is not uncommon, however, for a patient with an immune deficiency problem such as common-variable immunodeficiency syndrome (hypo- or agammaglobulinemia) to experience recurrent lung infections and develop disabling pulmonary disease from bronchiectasis before the diagnosis is entertained and treated. Another example of frequent respiratory infections from an underlying systemic disease is in patients with sickle-cell anemia, who exhibit a very high incidence of pulmonary infection by streptococci.

The lungs may be affected in an unusual manner, as exemplified by the neurogenic pulmonary edema following damage to the brain, aspiration pneumonia as a result of incompetent lower esophageal sphincter, respiratory distress syndrome following acute pancreatitis, pulmonary calcification noted in patients on long-term hemodialysis, pneumothorax associated with menses, or pulmonary hypertension in patients with acquired immunodeficiency syndrome.

Even in a single disease entity, there can be a multitude of intrathoracic manifestations. In rheumatoid arthritis, for example, the pulmonary system may demonstrate any or many of the following: pleural effusion, pulmonary nodules, interstitial pneumonitis and fibrosis, laryngeal nodules, bronchiolitis obliterans, or pulmonary vasculitis. The examples provided in the following chapters are not exhaustive but are sufficient to illustrate that the respiratory system provides a valuable indication of the presence and progress of many important systemic diseases.

The diseases and chapters in this section are arranged on the basis of subspecialty orientation in the practice of internal medicine. It is, however, difficult to pigeonhole certain disease entities into a specific organ system because many diseases overlap subspecialty or organ-system boundaries. Nevertheless, the discussions on diseases or disorders are included under the subspecialty area where they are commonly handled in clinical practice. Several topics have been shifted from their location in the previous edition so that now they appear under more appropriate chapters and subject titles. The discussion of noninfectious pulmonary complications in patients with acquired immunodeficiency syndrome has been deleted from this section and moved to Chapter 26. The readers may observe commission of an occasional redundancy. This, however, is unavoidable in a book of this magnitude and format and is preferable to total omission of a topic.

I am very grateful to my colleague and friend Thomas V. Colby, M.D., for contributing many of the photomicrographs that greatly strengthen the educational objectives of this section.

Preface

The need to publish a new edition of this book has been dictated by an increased understanding of the basic science and clinical aspects of pulmonary diseases.

Many chapters from the previous edition have been continued albeit some of them with new authors. A chapter on Molecular Biology of Pulmonary Disease has been added, reflecting the current emphasis on the genetic basis for an increasing number of abnormalities. Two chapters on Differential Diagnosis have been added to emphasize the clinical aspects and the roentgenologic aspects of common pulmonary syndromes. The chapters dealing with aerosols, theophylline, and surfactant reflect an increasing emphasis on Pulmonary Pharmacology.

The broader world view of tuberculosis is presented in the chapters dealing with mycobacterial disease, which have been written in this edition by the group from the New Jersey Medical School National Tuberculosis Center.

The selection of new authors reflects the trend towards the combination of youth and excellence that characterize the best in recent medical literature. Thus, it is our opinion that this edition of the Textbook is written by the very best clinician/scientists in the world of pulmonary medicine.

Two other circumstances deserve mention. Dr. Wolinsky retired as an editor after the last edition, and Drs. Celli, Crapo, and Karlinsky have joined Dr. Baum in producing what we all hope is a textbook worthy of our readers. And Lippincott-Raven has taken on the responsibility of publishing the book. Thus continuity of the technical excellence of the book is assured.

We all sincerely believe that this edition of the *Textbook of Pulmonary Diseases* maintains the high standard achieved in previous editions and will be of value to students, both undergraduate and those highly experienced in the field of pulmonary medicine.

GLB
JDC
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JBK

Preface to the First Edition

Why another textbook? A few years ago when this work began, I approached the prospective contributors and found that they felt, as I did, that the available compilations and texts were weak in one or another of the major areas in the field of chest diseases. It seemed that by using specialists whose major interests were in these areas and allowing them to be responsible for covering all that they felt belonged in their area, a more complete and current textbook would result. Thus, the authors were assembled with an overall plan to cover the field completely and in a coordinated way with current material being woven into concepts by each author.

The difficulties of such a project are apparent. As part of internal medicine, the study of pulmonary diseases involves a wide variety of disciplines. Anatomy, physiology, immunology, bacteriology, mycology, biochemistry, epidemiology, and pathology, among the basic sciences, must be blended with physical diagnosis, therapeutics, radiology, clinical pathology, physiatry, and psychiatry to present a complete picture of this field of medicine. In addition, emphasis must be placed on the more important problems in public health as they bear on each area. Putting this material into an orderly and readable form is crucial to the value of the book, and providing a complete but selective bibliography is essential to making this a true textbook and not just a review.

In many areas, such as allergic disease and interstitial diseases, extensive background discussions precede the actual clinical presentations. This was done in order to provide sound physiologic basis for the clinical expressions of pathology that direct the activities of the clinician. In addition, embryology of the lung is discussed within the areas of congenital, developmental, and hereditary diseases and in continuity with this material rather than in a remote part of the book where its application would not be directly apparent. For the same reason, details of bronchial and parenchymal anatomy are followed by well-illustrated chapters on emphysema and pulmonary insufficiency.

At the clinical level, the approach to the various infectious diseases is consistent, and it makes use of principles proven reliable in the field of clinical bacteriology as the basis of the approach to viral, rickettsial, and fungal diseases. The mycobacterioses are described in a fresh way which clearly integrates new knowledge of chemotherapy and rehabilitation with established pathogenetic and clinical principles. It is in this historically prime subject in the field of pulmonary diseases that this book offers something that has not been available before. The established treatises dealing with tuberculosis have merely modified and appended the old format to include the subjects of drug therapy, drug resistance, resectional therapy, and rehabilitation based on physical activity early rather than late in the course of treatment. No continuity of approach was projected in such an exposition. By contrast, in this textbook, Drs. Jenkins and Wolinsky have synthesized a discussion that deals with broad principles in light of current information on one hand and provide orderly presentation of details on the other.

Diagnosis is the first subject dealt with in this book, and this is appropriate. Drs. Smith and Kory have developed a unique set of tables at the end of their chapters which should be extremely useful to the student and to the practitioner alike. It is no coincidence that Drs. Amberson, Middleton, and Schwarz have each repeatedly stressed the primacy of accurate diagnosis to many generations of students.

The authors and I have attempted to make this book detailed and current enough to appeal to the sophisticated specialist and clinical researcher and orderly, clearly organized, and well indexed to be of use to the beginning student. Because this book deals with pulmonary diseases primarily, specific discussions of mediastinal diseases other than tumors or gastrointestinal diseases with thoracic manifestations have not been included. Finally, I have written nothing myself, but have devoted my efforts to organization of material and exhortation of the authors.

This textbook is only a beginning, since new work will make much of what is written here obsolete; possibly obsolescence will have set in before publication. Nevertheless, the soundness of the physiologic approach allows for the addition of current knowledge to that discussed here without loss of continuity.

I sincerely hope that this book will, through the authority of the authors' material, stimulate the most important ingredient of any textbook in any field: the curiosity of the student.

G.L.B.
Cincinnati

Acknowledgment

Of the many people involved in the production of this edition of the *Textbook of Pulmonary Diseases* who deserve our heartfelt thanks, none is in the league of Laurie Anello. This highly professional medical editor has worked with Dr. Wolinsky and Dr. Baum for two editions of the book and gave the sendoff to Drs. Celli, Crapo, Karlinsky, and Baum for this one.

We wish to express our gratitude to the editing staff at Little, Brown, especially Jo-Ann Strangis, who continued in their active and efficient efforts prior to the change in publishers. And since the changeover formally took place, the energetic approach taken by Joyce-Rachel John and Michelle LaPlante of Lippincott-Raven Publishers has been very impressive, and undoubtedly, responsible for this edition appearing on schedule and in the fine shape that it is in. Their help has been consistent, and the results impressive.

A word about Dr. Wolinsky must be said. As the previous editor of the Textbook, Dr. Wolinsky continued to help in the preliminary planning of this edition despite his formal retirement from editorship. His no-nonsense approach and his good sense is expressed in the best of this current edition.

And finally, all four editors wish to express their sincerest gratitude to our authors, new and veteran.

CHAPTER

1 Normal Anatomy and Defense Mechanisms of the Lung

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INTRODUCTION

Inhalation of approximately 10,000 L of air is necessary to meet the daily gas exchange requirements of the adult human lung. The normal lung has an extraordinary respiratory reserve. Arterial oxygenation commonly improves with exercise, and even under heavy work conditions, pulmonary gas exchange in a normal adult is rarely a cause of limitation to aerobic performance. To accomplish the efficient extraction of oxygen and exchange of carbon dioxide, the lung has an internal surface area approximately equal to that of a tennis court. The upper and lower respiratory tracts act to condition the inhaled air, and the lung has developed unique defense pathways to allow it to maintain its fine, delicate gas exchange surface while being continuously exposed to potentially injurious reactive or infectious agents in inhaled air. This chapter reviews the normal anatomy of the human lung and focuses on the unique structural characteristics that allow the lung to maintain normal function while being continuously exposed to inhaled reactive gases and particles.

THE NORMAL RESPIRATORY TRACT

Two normal adult lungs at maximal capacity contain 5 to 6 L of air and weigh an average of 850 g in men and 750 g in women. Blood makes up a substantial fraction of the lung weight, and *in vivo* the lungs have been estimated to contain as much as 360 mL of blood. Lung weight is approximately 1% of total body weight in a normal adult. Ninety percent of the volume of the lungs is made up of gas exchange regions or lung parenchyma, whereas lung weight is approximately equally divided between the parenchyma and structures other than parenchyma (airways and large vessels).

The right lung is commonly slightly larger than the left, comprising about 53% of the volume of both lungs on average. Each lung is completely covered by a visceral pleura. The visceral pleura subdivides each lung, although incompletely, into lobes. The right lung has three lobes, and the left is divided into two lobes. Incomplete fissures between the lobes commonly allow for some collateral ventilation between lobes. The bronchopulmonary segments are defined by the primary segmental bronchi that branch off the lobar bronchi. Lobar segments are not commonly subdivided by pleura. There are 10 segments in the right lung (Fig. 1) and eight in the left. Common terminology identifies 10 segments in each lung, with the first and second (apical posterior) segments of the left upper lobe being a combined segment and the anterior basal and medial basal segments being combined in the left lower lobe. The left lingula is anatomically part of the left upper lobe and is not commonly separated by a pleura-containing fissure. The fissure separating the right middle lobe from the right upper lobe is termed the *horizontal fissure* and can occasionally be recognized as a horizontal line on an anterior-posterior chest radiograph. The oblique or major fissures separating the upper and lower lobes of both the left and right lungs can be identified on lateral chest radiographs. The left major fissure commonly lies slightly apically and anteriorly to the right major fissure (Fig. 2). However, this apparent position can be easily altered by small variations in the orientation of a left lateral chest radiograph.

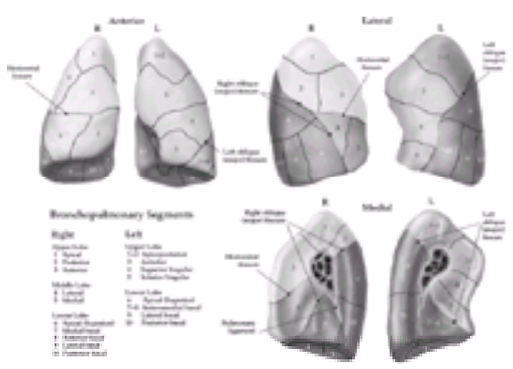

FIG. 1. Location of bronchopulmonary segments from anterior, lateral, and medial views. *See color plate 1.*

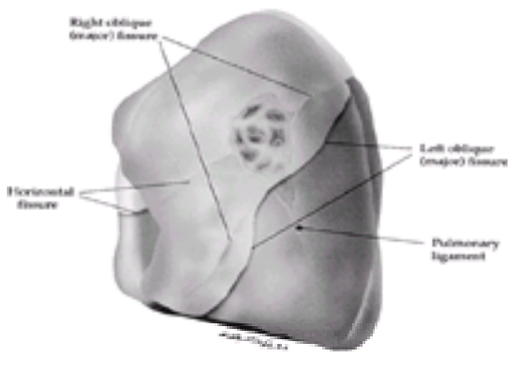

FIG. 2. Left lateral view of the lungs. Partially translucent image of the left lung allows the right lung to be seen. The location of the major fissures and the horizontal fissure of the right lung are illustrated in the positions in which they would appear on a left lateral chest radiograph. Note that the major fissure on the right side lies

slightly anterior and apical to the major fissure on the left side. *See color plate 2.*

A common variant in the lobation of the lung is the presence of a horizontal fissure partially demarcating the superior segment of either the right or left lower lobes. Another variant occurs when during development the azygos vein moves into the apical portion of the right pleural cavity. This displaces parietal pleura into the lung, producing a fissure in the apex of the upper lobe of the right lung. This partially separated lung lobe, known as an *azygos lobe,* occurs in slightly less than 1% of the population. The lingula of the left lung may also be demarcated by an anomalous fissure.

Contours along the lung surfaces for the heart, mediastinal structures, and major vessels are illustrated in Fig. 1. A fold of tissue containing connecting tissue and vessels that extends inferiorly from the hilum on both sides is termed the *pulmonary ligament.*

Pleura

The normal visceral pleura is a thin translucent sheet of mesothelial tissue. It is contiguous with the parietal pleura at the hilum, the parietal pleura being the surface covering of the chest wall. Pleural spaces are filled with a minimal amount of fluid ranging from 1 to 20 mL. The movement of fluid into and out of the pleural space depends on the combined effects of hydrostatic, colloid osmotic, and tissue pressures in the parietal and visceral pleura. The parietal pleura contains lymphatics that drain into the internal mammary artery, periaortic arteries, and diaphragmatic lymph nodes. Pleural fluid is thought to arise primarily from the capillaries lining the parietal pleura. This fluid circulates back across the parietal pleura, where it is cleared by lymphatics. Tracer studies have suggested that the parietal pleura accounts for most fluid movement into and out of the pleural spaces under normal conditions. Visceral pleural capillaries and visceral pleural lymphatics do not normally play a major role in fluid fluxes through the pleural space.

In total, the driving force withdrawing fluid from pleural spaces is greater than the net force moving fluid out of the pleural capillaries and into the pleural spaces. This results in the pleural space remaining relatively dry. Fluid does not normally accumulate in the pleural space unless hydrostatic pressure is elevated in the pulmonary capillary bed or an inflammatory condition of the pleura causes protein leakage into perivascular and pleural spaces, decreasing the oncotic pressure gradient and thereby the major force favoring extraction of fluid from the pleural spaces.

Anatomically, the pleura is made up of mesothelium. Mesothelial cells are characterized by their long microvilli, up to 2 μm in length. These cells contain desmosomal intracellular attachments (macular adherens) and also intermediate filaments in their cytoplasm (cytokeratin). Mesothelial cells have a well-developed endoplasmic reticulum, which suggests that they are metabolically active. Beneath the mesothelial cells is a thin, loose connective tissue structure containing both capillaries and lymphatics. There is also a deeper layer of elastic fibers between the relatively thin visceral pleura and the immediately subjacent alveolar septal tissues. The parietal pleura has a similar architecture, except that the underlying connective tissue layer is substantially thicker and overlies intercostal muscle, fat, and vascular structures.

Lung Lymphatics

Tissue fluids in the lung move centrally toward the hilum. In alveolar tissue, alveolar septal junctions create spaces through which fluid is thought to move until it reaches the walls of an airway or vascular structure in which lymphatic structures are present. These intrapulmonary lymphatics, termed *deep lymphatics,* drain the bronchovascular bundles toward the lung hilum. The superficial pleural lymphatics carry fluid along the pleural surfaces to the point at the hilum where the visceral pleura reflects into the parietal pleura. These superficial lymphatics also follow interlobular septa and thereby interconnect with the deep pulmonary lymphatic system. The deep pulmonary lymphatic system can be clearly identified anatomically beginning at about the level of respiratory bronchioles.

Lymph nodes are abundant in the pulmonary hilum and along the trachea and extrapulmonary bronchi. Lymphatic fluid drains through anastomosing channels that connect these lymph nodes and moves upward along the trachea. The lymphatics on the right side re-enter the systemic circulation through the subclavian vein near its junction with the jugular vein. Pulmonary lymphatics on the left side return to the systemic circulation through the thoracic duct or by directly emptying into the left subclavian vein.

Four major groups of lymph nodes exist in the lung. These include intrapulmonary nodes adjacent to lobar, segmental, and smaller bronchi and small nodes (1 to 3 mm) located in subpleural regions, often at junctions with interlobular septa. Extrapulmonary nodes are situated in the subcarinal region near the bifurcation of the main bronchi. They are also found along the walls of the trachea and main bronchi. The intrapulmonary nodes, which are part of either the pleura or small intrapulmonary airways, are termed *N1 nodes.* Extrapulmonary nodes along the main bronchi may also be termed *N1.* Subcarinal and ipsilateral tracheal nodes are termed *N2,* whereas contralateral hilar, tracheal, or bronchial nodes are termed *N3.*

The lung also can contain aggregates of lymphoid tissue along all levels of large and small airways. This tissue is called *bronchus-associated lymphoid tissue* (*BALT*). BALT contains lymphoid follicles with germinal centers but does not have the fibrous capsule and capsular sinus characteristic of lymph nodes. The question has been raised as to whether BALT occurs normally in humans or rather develops only after stimulation. Its specific role in immune regulation is not yet well defined.

Upper Respiratory Tract

The upper respiratory tract plays a critical role in conditioning air entering the lungs. Most of the air moving through the nasal cavity has turbulent flow characteristics. In addition, air moving downward into the trachea encounters a right-angle turn at the posterior nasopharynx (Fig. 3). Because of these characteristics of nasopharyngeal anatomy and air flow dynamics, most airborne particulate matter and highly reactive gases impact or are absorbed along the mucosal surfaces and so are removed in the upper airways. Aggregates of lymphoid tissue in the posterior pharynx (pharyngeal tonsils) also play a role in clearing the large amounts of airborne material deposited in the nose and other regions of the upper respiratory tract. Most airborne materials deposited in the upper airway tract are moved posteriorly along the nasal mucous coat to the posterior pharynx, where the secretions are eventually swallowed. The upper respiratory tract also plays a role in warming and humidifying the air. This process is continued in the large airways. For gases of low reactivity and particles of 1 μm in size, upper respiratory tract clearance is less efficient. A significant fraction of these airborne pollutants is deposited in the small airways and alveolar regions.

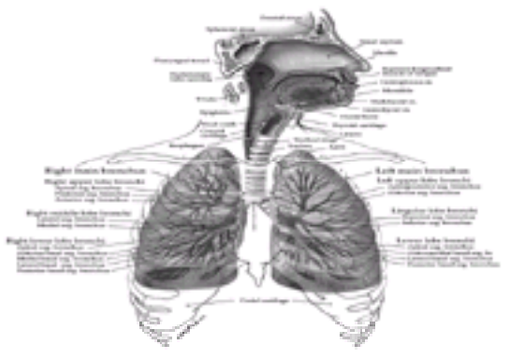

FIG. 3. Anatomy of the upper and lower respiratory tracts.

Trachea and Bronchi

The trachea and main bronchi contain U-shaped rings of hyaline cartilage. The dorsal wall of the trachea is made up of a smooth muscle coat (the trachealis muscle). The main bronchi are fully encircled with cartilage for only four to six generations. Thereafter, the cartilaginous rings of intrapulmonary bronchi contain islands of cartilage that are not contiguous. The number and size of these cartilaginous islands diminish as the airways become smaller and more peripheral. This organizational pattern of cartilage has the advantage of assisting in an effective cough mechanism. The cough is initiated when intrapulmonary pressure is raised against a closed glottis, causing the smaller bronchi to narrow in size. The abrupt opening of the glottis with the onset of cough leads to high pressure and rapid flow through narrow airways, which can facilitate removal of obstructing secretions. Under normal breathing conditions, the intrapulmonary bronchi do not collapse because they are tethered to surrounding alveolar tissue with elastic and cartilaginous interconnections. The incomplete cartilage rings provide support for the intrapulmonary airways

while still permitting them to narrow.

Intrapulmonary bronchi contain a subepithelial elastic layer. Outside this, smooth muscle bundles form a narrow spiral around the airways, with the smooth muscle extending to the level of the respiratory bronchiole. The tight spiral organization of the smooth muscle causes airway narrowing when the smooth muscle contracts. A loose connective tissue layer surrounds the muscular coat, and bronchial glands and cartilage plates lie in this space.

The bronchial epithelium is a stratified epithelium that includes a number of cell types. Predominant among these are secretory cells, which in the large airways are primarily mucus-secreting cells. Ciliated epithelial cells and nonciliated basal cells make up the other two major airway epithelial cell types. The bronchial epithelium also contains neurosecretory cells, termed *Kultschitsky cells* or *K cells.* They are similar to the Kultschitsky cells found in the gastrointestinal tract. These cells, which occur singly or in clusters of four to 10 cells termed *neuroepithelial bodies,* are thought to have a neuroendocrine secretory function. These endocrine cells are found in both bronchi and bronchioles. Kultschitsky cells are most distinctively recognized by their large numbers of fine, dense core granules aggregated in the basal part of the cells. The granules are secreted basally into the peribronchial connective tissue and surrounding smooth muscle. Various products identified with the neuroendocrine cells influence smooth muscle contraction, secretion of mucus, and ciliary beat.

Cilia are the principal means for clearing inhaled toxicants deposited in the mucous lining layers of the nasal passages and airways. Dysfunction in cilia is known to predispose individuals to respiratory infections and bronchiectasis. Ciliated cells are densely distributed in the airways, and the cilia greatly increase their apical surface area. The plasma membrane surface of the cilia accounts for approximately 80% of the plasma membrane surface in airways. Thus, the cilia themselves are a primary filter and/or target for inhaled toxicants that react with cell membranes. In the serous fluid layer in which they beat, the cilia make up 40%–50% of the volume. Each ciliated cell contains approximately 200 cilia; these beat in a biphasic stroke consisting of a fast forward flick and a slower recovery motion. Coordinated strokes by adjacent ciliated cells produce a proximally directed wave of motion in the mucous lining layer. The beating cilia produce mucociliary transport rates that vary from approximately 20 mm/min in the large bronchi to a distinctly slower rate of approximately 1 mm/min in the bronchioles. This gradient in transport rates has been assumed to be the result of a corresponding gradient in ciliary density, with fewer cilia in the small airways and greater numbers in the larger airways, to prevent piling up of mucus on the relatively small surface area of the larger airways. However, direct measurements of the density of ciliated cells and their cilia do not support this hypothesis. The mechanism or mechanisms responsible for the higher transport rate of mucus in larger airways remain to be determined.

Ciliated cells not only mechanically move mucus but also have a secretory function. These epithelial cells contain ion pumps that move sodium away from the bronchial lumen and chloride toward it. This allows water to follow the resulting osmotic gradient and thereby control the thickness and viscosity of the serous fluid layer. Proteins controlling this ion flux are encoded by the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene is a highly regulated chloride channel in the apical membrane of ciliated epithelial cells. Mutations in this gene cause cystic fibrosis.

Mucous cells (goblet cells) and mucous glands both produce mucus, but the volume coming from glands is substantially greater than that derived from mucous cells under normal conditions. The mucous glands are compound tubular glands lining the submucosa of the bronchi between cartilage plates. The glands are connected by a secretory tubule to the airway lumen. Plasma cells are often found around these secretory tubules. The plasma cells contain both IgA and IgG, although the primary immunoglobulin in mucus is 11S secretory IgA. Two IgA molecules, both of which are produced by plasma cells, are joined by the J protein. These molecules are then complexed with a secretory piece by epithelial cells lining the secretory tubules, and the complex is transported into the tubular lumen and into the mucous layer.

Examples of airway epithelium and mucous layer architecture from human bronchi are shown in the electron micrographs of Fig. 4. Characteristic profiles of ciliated and goblet cells are illustrated in Fig. 4A. In Fig. 4B, a goblet cell is in the process of secreting into the mucous lining layer. The mucous lining layer in this micrograph has a well-defined electron-dense surface film at the top of the sol layer. Examples of other secretory and basal cells in human airways are shown in Fig. 5. Secretory cells other than goblet cells are typically found in highly clustered groups, as illustrated in Fig. 5A, showing a group of secretory cells containing electron-dense granules. A basal cell with numerous desmosomes (*d*) and keratin filaments (*f*) appears in Fig. 5B. An intermediate cell (*I*) with the same features as a basal cell (i.e., desmosomes, keratin filaments, and a high nucleus-to-cytoplasm ratio) but no basement membrane contact is shown in Fig. 5C. The layered arrangement of cells in human bronchi is principally attributable to the basal cell layer, which accounts for approximately 90% of the cell surfaces making contact with the basement membrane. In the pseudostratified epithelium of human bronchi, the average basement membrane contact of a ciliated, goblet, or other secretory cell is significantly smaller than that of basal cells. The large concentration of keratin filaments and hemidesmosomes found in basal cells suggests that these cells play a primary role in the attachment of columnar cells to the basal lamina.

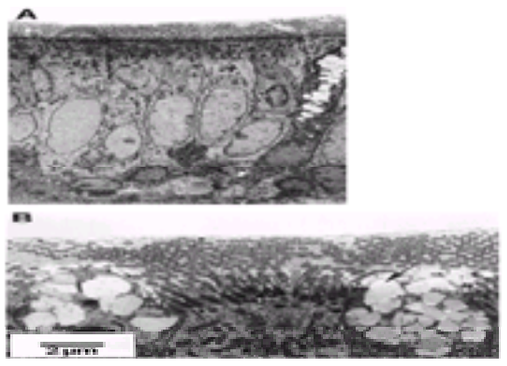

FIG. 4. Electron micrographs of the airway epithelium and mucous lining layers from human bronchi. **A:** Ciliated cells showing mitochondria concentrated in the apical portion of the cell and cilia extending into the mucous lining layer. One goblet cell is shown with its secretory granules distributed across the upper half of the cell. **B:** Two goblet cells in the process of releasing electron-lucent secretory granules from their apical surface into the mucous lining (*arrow*). This micrograph also illustrates a region in which the gel (or electron-dense) layer above the cilia is absent. (Reproduced with permission from Mercer RR, Russell ML, Roggli VL, Crapo JD. *Am J Respir Cell Mol Biol* 1994;10:613–624.)

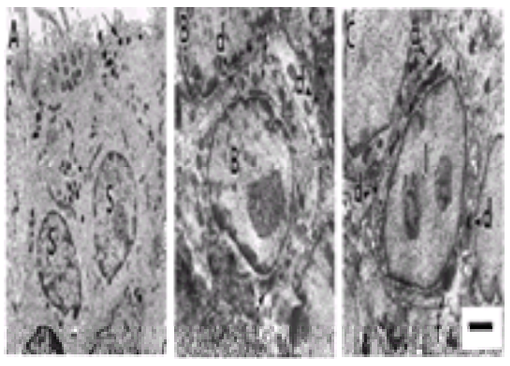

FIG. 5. Electron micrographs of secretory, basal, and intermediate cells from human bronchi. **A:** Secretory cells (*S*) containing electron-dense granules (*arrows*). **B:** Several desmosomes (*d*) and keratin filaments (*f*) of a basal cell (*B*). **C:** An intermediate cell (*I*) with the same features as a basal cell (i.e., desmosomes, keratin filaments, and a high nucleus-to-cytoplasm ratio) but no basement membrane contact. Whereas a prominent nucleolus is typically found in basal cell nuclei, two nucleoli, as illustrated in the intermediate cell in C, were noted only in intermediate cells. *Bar* at the bottom right represents 2 µm. (Reproduced with permission from Mercer RR, Russell ML, Roggli VL, Crapo JD. *Am J Respir Cell Mol Biol* 1994;10:613–624.)

Mucous Lining Layers

It has long been known that the lung clears or removes inhaled particulate matter by means of a mucociliary escalator mechanism. The mucous lining of the lung airways is composed of at least two physically and morphologically distinct layers: an underlying serous layer, in which the cilia beat (sol layer), is blanketed by a viscous layer (gel layer). Whether a continuous gel layer exists throughout the airways is a matter of debate. In general, studies focusing on the nasal epithelium and upper airways have found a continuous blanket, whereas studies focusing on more distal airways and bronchioles have not. More recent studies have demonstrated

that the mucous lining layer of the airways contains a surface-active film at the air-fluid interface in addition to the two layers originally described.

The bronchial epithelium plays a critical role in both producing and moving mucus out of the lung. The rate of movement of mucus is slowest in the small airways and fastest in the large bronchi and trachea. The normal adult produces substantial quantities of lung secretions daily, virtually all of which are transported by ciliary clearance to the posterior pharynx, where they are unconsciously swallowed. The outer layer of the mucous coat is a highly viscous gel containing glycoproteins with molecular weights of several million daltons. In addition to mucous glycoproteins, the airways secretions contain immunoglobulins (primarily IgA), proteinase inhibitors, and antibacterial proteins (lysozyme and lactoferrin). Sixty to eighty percent of the cells in the airway epithelium are ciliated cells; the remaining cells are either basal or secretory cells.

Methods for preserving the mucous lining layer have included direct visual observation on dissected airway specimens, fixation by immersion, vascular perfusion fixation, quick freezing, and osmium tetroxide vapor fixation. Of these different methods of preservation, vascular perfusion fixation is the most generally applicable, as mechanical disruption from immersion or airway instillation of fixative is eliminated. Because the extensive capillary bed of the lungs is used to place the fixative in the immediate vicinity of the fluid lining layers, this method has been shown to improve significantly the preservation of mucous lining layers in the airways and the surface-active film of the alveolar region. Figure 6 demonstrates the changes in the mucous lining layer along the respiratory tract of a lung fixed by a combination of osmium vapor and vascular perfusion fixation. The gel layer is present in the airways from the trachea to the bronchi. In the distal and terminal bronchioles, the gel layer is attenuated and not always present. Tubular myelin and other surfactant debris are commonly found in both the gel layer of the upper airways (trachea to bronchi) and near the surface of the sol layer of the more distal airways, where the gel layer may be absent.

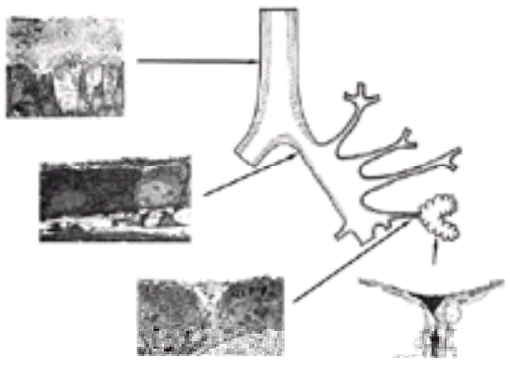

FIG. 6. Changes in the mucous lining layer along one airway path from trachea to alveolar surface. The thickness decreases from 10 to 20 μm in the trachea to 0.1 μm on the alveolar surface.

Bronchioles

Bronchioles are defined by the absence of cartilaginous structures in the bronchial wall. Smooth muscle continues along bronchiolar walls and reaches the terminal bronchioles. The bronchial smooth muscle spirals around the airways and does not form a continuous coat in the bronchial wall. Thus, there is no true muscular mucosa in bronchi. The connective tissue surrounding bronchial walls is termed the *lamina propria.* The lamina propria includes vascular structures, lymphatics, loose fibrous tissue, and modest numbers of inflammatory cells. Adipose tissue may also be found in the walls of bronchi, particularly in older individuals.

The airway epithelium of bronchioles is simple columnar and is made up of two primary types of cells, ciliated cells and nonciliated secretory cells. The latter cell type commonly is termed a *Clara cell.* Unlike the arrangement in the bronchial epithelium, ciliated cells and Clara cells in the bronchioles have extensive contact with both the luminal and basement membrane surfaces. Mucus-secreting cells are not found in bronchioles under normal conditions. Chronic exposure to tobacco smoke can cause proliferation of mucous cells, which are then found in bronchioles and likely account for the higher density of viscous small-airway secretions in smokers. The production of mucus in small airways in response to chronic irritation is an adaptive response that would have the effect of absorbing or reacting with inhaled pollutants, thereby providing better protection of the underlying bronchiolar epithelium. The function of Clara cells is still being defined. These cells are thought to be involved in production of the thin serous fluid that normally lines small airways, in the detoxification of chemicals depositing in small airways, and in regulating the immune or inflammatory responses in airways. Their products include surfactant apoproteins A, B, and D, antileukoproteinase, and a unique 10-kD protein that has been found to bind to environmental pollutants. Clara cells are also thought to be a stem cell involved in the regeneration or repair of epithelial injury in bronchioles.

The number of cells per unit area of epithelial basement membrane for human airways is shown in Fig. 7. The cells populating the airway epithelium change significantly as the airways narrow and a transition occurs from a pseudostratified epithelium (with an extensive population of basal and goblet cells) to a simple columnar epithelium in bronchioles. The pseudostratified arrangement of cells in the epithelium of human bronchi creates a total epithelial cell density almost twice that of the more distal bronchioles. In addition, the cell composition changes, from larger numbers of goblet and basal cells in bronchi to larger numbers of Clara cells in bronchioles.

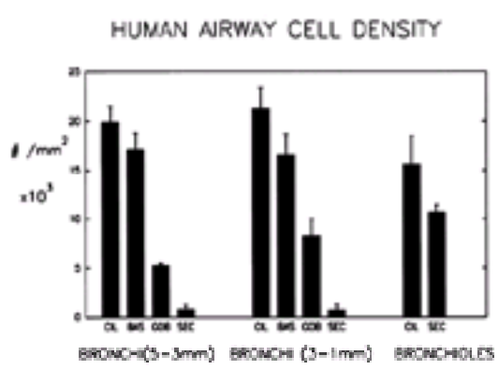

FIG. 7. The number of cells per unit area of epithelial basement membrane for human airways. Human airway cell populations change dramatically from the pseudostratified epithelium of bronchi, which have a large proportion of basal (*bas*) and goblet (*gob*) cells, to the simple columnar epithelium of bronchioles, composed primarily of ciliated (*cil*) and secretory (*sec*) cells.

Bronchial Branching

A terminal bronchiole represents, on average, 16 generations or branchings from the trachea. Most of the path lengths are shorter and can consist of as few as six to eight generations. The longest path length is the axial path to the posterior caudal tip of the right lower lobe, with 20 to 25 generations. Human lung airways are characterized by an asymmetric, dichotomous branching pattern in which the two (or three) daughter branches at most junctions are not of the same diameter and do not form a consistent, symmetric branching angle with the parent airway (Fig. 8). Pulmonary arteries follow the airways, whereas pulmonary veins lie in the boundaries between gas exchange units. This position allows the veins to accept blood from multiple adjacent gas exchange units (Fig. 9). An important result of the vascular supply following the airways is that each segmental bronchus with its pulmonary segment has its own vascular supply. Thus, a pulmonary segment can be resected as an anatomically discrete subdivision. Resection of one or more pulmonary segments does not compromise the blood flow to adjacent lung segments.

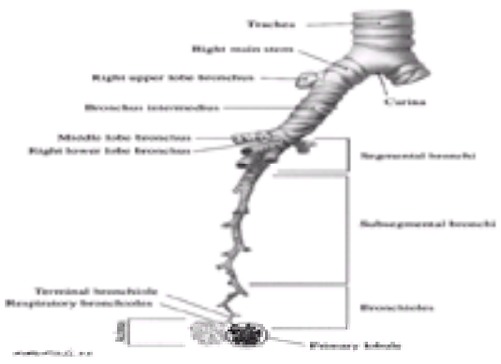

FIG. 8. Airway anatomy of the human tracheobronchial tree. This figure illustrates typical branching along one of the longer paths to a right lower lobe segment. In the normal human lung, there are approximately five to 15 branch points from a segmental bronchus to a terminal bronchiole. In a completely binary, symmetric branching system, 14 to 15 branch points from the trachea would be required to create the 40,000 terminal bronchioles in a human lung. Because many paths are shorter, there are also path lengths with greater than 15 branch points from the trachea. Segmental bronchi are characterized by the presence of cartilaginous plates in their walls, whereas bronchioles contain smooth muscle in their walls but no cartilage. *See color plate 3.*

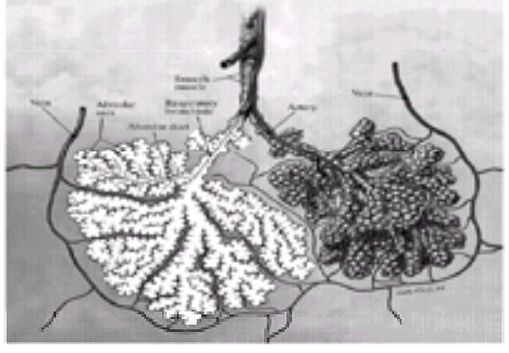

FIG. 9. Vascular supply and branching anatomy of the human acinus. Respiratory bronchioles typically show up to three branch points, whereas alveolar ducts have up to nine branches. Pulmonary arterioles travel with the respiratory bronchioles and alveolar ducts into the center of the acinus. The capillary network radiates outward from the arterioles to form anastomoses with the venous system, for which the major channels lie on the surface of the acinus.

Acini

All the gas exchange structures distal to a single terminal bronchiole represent an acinus. Thus, an acinus is a parenchymal lung unit in which all structures participate in gas exchange. The human lung fairly consistently has three generations of respiratory bronchioles that are followed by a number of divisions of alveolar ducts. Rats have from three to 13 divisions of alveolar ducts, and the human lung has a similar alveolar ductal architecture, with approximately nine generations of alveolar ducts.

A typical normal human lung contains approximately 30,000 to 40,000 terminal bronchioles and, by definition, the same number of acini. Each acinus is approximately 6 mm in diameter and has a volume of approximately 0.50 mm^3. Acini vary substantially in size and typically contain 10,000 to 12,000 alveoli (Table 1).

Volumes (gas)	
Upper respiratory tract	20 cm^3
Airways	
Bronchi	88 cm^3
Bronchioles	23 cm^3
Alveolar region	5018 cm^3
Numbers	
Terminal bronchioles	30–40,000
Acini	30–40,000
Alveoli	500×10^6
Cells (alveolar region)	20×10^9
Epithelial cells	
Upper respiratory tract	560×10^6
Bronchi	7200×10^6
Bronchioles	3300×10^6
Alveolar region	$52,000 \times 10^6$
Surface areas	
Upper respiratory tract	104 cm^2
Bronchi	1300 cm^2
Bronchioles	1100 cm^2
Alveolar epithelium	1,022,000 cm^2
Alveolar capillaries	720,000 cm^2
One alveolus	121,000 μm^2

TABLE 1. *Structural characteristicsof the normal human lung*

In older literature, divisions of the lung into primary and secondary lobules is described. The primary lobule refers to all respiratory tissue distal to a final respiratory bronchiole, and thus contains only alveolar ducts and alveolar sacs. Some animal species, such as the rat, have only rudimentary respiratory bronchioles, and in this situation a primary lobule is a useful concept to define aspects of ventilation and gas distribution in specific lung units. In the human, the primary lobule is not a very useful concept, because the acinus divides into multiple respiratory bronchioles and a high degree of collateral ventilation occurs between these subunits. Secondary lobules are lung units delineated by connective tissue septa; they are about 1 cm^3 in size. They form structures that are clearly visible on the pleural or cut surface of the lung. The secondary lobule is supplied by a bronchiole with a diameter of about 1 mm that divides into five to 12 terminal bronchioles, and thus into a similar number of acini.

Alveoli

The gas exchange region of the lung is made up of approximately 500,000,000 alveoli having a total surface area of approximately 100 m^2. These alveoli are highly vascularized, with the alveolar septal capillary bed having a vascular surface area of approximately 70 m^2. The normal alveolar septa are approximately 10 µm thick. The alveolar air-capillary barrier is made up of variable thin and thick segments. The thin segment is composed of an alveolar epithelium, a fused epithelial and endothelial basement membrane, and a capillary endothelium. Because both type I epithelial cells and capillary endothelial cells are highly attenuated, the combined thickness of this air-blood barrier can be as little as 0.5 µm. The alveolar walls contain connective tissue, primarily collagen, which weaves through the capillary mesh. This and other cellular and acellular components of the interstitium create the thicker portions of the alveolar septal walls. Three-dimensional reconstructions of alveolar septal walls from rats have demonstrated that the alveolar entrance rings are particularly rich in both collagen and elastin. Alveolar mouths form the boundary of alveolar ducts (Fig. 10), and their entrance rings are linked together into a connective tissue structure that spirals down alveolar ducts, providing a connection between the openings or mouths of individual alveoli. Elastic tissue is most prominent along the alveolar duct openings. Collagen strands or fibers interlace across the alveolar walls and connect adjacent alveoli along a single alveolar duct as well as connect alveoli between two adjacent alveolar ducts.

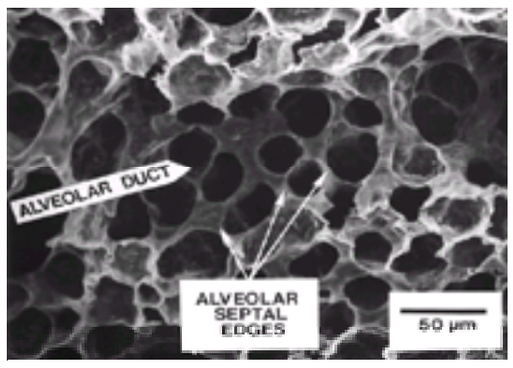

FIG. 10. Scanning electron micrograph of the alveolar duct region from a rat lung. The alveolar duct walls are made up of alveolar mouth openings surrounded by flattened alveolar septal edges forming the entrance rings around the alveolar openings. The primary collagen and elastin network lining the alveolar ducts is under tension in this fully expanded lung.

Based on morphologic evidence of collagen and elastin distributions and the effects of surfactant depletion on the structure of alveoli and alveolar ducts, Wilson and Bachofen developed a model of lung micromechanics comparing the contributions of alveoli and alveolar ducts to lung elasticity. This model suggests that elastic components abundant in the walls of alveolar ducts are primarily responsible for the function of alveolar ducts, whereas surface tension effects are primarily responsible for the tension in alveoli. Three-dimensional reconstructions of alveoli and alveolar ducts as transpulmonary pressure is raised from 0 to 30 cm H_2O demonstrate that at low lung volumes alveoli make up 80% of the parenchymal lung volume and dominate the gas volume changes. As pulmonary pressure increases, the contributions to changes in volume by both alveoli and alveolar ducts converge (Fig. 11). This suggests that at high lung volumes connective tissue elements, both between and within the alveolar ducts, come under tension and act to equalize further changes in volume between alveoli and alveolar ducts. This both limits overextension of alveoli and enhances lung stability by distributing stress among all contributing units of an alveolar duct interconnected by elastic and collagenous structures.

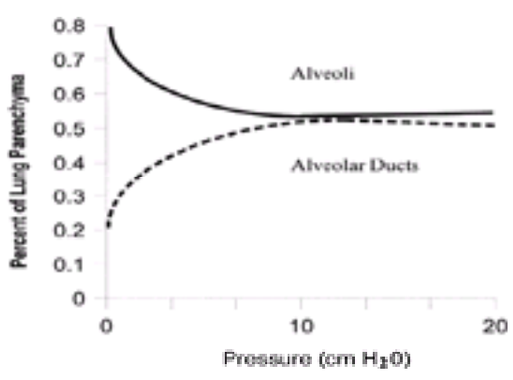

FIG. 11. Volume ratios of alveoli and alveolar ducts as a function of the transpulmonary extending pressure. These pressure-volume relationships were determined using morphometric point-counting procedures to estimate the relative contributions of alveoli and alveolar ducts during lung expansion. At low lung volumes, alveoli make up the majority (80%) of the lung parenchyma. As lung volume increases, alveolar ducts initially show the greatest change in volume, and they increase from 20% to almost 50% of the volume of the lung parenchyma. At about 10 cm of water pressure, the two curves converge, showing that changes in volume of these two compartments are proportionally similar from intermediate to high lung volumes or pressures. The convergence of these two curves at higher pressures suggests that the connective tissue elements within and between the alveolar ducts are under tension and help stabilize the lung by equally distributing further increases in lung volume.

The alveolar epithelium is covered primarily by type I and type II epithelial cells. The characteristics of the alveolar septal wall in normal human lung is shown in Fig. 12. Type I epithelial cells are thin squamous epithelial cells having an average surface area of approximately 7000 μm^2 (Table 2). Their highly attenuated cytoplasm has an average thickness of only 0.36 µm. The alveolar epithelium contains approximately equal numbers of type I and type II cells. The type II cell is cuboidal in shape and is commonly found at junctions of alveolar septa and along the alveolar surfaces surrounding intrapulmonary vascular and airway structures. Alveolar type II epithelial cells have conspicuous mitochondria and an extensive Golgi apparatus, indicating a high synthetic role for these cells. They are characterized chiefly by the presence of large numbers of small microvilli on the apical surface (Fig. 13) and of unique secretory granules, known as *lamellar bodies.* Each type II cell contains 100 to 200 lamellar bodies. These are composed of tightly packed whirls of surfactant, which give these bodies their lamellar appearance on cross-section. The continued secretion of lamellar contents replenishes surfactant at the alveolar air-liquid interface. Alveolar type II cells are connected to adjacent type I cells with a relatively impermeable tight junction. These junctions contain three to five junctional strands on electron microscopy of freeze-fracture replicas. Type II cells have four known primary functions: (1) They secrete surfactant. (2) They act as an ion pump, moving fluid from the alveolar spaces into the subjacent interstitial spaces. Type II cells move sodium from the alveolar lumen to the interstitium via an apical sodium channel regulated by cyclic AMP. Water passively follows the sodium movement. (3) They repair alveolar injury. These cells are the progenitor cells for alveolar epithelium and can regenerate alveolar type I epithelium. (4) They control alveolar inflammation. Type II alveolar epithelial cells secrete antiinflammatory cytokines. They also secrete antioxidants, including the extracellular superoxide dismutase enzyme. Type II cells have been shown to secrete nitric oxide by the activation of nitric oxide synthase. The secretion of both antioxidant enzymes and nitric oxide by type II cells is induced by the proinflammatory cytokines interferon-g and tumor necrosis factor-a, suggesting a role for these cells in the control of inflammatory functions.

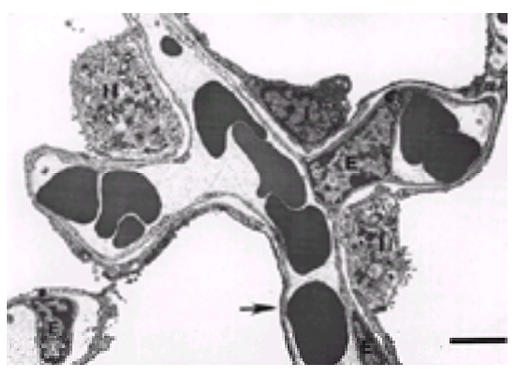

FIG. 12. Transmission electron micrograph showing the alveolar septum from a normal human lung. An efficient exchange of O_2 and CO_2 between inspired air and red blood cells is promoted by the large gas exchange surface with minimal distances (*arrow*) across the epithelial, interstitial, and endothelial components of the alveolar septa. *I,* type I alveolar epithelial cell; *II*, type II alveolar epithelial cell; *c*, capillary endothelial cell. Bar = 1 µm. (Reproduced with permission from Crapo et al. *Am Rev Respir Dis* 1982; 125:740–745.)

	No. in both lungs	Average cell surface area	Average cell volume
Alveolar epithelial cells			
Type I	19×10^9	6900 μm^2	2400 μm^3
Type II	32×10^9	250 μm^2	800 μm^3
Capillary endothelial cells	73×10^9	1000 μm^2	600 μm^3

TABLE 2. *Characteristics of alveolar septal cells in normal human lung*

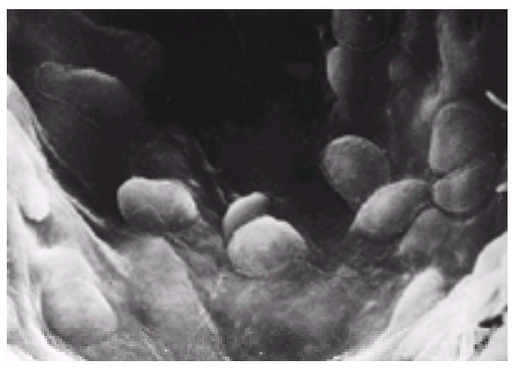

FIG. 13. Scanning electron micrograph of the alveolar septal surface showing several type II alveolar epithelial cells surrounded by type I epithelium. Type II cells are identified by their distinctive microvilli. In this micrograph, the overlying surfactant layer was removed by fixatives.

The shape of alveoli *in vivo* approximates a smooth partial circle. Smoothing of the folds on the alveolar surface is accomplished by folding of alveolar septal membranes into the capillaries and by filling of tissue depressions with alveolar lining fluid containing surfactant at its surface. Changes in alveolar size are thought to occur primarily by folding and unfolding of the alveolar pleats, and this process minimizes stress tension on alveolar septal cells.

Stability of alveoli with their small radius of curvature requires a highly surface-active material at the air-liquid interface. La Place's Law describes the relationship of the alveolar pressure (P) required to keep an alveolus open with alveolar surface tension (t) and radius of curvature (r):

$$P = 2\ \tau/r$$

According to this principle, as the radius falls during exhalation, the surface tension must also fall, or the required pressure to maintain open alveoli would rise. As alveolar pressure falls during exhalation, this scenario would result in alveolar collapse with each breath. Surfactant prevents alveolar collapse. As the radius of alveoli decreases, the surfactant phospholipids are packed more tightly and surface tension is reduced. Thus, alveolar surface tension and the radius of alveoli *in vivo* fall synchronously, and alveolar stability is maintained.

Surfactant is a complex mixture of lipids and proteins synthesized by alveolar type II epithelial cells. The primary lipids include saturated phosphatidylcholine and phosphatidylglycerol. Surfactant also contains a number of proteins, three of them identified as surfactant proteins A, B, and C. Each of these facilitates the spreading and recycling of surfactant. A fourth surfactant protein, SP-D, is produced and secreted by type II cells but is not known to be a part of surfactant. It is thought to play a role in antibacterial defense.

The proportion of the alveolar septum of the human lung that is interstitium is substantially greater than in many other species, as shown in Fig. 14. The alveolar interstitium increases as a function of age in both rodents and humans. The high amount of interstitium in the human lung likely reflects the substantially longer life span of the human and exposure to environmental air pollutants. The lungs of children have substantially less interstitial connective tissue and interstitial matrix elements than do adult human lungs (Fig. 14.) The alveolar macrophages on the alveolar surfaces in a normal nonsmoking human make up only about 3% of total alveolar cells. The number of alveolar macrophages is substantially elevated in smokers and can be 10% of the alveolar septal cells. The normal human alveolus has a diameter of about 225 µm and a surface area of 120,000 μm^2; it is made up of 148 endothelial cells, 106 interstitial cells, and 107 epithelial cells (types I and II) and contains 12 alveolar macrophages. The comparative cellular anatomy of an average alveolus from the mouse to the human is shown in Fig. 15. The relative cell composition of the alveolar septa is similar across species. The larger alveoli of larger species are generally contain more cells of the same average size rather than larger cells. The differences in cellular size and shape between cells of different function are dramatic, as shown in Table 2, with the alveolar type I epithelial cell being four times larger than a capillary endothelial cell and having a sixfold greater surface area. Thus, cellular function, not species or organ size, determines characteristics of each class of cell.

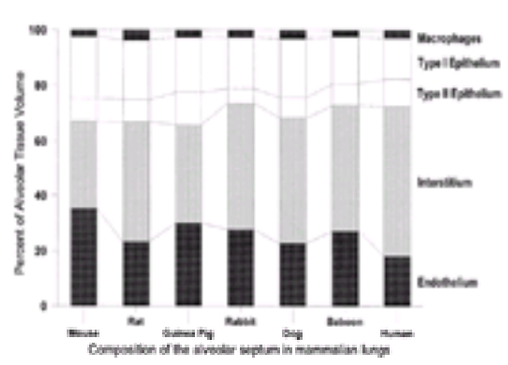

FIG. 14. Composition of the tissues of the alveolar region in mammalian lungs. The ratios of endothelium, interstitium, epithelium, and alveolar macrophages are shown. Note that the human lung has proportionally more interstitium than do the other species illustrated. This is likely related to the extensive environmental pollutants to which human lungs are exposed, leading to microscopic fibrotic interstitial reactions.

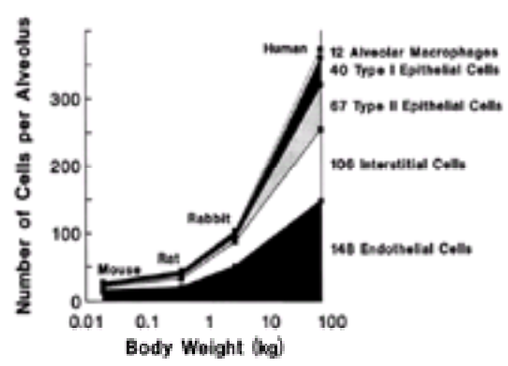

FIG. 15. The cellular makeup of alveoli in mouse, rat, rabbit, and human. Numbers along the right vertical axis correspond to the data for human lungs. The typical human alveolus is made up of almost 400 cells.

Pulmonary Circulation

The main pulmonary artery and the next several generations of pulmonary arteries with diameters greater than 0.5 cm are called *elastic arteries.* The walls of these vessels contain multiple concentric elastic lamina as well as smooth muscle and collagen layers. These vessels enter the lung at the hilum and lie adjacent to and branch with each of the bronchi. Arteries with diameters ranging from 0.1 to 0.5 cm are termed *muscular pulmonary arteries.* These vessels contain circular smooth muscle located between an internal and external elastic lamina. Muscular pulmonary arteries begin at the level of smaller bronchi, have the same approximate diameter as the bronchi, and travel and branch with the bronchi. These arteries continue to follow bronchioles and respiratory bronchioles and enter into the center of the acinus, branching with alveolar ducts. Their size decreases as they move peripherally, and by the time they reach the acinus they are substantially smaller than the alveolar ducts.

Pulmonary veins travel in the peripheral walls of acini and along the connective tissue planes of sublobular and lobular septa. Thus, blood enters the acinus alongside the airways and then moves outward across the acinus to the periphery, where pulmonary veins collect blood from multiple adjacent acini. Each vein drains a much larger zone than is supplied by a single small muscular pulmonary artery.

A separate circulation and nutrient supply to the bronchi and the walls of their adjacent pulmonary arteries arises from the systemic circulation via bronchial arteries. These arteries come directly from the aorta or from the internal mammary, subclavian, or intercostal arteries. This systemic arterial supply to the bronchi travels as small vessels in the walls of the bronchi and extends to the level of the bronchioles. Bronchial veins exist only in the most central bronchi and empty into the azygos and hemiazygos veins. The remainder of the bronchial arterial circulation drains into pulmonary veins and moves by that circuit to the left atrium.

The relative surface areas and volumes of different components of the pulmonary vascular bed are given in Table 3. The volume of blood in the lung is normally approximately equally distributed between the arterial system, capillary network, and venous system. Ninety-six percent of the pulmonary vascular surface area is in the capillary bed. The capillary network has the capacity for substantial expansion if all capillary beds are recruited and functional, as under conditions of exercise. When the capillary network is fully recruited, the proportion of the pulmonary blood volume in the capillary bed can increase from 30% to 50%–60%.

Vessel	Surface area	Volume
Arteries > 500 μm	0.4 m^2	68 cm^3
Arterioles 13–500 μm	1.0 m^2	18 cm^3
Capillaries	70 m^2	60–200 cm^3
Venules 13–500 μm	1.2 m^2	13 cm^3
Veins > 500 μm	0.1 m^2	58 cm^3

TABLE 3. *Human pulmonary vascular system*

The pulmonary vascular system is a low-pressure circulation, and the pulmonary arteries are substantially more distensible than are systemic arteries. Pulmonary veins are also highly distensible at relatively low transmural pressures. Distensibility of the pulmonary vascular bed makes it possible for the blood volume to change readily in response to vasomotor stimuli or hydrostatic/orthostatic conditions. The pulmonary vascular bed acts as a capacitance reservoir for the left side of the heart. Sufficient blood is contained in the elastic reservoir to support two to three heartbeats. Pulmonary blood volume can increase 30% during a change of position from standing to lying. Up to half of the pulmonary blood volume can be forced out of the lungs by Valsalva's maneuver (increasing intrathoracic pressure against a closed glottis).

The vertical height of a normal human lung is about 25 cm, with the hilum situated about one-third the distance from the top of the lungs (Fig. 2). Pulmonary capillary pressure varies from the top to the bottom of the lung. With an average pulmonary arterial pressure of 20 cm H_2O, the pulmonary arterial pressure from the top to the bottom of the lung varies from 12 cm H_2O to 36 cm H_2O. Pulmonary venous pressure varies from approximately 0 at the top of the lung to 24 cm H_2O at the bottom, with a mean pressure of 6 to 8 cm H_2O at the hilum. Thus, with a highly distensible pulmonary vascular bed, pulmonary blood volume is preferentially distributed toward the dependent portions of the lung. The effects of gravity and distensibility are balanced by vasomotor tone regulating blood flow across the pulmonary vascular bed. Because muscular arteries extend into the acinus, local vasomotor control can influence distribution of blood flow to each lung unit and thereby determine the ventilation-perfusion ratio of each of these units.

Blood flow in the pulmonary capillaries is pulsatile except under conditions of severe pulmonary hypertension. Blood flow in the capillary network has been estimated to have a velocity averaging about 1000 μm/sec.

The pulmonary capillary bed is made up of an extensive network of interconnected small tubules. There has been substantial debate regarding whether pulmonary capillary blood flow is best modeled as tubular flow or sheet flow. Anatomically, as illustrated in Fig. 16, the capillary bed is a combination of the two. The capillary network crosses multiple alveoli as blood flows from the central arteriole in an acinus to the venules at the acinar margins. This creates a fairly long path length over which gas exchange can occur. The average transit time of a red cell through the pulmonary capillary bed has been estimated to be 0.1 to 0.5 sec. Under normal resting conditions, red blood cells are fully saturated with oxygen during the first third of their transit through the pulmonary capillary bed. The lung has a sufficient gas exchange reserve that even heavy exercise does not produce arterial desaturation, and in fact increased blood flow throughout the entire capillary bed generally results in an increased arterial partial pressure of oxygen (PaO_2) under conditions of exercise. Red cells are likely to leave the capillary bed not fully saturated with oxygen only when the inspired oxygen tension is low or when disease prevents adequate ventilation of individual gas exchange units. One of the important ventilation-perfusion regulatory pathways in the lung is hypoxic pulmonary vasoconstriction. Relative hypoxemia in small gas exchange units leads to constriction of the corresponding muscular pulmonary arteries, which maintains balanced ventilation-perfusion ratios. The pulmonary venous system also contains smooth muscle and has been shown to be equally sensitive to vasoactive mediators, thus regulating venous pooling in the lung.

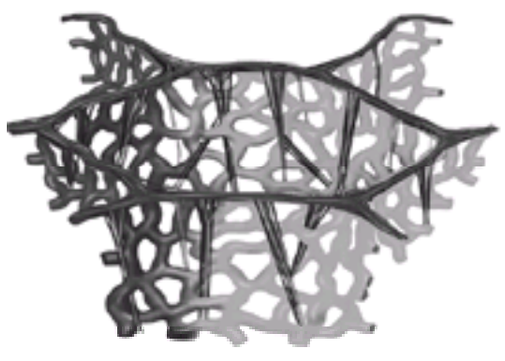

FIG. 16. Schematic illustration of the pulmonary capillary bed showing the high density of short, highly interconnected capillary segments in the alveolar walls. The distribution of collagen and elastin fibers in the lung parenchyma is also shown. The drawing illustrates the high concentrations of connective tissue fibers along the alveolar duct septal edges that form the alveolar duct walls. Elastin fibers tend to be located over the major collagen bundles lining the alveolar entrance rings. Thus, the alveolar entrance rings are rich in both elastin and collagen. The alveolar walls contain thin collagen strands that interconnect adjacent alveoli by weaving between

capillary segments.

The pulmonary capillary bed acts as an efficient filter of the systemic vascular system. Approximately three quarters of the blood volume of the body is contained in the systemic venous system. This blood passes through the pulmonary capillary bed on each circulation, and any microemboli forming in the systemic venous system will therefore be filtered by the lung. These microemboli produce no dysfunctional or pathologic effects in the lung and are rapidly cleared by lytic pathways or the pulmonary reticuloendothelial system. The physiologic effects of resection of one lung clearly demonstrate that up to half the pulmonary vascular system can be obstructed or removed without serious change in the hemodynamics of the remaining pulmonary vascular bed. This design of the pulmonary vascular system allows it to be an efficient filter of the body's blood supply.

Capillary endothelial cells form a continuous lining of alveolar capillaries. These cells are connected by tight junctions that, however, are more permeable to macromolecules than are the junctions between airway epithelial cells. Endothelial cell junctions contain one to three junctional strands, in which discontinuities exist. In comparison, airway epithelial cell junctions have three to five junctional strands. In addition, because alveolar type I epithelial cells are substantially larger (Table 2) and cover a much greater surface area per cell than do capillary endothelial cells, the total junctional area over which fluid and macromolecular transport can occur is substantially lower at the alveolar epithelium than it is along the pulmonary capillary endothelium. The impermeability of the alveolar epithelium to fluid and electrolyte movement explains why pulmonary vascular congestion (failure of the left side of the heart) leads to pulmonary interstitial edema substantially sooner than intra-alveolar pulmonary edema occurs.

The pulmonary capillary epithelium has a number of metabolic functions. Because it is the only capillary bed that receives the entire blood flow of the body during each circulation, the pulmonary capillary bed is in a critical position to regulate reactive bloodborne materials. Pulmonary endothelium plays a role in either activating or degrading a number of vasoactive mediators. Some substances are metabolized by enzymes on the capillary endothelial cell surface, whereas others require uptake into the endothelial cells. For example, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II on the surface of pulmonary capillaries, producing a vasoconstrictive molecule of substantially greater physiologic potency. The same enzyme, ACE, inactivates bradykinin. Bradykinin is a highly potent, locally released vasodilator, and its inactivation in the lung prevents it from causing systemic hypotension. Other mediators, such as serotonin and norepinephrine, are metabolized by endothelial cells but require uptake into the cellular cytoplasm. Pulmonary capillary endothelium also synthesizes prostacyclin and tissue plasminogen activator. These cells are a rich source of thrombomodulin, a cell surface protein with anticoagulant properties. The endothelium secretes nitric oxide, a local vasorelaxant, and secretes endothelins, which are potent vasoconstrictor peptides. Vascular endothelium metabolizes adenonucleotides and both prostaglandins E_2 and F_{2a}. Vascular endothelium also plays a role in regulating phagocytic cell function via the expression of cell surface adhesion molecules. The adhesion molecules interact with receptors on phagocytic cells and regulate the movement of phagocytic cells through the vascular bed as well as their migration into subjacent tissues.

Alveolar Macrophages

Alveolar macrophages are the principal means by which the lungs process the normal burden of inhaled particles. Alveolar macrophages are also secretory and regulatory cells and prevent injurious actions of other lung cells. For instance, it has recently been demonstrated that macrophage engulfment of neutrophils significantly contributes to the resolution of pulmonary inflammation. Once phagocytosis of the ingested particle has been accomplished by alveolar macrophages, the cell and/or toxicant is eliminated by internal digestion or mucociliary transport of the macrophage to the oropharynx. In an additional mechanism, particle-laden macrophages have been shown to traverse the interstitial spaces to reach the mediastinal lymph nodes. Figure 17 demonstrates an airway macrophage beneath the electron-dense lining layer of a rat bronchiole. Airway macrophages are approximately five times more numerous per unit of airway surface area than they are per unit of alveolar surface (Table 4). However, because of the large surface area of the alveolar gas exchange region, alveolar macrophages account for approximately 99% of total air space macrophages.

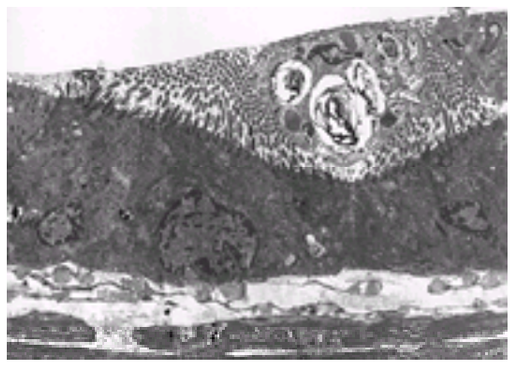

FIG. 17. Electron micrograph of an airway macrophage beneath the electron-dense lining layer of a rat bronchiole.

Region	Density on surface (No./cm^2)	Total No. (millions per both lungs)
Airways	25,000 ± 6400	62 ± 8
Alveoli	5861 ± 1860	5990 ± 1900

TABLE 4. *Macrophage distribution and number*

Alveolar macrophages are unique mononuclear phagocytes. These cells contain numerous lysosomes in their cytoplasm, consume oxygen and secrete neutral proteases at a high rate, and are more active than other tissue macrophages. Although these cells are individually active, they are poor antigen-presenting cells and poor accessory cells. The primary antigen-presenting cell in the lung is a dendritic cell. The primary role of alveolar macrophages is thought to be in defense of alveoli against dust and pathogens. They appear to be able to carry out this role without activating excessive inflammatory processes in the alveolar septa. The vast majority of antigens reaching the small airways and alveolar septa are processed without activation of lymphocyte-based immune recognition and neutrophils. The lung contains very few lymphocytes in alveolar septa.

Alveolar macrophages arise in bone marrow. There is also an interstitial macrophage pool in the lung, and alveolar macrophages proliferate on the alveolar surfaces. Regeneration of the alveolar macrophage population has been shown to occur in all three of these sites.

Mast Cells

Mast cells are a normal, albeit small, component of lung cells. They are identified by the presence of numerous membrane-bound intracytoplasmic granules with variable intragranular inclusions. These granules are 0.6 to 0.8 µm in diameter. The cells also have long filiform microvilli on the surface. Mast cells have high-affinity IgE membrane-bound receptors that are specific for inhaled allergens. On activation, these cells release allergic mediators, such as histamine, prostaglandin D_2 (PGD_2) and leukotriene C_4 (LTC_4). Mast cells also produce neutral proteases (tryptase and chymase), lysosomal enzymes, myeloperoxidase, eosinophil chemotactic factor of anaphylaxis, high-molecular-weight neutrophil chemotactic factor, and heparin. Although the specific role of mast cells is unclear, they clearly play a role in airways secretory and bronchoconstrictor responses of hypersensitivity reactions such as anaphylaxis, hay fever, and asthma. Increased numbers of mast cells are found in

pulmonary edema and pulmonary fibrosis.

Neutrophils

Neutrophils are terminally differentiated cells that are distributed in the bone marrow, blood, and tissue compartments. In the normal lung, neutrophils are almost exclusively found within the circulation, and almost half of the total body circulating neutrophils may be marginated along the walls of pulmonary capillaries and venules. Neutrophils are found in significant numbers in the pulmonary tissue spaces only in cases of pulmonary inflammation, such as in the adult respiratory distress syndrome (ARDS). Migration into tissue spaces occurs in response to chemotactic agents produced by invading microorganisms, toxin-derived products, and complement-activated chemoattractants, such as C5. Following phagocytosis, invading organisms are killed within neutrophils by an oxidant-mediated mechanism, by microbicidal proteins contained in neutrophil granules, or both. In the oxidant-mediated process, a membrane-bound NADPH oxidase generates O_2^-, which can enzymatically or spontaneously dismute to generate H_2O_2. These species react to form hydroxyl radical, another potent oxidant. These agents individually or in combination kill bacteria. Neutrophil granules contain a host of bactericidal agents, including myeloperoxidase, cathepsin G, acid hydrolases, elastase, and lysozyme.

Eosinophils

Eosinophils are not normally present in lung tissue spaces. However, the presence of significant numbers of these cells and their synthesis products has been shown to occur in allergically induced lung inflammation, and they are believed to play a major role in the development of reactive airways disease.

Eosinophils develop in the bone marrow and are transported via the circulation to the tissue spaces of the gastrointestinal and respiratory tracts. The host defense function is less well defined for eosinophils than for neutrophils. Eosinophils may be capable of some bactericidal activity. However, the principal function of these cells is likely their antiparasitic activity. Eosinophils synthesize and secrete potent inflammatory mediators, such as platelet-activating factor and LTC_4.

Innervation of the Lung

Motor neurons in the pulmonary nervous system influence airway tone, pulmonary blood flow, and secretion of mucus. Sensory neurons modulate the cough reflex, the Hering-Breuer reflex, and responses to irritant dusts and gases, and they may respond to interstitial fluid pressure. In addition, a variety of neural peptides released by afferent nerves may modulate airway tone, vascular tone, and airway secretions.

The primary motor and sensory innervation of the lung comes from the vagus nerve (cranial nerve X). In addition, sympathetic fibers arising from the second to the fourth thoracic sympathetic ganglia innervate the lung. Fibers from both the vagus nerve and the thoracic sympathetic plexus comingle as they enter the hilum of the lung and then divide into plexuses that follow bronchi, arteries, and veins. Along the airways, the nerve plexuses lie both internally and externally to the cartilage, with the larger external plexus containing ganglia along the first three bronchial divisions. Nerve fibers continue in airway walls to the level of respiratory bronchioles.

The arterial nerve plexus travels in the media and distally reaches the full extent of muscular arterioles. The venous nerve plexus reaches all the way to the visceral pleura and even supplies subpleural alveolar walls.

In addition, small unmyelinated nerve fibers have been identified in alveolar walls. They are rare, and their source has not been clearly identified. These fibers are thought to represent J (juxtacapillary) receptors, which in animals have been shown to respond to interstitial fluid pressure and certain chemicals. They cause a transitory reflex apnea and shallow rapid respiration.

The primary motor innervation for the lung is parasympathetic (cholinergic). Stimulation of the vagus nerve leads to bronchoconstriction and enhanced secretion of mucus. These actions are blocked by atropine. Parasympathetic nerves arising from the vagus nerve synapse in the ganglia of the first generations of intrapulmonary bronchi. The primary neural inhibitor of bronchial muscular tone is vasoactive intestinal peptide (VIP). This neuropeptide is stored and released by parasympathetic neurons and may coexist with acetylcholine. Thus, the same group of neurons may release acetylcholine, which contracts airway smooth muscle, and VIP, which counteracts the action of acetylcholine to act as a bronchodilator. There are multiple examples of neurotransmitters with opposing actions being released from common nerve elements in the lung; for example, neuropeptide Y, a bronchial and vascular constrictor, coexists in pulmonary adrenergic nerves with norepinephrine. The complex interactions of the parasympathetic, sympathetic, and nonadrenergic, noncholinergic (NANC) nervous systems in the lung and the coexistence of opposing neurotransmitters has made the study of neural control of lung function difficult. It is clear, however, that motor innervation of the airways is predominantly parasympathetic and that there is no significant direct adrenergic innervation of bronchial smooth muscle.

The NANC nerve supply to the lung is thought to regulate primarily mucous secretion and bronchial blood flow. NANC nerves can be either inhibitory or excitatory, and their function is not yet well characterized. The inhibitory functions include relaxation of bronchial smooth muscle, perhaps by the release of nitric oxide or VIP. VIP is a potent relaxant of human bronchi *in vitro* but appears to have little effect on smaller airways. Excitatory responses of the NANC system include bronchoconstriction, possibly mediated by the release of tachykinins, such as substance P. By means of neural stains and electron microscopy, unmyelinated nerve fibers have been shown to pass through the airway epithelial basement membrane and be distributed between columnar bronchial epithelial cells. These fibers contain neuropeptides thought to be released as a reflex response to activation of local irritant receptors. The major neuropeptides identified in the lung are shown in Table 5. In addition, Kultschitsky neuroendocrine cells may play a role in afferent nerve function. These cells have been found to release neuroactive peptides, including serotonin, calcitonin, and bombesin.

Neuropeptide	Functions
Vasoactive intestinal peptide	Enhanced secretion Bronchorelaxation
Peptide histidine methionine	Bronchorelaxation Vasorelaxation
Neurokinin A	Vasorelaxation
Substance P	Enhanced secretion
Calcitonin gene-related peptide	Enhanced secretion
Neuropeptide K	Bronchoconstriction
Neuropeptide Y	Bronchoconstriction Vasoconstriction Decreased secretion

TABLE 5. *Neuropeptides in the human lung*

Neural control of the pulmonary vascular system has been a substantial area of investigation. Despite this, the role of the nervous system in regulating blood flow in the human lung is not well understood. Nerves arising from both the sympathetic and parasympathetic systems innervate the pulmonary vascular system. In most animals, adrenergic supply of the pulmonary arterial system predominates over cholinergic innervation. Electric stimulation of the nerves of the lung has been shown to cause both vasoconstriction and vasodilation. Pulmonary arterioles are thought to be the primary site for pulmonary vascular resistance. The pulmonary venous system is well innervated and may also play a role in regulating resistance and capacitance of the pulmonary vascular system. Sympathetic stimulation in animals has been shown to cause pulmonary venous constriction.

The sensory system in the lung travels upward through both the vagus nerve and the thoracic sympathetic plexus. Receptors in the main bronchi mediate the cough reflex. Small airways contain irritant receptors that respond to irritant gases, irritant dust, and mechanical stimuli to produce bronchoconstriction, hyperventilation, and chest discomfort. The Hering-Breuer reflex involves mechanoreceptors located in airway walls. These receptors increase their rate of firing under stretch and thus inhibit the central inspiratory center as a progressive reflex response to lung expansion. The nerves mediating this reflex are thought to be located in the smooth muscle of the bronchial walls.

RESPIRATORY TRACT DEFENSE MECHANISMS

For the exchange of gases, conditioning of inspired air, and defense against inhaled toxicants to be accomplished simultaneously, highly synergistic interactions between respiratory tract clearance and secretion and biochemical and cellular defense mechanisms are required. In the normal lung, defense functions are mediated by epithelial cells of the airways and alveolar regions, resident alveolar macrophages, and numerous proteins in the extracellular spaces and mucous lining layers.

Resident lung macrophages carry out the normal tasks of lung defense by selective phagocytosis of foreign particles; secretion of proteases, oxygen free radicals, and cytokines; and antigen presentation. In the presence of toxicants or other pathologic conditions, infiltration of bloodborne phagocytes, such as neutrophils, and toxicant-specific immunologic mechanisms, such as antibody production by B lymphocytes and cellular cytotoxic actions by T lymphocytes, augment the normal defense functions. Inflammatory cells recruited into the lungs tend to produce indiscriminate injury to resident lung cells and tissues by nonselective release of proteases, oxygen free radicals, and other cytotoxic agents. The lung appears to be designed to clear normal levels of inhaled pollutants without activating these inflammatory patterns, but it can activate them when more severely stressed.

Deposition of Inhaled Gaseous Toxicants

Because the physical mechanisms of transport and chemical uptake vary significantly between different airborne toxicants, no single approach can be used to estimate the pulmonary uptake of all inhaled agents. For instance, formaldehyde and ozone are both highly reactive gaseous toxicants with an inspiratory uptake of greater than 90%. However, the solubility of formaldehyde in aqueous biologic solutions is approximately 12 times greater than that of ozone. Because of their different solubilities, the critical target sites of injury for formaldehyde and ozone are at opposite ends of the respiratory tract. The major sites of uptake and toxic reactions of formaldehyde are in the nose and other parts of the upper respiratory tract. The uptake of formaldehyde in the upper respiratory tract is so rapid that virtually none of it reaches the lower respiratory tract. In contrast, because of the lower solubility of ozone, more of it reaches the lower respiratory tract. Significant uptake of ozone does occur in the nasal passages and upper respiratory tract; however, this uptake is associated with reaction of ozone with components of the thick mucous layer lining this region. The site of greatest injury from inhalation of ozone, and similar oxidant gases, is the alveolar epithelium at the transition between airways and the gas exchange region. In this region, the surface lining fluids are thin, so that the probability of ozone reacting directly with the underlying alveolar epithelial cells is greater. The critical respiratory targets and the toxic responses to all airborne pollutants depend on their inhaled concentrations, the resulting concentration gradient in different regions of the respiratory tract, and the effects of scrubbing and/or detoxification of the reactive gas by the mucous lining layer overlying the epithelial layer in each region.

Deposition of Inhaled Particles

The alveolar septal region is continually bombarded by a variety of organic and inorganic materials ranging from transition metals to animal and human proteins. Although the upper respiratory tract and upper airways filter most inhaled particulate matter, it is well documented that particles of 1 µm in size are not effectively filtered by the upper respiratory tract and that a significant fraction of these particles deposit on the intrapulmonary airways or reach the alveolar region. Normal ambient air can contain on the order of 10,000 respirable particles, defined as less than 10 µm in size with a mass median aerodynamic diameter (MMAD) of 0.3 µm, per cubic centimeter. Up to 30% of these particles deposit on medium and small airways, and about 10% deposit in the alveolar region. Thus, if a minute ventilation of 10 L is assumed, 30 million particles deposit per minute on smaller airways and 10 million particles deposit per minute on alveoli and alveolar ducts. Although the human lung contains 500 million alveoli, the particles tend to deposit proximally, and the load can be estimated to be up to one particle per minute per alveolus in the proximal alveolar ducts. The lung handles this steady, normal load of particulate matter without inducing inflammatory amplification.

These same pollutants would cause a strong inflammatory reaction if injected into another organ, yet they appear to cause virtually no reaction in alveolar septa in normal lungs. This is remarkable when one considers that the alveolar-capillary gas exchange membrane in most regions is thinner than 1 µm. If the organic and inorganic materials reaching the airways and alveolar surface were to stimulate the type of inflammatory reactions that occur in many other tissues, white cells would be rapidly recruited into these spaces and a progressive inflammation would result, leading to acute bronchitis, acute alveolitis, and/or interstitial fibrosis. The absence of an injurious response to normal lung particle burdens appears to be the result, in part, of the unique role of resident lung defense cells, such as alveolar macrophages. Each alveolus contains an average of 12 macrophages, which are thought to process all particles reaching this region under normal conditions. Alveolar macrophages have been shown to have a blunted capacity for antigen presentation and mitogen production compared with other monocytic phagocytes, and thus they are able to process inhaled particles without stimulating excessive immunologic responses or lung inflammation. The lipids and/or proteins of the alveolar surface lining layer have been shown to have anti-inflammatory actions. High particle loads given experimentally have been shown to overload these and other anti-inflammatory defense mechanisms and induce alveolar inflammation. The dose-response relationship for the onset of particle-induced inflammation is not known, nor are the mechanisms controlling this process.

Pulmonary disorders in which particle deposition and/or clearance plays a major role include hypersensitivity pneumonitis, silicosis, asbestosis and other mineral fiber disorders, and a number of metal- and organic antigen-specific disorders. In most of these cases, the biologic association between toxicant dose and health effects has been clearly demonstrated.

Epidemiologic studies demonstrate a significant association between particulate exposure and increases in hospital admissions, morbidity, and mortality. Children, whose small airways are potentially more susceptible to particle-induced inflammation and limitations of air flow, are thought to be at high risk. Airborne particulate levels as low as 150 µg/m^3 are statistically associated with increases in elementary school absenteeism. The association between particle concentration and increased mortality appears to be maximal when the experimental results are averaged over a 3- to 5-day period. Such studies have been the primary means of identifying human health risks associated with particle inhalation. These studies taken as a whole suggest that ambient levels of particles on the order of 100 µg/m^3 are associated with adverse health effects. Each increase of 10 µg/m^3 in the PM_{10} (particulate matter with an aerodynamic diameter of 10 µm) is associated with an approximate 1% increase in mortality. The increased mortality appears to occur largely among the sick and elderly. The underlying biologic mechanisms responsible for these epidemiologic associations have not been determined. Interactions between particles and other pollutants, such as sulfur dioxide and nitrogen dioxide, and the effects of climate have been suggested as critical factors. High levels of trace metals in the particulate matter from urban and industrial sources have been suggested as possible causative agents. Table 6 illustrates the significant differences that exist in trace element composition between air sampled at a remote natural site and in various North American cities. In cities with a large number of anthropogenic sources, the potentially toxic trace elements of nickel, copper, and zinc are present at substantial levels. Particle samples from natural sites that are not contaminated by anthropogenic sources do not contain significant levels of these elements.

Trace element	Grand Canyon, Arizona	Houston, Texas	Washington, D.C.	Ottawa, Canada
Nickel, ng/m^3	0.1	5.0	1.0	4.4
Copper, ng/m^3	0.3	16.0	3.4	73.0
Zinc, ng/m^3	0.6	122.0	13.9	114.0
Selenium, ng/m^3	0.2	0.2	2.5	0.3
Arsenic, ng/m^3	0.2	0.1	0.6	0.5
Total mass PM_{10}	9400.0	29,000.0	34,900.0	44,500.0

PM_{10}, particulate matter <10 µm in aerodynamic diameter (ng/m^3).

TABLE 6. *Comparison of ambient dust concentrations*

Deposition of inhaled particles occurs according to physical mechanisms of inertial impaction, gravitational sedimentation, diffusion, and interception. A variety of factors, such as aerosol particle size, density, shape, hygroscopic/hydrophobic character, and electrostatic charge, may also play important roles in determining how these mechanisms control the location and efficiency of deposition in the lungs. Because particles are present in a range of sizes and shapes, an aerosol is typically described by a size distribution or a mass/count weighted mean. In toxicologic evaluations, the Mass Median Aerodynamic Diameter (MMAD) is typically used to describe an aerosol in terms of the aerodynamic behavior of its particles, site(s) of particle deposition, and deposited mass. Particles in the size range of 1 to 10 µm deposit with relatively high efficiency in the upper respiratory tract and large airways, where inertial deposition is driven by high flow rates. Particles in the size range of 0.01 to 0.1 µm deposit by diffusion and are primarily taken up in the alveolar regions, where the large surface area enhances deposition by diffusion and sedimentation. The small airways do not have a single dominant mechanism of deposition.

Both empiric and mathematical approaches have been used to assess the dosimetry of inhaled particles. Direct measurements of deposition demonstrate that the human upper respiratory tract efficiently removes particles with an Mass Median Aerodynamic Diameter (MMAD) of approximately 5 µm. For particles in the 1- to 5-µm range, the total respiratory tract (upper respiratory tract plus conducting airways plus gas exchange region) deposition efficiency is on the order of 20%. Mathematically based estimates of the alveolar deposition efficiency of inhaled 1- and 5-µm aerosol particles are 5.2% and 17%, respectively.

Because of the nature of the mechanisms of deposition, deposited particles are not uniformly distributed on respiratory tract surfaces. Aerosols have been shown to deposit preferentially on the ridges of airway bifurcations, both in theoretical models and in direct observation of aerosol behavior using airways casts. Experimental observations of ciliary activity and mucous flow suggest that the concentration of particles on the ridges of airway bifurcations could, in part, result from trapping of

particles on these ridges as they are cleared from more distal airways. Particles on airway ridges or branch points are cleared with a half-life of approximately 1 hour.

Particles deposited in the airways are rapidly cleared by the mucociliary escalator and by airway macrophages. Within 24 hours, most particles with a diameter of 1 µm are cleared from the airways. Particles initially deposited in the alveolar region are primarily cleared by macrophage phagocytosis. Clearance from the alveolar region is considerably slower than clearance from the airways, and removal of insoluble particles may require weeks to months.

Immunologic Responses

Immunologic responses can be classified as nonspecific or innate immune responses (actions of macrophages, monocytes, lymphocytes, and granulocytes) or agent-specific immune responses (immunologic memory of T and B cells). The innate defense mechanisms include a combination of phagocytosis and cytotoxic effects by effector cells and activation of the complement cascade. In the adaptive response, a large population of antigen-specific lymphocytes is produced that results in a potentially greater and prolonged immune system response. The adaptive response occurs when an antigen derived from the toxicant exposure is processed and presented by a dendritic cell, macrophage, or monocyte to a lymphocyte. The lymphocyte then undergoes clonal expansion to produce large numbers of cells that are specific for the particular toxic agent. Cytotoxic T-cell production occurs by this process when major histocompatibility (MHC) is expressed by the antigen-presenting cells in association with toxicant-derived antigen. Activated T cells produce numerous cytokines, such as tumor necrosis factor, that significantly enhances the immune response and the inflammatory responses of resident lung cells. Antibodies specific to the antigen are produced by B cells, which are stimulated by the interleukins to produce memory cells and plasma cells.

The effects of inhaled particles on human health are likely to involve inflammation, hypersensitization, and immunologic memory of T and B cells. These mechanisms are capable of amplifying injury initiated by repeated, low-dose exposures to antigens and therefore have the potential to produce significant effects at ambient levels of exposure. The pulmonary immune system differs from the systemic immune system in its ability to produce localized cell-mediated immune responses on repeated exposure to inhaled antigenic materials. Such localized response may play a significant role in hypersensitivity pneumonitis. Particles that contain metals have been shown to produce these responses. For instance, nickel and other transition metals are highly toxic and known to produce delayed hypersensitivity. Recent studies indicate that T-cell recognition of metal-complexed haptens plays a role in T-lymphocyte immune responses.

The airway epithelium and the alveolar epithelium are the primary lung surfaces on which inhaled toxicants may be initially distributed and/or react. The airway epithelium is a likely critical target site for an inhaled toxicant, as it is the first cellular barrier to inhaled toxicants and the most densely populated of the target surfaces. These aspects are offset to a large extent by the protection afforded by the thick mucous layer overlying airway epithelial cells and the efficient ciliary propulsion system. The alveolar epithelium of the gas exchange region has a large surface with a relatively low density of cells covered by a thin surface film. The thin surface film of the alveolar epithelial layer constitutes a critical site of possible action for pollutants not filtered by proximal airways. The outermost region of the respiratory path is the pleura, and this site is typically involved in toxic processes only after secondary transport following initial uptake of the reactive substance in more proximal air spaces. At each level, the presence or absence of adverse effects of inhaled particles and reactive gases is primarily determined by the unique immune response system in the lung.

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CHAPTER

2 Control of Ventilation

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INTRODUCTION

The respiratory system, along with cardiovascular structures, operates as part of an intricate organization controlled by the central nervous system (CNS) to ensure optimal cell performance, providing sufficient oxygen to meet metabolic requirements and removing enough carbon dioxide so that cell function is not impaired by excessive changes in hydrogen ion concentration. The major function of the respiratory system is to maintain the arterial tension of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) within acceptable limits in the face of changing metabolic needs and environmental conditions. To achieve this, the system is equipped with multiple sensors that monitor changes in blood chemistry (chemoreceptors) and changes in the mechanical properties of the lung and chest wall (mechanoreceptors). The chemoreceptors and mechanoreceptors allow ventilation to be continuously readjusted in accordance with metabolic needs, despite changes in body posture that alter the mechanical advantage or movement of the respiratory muscles. In addition, these receptors coordinate the contraction and relaxation of the respiratory muscles, so that adequate gas exchange is carried out with minimum expenditure of energy.

In addition, the respiratory chemoreceptors and mechanoreceptors participate in a protective network that adjusts the pattern of breathing and the mechanical conditions of the airways to minimize the deleterious effects on the lung of inhaled, noxious material.

Ventilation, unlike blood pressure and cardiac output, can be controlled consciously (voluntarily) as well as automatically (involuntarily). Indeed, the pathways for voluntary and automatic control of the respiratory muscles are anatomically separate. Voluntary as well as automatic control is essential for using the respiratory muscles in speech. In humans, afferent information continuously fed back to the CNS by mechanoreceptors in the airways, lungs, and chest wall allows the force of contraction of the respiratory muscles to be coordinated smoothly in volitional acts.

Besides inputs from respiratory system sensors, ventilation is influenced by projections from the vasomotor neurons to respiratory neurons and by signals received from thermoreceptors and vascular receptors. The multiplicity of inputs to the respiratory neurons ensures that ventilation is maintained when disease affects one or more afferent pathways or when the perception of some sensory cue is blunted by a depressed state of consciousness (e.g., sleep or anesthesia). However, conflicting demands and signals from different receptors may be responsible for dyspnea, a common symptom in respiratory disease.

CENTRAL RESPIRATORY NEURONS

The precise organization of the central respiratory neurons is still a matter of contention. Although there may be respiratory pacemaker cells in which spontaneous changes in transmembrane potential occur, in the intact system, the respiratory rhythm depends on interconnections between different respiratory neurons.

Because breathing is preserved in anesthetized animals even after removal of the brain rostral to the pons, it is believed that the neurons on which respiratory rhythm critically depends are located in the bulbopontine region. Many investigators believe that the essential features of the respiratory rhythm remain even after separation of the pons from the medulla, and that the central pattern generator must be anatomically located within the confines of the medulla. There is evidence, however, that pontine neurons, particularly the complex composed of the nucleus parabrachialis medialis (NPBM) and the Kölliker-Fuse nucleus (KFN), as well as nuclei in the tegmentum (magnocellular and gigantocellular nuclei), significantly modify breathing.

In addition to these pontine and medullary respiratory neuronal aggregates, neurons with activity that is modulated by respiration can be found all through the brain stem intermixed with nonrespiratory neurons. It also has been shown that when breathing is stimulated, respiratory modulation of the activity of these neurons decreases according to level of anesthesia and sleep state.

A number of neurons whose firing patterns demonstrate a respiratory modulation but whose phase relationships with phrenic motor activity and with one another differ have been identified in the brain stem. Some of these neurons project to the spinal cord (bulbospinal) and are therefore true premotor cells. The remainder have axons that project to other parts of the brain (propriobulbar). Only the function of the bulbospinal neurons has been determined with any degree of certainty. It is generally believed, however, that the propriobulbar cells actively inhibit or excite other neurons involved in the respiratory cycle. The precise function of these propriobulbar neurons remains under investigation, although it is generally agreed that they are organized into networks whose complicated interactions determine the level of excitation of the bulbospinal neurons and produce respiratory phase switching.

MEDULLARY RESPIRATORY NEURONS

The respiratory neurons in the medulla seem to be aggregated into two groups (Fig. 1). One collection, the ventral respiratory group (VRG), forms a longitudinal column of neurons in the ventrolateral part of the medulla. It extends rostrally from the upper border of the spinal cord almost to the bulbopontine boundary. The other group, the dorsal respiratory group (DRG), is more circumscribed anatomically. It is located in a more medial and dorsal part of the medulla in the region of the ventrolateral nucleus of the tractus solitarius (NTS) and extends from the obex about 2.5 mm rostrally.

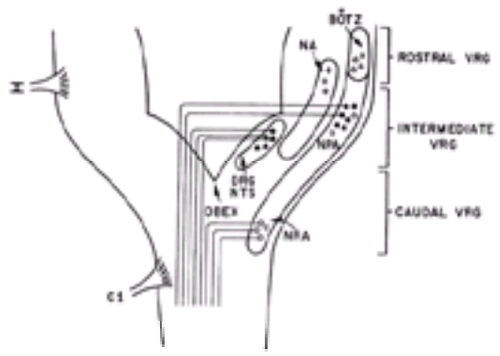

FIG. 1. Schematic depicting the organization of medullary respiratory neurons in the dorsal and ventral respiratory groups (DRG and VRG, respectively). Structures on one side only are shown. Axons from inspiratory bulbospinal neurons in the nucleus tractus solitarius (NTS) and the nucleus para-ambigualis (NPA) decussate rostral to the obex and extens caudally in the contralateral cord. Axons from expiratory bulbospinal neurons in the nucleus retroambigualis (NRA) decussate caudal to the obex. Bötz = Bötzinger complex in the nucleus retrofacialis; NA = nucleus ambigualis.

The nuclei of the solitary tract appear to function as relay stations for important respiratory and cardiovascular information. Afferents from pulmonary stretch receptors and carotid chemoreceptors and baroreceptors appear to synapse for the first time in the brain at this location.

Dorsal Respiratory Group

The DRG contains almost entirely inspiratory neurons. One kind of inspiratory neuron, the I_a neuron, like the phrenic motor neurons, demonstrates an augmenting pattern of firing that peaks at end-inspiration. Axons from these cells decussate in the medulla at or immediately rostral to the obex and connect with phrenic and inspiratory intercostal motor neurons in the spinal cord. Collaterals are sent to the ipsilateral inspiratory neurons in the VRG, but a few also are distributed to the expiratory neurons in the VRG.

The firing of I_b neurons, as of I_a neurons, occurs primarily in inspiration but, in contrast to the discharge of I_a neurons, is augmented by inputs from pulmonary stretch receptors. In animals, the discharge peak of I_b is not as sharp and the decline in activity during expiration is slower than for I_a. In the absence of excitatory input from vagal stretch receptors, however, the discharge patterns of I_a and I_b neurons are similar.

Like I_a neurons, some of the I_b neurons project to the spinal cord. Those I_b neurons that do not project to the cord appear to undergo extensive axonal arborization in the NTS. I_b neurons seem to be responsible for the shortening of inspiratory time induced by lung inflation. Their responsiveness to stretch-receptor input is less during expiration than during inspiration.

The DRG also contains late-onset inspiratory neurons that reach their peak firing rate in the transition from inspiration to expiration. Their activity, like that of I_b neurons, is facilitated by stretch-receptor activity. These neurons may participate in the short phase of graded inhibition of inspiratory activity seen with volume changes occurring toward the terminal portion of inspiration.

Recently, a small number of early-expiratory neurons have been observed in the DRG (and possibly also in the VRG) intermingled with inspiratory cells. They begin their firing shortly before the end of inspiration and reach peak discharge rates quickly, and then their activity slowly diminishes during expiration, disappearing before inspiration begins. Increases in lung volume slow the rate of decline in activity of these cells, whereas prevention of lung inflation does the opposite. The activity of these neurons is related to postinspiration inspiratory activity (PIIA), which occurs in the diaphragm and intercostal and laryngeal muscles and retards expiratory flow and the rate of lung deflation.

Ventral Respiratory Group

The VRG in the medulla comprises several anatomically and probably functionally distinct populations (Fig. 1). One classification divides the neurons of the VRG into three aggregates: the nucleus retroambigualis (NRA), the nucleus para-ambigualis (NPA), and the nucleus retrofacialis (NRF).

The nucleus ambigualis (NA) is composed primarily of subnuclei of motor neurons innervating the laryngeal, pharyngeal, and facial muscles. This nucleus also contains the vagal motor neurons innervating the bronchial smooth muscles and the smooth muscles of the thoracic and abdominal viscera. These neurons are almost completely inactive during deep anesthesia, suggesting that they are not essential to respiratory rhythmogenesis.

The NPA is located in the region medial to the NA and 1 mm caudal to 3.5 mm rostral to the obex. The NPA is composed primarily of premotor inspiratory neurons, but some expiratory cells are present.

Most of the inspiratory neurons of the NPA (like I_a cells in the DRG) fire in a ramplike fashion, with peak activity occurring at the conclusion of the inspiratory phase. The NPA also contains a few inspiratory propriobulbar, so-called early-burst neurons. These cells begin to discharge slightly before the onset of the phrenic discharge, peak rapidly, and then demonstrate a decline and disappearance of activity in the latter half of inspiration. They send no projections to spinal motor neurons, but they have a rich pattern of arborization with expiratory neurons in the contralateral NRA, whose activity they appear to inhibit.

The activity of other neurons in the VRG (located in the NRA and NRF) is mainly directed to expiration. The expiratory neurons in the NRA demonstrate a slowly augmenting pattern of activity, with peak discharge late in expiration. Input from pulmonary stretch receptors prolongs the time of firing of these neurons. Hypercapnia causes these neurons to discharge earlier in inspiration and increases the steepness with which their rate of discharge rises. Lesioning experiments indicate that neurons in the NRA are the sole source of expiratory premotor neurons but are not of fundamental importance in generating the respiratory rhythm.

Respiratory neurons in the NRF (also called the *Bötzinger complex*) and in an area immediately rostral to it, called the *pre-Bötzinger complex,* have been described. Bötzinger neurons discharge mainly in expiration with a slowly augmenting firing pattern that peaks at end-expiration. They send projections to the DRG on the opposite side and seem to inhibit the inspiratory neurons located there. On the other hand, pre-Bötzinger neurons fire during inspiration, demonstrate pacemaker-like activity, and appear to be exclusively propriobulbar in type. In the neonatal rat, lesions in this pre-Bötzinger complex eliminate respiratory rhythmogenesis. Some pharyngeal motor neurons also can be found in the NRF.

Interrelationship Between Dorsal and Ventral Respiratory Groups

The precise interactions between the DRG and VRG remain unclear. Earlier studies indicated that inspiratory neurons of the DRG projected to the VRG, but a reciprocal connection was not apparent. These studies suggested that the central pattern generator was composed only of inspiratory cells and was located in the DRG. In this view, the DRG was the prime mover in the genesis of the respiratory rhythm, dominating the cells in the VRG and governing their activity. More recent studies indicate that cells from the VRG (Bötzinger complex) may inhibit inspiratory neurons in the DRG. Ablation experiments eliminating either the entire DRG or the Bötzinger complex in the VRG do not eliminate rhythmogenesis, indicating that substantial redundancy is present in the system.

The functional significance of the interconnections between groups of inspiratory cells in the DRG and VRG is also unclear. These interconnections may serve to synchronize the timing of neuronal firing in anatomically separate locations. For example, midline incisions through the medulla are associated with asynchronous firing of the two phrenic nerves.

TIMING OF RESPIRATORY MOTOR ACTIVITY

During inspiration, firing rates increase monotonically in both inspiratory propriobulbar and bulbospinal neurons. Early in expiration, inspiratory propriobulbar neurons are silenced, but the activity of inspiratory bulbospinal neurons stops only momentarily, reappearing after a brief period of silence and then gradually declining as expiration proceeds. This PIIA corresponds in time to the period of firing of early-expiratory neurons in the DRG and VRG. Expiratory bulbospinal neurons are silent during this early phase of expiration, whereas inspiratory propriobulbar neurons are actively inhibited. Furthermore, because the time course of inhibition of the

respiratory propriobulbar neurons is similar to the time course of activity of the early-expiratory units, it has been suggested that the respiratory rhythm is caused by inhibition of an inspiratory ramp generator by these early-expiratory neurons.

Based on these observations, it has been proposed that expiration be divided into two phases, E_I and E_{II}. The E_I phase corresponds to the period of PIIA, whereas the E_{II} phase corresponds to the period in which PIIA is absent and expiratory neuronal activity may be present. In some situations, PIIA may extend throughout expiration, suggesting that the respiratory rhythm does not depend on the occurrence of activity in expiratory neurons.

PIIA appears to be associated with “braking” of expiratory air flow by contraction of the inspiratory muscles. Increases in PIIA and prolongations in E_I occur, for example, when the larynx is bypassed so as to decrease upper airway resistance. PIIA (E_I) is markedly reduced or eliminated by vagotomy, suggesting that mechanoreceptors that sense lung volume and/or tracheal air flow are important inputs. Hypercapnia decreases the duration of E_I, whereas hypoxia appears to do the reverse. Increases in PIIA may contribute to the increase in functional residual capacity (FRC) observed during hypoxia.

Respiratory timing can be significantly affected by the rostral pontine pneumotaxic center, which comprises the NPBM and KFN. This structure contains a number of neurons that have different patterns of firing: inspiratory, expiratory, or phase-spanning. When the vagi are intact, discharge patterns in the NPBM are mainly tonic, but they become more clearly phasic after vagotomy. Both the VRG and the DRG send projections to the pneumotaxic center, so that the respiratory activity seen in this center appears to be of medullary origin. Depending on the region involved, stimulation of the pneumotaxic center can either terminate or prolong inspiration. Stimulation of the dorsolateral region terminates inspiration. The earlier in inspiration the stimulation is applied, the stronger is the stimulus needed. If the pneumotaxic center is lesioned and the vagi are cut, an apneustic breathing pattern develops in anesthetized animals that is characterized by prolonged inspiratory time. If time is allowed for recovery, however, and the animal regains consciousness, breathing loses its apneustic quality. If the animal is then given anesthesia or allowed to go to sleep, the apneustic pattern returns. These observations suggest the lack of importance of the pneumotaxic center in generating the respiratory pattern, and indicate that an interaction between states of alertness and the activity of higher brain centers and the brain stem bulbopontine respiratory neurons can significantly affect respiratory rhythm.

It is not clear whether some or any of the different respiratory neurons described in fact make up the central pattern generator. Three different ways in which the central respiratory pattern may be produced in the brain have been proposed. In one, the pattern generator is composed only of inspiratory neurons; an inspiratory ramp continues until it is terminated by the activity of off-switch neurons. The off-switch neurons are triggered after some predetermined time or after the inspiratory ramp reaches some threshold level of activity. Both trigger and ramp neurons could be stimulated by hypoxia and hypercapnia. In this scheme, inspiration is a self-terminating process carried out by cells whose activity is confined to inspiration.

In a second hypothesis, the central pattern generator may include both inspiratory and expiratory cells affected by chemical drives causing tonic increases in the activity of each. The increasing ramplike discharge seen in inspiratory intercostal and phrenic nerves may result from a gradual decline in inhibition rather than a gradual increase in excitation. This hypothesis is based on the observation that during apnea induced by hypocapnia, decreases in PO_2 elicit inspiratory tonic activity. Progressive decreases in PO_2 during apnea elicit progressive increases in tonic inspiratory activity until at a critical level of hypoxia the respiratory rhythm reappears. On the other hand, hypocapnia under hyperoxic conditions produces continuous firing of expiratory neurons, which increases as PCO_2 rises until rhythmic breathing resumes. This suggests hypoxia exerts an excitatory effect predominantly on inspiratory activity, and that hypercapnia affects expiratory motor activity.

The third idea is that respiratory rhythmogenesis arises in the antagonistic activity of inspiratory and early-expiratory neurons and does not depend on the activity of conventional expiratory neurons that peaks late in the expiratory phase.

PATTERN OF MOTOR OUTFLOW TO THE INSPIRATORY MUSCLES

The firing of the bulbospinal inspiratory neurons projecting to the diaphragm and intercostal muscles increases progressively throughout inspiration and is terminated abruptly (off-switching). The ramplike increase in activity of these bulbospinal neurons (the central inspiratory activity) causes a progressive increase in excitation of the inspiratory muscles and hence their force of contraction (Fig. 2). The electrical and mechanical analogues of central inspiratory activity are, respectively, the integrated activity of the phrenic neurogram and diaphragmatic electromyogram (EMG) and the pleural pressure waveform. The progressively augmenting shape of central inspiratory activity allows the inspiratory musculature to overcome the progressive increase in elastic recoil of the lung during inspiration despite progressive shortening and a decrease in the intrinsic ability of the inspiratory muscles to generate force (i.e., the length-tension relationship).

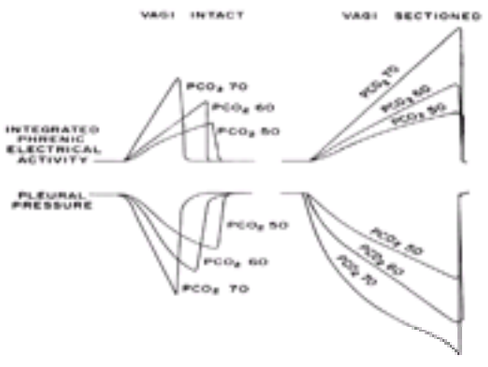

FIG. 2. Effect of hypercapnia on the duration of the phrenic nerve electrical activity integrated as a moving time average and its rate of increase and the pleural pressure waveform. Note the similarity in shape of the integrated phrenic neurogram and the pleural pressure tracing. Following bilateral vagotomy, the duration of inspiration remains relatively constant despite the progressive increase in PCO_2.

Control of the rate of rise in central inspiratory activity and hence the rate of lung inflation differs from control of inspiratory off-switching. Both chemical (e.g., hypoxia and hypercapnia) and nonchemical (e.g., thermal and mechanoreceptor afferents) inputs affect the steepness of the ramp of central inspiratory activity. On the other hand, the timing of inspiratory off-switching depends largely on inputs from pulmonary stretch receptors and from higher CNS structures, such as the NPBM and the KFN.

In anesthetized animals, phasic increases in lung volume resulting from the ramp of central inspiratory activity progressively increase pulmonary stretch-receptor activity. Integration of inputs from pulmonary stretch receptors and projections reflecting the intensity of the central inspiratory activity by as yet incompletely described pools of neurons terminates inspiration. Vagotomy eliminates stretch-receptor input, prolonging inspiration and increasing tidal volume, but the rate of rise in central inspiratory activity and hence the rate of inspiratory air flow are virtually unchanged. On the other hand, hypoxia and hypercapnia increase the steepness of the ramp of inspiratory activity and hence increase the rate of inspiratory air flow and tidal volume, but they have little effect on the duration of inspiration and frequency of breathing.

When the vagus is intact, so that respiratory neurons receive input from the stretch receptors as well as inputs reflecting central inspiratory activity, the duration of inspiration is reduced, because the inspiratory off-switch is activated earlier. Because central inspiratory activity increases with time, more stretch-receptor input (i.e., a greater change in lung volume) is needed early in inspiration to terminate a breath. This accounts for the curvilinear relationship between tidal volume (V_t) and inspiratory time (t_{insp}) that has been noted in studies of anesthetized animals (Fig. 3).

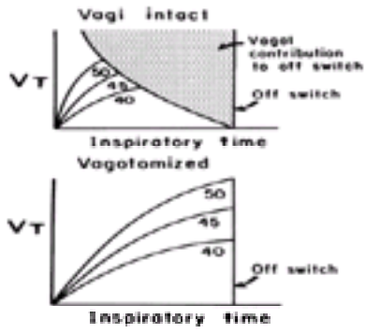

FIG. 3. Effect of lung volume information in determining off-switch and, hence, t_{insp}. Vagal input allows the off-switch threshold to be reached earlier in inspiration. The numbers refer to the PCO_2 with the vagi intact. Inspiratory time declines and tidal volume rises with increasing hypercapnia. Without lung volume information (vagotomy), t_{insp} is fixed.

Consistent with these observations is the idea that ventilatory responses to hypercapnia and hypoxia depend on the sensitivity of both stretch receptors and chemoreceptors. Chemoreceptor sensitivity, because it influences the rate of increase in central inspiratory activity, is more closely related to the average level of air flow during inspiration than to minute ventilation. That is, the change in the ratio of tidal volume to inspiratory time, rather than the change in ventilation itself, most closely reflects chemical drive. On the other hand, the change in inspiratory time as a fraction of total breath duration indicates the activity of stretch receptors.

Although ventilation is conventionally thought to be equal to tidal volume times frequency (f), the concept of central respiratory neuronal organization suggests that ventilation should more realistically be considered to be the product of the following:

$$\frac{V_T}{t_{insp}} \times \frac{t_{insp}}{t_{insp} + t_{exp}}$$

where t_{insp} is inspiratory time and t_{exp} is expiratory time.

Some studies in humans have tried to separate neural and chemical responses to hypoxia and hypercapnia by analyzing ventilatory responses with this approach. In some cases, depressed ventilatory responses to CO_2 seem to be caused by altered mechanoreceptor function rather than by depressed chemosensitivity.

It is important to remember that this concept originated from experiments carried out in anesthetized animals and accordingly does not include the effects on breathing of inputs eliminated by anesthesia. These additional inputs, occurring during both wakefulness and sleep, may greatly distort the basic relationships between the medullary respiratory neurons observed in animals during anesthesia. Thus, in awake humans, increases in breathing frequency produced by hypercapnia and hypoxia are associated mainly with a shortening of expiratory time, whereas inspiratory time remains relatively constant. Rapid-eye-movement (REM) sleep is associated with an irregular breathing pattern and seems to eliminate ventilatory increases to hypercapnia, but not to hypoxia. In non-REM sleep, breathing is more regular, but responses to changes in CO_2 remain lower than during wakefulness.

Even in anesthetized animals, influences from thermal and circulatory receptors can affect breathing. For example, temperature increases accelerate the frequency of breathing without changing tidal volume.

CENTRAL CHEMORECEPTORS

When CO_2-enriched gas is inspired, ventilation increases. The increase in ventilation tends to minimize the rise in $PaCO_2$. Because the amount of CO_2 delivered to the chemoreceptors depends on the CO_2 carried to them by the arterial blood, the $PaCO_2$ determines the PCO_2 in the immediate environment of the chemoreceptors.

The effect of increases in ventilation on $PaCO_2$ can be determined by the following equation:

$$PaCO_2 = \frac{\dot{V}CO_2 \times K}{\dot{V}_A} + PICO_2$$

where $\dot{V}CO_2$ is the metabolic production of CO_2 each minute, $\dot{V}_A$ is the alveolar ventilation, $PICO_2$ is the partial pressure of inspired CO_2, and K is a proportionality constant.

It can be seen that the greater the increase in ventilation caused by a change in $PICO_2$, the lower is the $PaCO_2$. In conscious humans, central chemoreceptors located within the medulla account for 70%–80% of the increase in ventilation. The peripheral chemoreceptors account for the remainder of the increase in ventilation when CO_2-enriched gas is inspired and for all the increase in ventilation produced by hypoxia.

The exact location of the central chemoreceptors is still disputed, although most experimental data indicate that they (1) are distinct from the inspiratory motor neurons themselves, (2) are not located in the dorsal and ventral groups described earlier, and (3) respond to changes in hydrogen ion concentration of brain interstitial fluid but also may respond directly to changes in PCO_2 (perhaps through a change in intracellular pH).

Studies in which drugs and temperature probes have been applied to the ventrolateral surface of the medulla have demonstrated abrupt and striking ventilatory effects, suggesting that many of the neurons comprising the central chemoreceptors or their associated axons may be located near the surface. Chemoreceptor activity can be influenced from three different superficial areas (Fig. 4). Recent studies suggest that respiratory cells near the ventral surface are intermingled with cells that also have significant vasomotor effects. Many agents that increase ventilation when applied superficially to the ventral medullary surface (e.g., nicotine, acetylcholine, kainic acid) also raise blood pressure. On the other hand, agents that decrease respiration when similarly applied (e.g., t-amino butyric acid, taurine, enkephalins) also decrease blood pressure. Nonetheless, discrete areas have been described from which either respiratory or vasomotor effects predominate (e.g., the nucleus paragigantocellularis, a collection of cells close to the ventral medulla).

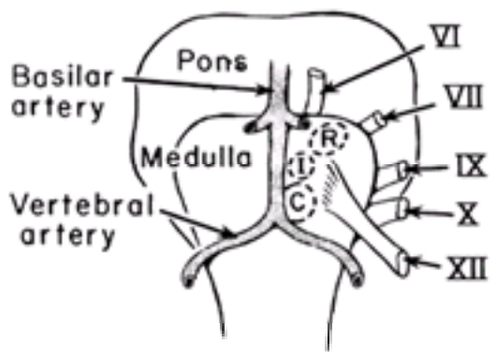

FIG. 4. Ventrolateral medulla and its rostral (R), intermediate (I), and caudal (C) chemosensitive areas.

The crucial experiments in which activity from the central chemoreceptors would be directly recorded have never been performed. Hence, it has been possible to evaluate central chemoreceptor activity only indirectly. This is usually accomplished by measuring the increase in ventilation or phrenic nerve activity produced when the P_ICO_2 is changed. Changes in ventilation theoretically should be related to changes in hydrogen ion concentration in the brain, but this concentration cannot be measured easily, either in humans or in animals. Instead, changes in ventilation are conventionally related to the measured levels of $PaCO_2$. This kind of indirect estimation of central chemoreceptor activity is valid only under restricted circumstances and only if certain assumptions are made. It is assumed, for example, that in a steady state, after CO_2 has been inspired for 10 to 20 minutes, changes in $PaCO_2$ reflect changes in the hydrogen ion concentration of the brain. By the Henderson-Hasselbalch equation, hydrogen ion concentration in the brain, as in other tissues, varies according to the ratio PCO_2/ HCO^-_3, where PCO_2 is the partial pressure of CO_2 at the chemoreceptor in the interstitial fluid and HCO^-_3 is the bicarbonate concentration of the medullary interstitial fluid. Hence, increases in bicarbonate concentration decrease hydrogen ion concentration, whereas decreases in bicarbonate concentration have the opposite effect.

The relationship between arterial PCO_2 and PCO_2 in the brain interstitial fluid depends on cerebral venous PCO_2 and therefore on cerebral blood flow. The greater the cerebral blood flow, the smaller the difference between PCO_2 in arterial blood and in interstitial fluid. As cerebral blood flow increases with PCO_2, the change in ventilation produced by a change in $PaCO_2$ depends on the CO_2 responsiveness of cerebral blood vessels as well as on the sensitivity of the central chemoreceptors. This may be a significant factor in patients with cerebrovascular disease.

Changes in blood bicarbonate levels are not immediately mirrored in the brain interstitial fluid. In addition, evidence suggests that hydrogen ion concentration in interstitial fluid is actively regulated by cellular pumps at the blood-brain barrier or by the metabolism of brain cells. This means that in metabolic acidosis or alkalosis, neither $PaCO_2$ nor hydrogen ion concentration in blood may reliably indicate the status of hydrogen or bicarbonate ion concentrations in interstitial fluid.

The stimulatory effect of acid injected into the blood on the peripheral chemoreceptors lowers PCO_2. Because the transfer of PCO_2 between blood and brain interstitial fluid is faster than the transfer of hydrogen or bicarbonate ions, the brain interstitial fluid may actually become alkaline when the blood PCO_2 is acutely made acidic. Direct administration of acid into the cerebrospinal fluid to bypass the blood-brain barrier increases the hydrogen ion concentration in brain interstitial fluid and drives the $PaCO_2$ down by stimulating central chemoreceptors.

With chronic acid-base disturbances, hydrogen ion changes in cerebrospinal fluid are usually qualitatively the same as those in the blood but are quantitatively less.

The effect of chronic metabolic acidosis and alkalosis on ventilatory responses to CO_2 is shown in Fig. 5. It can be seen that in metabolic acidosis the level of ventilation is greater at any given level of PCO_2, whereas in metabolic alkalosis ventilation decreases. These changes in ventilation reflect the altered level of bicarbonate in the brain interstitial fluid. If the same ventilation results are plotted as a function of hydrogen ion concentration in brain interstitial fluid, the response lines are identical.

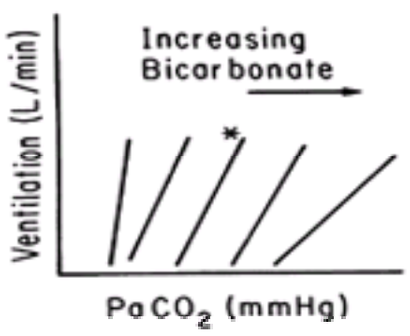

FIG. 5. Effect of changes in blood bicarbonate on the relationship between ventilation and PCO_2. The asterisk indicates the response line at the usual level of HCO^-_3.

In humans and animals, increases in PCO_2 over a wide range cause a virtually linear increase in ventilation. At levels of $PaCO_2$ >80 to 100 mmHg, the response to hypercapnia diminishes and may plateau. Decreases in $PaCO_2$ below the usual level depress ventilation. In anesthetized and sleeping animals and humans, artificial hyperventilation with progressively reduced PCO_2 eventually produces apnea. In a normal, awake human, however, active voluntary hyperventilation rarely causes apnea. In most cases, when voluntary hyperventilation is suspended, the increase in ventilation persists for perhaps 30 to 50 seconds. The persistence of ventilation in awake subjects at low levels of PCO_2 has been attributed to a “wakefulness drive” caused by the continued impingement of other stimuli (e.g., noise, mechanoreceptor input, and light input) on the respiratory neurons. However, continuation of phrenic nerve activity at low levels of PCO_2 has been described even in anesthetized animals made to hyperventilate actively by electrical stimulation of the carotid body nerves. This effect, which has been attributed to persisting reverberations in medullary respiratory neuron circuits, probably contributes to the wakefulness drive and helps stabilize breathing.

PERIPHERAL CHEMORECEPTORS

Sensors in both the carotid body (innervated by the ninth cranial nerve) and the aortic body (innervated by the tenth cranial nerve) respond to hypoxia by increasing ventilation. If the carotid and aortic bodies are removed, hypoxia depresses breathing. In most species, the increase in ventilation with hypoxia is more a consequence of carotid than of aortic body activity. The carotid body also responds, to a limited extent, to changes in PCO_2 and hydrogen ion concentration, and it appears to be particularly important in the immediate increase in ventilation seen in metabolic acidosis. However, the increase in peripheral chemoreceptor activity caused by CO_2 appears to be inconsequential under hyperoxic conditions.

With decreases in PaO_2, afferent fibers from the carotid body increase their discharge hyperbolically. Reduction in PO_2 rather than in O_2 content in the arterial blood is mainly responsible for the increasing activity. The biochemical and physiologic mechanism that allows the carotid body to respond to even relatively mild hypoxia has not been completely elucidated, but some details are known. Although blood flow in the carotid body is unusually high, so is the metabolic rate. Vascular shunts through the carotid body as well as its high metabolic rate may produce areas of hypoxia within the carotid body, even when the arterial blood is fully saturated with O_2. Measurements of carotid body PO_2 have shown some extremely low tensions, but the range of tensions is wide. Cytochrome enzymes within the carotid body may have an especially low affinity for O_2, thus accounting for the sensitivity of the carotid body to changes in PO_2. Although the primary function of the peripheral arterial chemoreceptors is to transduce changes in arterial PO_2, PCO_2, and/or hydrogen ion levels into nerve signals, there is no general agreement as to how this is accomplished, nor is it known whether all stimuli act through a common mechanism.

Ultrastructural studies of the carotid and aortic bodies demonstrate the presence of two distinct types of cells. Afferent nerve terminals from the carotid sinus nerve appose type I glomus cells, which contain abundant, dense, clear-cored synaptic vesicles, mitochondria, and conspicuous rough endoplasmic reticulum. The cytology of type II (sustentacular) cells resembles that of Schwann cells. They envelop the afferent terminal-glomus cell complex.

Whereas it was originally proposed that the afferent terminals are chemosensitive and that the type I cells function as modulatory interneurons, subsequent studies have suggested that the integrity of the glomus cells (type I and perhaps type II cells) is essential for the process of chemoreception. After the glomus cells are destroyed, nerve endings alone seem unable to respond to physiologic stimuli.

Glomus cells (type I cells) contain a variety of agents, including acetylcholine, norepinephrine, dopamine, and 5-hydroxytryptamine. Recent immunocytochemical studies also have shown the presence of at least three polypeptides in the carotid body of cats and rats (i.e., substance P, vasoactive intestinal polypeptide [VIP], and enkephalins), suggesting that neuropeptides may play important roles in the transmission of nerve signals. Substance P, a member of the tachykinin group of polypeptides, has been proposed as a general transmitter/modulator for primary afferent fibers sensing nociceptive stimuli. In addition, substance P enhances the discharge of carotid body preparations in vivo and in vitro. These excitatory effects of substance P are dose-dependent, seem to be slow in onset, and last several seconds after intracarotid administration. Hypoxic excitation of the carotid body is markedly attenuated by substance P antagonists. The mechanism(s) for sensing O_2

in the carotid body remains unclear. However, hypoxia depolarizes type I cells and increases cytosolic calcium, perhaps through effects on O_2-sensitive, voltage-gated potassium channels and cytochrome protein(s) with a low affinity for O_2. Depolarization of glomus cells in turn causes neurotransmitter release and activation of sinus nerve afferent terminals.

Efferent discharge to the carotid body from the CNS depresses afferent activity provoked by hypoxia. This efferent inhibition may prevent saturation of the carotid body response, allowing the carotid body to respond to a wider range of PO_2 than it could otherwise. In part, efferent control depends on sympathetic nervous regulation of carotid body blood flow. However, other inhibitory efferent fibers that have no effect on the carotid body vasculature are also present.

With hypoxia, ventilation, like carotid body activity, increases hyperbolically (Fig. 6). Also, changes in PCO_2 seem to enhance the ventilatory response to hypoxia, and vice versa (i.e., CO_2 and hypoxia interact multiplicatively). Single carotid body fibers respond to both CO_2 and hypoxia, so that some of the interaction of hypoxia and hypercapnia occurs at the cellular level in the sensor itself. However, other evidence suggests that convergence of input from central and peripheral chemoreceptors at the level of the CNS helps enhance the interaction of hypoxia and hypercapnia as ventilatory stimulants. Experimental studies on the effect of carotid nerve stimulation in different phases of breathing show that carotid body discharge is more effective in stimulating breathing during inspiration than during expiration. Carotid body discharge varies spontaneously during the breathing cycle as a result of variations in PaO_2. The relationship between oscillations in carotid body activity and phase of breathing depends on the circulation time between the lungs and the carotid body. Thus, changes in cardiac output theoretically might affect both the level and pattern of breathing. When central chemoreceptor activity and the response to CO_2 have been eliminated by destruction of the ventrolateral medullary surfaces, input from the carotid body alone is sufficient to maintain rhythmic breathing. Both central and peripheral chemoreceptors respond proportionally as the level of PCO_2 is altered. Some studies suggest that increases in the rate of change of CO_2 but not in the rate of change of PO_2 also stimulate the carotid body.

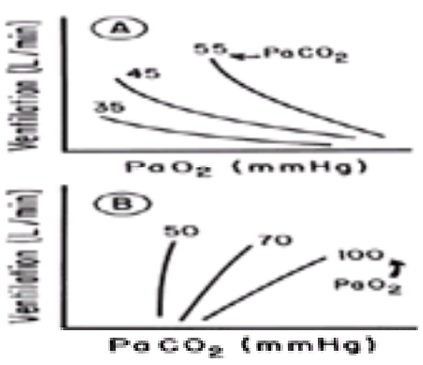

FIG. 6. Effect of changing $PaCO_2$ on (A) the ventilatory response to hypoxia and (B) the ventilatory response to hypercapnia.

RESPIRATORY SENSORY RECEPTORS

The receptors of the lungs and airways are innervated through the vagi and superior laryngeal and trigeminal nerves, and respond, as in other hollow visceral structures, to irritation of the lining layers and changes in distending forces. The mechanoreceptors associated with the respiratory muscles are innervated by spinal nerves and, like those in other skeletal muscles, monitor changes in joint movement and in the length and tension of the muscle itself.

Pulmonary Receptors

There are basically three types of pulmonary receptors: stretch receptors in the smooth muscles of the airway, irritant receptors in the airway epithelium, and J (juxtacapillary) receptors situated in the lung interstitium.

Stretch Receptors

Stretch receptors are innervated by large myelinated fibers. As the lung is inflated, these receptors inhibit inspiration, promote expiration, and initiate the Hering-Breuer reflex. In animals, lung inflation cuts short inspiration and produces expiratory apnea; the duration of apnea is proportional to the degree of inflation.

Direct measurements of stretch-receptor activity indicate that stretch receptors in humans are excited by even small changes in lung volume during quiet breathing. In humans, however, unlike what occurs in animals, vagal blockade to abolish stretch-receptor input does not affect breathing frequency or tidal volume at rest. Vagal blockade in both humans and animals does, however, prevent the increase in breathing frequency that occurs when ventilation is stimulated by hypercapnia or hypoxia and tidal volume is larger.

In animals, stretch-receptor activity helps to preserve tidal volume whenever the usual movements of the lung are hindered by changes in airways resistance or respiratory system compliance. Anything that retards lung inflation diminishes inspiratory inhibitory stretch-receptor activity. Therefore, inspiration is prolonged and tidal volume tends to approach its usual level when the airway is obstructed or respiratory compliance is reduced, despite mechanical interference. When expiration is hindered and lung deflation slowed, increased stretch-receptor activity heightens the force of contraction of the expiratory muscles and also prolongs expiratory time. Both these stretch-receptor actions tend to prevent mechanical impediments to expiration from increasing end-expiratory volume and, as a consequence, decreasing the resting length of the inspiratory muscle. Stretch-receptor activity, by promoting full expiration, helps preserve inspiratory muscle function.

Although stretch receptors are not important in humans in shaping resting breathing patterns, they may help maintain tidal volume when breathing is stimulated or lung or chest-wall mechanical performance is impaired. The increase in breathing frequency caused by stretch-receptor activity in animals and during stimulated breathing in humans decreases the work of breathing of the respiratory muscles, conserving the energy that has to be expended to produce gas exchange. Although it is well-known that peripheral inputs from lung mechanoreceptors strongly affect the timing of respiratory motor activity, at the present time it is difficult to separate clearly the ventilatory effects of the pulmonary stretch-receptor afferents from those of other vagal sensory components (e.g., irritant and C-fiber afferents). However, changes in vagal afferent activity elicited by phasic lung volume changes seem to control predominantly the duration of inspiration, whereas tonic inputs predominantly affect the duration of expiration.

Irritant Receptors

Irritant receptors, like the stretch receptors, are innervated by myelinated fibers, whereas unmyelinated fibers supply the J receptors. Unlike the stretch receptors, both irritant and J receptors are rapid-adapting (within seconds). Neither irritant nor J receptors have a pattern of firing that is related to the phases of inspiration and expiration. Consequently, it is believed that neither receptor has an important influence in determining the pattern of breathing at rest.

Mechanical stimulation of the airways or the inhalation of potentially noxious agents (e.g., particulate matter, nitrogen dioxide, sulfur dioxide, ammonia, and antigens) seems to excite irritant receptors and produce airway constriction. Stimulation of irritant receptors augments the activity of the inspiratory neurons and, by interaction with the stretch receptors, promotes rapid, shallow breathing. This pattern of breathing, in combination with airway constriction, may limit penetration of dangerous agents into the lung and prevent them from reacting with the gas-exchanging surfaces.

The inspiratory augmenting effect of irritant-receptor excitation and the increase in breathing frequency it produces may help maintain ventilation in asthmatic patients, even when the work of breathing is massively increased.

Irritant receptors can be excited by traction on the airways and are stimulated if atelectasis reduces lung compliance. These receptors seem to cause augmented breathing and the large sighs that occur sporadically during normal breathing, and help to open collapsed areas of the lung. As a consequence, irritant receptors help maintain adequate gas exchange.

J Receptors

J receptors are stimulated by pulmonary interstitial edema, but they also can be activated by various chemical agents, such as histamine, halothane, and phenyldiguanide. Activation of the J receptors causes laryngeal closure and apnea, followed by rapid, shallow breathing. When pulmonary edema develops as a result of exercise, J receptors seem to depress the activity of the exercising limbs by a somatic reflex involving cingulate gyrus. J receptors, together with irritant receptors, may be responsible for the tachypnea seen in patients with pulmonary embolus, pulmonary edema, and pneumonia.

Laryngeal Receptors

Mechanoreceptors and chemoreceptors in the upper airway reflexively affect the level and pattern of breathing, motor outflow to the upper airway and chest-wall muscles, and airway tone. The best-studied of the upper airway receptors are the laryngeal receptors. In fact, all areas of the laryngeal mucosa and deeper structures contain sensory nerve endings. Several types of laryngeal receptors have been described: (1) pressure receptors, (2) “drive” receptors, and (3) cold receptors.

Pressure receptors, the most numerous of the laryngeal receptors, are activated by increases in negative (intraluminal less than extraluminal pressure) or positive transmural pressure. Pressure receptors fire in response to both dynamic and static pressure changes, and are slow-adapting. Approximately, two thirds of the pressure receptors respond to negative pressure; the remaining third respond to positive pressure. Approximately one half of laryngeal pressure receptors demonstrate a respiratory modulation in the absence of air flow in the isolated, bypassed upper airway, suggesting that they respond to laryngeal muscle shortening in response to descending motor drive. These so-called drive receptors fire primarily during inspiration. Their firing pattern is diminished by paralysis of the intrinsic muscles of the larynx.

Reflexes elicited by laryngeal pressure receptors tend to stabilize the upper airway, retard its tendency to collapse in response to subatmospheric pressure, and re-establish its patency following occlusion. Laryngeal pressure receptors reflexively activate upper airway muscles while inhibiting inspiratory muscles of the chest wall. Negative transmural airway pressure reflexes increase the activity of inspiratory upper airway muscles (e.g., genioglossus, sternohyoid, cricothyroid, levator alae nasi, posterior arytenoids), advance the onset of the upper airway-muscle EMG relative to that of the diaphragm, increase the duration of inspiration and expiration, and decrease the average rate of rise of diaphragmatic and inspiratory intercostal EMG activity. (Normally, activation of upper airway muscles occurs 50 to 100 ms before the outset of diaphragmatic activation.) Reflex responses to negative pressure in the upper airway mediated by pressure receptors may explain the greater tidal volume, expiratory time, and ventilation during nasal than in tracheostomy breathing in conscious animals and humans.

In contrast to pressure receptors, laryngeal cold receptors are silent near body temperature but are activated by decreases in laryngeal temperature to 34°C or below. When active, cold receptors demonstrate a phasic, inspiratory firing pattern and, in contrast to pressure receptors, appear to adapt rapidly. Cold receptors appear to be located superficially in the mucosa on the edge of the vocal cords near the arytenoid process. Increases in lower airway resistance elicited by laryngeal cooling may be mediated by these receptors.

Finally, mechanical or chemical irritation of the larynx (e.g., probe contact or application of acid) elicits cough, laryngeal closure, bronchoconstriction, an increase in tracheal production of mucus, and a decrease in heart rate and blood pressure. These reflex responses to laryngeal irritation suggest that laryngeal chemoreceptors and mechanoreceptors function to protect the lower airway from aspiration or inhalation of toxic fumes.

Of interest, reflex responses to laryngeal stimulation appear to be state-dependent and are qualitatively different during wakefulness and sleep. For example, in the dog, application of distilled water to the larynx during wakefulness consistently elicits cough and bronchoconstriction. In contrast, the same maneuver performed during REM sleep does not stimulate cough, but rather elicits apnea and bradycardia.

Chest-Wall Receptors

Three types of receptors in the chest wall—joint, tendon, and spindle receptors—signal changes in the force exerted by the respiratory muscles and movement of the chest wall. Specialized Ruffini receptors, as well as pacinian and Golgi organs, are present in joints. Joint-receptor activity, which can be consciously perceived, varies with the degree and rate of change of rib movement.

Inputs arising from muscular receptors, both proprioceptive (particularly muscle spindle) and nociceptor afferent (types III and IV) endings, influence the level and timing of respiratory activity. Proprioceptor afferents (chiefly from the intercostal and abdominal muscles) project to the phrenic motor neurons, where their effect is on firing rate only, and to medullary respiratory neurons in the DRG and NRA, where their predominant effect is on respiratory timing.

Tendon organs in the intercostal muscles and diaphragm monitor the force of muscle contraction and produce an inspiratory inhibitory effect. It was once thought that tendon organ activity was provoked only by unusual levels of muscle force, but it is now believed that tendon organs are stimulated by even small changes in force. Tendon organ input may be important in regulating both intercostal muscle and diaphragmatic contraction during breathing at rest.

Muscle spindles, which are abundant in the intercostal muscles but scarce in the diaphragm, are involved in several kinds of intercostal respiratory reflexes and also help coordinate breathing during changes in posture and speech.

Figure 7 shows schematically the operation of the spindle and its neural connections. Spindles are located on intrafusal muscle fibers aligned in parallel with extrafusal fibers, which move the ribs. Motor innervation of the extrafusal fibers originates in alpha motor neurons, whereas the intrafusal fibers receive motor innervation from gamma (fusimotor) motor neurons. Passive stretch of an intercostal spindle by lateral flexion of the trunk, for example, increases spindle afferent activity and activates a monosynaptic segmental reflex that causes contraction of the parent extrafusal fiber and restores the upright position. The spindles also can be stretched by an efferent fusimotor discharge, which causes contraction and shortening of the intrafusal fiber itself. Some fusimotor fibers fire phasically, so that their rate of discharge rises during inspiration and falls during expiration; other fusimotor fibers are tonically active. The cerebellum determines the balance between tonically and phasically active fusimotor fibers. Without phasic fusimotor activity, spindle discharge would decrease when the extrafusal fibers contract during inspiration. Simultaneous activation of fusimotor and alpha motor neurons causes the spindles to be under continuous stretch during inspiration and enhances the contribution made by the intercostal muscles to respiration. If inspiratory movements are impeded, afferent activity from a spindle innervated by a phasically active fusimotor fiber is enhanced, thus increasing inspiratory muscle force and helping to preserve tidal volume. Activity from lower intercostal muscle spindles, through an intersegmental spinal reflex, also enhances diaphragmatic contraction, allowing the diaphragm to contribute to the compensatory increase in muscle force that occurs when respiratory movements are hindered. In contrast, stretch of the intercostal spindles in the midthoracic region of the chest decreases the duration of inspiration and diminishes the force of inspiratory muscle contraction. This reflex may cut short ineffective inspirations. Ineffective inspirations sometimes are seen in the newborn when the negative intrathoracic pressure produced by powerful diaphragmatic contraction causes paradoxical inward movement of the flexible infant rib cage.

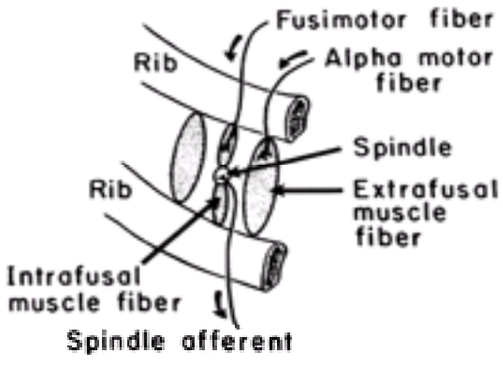

FIG. 7. Intercostal muscle spindle.

Of considerable importance, spindle afferents reach the highest level of the central nervous system, the sensorimotor cortex. Projection of spindle afferent activity to the cerebral cortex allows respiratory muscle length and tension to be sensed consciously and modulated with great precision, thereby allowing complex volitional acts to be performed (e.g., speaking, playing a wind instrument). Spindle afferent activity also likely contributes to the sense of breathlessness. It has been suggested that dyspnea occurs when spindle afferent activity is “high” relative to the intensity of central motor activity to the inspiratory muscles. This concept, which has been termed *length-tension inappropriateness,* explains the dyspnea that arises in the setting of lung diseases that increase inspiratory muscle load and impede muscle shortening. Of interest, the sense of breathlessness can be affected in patients with chronic obstructive pulmonary disease (COPD) by application of vibratory stimuli to the

intercostal muscles, which changes spindle afferent activity. Dyspnea is ameliorated by vibratory stimuli applied in phase with muscle contraction and worsened when the vibratory stimulus is applied out of phase with muscle contraction.

Integration of Afferent Input

Although it is clear that afferent input to the medullary respiratory neurons from mechanoreceptors in the lungs, respiratory muscles, and cardiovascular and thermal regulatory systems (and even the exercising limbs) have significant effects on breathing, the precise manner in which these inputs are integrated is poorly understood. However, the changes in respiratory motor activity elicited by changes in these inputs are not stereotyped. The reflex responses to these inputs may affect the motor output to some respiratory muscles more than others. Pulmonary stretch-receptor input inhibits chest-wall muscle activity (i.e., diaphragm and external intercostal muscles) but increases the activity of the upper airway-dilating muscles (i.e., posterior cricoarytenoid) and the chest-wall expiratory muscles. Even more interesting, some receptors seem to have opposing effects on muscles that normally act as agonists. For example, stimulation of esophageal mechanoreceptors by balloon distension of the distal esophagus reflexively inhibits diaphragmatic activity, both costal and vertebral, but enhances external intercostal activity.

CONTROLLED SYSTEM EFFECTS ON REGULATION OF BREATHING

The translation of the output of the inspiratory neurons to ventilation involves, as shown in Fig. 8, the successive transformation of nerve impulses to muscle electrical activity, muscle shortening, force, and then ventilation. Usually, moderate changes in the mechanical properties of the muscles or chest bellows have little or no effect on the resting blood gas tensions. Compensating effects by the chemoreceptor and mechanoreceptor reflexes, conscious adjustments, and the intrinsic force-velocity relationships of the muscles themselves allow the force of contraction to increase whenever the rate of contraction is slowed. In the presence of sufficiently severe chest disease, however, gas exchange is inadequate despite all efforts to compensate.

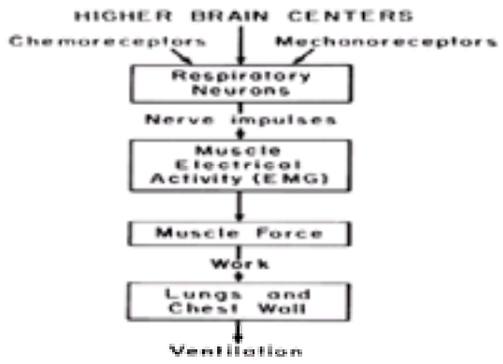

FIG. 8. Steps by which respiratory neural activity is translated into ventilation.

Even when the compensatory responses prove ultimately to be adequate, changes in mechanical conditions (or metabolic rate) cause a transient period in which gas exchange is disturbed and gas tensions are abnormal. The degree to which blood gas tensions deviate from normal in such situations depends on the volume and arrangement of the body stores of O_2 and CO_2.

CO_2 is contained in the body in large amounts as gas in the lungs, but mainly in the form of bicarbonate and carbonate solutions in blood and tissues. O_2, on the other hand, is stored in much smaller amounts in alveolar gas, in solution, and in combination with hemoglobin and myoglobin. Disturbances in gas exchange cause small changes in PCO_2 because of the large size of the CO_2 stores, but large changes in PO_2.

Rates of change of PO_2 and PCO_2 depend not only on the volume of gas stores, but also on organization—that is, the way O_2 and CO_2 contained in different body tissue compartments are linked by the circulation, rates of perfusion, and metabolic rates in the various body compartments—and the ability of the tissues in each compartment to bind CO_2 and O_2.

The rate at which peripheral and central chemoreceptors respond to changes in inspired CO_2 and O_2 depends on the arrangement of the body gas stores. The small size of the arterial compartment and the high rate of carotid body blood flow allow peripheral chemoreceptors to respond quickly to changes in both O_2 and CO_2. The larger CO_2 stores of the brain cause the central chemoreceptors to respond more slowly to changes in inspired CO_2. This difference in response time of central and peripheral chemoreceptors has been used to distinguish the contribution of each receptor to the CO_2 response.

TESTS OF CHEMORECEPTOR SENSITIVITY

When lung function is normal, the sensitivity of the peripheral and central chemoreceptors to CO_2 can be evaluated by measuring the ventilatory response to inspired CO_2. In the conventional steady-state test, the inspired CO_2 is increased in steps, and ventilation at each step is related to the change in $PaCO_2$. Sensitivity to CO_2 is determined from the slope of the line relating ventilation to CO_2. Although the central chemoreceptors are readily accessible to CO_2, the size of cerebral CO_2 stores increases the time required for ventilation to reach a steady state when PCO_2 changes. Usually, the inspired CO_2 concentrations at each step must be maintained constant for 10 to 20 minutes to ensure equilibration. Relative rates of equilibration of PCO_2 in arterial and brain venous blood (Fig. 9) indicate that $PaCO_2$ reaches its steady-state level long before the venous PCO_2. It is apparent from Fig. 9 that if ventilation, which closely tracks cerebral venous PCO_2, is measured too soon, chemosensitivity will be underestimated.

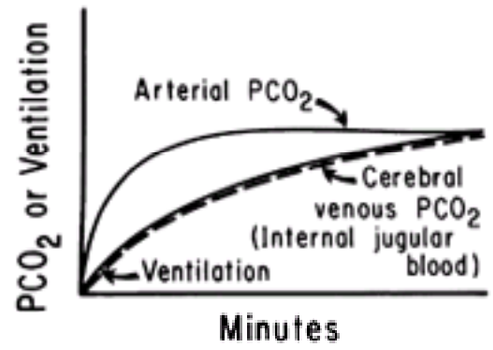

FIG. 9. Changes of ventilation, $PaCO_2$, and cerebral venous $PaCO_2$ when inspired CO_2 is changed.

When CO_2 is rebreathed from a bag containing CO_2 at the mixed venous level together with O_2, arterial and venous blood equilibrate more rapidly. After a brief transition period, PCO_2 at all sites in arterial, cerebral, and mixed venous blood and alveolar air rises at the same rate. Consequently, the rate of change of PCO_2 in alveolar air can be used as an index of the rate of change in PCO_2 in the central chemoreceptors. The exact length of the transition period depends on the size of the rebreathing bag. When the volume of the rebreathing bag is about the same as the vital capacity, chemosensitivity can be estimated by continuous recording of ventilation and PCO_2 after 45 to 60 seconds of rebreathing. Measurements for wide variations in PCO_2 can be obtained in a few minutes. Estimates obtained by this rebreathing method agree with those obtained by the more prolonged steady-state technique. However, the rebreathing tests measure CO_2 sensitivity at much higher levels of PCO_2 than are usually encountered. Moreover, differences have been noted between rebreathing and steady-state ventilatory response to CO_2 when

metabolic acidosis or alkalosis is present. With the steady-state technique, moderate alkalosis and acidosis produce larger changes in the position of the ventilatory response line but relatively small changes in its slopes, whereas the reverse is true in the rebreathing tests. The explanation for this difference is obscure, but it may be related to the different levels of PCO_2 at which steady-state and rebreathing tests are performed.

The average ventilatory response to CO_2 is about 2.5 L/min/mmHg in normal adult men. It is somewhat less in women than in men and tends to decline with advanced age. It varies greatly between individuals but is much more constant in repeated measurements from a single subject. Some of this variability is caused by differences in personality, genetic makeup, and body size, and it is reduced when the CO_2 response is corrected for differences in vital capacity.

Cortical activity is known to affect the response to CO_2. Ventilatory responses to CO_2 measured with the subject's eyes open are greater than ventilatory responses to CO_2 measured with the subject's eyes shut.

TESTS OF PERIPHERAL CHEMORECEPTORS

The peripheral chemoreceptors also respond to CO_2 and contribute about 20%–30% of the total ventilatory increase observed when CO_2 is inhaled. Because peripheral chemoreceptors react rapidly to changes in CO_2, peripheral chemoreceptor responses have been evaluated by measuring the immediate increase in ventilation caused by a few breaths of inspired CO_2 or by measuring the immediate decrease in ventilation observed when CO_2 is abruptly removed.

The response to hypoxia, like the response to hypercapnia, can be measured by either rebreathing or steady-state techniques. Because of the prominent effects of CO_2 on breathing, it is important to keep the CO_2 constant while the response to hypoxia is measured. Because O_2 stores are small, the peripheral chemoreceptor response to O_2 also can be evaluated by measuring the effect on ventilation of a few breaths of N_2 or 100% O_2.

No matter how it is measured, the ventilatory response to hypoxia is curvilinear, making quantitation difficult. The response can be made linear, however, by relating ventilation to the reciprocal of PO_2 or to the arterial O_2 saturation.

There are insufficient data to establish the range of normal values of the ventilatory response to hypoxia; however, available information indicates that it is closely related to the metabolic rate and is at least as variable as the CO_2 response.

Prolonged periods of hypoxia, particularly early in life, are associated with depression of the chemoreceptor response to hypoxia. The ventilatory response to hypoxia is reduced in native residents of regions at high altitudes and in children with congenital cyanotic heart disease. The carotid body appears to be larger in native residents of high altitudes. The change in size may be caused by increased carotid body vascularity, which raises PO_2 and decreases responsiveness.

In the newborn, hypoxia causes only a transient increase in ventilation, which then subsides to nearly prehypoxic levels. It has been recently appreciated that in adult humans, hypoxia lasting for as short a time as 5 minutes produces a gradual reduction in ventilation from its initial peak level.

The initial increase in ventilation is of course mediated by the carotid body. The subsequent decrease seems to represent a depressant effect of hypoxia on central respiratory neurons by hypoxia-induced increases in cerebral blood flow and probably the release of inhibitory neuromodulators, such as adenosine.

Lung disease or respiratory muscle weakness can depress ventilatory responses to chemical stimuli. The depressant effect seems to be greater for the response to CO_2 than for the response to hypoxia. As a result of studies in which airway resistance was increased by requiring subjects to breathe through external resistance, either during inspiration or expiration, it was suggested that the inspiratory work of breathing at a given level of PCO_2 is fixed, so that when the ratio of inspiratory muscle work to ventilation is increased by disease, ventilation decreases. The hypercapnia observed in severe obstructive lung disease was explained by the increase in flow-resistive work associated with chronic airway obstruction.

More recent studies have indicated that small increases in airway resistance have little effect on resting ventilation or CO_2 response in normal subjects and may even heighten ventilation. The mechanisms responsible for the preservation of ventilation under these circumstances could include intrinsic properties of the respiratory muscles, increased inspiratory augmenting output from lung and chest-wall mechanoreceptors, readjustment in the sequence of contractions of the respiratory muscles so that mechanical advantage of the muscles and their coordination is improved, and increased inspiratory drive originating from the motor cortex. This last mechanism may depend on the conscious perception of changes in airway resistance. It is interesting that the ability to detect changes in airway resistance varies, decreasing with increasing airway resistance, and that it decreases further when airway obstruction is chronic than when it is acute.

Because mechanical changes may limit the ventilatory response to chemical stimuli, other methods of assessing the output of respiratory motor neurons have been devised. Two methods have been employed: measurement of occlusion pressure and EMG of the diaphragm. Neither is perfect, but both are useful under certain circumstances.

In the measurement of occlusion pressure, the force of contraction of the inspiratory muscles under quasi-isometric conditions is determined as follows: The airway is momentarily blocked at the beginning of inspiration, and the negative pressure developed during inspiration is measured. In conscious subjects, the reproducibility of the response is greater when the airways are occluded for just a fraction of a second. The occlusion pressure increases with hypercapnia and hypoxia and can be related to change in PCO_2 and PO_2 to estimate chemosensitivity.

Airway occlusion at FRC produces a no-flow state at the relaxed position of the respiratory system. The absence of air flow and prevention of significant volume change during inspiration prevent increases in airway resistance or decreases in compliance from affecting this index of respiratory output. In patients with mechanical abnormalities of the ventilatory pump caused by diseases of the lung or chest wall, occlusion pressure therefore more accurately reflects the neuromuscular drive to breathe than does ventilation.

Because the tensions developed by the inspiratory muscles theoretically depend on their initial length, the occlusion pressure in patients with lungs hyperinflated by disease may not reflect respiratory drive accurately. Increased FRC in animals reduces occlusion pressure responses. However, studies in conscious humans in whom FRC has been changed by altering body position show little effect on occlusion pressure, even when changes in FRC are fairly large (1000 mL). A conscious person apparently maintains constant muscle tension successfully, despite changes in initial muscle length, by altering neural output.

Measurement of the electrical activity of the diaphragm is probably the most direct way of evaluating respiratory neuronal output. This can be accomplished by passing a catheter containing electrodes down the esophagus and positioning the electrodes so that they straddle both surfaces of the diaphragm.

Various ways have been devised to quantitate diaphragmatic electrical activity measured this way. In the method most used currently, diaphragmatic activity is integrated over small intervals of time (100 to 200 ms), and the average activity per time limit is recorded (the so-called moving average). Electrical activity measured in this way depends on the exact positions of the electrodes in relation to the diaphragm during breathing, so that it is difficult to compare one individual with another. It is possible, however, to use this method to determine the effect of different therapeutic interventions in the same person.

CLINICAL IMPLICATIONS

The most important cause of respiratory failure is derangement of lung mechanics. However, respiratory failure does not develop in all patients, even those with severe impairment of pulmonary function. It has long been suspected that those patients who have the poorest chemosensitivity are the ones in whom CO_2 retention is most likely to develop when the performance of the chest bellows is reduced. The evidence for this is indirect. For example, normal offspring of hypercapnic subjects with COPD demonstrate significantly lower ventilatory and occlusion pressure responses to hypoxia and hypercapnia (~60% lower) than do normal offspring of eucapnic subjects with COPD.

The CO_2 sensitivity of children who have retained CO_2 because of upper airway obstruction resulting from hypertrophy of the adenoids and tonsils is depressed, even after the tonsils and adenoids have been removed. Asthmatic patients who have retained CO_2 during an asthmatic attack also show persistently low ventilatory responses to CO_2, even after recovery from the asthmatic episode. Moreover, subjects who have had asphyxial, near-fatal episodes of asthma display lower ventilatory and occlusion pressure responses to hypoxia than do either age-matched normal subjects or asthmatic subjects with no history of near-fatal episodes.

There is also a small group of subjects who retain CO_2 even though lung function is normal. In some of these patients, the cause of the depressed CO_2 sensitivity is not known, but in others it seems to be associated with specific diseases, certain metabolic abnormalities, such as alkalosis, or the long-term administration of respiratory depressant drugs, such as methadone. These conditions are summarized in Table 1. In a few conditions listed in Table 2, only the ventilatory response to hypoxia is depressed. Individuals with these conditions are able to maintain blood gas tensions within usual limits because of their normal CO_2 drive. However, when CO_2 sensitivity is reduced by the administration of drugs (e.g., premedication before surgery), significant hypoxemia can develop. Depressed ventilatory responses to hypoxia may also increase the tendency for CO_2 retention to develop in COPD and may be a risk factor for acute mountain sickness.

Genetic factors
Obesity-hypoventilation syndrome
Bulbar poliomyelitis
Metabolic alkalosis
Parkinson's disease
Narcotic addictions (temporary)
Myxedema
Bilateral spinothalamic lesions
Severe hepatic failure

TABLE 1. *Conditions sometimes associated with depressed responses to hypercapnia and hypoxia*

Narcotic addictions (long-term)
Carotid endarterectomy
Cyanotic congenital heart disease
Familial dysautonomia
Semistarvation
Arnold-Chiari syndrome

TABLE 2. *Conditions associated mainly witha decreased response to hypoxia*

Certain conditions seem to predispose to heightened responses to CO_2 or hypoxia, even when the lungs are normal. These conditions are listed in Table 3.

Hyperthyroidism
Salicylism
Fever
Hemodialysis for uremia
Luft's syndrome
Pregnancy
Mild hepatic failure

TABLE 3. *Conditions associated with increased responses to carbon dioxide and/or hypoxia*

Abnormalities in mechanoreceptor function also can influence gas exchange. Patients with chronic airway obstruction who breathe with small tidal volumes tend to retain CO_2, whereas those who breathe with larger tidal volumes do not. The small tidal volumes are caused by abbreviated inspiratory time and perhaps by heightened pulmonary or chest-wall receptor activity. Heightened mechanoreceptor activity may also be responsible for dyspnea in some patients with interstitial lung disease, as vagal blockade at times alleviates this sensation.

EFFECTS OF SLEEP ON VENTILATION

State-related changes in CNS activity associated with the transition from wakefulness to sleep exert complex effects on ventilatory control that profoundly affect the level and pattern of breathing. In general, withdrawal of cortical and higher CNS influences that provide excitatory inputs to the medullary respiratory neurons during wakefulness cause the chemical regulation of ventilation to assume greater importance.

The transition from wakefulness to slow-wave sleep (i.e., stages 1, 2, 3, and 4 non-REM) is associated with increases in $PaCO_2$ and decreases in PO_2, an increase in the threshold of the ventilatory response to CO_2, and elimination of the "dog leg" in the ventilatory response to CO_2 attributable to the wakefulness drive. In normal subjects, elimination of wakefulness drives and decreases in chemosensitivity typically increase $PaCO_2$ and decrease PO_2 by 4 to 8 mmHg. Small reductions in PCO_2 in the order of 4 to 6 mmHg regularly induce apnea in normal subjects, in contrast to what occurs during wakefulness, when breathing persists despite marked hypocapnia. Steady-state changes in PCO_2 during slow-wave sleep appear to be inversely related to the magnitude of the ventilatory response to CO_2 during wakefulness.

Breathing during stages 1 and 2 of slow-wave (i.e., light) sleep is frequently periodic and often characterized by apnea (i.e., cessation of air flow for >10 seconds) with or without occlusion of the airway (see below). Periodic breathing resembles the Cheyne-Stokes respiration occurring during wakefulness. On the other hand, stages 3 and 4 of non-REM sleep are generally characterized by a slow, deep, regular pattern of breathing. Interestingly, this phase of sleep is associated with a greater depression of ventilatory responses to CO_2 and O_2 than are stages 1 and 2.

Breathing during REM sleep is rapid and irregular, with marked variation in the duration of inspiration and expiration, tidal volume, and average inspiratory air flow rate. Periods of hyperpnea appear to coincide with REM sleep. Electrical activity (EMG) of the rib cage and upper airway respiratory muscles is profoundly depressed in REM sleep, in keeping with the marked muscular atonia observed in the limb muscles. Diaphragmatic EMG activity is relatively spared, but abrupt, irregular periods of inhibition during inspiration may occur. A disproportionate reduction in intercostal relative to diaphragmatic activity in REM sleep leads to paradoxical inward movement of the rib cage on inspiration. Profound inhibition of upper airway muscle electrical activity considerably increases upper airway resistance. Ventilatory responses to CO_2 and O_2 are at their lowest during this stage of sleep. In subjects with underlying lung disease, the greatest disturbances in PaO_2 and $PaCO_2$ occur during this stage of sleep, presumably because of the rapid, shallow pattern of breathing, increased ratio of volume of dead space to tidal volume, and uncoordinated pattern of rib cage

and abdominal movement.

Periodic Breathing During Sleep

Recent studies have suggested several possible mechanisms for the periodic breathing and airway occlusion that occur during the transition from wakefulness to light sleep, each of which causes instability in the ventilatory control system. First, removal of the wakefulness drive depresses ventilation, with concomitant large and rapid increases in PCO_2 and reductions in PO_2 that stimulate peripheral and central chemoreceptors. Second, alterations in blood gas tensions and mild reductions in metabolic activity that decrease CO_2 production and O_2 consumption increase plant gain—that is, the change in blood gas tensions induced by a given change in ventilation. Increased plant gains in stage 1 and stage 2 sleep may offset the mild reductions in ventilatory responses to CO_2 and O_2 that occur during these stages and increase controller gain. Third, progressive increases in respiratory effort during occlusive apnea lead to arousal, the primary mechanism whereby occlusive apnea is terminated. Collapse of the upper airway and arousal destabilize breathing by producing large and rapid changes in PCO_2 and PO_2. Fourth, arousal may be followed by a rapid return to sleep, removal of the wakefulness drive, and rapid deterioration in blood gases. Cycles of airway occlusion and arousal superimposed on sleep-related changes in controller gain may be mutually reinforcing and lead to sustained, progressively amplifying oscillations in breathing and blood gas tensions. Breathing in stages 3 and 4 of sleep is likely to be more stable than in stages 1 and 2, because overall controller gain may be diminished and because changes in ventilation caused by external stimuli are less likely than in stages 1 and 2. Depression of CO_2 and O_2 chemosensitivity in stages 3 and 4 may more than offset increases in plant gain.

Changes in respiration with periods of apnea, profound arterial desaturation, and disturbed sleep appear to be especially common in patients with congestive heart failure. Periodic breathing in these subjects may be explained by a prolongation in circulation time with information delays and increases in plant gain as a result of decreases in pulmonary stores of O_2 related to pulmonary edema.

Airway Occlusion During Sleep

The pathogenesis of airway occlusion during sleep has now been elucidated. Patency of the upper airway during sleep depends on a balance between the subatmospheric “sucking” pressures in the posterior nasopharyngeal space generated by the inspiratory muscles of the chest wall and the opposing dilating forces generated by the upper inspiratory airway muscles, which tend to enlarge and “stiffen” the upper airway. In essence, collapse of the upper airway during inspiration occurs when there is an imbalance of forces in favor of the subpharyngeal pressures. Collapse of the upper airway therefore depends on three factors: (1) activity of the dilator muscles, (2) intraluminal airway pressure, and (3) mechanical properties of the passive upper airway.

The activity of the respiratory skeletal muscles of the upper airways, which originate on the mandible, tongue, larynx, and hyoid bone and dilate the upper airway (i.e., genioglossus, geniohyoid, sternohyoid, posterior arytenoids, cricothyroid), demonstrate a respiratory modulation—that is, the EMG and tension of these muscles increase during inspiration, thereby augmenting the caliber of the upper airway and its tendency to remain patent. Hypercapnic and hypoxic chemical stimuli to breathing increase upper airway muscle electrical activity (e.g., genioglossus, posterior arytenoids) in a manner qualitatively similar to that seen in the pump muscles of the chest wall. All stages of sleep are associated with depression of EMG activity of upper airway muscles at any given level of PO_2 or PCO_2 out of proportion to changes in chest-wall muscle EMG. REM sleep is associated with the greatest inhibition of upper airway muscle electrical activity, in keeping with the generalized muscular atonia that occurs during this stage of sleep. Airway collapse during sleep is favored, therefore, by depression of the electrical activity of dilating upper airway muscles. Re-establishment of airway patency in the setting of obstructive apnea requires arousal and increases in upper airway EMG activity. Of interest, administration of alcohol in amounts that have no effect on ventilation or pattern of breathing depress genioglossus EMG activity during eucapnia or hypercapnia. This finding may explain the greater tendency for obstructive sleep apnea to develop after alcohol ingestion or sedative use.

In addition, end-expiratory lung volume (FRC) oscillates during periodic breathing and demonstrates progressive reduction during the several breaths preceding occlusion. Reductions in lung volume *per se* reduce the cross-sectional area of the posterior nasopharynx and increase the mechanical advantage of the inspiratory muscles of the chest wall (i.e., the inspiratory pressure generated for a given EMG activity is increased).

Classic control system theory indicates that increased controller gain predisposes to control system instability and oscillation. However, it seems likely that the precise mechanisms by which periodic breathing with apnea develop during sleep vary from individual to individual and may depend on the magnitude of the wakefulness drive, the propensity to awaken and undergo rapid, state-related changes in ventilation, and the proclivity of the upper airway to collapse.

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CHAPTER

3 Respiratory Functions of the Lung

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INTRODUCTION

When the human body is at rest, the lungs receive 5 L of pulmonary blood flow and nearly 5 L of fresh gas/min. The blood in the circulation exchanges metabolic gases within the lung's approximately 300 million alveoli, each of which is about 300 μm in diameter. The alveoli provide a huge surface area of approximately 75 m^2 for gas exchange, with a thickness of <0.5 μm. The alveoli are intertwined with a complex pulmonary capillary network having a surface area of approximately 50 m^2. In the pulmonary capillaries, the erythrocytes traverse the microcirculation in about three quarters of a second. Within the first third of this brief transit time, oxygen and carbon dioxide exchange is such that as the blood exits from the pulmonary capillaries, the concentrations of oxygen and carbon dioxide in the erythrocyte are in equilibrium with those of the alveoli. This system is relatively simple but highly efficient and capable of accommodating as much as a sixfold increase in the rate of blood flow and a twenty-fold increase in the rate of oxygen consumption by the body. The first portion of this chapter describes how the lungs match ventilation with blood flow to insure efficient gas exchange under normal and diseased conditions.

VENTILATION

The adult human lung is described most simply as a system containing conducting airways and the air spaces, or alveoli. The conducting airways consist of bronchi (cartilaginous airways) and bronchioles (noncartilaginous airways), but they contain no alveoli and therefore do not participate in gas exchange. They constitute the “anatomic dead space.” Generally speaking, beginning with the trachea, the conducting airways comprise the first 19 generations of bronchi, ending in terminal bronchioles (Fig. 1). Each terminal bronchiole subtends a terminal respiratory unit, or acinus. The acinus consists of respiratory bronchioles that have alveoli arising from their walls, and alveolar ducts that are lined with alveoli. These structures constitute the “respiratory zone” of the lung, and comprise generations 20 through 27 in Fig. 1. The respiratory zone makes up most of the lung, and for the adult, its volume is approximately 3000 mL.

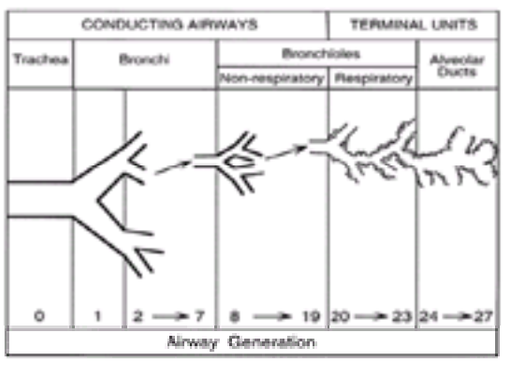

FIG. 1. Weibel's lung model. Note that generation number begins with the trachea. For details, see text. (Adapted and reprinted with permission from Weibel ER. *Morphometry of the Human Lung.* Berlin: Springer-Verlag; 1963:111.)

The Weibel lung model of Fig. 1 conveniently includes some obvious simplifications. For example, some respiratory bronchioles conduct gas in series to more distal respiratory bronchioles and their alveolar ducts and alveoli. In some regions of the human lung, there are fewer than 27 bifurcations from the trachea to the alveoli, whereas other regions contain more than 27 bifurcations. This type of airway branching is known as an *irregular dichotomous pattern.* The presence of shorter pathways may be one of the mechanisms by which gas exchange is sufficient to support life even when tidal volume is less than the dead space, as occurs during

high-frequency ventilation.

Despite its limitations, the simple lung model works quite well for simulating the gas exchange behavior of the lung under resting conditions. The utility of the approach is shown in Fig. 2, where the Weibel model is used to examine the nature of gas flow in the lung. The model indicates little change in the total cross-sectional area of the airways until the terminal bronchioles are reached, where the cross-sectional area increases dramatically. The physical effect of this rapid increase in cross-sectional area is to decrease the forward velocity of the gas flow dramatically, such that the primary mechanism of gas transport changes from convective to "diffusive" in the regions of terminal bronchioles. Indeed, molecular diffusion of the gas phase is essentially the only mechanism of gas entry into the alveoli.

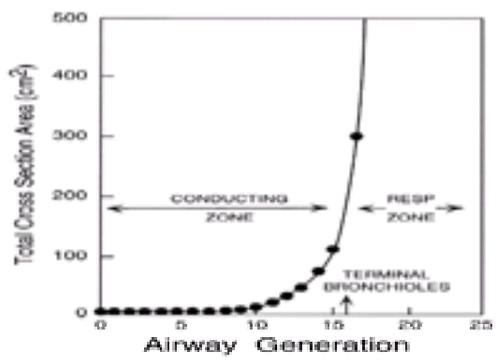

FIG. 2. Diagram of total cross-sectional area of the airways in the respiratory (*resp*) zone. The rapid increase in cross-sectional area in the respiratory zone is predicted from Weibel's model (Fig. 1). (Reprinted with permission from West JB. *Respiratory Physiology—The Essentials.* 4th ed. Baltimore: Williams & Wilkins; 1990.)

Alveolar Ventilation and Dead Space

The alveolar ventilation ($\dot{V}_A$) is the amount of fresh inspired air reaching the alveoli per minute. It can be calculated by subtracting the ventilation not involved in gas exchange (dead space ventilation, $\dot{V}_D$) from total ventilation (or minute ventilation, $\dot{V}_E$).

$$\dot{V}_A = f(V_T - V_D) = \dot{V}_E - \dot{V}_D$$

where f is the respiratory rate; V_T is tidal volume; and V_D is the dead space. Because an appreciable part of each tidal volume does not reach the regions of the lungs in which gas exchange occurs, this fraction of the tidal volume is exhaled largely unchanged and comprises the dead space of the breath. Therefore, it is useful to think of dead space as a fraction of the tidal volume (V_D/V_T) when evaluating the efficiency of carbon dioxide elimination.

Another way to measure the alveolar ventilation in normal subjects is by way of the alveolar ventilation equation:

$$\dot{V}_A = \dot{V}CO_2/P_ACO_2 \times K$$

where $\dot{V}CO_2$ is the volume of CO_2 exhaled per minute, P_ACO_2 is the partial pressure of CO_2 in the alveoli, and K is a proportionality constant (0.863). Because in normal lungs the PCO_2 of alveolar gas and that of arterial blood ($PaCO_2$) are virtually identical, the $PaCO_2$ can be used in the equation to substitute for the P_ACO_2. The same equation also can be used in patients with underlying lung disease, but the solution would yield the "effective" alveolar ventilation. This value is not the same as the alveolar ventilation defined by the anatomic dead space. The "effective" alveolar ventilation would be the volume of fresh inspired gas involved in gas exchange with the capillary blood. Regardless of how it is measured, it is the alveolar ventilation, and not the total ventilation, that determines the effectiveness of CO_2 elimination. This principle can be illustrated by the example of a patient with severe lung disease requiring mechanical ventilation. Such a patient may require as much as 20 L/min of total ventilation to maintain an acceptable PCO_2, because the majority of the gas is used to ventilate air spaces in the lung that are not perfused with pulmonary arterial blood.

Components of the Dead Space

The *anatomic dead space* is the internal volume of the conducting airways from the nose and mouth to the terminal bronchioles. In adults, the anatomic dead space in milliliters is approximately equal to the ideal body weight in pounds. The value increases slightly as lung volume increases or with agents that relax smooth muscle and dilate the airways. Anatomic dead space is also greater during hyperventilation and during exercise, because radial traction is exerted on the bronchi by the surrounding parenchyma of the lung. This traction increases the caliber of the conducting airways.

The volume of the anatomic dead space can be determined easily by Fowler's method (Fig. 3). For this measurement, the patient takes a single inspiration of 100% oxygen, and the nitrogen concentration at the mouth is measured during a slow exhalation. Initially, pure oxygen from the dead space is measured (phase I); nitrogen concentration begins to rise as the dead space gas is washed out by the alveolar gas (phase II). Then, an almost uniform gas concentration is recorded, which represents alveolar gas (phase III). The nitrogen concentration of the final part of the expiration (phase IV) rises because the small airways progressively close at the bases of the lungs. The anatomic dead space is calculated by transforming phase II into an ideal square front (vertical dashed line) and determining the expired volume on the abscissa. The anatomic dead space is not measured routinely in the clinical pulmonary function laboratory because it has little diagnostic value.

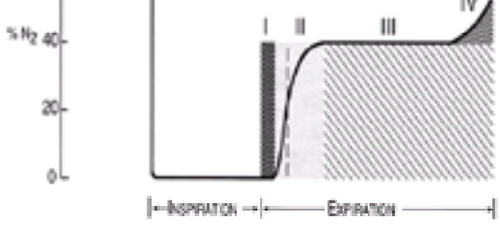

FIG. 3. A single-breath N_2 washout analysis to calculate anatomic dead space. The subject is requested to take a deep breath of O_2 and breathe out slowly and evenly. At the beginning of expiration, pure O_2 (0% N_2) is expired (phase I). This is followed with a rapidly rising N_2 concentration, which represents the washout of the remainder of the dead space gas by alveolar gas, and then by pure alveolar gas (phase III). The N_2 concentration in the last part of the expiration (phase IV) rises because of the progressive closure of the small airways at the bases of the lungs. The anatomic dead space is calculated by transforming phase II into a rectangle and determining the expired volume on the abscissa. (Reproduced with permission from Forster RE, et al., eds. *The Normal Lung: Physiological Basis of Pulmonary Function Tests.* 3rd ed. Chicago: Year Book; 1986.)

Whereas anatomic dead space is determined solely by the structure of the lung, physiologic dead space represents the part of the lungs not involved in carbon dioxide elimination. It is equivalent to the "wasted" ventilation, a term preferred by some authors because physiologic dead space is neither "physiologic" nor "dead." Physiologic dead space can be calculated from the Bohr equation:

$$V_D/V_T = (P_ACO_2 - P_ECO_2)/P_ACO_2$$

where A and E refer to alveolar and mixed expired gas, respectively. In subjects with normal lungs, the PCO_2 of alveolar gas (P_ACO_2) and that of arterial blood ($PaCO_2$) are virtually identical, so that the $PaCO_2$ is often substituted for the P_ACO_2.

The volume of the physiologic dead space is about the same as the anatomic dead space for the normal lung. In the presence of ventilation-perfusion mismatch, however, physiologic dead space increases, mainly from ventilation of lung units with abnormally high ventilation-perfusion ratios. The inspired air that enters these lung units is less effective in eliminating carbon dioxide from the venous blood and produces marked inefficiency of exchange between the blood and gas phases.

Distribution of Ventilation

Regional Distribution of Ventilation

In normal human lung, the alveolar ventilation is not distributed uniformly throughout the air spaces. Using a radioactive tracer gas (e.g., ^{133}Xe) to assess gas distribution, the ventilation per unit volume of the lung in normal upright individuals is found to be the greatest near the base and becomes progressively lower toward the apex. When the subject lies supine, this difference decreases, but the ventilation of the dependent (posterior) lung exceeds that of the nondependent (anterior) lung. In the lateral decubitus position, the dependent lung also is ventilated more effectively.

The topographic distribution of ventilation in the upright lung may be explained by the pleural pressure gradient (Fig. 4). Experimental studies in the upright position show that there is a gradient of intrapleural pressure of 0.6 to 0.7 cm H_2O per centimeter of vertical distance such that the intrapleural pressure is more negative in the upper compared with the lowermost regions of the lungs. The lower transpulmonary pressure (intra-alveolar pressure minus intrapleural pressure) at the base of the upright lung produces two effects: First, the volume of the alveoli at the base is lower, as indicated by the pressure-volume curve at the bottom of Fig. 4. Second, the change in volume for a small change in transpulmonary pressure is greater, because the alveoli are operating on a steeper part of the pressure-volume curve (i.e., the compliance is greater). Thus, the ventilation measured as change in volume per resting volume is greater at the base than at the apex.

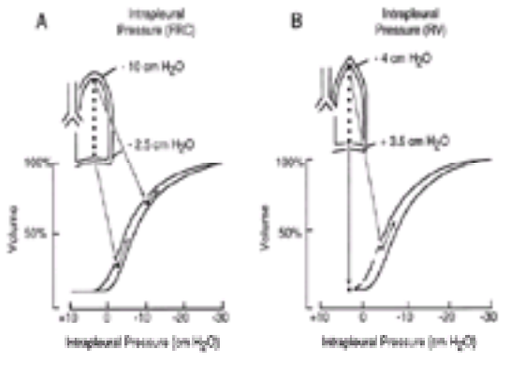

FIG. 4. The topographic distribution of ventilation of the upright lung. **A:** An inspiration from FRC. **B:** An inspiration from RV. (Reproduced with permission from West JB. *Respiratory Physiology—The Essentials.* 4th ed. Baltimore: Williams & Wilkins; 1990.)

The dependent portion of the lung receives more ventilation when a breath is initiated from the functional residual capacity (FRC). If a normal subject makes a small inspiration from residual volume (RV), however, most of the ventilation goes to the apex of the upright lung. This is because the intrapleural pressures in the lowermost lung regions become positive and exceed intra-alveolar pressure, causing the small airways to close. A small decline in transpulmonary pressure that does not exceed the critical opening pressure of the small airways does not allow gas to enter the extreme base of the lung, and only the apex is ventilated (Fig. 4).

The volume at which the basal airways close on exhalation (probably in the region of the respiratory bronchioles) is called the *closing volume.* This closure occurs only at lung volumes below FRC in young normal subjects, but the lung volume at which closing begins increases with advancing age and obesity. This is one of the reasons why the dependent portions of the lungs of older and heavier individuals are more susceptible to atelectasis under conditions that decrease the FRC, such as general anesthesia.

The factors that contribute to vertical gradient of intrapleural pressure are complex. In small animals with compliant thoracic cages, the effects of gravity on the shape of the chest wall appears to be the major determinant of the pressure gradient. In contrast, in large animals with less compliant rib cages, the weight of the lung appears to be the major factor causing the regional gradient of intrapleural pressure and, hence, regional variations in transpulmonary pressure. It also should be noted that in large animals, factors other than lung weight also contribute to the regional distribution of ventilation. For example, the vertical gradient of intrapleural pressure evident in dogs studied in the supine position disappears when they are turned to the prone position. Voluntary breathing with different groups of respiratory muscles also affects the distribution of intrapleural pressure and regional ventilation. Thus, a complete explanation for the nonuniformity of ventilation and the regional differences in intrapleural pressure should take into account the effects not only of lung weight but also of the physical stresses on the lung tissue and thorax.

Unlike the topographic distribution of ventilation, the distribution of ventilation in small regions of the lung cannot be measured easily, because it is beyond the resolution of existing external detectors, such as gamma cameras. Several physiologic factors cause uneven ventilation at the lobular or even the acinar level of the lung.

Time Constants

The time constant of a unit of the lung is determined by the product of its resistance and compliance. Lung units with different time constants inhale and exhale at different rates. A lung unit with a long time constant (i.e., greater resistance and compliance) does not completely fill by the end of inspiration and empties slowly during expiration. In contrast, a lung unit with a short time constant (i.e., smaller resistance and compliance) fills and empties rapidly. The higher the respiratory rate, the greater the discrepancy in filling and emptying between these two kinds of units, and thus the greater the inhomogeneity of ventilation.

When a lung unit with a long time constant is located adjacent to a lung unit with a short time constant, the unit with the long time constant may withdraw gas from the adjacent lung unit with a short time constant rather than fresh inspired gas. This “to and fro” behavior is known as *pendelluft,* and it can occur in abnormal lungs. In addition, a lung unit with a short time constant may receive a higher proportion of dead space gas, which reduces its alveolar ventilation. This effect is prominent in chronic obstructive lung disease, in which compliant lung units with extremely long time constants behave essentially as dead space.

Structural Asymmetry

The inherent asymmetry of the anatomy of the lung produces lung units of different sizes. As expected, smaller lung units receive greater penetration of gas by diffusion than larger units. As a consequence, incomplete mixing of gases may occur in the larger unit, a behavior functionally similar to that caused by stratified inhomogeneity (see below). This mechanism becomes most prominent in bullous lung diseases.

Stratified Inhomogeneity

Another reason for uneven ventilation of small lung units is a gradient of gas concentration along the small airways. This condition is called *stratified inhomogeneity.* Inspired gas reaches approximately the region of the terminal or respiratory bronchioles by convective flow, but gas flow over the rest of the distance to the alveoli is accomplished principally by molecular diffusion within the airways. When airway calibers are altered (e.g., in centrilobular emphysema), the process of gas diffusion may be incomplete for each breath. Thus, alveoli more distal to the conducting airways are less well ventilated than proximal alveoli.

The overall inhomogeneity of ventilation of the lung can be estimated in the laboratory using single-breath or multiple-breath washout techniques. For example, a single breath of air can be inspired containing a small concentration of a chemically inert, relatively insoluble gas (e.g., helium or methane) and then slowly and evenly exhaled into a spirometer or flow meter while concentration of the tracer gas is recorded continuously. Nonuniformity of ventilation can be assessed by measuring the slope of the alveolar plateau (phase III) in Fig. 3. A multiple-breath technique also can be used based on the rate of washout of nitrogen gas when pure oxygen is breathed (nitrogen washout). Inhomogeneity can be judged by the number of breaths required to obtain 90% of the equilibrium value compared with the number

calculated assuming the tidal gas is distributed uniformly.

Factors Counteracting Ventilation Inhomogeneity

Several mechanisms tend to preserve the uniform distribution of ventilation in the lung. One of these mechanisms is the *pendelluft* phenomenon described above. Another mechanism is gas exchange through collateral air channels between adjacent lung units. *Collateral ventilation* can occur between alveoli (pores of Kohn), neighboring terminal units, contiguous lobules (canals of Lambert), and foramina of Martin. The factors affecting flow through these channels, including lung volume and the PCO_2 in alveolar gas, have been studied in several species of experimental animals. Studies in humans, however, are limited. It appears that in normal subjects breathing near FRC there is little gas flow going through collateral channels. Collateral flow becomes more important in determining the mechanical behavior and distribution of ventilation of lungs with airway obstruction.

Another factor that tends to improve uniformity of ventilation is the *interdependence* of peripheral lung units. This concept originates from the observation that contiguous lung units are attached integrally to each other by the connective tissue framework of the lung parenchyma. The behavior of one unit must therefore influence the behavior of its neighbors. This framework serves to offset the tendency for regional differences in compliance to make lung units larger or smaller than they should be for optimal performance. Finally, the pulsatile action of the heart promotes mixing of gas by imparting physical motion to the surrounding lung tissue. The effects of such *cardiogenic mixing* on distribution of ventilation, however, are probably quite small compared with the other factors mentioned above.

PERFUSION

The pulmonary circulation consists of a pump (the right ventricle), a distribution system (arteries and arterioles), a gas exchange surface (the capillary bed), and a collecting system (venules and veins). In a normal-sized adult, the pulmonary circulation contains about 500 mL of blood, of which approximately 150 mL is in the capillary bed. The capillary bed opposes the alveolar epithelium and provides an extensive interface for the uptake of oxygen and elimination of carbon dioxide. It is a readily expandable bed that can tolerate blood flow of several times the resting cardiac output with only a small rise in the pressure (Table 1).

Condition	Rest (sitting)	Exercise
Oxygen consumption	300	2000 mL/min
Blood flow		
Cardiac output	6.3	16.2 L/min
Heart rate	70	135 beats/min
Stroke volume	90	120 mL/beat
Intravascular pressure		
Pulmonary arterial pressure	20/10	30/11 mmHg
Mean	14	20 mmHg
Left atrial pressure, mean	5	10 mmHg
Brachial arterial pressure	120/70	155/78 mmHg
Mean	88	112 mmHg
Right atrial pressure, mean	3	1 mmHg
Resistances		
Pulmonary vascular resistance	1.43	0.62 units[a]
Systemic vascular resistance	13.5	6.9 units[a]

[a] Units = mmHg/L/min.

TABLE 1. *Pulmonary and systemic hemodynamic variables during rest and moderate exercisein a normal adult man*

Hemodynamic Properties of the Pulmonary Circulation

The pressure within the pulmonary circulation is quite low (about one fifth of that of the systemic circulation), although the blood flow to the lungs is comprised of the entire cardiac output. This feature of the pulmonary circulation is responsible for much of its special behavior. A comparison of pulmonary and systemic hemodynamic variables at rest in the normal adult is given in Table 1. The following three concepts about pressure in the pulmonary vessels are important to understanding the behavior of the pulmonary circulation.

Intravascular Pressure

The actual blood pressure inside the lumen of any vessel referenced to atmospheric pressure is the intravascular pressure. Some intravascular pressures, such as pulmonary arterial pressure and pulmonary venous pressure, can be measured directly by placing catheters into the bloodstream at specific points. Pulmonary capillary pressure, on the other hand, is difficult to measure directly. In fact, there is still uncertainty about the exact values of capillary pressure in the pulmonary circulation. Obviously, as blood flows from the pulmonary arterioles through the capillaries to the pulmonary venules, the capillary pressure must be less than arteriolar and greater than venular pressure. In clinical practice, capillary pressure can be estimated by wedging a catheter into a lobar branch of pulmonary artery. The “wedge” pressure measured under conditions of “no flow” reflects pressure downstream within the vascular network at the site of the next freely communicating channels, that is, pulmonary capillaries or small pulmonary venules.

Transmural Pressure

Transmural pressure is the difference between the pressure inside a vessel and the pressure in the tissue around it (perivascular pressure). Transmural pressure is related to the diameter of the vascular lumen. For example, the pressure around the pulmonary arteries and veins is approximately equal to the intrapleural pressure. The pressure around the capillaries is approximately the intra-alveolar pressure. It is this difference in transmural pressure that leads to the different behavior of alveolar and extra-alveolar vessels under conditions such as lung inflation (discussed later). At the capillary level, the transmural pressure is also an important determinant of the rate of transudation of fluid across the capillary bed.

Pulmonary Driving Pressure

Driving pressure is the difference in intravascular pressure between one point in a vessel and another point downstream. It is the pressure involved in overcoming the frictional resistance that impedes blood flow between two points. The driving pressure for the pulmonary circulation is the difference between the intravascular pressure in the main pulmonary artery and that immediately after the pulmonary circulation in the left atrium.

It is important to recognize the differences among these three pressures. For example, if mean pulmonary arterial pressure is 15 mmHg and mean left atrial pressure is 5 mmHg, the driving pressure across the lung would be 10 mmHg (15 – 5). In the presence of mitral stenosis, the mean left atrial pressure may rise to 20 mmHg and the mean pulmonary pressure to 30 mmHg. In this case, the driving pressure for the pulmonary circulation remains at 10 mmHg, but the behavior of the circulation has changed dramatically. The work of the right ventricle has doubled and the transmural pressure at each point along the pulmonary circulation is increased (assuming no change in extravascular pressures), so that pulmonary edema is more likely to develop. There are also situations in which increased pulmonary arterial pressure is associated with normal pulmonary capillary pressure (e.g., primary pulmonary hypertension). In such cases, there is unusually high resistance in the arteries or arterioles. There may be evidence of severe right ventricular strain and failure without an additional tendency for fluid transudation across the pulmonary capillary bed.

Because the pulmonary circulation is a low-pressure system, the pulmonary arteries, both large and small, contain much less smooth muscle than comparable vessels in the systemic circulation. Two exceptions to this generalization occur in the normal lung. One exists in the fetus, where the pulmonary artery connects with the aorta via the patent ductus arteriosus, and therefore the pulmonary artery is exposed to systemic pressures. Another exception occurs in long-term residents of high altitudes, who have elevated pulmonary arterial pressures through the mechanism of chronic hypoxic pulmonary vasoconstriction. As a consequence, these individuals have increased amounts of smooth muscle in the walls of their pulmonary arteries. The extension of vascular smooth muscle into distal pulmonary arteries is found in arterioles as small as 20 μm in diameter.

Different segments of the pulmonary vessels are subject to different perivascular pressures, which strongly influences their internal calibers. This effect occurs because intravascular pressures in the pulmonary circulation are low and vascular diameter depends heavily on transmural pressure. Extrapulmonary vessels are exposed to subcostal pleural pressure modified by local mechanical effects. These extrapulmonary vessels include the large pulmonary arteries and pulmonary veins. Intrapulmonary vessels, on the other hand, can be exposed to perivascular pressures ranging from those at the pleura to those at the alveolus, depending on their anatomic location.

Intrapulmonary Vessels

Differences in the behavior of intrapulmonary vessels were first observed by Macklin, who showed that the volume of the larger vessels increased with lung inflation and decreased with deflation. These observations were extended by Howell and associates, who used the surface tension differential produced by kerosene to separate larger from smaller vessels. These investigators observed that positive-pressure inflation of the lungs compressed small vessels, which were not filled by kerosene, while larger kerosene-containing vessels were expanded.

Intrapulmonary vessels can be divided into alveolar, corner, and extra-alveolar vessels, depending on the perivascular pressures to which they are exposed. The *alveolar vessels* are largely capillaries contained within the interstitium that separates adjacent alveoli. The pressure to which they are exposed is very close to alveolar pressure. When the lung expands, the alveolar walls unfold and the connective tissue elements around them are rearranged. This process compresses the alveolar vessels.

Corner vessels are located at sites where three alveoli meet and therefore are insulated from the surrounding alveolar pressure. These corner vessels are usually about 30 µm in diameter. Morphologic evidence suggests that corner vessels are contained within pleats in the alveolar septa. At low lung volume, the cell structures and connective tissue elements are displaced inward away from the surface of the alveoli. Thus, the enfolded capillaries behave like extra-alveolar vessels, because they are not exposed to alveolar pressure. When the septa unfold, however, the same capillaries behave like alveolar vessels, because the pressure around them is now much closer to the pressure in the adjacent alveoli. Functionally, such corner vessels are probably the vessels that remain open in the zone 1 lung (see below).

The *extra-alveolar vessels,* by definition, are vessels not affected by changes in alveolar pressure but that do enlarge during lung inflation. These vessels can be arteries, arterioles, veins, venules, or precapillaries. The key anatomic feature of the extra-alveolar vessels is their location within a perivascular interstitial space surrounded by a connective tissue sheath. Measurements of pressure with micropipettes inserted into the perivascular interstitial spaces have revealed pressures that are slightly more negative than pleural pressure. The perivascular interstitial pressures become even more negative as the lungs inflate, resulting in dilation of extra-alveolar vessels.

Pressure-Flow Relationships in the Lung

In the upright position, the relationship between pressure and flow in the normal pulmonary circulation is not linear. This is a consequence of the distensibility of the vessels and recruitment of additional vessels when flow is increased. This principle is readily demonstrated in the isolated lung preparation. If pulmonary blood flow is plotted against pulmonary arterial pressure while pulmonary venous pressure and transpulmonary pressure (alveolar pressure minus intrapleural pressure) are held constant (thus fixing lung volume), the slope of the line describing the pulmonary vascular resistance decreases until it reaches a constant value.

Two mechanisms are responsible for the fall in pulmonary vascular resistance in the above system. These are vascular recruitment, that is, the opening of previously closed blood vessels, and distention, or an increase in the caliber of the open vessels. Figure 5 shows experimental data from lungs (of dogs) quick frozen in situ that indicate the importance of recruitment as the pulmonary arterial pressure is raised from low values. The number of open capillaries per millimeter of length of alveolar wall increased from about 25 to >50 as the pulmonary arterial pressure was raised from 0 to nearly 15 cm H_2O. Figure 5 also shows the importance of distention of pulmonary capillaries. The mean width of the capillaries increased from about 3.5 to nearly 7 µm as the capillary pressure was increased to approximately 50 cm H_2O. Beyond that, very little change in diameter occurs with increases in pressure.

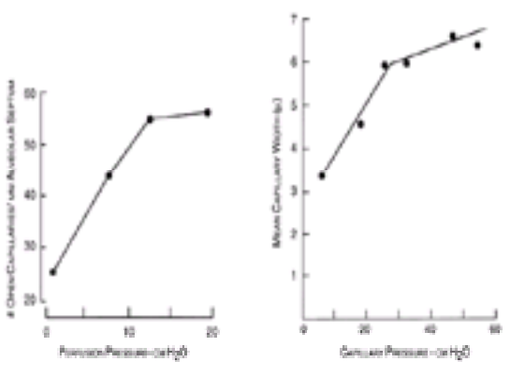

FIG. 5. Left panel: Importance of recruitment of pulmonary capillaries as the pulmonary arterial pressure is raised. (Reproduced with permission from Warrell DA, Evans JW, Clarke RO, Kingaby GP, West JB. Pattern of filling in the pulmonary capillary bed. *J Appl Physiol* 1972;32:346–356.) **Right panel:** Importance of distention of pulmonary capillaries as their pressure is increased. (Reproduced with permission from Glazier JB, Hughes JMB, Maloney JE, West JB. Measurements of capillary dimensions and blood volume in rapidly frozen lungs. *J Appl Physiol* 1969;26:65–76.)

The mechanisms of recruiting pulmonary capillaries are not fully understood. As the pulmonary arterial pressure is increased, it has been suggested that the critical opening pressures of various arterioles are overcome successively. In a dense network of numerous interconnected capillary segments, it can be shown that individual capillary segments require a very small critical pressure before flow begins. Because the network contains a distribution of these critical pressures, recruitment can occur over a large range of arterial pressures. For example, in a network with as many elements as the human pulmonary capillary bed, a critical pressure on the order of only 0.02 cm H_2O for individual segments would be required to recruit vessels over a range of arterial pressures from 0 to 30 cm H_2O. Such a very small critical pressure could result from the basic flow properties of blood, especially when red blood cells fill the capillary lumen.

Just where and how critical opening occurs in pulmonary microvessels is debatable. The variation in red blood cell concentration within areas supplied by single arterioles is probably sufficient to account for the variation between areas supplied by different arterioles. This suggests that recruitment may occur at the capillary rather than the arteriolar level. This would be consistent with the notion that blood flow to the gas-exchanging regions of the lung is regulated at the alveolar level. Thus, under special conditions (e.g., regional gas trapping and edema), closure of alveolar vessels by pericapillary forces may divert blood flow from one pulmonary capillary to another.

The mechanism by which pulmonary capillaries distend is related simply to the ability of the alveolar wall to bulge when the transmural pressure is raised in the capillaries. It has sometimes been argued that the mechanism of distention of pulmonary capillaries cannot be analogous to the behavior of some systemic capillaries. For example, in frog mesentery, the intracapillary pressure can be raised to 100 mmHg without measurable distention. This apparent capillary rigidity, however, can be explained by the support offered by the surrounding interstitial tissue rather than by the stiffness of the capillary walls themselves. This kind of support for the capillaries by the interstitial tissue is lacking in the alveolar region of the lung. One analogy sometimes used to describe the pulmonary capillary network is that of Swiss cheese: the open holes are supported by the cheese around them. Indeed, photomicrographs of pulmonary capillaries in rapidly frozen lungs at high intracapillary pressures show remarkable distention. This finding supports the notion that pulmonary capillaries are passively distensible with increased transmural pressure.

When the capillary pressure is raised to very high levels, the capillary walls are damaged. This damage allows protein or red blood cells to leak out, causing high-permeability pulmonary edema or even frank hemorrhage. In rabbits, this occurs at a capillary transmural pressure of about 40 mmHg, and the ultrastructural changes in the lungs include disruption of the capillary endothelial layer, the alveolar epithelial layer, or both. Because the calculated stress across the interstitium is very high under these conditions, the phenomenon is known as *stress failure.*

There are five conditions in which stress failure of capillaries may be involved. These are as follows: (1) Increased pressure causes high-permeability edema—for example, neurogenic pulmonary edema or high-altitude pulmonary edema (HAPE)—in which the pulmonary edema is of the high-permeability type despite an increased capillary pressure. In neurogenic pulmonary edema, the increased capillary pressure is related to excessive sympathetic activity. In HAPE, intense hypoxic vasoconstriction raises pressure in small pulmonary arterioles. The vasoconstriction, however, is heterogeneous, and some capillaries are not protected by arterial constriction and are exposed to high pressure. The stress failure hypothesis in HAPE is supported by the patchy distribution of pulmonary edema and the observation that exercise at high altitude is a provocative factor. (2) Increased pressure causes hemorrhage—for example, exercise-induced pulmonary hemorrhage in race horses and possibly top-notch human athletes. Pulmonary systolic pressures as high as 120 mmHg can develop in race horses while galloping. The fact that increased capillary pressure causes bleeding rather than high-permeability edema may be related to the very abrupt rise in pressure. (3) Increased pressure causes edema and hemorrhage—for example, in mitral stenosis and pulmonary veno-occlusive disease. (4) Overinflation or hyperinflation of the lung increases the longitudinal tension in the alveolar wall, some of which is transmitted to the capillary wall. This could explain the increased capillary permeability at high lung volumes. The increased

permeability is caused by high lung volume rather than alveolar pressure, because banding the chest prevents the increased permeability. (5) In cases of an abnormal extracellular matrix—for example, Goodpasture's syndrome—the strength of the capillary wall is diminished by the attack by antibodies on the collagen of the basement membrane. Alveolar hemorrhage may occur even at normal vascular pressures.

Pulmonary Vascular Resistance

A variety of approaches have been used to measure changes in pulmonary vascular resistance *in vivo.* These include measurement of pressure-flow curves and the pressure gradient across the pulmonary vascular bed at end-diastole. Pulmonary vascular resistance for the pulmonary circulation is calculated from the following equation:

$$R = (P_{pa} - P_{pv})/\dot{Q}$$

where R is pulmonary vascular resistance; P_{pa} is mean pulmonary arterial pressure (mmHg); P_{pv} is mean pulmonary venous pressure (mmHg; often the pulmonary wedge pressure is used), and $\dot{Q}$ is pulmonary blood flow (L/min). For the normal pulmonary circulation the value for R is approximately 2.0 mmHg/L/min. To express pulmonary vascular resistance in dynes sec^{-1} cm^{-5}, the numerator of the equation is multiplied by 80 (1.332 × 60 sec); the normal value is then »160.

Although the resistance equation has the form of Ohm's Law for electrical circuits (voltage difference divided by current flow), the resistance of an electrical resistor does not depend on either the voltage drop or the flow of current. This is not true for the pulmonary vascular resistance, which is affected by both driving pressure and blood flow. For example, in the normal pulmonary circulation, as pulmonary arterial pressure is increased at constant left atrial pressure, pulmonary vascular resistance falls. Of course, this is associated with an increase in pulmonary blood flow (Fig. 6). Also, pulmonary vascular resistance decreases when venous pressure is raised (with pulmonary arterial pressure held constant). In this case, however, pulmonary blood flow decreases (Fig. 6). Thus, it should be apparent that a single value for pulmonary vascular resistance is an incomplete description of the pressure-flow properties of the pulmonary circulation. Nonetheless, pulmonary vascular resistance measurements are useful in clinical practice for the diagnosis of pulmonary vascular diseases and for monitoring therapeutic interventions.

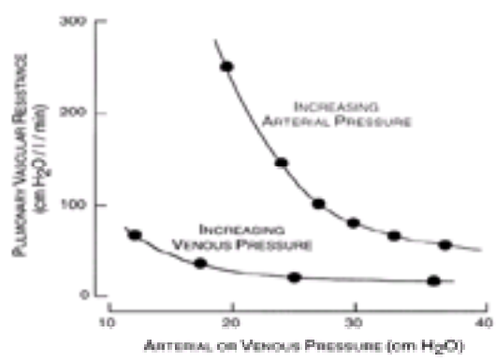

FIG. 6. Relationship between pulmonary vascular resistance and pulmonary arterial or venous pressure. Experiments in a dog lung preparation in which one pressure was changed while the other was held constant. (Reproduced with permission from West JB. *Respiratory Physiology—The Essentials.* 4th ed. Baltimore: Williams & Wilkins; 1990.)

In humans, the pressure drop across the pulmonary vascular bed is »10% of the pressure drop across the systemic circulation. Different approaches have been used to determine the pattern of pressure drop along the pulmonary blood vessels. These include measuring the transudation pressure on the pleural surface of isolated lung; measuring the pressure transient resulting from the injection of a bolus of low- or high-viscosity blood into the pulmonary artery; measuring transient pressure following rapid occlusion of the venous outflow, the arterial inflow, or both; determining pressure-flow curves under zone 2 conditions, and direct puncture of different-sized vessels along with direct measurement of hydrostatic pressure. The values obtained from the various measurements are surprisingly consistent; in the normal lung, precapillary and postcapillary resistances are about equal, favoring a slightly higher precapillary resistance. Morphologically, the major site of pulmonary vascular resistance is in the small muscular arteries (100–1000 µm) and arterioles (<100 µm), because the cross-sectional area of the vascular network expands suddenly at the precapillary level.

Effect of Lung Volume on Vascular Resistance

The pulmonary vascular resistance depends greatly on the degree of inflation of the lung. The relationship between lung volume and pulmonary vascular resistance is shown in Fig. 7. The *solid line* in Fig. 7 indicates the total vascular resistance. *Two dashed lines* denote vascular resistances contributed by alveolar and extra-alveolar vessels. The lung normally operates near the minimal value of vascular resistance, which occurs at approximately FRC. Both increases and decreases in lung volume from the resting position are associated with increased resistance to blood flow. As shown in Fig. 7, increasing pulmonary vascular resistance with decreasing lung volume results mainly from increases in the resistance of extra-alveolar vessels. This is most likely related to the decrease in caliber of the extra-alveolar vessels caused by decreases in the forces of radial traction exerted by the surrounding parenchyma. At states of high lung inflation, the increase in pulmonary vascular resistance is probably caused by distortion of the pulmonary capillaries. This distortion increases the resistance of blood moving through it. Direct measurements on frozen lungs of dogs show that the average width of the capillaries decreases greatly at high levels of lung inflation.

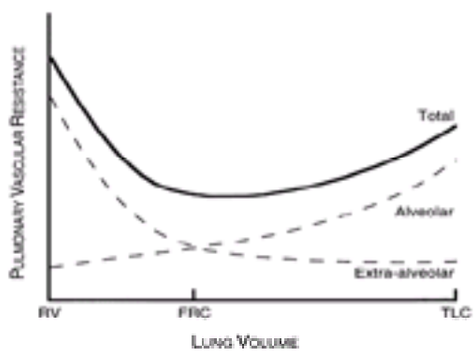

FIG. 7. Relationship between lung volume and pulmonary vascular resistance. The effects of changes in vital capacity on total pulmonary vascular resistance and the contributions to the total afforded by alveolar and extra-alveolar vessels are depicted. Note that changes in total pulmonary vascular resistance form a U-shaped curve during lung inflation, with the nadir at FRC. *RV,* residual volume; *TLC,* total lung capacity. (Reprinted with permission from Murray JF. *The Normal Lung.* 2nd ed. Philadelphia: WB Saunders; 1986.)

Active Versus Passive Modulators of Pulmonary Vascular Resistance

Pulmonary vascular resistance is modulated by various factors that can be divided conveniently into “passive” and “active” processes. Passive factors change the caliber of pulmonary blood vessels without a significant response in the tone of vascular smooth muscle. Table 2 summarizes the pertinent passive factors. Of these passive factors, the effect of blood viscosity on pulmonary vascular resistance is the most difficult to quantify, but it appears to depend on the capillary hematocrit, the physical properties of red blood cells, and the composition of plasma. In the isolated lung, as hematocrit increases, progressively greater pressure is required to overcome the contribution of blood viscosity to resistance and to maintain the blood flow. In contrast, active factors alter pulmonary vascular resistance by contracting or relaxing the smooth muscles of blood vessel walls. These factors can be humoral, neural, or chemical in nature. Some of the important active factors are shown in Table 3.

Factor	Response
Pulmonary arterial pressure (P_{PA})	Increased P_{PA} causes decreased PVR
Left atrial pressure (P_{LA})	Increased P_{LA} causes decreased PVR
Transpulmonary pressure (P_t)	Increase and decrease of P_t from value at FRC cause increased PVR
Total interstitial pressure (P_{is})	Increased P_{is} causes increased PVR
Pulmonary blood volume	Shift of blood from systemic vessels into lung vessels causes decreased PVR
Whole-blood viscosity	Increase in viscosity causes increased PVR

PVR, pulmonary vascular resistance; FRC, functional residual capacity.

TABLE 2. *Factors causing "passive" changes in pulmonary vascular resistance and direction of responses*

Factor	Response
Neurogenic stimuli	
Sympathetic stimulation	Increases PVR in experimental animals; no effect in humans
Parasympathetic stimulation	Decreases PVR in experimental animals with pre-existing vasoconstriction; no effect in humans
Humoral stimuli	
Norepinephrine, serotonin, histamine, angiotensin, fibrinopeptides, prostaglandin $F_{2\alpha}$	Vasoconstriction
Acetylcholine, bradykinin, prostaglandin E_1, prostacyclin (prostaglandin I_2)	Vasodilation; bradykinin affects humans with pulmonary hypertension
Nitric oxide	Vasodilation
Chemical stimuli	
Alveolar hypoxia	Increases PVR
Alveolar hypercarbia	Increases PVR in experimental animals; no effect in humans
Acidemia (decreased pH)	Increases PVR

PVR, pulmonary vascular resistance.

TABLE 3. *Important causes of "active" changes in pulmonary vascular resistance and direction of responses*

The pulmonary circulation is exposed constantly to passive influences, making it sometimes difficult to demonstrate that changes in pulmonary vascular resistance are caused by active pulmonary vasoconstriction or dilation. Notable exceptions occur when the vasomotor responses are opposite to and prevail over responses to passive factors. Similarly, changes in pulmonary arterial pressure alone cannot be interpreted as indicating changes in pulmonary vascular resistance unless left atrial pressure and cardiac output are known.

Advanced lung diseases such as pulmonary fibrosis and pulmonary emphysema can cause increases in pulmonary vascular resistance and thus pulmonary hypertension. Pulmonary vasoconstriction is caused by alveolar hypoxia, but distortion of lung architecture by the disease processes and increased interstitial fluid in the perivascular spaces of the extra-alveolar vessels (pulmonary edema) also play important roles. When edema is severe, fluid also may accumulate in the interstitium of the alveolar wall, thus encroaching on alveolar vessels and increasing their vascular resistance.

Distribution of Perfusion

The distribution of pulmonary blood flow can be measured with tracer methods. Radioactive carbon dioxide ($C^{15}O_2$) was the first test substance to be used to study the distribution of pulmonary blood flow. After the tracer gas is breathed into the lung, regional perfusion can be determined by monitoring the disappearance of the gas, whose uptake from alveoli depends on the blood flow to the alveoli. Insoluble tracer gases such as ^{133}Xe also can be dissolved in saline solution and injected into a peripheral vein. When the xenon reaches the pulmonary capillaries, it is transferred into the alveolar gas. The tracer pattern within the lung then reflects the perfusion of gas-filled alveoli in various regions. The distribution of blood flow also can be measured with labeled particles, such as radioactive- or fluorescent-labeled microspheres. These particles are sized appropriately to be trapped within small pulmonary vessels as they pass into the pulmonary circulation.

Each of these procedures has advantages and disadvantages, but all have detected the presence of a vertical gradient of blood flow in a normal upright lung. The vertical gradient is largely the consequence of differences in hydrostatic pressure in the pulmonary circulation associated with gravity. As the adult upright human lung is about 30 cm high, the hydrostatic difference in pressure between the extreme apex and the bottom of the base can be as much as 30 cm of blood (23 mmHg). This means that the intravascular pressure in vessels at the lung base can be higher than that in apical vessels by as much as 23 mmHg. When the pulmonary venous pressure and intra-alveolar pressure are held constant, this translates to a greater transmural pressure for the vessels at the base. As a result, the diameter of blood vessels at the base of the lung is greater and more blood flows through them. The difference between apical and basal blood flow no longer exists when the lung is supine, but a perfusion gradient can be detected between the independent (uppermost) and dependent (lowermost) regions of the lung. In the upright position, exercise increases apical blood flow more than basal blood flow because of the recruitment of collapsed vessels (West zone 1; see below), and the perfusion gradient is reduced greatly.

Gravity-Dependent Distribution of Blood Flow

The intravascular pressures of the pulmonary circulation are influenced by the hydrostatic pressure created by gravity. As alveolar pressure is relatively independent of gravity, the relationships among pulmonary arterial, pulmonary venous, and alveolar pressures must also influence the distribution of pulmonary blood flow. This principle was predicted by Dock. West subdivided the lung into four zones with differing patterns of blood flow. Figure 8 shows this zonal distribution.

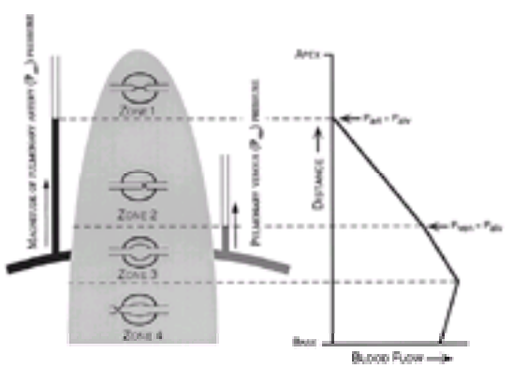

FIG. 8. Schematic representation of the four zones of the lungs in which different hemodynamic conditions govern blood flow. Alveolar pressure (P_{alv}) is assumed to be 0; the heights of the *blue column* and the *red column* represent the magnitude of pulmonary arterial (P_{art}) and pulmonary venous (P_{ven}) pressures, respectively. (Reprinted with permission from Hughes JM, et al. Effect of lung volume on the distribution of pulmonary blood flow in man. *Respir Physiol* 1968;4:58–72.)

Zone 1 is the region of the lung wherein alveolar pressure exceeds both the pulmonary arterial and venous pressures. In zone 1, the alveolar vessels are collapsed and there is no pulmonary blood flow. In the presence of corner vessels that are protected from alveolar pressure, however, some flow still occurs in this zone.

Zone 2 is the part of the lung in which pulmonary arterial pressure exceeds alveolar pressure, but alveolar pressure exceeds venous pressure. Under these conditions, the resistance to blood flow is determined by the difference between pulmonary arterial and alveolar pressures, rather than by the expected arterial-venous pressure difference. This behavior has been referred to variously as the *waterfall* or *sluice effect* and can be simulated in a Starling resistor model made of rubber tubing. The

flow properties of capillaries, however, are very different from those of a Starling resistor. For one thing, capillary flow tends to be laminar. This differs from the Starling resistor, which usually oscillates and creates turbulent flow. In addition, the capillaries contain trains of red blood cells that essentially fill the diameter of the small vessels. These vessels cannot collapse in the same way as a rubber tube. Nevertheless, the lung in zone 2 conditions has essentially the same pressure-flow characteristics as a Starling resistor. Also in zone 2, blood flow increases progressively down the lung because of the increasing hydrostatic effect on pulmonary arterial pressure, which increases the driving pressure in this region (pulmonary arterial pressure minus alveolar pressure).

Zone 3 is the part of the lung in which pulmonary venous pressure exceeds alveolar pressure. Blood flow also increases down this zone, although the rate of increase in relation to distance is less than in zone 2. Because the arterial-venous pressure difference is responsible for flow and is constant, it is not immediately apparent why blood flow would increase down this zone. Because the transmural pressure across the vessel wall increases with distance down zone 3, however, pulmonary arterial and venous pressures both increase while alveolar pressure remains constant. Thus, if the vessels are distensible, their caliber will increase and their vascular resistance will decrease down the zone. Indeed, micrographs of rapidly frozen lung confirm an increase in vessel caliber down zone 3. It is also possible that retrograde recruitment of capillaries contributes to the increase in blood flow.

In zone 4, the relationships between intravascular and alveolar pressures are the same as in zone 3, but the blood flow decreases. Zone 4 occurs in the lowermost region of the upright human lung and diminishes as lung volume increases. Conversely, as lung volume decreases, this region of reduced blood flow extends farther and farther up the lung, so that at FRC blood flow decreases progressively down the bottom half of the lung. At residual volume, zone 4 extends nearly all the way up the lung, so that blood flow at the apex exceeds that at the base. This condition obviously cannot be explained by the interactions among the pulmonary arterial, venous, and alveolar pressures. Instead, the reduced blood flow in zone 4 can be attributed to narrowing of extra-alveolar vessels at the lung base that results from lower lung inflation. The increased contribution of extra-alveolar vessels to pulmonary vascular resistance results in the presence of a zone of reduced blood flow in that region. This explanation is supported by the observation that vasoconstrictor drugs such as serotonin cause zone 4 to extend farther up the lung. The opposite effect is seen when vasodilator drugs are infused into the pulmonary circulation.

Zone 4 would be expected to increase in the presence of interstitial pulmonary edema, because the edematous fluid increases interstitial pressure in the vascular sheath and thereby narrows the extra-alveolar vessels. This is a plausible mechanism for the inverted distribution of blood flow (cephalization of pulmonary vasculature on chest x-ray) in pulmonary edema. The interaction of interstitial edema with blood flow distribution, however, remains poorly understood.

Gravity-Independent Distribution of Blood Flow

Not all the inhomogeneity of blood flow in the lung can be explained by gravitational effects. In normal people flying Keplerian arcs in aircraft, where periods of up to 25 sec of microgravity are possible, much of the normal topographic inhomogeneity disappears. Indirect measurements of inhomogeneity of pulmonary blood flow have been made in astronauts in space shuttles by monitoring the magnitude of cardiogenic oscillations on the expired carbon dioxide tracing. A striking reduction in inhomogeneity of blood flow was detected during weightlessness compared with that observed in the upright posture before or after the flight. Interestingly, substantial inhomogeneity of blood flow still remained, indicating that some gravity-independent mechanism was also present. Variations in the length of the pathways from the main pulmonary artery to the terminal respiratory units and variations within a single terminal respiratory unit may contribute to this process. The unequal length of pathways leads to different transit times for red blood cells and earlier perfusion of first-order respiratory bronchioles and their alveoli than of the more distal ones. Another suggestion is that regions of intrinsically high resistance (low conductance) exist normally because of differences in caliber or geometric features of the pulmonary vascular bed. Evidence for this has been obtained in isolated dog lungs. It also has been suggested that isogravitational inhomogeneity of blood flow can be explained by fractal geometry. According to this concept, the inhomogeneity is a consequence of a fractal configuration of vascular branching that is replicated from larger to smaller blood vessels. Such a fractal model might also explain the radial gradient of perfusion and the regional differences in conductance mentioned above.

Pulmonary Blood Flow in Cardiopulmonary Diseases

The normal distribution of pulmonary blood flow is altered by many cardiopulmonary diseases. The redistribution of blood flow frequently increases mismatching of ventilation and perfusion and may result in hypoxemia or increases in dead space (see below, Ventilation-Perfusion Distribution and Gas Exchange). For example, localized structural lung disease resulting in the formation of bullae or cysts usually causes local reductions in flow. The same is also true of pulmonary embolism, in which the local blood flow is obstructed by the presence of clots. Such abnormalities of perfusion are usually coupled with normal ventilation and hence increase the dead space. This pattern of ventilation-perfusion abnormality provides an important diagnostic clue on ventilation-perfusion scan. The blood flow to the lung on the side of a pneumothorax may be compromised because of compression or kinking of large or small pulmonary vessels. Blood flow may be reduced to some parts of the lung because of destruction of the pulmonary vasculature or distortion of pulmonary vascular geometry in diffuse lung diseases such as pulmonary fibrosis or chronic obstructive pulmonary disease. In patients with pulmonary hypertension or increased blood flow secondary to left-to-right shunts, the blood flow is usually distributed more uniformly. During severe hypotension and circulatory shock, perfusion to the lung apices is reduced significantly. Increased pulmonary venous pressure, as in mitral stenosis, initially causes a more uniform distribution than normal. In more advanced disease, inversion of the normal distribution of blood flow is frequently seen, with more perfusion to the upper than to the lower lung zones. The mechanism for this shift is not understood fully, but, as indicated earlier, it may be related to perivascular edema causing an increased resistance within the extra-alveolar vessels.

Control of the Pulmonary Circulation

The distribution of pulmonary blood flow and the pressure-flow relations of the pulmonary circulation are highly influenced by the “passive” factors shown in Table 2. Thus, gravity and the mechanisms of recruitment and distention can account for most of the behavior of the normal circulation. By contrast, when the amount of smooth muscle is increased—for example, in the lungs of fetuses, of long-term residents of high altitudes, or of patients with prolonged pulmonary hypertension—“active” regulatory factors begin to play a more significant role in the control of the pulmonary circulation.

One example of active control of the pulmonary circulation is hypoxic pulmonary vasoconstriction. The precise mechanism of this response is unknown. It clearly does not depend on central nervous system input, as it occurs in excised isolated lungs. Furthermore, the local action of hypoxia on the artery itself is important, because excised segments of pulmonary artery can be shown to constrict in hypoxic environments. It is also known that hypoxic pulmonary vasoconstriction can be elicited by lowering the partial pressure of oxygen (PO_2) in the alveolar gas or mixed venous blood.

The stimulus-response curve for hypoxic pulmonary vasoconstriction is very nonlinear. When the alveolar PO_2 is altered in the region above 100 mmHg, little change in vascular resistance is seen; however, when alveolar PO_2 is reduced to 60 mmHg, vasoconstriction may occur. At PO_2 values approaching that of mixed venous blood, local blood flow may be almost abolished. The intensity of hypoxic vasoconstriction varies from subject to subject, among different species, and in different parts of the same lung.

The site of hypoxic vasoconstriction is still not certain, but some evidence suggests it occurs in pulmonary precapillary vessels (small muscular pulmonary arteries and arterioles). Some studies also suggest alveolar vessels may be, at least in part, responsible for the increased resistance, and contractile cells have been described in the interstitium of the alveolar wall; these cells conceivably could distort capillaries and increase their resistance.

The cellular mechanisms of hypoxic pulmonary vasoconstriction remain obscure despite a great deal of research. Some chemical modulators of the response, including catecholamines, histamine, angiotensin, and prostaglandins, have been studied extensively. None of these substances, however, meets all the necessary criteria for the mediator of hypoxic pulmonary vasoconstriction. Recently, it has been suggested that inhibition of endothelium-derived relaxing factor (EDRF) or nitric oxide may be involved. As the biosynthesis of nitric oxide requires molecular oxygen, hypoxic vasoconstriction may in part represent loss of vasodilator effects normally provided by nitric oxide.

Hypoxic pulmonary vasoconstriction has the effect of directing blood flow away from hypoxic regions of lung. This tends to reduce the extent of ventilation-perfusion mismatching in diseased lungs and limits the decline in the arterial PO_2. A good illustration of this effect is seen in patients with pulmonary hypertension who are treated with systemic vasodilators, such as calcium channel blockers, in an attempt to reduce pulmonary arterial pressure. This treatment can be associated with nonspecific vasodilation that causes an increase in blood flow to poorly ventilated areas. The process may lead to a reduction in arterial PO_2. Hypoxic pulmonary vasoconstriction also occurs in both newcomers and in permanent residents of high altitudes. At altitude, the increase in pulmonary arterial pressure is especially marked during exercise. These responses result in improvement in gas exchange.

GAS EXCHANGE

The composition of normal gas changes in various lung compartments during inspiration (Fig. 9). As can be seen, the partial pressure of oxygen (PO_2) decreases as soon as the ambient gas reaches conducting airways. This is caused by warming of the inhaled air and its saturation with water vapor. These processes dilute the inspired mixture of N_2 and O_2. At body temperature of 37°C, water vapor pressure adds 47 mmHg of pressure to dry gas. Once the inspired gas reaches the terminal respiratory units, gas exchange takes place. Slightly more O_2 is removed than carbon dioxide (CO_2) is added (at a normal respiratory exchange ratio of 0.8), which

causes the volume of each gas exchange unit to diminish slightly and raises the concentration of N_2 within the alveoli slightly. The gas composition of the blood in the pulmonary capillaries leaving the alveoli is approximately the same as the gas phase of the terminal units. The PO_2 in the arterial blood is slightly lower because local matching of ventilation and perfusion in normal lungs is imperfect and unoxygenated blood is added to capillary blood from postpulmonary shunt.

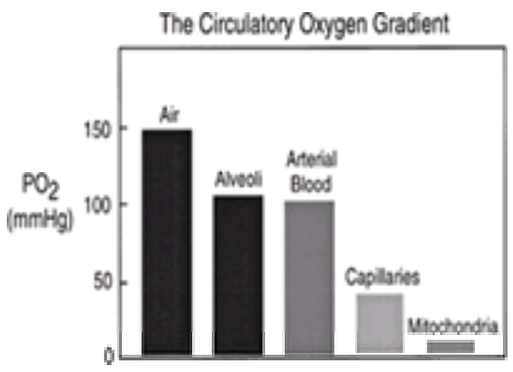

FIG. 9. The O_2 gradient from the alveolar space to the mitochondria. Note that there is a stepwise decrement in PO_2 from 100 mmHg in the alveolar space to values of a few mmHg at the mitochondria, where most of the O_2 is consumed.

Ventilation-Perfusion Distribution and Gas Exchange

Exchange of O_2 and CO_2 between blood in the pulmonary arterial system and alveolar gas occurs continuously in more than 100,000 terminal respiratory units of the lungs. The adequacy of function of each gas exchange unit is determined by local matching of ventilation and perfusion ($\dot{V}_A/\dot{Q}$). In general, inadequate ventilation relative to perfusion (i.e., low $\dot{V}_A/\dot{Q}$ regions and shunt) has the greatest effect on O_2 uptake by the lung and thus may result in hypoxemia. On the other hand, excessive ventilation relative to perfusion (i.e., high $\dot{V}_A/\dot{Q}$ regions and dead space) has more influence on CO_2 elimination by the lung and predisposes to hypercapnea.

The effects of $\dot{V}_A/\dot{Q}$ matching on the efficiency of gas exchange in the lung can be understood using the two-compartment lung model. In an ideal lung consisting of two alveolar units (A and B), each receiving 2.0 L/min of alveolar ventilation and 2.5 L/min of blood flow, the $\dot{V}_A/\dot{Q}$ ratio is 0.8 for the individual units A and B, and 0.8 for the entire lung. Assuming no barrier to diffusion of O_2 and a normal PO_2 in the pulmonary artery, the PO_2 of alveolar gas is the same as the PO_2 of end-capillary and arterial blood. There is no O_2 gradient from alveolus to capillary (alveolar-arterial PO_2 difference). A “normal” lung has a slight degree of $\dot{V}_A/\dot{Q}$ mismatch, which is caused primarily by the greater effects of gravity on the distribution of perfusion than on ventilation (Fig. 10). Thus, in the “normal” lung, while the $\dot{V}_A/\dot{Q}$ ratio for the whole lung remains at 0.8, the $\dot{V}_A/\dot{Q}$ ratios for the two units A and B are 1.0 and 0.6, respectively. This causes the mean PO_2 in the blood leaving the lung to decrease slightly and produces an alveolar-arterial PO_2 difference of 4.4 mmHg. Uneven distribution of blood flow may also result in similar effects, especially in the upright lung.

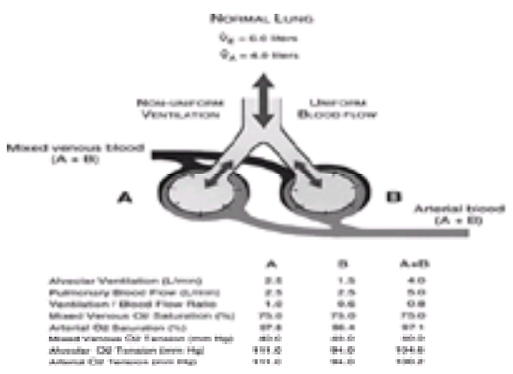

FIG. 10. Ventilation-perfusion relationship of a normal lung is illustrated using a two-compartment model. Note that the ventilation-perfusion maldistribution is responsible for an alveolar-arterial PO_2 difference of about 4.4 mmHg; the remainder of the normal PO_2 difference is caused by postpulmonary shunts (ignored in this illustration). (Reproduced with permission from Forster RE, et al., eds. *The Normal Lung: Physiological Basis of Pulmonary Function Tests.* 3rd ed. Chicago: Year Book; 1986.)

Assessment of Abnormalities in Gas Exchange

The effectiveness of gas exchange (and thus the distribution of $\dot{V}_A/\dot{Q}$ ratios) can be assessed by several methods. The simplest approach is to sample the composition of arterial blood and alveolar gas. More complicated approaches rely on tracer gases and modeling of gas exchange—for example, the multiple inert gas elimination technique. No measurement technique, however, allows an exact description of the complex behavior of gas exchange in the lung.

Arterial PO_2

The arterial PO_2 certainly provides some information about the degree of ventilation-perfusion matching. The major advantage of the measurement is its simplicity. In general, a low PO_2 almost always indicates the presence of $\dot{V}_A/\dot{Q}$ mismatch or shunt, but a normal PO_2 (greater than 80 mmHg) does not necessarily imply that the $\dot{V}_A/\dot{Q}$ distribution of the lung is “normal.”

Alveolar-Arterial PO_2 Difference

The alveolar-arterial PO_2 difference ($A–aDO_2$) is calculated readily from the alveolar PO_2 (P_AO_2) and the arterial PO_2 (PaO_2). The alveolar PO_2 is computed from the alveolar gas equation:

$$P_AO_2 = F_IO_2 (P_B - PH_2O) - (P_ACO_2/R)$$

where P_B is barometric pressure; PH_2O is water vapor pressure at body temperature (47 mmHg at 37°C); F_IO_2 is the fractional concentration of O_2 in inspired gas (0.21 in air); and R is the respiratory exchange ratio. The equation simplifies to

$$P_AO_2 = F_IO_2 (713) - 1.25\ PaCO_2$$

by substituting the arterial for alveolar PCO_2 and 0.8 for the respiratory exchange ratio. The alveolar-arterial PO_2 difference is more informative than the arterial PO_2

alone because it takes into account the level of ventilation.

The alveolar-arterial PO_2 difference in healthy adults breathing room air increases with age. As a general rule, the alveolar-arterial PO_2 difference for an individual should be no more than half of the chronologic age, with a maximum of 25 mmHg. The alveolar-arterial PO_2 difference is caused by the combination of $\dot{V}_A/\dot{Q}$ mismatch and right-to-left postpulmonary shunting of blood. Each of these mechanisms is responsible for about half of the total alveolar-arterial PO_2 difference in normal adults. None of the alveolar-arterial PO_2 difference at normal barometric pressure is caused by failure of diffusion equilibrium to occur, even during heavy exercise. Diffusion disequilibrium may occur during exercise at high altitudes.

The alveolar-arterial PO_2 difference increases with increasing alveolar PO_2, in part because the upper part of the oxygen-hemoglobin dissociation curve is concave. The alveolar-arterial PO_2 difference reaches a maximum and then decreases at higher PO_2. The decline in the alveolar-arterial PO_2 difference occurs when inspired PO_2 exceeds 350 to 450 mmHg, because alveolar PO_2 rises to more uniform levels despite the nonuniform distribution of $\dot{V}_A/\dot{Q}$ ratios.

Physiologic Shunt

The presence of right-to-left shunt can be differentiated from low $\dot{V}_A/\dot{Q}$ causes of hypoxemia by having the patient breathe 100% O_2. While the patient is breathing pure O_2, the alveolar PO_2 in different lung units differs according to differences in alveolar PCO_2. Lung units with low $\dot{V}_A/\dot{Q}$ ratios, even though they may be ventilated only poorly via collateral pathways or intermittently at high lung volumes, will show an increase in PO_2 nearly maximally with elevation of the inspired PO_2. This response also occurs with impairment of diffusion for O_2 between alveolar gas and capillary blood. This maneuver usually increases the arterial PO_2 to >600 mmHg. The size of the shunt can be calculated using the following equation:

$$Q_s/Q_T = (CcO_2 - CaO_2)/(CcO_2 - C\bar{v}O_2)$$

where Q_s/Q_T is the shunt as a fraction of cardiac output; CcO_2 is end-capillary O_2 content; CaO_2 is arterial O_2 content; and $C\bar{v}O_2$ is mixed venous O_2 content. End-capillary blood is assumed to have a PO_2 equal to that in the alveolar gas. The O_2 contents are measured in samples of arterial and mixed venous blood. Alternatively, a value for the arterial-mixed venous difference in O_2 content, which is relatively constant among patients, normally can be assumed to be 5 mL/dL. Healthy individuals have a small “anatomic shunt” that amounts to 2%–5% of the cardiac output. This shunt occurs because some venous blood normally drains into pulmonary veins, left atrium, or left ventricle from bronchial and myocardial (thebesian) circulation.

The use of 100% O_2 to measure Q_s/Q_T can exclude shunt as a cause of hypoxemia. The procedure does not determine the location of a shunt, which may be intracardiac or intrapulmonary. Alveoli with low $\dot{V}_A/\dot{Q}$ ratios (<0.1) also may collapse completely during O_2 breathing if O_2 diffuses into the blood faster than fresh gas is added by ventilation. These collapsed alveoli can lead to overestimation of the true shunt fraction, as they allow pulmonary arterial blood to bypass the alveoli.

Physiologic Dead Space

Whereas physiologic shunt reflects the amount of blood flow going to lung units with near-zero ventilationperfusion ratios ($\dot{V}_A/\dot{Q} = 0$), physiologic dead space is a measure of the amount of ventilation going to units with unusually high ventilation-perfusion ratios ($\dot{V}_A/\dot{Q} \gg ¥$). The physiologic dead space can be computed from the Bohr equation:

$$V_D/V_T = (P_ACO_2 - P_ECO_2)/P_ACO_2$$

where V_D is physiologic dead space, V_T is tidal volume, P_ECO_2 is expired PCO_2, and P_ACO_2 is alveolar PCO_2. The P_ACO_2 is assumed to be equal to the $PaCO_2$. The Bohr equation requires a measurement of mixed expired gas, which is not conveniently obtained in many clinical settings. Instead, V_D/V_T can be estimated from the $\dot{V}_E$ and $PaCO_2$ using an isopleth nomogram (Fig. 11).

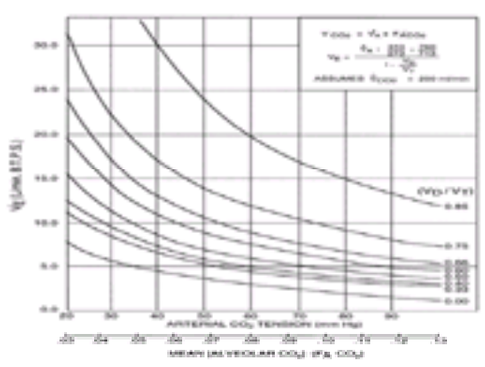

FIG. 11. An isopleth nomogram for estimating V_D/V_T from minute ventilation ($\dot{V}_E$) and arterial PCO_2. Assumptions and calculations are given in the *box in the right upper corner.*

Distribution of Ventilation-Perfusion Ratios

It has long been recognized that the lungs must contain some sort of distribution of ventilation-perfusion ratios. Major conceptual advances became possible with the introduction of the multiple inert gas elimination technique (MIGET). The MIGET is based on the straightforward principles governing inert gas elimination by the lung. When an inert gas in solution is steadily infused into the venous circulation, the proportion of gas that is eliminated by ventilation from the blood by a unit of the lung depends only on the solubility of the gas and the ventilation-perfusion ratio. The relationship is given by the following equation:

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

where Pc´ is the partial pressure of the gas in end-capillary blood and l is the blood-gas partition coefficient. The end-capillary partial pressure divided by the mixed venous partial pressure ($P\bar{v}$) is known as the *retention.*

In practice, a saline solution containing low concentrations of six gases (such as sulfur hexafluoride, ethane, cyclopropane, halothane or isofluorane, diethyl ether, and acetone) of differing solubilities is infused slowly into a peripheral vein until a steady state is reached (about 20 min). During measurements, simultaneous samples of arterial and mixed venous gases and expired gas are collected and analyzed for the inert gases by gas chromatography. Retention and excretion values for the inert gases are graphed against their solubility in blood, as shown in Fig. 12. The data for inert gas retention plotted against solubility are joined by a *broken line* in the upper panel of Fig. 12. Below this are the data points for excretion against solubility, also joined by the *broken line.* The *two solid lines* show how retention and excretion would behave for an ideal lung with no ventilation-perfusion maldistribution but with the same overall ventilation and blood flow. The *broken* and *solid lines* are very close together in normal lung (Fig. 12).

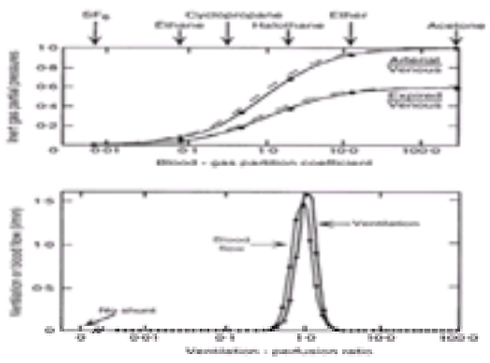

FIG. 12. Distribution of ventilation-perfusion ratios determined by the multiple inert gas elimination technique. Data from a 22-year-old normal subject are illustrated. **Upper panel:** Data points for inert gas retention (*upper curve*) and excretion (*lower curve*). *Broken lines* join the points. The *two solid lines* show the values of retention and excretion for a lung with no ventilation-perfusion inequality. **Lower panel:** Recovered distribution of ventilation-perfusion ratios. SF_6, sulfur hexafluoride. (Reproduced with permission from Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2. *J Clin Invest* 1974;54:53–68.)

The retention-solubility plots from the MIGET contain information about the distribution of $\dot{V}_A/\dot{Q}$ ratios in the lung. For example, a lung containing units that are perfused but not ventilated (shunt) will show increased retention of the least soluble gas, sulfur hexafluoride. Conversely, a lung having large amounts of ventilation to lung units with very high $\dot{V}_A/\dot{Q}$ ratios will show increased retention of the high-solubility gases, ether and acetone. In practice, the distribution of ventilation-perfusion ratios that best fits the pattern of inert gas retention and excretion based on a 50-compartment model can be obtained by an iterative process using a computer.

The use of the multiple gas elimination technique requires certain assumptions about the behavior of the lung. The method assumes no diffusion barrier for O_2 and negligible O_2 consumption by the lung. The fitted $\dot{V}_A/\dot{Q}$ distribution from a set of measurements is not unique, but in most cases the range of possible distributions compatible with the data is small. Also, more than three modes of a distribution can be recovered, and only smooth distributions can be obtained. Despite these limitations, the technique provides much more information about the distribution of $\dot{V}_A/\dot{Q}$ ratios in patients with lung disease than was previously available. In addition, the MIGET is very sensitive. A shunt of only 0.5% of the cardiac output approximately doubles the arterial concentration of sulfur hexafluoride.

The retention and excretion solubility curves and the derived distribution of ventilation-perfusion ratios from a 22-year-old normal volunteer is shown in Fig. 12. It is apparent from Fig. 12 that the recovered distributions for both ventilation and blood flow (*lower panel*) are narrow and span only one log of ventilation-perfusion ratios. Essentially no ventilation or blood flow occurs outside the range of approximately 0.3 to 3.0 on the ventilation-perfusion ratio scale, and no significant intrapulmonary shunt (i.e., regions with blood flow but no ventilation) is detected.

In older normal subjects, the dispersion of the $\dot{V}_A/\dot{Q}$ distribution has been found to increase. For example, some older people with apparently normal lungs have a “shoulder” to the left of the main blood flow distribution, with some 10% of the total blood flow going to lung units with ventilation-perfusion ratios of <0.1. Despite this region of low $\dot{V}_A/\dot{Q}$, there may still be no shunt. The cause of such age-related $\dot{V}_A/\dot{Q}$ mismatch is believed to be degenerative processes in the small airways with aging.

Ventilation-Perfusion Distributions in Lung Disease

The distribution of ventilation-perfusion ratios from a patient with chronic obstructive lung disease is shown in Fig. 13. The $\dot{V}_A/\dot{Q}$ distribution is typical of that seen in patients believed to have predominantly emphysema. The $\dot{V}_A/\dot{Q}$ distribution is bimodal, and large amounts of ventilation go to lung units with extremely high $\dot{V}_A/\dot{Q}$ ratios (alveolar dead space) (Fig. 13A). Presumably, the high $\dot{V}_A/\dot{Q}$ regions reflect ventilation to lung units in which many capillaries have been destroyed by the emphysematous process. The presence of a small shunt (3.1%) and slight shift to the left of the main mode of blood flow can explain mild arterial hypoxemia found in this patient (PaO_2 of 63 mmHg).

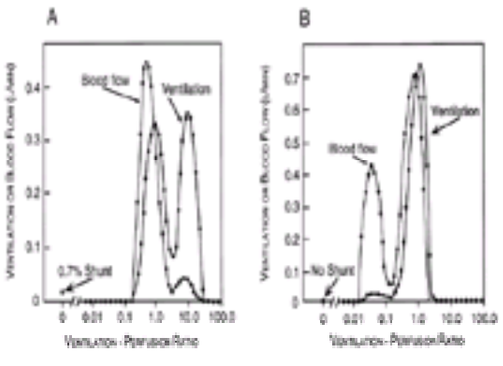

FIG. 13. Examples of the distribution of ventilation-perfusion ratios in patients with chronic obstructive pulmonary disease. **A:** Type A (patients with predominantly emphysema) tends to have areas of very high $\dot{V}_A/\dot{Q}$. **B:** Type B (patients with predominantly chronic bronchitis) often has areas of very low $\dot{V}_A/\dot{Q}$. Shunt ($\dot{V}_A/\dot{Q} = 0$) is rarely seen in either type. (Reproduced with permission from Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest* 1977;59:203–216.)

Patients with chronic obstructive lung disease who have predominantly bronchitis generally show a different pattern of $\dot{V}_A/\dot{Q}$ distribution (Fig. 13B). The main abnormality in these patients is the large amount of blood flow distributed to lung units with very low $\dot{V}_A/\dot{Q}$ ratios, between 0.003 and 0.1, explaining the more severe hypoxemia generally found in this type of patient. Presumably, the low ventilation-perfusion ratios in chronic bronchitis are the result of diseased airways blocked by retained secretions. It also should be emphasized that the $\dot{V}_A/\dot{Q}$ distributions found in severe chronic bronchitis show considerable variability.

Ventilation-Perfusion Mismatch and Carbon Dioxide Retention

It is important to appreciate that ventilation-perfusion mismatch interferes with the efficiency of CO_2 elimination by the lung, although patients with ventilationperfusion mismatch often have a normal or even low $PaCO_2$. The reason for this is that the regulatory chemoreceptors increase the ventilatory drive whenever they sense a rising $PaCO_2$. Such patients can maintain a normal PCO_2 by increasing the total ventilation at a cost of increasing the work of breathing. A significant portion of this increased ventilation, however, goes to lung units with high $\dot{V}_A/\dot{Q}$ ratios, which are inefficient at eliminating CO_2 (physiologic dead space).

When high $\dot{V}_A/\dot{Q}$ areas predominate in diseased lungs, the capacity to hyperventilate is readily exceeded and CO_2 retention may ensue. Patients with CO_2 retention are sometimes said to be “hypoventilating” as a result of the hypercapnia. Such patients with chronic lung disease and ventilation-perfusion mismatch, however, actually have “relative” hypoventilation, because the total ventilation is almost always increased.

Regulatory Control of Ventilation-Perfusion Matching

The alveolar PO_2 appears to be the most important factor involved in regulating the distribution of ventilation-perfusion within the lung. In this respect, hypoxic pulmonary vasoconstriction can be considered as part of a negative feedback loop. For example, in lung units with low $\dot{V}_A/\dot{Q}$ ratios, there is a fall in the local alveolar PO_2, and constriction of the associated microvessels reduces the local pulmonary blood flow. This tends to restore the local $\dot{V}_A/\dot{Q}$ ratio toward its normal value. This effect can be appreciated in residents of high altitudes, who are exposed constantly to lower ambient O_2 concentrations. Residents of high altitudes have better $\dot{V}_A/\dot{Q}$ matching than sea level residents, as reflected by a smaller alveolar-arterial PO_2 difference. The intensity of hypoxic pulmonary vasoconstriction varies among different lung regions, and probably depends on the smooth muscle tone in different vessels. The effectiveness of hypoxic pulmonary vasoconstriction on preserving $\dot{V}_A/\dot{Q}$ ratios also depends on the type of inhomogeneity. For example, when collateral ventilation is present, the regulatory effectiveness of hypoxic vasoconstriction may be greater than it would be if there were a parallel ventilatory arrangement between lung units. More recently, a role for nitric oxide in regulating local ventilation-perfusion matching has been suggested. The hypothesis is reasonable for the following reasons: (1) Nitric oxide is produced endogenously by endothelial cells and may regulate the local blood flow through its vasodilating effect, and (2) nitric oxide inhibits hypoxic pulmonary vasoconstriction. The nitric oxide-mediated mechanism may be especially important in patients with inflammatory lung diseases, in whom production of nitric oxide is increased. The loss of local hypoxic vasoconstriction would worsen ventilation-perfusion mismatch.

DIFFUSION CAPACITY

O_2 from the ambient air is carried into the lungs by two physical processes: bulk flow, which occurs in the conducting airways, and molecular diffusion, which is the main mechanism of gas transfer in the distal alveolar units. From the alveolar region, O_2 must diffuse across the alveolar-capillary membrane and enter the plasma and red cell membrane before it reacts with hemoglobin. The diffusion gradient for O_2 is determined by the PO_2 difference between alveolar gas and mixed venous blood at the entry to the pulmonary capillaries. Because of the high affinity of hemoglobin for O_2, the PO_2 in the capillary blood quickly rises to that in the alveolar gas, and the diffusion gradient for O_2 falls from approximately 60 mmHg to almost nil. At rest, this diffusion process is virtually complete in the first third of the mean capillary transit time of 0.75 sec.

The physical process of diffusion of gases across the alveolar capillary membrane behaves according to Fick's Law of Diffusion. Fick's Law states that for a given gas, the amount of gas transferred across a tissue sheet ($\dot{V}_{gas}$) is proportional to the area (A), a diffusion constant, and the difference in partial pressure ($P_1 - P_2$), and is inversely proportional to the thickness of the barrier (T):

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

where D is a diffusion constant that depends on the properties of the tissue and the particular gas.

The lung is too complex to determine the area and thickness of the blood-gas barrier during life. Instead, the diffusion equation is written to combine the factors A, T, and D into one constant, D_L, as follows:

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

where D_L is called the *diffusing capacity of the lung.* The diffusing capacity includes the area, thickness, and diffusion properties of the membrane as well as the properties of the diffusing gas. Thus, the diffusing capacity for a gas is given by the following equation:

$$D_L = \frac{\dot{V}_{gas}}{(P_A - P_C)}$$

where P_A and Pc are the partial pressures of the gas in alveolar space and capillary blood, respectively.

Carbon monoxide (CO) is usually the gas of choice for measuring the diffusion properties of the lung, because its transfer is limited almost entirely by diffusion. The partial pressure of CO in capillary blood is very low because of its high affinity for hemoglobin (200 times greater than that of O_2), so that Pc in the above equation can generally be neglected. In this case, the above equation can be simplified as follows:

$$D_LCO = \frac{\dot{V}CO}{P_ACO}$$

The diffusing capacity of the lung for carbon monoxide (D_LCO) is thus expressed in units of milliliters of CO transferred per minute per millimeter of mercury of alveolar partial pressure. Of note, this unit is analogous to that for conductance. Some people—heavy cigarette smokers, for example—have sufficient carboxyhemoglobin in their blood that the partial pressure of CO in the pulmonary capillaries cannot be neglected. In this case, the partial pressure of CO can be measured in alveolar gas using a rebreathing technique and a correction made for back-diffusion of CO during the D_LCO maneuver.

The capacity for O_2 diffusion in the lungs can be estimated by multiplying the diffusing capacity for CO by 1.25. The uptake of O_2 by the lung is typically limited by perfusion under normal conditions. This process becomes limited partly by perfusion and partly by diffusion under hypoxic conditions. For this reason, measurements of diffusion using O_2 are often difficult to interpret.

The diffusing capacity of the lung can be separated into two components: (1) the alveolar-capillary membrane plus the erythrocyte cell membrane and (2) the reaction with hemoglobin (Fig. 14A). These components can be regarded as “resistances” in series to the transfer of O_2. This type of analysis was carried out by Roughton and Forster, who showed that the following relationship exists:

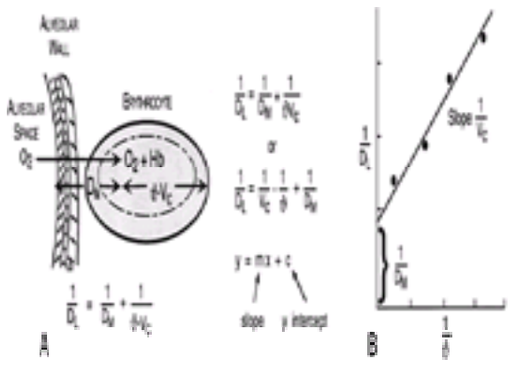

FIG. 14. The two components of the measured diffusing capacity (D) of the lung. **A:** Components attributable to the diffusion process itself and the time taken for O_2 (or CO) to react with hemoglobin. **B:** The graphic solution of DM and Vc according to the Roughton and Forster analysis. DM and Vc are derived by plotting against 1/DL. (Reproduced with permission from West JB. *Textbook of Respiratory Medicine.* 2nd ed. Philadelphia: WB Saunders; 1994.)

$$1/D_L = 1/D_M - 1/\theta Vc$$

where D_L refers to the diffusing capacity of the lung, D_M is the diffusing capacity of the membrane (which includes the plasma and red cell membrane), q is the rate of reaction of O_2 (or CO) with hemoglobin, and Vc is the volume of blood in the pulmonary capillaries. In the equation, values for D_M and Vc can be obtained graphically by measuring the diffusing capacity for CO at both high and normal alveolar PO_2 values (Fig. 14). Increasing the alveolar PO_2 reduces the value of q for CO, because the CO has to compete with a higher pressure of O_2 for the hemoglobin. When the values of $1/D_L$ obtained at two different values of PO_2 are plotted against 1/q, as shown in Fig. 15, the slope of the line is 1/Vc and the intercept on the vertical axis is $1/D_M$.

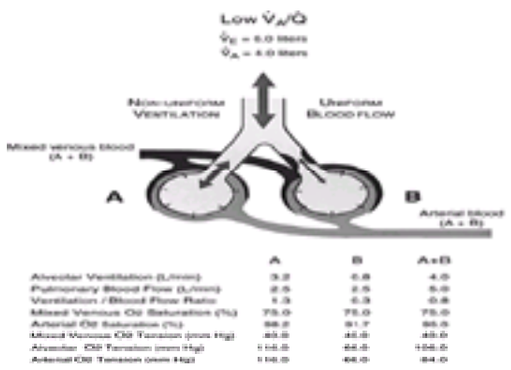

FIG. 15. Effects of nonuniform distribution of ventilation with uniform blood flow on gas exchange in a two-compartment lung model. Note that uneven ventilation produces a low $\dot{V}_A/\dot{Q}$ unit (*unit B*) and results in an alveolar-arterial PO_2 difference of 22 mmHg. (Reproduced with permission from Forster RE, et al., eds. *The Normal Lung: Physiological Basis of Pulmonary Function Tests.* 3rd ed. Chicago: Year Book; 1986.)

The Roughton-Forster equation is useful to demonstrate the factors that influence the diffusing capacity of the lung. Thus, the diffusing capacity can be reduced if D_M is increased, as when the thickness is increased or the area is reduced. The diffusing capacity also can be altered if the rate at which CO combines with blood (q) is reduced (e.g., in anemia) or if capillary blood volume (Vc) is reduced (e.g., in pulmonary embolism).

According to the Roughton-Forster equation, the term D_M should be just as important as qVc in determining the diffusing capacity of the lung. In clinical practice, however, the most important factor affecting the diffusing capacity is Vc; this is true in normal subjects as well as in many patients with pulmonary diseases. Changes in D_M are much less significant. It can be shown that raising the pulmonary arterial pressure when left atrial pressure is low increases the D_L substantially. This occurs because higher perfusion pressure recruits and distends pulmonary capillaries, and thus increases Vc. This effect is diminished if left atrial pressure is already elevated. Capillary recruitment and thus increased Vc probably also account for the increase in D_L measured during exercise and during changes from the upright to the supine position. Similarly, changes in D_L induced by certain drugs can be explained best by their effects on Vc. This is also true in diseases associated with increased thickness of the alveolar membrane (e.g., idiopathic pulmonary fibrosis). The reduced diffusing capacity under these conditions usually can be attributed to decreased Vc that results from decreased lung volume caused by destruction and distortion of lung parenchyma. In addition to desaturation of the test gas, a decreased D_L is seen in emphysema, partly because destruction of pulmonary capillaries decreases the Vc.

Measurements of Diffusing Capacity

Single-Breath Method

The single-breath method was first described by Marie Krogh in 1914. The patient performs a single inhalation of a dilute mixture (about 0.3% each) of CO and an inert tracer gas (e.g., helium or methane), followed by a 10-sec breath-hold. The rate of disappearance of CO from the alveolar gas during the 10-second breath-hold is calculated. At the end of the breath-holding period, a sample of alveolar gas is obtained after discarding the dead space. The exhaled sample is then analyzed for CO using an infrared analyzer. The inert tracer gas is used to measure alveolar volume by dilution. The single-breath equation is as follows:

$$D_LCO_{sb} = K \times V_A \times \ln\left(\frac{F_ACO_i/F_ACO_s}{F_AHe_i/F_AHe_s}\right) \{(P_B - 47) \times t\}$$

where V_A is the alveolar volume in liters, t is breath-holding time in sec, and K is a constant. The fractional concentrations of CO and helium in inspired and sample gas (F_ACO_i/F_ACO_s and F_AHe_i/F_AHe_s, respectively) are indicated by the appropriate terms.

The analysis of data based on the single-breath method involves several assumptions. The inhalation is assumed to be instantaneous, although in reality it is not. As the alveolar concentration of CO continues to decrease during breath-hold period, calculation of D_L can be affected by the breath-hold time. Alternative methods have been proposed to circumvent these problems. For example, equations for changes in the alveolar concentrations of CO can be developed to fit each of the three phases of the single-breath maneuver (inhalation, breath-hold, and exhalation). The three-equation method appears to give a more accurate measurement of the diffusing capacity.

In many patients with lung diseases, the single-breath diffusing capacity is reduced. The decrease in D_LCO is usually caused by uneven ventilation-perfusion distribution and diffusion-perfusion properties in diseased lungs rather than by true changes in diffusion across the alveolar-capillary membrane. Such diseased lungs tend to empty unevenly, and the post-dead space sample of expired gas that is analyzed for CO is not representative of the whole lung. For this reason, the diffusing capacity is sometimes referred to as the *transfer factor* (especially in Europe), to emphasize that it is more a measure of the lung's overall ability to transfer gas into the blood than a specific test of diffusion. Nevertheless, the test gives considerable information about gas exchange in the normal lung. Even in patients with severe disease, the results are useful for assessing the severity and type of lung disease in the pulmonary function laboratory.

Steady-state Method

In this method, the subject breathes a low concentration of CO (about 0.1%) for about 30 sec, until a steady state of gas exchange has been reached. The constant rate of disappearance of CO from alveolar gas is then measured for a further short period, along with the alveolar concentration of the gas. This technique is better suited for measurements during exercise, when breath-hold becomes a problem. The normal value of the diffusing capacity for CO depends on age, sex, and height (as is the case for most pulmonary function tests), and appropriate regression equations are available.

Intrabreath Method

More recently, with the development of rapidly responding infrared analyzers, the diffusing capacity can be measured using a single-breath–slow exhalation, or “intrabreath,” technique. The gas concentrations are monitored continuously during slow inhalation and exhalation. Multiple estimates of D_L can be made during a single exhalation, giving D_L as a function of lung volume. Alternatively, a single estimate of D_L can be obtained by applying a linear regression to exhaled CO concentration continuously measured during slow exhalation. Regression equations for the “intrabreath” diffusing capacity for CO based on age and height have been published.

Distribution of Diffusing Capacity

The Roughton-Forster approach to analyzing diffusing capacity assumes a homogeneous pulmonary system. The interpretation of the results is affected by heterogeneity in alveolar ventilation, alveolar lung volume, alveolar perfusion, and pulmonary diffusing capacity. The relative importance of heterogeneity in each of these factors and their interactions vary according to individual characteristics and the particular method chosen to measure D_L.

A single acinus is sufficiently small so that ventilation and perfusion within such units can be assumed to be homogeneous. In the whole lung, however, perfusion depends on gravity as well as other regional stress factors. The higher perfusion pressure in the bottom of the lung results in greater recruitment of capillaries and

therefore a larger capillary volume and capillary surface area for diffusion. In addition, larger regional differences in lung volume and alveolar ventilation are known to occur. These variations may result in significant local variations in diffusing capacity. This was demonstrated experimentally by Hamer, who showed, using a breath-hold technique, that overall D_L, D_M, and Vc vary as a function of lung volume. Using a single-exhalation technique, Denison et al. measured regional $\dot{V}_A$, $D_L/\dot{V}_A$, and $\dot{Q}/\dot{V}_A$ through a bronchoscope within individual lobes of the lungs of normal human subjects. They found a vertical gradient for $D_L/\dot{V}_A$ in the sitting position. $D_L/\dot{V}_A$ ranged from 0.86 in the upper lobe to 1.13 in the lower lobe. Clinically, diffusing capacity measured by the breath-hold method gives little information about its distribution in the lung. Since use of the rapid infrared analyzer has been combined with the single-exhalation method, the regional distribution of diffusing capacity can be measured in the lung.

MECHANISMS OF HYPOXEMIA

An arterial PO_2 value below the range for normal subjects of the same age establishes the presence of hypoxemia. In general, arterial hypoxemia is defined by PO_2 values of <80 mmHg in adults breathing room air at sea level.

Hypoventilation as a Cause of Hypoxemia

The simplest derangement of gas exchange occurs when insufficient fresh air is breathed. Such hypoventilation decreases the arterial PO_2 and increases the arterial PCO_2. If $\dot{V}_A/\dot{Q}$ distribution remains uniform, no alveolar-arterial difference develops for either O_2 or CO_2. The common causes of hypoventilation-associated hypoxemia are anesthetics or narcotics that depress the central nervous system, and neuromuscular diseases that affect respiratory muscle function.

Ventilation-Perfusion Mismatch as a Cause of Hypoxemia

Ventilation-perfusion mismatch (low $\dot{V}_A/\dot{Q}$ regions) is the most common cause of hypoxemia in lung disease. Figure 15 illustrates the effects of $\dot{V}_A/\dot{Q}$ mismatch on hypoxemia using a two-compartment lung model. If the total ventilation remains constant at 4 L/min but unit A receives four times as much ventilation as unit B (3.2 L/min vs. 0.8 L/min), and if the distribution of perfusion is uniform (2.5 L/min for each unit), the $\dot{V}_A/\dot{Q}$ ratio for unit A becomes 1.3, whereas that for unit B is 0.3. O_2 tension and saturation must decrease in blood leaving the hypoventilated unit B; O_2 saturation must rise in blood leaving the hyperventilated unit A. Because of the nearly linear nature of the hemoglobin dissociation curve, the final PO_2 in the pulmonary venous blood, which is derived from the blood flow-weighted average of O_2 content, has to decrease. Thus, the high PO_2 in the blood leaving high $\dot{V}_A/\dot{Q}$ unit A is not sufficient to compensate for the low PO_2 contributed by low $\dot{V}_A/\dot{Q}$ unit B. The arterial blood would then have a PO_2 of 84 mmHg instead of 100 mmHg, as in the normal lung.

Right-to-Left Shunt as a Cause of Hypoxemia

A shunt is defined as a region where there is blood flow from the right side of the heart to the left, but no ventilation ($\dot{V}_A/\dot{Q} = 0$). The effects of a right-to-left shunt on gas exchange are shown schematically in Fig. 16. In this example, 33% of the total blood flow (2.0 L/min) is shunt. Although gas exchange in units A and B is unimpaired, the net result from mixing of blood from these two units and the shunt pathway is a reduction of arterial PO_2 and the creation of the alveolar-arterial O_2 gradient. This effect on PO_2 is similar to that caused by $\dot{V}_A/\dot{Q}$ mismatch. In fact, a shunt in mathematical terms is the ultimate ventilation-perfusion mismatch, one in which there is perfusion but no ventilation. Because of the absence of ventilation, hypoxemia resulting from shunt cannot be corrected by breathing 100% O_2. This technique allows $\dot{V}_A/\dot{Q}$ mismatch to be differentiated from shunt as the cause of hypoxemia.

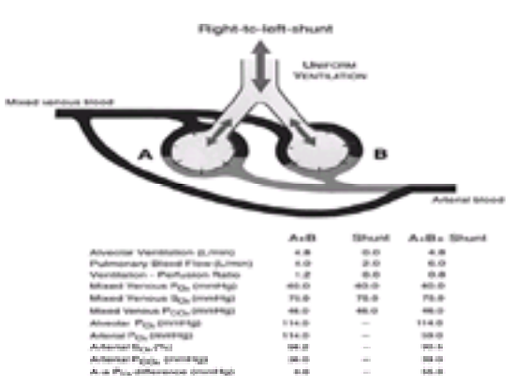

FIG. 16. Effects of right-to-left shunt on gas exchange in a two-compartment lung model. (Reproduced with permission from Forster RE, et al., eds. *The Normal Lung: Physiological Basis of Pulmonary Function Tests.* 3rd ed. Chicago: Year Book; 1986.)

When a normal, healthy person breathes 100% O_2, an alveolar-arterial PO_2 difference of between 30 and 50 mmHg can usually be detected. This is consistent with the presence of a right-to-left shunt of approximately 2%–3% of the cardiac output. The multiple inert gas method, which measures only intrapulmonary shunt, indicates virtually no right-to-left shunt through the normal lung. These two results, taken together, imply that most of the shunt in normal subjects occurs distally to the gas exchange units (i.e., “postpulmonary shunt”). The main sources of the normal postpulmonary shunt are bronchial and mediastinal veins that empty into pulmonary veins and the Thebesian vessels of the left ventricle, which empty directly into the left ventricular cavity. When shunt occurs in patients with lung disease, it is usually accounted for by the perfusion of nonventilated lung regions through relatively normal vascular channels. Sometimes, shunt flow may occur through intracardiac communications, as in patent foramen ovale, when pressure in the right atrium is increased—for example, from pulmonary hypertension.

Diffusion Impairment as a Cause of Hypoxemia

In normal subjects at rest, O_2 equilibrates quickly between the blood and gas phases in the alveolar region of the lung, and there is no diffusion limitation. This is true for healthy persons at sea level and at low altitude. During exercise at higher altitudes (>10,000 ft), the alveolar-arterial PO_2 difference can increase due to diffusion disequilibrium (Fig. 17).

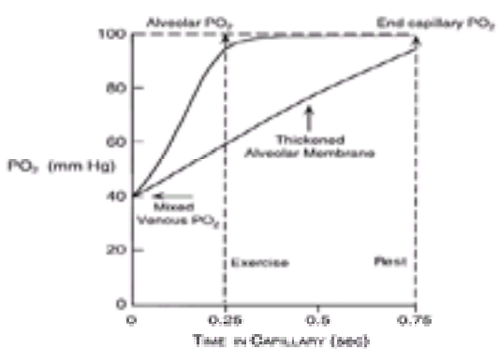

FIG. 17. Typical time courses for the change in PO_2 in the pulmonary capillary when diffusion is normal and the blood-gas barrier is abnormally thick. The time course for CO uptake is also shown.

Many patients with lung disease have abnormal diffusing capacity measured by the single-breath CO method. A diffusion impairment causing an increased alveolar-arterial PO_2 difference is unusual in these patients while at rest. As mentioned earlier, the major reason for a decreased diffusion capacity measured in the pulmonary function laboratory in patients with lung disease is maldistribution of ventilation-perfusion. Abnormal diffusion as a cause of an increased alveolar-arterial PO_2 difference is much more likely during exercise in these patients. Exercise-induced diffusion abnormalities result from lengthening of the diffusion pathway across the alveolar-capillary membranes or, more commonly, from a decrease in pulmonary blood volume in combination with an increase in the rate of blood flow, thus shortening the capillary transit time for the erythrocytes. Similar to hypoxemia caused by $\dot{V}_A/\dot{Q}$ mismatch, hypoxemia caused by diffusion impairment can be corrected by having the patient breathe 100% O_2.

Decreased Mixed Venous Oxygen Content as a Cause of Hypoxemia

The O_2 content of pulmonary arterial (mixed venous) blood usually has little effect on arterial PO_2 in persons with normal lungs. In patients with very low cardiac output (e.g., patients in cardiogenic shock), a decrease in $C\bar{v}O_2$ contributes substantially to hypoxemia provided the amount of venous admixture is small. In the presence of lung disease with a substantial amount of venous admixture, resulting from either ventilation-perfusion abnormality, a large right-to-left shunt, or both, the O_2 content in the mixed venous blood has a considerable effect on arterial PO_2. For a given amount of ventilation-perfusion mismatch, the lower the mixed venous O_2 content, the lower the arterial PO_2. This mechanism of hypoxemia is particularly important in critically ill patients with serious cardiopulmonary diseases.

MECHANISMS OF HYPERCAPNIA

Ideally, CO_2 exchange should be characterized by (1) complete equilibration between aqueous and gaseous phases before blood leaves the pulmonary capillary, (2) identical PCO_2 in mixed alveolar gas and arterial blood, and (3) an inverse relationship between these gas tensions and the amount of ventilation of the alveolar spaces. Although it is not likely that all three postulates are ever achieved completely, CO_2 exchange is so close to the ideal that for practical purposes they can be assumed to hold true in the normal lung. This situation is certainly not the case for the abnormal lung.

Increased Dead Space as a Cause of Hypercapnia

As ventilation in the lung is cyclical—that is, gas enters and leaves by the same conduit—a portion of the inhaled gas never reaches the exchange surface. The last portion of each inspired breath remains in the tracheobronchial tree and is exhaled without its participating in either O_2 or CO_2 exchange. This portion of each tidal volume, V_D/V_T, is calculated from the difference between the PCO_2 of arterial blood and mixed expired gas and is expressed by the Bohr equation (see above). If tidal volume itself is measured, physiologic dead space can be described as a volume rather than a ratio. The *anatomic dead space* varies little in disease but does vary moderately with tidal volume, as airway volume increases slightly at higher lung volumes. The volume of anatomic dead space is important to consider when assessing ventilation, particularly during mechanical ventilation, but it does not need to be measured, because its size is not affected by disease.

Alveolar dead space for the most part is a conceptual space rather than an actual anatomic volume. A complete lack of gas exchange is present only in alveoli in which $\dot{V}_A/\dot{Q}$ equals infinity (i.e., ventilated but not perfused at all). This situation is relatively rare. Far more commonly, alveoli have an excess of ventilation in relation to blood flow, and all the ventilation to such alveoli participates in gas exchange, but with lower efficiency than normal. This decrease in efficiency, measured in terms of its effect on CO_2 exchange, contributes to the alveolar dead space.

It is difficult to separate alveolar from anatomic dead space because of the difficulty of obtaining an expired gas sample that represents alveolar gas. Nor is it important, because both are factors in gas exchange and must be taken into consideration. Physiologic dead space (V_D/V_T) represents the sum of the anatomic dead space and the alveolar dead space, the latter usually resulting from ventilation-perfusion imbalance. The V_D/V_T describes CO_2 exchange as if the tidal volume were divided into a portion that does not participate at all in CO_2 exchange (physiologic dead space) and a remaining volume that exchanges CO_2 in a completely normal fashion. In reality, almost all the tidal volume, exclusive of the anatomic dead space, participates in CO_2 exchange, but to a degree that varies with the local $\dot{V}_A/\dot{Q}$. In the sitting position, V_D/V_T is about 30% and varies little with age. It can increase to 60% or more in disease, reflecting gas exchange units with elevated $\dot{V}_A/\dot{Q}$. In the normal individual, V_D/V_T decreases with exercise, because changes in the physiologic dead space volume are small compared with the increases in tidal volume accompanying exercise. The responses of V_D/V_T to exercise in disease are variable, but usually V_D/V_T decreases, although not generally to normal levels.

Because physiologic dead space is a clearance index, it is affected by any factor that influences the efficiency of CO_2 exchange. It is useful in assessing $\dot{V}_A/\dot{Q}$ inequality only because this abnormality has a far greater effect on CO_2 exchange than all other factors combined.

Ventilation-Perfusion Mismatch as a Cause of Hypercapnia

Although maldistribution of ventilation and blood flow is not usually characterized by hypercapnia, there is no question that CO_2 exchange is affected by $\dot{V}_A/\dot{Q}$ imbalance. As $\dot{V}_A/\dot{Q}$ falls, local PCO_2 rises, reaching the value of the mixed venous PCO_2 when $\dot{V}_A/\dot{Q}$ equals zero. The maximum increase is slight in terms of gas tension but represents a considerable change in content because of the steep slope of the CO_2 dissociation curve. Besides the direct effect of the decrease in ventilation on CO_2 excretion, the simultaneous failure to oxygenate blood completely further hinders CO_2 exchange. With oxygenation, the carrying capacity of blood for CO_2 decreases, facilitating CO_2 excretion (Haldane effect). A quantity of CO_2 equal to that retained in alveoli with low $\dot{V}_A/\dot{Q}$ must be excreted in other gas exchange units to avoid hypercapnia. As noted previously, this can be accomplished in alveoli in which $\dot{V}_A/\dot{Q}$ is higher than normal. Because CO_2 is excreted less efficiently in these alveoli, alveolar dead space is increased, and the total ventilation must be increased to keep the alveolar exchange at a normal level. The incremental ventilation is achieved rapidly because of the sensitivity of central chemoreceptors to altered levels of PCO_2.

The ventilatory work required for this compensation is usually small, as can be illustrated by an extreme example. If one-half the cardiac output went to alveoli that were no longer ventilated, the remaining alveoli would have to excrete twice the normal amount of CO_2 to prevent hypercapnia. This could be accomplished by maintaining a PCO_2 in the low 30s in these units, and it would require an increase in ventilation of 25%–30% over that needed to exchange the same quantity of CO_2 with an ideal ventilation-perfusion distribution. This is only a small fraction of the normal ventilatory reserve. The ease of this compensation and the magnitude of normal ventilatory reserve account for the low incidence of hypercapnia in patients with $\dot{V}_A/\dot{Q}$ disturbances. As the disparity of $\dot{V}_A/\dot{Q}$ throughout the lung becomes greater, however, compensation becomes more difficult to achieve. In the previous example, if retained CO_2 was excreted in only 10% rather than 50% of the alveoli, a much higher $\dot{V}_A/\dot{Q}$ would be present in the compensating alveoli, and alveolar dead space would increase correspondingly. In this circumstance, a 200% increase in ventilation would be required to maintain normocapnia. Although it is unlikely that normal ventilatory reserve would be exceeded except in an extreme $\dot{V}_A/\dot{Q}$ disturbance, the reserve may be minimal in disease. Moreover, the work of breathing can be increased substantially in disease. CO_2 produced by respiratory muscles may place an undue burden on the lungs when increments in ventilation require high levels of muscular work. Thus, a decreased ventilatory reserve combined with a high work of breathing and severe $\dot{V}_A/\dot{Q}$ imbalance can lead to an increase in alveolar dead space that cannot be overcome easily. These processes result in hypercapnia.

Hypoventilation as a Cause of Hypercapnia

In the homogeneous lung, the definition of alveolar ventilation is quite simple. Under these conditions, alveolar dead space does not exist, because early inspired gas in the anatomic dead space does not exchange CO_2. A discussed earlier in this chapter, alveolar ventilation can be defined as follows:

$$\dot{V}_A = \dot{V}CO_2/P_ACO_2 \times 0.863$$

where $\dot{V}CO_2$ is CO_2 output and P_ACO_2 is alveolar PCO_2 (assumed to be the same as arterial PCO_2). The definition of alveolar ventilation becomes more difficult when the lung is not ventilated uniformly. Alveolar and arterial PCO_2 are then no longer identical, and it is not possible to obtain an expired sample that is known to represent

alveolar gas. Indeed, the term *alveolar gas* is misleading, as the composition of gas in the alveoli varies widely depending on local $\dot{V}_A/\dot{Q}$ relationships. Classically, the response to this problem has been to define alveolar ventilation in a functional manner by using the right side of the above equation. Hence, if arterial PCO_2 is elevated, alveolar ventilation is decreased and insufficient to excrete CO_2 in a normal fashion. Likewise, hyperventilation is signaled by a less-than-normal arterial PCO_2. With this approach, alveolar ventilation is equal to the difference between total expired ventilation and the physiologic dead space. In this context, there are two reasons for alveolar hypoventilation (i.e., arterial hypercapnia). First, if total minute ventilation is decreased, the alveolar component decreases and arterial PCO_2 rises. Second, alveolar hypoventilation occurs if physiologic dead space increases because of ventilation-perfusion imbalance and the necessary increase in total ventilation cannot be sustained to compensate for the change in dead space. In the latter circumstance, the $\dot{V}_A/\dot{Q}$ disturbance can be so severe that hypercapnia may be present, even though the total minute ventilation measured at the mouth is greater than normal. This is the result of defining alveolar ventilation in terms of alveolar PCO_2.

West has challenged this functional definition, arguing that the quantity of ventilation of the alveolar space is normal in $\dot{V}_A/\dot{Q}$ mismatch and that the approach based on arterial PCO_2 overlooks the underlying problem. This viewpoint defines alveolar ventilation in an anatomic rather than a functional manner by making use of the concept of *effective ventilation* when the arterial PCO_2 is used as an index of ventilation. The term *alveolar ventilation* has a long tradition and is unlikely to be changed, although it would be more useful to identify the precise mechanisms involved in producing hypercapnia. No simple bedside techniques are available, however, to sort out accurately the degree of hypercapnia resulting from inadequate ventilation and that caused by severe ventilation-perfusion mismatch.

BLOOD GAS TRANSPORT

In air-breathing vertebrates, the metabolic processes of the body are supported by the integrated functions of the heart, lungs, and blood. Atmospheric oxygen, brought into proximity with the blood in the alveolar capillaries of the lungs, diffuses into the erythrocyte and is bound reversibly to hemoglobin. The erythrocyte circulates to the tissue capillaries, where oxygen dissociates from hemoglobin and diffuses down its concentration gradient into the cells to be consumed by mitochondria. The erythrocyte then carries carbon dioxide generated in the mitochondria to the alveolar capillaries, where it diffuses down its concentration gradient into the air spaces of the lung. These physiologic processes make use of the physical processes of diffusion, chemical reaction, convection, and diffusion again. This portion of the chapter describes the remarkable properties of the blood that enable it to carry oxygen and carbon dioxide and maintain acid-base homeostasis. It also summarizes the processes of convective oxygen transport to the microcirculation, diffusion of oxygen into the tissues, and cellular respiration. Examples have been selected to describe the effects of disease processes such as anemia, hypoxemia, ischemia, and heterogeneity of blood flow on oxygen delivery and cellular metabolism.

The Metabolic Milieu of the Body

The gas transport mechanisms in the blood are designed primarily to handle large quantities of the metabolic gases O_2 and CO_2, although soluble inert gases, such as N_2, also are transported in dissolved form. The circulation supports a basal metabolic rate for O_2 of about 3.0 mL/min and a CO_2 production rate of 2.4 mL/min per kilogram of body weight for the adult human. The demands on the circulation, however, can increase as much as 20-fold under conditions of extreme exercise. The large size and high metabolic requirements of vertebrate animals for molecular O_2 confounds diffusion as a transport mechanism, because the distances and the rates of O_2 consumption become too great. These requirements can be met only by an efficient convective transport system to deliver O_2 to more dense regions of the circulation, where diffusion again becomes an effective process for its distribution. In addition, having a carrier molecule for O_2 is adaptive, because the amount of the gas that can be dissolved in the blood at normal barometric pressures is not adequate to meet the metabolic requirements of higher organisms.

When the plasma comes in contact with a gas such as O_2, its concentration rises to a value determined by the partial pressure of the gas and the solubility coefficient of plasma for O_2. As the solubility of O_2 in plasma is quite low (0.0224 mL O_2 per milliliter of plasma at body temperature), the amount of O_2 dissolved in plasma at normal barometric pressure is quite low. The number of milliliters of dissolved O_2 in a liter of blood plasma at STPD (standard temperature and pressure, dry) is given by the following simple relationship:

$$\begin{aligned}\text{Dissolved } O_2 &= [0.0224\ PO_2\ (P_B - PH_20)] \times 100\ \text{mL} \\ &= [0.0224\ PO_2\ (760 - 47)] \times 100\ \text{mL} \\ &= 0.0031\ PO_2\end{aligned}$$

where P_B is the barometric pressure, PH_2O is water vapor pressure, and PO_2 is the partial pressure of O_2 in the blood. Hence, for a PO_2 in the blood of 100 mmHg, the dissolved O_2 content is only 0.3 mL/dL or 3.0 mL/L of blood. To meet a basal requirement for O_2 of 3 mL/kg/min, the minimum cardiac output would have to be 1.0 L/kg/min, or, for an adult of normal size, about 70 L/min. During exercise at an O_2 consumption rate of 3.0 L/min, the cardiac output would have to increase to an amazing 1000 L/min. To circumvent this problem, hemoproteins capable of carrying large quantities of O_2 have evolved in higher animals. These hemoproteins are the hemocyanins of invertebrates and the hemoglobins of vertebrates.

Structural Biology and Molecular Properties of Hemoglobin

Hemoglobin is the major protein of erythrocytes. It allows vertebrates to transport molecular O_2 from the lungs to the tissues and CO_2 from the tissues to the lungs. Human hemoglobin is a tetramer of two a and two b polypeptides, each containing a heme moiety. The tetramer consists of 547 amino acids and has a molecular weight of 64,800 Da. The heme and the globin interact with each other in a way that determines the O_2-binding characteristics of hemoglobin. The heme groups to which the O_2 binds are harbored within the protein parts of the molecule. Heme is the complex of chelated iron in a cyclic tetrapyrrole (porphyrin) ring. The porphyrin of hemoglobin is called *protoporphyrin IX.* The iron atom is kept in the center of the porphyrin ring between four nitrogen atoms. The porphyrin carries side chains that maintain the heme group in the proper orientation within the protein portion of the hemoglobin molecule. Double bonds in the heme moiety cause hemoglobin to have a bright red color when oxygenated and a purple color when deoxygenated.

The location of the heme group in the globin portion of the molecule is important for maintaining the iron in a ferrous valence state (Fe^{2+}). Normally, when iron reacts with O_2, the iron valence state changes to ferric (Fe^{3+}) and an oxide (rust) is formed. In the folds of the globin chain, ferrous iron is protected and its reaction with O_2 is reversible. One important part of this mechanism is the linkage of the heme iron to the amino acid histidine, which supplies a negative charge and enables the iron to form a weak bond with O_2. Thus, the interactions between heme and globin in the molecule are responsible for the reversible linkage of O_2 with the heme group. The basic features of the molecular physiology of hemoglobin, including the interactions of heme with globin, are summarized below, along with the chemical mechanisms for inducing conformational changes in hemoglobin in the presence of O_2, organic phosphates, protons, and CO_2.

Hemoglobin consists of four globin molecules: two identical a subunits and two identical b subunits. In the evolution of the globin molecule in higher vertebrates, the amino acids responsible for proper heme orientation and cooperative O_2 binding have been conserved. The secondary structure of a and b subunits of hemoglobin is characterized by a high content of a helices (about 75%), which vary in length between 7 and 23 amino acids. The surfaces of the a and b subunits have nonpolar regions that allow them to form an a_2b_2 tetramer. The four subunits make a total of six contacts and are held together by hydrophobic interactions, by hydrogen bonds, and by electrostatic interactions of salt bridges. These noncovalent interactions allow the subunits to move easily during reversible binding of O_2 with the heme group. Among the contacts between the subunits, only the most extensive one, the a_1b_1 contact, remains the same on O_2 binding. The surface of the hemoglobin molecule contains many polar groups that are all hydrated and therefore contribute to the high water solubility of hemoglobin. This feature allows dense packing of hemoglobin within erythrocytes, each of which contains about 3 trillion molecules of tetrameric hemoglobin.

The binding of O_2 to the heme iron provides the crucial triggering mechanism for the conformational change of the globin part of hemoglobin (Fig. 18). Molecular O_2 is bound to the iron atom by an end-on geometry with an Fe-O-O angle of 155°. Iron in deoxyhemoglobin is five-coordinated with the four pyrrole nitrogens of porphyrin and the imidazole nitrogen of the proximal histidine, resulting in four unpaired electrons in the iron atom. In oxyhemoglobin, the iron is six-coordinated, leading to a state in which all the electrons are paired. This pairing of electrons leads to a reduction of magnetic moment in oxyhemoglobin compared with that in deoxyhemoglobin. The magnetic changes in iron accompanying the binding of O_2 give rise to stereochemical changes in the heme that produce the conformational changes in globin responsible for cooperative O_2 binding and allosteric effects, such as the Bohr effect. The mechanism that triggers the changes in the structure of the hemoglobin molecule when O_2 is bound or released is the movement of the heme iron. When heme iron reacts with O_2, it reorients the iron in the porphyrin ring. The bond between the imidazole nitrogen is shortened in deoxyhemoglobin by about 0.6 Å compared with that of oxyhemoglobin. In addition, the porphyrin structure is flexed in deoxyhemoglobin but not in oxyhemoglobin. These changes in electronic configuration are transmitted to the globin part of the molecule.

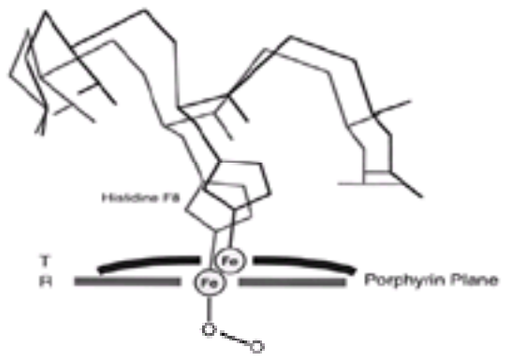

FIG. 18. Schematic illustration of the hemoglobin molecule. Changes in globin structure with O_2 binding to heme in hemoglobin are shown for the R (oxy) and T (deoxy) states.

A standard terminology is used for the different properties of deoxyhemoglobin and oxyhemoglobin to describe how changes in the heme structural affect the globin. Deoxyhemoglobin is said to be in the T or tense state, and oxyhemoglobin is said to be in the R or relaxed state. The T state of hemoglobin has a low O_2 affinity, whereas the R state has an O_2 affinity about 150 times greater than that of the T state. The transition between these conformational states is induced by the shift of the heme iron when O_2 is bound or released. The most important changes that occur in hemoglobin on binding or release of O_2 occur in the a_1b_2 and a_2b_1 contacts. These contacts fit together, and the respective hydrogen donor and acceptor sites are constructed so that only two positions of the two subunits are stable. This is the structural basis for the two-state model that explains most of the physiologic properties of hemoglobin. The cooperativity of O_2 binding is also a direct consequence of the fact that hemoglobin assumes only these two stable structures: the R structure whose O_2 affinity is high and the T structure whose O_2 affinity is lowered by molecular interactions such as salt bridges and the binding of organic phosphates.

Diphosphoglycerate

The erythrocytes of humans and most other mammals contain high concentrations of the glycolytic intermediate 2,3-diphosphoglycerate (DPG). Its concentration within human erythrocytes is normally about 5 mmol/L of erythrocytes, equivalent to the concentration of tetrameric hemoglobin. DPG is negatively charged at physiologic pH values and binds to deoxyhemoglobin in a 1:1 molar ratio. It binds to deoxyhemoglobin much more tightly than to oxyhemoglobin. The overall reaction is as follows:

$$Hb_4(DPG) + 4O_2 \rightleftharpoons Hb_4(O_2)_4 + DPG$$

Deoxyhemoglobin has a DPG binding site that is complementary in shape and charge to the phosphate that is able to stabilize the T structure of hemoglobin. The binding of O_2 results in a loss of complementarity and expulsion of the DPG molecule. The presence of O_2 decreases the binding constant of DPG and hemoglobin by two orders of magnitude at physiologic pH, temperature, and salt concentrations. O_2 binding changes the quaternary structure of deoxyhemoglobin by increasing the distance between the partners of the salt bridges, causing them to break. When a salt bridge is broken, the apparent pK value of the two partners falls. Therefore, protons tend to be set free by oxyhemoglobin and taken up by deoxyhemoglobin. This difference in proton binding between oxyhemoglobin and deoxyhemoglobin is the basis for the dependence of the O_2 affinity of hemoglobin on pH, also known as the *Bohr effect.* Quantitatively, about 2.0 H^+ are set free on oxygenation at neutral pH in the absence of DPG according to the following reaction:

$$Hb_4(H)_2 + 4O_2 \rightleftharpoons Hb_4(O_2)_4 + 2H^+$$

Protons are released from four pairs of salt bridges on O_2 binding. The sum of the changes in the apparent pK of these groups gives rise to the Bohr effect (effect of pH on O_2 affinity) and to the difference in proton binding between oxyhemoglobin and deoxyhemoglobin (Haldane effect).

Carbon Dioxide

The hemoglobin molecule, like other proteins, directly binds CO_2. The chemical interaction of CO_2 with the unprotonated forms of protein amino groups occurs according to the following reactions:

$$Hb{-}NH_2 + H^+ \rightleftharpoons Hb{-}NH_3$$
$$Hb{-}NH_2 + CO_2 \rightleftharpoons Hb{-}NHCOO^- + H^+$$

The carbon atom of CO_2 and the amino group of hemoglobin form a complex known as a *carbamate.* Carbamate formation proceeds only when the amino group is unprotonated; therefore, 50% of the N-terminal a-amino groups but less than 1% of the e-amino groups within the protein can bind with CO_2 in the physiologic pH range. Deoxyhemoglobin binds more CO_2 as carbamate than does oxyhemoglobin, and about 80% of this oxygen-labile carbamate is confined to the b subunits at physiologic pH. The pK value of the a-amino groups of the a subunits increases with deoxygenation from 7.0 to 7.8, thereby inhibiting carbamate formation. The pK value of the N-terminal a-amino groups of the b subunits remains nearly constant at around 7.0, regardless of oxygenation. Carbamates formed at the N-terminal a-amino group of the b subunits is stabilized by positively charged groups near the N-termini of the b subunits in deoxyhemoglobin. During the process of oxygenation, these positively charged groups move apart, destabilizing the carbamate and releasing CO_2 from the binding sites. This process is discussed in more detail in the section on CO_2 transport.

The Oxygen Equilibrium Curve of Hemoglobin

The relationship between the fractional saturation of hemoglobin with O_2 and the PO_2 under equilibrium conditions is the sigmoid O_2 equilibrium curve (OEC) of hemoglobin (Fig. 19). The sigmoid shape of the hemoglobin OEC determines the loading and unloading of O_2 under physiologic conditions. Its position is often expressed by the PO_2 at half-saturation (P_{50}). The normal P_{50} for human hemoglobin is approximately 27 mmHg. When the O_2 affinity increases, the OEC shifts to the left (reduced P_{50}). When the O_2 affinity decreases, the OEC shifts to the right (increased P_{50}). The principal physiologic determinants of the functional OEC within erythrocytes are H^+, 2,3,-DPG, and CO_2. Other effectors, such as Cl^- and adenosine triphosphate (ATP), also decrease O_2 affinity, but their physiologic roles are minor. One of the most powerful ways to decrease O_2 affinity is to bind CO to hemoglobin. CO has 200 times the affinity for heme as does O_2, and when CO binds to one heme site, it increases the O_2 affinity of the other binding sites. The OEC is also very sensitive to changes in temperature; hypothermia decreases the P_{50} approximately 2 mmHg per degree centigrade.

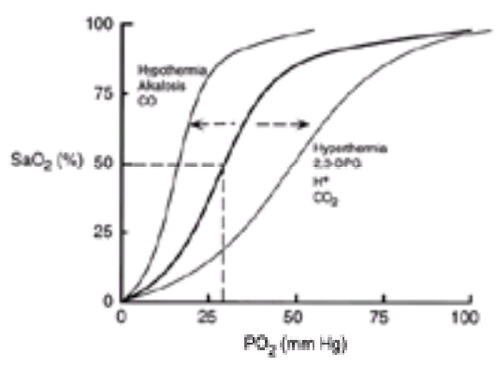

FIG. 19. OEC of hemoglobin. The normal P_{50} value is indicated by the *dashed lines.* The changes in position of the OEC associated with various effector molecules are indicated by the *dashed arrows.*

The first physiologists to observe the sigmoid nature of the OEC concluded that O_2 affinity increased during progressive oxygenation. They called this phenomenon *cooperativity.* This cooperativity was described mathematically by Hill using an equation that empirically relates hemoglobin saturation to O_2 tension. The Hill plot for the OEC falls on a straight line with a slope determined by the degree of cooperativity. This empiric description of the OEC, however, provides no information about the mechanism of O_2 binding. A more general approach to the quantitation of the oxygenation of hemoglobin was made by Adair, who recognized that hemoglobin was made up of four subunits, each of which could bind a single O_2 molecule. Adair derived equations for the stepwise oxygenation of hemoglobin:

$$Hb(O_2)i + O_2 \rightarrow Hb(O_2)i + 1$$

where i ranges from 0 to 3. The association constants for the sequence of equilibrium reactions are difficult to determine experimentally because of the interdependence among the parameters. In addition, the approach says nothing of molecular structure; thus, it is not useful for understanding structure-function relationships.

The two-state model provides a better functional description of the physiologic behavior of hemoglobin, because each of the two states of hemoglobin, R (relaxed) and T (tense), has its own unique O_2 affinity. The equilibrium constants for their reactions with O_2 are K_R and K_T. The ratio of these constants,

$$C = K_T/K_R$$

is less than 0.01 for human hemoglobin A; that is, the affinity of molecules in the R state for O_2 is much greater than the affinity of those in the T state. The constant C is characteristic of a given hemoglobin structure. The equilibrium between the two conformations is given by the allosteric constant:

$$L = [Hb]_T/[Hb]_R$$

This is influenced by mutations in the globin chains and by several small allosteric molecules. These small molecules react with hemoglobin at nonheme sites in such a way as to stabilize the T conformation. Thus, a mixture of R and T hemoglobin molecules will show a reactivity with O_2 related to the position of the T-R equilibrium. For deoxyhemoglobin, the equilibrium is almost entirely on the T side. The T (deoxygenated) state is constrained by salt and hydrogen bonds to a much greater degree than the R state. Successive oxygenation of the heme groups causes some of these bonds to break, decreasing the stability of the T structure. When the molecules transit from the T to the R state, the constraints are released and the oxygen affinity increases. The shift from T to R during oxygenation accounts for cooperativity of O_2 binding. For normal hemoglobin, the shift from T to R occurs primarily between binding of the second and third O_2 molecules; hence, the OEC is steepest in the middle part of the curve.

The behavior of the OEC can affect O_2 transport to tissues. For instance, certain genetic alterations in the hemoglobin molecule may lead to polycythemia. A reduced O_2 affinity may improve O_2 delivery to tissues when arterial oxygenation is inadequate. In animals, chemical modifications of hemoglobin that shift the OEC to the right will increase PO_2 in the tissues during normoxia. During CO poisoning, the OEC is shifted to the left by CO binding to hemoglobin. This leftward shift exacerbates the tissue hypoxia resulting from the CO-mediated decrease in O_2 carrying capacity. An extreme leftward shift in the OEC caused by respiratory alkalosis is also a feature of O_2 transport in humans at high altitude. The effects of other changes in the position or shape of the OEC on O_2 transport, however, have been difficult to demonstrate in humans.

The actual shape and position of the OEC in vivo is influenced most strongly by hydrogen ion concentration, although O_2 and CO_2 also interact with hemoglobin in a very complex way to regulate the position and shape of the OEC. Hydrogen ion effects are regulated by PCO_2 and the buffering capacity of hemoglobin. Buffering by hemoglobin, in turn, is determined by hemoglobin concentration and the degree of O_2 saturation. The O_2 saturation is determined by the PO_2 and O_2 affinity of hemoglobin. These complex interactions are difficult to sort out in the efficiency of gas exchange by blood. Other properties of erythrocytes that affect O_2 transport include the rates of binding of physiologic ligands (O_2, CO_2, H^+, 2,3-DPG), buffering capacity, the barrier to diffusion of the red blood cell membrane, the unstirred plasma layer immediately surrounding the cell, and the blood viscosity.

An increase in 2,3-DPG normally augments tissue oxygenation by shifting the OEC to the right. At high altitude, if O_2 uptake by the lung is limited by diffusion, a lower O_2 affinity of hemoglobin would limit O_2 loading of hemoglobin, whereas a higher O_2 affinity would augment it. Whether or not the latter effect would be offset by lower tissue unloading remains unclear, because few measurements of venous PO_2 are available under severely hypoxic conditions. The 2,3-DPG effect does not seem well suited to O_2 delivery at high altitude, but the traditional view that shifting the OEC to the right facilitates O_2 unloading in tissue sites also may not be appropriate under certain conditions. Barcroft et al. first proposed that increased O_2 affinity was an important adaptation to high altitude based on analogy with the placental circulation, in which fetal blood has a higher affinity than that of the mother. Chemical modification of hemoglobin to increase its O_2 affinity confers better survival in hypoxic rats, and mutant hemoglobins with increased O_2 affinity may protect against the effects of hypoxia. On the summit of Mt. Everest, respiratory alkalosis decreases the P_{50} of whole blood to about 19 torr, a value that would help maintain the O_2 saturation of arterial blood. The arterial desaturation during exercise in extreme hypoxia might be ameliorated by the increase in the O_2 affinity of hemoglobin, although its effects on O_2 release to the tissues are uncertain.

Carbon Dioxide Transport and the Carbon Dioxide Dissociation Curve

The CO_2 dissociation curve of hemoglobin describes overall CO_2 transport as a function of CO_2 tension. The CO_2 dissociation curve is relatively steep in comparison with the O_2 equilibrium curve (Fig. 20). Consequently, large volumes of CO_2 can be exchanged by the lungs with relatively small changes in blood PCO_2. These small changes in blood PCO_2 minimize oscillations in blood pH, and the hydrogen ion concentration of blood at rest varies only 10% between arterial and mixed venous values. The steepness of the CO_2 dissociation curve also permits continued excretion of CO_2 even in the presence of significant mismatching of pulmonary ventilation and blood flow.

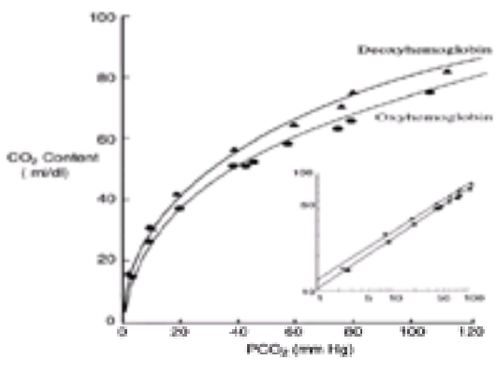

FIG. 20. CO_2 dissociation curve of blood. *Inset* shows log arithmetic transformation of the curve that linearizes the relationship between CO_2 content and PCO_2.

Most of the CO_2 in blood exists in the form of bicarbonate ion. CO_2 also is transported in a physically dissolved state in blood, and it is bound to amino groups of

proteins as carbamate compounds. Although CO_2 has an aqueous solubility approximately 20 times that of O_2, CO_2 dissolved in physical solution accounts for only 5% of the CO_2 content of arterial or venous blood. Dissolved CO_2, however, is important for CO_2 transport and exchange because the bicarbonate and carbamate pools are linked through dissolved CO_2. Molecular CO_2 is highly lipid-soluble and diffuses rapidly across cell membranes. Exchange of CO_2 in both the lung and peripheral tissues occurs via diffusion of molecular CO_2 across the vascular endothelium. CO_2 diffuses across the alveolar capillary membrane so rapidly that limitation of the process cannot be measured in vivo.

Hydration of CO_2 produces carbonic acid (H_2CO_3), which is almost completely ionized to hydrogen and bicarbonate in blood because the pK of carbonic acid (»3.8) is much lower than the pH of blood:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^- \quad \textbf{(1)}$$

This process involves two steps. The first step is the hydration of CO_2 to carbonic acid, and the second step is the ionization of carbonic acid to bicarbonate. Bicarbonate ion can further dissociate into hydrogen and carbonate ions; however, little carbonate is formed in the body, because the pK of this reaction is greater than 10.0. CO_2 is hydrated to H_2CO_3 inside erythrocytes at a very slow rate. This reaction when catalyzed by carbonic anhydrase in the erythrocyte, however, occurs so quickly that the process is completed during the passage of the red cell through the peripheral capillaries. The reverse reaction, the dehydration of H_2CO_3 to CO_2, occurs during pulmonary excretion of CO_2 and similarly requires enzymatic catalysis. Carbonic anhydrase is present within the erythrocyte in high concentrations but is virtually absent from plasma. Carbonic anhydrase also is found in the capillary endothelium of the lung and other organs, but the quantity of enzyme there is small.

Human erythrocytes contain two isoforms of carbonic anhydrase. Carbonic anhydrase I is a low-activity enzyme that is inhibited by anions such as chloride. This isoform probably does not catalyze reactions of CO_2 in vivo. The other isoform, carbonic anhydrase II, has high catalytic activity and is resistant to anion inhibition. Human carbonic anhydrase II is comprised of 259 amino acids and has modest homology with carbonic anhydrase I. All isoforms of carbonic anhydrase contain a zinc atom that is essential for enzymatic activity. Activity is lost with binding of an unsubstituted—SO_2 NH_2 group of aromatic sulfonamides to the zinc ion. Acetazolamide is the most widely known of these inhibitors.

CO_2 and hydrogen ions reversibly bind to uncharged amino groups of proteins as described for hemoglobin:

$$R—NH_2 + H^+ \rightarrow R—NH_3^+$$

$$R—NH_2 + CO_2 \rightarrow R—NHCOOH$$

where R represents the protein moiety and R—NHCOOH is the carbamic acid. Under physiologic conditions, carbamic acids release protons and form carbamate ions, $R—NHCOO^-$. Because both molecular CO_2 and protons compete for uncharged amino groups, carbamate formation is pH-dependent and increases with alkalinity. Transport of CO_2 as carbamates is also influenced by PCO_2 and by the pK of the amino groups on the protein. The pK values of a-amino groups of the N-termini of blood proteins lie within the physiologic range of pH. Therefore, these frequently exist in the uncharged $R—NH_2$ form and are available to bind CO_2. In contrast, e-amino groups, which are located throughout the protein chains, have a pK well above the physiologic pH range. This means that most e-amino groups are bound to hydrogen ions and cannot bind CO_2. The concentration of carbamates in plasma is approximately 0.6 mM, and binding of CO_2 to a-amino groups accounts for 60% of this quantity. Plasma carbamates, however, do not participate in CO_2 exchange, because the steep slope of the CO_2 dissociation curve minimizes changes in pH and PCO_2 between arterial and venous blood. This effect in turn minimizes changes in plasma carbamate concentration in the lung and systemic capillaries.

Under physiologic conditions, binding of CO_2 to a-amino groups of hemoglobin is an important factor in CO_2 exchange. The total concentration of hemoglobin-carbamates in blood is relatively low, but as pointed out earlier, deoxyhemoglobin binds more CO_2 as carbamate than does oxyhemoglobin. The difference in bound CO_2 between the deoxygenated and oxygenated hemoglobin, or “oxylabile carbamate,” has a role in CO_2 exchange. When O_2 is released by hemoglobin in the tissues, it is accompanied by increased binding of CO_2 to a-amino groups. Conversely, oxygenation of hemoglobin in the lung promotes release of CO_2 bound as carbamate. The presence of 2,3-DPG decreases the total CO_2 content, and binding of oxylabile carbamate to hemoglobin relates inversely to 2,3-DPG concentration. The interaction between 2,3-DPG and CO_2 binding involves inhibition of carbamate formation when 2,3-DPG is bound to the N-terminal amino groups of the b chains of hemoglobin. Because the a chains of hemoglobin do not bind 2,3-DPG, organic phosphates do not affect carbamate formation in these subunits of the molecule. Carbamate binding measurements indicate that both the a and b chains of hemoglobin participate equally in oxylabile carbamate formation at physiologic PCO_2 in the presence of 2,3-DPG. This effect of organic phosphates on oxylabile carbamate formation decreases the role of this pathway in CO_2 exchange. The oxylabile carbamate accounts for perhaps 10% of total CO_2 exchange.

The CO_2 content of deoxygenated blood is greater than that of oxygenated blood at any PCO_2. This feature of CO_2 transport is referred to as the *Haldane effect.* The CO_2 dissociation curve of blood is nonlinear, but when plotted on logarithmic axes it becomes linear (Fig. 20). The slope of the line depends on the hemoglobin concentration of blood. The logarithmic expression of the CO_2 dissociation curve also permits definition of the curve by measuring a single experimental point and the hemoglobin concentration. The most important physiologic value is the slope of the CO_2 dissociation curve, as this determines the efficiency of CO_2 exchange. The slope of the CO_2 dissociation curve is essentially constant at a constant hemoglobin concentration. Thus, calculations of arterial-venous content differences and other parameters of gas exchange from CO_2 dissociation curves are correct as long as the appropriate slope and hemoglobin concentration are used.

Two thirds of the total CO_2 contained in whole blood is distributed in the plasma, and one third in erythrocytes at equilibration. The CO_2 in circulating blood is increased by the large internal buffering capacity of erythrocytes, the presence of cellular carbonic anhydrase, and the exchange of bicarbonate and chloride ions across the erythrocyte membrane. Similarly, two thirds of the bicarbonate in blood is distributed in the plasma and one third in the erythrocytes. The plasma volume is about 55% and the erythrocyte volume about 45% of whole blood, and bicarbonate ion is transported primarily in the aqueous phase. Plasma also has a greater fraction of water than do the erythrocytes, owing to the high concentration of hemoglobin inside the red cells. The Donnan effect, a consequence of charge restriction by negatively charged hemoglobin molecules inside the erythrocyte, also leads to a lower intracellular concentration of diffusible anions, such as bicarbonate.

Despite the lower bicarbonate content of erythrocytes, they are essential for almost all bicarbonate transport. CO_2 entering the blood from the tissues diffuses into the erythrocytes, where the large buffering capacity favors bicarbonate formation. Formation of bicarbonate from CO_2 is catalyzed rapidly by carbonic anhydrase within the erythrocytes, and CO_2 in minimal amounts remains hydrated as carbonic acid during the short period of capillary transit. The erythrocyte membrane facilitates the rapid exchange of intracellular bicarbonate ions for extracellular chloride ions, thereby shuttling bicarbonate ions produced within the erythrocyte into the plasma. Coupling of bicarbonate and chloride in the exchange process is accomplished via a transport protein, so that transmembrane potential is not altered and electrical potentials are not established that would prevent bicarbonate from moving out of the erythrocyte. This facilitated transport permits rapid exchange of bicarbonate across the cell membrane during the short period of capillary transit. Thus, even though the majority of bicarbonate is carried within the plasma, it is almost exclusively formed within the red cells. The entire process is reversed in the lungs as bicarbonate is converted to molecular CO_2, which is able to cross the alveolar-capillary membrane.

The facilitated exchange of bicarbonate and chloride across the erythrocyte membrane is mediated by an anion exchange protein (AE1, formerly band 3 protein). There are approximately 10^6 molecules of AE1 in each erythrocyte membrane. A variety of anions are transported by this carrier transmembrane, but bicarbonate and chloride ions exhibit the fastest rates of exchange. The actual mechanism of the exchange is characterized by 1:1 bidirectional anion flux associated with a conformational change in the protein structure.

The influence of O_2 on the CO_2 dissociation curve, the Haldane effect, has received less attention than the converse relationship, the effect of CO_2 on the O_2 dissociation curve of blood, the Bohr effect. The Bohr effect is responsible for only 2% of total O_2 exchange in the tissues, whereas the Haldane effect accounts for nearly half of resting CO_2 exchange. Oxygen-dependent exchange of CO_2 occurs via both the carbamate and bicarbonate pathways and is a function of pH, PCO_2, and the concentration of 2,3-DPG. With normal 2,3-DPG concentrations, the Haldane effect increases with increasing pH, reaching its maximal value under normal acid-base conditions. The importance of the carbamates in this process increases as the pH increases, because carbamate formation is promoted by the lack of protons and by less 2,3-DPG binding at higher pH. The contribution of the bicarbonate pathway to CO_2 transport peaks in the physiologic range of pH, but it decreases at higher pH as a result of increasing prominence of carbamates. When protons are released from deoxyhemoglobin on O_2 binding, some are consumed by the carbamate reaction, thereby leaving fewer protons to combine with bicarbonate ion to form CO_2. CO_2 exchange would occur without a functioning Haldane effect despite the fact that half of CO_2 excretion normally occurs by this mechanism. The cost of such a loss would be greater changes in arterial-venous CO_2 content,

increased tissue hypercarbia, and altered acid-base status.

ACID-BASE PHYSIOLOGY

A discussion of respiratory acid-base problems requires a basic understanding of the chemical behavior of acids and bases in aqueous solution. Chemical reactions proceed at a velocity that is proportional to the active concentrations, or "activities," of the reactants. In a reaction that may proceed in either direction, the Law of Mass Action may be written as follows:

$$[A] + [B] \rightleftharpoons [C] + [D]$$

Rate constants of the reactions in both the forward (k_1, [A] + [B] ® [C] + [D]) and reverse (k_2, [C] + [D] ® [A] + [B]) directions determine the concentrations of reactants until chemical equilibrium is reached, when

$$k_1/k_2 = [C][D]/[A][B]$$

The term k_1/k_2 is the equilibrium constant, K_e. For an acid in solution, the equilibrium constant is known as the dissociation constant:

$$K_a = [H^+][A^-]/[HA]$$

K_a determines the concentration of hydrogen ion, $[H^+]$. If the acid is "strong," K_a is large and $[H^+]$ and $[A^-]$ are much higher than [HA].

In 1909, L. J. Henderson used the Law of Mass Action to express the hydrogen ion equilibrium for carbonic acid:

$$[H^+] = K \times [CO_2]/[HCO_3^-]$$

Using the convention in which $[H^+]$ is expressed as pH, in which p is the negative power of 10, Hasselbalch rearranged Henderson's equation and applied it to the carbonic acid buffer system to obtain the following:

$$pH = pK + \log([HCO_3^-]/[CO_2])$$

When methods for the measurement of PCO_2 became available, $[CO_2]$ was replaced by PCO_2 and the equation written as follows:

$$[H^+] = 24\ PCO_2/[HCO_3^-]$$

where $[H^+]$ is in nEq/L, PCO_2 is in mmHg, and $[HCO^-_3]$ is in mEq/L. The familiar form of the Henderson-Hasselbalch equation is obtained by substituting 6.1, the pK_a of the system, and 0.0301, the solubility constant for CO_2 in plasma, into the equation:

$$pH = 6.1 + \log([HCO_3^-]/0.0301\ PCO_2)$$

As the PCO_2 of arterial plasma is regulated by alveolar ventilation, it is used to indicate the respiratory component of the acid-base state. The $[HCO^-_3]$ is an estimate of the nonrespiratory, or "metabolic," contribution to $[H^+]$. Although the Henderson-Hasselbalch equation accurately describes the equilibrium relationships between these variables, it does not describe how acid-base balance is regulated. The regulation of acid-base balance could be described by the Henderson-Hasselbalch equation only if both PCO_2 and $[HCO^-_3$ acted independently without influencing each other significantly or being affected by the other systems involved in acid-base control. This assumption is not valid, because the bicarbonate buffer system is influenced by the independent and direct effect of PCO_2 on $[HCO^-_3]$. Hence, changes in $[HCO^-_3]$ do not indicate "metabolic" changes alone. This difficulty was addressed by titration studies of plasma to produce the Siggaard-Andersen nomogram, along with normalizing the PCO_2 to 40 mmHg. This approach produced the concept of "base excess," the excess $[HCO^-_3]$ in arterial plasma that accounts for changes in ventilation. The concept of the base excess, however, did not hold when applied to whole blood or to plasma changes in which the acid-base adjustments were made *in vivo.* This issue required standardizing in vitro data to whole blood having a constant hemoglobin concentration.

The contribution of strong electrolytes to $[H^+]$ in the blood is another problem that has been approached conventionally by analyzing the difference between the concentrations of anions and cations. In plasma, cations predominate and exert a basic, or alkalizing, effect. The effect of strong ions other than Na^+, K^+, and Cl^- is expressed as the "anion gap," the anion concentration that cannot be explained by the inorganic anions and bicarbonate ($[Na^+] + [K^+]$) – ($[Cl^-] + [HCO^-_3]$). An excessive anion gap represents unmeasured anions, such as lactate or ketones. The working principle of the strong ion difference ([SID]) is similar to that of the anion gap, but it has the advantage of functioning as an independent variable in acid-base regulation.

The Physicochemical Approach to Acid-Base Interpretation

Acid-base problems are best approached by identifying and assessing changes in the buffer systems that contribute to changes in $[H^+]$. The recognition of both independent variables (those not altered by changes outside the system) and dependent variables (those influenced by the independent variables and by changes in other systems) can be described in a series of equations in which the independent variables are specified. This physicochemical approach identifies the dependent and independent variables that determine the acid-base status of plasma, cells, and body fluids.

Because body fluids are dilute aqueous solutions, the chemical behavior of water underlies all acid-base physiology. There is a small dissociation in pure water expressed in the following reaction:

$$2H_2O \rightleftharpoons H_3O^+ + OH^-$$

The extent of the dissociation defined by the Law of Mass Action is as follows:

$$K_W = [H^+][OH^-]/[H_2O]$$

In this equation, $[H_2O]$ in pure water is 55 mol/L, and because $[H^+]$ and $[OH^-]$ are 10^{-7} Eq/L or less, the $[H_2O]$ is effectively a large constant, and

$$K'_W = [H^+][OH^-]$$

where K'_W, the ion product for water, is $K_W \times [H_2O]$. In pure water, H^+ and OH^- are the only ions and are equal in concentration (neutral pH). At 25°C, K'_W has a value of 1.008×10^{-14} Eq_2-L^{-2}. This value is usually rounded off to 1.0×10^{-14}; thus,

$$K'_W = [H^+][OH^-] = 10^{-14}$$

and

$$[H^+] = [OH^-] = 10^{-7}$$

Neutral $[H^+]$ is 10^{-7} (pH = 7.0) at 25°C. At body temperature (37°C), however, neutral $[H^+]$ is not be 10^{-7} Eq/L because

$$K'_w = 4.4 \times 10^{-14}$$

and

$$[H^+] = (4.4 \times 10^{-14})/[OH^-] \text{ Eq/L} \quad \textbf{(1)}$$

Thus, neutral $[H^+]$ is the square root of 4.4×10^{-14}, or 2.1×10^{-7} (pH = 6.68).

In aqueous solutions, strong electrolytes are dissociated completely, and they are defined as having K values that are greater than 10^{-4} (strong acids) or less than 10^{-12} (strong bases). In blood and body fluids, K can be ignored for strong electrolytes because they are dissociated; that is, strong acids (HA) exist only as H^+ and A^-, and strong bases (BOH) exist only as B^+ and OH^-. In physiologic fluids, the main strong electrolytes are Na^+, K^+ and Cl^-. These strong ions influence $[H^+]$ by the Law of Electrical Neutrality and the dissociation of water. This means that in any system at equilibrium the net charge must be zero; thus, in a solution of Na^+, K^+, and Cl^- in water,

$$[Na^+] + [K^+] + [H^+] - [Cl^-] - [OH^-] = 0$$

The effect of strong ions may be lumped into a single term that expresses the net negative or positive charge that they exert. This is the “strong ion difference” ([SID]), which in plasma is normally $[Na^+] + [K^+] – [Cl^-]$. Strong organic ions, such as lactate or ketones, also contribute to [SID], as they may be present in high concentrations. Other strong inorganic ions are usually ignored, as they are present in low concentrations. Therefore,

$$[SID] + [H^+] - [OH^-] = 0$$

where the independent variable is the [SID] and the dependent variables are $[H^+]$ and $[OH^-]$. In normal plasma, $[Na^+]$ is 140 mEq/L, $[K^+]$ is 4 mEq/L, and $[Cl^-]$ is 104 mEq/L. Thus, the normal [SID] is approximately 40 mEq/L. Without bicarbonate or other basic electrolytes in plasma, $[OH^-]$ would have to be close to 40 mEq/L (4×10^{-2} Eq/liter). If true, then

$$[H^+] = 4.4 \times 10^{-14}/4 \times 10^{-2} \text{ Eq/L}$$
$$= 1.1 \times 10^{-12} \text{ Eq/L}$$

or a pH of nearly 12. This calculation shows how important strong ions, weak acids, and the HCO^-_3 buffer system are for the control of $[H^+]$ in body fluids. With these systems in plasma, the $[H^+]$ is 4×10^{-8} (pH = 7.4).

Total weak acids (A_{tot}) are the buffers present in a partially dissociated state in the physiologic pH range. These acids have dissociation constant (K_a) values between 10^{-4} and 10^{-12}; however, only weak acids with a K_a close to pH 7.4 are effective buffers. Buffer systems include plasma proteins ($K_a = 3 \times 10^{-7}$), proteins and phosphates in cells ($K_a = 5.5 \times 10^{-7}$), and hemoglobin in red cells. The K_a of the imidazole group of the histidine residues in proteins is virtually identical to the neutral $[H^+]$ of water, while in hemoglobin, the imidazole groups are associated closely with the heme, and the imidazole groups become less acidic when the heme structure tenses on the release of O_2. For oxyhemoglobin, K_a is 2.5×10^{-7}, and for deoxyhemoglobin, it is 6.3×10^{-9}. For plasma proteins at 37°C:

$$[H^+] \times [A^-] = (3 \times 10^{-7}) \times [HA] \text{ Eq/L} \quad \textbf{(2)}$$

The effectiveness of weak acids as buffers depends not only on the dissociation constant, but also on total concentration ($[A_{tot}]$) of the acid. The sum of the dissociated (A^-) and undissociated (HA) forms of any weak acid remains constant:

$$[HA] + [A^-] = [A_{tot}] \text{ Eq/L} \quad \textbf{(3)}$$

where $[A_{tot}]$ is an independent variable and [HA] and $[A^-]$ are dependent variables. In plasma, $[A_{tot}]$ represents the ionic equivalent of the plasma proteins and may be estimated by multiplying the protein content by 0.24. Thus, at a normal total protein levels of 70 g/L, $[A_{tot}]$ is 17 mEq/L. This value is comprised of $[A^-]$ of 15 mEq/L and [HA] of 2 mEq/L at pH 7.4. Hence, even though plasma proteins behave as weak acids, they are mostly dissociated (15/17) at normal arterial pH.

Carbon Dioxide and the Bicarbonate Buffer System

The CO_2 buffer system acts mainly through variations in total CO_2 content brought about by variations in PCO_2 and $[H^+]$. As indicated earlier, the two components of the system are hydration of CO_2 and the dissociation of carbonic acid into HCO^-_3 and H^+. These two equations can be combined and solved for $[H^+]$ to yield an equation containing two constants and $[H_2O]$. These constants may all be incorporated into a single overall ionization constant (K'_a) to obtain:

$$[H^+] = K'_a[CO_2]/[HCO^-_3]$$

where $[CO_2]$ is the concentration of dissolved CO_2 and is related to the PCO_2 by the solubility constant for CO_2 (3.01×10^{-5} Eq/L/mmHg). Substituting the solubility constant into the equation:

$$[H^+] = K'_a (3.01 \times 10^{-5} PCO_2)/[HCO^-_3] \text{ Eq/L}$$

For K'_a of 7.94×10^{-7} the single constant can be used:

$$K_c = (7.94 \times 10^{-7}) \times (3.01 \times 10^{-5})$$
$$= 2.4 \times 10^{-11}$$

Thus,

$$[H^+] = (2.4 \times 10^{-11}) \times PCO_2/[HCO^-_3] \text{ Eq/L} \quad \textbf{(4)}$$

For PCO_2 expressed in torr and $[HCO^-_3]$ in mEq/L,

$$[H^+] = 24 \times PCO_2/[HCO^-_3] \text{ nEq/L}$$

This is Henderson's equation. PCO_2 is the independent variable of the CO_2 system, whereas $[H^+]$ and $[HCO^-_3]$ are both dependent variables. Using the pK_a of the bicarbonate system in the expression yields the Henderson-Hasselbalch equation. At a normal $PaCO_2$ of 40 mmHg, if $[H^+]$ is 40 mEq/L, then $[HCO^-_3]$ is 24 mEq/L.

The hydration of CO_2 to carbonic acid in aqueous solution is a slow process, but as noted earlier, it is accelerated greatly by carbonic anhydrase. Carbonic acid

dissociates into H^+ and bicarbonate, and bicarbonate itself dissociates into H^+ and carbonate ion. The equilibrium equation is as follows:

$$[H^+] = (6 \times 10^{-11})[HCO_3^-]/[CO_3^{2-}] \text{ Eq/L} \quad \textbf{(5)}$$

where 6×10^{-11} is the K_a for the reaction. All three variables in this equation depend on changes in the CO_2 and other systems.

The interactions between the different buffer systems in the body must satisfy the Law of Electrical Neutrality when the systems are in equilibrium. Hence, all the charges of ions in the systems must be summed, including $[H^+]$ and $[OH^-]$ for water, the net positive charge of [SID] for strong electrolytes, $[A^-]$ for weak electrolytes, and CO_2, $[HCO^-_3]$, and $[CO^{2-}_3]$. Thus,

$$[SID] + [H^+] - [HCO_3^-] - [CO_3^{2-}] - [A^-] - [OH^-] = 0 \quad \textbf{(6)}$$

The $[H^+]$ and $[OH^-]$ in plasma cannot be computed from this equation because the [SID], $[HCO^-_3]$, and $[A^-]$ are orders of magnitude greater than $[H^+]$ and $[OH^-]$ in body fluids. The equation must be satisfied, however, to quantify the effects of the variables governing electrolyte physiology. The calculated $[H^+]$ and $[OH^-]$ also have to satisfy each equation in which they appear as dependent variables. Because the relationships between the variables are complicated, the six numbered equations (Eq. 1,Eq. 2,Eq. 3,Eq. 4,Eq. 5 and Eq. 6) must be solved simultaneously to account fully for all the interactions. The three independent variables only appear once in the series: $[A_{tot}]$ (Eq. 3), PCO_2 (Eq. 4), and [SID] (Eq. 6). The dependent variables appear in more than one equation: $[H^+]$, $[OH^-]$, $[HCO^-_3]$, $[CO^{2-}_3]$, and $[A^-]$.

The equations can be solved simultaneously for any values of [SID], $[A_{tot}]$, and PCO_2 in plasma, or by changing parameters to fit the acid-base status of any other body fluid or any other conditions. Also, the equations may be combined into a single fourth-order polynomial from which $[H^+]$ can be computed. This computation has no practical role in the assessment of the acid-base status of plasma, in which pH can be measured directly, but the measured $[H^+]$ and calculated $[H^+]$ generally agree because the acid-base systems have been defined rigorously in terms of their dependent and independent components. This enables identification of the mechanisms that lead to changes in $[H^+]$ in plasma, cells, and interstitial fluid. Calculations of “base excess” and the “anion gap” are replaced by the variables [SID] and $[A^-]$. This approach also clarifies some fuzzy concepts, including the use of the Henderson-Hasselbalch equation to imply that $[H^+]$ is controlled by changes in $[HCO^-_3]$, the concept of protons being produced or eliminated, and concepts implying that $[HCO^-_3]$ may be produced, removed, or retained (by the kidneys), or administered as a useful therapy.

The use of graphs or solutions of the equations to obtain the variables that satisfy the measured arterial $[H^+]$ and PCO_2 are useful clinically. Also, plasma electrolyte measurements yield a measured inorganic [SID] ($[Na^+] + [K^+] – [Cl^-]$) that may be compared with the value of [SID] that satisfies $[H^+]$ and PCO_2 for possible effects of other strong ions. A difference between the inorganic [SID] and total [SID] indicates the presence of unmeasured ions, such as lactate or ketoacids. This exercise is similar to the calculation of the anion gap, except that $[A^-]$ is a variable rather than a constant. Because $[H^+]$, $[OH^-]$, and $[CO^{2-}_3]$ are in micromolar concentrations or less, Eq. 6 may be simplified as follows:

$$[SID] - [HCO_3^-] - [A^-] = 0$$

This simplification makes it possible to evaluate the effects of the three independent variables ([SID], PCO_2, and protein) and to determine whether unmeasured strong anions are contributing to the acid-basis status.

Variations in the relative magnitude of the independent variables involved in control of acid-base status produce differing effects in different fluid compartments and different tissues (Fig. 21). In intracellular fluid, [SID] is large and dominated by a high $[K^+]$. Large protein and phosphate concentrations (A_{tot}) also minimize the effects of reductions in [SID] resulting from falls in $[K^+]$ or accumulation of strong organic ions such as lactate. In tissues, PCO_2 is high and increased by metabolism, but $[HCO^-_3]$ is low. Changes in PCO_2 in tissue influence $[H^+]$ much less than in plasma. Control of intracellular $[H^+]$ is achieved through buffering by A_{tot} and exchange of strong ions with extracellular fluid, thereby changing the [SID], and by diffusion of CO_2 out of the cell. In interstitial fluid and other ultrafiltrates of plasma, such as lymph or cerebrospinal fluid, $[H^+]$ is influenced only by changes in [SID] and PCO_2, because protein is virtually absent and there is no role for the weak acid system. In plasma, the [SID] also tends to regulate the pH, but variations in PCO_2 may bring about large and rapid changes in arterial $[H^+]$.

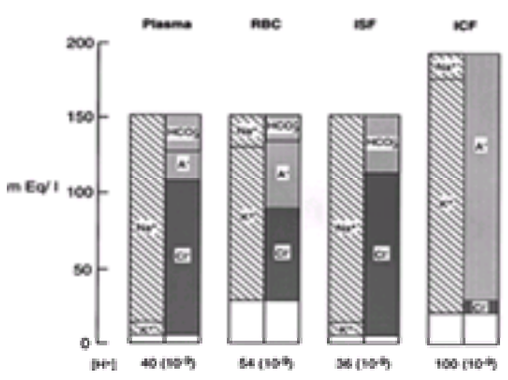

FIG. 21. Diagrams of ionic status of various body fluid compartments: *RBC,* red blood cell; *ISF,* interstitial fluid, *ICF,* intracellular fluid. Electrical neutrality is shown by equal heights of the two panels in each plot. The strong ion difference [SID] is occupied by the $[A^-]$ and $[HCO^-_3]$. The $[H^+]$ is shown beneath each plot.

Inside erythrocytes, all three systems have similar values, because [SID] and $[A_{tot}]$ are high and PCO_2 is in equilibrium with the PCO_2 of the surrounding plasma. The situation is also complicated because the state of oxygenation influences the dissociation constant. These considerations emphasize the importance to acid-base balance of fluid, strong ion, and CO_2 shifts between the different body compartments, because the molecules making up A_{tot} (e.g., proteins) do not move readily.

Intracellular pH and the Alphastat Hypothesis

For many years, partly because of the difficulty in studying pH changes within tissues, acid-base physiology has dealt primarily with the status of the blood. Marked changes in biochemical and physiologic function, however, accompany alkalosis and acidosis in the systemic organs. For example, alkalosis stimulates glycolysis, whereas increases in $[H^+]$ impair membrane function, blunt hormonal responses, and inhibit enzyme activity. Such effects appeal to the concept of control of the intracellular $[H^+]$; however, good evidence in living systems suggests that regulatory mechanisms are attempting to keep a constant state of protein ionization. This concept is based on the parallel effects of temperature on tissue pH and on the pK of the imidazole group of histidine in proteins, which is very close to neutral pH. This principle was first pointed out by Rahn et al., who suggested that regulation protected the fractional dissociation of the cellular imidazole—NH groups. They termed the fractional dissociation *alpha,* and they called the control mechanism the *alphastat.* The close involvement of imidazole groups in enzyme regulation, receptor function, and the operation of membrane pores and ion exchangers explains many physiologic effects of acid-base perturbations previously explained by changes in $[H^+]$.

In clinical circumstances, intracellular acid-base measurements are not usually available; however, intracellular $[H^+]$ is important because of its influence on cellular metabolic processes. Large variations clearly exist in pH in different tissues in different clinical situations. Experimental studies in animals and humans have attempted to establish the magnitude of intracellular fluid (ICF) changes relative to those of extracellular fluid (ECF). Studies in which arterial PCO_2 has been raised or lowered have shown that ICF $[H^+]$ is well defended in a range of arterial PCO_2 between 40 and 80 mmHg. This can be explained in terms of the differences in [SID] and $[A_{tot}]$ between ICF and ECF. Studies of metabolic acidosis and alkalosis have similarly shown good control of $[H^+]$ in ICF, but the defense against alkalosis appears to be less effective than that against acidosis. The reasons for this difference probably lie in the different extent to which ECF changes in [SID] are capable of influencing the

[SID] in the ICF.

Erythrocytes and Acid-Base Control

Erythrocytes buffer sudden changes in ions or PCO_2 and help maintain relatively constant conditions in plasma and thus in the ECF. The ICF composition of the erythrocyte lies between that of ICF and plasma. The $[K^+]$ is not as high as in ICF, but $[Na^+]$ and $[Cl^-]$ are higher, although still well below plasma values. The erythrocyte [SID] is 60 mEq/L, compared with 130 mEq/L in ICF. Hemoglobin also provides an $[A_{tot}]$ of 60 mEq/L, which compares with 20 mEq/L in plasma and 200 mEq/L in ICF. The R and T forms of hemoglobin also provide a variable K_a, which enables deoxyhemoglobin to buffer venous acidity more effectively. The carbonic anhydrase in the erythrocyte enables the hydration of CO_2 to proceed rapidly, and carbonate formation enhances CO_2 content without a comparable increase in $[H^+]$. Cell membrane transport systems also facilitate ion exchange between the plasma and erythrocyte while controlling erythrocyte volume.

When O_2 dissociates from hemoglobin, $[H^+]$ inside the erythrocyte tends to decrease. As CO_2 enters the erythrocyte, this decrease in $[H^+]$ is offset by the ionization of carbonic acid. Bicarbonate moves out of the cell, and Cl^- moves into the cell. This tends to increase plasma [SID] and leads to a rise in plasma $[HCO^-_3]$. At the same time, CO_2 forms carbamates very rapidly. This reaction is facilitated by deoxygenation, which allows the a-amino groups of the b chain of deoxyhemoglobin to form carbamates. In addition to these reactions associated with the deoxygenation of hemoglobin and CO_2 content of venous blood, the erythrocyte can modulate rapid changes in plasma ion concentration.

Ventilation and Acid-Base Control

The PCO_2 in arterial plasma is controlled mainly by changes in ventilation, as shown in the alveolar ventilation equation, which expresses the simple inverse relationship between $PaCO_2$ and $\dot{V}_A$. The equation is useful because neither metabolic rate nor ventilation needs to be measured to assess the adequacy of breathing in relation to metabolic demand. Arterial PCO_2 represents the balance between metabolic CO_2 production and ventilation. In tissues and venous blood, PCO_2 is regulated primarily by the balance between metabolism and blood flow. The extent to which arterial PCO_2 reflects the adequacy of ventilation also depends on the activity of carbonic anhydrase in allowing rapid equilibration of PCO_2 between pulmonary capillary blood and alveolar gas. Thus, it is affected by carbonic anhydrase inhibition.

The alveolar ventilation equation expresses the combined effects of changes in $\dot{V}_A$ and $\dot{V}CO_2$ on $PaCO_2$. In patients with severely impaired ventilatory capacity, respiratory failure may be worsened by changes in $\dot{V}CO_2$. In patients with an increase in PCO_2, several factors may contribute to underventilation, including inefficient gas exchange leading to dead space ventilation ($\dot{V}_D$), increased work of breathing, impaired respiratory muscle strength and endurance, and disorders of respiratory control. The ventilatory responses to acid-base disorders of nonrespiratory origin are extremely important for regulating $[H^+]$, because they may change rapidly. In long-term responses to acid-base disturbances, the response of the central medullary chemoreceptors is the most important factor in the ventilatory set point. The major effector is the $[H^+]$ in cerebrospinal fluid, and because cerebrospinal fluid is protein-free, the PCO_2 and [SID] are the two important independent variables in central control of ventilation.

The Kidneys and Acid-Base Control

The kidneys influence acid-base status mainly by changing the [SID] of the plasma. In the glomerulus, Na^+ reabsorption from plasma ultrafiltrate in the tubules is an active process that lowers both $[Na^+]$ and osmolality in the tubules, leading to water reabsorption. This process in the distal tubule is under the control of antidiuretic hormone. Chloride reabsorption is mediated in part electrically and in part by an active process related to ATPase-driven membrane pumps on renal tubular cells. If Cl^- is reabsorbed less rapidly than Na^+, urinary $[Cl^-]$ increases relative to $[Na^+]$ and urinary [SID] falls and increases urinary $[H^+]$. If Na^+ is less rapidly reabsorbed than Cl^-, the opposite occurs. In the tubular lumen, a fall in [SID] and an increase in $[H^+]$ tend to increase PCO_2. The increase in PCO_2 occurs because the tubule is partly closed to the circulation and the removal of CO_2 by the renal capillary blood flow may not keep pace with its production. The $[HCO^-_3]$ tends to fall with the increase in $[Cl^-]$, and when urinary pH has fallen to <6, urinary $[HCO^-_3]$ is very low. In this way, the excretion of Cl^- in excess of Na^+ and K^+ contributes to control of plasma [SID] and $[H^+]$.

When $[H^+]$ has increased because of accumulation of organic anions such as lactate, the renal tubular cells can excrete the lactate, Cl^-, or both. Because the reabsorption of strong organic anions is less efficient, Cl^- is reabsorbed in preference to lactate, resulting in a very high urinary $[La^-]$ and low $[Cl^-]$. In this situation, the kidney prevents urinary pH from becoming too low by excreting more water and Na^+, if they are available, and by excreting ammonia and phosphates. This allows reabsorption of Na^+ or excretion of Cl^- without an increase in urinary $[H^+]$. Both effects tend to increase plasma [SID] and decrease plasma $[H^+]$. As ammonia and phosphate excretion have limited capacities, adequate Na^+ and water delivery to the distal tubule in an organic acidosis is very important. The kidneys normally are able to adjust to ranges of water excretion between 0.5 and 25 L/d and to ranges of Na^+ excretion between 0.05 and 25 g/d.

Disorders of Acid-Base Physiology

The primary acid-base disorders may be thought about in terms of abnormalities in the three acid-base variables capable of independent action: the [SID], $[A_{tot}]$, and PCO_2 in arterial blood. Primary acid-base changes are modified by “compensatory” changes that, to be effective, have to involve independent variables—for example, changes in ventilation leading to changes in PCO_2, or movement of strong ions into cells or urine to modify [SID].

Primary Metabolic Acidosis and Alkalosis

Processes that reduce [SID] (e.g., an increase in $[Cl^-]$) tend to increase $[H^+]$, leading to a primary metabolic acidosis (Table 4). A number of compensatory responses take place to minimize this effect. Reductions in [SID] may be offset by responses to increase [SID]; for example, in diabetic acidosis, dehydration may increase $[Na^+]$, and more Cl^- excretion in urine may help to reduce plasma $[Cl^-]$. These two changes help compensate for the effects of the increase in plasma ketoacid concentration. In disease states (e.g., uremic acidosis), these adaptive responses may not be available. Measurement of urinary electrolyte excretion may be helpful in assessing the role of the kidneys in an acidosis. A tendency for $[H^+]$ to increase also leads to an association of weak acids (plasma proteins, A_{tot}) and thus to a reduction in $[A^-]$, which may amount to 3 to 4 mEq/L (slightly more in very severe acidosis). Increases in $[H^+]$ also stimulate ventilation, leading to a decrease in $PaCO_2$. The effectiveness of this response depends on the ventilatory capacity, the efficiency of pulmonary gas exchange, and ventilatory control mechanisms. If none of these physiologic mechanisms is impaired, the increase in $[H^+]$ expected for a given reduction in [SID] may be used to identify the adequacy of the responses.

TABLE 4. *Causes of primary metabolicacidosis and alkalosis*

An increase in [SID] (e.g., a decrease in $[Cl^-]$) tends to reduce $[H^+]$, producing a metabolic alkalosis. The causes of primary metabolic alkalosis are given in Table 4. The compensatory responses to an increase in [SID] may be considered in terms similar to those seen in low [SID] states. These are retention of Cl^- by the kidneys in patients with normal renal function, and sometimes movement of Na^+ into ICF. Although $[H^+]$ may be defended by dissociation of weak acids with an increase in $[A^-]$,

this effect usually amounts to 1 mEq/L or less. Decreases in plasma [H^+] are usually accompanied by a reduction in ventilatory responsiveness, and $PaCO_2$ rises by about 1.0 mmHg for each increase in [SID] of 10 mEq/L. In some cases of metabolic alkalosis, severe loss of K^+ may accompany Cl^- in the kidneys, leading to depletion of intracellular [K^+] and a fall in ICF [SID]—an intracellular acidosis complicating the extracellular alkalosis. This effect may lead to respiratory muscle weakness.

Plasma Proteins and Total Weak Acid Concentration

Normally, the weak acid concentration [A_{tot}] is determined by the plasma protein concentration alone. The [A_{tot}] may increase if plasma proteins or other weak acids (such as phosphate) increase. Increases of more than 2 or 3 mEq/L in [A_{tot}] are uncommon, but because they act as weak acids, the effect of increasing [A_{tot}] is similar to a reduction in [SID]—a metabolic acidosis. The effects of increases in plasma proteins, as in multiple myeloma, vary depending on the isoelectric points of the class of globulin involved. Most globulins have isoelectric points similar to that of albumin, a pK of around 6.5, and thus act as weak acids. The IgG class has an isoelectric point that is close to pH 9.0.

When plasma protein concentration is reduced, the [A_{tot}] is reduced, leading to a fall in [A^-]. The effects are similar to increases in [SID] of equimolar size—a metabolic alkalosis. Quantitatively, the effect may be assessed by multiplying the total protein concentration in grams per liter by 0.24 [A_{tot}] and by taking 0.9 of this value as [A^-], as A_{tot} is about 90% dissociated in most situations. This value may then be added to [Cl^-] and [HCO^-_3] to identify the presence of any unmeasured anions. The major exception is an increase in IgG paraproteins in myeloma; these act as weak bases because of the basic amino acids lysine and arginine, whose isoelectric points are close to pH 9.0. They have a weak positive charge in the physiologic pH range, and [A_{tot}] and [A^-] appear falsely low their presence.

Primary Respiratory Acidosis and Alkalosis

An elevated $PaCO_2$ indicates alveolar hypoventilation, and when it is not a response to a metabolic alkalosis, it is termed a *primary respiratory acidosis.* The common cases of alveolar hypoventilation are shown in Table 5. The potential effect of an increase in $PaCO_2$ on plasma [H^+] may be seen by moving to the right along the normal [SID] isopleth in a plot of [H^+] versus $PaCO_2$ (Fig. 22). Similarly, it may be seen that the effect of an increase in $PaCO_2$ may be minimized by an increase in [SID]. Virtually the only compensatory mechanism that is effective and well tolerated is a reduction in plasma [Cl^-]. Acutely, this occurs through a shift of Cl^- into erythrocytes; over a longer time, excretion of Cl^- in excess of Na^+ and K^+ in urine leads to a fall in plasma [Cl^-]. In general, [Cl^-] falls acutely by 1 mEq/L and in chronic states by 3 to 4 mEq/L for each increase of 10 mmHg in $PaCO_2$. These changes in [$C1^-$] are accompanied by increases in [HCO^-_3] of similar magnitude.

Causes of CO_2 retention and respiratory acidosis
With normal lungs
Anesthesia
Sedative drugs
Neuromuscular disease (e.g., poliomyelitis, myasthenia gravis, Guillain-Barré syndrome)
Obesity-hypoventilation syndrome
Brain injury
With abnormal lungs
Chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema)
Diffuse interstitial pulmonary disease (late)
Severe kyphoscoliosis
Causes of excess CO_2 elimination and respiratory alkalosis
With normal lungs
Anxiety
Fever
Drugs (e.g., salicylates)
Hypoxemia (e.g., high altitude)
Central nervous system lesions (e.g., tumors, meningitis)
Sepsis
Hormonal excess (e.g., progesterone, thyroxine)
With abnormal lungs
Pneumonia
Diffuse interstitial pulmonary disease (early)
Acute bronchial asthma
Pulmonary vascular disease
Congestive heart failure

TABLE 5. *Causes of primary respiratoryacidosis and alkalosis*

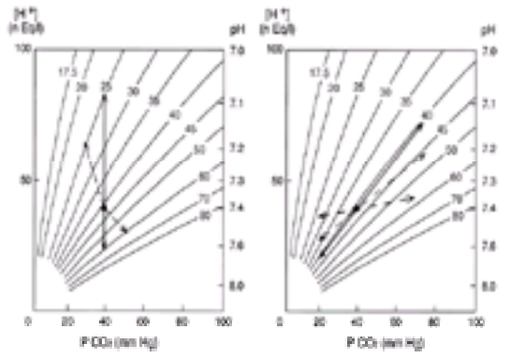

FIG. 22. Acid-base isopleths. Isopleths are for different values of [SID] in mEq/L at a normal weak acid concentration. **Left panel:** Changes in [H^+] accompanying changes in [SID] without respiratory compensation (*solid black arrow*) and with respiratory compensation (*dashed red arrow*). **Right panel:** Changes in $PaCO_2$. *Solid arrow* shows [H^+] changes with $PaCO_2$ in absence of changes in [SID]. *Dashed arrows* show changes in [SID] with acute (*red*) and chronic (*blue*) respiratory acidosis and alkalosis.

The effectiveness of increases in [SID] in limiting increases in [H^+] also may be appreciated by looking at Fig. 22. The figure may be used to assess the presence of superimposed metabolic acidosis, in which [SID] increases are less than expected for the rise in $PaCO_2$, or metabolic alkalosis, in which [SID] increases are more than expected. In recovery from ventilatory failure, resolution of the changes in [SID] is also time-dependent. If the reduction in $PaCO_2$ toward normal occurs rapidly, there is a delay in the increase in [Cl^-] (*posthypercapnic metabolic alkalosis*).

Reductions in $PaCO_2$ are caused by hyperventilation. When the reduction in $PaCO_2$ is the primary disturbance, the condition is termed *primary respiratory alkalosis.* Conditions that give rise to this situation are shown in Table 5. Reductions in $PaCO_2$ tend to reduce [HCO^-_3] in plasma, but unless a decrease occurs in [SID], this reduction is quite limited and a marked fall in [H^+] results, especially in acute hyperventilation. Reductions in [SID] minimize the fall in [H^+], and they are the result of two compensatory responses. These are retention of Cl^- through a fall in its renal excretion and a small accumulation of lactate resulting from the stimulation of glycolysis in erythrocytes and liver. Retention of Cl^- tends to characterize chronic states of hyperventilation, but increases in [La^-] may occur very rapidly. These compensatory changes are associated with increases in [H^+] toward normal and a fall in [HCO^-_3]. The usual reduction in total [SID] that results from an increase in both [Cl^-] and [La^-] accompanying an acute fall in $PaCO_2$ amounts to only 1 to 2 mEq/L for each fall of 10 mmHg in $PaCO_2$; this increases to 3 to 4 mEq/L when hyperventilation is sustained for several days. The reductions in $PaCO_2$ and [H^+] in hyperventilation are accompanied by a surprisingly large increase in [CO^{2-}_3], predisposing to hypocalcemia and tetany.

Complicated Acid-Base Disorders

Complicated acid-base disturbances are those disorders defined as either mixed (acidosis plus alkalosis) or combined (respiratory plus metabolic acidosis, or respiratory plus metabolic alkalosis). Not infrequently, complicated problems occurs in which the expected compensatory responses are inefficient or absent because of coexisting impairment of function. The most common functional impairments are the presence of renal disease or ventilatory failure. Usually, such situations have to be considered within the clinical context and need to be identified by the response to the primary disorder. For example, a patient with a metabolic acidosis resulting from poor control of diabetes may have a $PaCO_2$ that is higher than expected in response to the accumulation of ketoacids that reduces the [SID]. The poor ventilatory response may be caused by impaired ventilatory capacity resulting from air flow obstruction or respiratory muscle weakness. Poor renal function also may lead to an inappropriate compensatory response. For example, in chronic respiratory failure, the kidneys may be unable to excrete Cl^-, adding a metabolic acidosis to the

respiratory acidosis. Urinalysis, including measurement of electrolytes and pH, may be valuable in assessing these situations.

OXYGEN TRANSFER FROM BLOOD TO MITOCHONDRIA

Convective Oxygen Delivery

The net uptake of O_2 from the lungs to the body tissues is determined by the blood flow rate multiplied by the difference between the O_2 contents of arterial and venous blood ($avDO_2$). This relationship is expressed as Fick's First Principle:

$$\dot{V}O_2 = \dot{Q}_T [CaO_2 - C\bar{v}O_2]$$

where $\dot{V}O_2$ is the O_2 consumption of the body, $\dot{Q}_T$ is the cardiac output, and CaO_2 and $C\bar{v}O_2$ are the values for arterial and mixed venous O_2 content, respectively. The O_2 content (CO_2) of blood is determined as follows:

$$CO_2 = [Hb]\ (1.34)\ (SO_2) + 0.0031 \times PO_2$$

where [Hb] is hemoglobin concentration in grams per deciliter, 1.34 is the binding capacity of hemoglobin for O_2 in mL (O_2) per gram (Hb), and SaO_2 is the O_2 saturation of hemoglobin as a fraction of 1.0. The term 0.0031 PO_2 represents the dissolved O_2 per mmHg of O_2 partial pressure. At the resting metabolic rate with a cardiac output of 5 L/min (50 dL/min) and an arterial-venous difference in O_2 content of 5 mL/dL,

$$\begin{aligned}\dot{V}O_2 &= 50\ \text{dL/min} \times 5\ \text{mL}\ O_2\text{/dL} \\ &= 250\ \text{mL/min}\end{aligned}$$

The convective delivery of O_2 to the body tissues ($\dot{D}O_2$) is defined as $\dot{Q}_T \times CaO_2$. Solving the Fick equation, this is normally

$$\begin{aligned}&(50\ \text{dL/min})\ (15\ \text{g/dL})\ (1.34\ \text{mL}\ O_2\text{/dL})\ (1.0) \\ &\quad = 50 \times 20\ \text{mL}\ O_2\text{/min} \\ &\quad = 1000\ \text{mL}\ O_2\text{/min}\end{aligned}$$

At an $avDO_2$ of 5 mL/dL, approximately 250 mL O_2 is extracted by the body per minute. This results in a mixed venous hemoglobin saturation of 75% and an O_2 extraction ratio of 250 mL O_2/1000 mL O_2, or 0.25. In other words, only one fourth of the O_2 delivered to the tissues is utilized by the body at rest. During work, increased metabolic demands by the tissues for O_2 can be met by increasing $\dot{D}O_2$, the O_2 extraction ratio, or both. $\dot{D}O_2$ can be altered by changes in any of the variables in the Fick equation, including cardiac output, hemoglobin concentration, changes in O_2 binding capacity of hemoglobin, and hemoglobin O_2 saturation. In general, alterations in one of these parameters is compensated for by adjustments in one or more of the others to maintain “adequate” $\dot{D}O_2$ to the tissues. For example, anemia is compensated for by increases in cardiac output, whereas chronic hypoxia causes increases in both cardiac output and hemoglobin concentration. At extremes of exercise, the $\dot{D}O_2$ can increase as much as sixfold and the O_2 extraction ratio as much as threefold.

The distribution of cardiac output to the different tissues of the body under normal conditions is determined by the local metabolic needs. Normally, the O_2 consumption of tissues is independent of $\dot{D}O_2$ provided that more than the critical amount of O_2 is delivered. For example, the human brain receives approximately 20% of the cardiac output to support its normal O_2 requirement. Increasing $\dot{D}O_2$ to the normal brain (e.g., during hypercapnia) does not increase the metabolic consumption of O_2 by the brain. Under pathologic conditions such as hypovolemia, however, the cardiac output is redistributed by autonomic mechanisms to tissues with high obligatory needs for O_2. This response preserves the functions of the heart and brain at the expense of blood flow to skin, skeletal muscle, and splanchnic organs.

In some diseases, such as adult respiratory distress syndrome (ARDS) and sepsis, concerns have been raised about whether at a particular $\dot{D}O_2$ the body can extract O_2 adequately to meet the needs of the tissues. If not, O_2 consumption will fall if O_2 delivery falls. This situation is called *pathologic supply dependence of O_2 consumption.* It is distinguished from physiologic supply dependence, which occurs when O_2 delivery falls below the point at which normal O_2 extraction has reached its maximal limit of approximately 75% (Fig. 23). Pathologic O_2 supply dependence has been reported in a variety of clinical conditions; however, the finding is difficult to interpret under most circumstances. It is difficult to determine the clinical significance of small changes in systemic $\dot{V}O_2$ without sensitive methods for measuring the adequacy of oxidative metabolism in individual tissues. Therapeutic attempts to improve systemic O_2 consumption by increasing O_2 delivery in septic shock and ARDS have met with limited success once the circulatory blood volume has been restored adequately. The pathophysiologic mechanisms that may contribute to pathologic O_2 supply dependence are discussed later in this chapter.

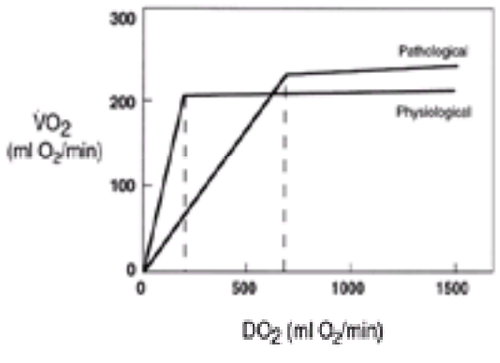

FIG. 23. Relationship between O_2 delivery and O_2 consumption for the body. Physiologic O_2 supply dependence shows a lower critical delivery than pathologic O_2 supply dependence. $\dot{D}O_2$, delivery; $\dot{V}O_2$, consumption.

In the intensive care unit, measurements of cardiac output by thermodilution, mixed venous oxygen content, and systemic O_2 consumption are made routinely using a flow-directed, balloon-tipped pulmonary arterial catheter (Swan-Ganz catheter). Alternatively, the $\dot{V}O_2$ can be measured by respiratory gas analysis. The $\dot{V}O_2$ represents the sum and venous O_2 content represents the flow-weighted average of all the tissues of the body. The measurements contain a number of potentially serious pitfalls in regard to interpretation, and misconceptions are common about the clinical utility of the information obtained from them. This is particularly true for an increase in the mixed venous O_2 saturation, which cannot be interpreted as an improvement in the hemodynamic status of a critically ill patient.

The coefficient of variation for the measurement of cardiac output by thermodilution is approximately 15%. Very few tissues of the body require 15% of the cardiac output to meet their normal O_2 requirements (the brain being a notable exception). As shown from the Fick equation, the cardiac output and $avDO_2$ can both be used to compute the systemic O_2 consumption. When pulmonary arterial catheter measurements are used to compute the $\dot{V}O_2$, then the $\dot{D}O_2$ measurement and $\dot{V}O_2$ measurement are linked mathematically, and errors in the measurement of cardiac output can produce systematic errors in $\dot{V}O_2$. This is the source of some of the

association between decreased $\dot{D}O_2$ and decreased $\dot{V}O_2$ in critically ill patients (O_2 supply dependence).

As systemic $\dot{D}O_2$ falls, mixed venous O_2 saturation also falls, because normal organ systems attempt to maintain $\dot{V}O_2$ by increasing O_2 extraction. If the organ system fails to extract O_2, systemic measurements show a fall only in the systemic $\dot{V}O_2$. If the $\dot{V}O_2$ of the organ system is low (e.g., for the kidney), then the change in systemic $\dot{V}O_2$ will be within the measurement error by thermodilution for the cardiac output. If an organ system with failing blood flow had been extracting O_2 nearly maximally, the complete loss of its perfusion will cause the mixed venous O_2 saturation to rise, not fall (Fig. 24). In this circumstance, the increase in venous O_2 saturation reflects the loss of the perfusion to the organ and not an improvement in tissue oxygenation. In other words, the mixed venous O_2 saturation is useful only as a measure of the degree of stress on the O_2 extraction mechanism; it cannot be used as a means to determine adequacy of tissue oxygenation. Thus, under most clinical circumstances in critically ill patients, a low mixed venous O_2 saturation indicates inadequate $\dot{D}O_2$ to some vascular bed(s); a normal mixed venous O_2 saturation means only a normal average O_2 extraction for tissues that are using O_2 at the time the measurement is taken. Tissues that are no longer extracting oxygen (e.g., because of ischemia or anoxia) are no longer represented in the mixed venous O_2 saturation value.

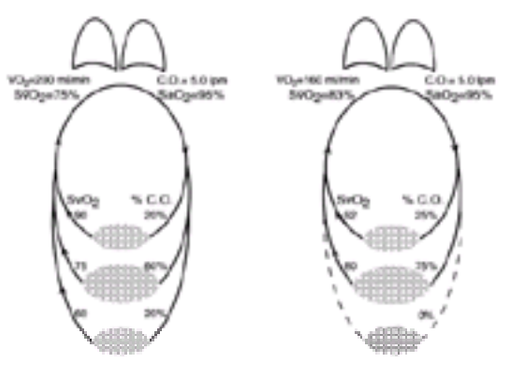

FIG. 24. Effects of loss of tissue perfusion on the mixed venous SaO_2 and O_2 consumption by the body. Note that SaO_2 increases when loss of perfusion occurs in a tissue previously extracting a large amount of O_2.

The Partial Pressure of Oxygen in Tissues

The convective delivery of O_2 from the lungs to the other body tissues produces a measurable PO_2 in the tissues. Measurements of PO_2 in living tissue, however, are difficult to make and difficult to interpret because of variability of the results. Predictions of tissue PO_2 from theoretical calculations also have led to conclusions that are sometimes inconsistent with experimental measurements. There is controversy concerning the effects of the serial resistances to O_2 transport from the erythrocyte to the mitochondria, and in particular concerning the question of whether the primary resistance resides at the capillary level or within the tissue. Although many aspects of this problem have been investigated, our understanding of tissue oxygenation is still quite incomplete, particularly for disease states.

The diffusion of O_2 from the capillaries into the tissues produces an O_2 distribution profile in the tissues. Tissue measurements of PO_2 with surface electrodes or indwelling microelectrodes usually yield very irregular PO_2 profiles. When various PO_2 values are plotted as percentages of their frequencies, a PO_2 histogram is obtained; the range and the peak PO_2 values provide an estimate of the dispersion of PO_2 values in the tissue. An example of a PO_2 histogram is provided in Fig. 25. The implications of the distribution of PO_2 values within a tissue are discussed below.

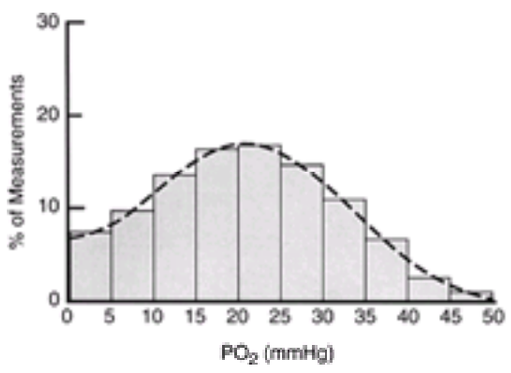

FIG. 25. PO_2 histogram of brain tissue. Measurements made in the brain of an anesthetized cat using platinum needle electrodes.

Before experimental measurements of tissue PO_2 became possible, the theoretical approach of Krogh, with his model of a tissue cylinder around a central capillary running parallel to resting muscle fibers, was used to calculate the PO_2 in an ideal tissue. Although it is quite simple, the Krogh model has been conceptually useful to describe the principles of tissue O_2 transport. In the Krogh tissue cylinder, the critical location for O_2 supply is at the periphery of the venous end of the cylinder. This is called the *lethal corner* (Fig. 26). Other models have been devised, in which O_2 is supplied to a solid cylinder from a homogeneous peripheral sheet of blood (Hill model) or, more realistically, from a number of peripheral capillaries. Most models assume an ideal cylindrical geometry and, for the most part, the delivery of O_2 from a uniform source of capillaries. In the Krogh cylinder, a single cylinder and capillary are considered assuming homogeneity of the tissue and its microcirculation; more complex models admit the possibility of differing numbers, distributions, and types of capillaries.

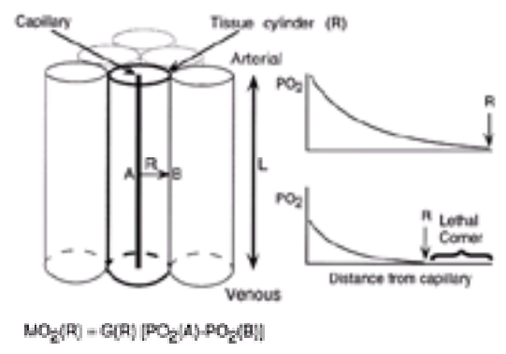

FIG. 26. Model of tissue oxygenation based on the Krogh cylinder. The predicted O_2 gradient in two regions of a single capillary and tissue cylinder are shown. The model assumes constant and uniform $\dot{V}O_2$ throughout the tissue cylinder. The diffusion of O_2 is given by the O_2 conductance (*G*) of the tissue and the difference in O_2 partial pressures between *points A* and *B* on the model.

The PO_2 gradient from capillary blood to tissue depends on the sum of convective and diffusive resistances to O_2 transport. The Krogh and Hill models stipulate a limitation by diffusion; however, there are circumstances in which $\dot{V}O_2$ may be limited not by diffusion but by O_2 delivery. The Krogh model also does not predict O_2 supply dependence because of its assumptions or its inherent limitations. The ideal $\dot{D}O_2/\dot{V}O_2$ relationship appears to be similar for anemic, hypoxic, and stagnant hypoxia as long as the intercapillary distance (ICD) is small (below 80 µm). The calculated O_2 extraction ratio, however, is too high. The high O_2 extraction predicted by the Krogh model may be caused by the assumption of tissue homogeneity and can be made more realistic by including an O_2 shunt of about 30%. Such precapillary O_2 loss has been demonstrated experimentally; however, its true magnitude is unknown. The O_2 extractions predicted by the Krogh model improve when ICD is increased (above 80 µm), but the critical point becomes higher for hypoxic hypoxia, indicating an effect of diffusion at large distance.

Support for the Krogh diffusion theory of capillary exchange has been found in controlled animal experiments suggesting that $\dot{V}O_{2max}$ is limited by O_2 diffusion during normoxia. It is not possible, however, to determine the location of the limiting resistance to diffusion from such experiments. Intracellular PO_2 values in working muscle also have been deduced from the myoglobin (MbO_2) dissociation curve in animal experiments. The MbO_2 saturation measured by cryomicrospectroscopy *ex vivo* suggests that the intracellular PO_2 is only a few torr and evenly distributed at $\dot{V}O_{2max}$. This finding has been ascribed to Mb-facilitated O_2 and a low apparent K_m for O_2 (PO_2 for half-maximal O_2 consumption) similar to that of isolated mitochondria. These findings suggest there is no lethal corner—that is, the muscle is "well stirred," tissue PO_2 is much lower than $P\bar{v}O_2$, and the main PO_2 gradient occurs across the capillary endothelium. In contrast, measurements of oxidized cytochrome a,a_3 in mitochondria in situ versus MbO_2 saturation diverge as $\dot{V}O_2$ increases *in vivo,* indicating the PO_2 gradient between cytosol and mitochondria increases with increasing $\dot{V}O_2$. Thus, the apparent behavior of the tissue PO_2 differs greatly between normal, isolated and *ex vivo* experiments. Isolated cells and tissues also differ from intact tissue, in which $\dot{V}O_2$ varies with the metabolic needs of the tissue. In living tissues, the functional microcirculation regulates many of the factors influencing the O_2 supply of tissues. These features of the microcirculation are summarized briefly in the following sections.

Effect of Oxygen Equilibrium Curve

Normally, only one fourth of the O_2 carried by oxyhemoglobin is unloaded in the tissues; however, because of countercurrent exchange of O_2 in precapillary vessels, hemoglobin in the capillaries probably operates closer to the steep, middle portion of the OEC. The effect of a shift of the OEC on O_2 unloading in tissues depends on the level of oxygenation. High P_{50} increases and low P_{50} decreases venous saturation in normoxia and mild hypoxia, whereas the opposite occurs in severe alveolar hypoxia. It is the steepness of the OEC that determines this difference. A P_{50} inadequate for a particular O_2 requirement can be compensated for by an increase in blood flow. The effect of a shift of the OEC on tissue oxygenation has been confirmed in many studies, but the significance of moderate shifts is often questioned. At normoxia, an increase in P_{50} (e.g., from the Bohr effect) makes the capillary blood maintain a higher PO_2 toward the venous end of the capillary.

Capillary Transit Time and Oxygen Shunting

Heterogeneous capillary geometry (e.g., variable spacing) leads to variable volume of perfused tissue, and variability of capillary transit time results in differing PO_2 patterns in various volumes of tissue. Capillaries with long transit times (low flow) are vulnerable to stagnant conditions with rapid depletion of O_2; capillaries with very short transit time (high flow) are prone to O_2 shunting. There must be optimal transit times for gas exchange somewhere in between these extremes for various tissues. There is also significant countercurrent exchange of O_2 between small arterioles and venules in some tissues (precapillary O_2 loss).

Heterogeneity of Perfusion

Many of the relevant variables that determine the adequacy of tissue O_2 availability are distributed inhomogeneously in the tissues. These variables include capillary density, capillary length and diameter, blood flow, transit time of erythrocytes through the capillary, $\dot{V}O_2$, and hemoglobin and myoglobin O_2 saturation values. The following example illustrates the problem. In resting skeletal muscle, most of the capillaries are perfused; however, blood flow rates in individual capillaries are inhomogeneous and often intermittent. This provides a physiologic reserve of capillaries in which the distribution of blood flow regulates tissue PO_2 over a range of changes in O_2 supply and/or $\dot{V}O_2$. In normal skeletal muscle, perfusion inhomogeneity may even increase during contraction and relaxation. Under conditions of submaximal exercise, however, all capillaries are open and flow is more homogeneous. Capillary heterogeneity during exercise, however, may decrease or increase at very high workloads. Heterogeneity also may markedly affect the O_2 supply at high $\dot{V}O_2$. On the other hand, local heterogeneity in O_2 delivery may be reduced by diffusion of O_2 between adjacent capillaries, particularly under conditions of high blood flow.

Capillary Hematocrit

The role of the capillary hematocrit in tissue gas exchange remains poorly understood. It is generally accepted, however, that capillary hematocrit is much lower than systemic hematocrit (perhaps as low as 10%), and it bears little relation to systemic hematocrit. Capillary hematocrit fluctuates in parallel with $\dot{V}O_2$ and the contractile state of the arterioles, which suggests it is a regulated variable in the maintenance of tissue oxygenation.

Venous PO_2 Versus Tissue PO_2

The venous PO_2 and mean tissue PO_2 generally agree for an organ under normal conditions, but there are significant deviations when changes occur in capillary density, $\dot{V}O_2$, hemoglobin concentration, and cardiac output. The change in venous PO_2 after an increase in capillary density provides a good estimate of mean tissue PO_2, even in conditions deviating from normal resting conditions. Misleadingly high venous PO_2 values, however, occur in the presence of functional arteriovenous O_2 shunting resulting from countercurrent blood flow, very short capillary transit times, preferential flow channels, or shock. Some of these problems have been discussed earlier in the context of clinical interpretation of the mixed venous O_2 saturation.

Oxygen Supply Dependence of Respiration

One of the simplifying concepts often used in thinking about tissue oxygenation is that cellular O_2 uptake has zero-order kinetics—that is, it is independent of PO_2 throughout the tissue. This assumption is based on the observation that the Michaelis-Menton constant (K_m) for O_2 is very low in well-stirred mitochondrial suspensions (order of 0.1 torr). Longmuir first showed that $\dot{V}O_2$ of cells depends on PO_2 up to considerably higher values than expected from zero-order kinetics; he ascribed this to intracellular resistance to O_2 diffusion. Slices of liver follow Michaelis-Menten kinetics rather than zero-order kinetics, with an apparent K_m about 100 times higher than that for mitochondrial suspensions. Thus, the difference between "true" mitochondrial K_m and "apparent" K_m for O_2 in cells and tissues must be appreciated.

In intact tissues, the mitochondrial oxidation-reduction state depends on PO_2 over a physiologic range of PO_2; thus, metabolic adjustment ensures a reasonably constant ATP supply and $\dot{V}O_2$ with decreasing PO_2. These findings imply that the critical PO_2 in intact cells is very low, and they diminish the potential effect of O_2 gradients on respiration rate. O_2 diffusion would be expected to limit $\dot{V}O_2$ only during an extreme lack of O_2 (e.g., ischemia or profound hypoxemia) or at extremes of $\dot{V}O_2$ with mild to moderate hypoxemia. Isolated small muscles and muscle slices in vitro show O_2 supply dependency, presumably caused by very low PO_2 values in the center of the tissue.

As discussed earlier, physiologic O_2 supply dependence is defined as a condition in which $\dot{V}O_2$ decreases with diminishing O_2 delivery below a low critical threshold. The slope below the critical threshold indicates optimal O_2 extraction. Above the critical threshold there is a horizontal plateau; decreases in O_2 delivery do not lower $\dot{V}O_2$ in the plateau region because O_2 extraction increases proportionately. When O_2 supply is reduced below the critical threshold, $\dot{V}O_2$ falls because O_2 extraction no longer increases proportionately and cannot compensate for the reduction in O_2 delivery (Fig. 23).

Pathologic O_2 supply dependence of $\dot{V}O_2$ has been reported over a wide range of O_2 delivery values in ARDS patients. This form of O_2 supply dependence is characterized by a higher critical O_2 supply, a lower slope below the critical PO_2, and a higher supercritical plateau or no plateau at all (Fig. 23). The lower slope indicates a deficiency in O_2 extraction from the blood with an increase in mixed venous PO_2. The underlying mechanisms that can contribute to this deficiency are complex and multifactorial. They include vascular microembolization, disruption of endothelial function resulting in a protein-rich permeability edema, microvascular dysregulation, and loss of mitochondrial function. Experimental injuries that produce O_2 supply dependency are characterized by a decrease in capillary reserve, an increase in capillary distances (loss of open capillaries and edema), heterogeneity of capillary distribution and flow, and an increase in capillary shunts. These problems contribute to derangements of the microvascular function and impaired O_2 extraction from the blood, with compromise of O_2 supply to the tissue.

CELLULAR ENERGY METABOLISM

Cellular Energy Requirements

The immediate energy source for practically all the energy-requiring processes in the cell is the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (P_i). ATP is replenished continuously by the cell through the processes of glycolysis and oxidative phosphorylation. In these processes, sequences of chemical reactions partially trap changes in chemical free energy in the synthesis of ATP. The ATP-ADP cycle (Fig. 27) constitutes a basic feature of energy metabolism in all cells and functions as the link between the energy-utilizing and the energy-consuming processes. The rate of ATP utilization can increase more than 100 times during exercise, utilizing the whole muscle store of ATP in about 3 seconds. For cellular homeostasis, the rate of ATP regeneration generally equals the rate of ATP utilization, and the cellular ATP content remains approximately constant. Of all the tissues of the body, cardiac and skeletal muscle are faced with the most intricate problems of metabolic regulation because of their unique need to change metabolic rate.

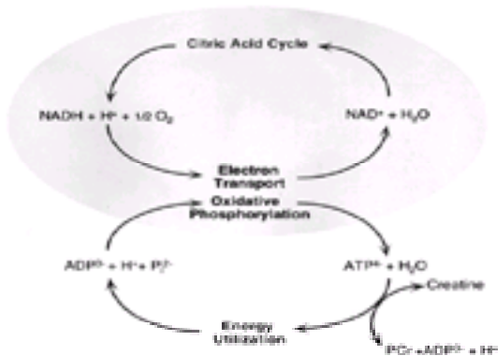

FIG. 27. The ATP-ADP cycle. The major means of conserving energy in the cell is oxidative phosphorylation, which is coupled to electron transport in the mitochondrion (*shaded area*). Oxidative phosphorylation generates ATP from ADP and P_i to support the energy needs of the cell. Additional energy can be stored in the form of PCr, which can be used later to phosphorylate ADP and regenerate ATP.

The ultimate and most efficient process for ATP formation in aerobic cells is the intramitochondrial oxidation of substrates by the citric acid cycle, with conservation of free energy by the coupled processes of electron transport and oxidative phosphorylation. In the final process, molecular O_2, the ultimate electron acceptor, is reduced to water. For a limited period of time, however, ATP can be produced through processes that do not require O_2 (e.g., glycolysis). Some species have evolved with a special ability to survive for a prolonged period under anaerobic conditions. The physiologic relationship between aerobic and anaerobic energy production is well illustrated by a discussion of exercise metabolism.

Metabolism During Exercise

Progressive muscular exercise is accompanied by proportional increases in $\dot{V}O_2$ until the maximal aerobic capacity is reached ($\dot{V}O_{2max}$). Workloads beyond those required to reach $\dot{V}O_{2max}$ produce no further increase in O_2 consumption. A major determinant of the $\dot{V}O_{2max}$ during exercise under normoxic conditions is the cardiac output. The cardiac output sets an upper limit of the capacity to deliver O_2 to the tissues. Heavy exercise with only 10 kg of muscle may be sufficient to elicit an average person's maximal O_2 uptake; however, the system for convective O_2 delivery also can be seen as being well matched to the ability of the muscle to consume O_2. At high muscle blood flow rates and extraction ratios, the availability of O_2 to the mitochondria may be limited by diffusion.

The type of fuel utilized during physical activity is determined by work intensity, duration, training status, and substrate availability. The major part of the energy demand during low-intensity exercise is supplied by oxidation of fat, whereas oxidation of carbohydrates is required during exercise at higher intensities. The amount of ATP that can be produced by glycolysis corresponds to about 20 seconds of maximal work. This limitation is caused by depletion of the store of creatine phosphate (PCr) and the accumulation of lactic acid in the muscles. ATP formed by glycolysis is therefore important during short bursts of high-intensity exercise or during ischemic conditions, but it is negligible in terms of energy provision for sustained exercise. During sustained exercise at low or moderate intensities, the rate of pyruvate oxidation is similar to the rate of glycolysis, but at higher intensities the entry of pyruvate into the mitochondrion is incomplete and lactic acid is formed and accumulates in the body fluids. Accumulation of lactate in muscle and blood begins at about 50%–70% of $\dot{V}O_{2max}$. At 100% of $\dot{V}O_{2max}$, 10%–20% of the total energy production is provided by glycolysis with lactate formation. Accumulation of lactate in blood is accompanied by an increased ventilation and CO_2 exchange. The exercise intensity when blood lactate and ventilation increase more than the increase in intensity and $\dot{V}O_2$ has been termed the *anaerobic threshold* or *lactate threshold.* This value is widely used in exercise physiology to define the training status of subjects.

During muscular work, the major store of high-energy phosphates in the cell is PCr. PCr can maintain the cellular ATP concentration approximately constant despite fluctuating energy demands. During maximal short-term exercise, the muscle content of PCr can become depleted, and the amount of energy provided corresponds to about 0.3 mol of ATP. The classic view of PCr is that it serves as a high-energy phosphate buffer during periods of high demand for energy. The concept is valid, but changes occur in the PCr level under other conditions. It has been shown that PCr decreases during submaximal exercise in relation to the intensity of the exercise. The decline in PCr occurs at the onset of exercise, and its value remains practically constant during the exercise.

The relative concentrations of ATP, ADP, and the other adenine nucleotides are important for the control of bioenergetic processes. Their concentrations are determined by the energy potential of the system and the adenylate kinase (AK) reaction. AK is considered to be close to equilibrium:

$$2\ ADP \overset{AK}{\leftrightarrow} AMP + ATP$$

The total cellular concentrations (including both the free and bound nucleotides) of AMP, ADP, and ATP are related to each other in a ratio of roughly 1:10:100. The cellular concentration of ATP remains fairly constant during most physiologic conditions, but because it is present in much greater concentrations than the other adenine nucleotides, a small decrease in ATP results in a large relative increase in ADP and in an even more pronounced increase in the relative concentration of AMP. The availability of ADP is a primary determinant of the mitochondrial respiratory rate.

Breakdown of PCr is catalyzed by creatine kinase, and because the enzymatic activity in muscle is high, the reaction appears to be close to equilibrium under most conditions. An increase in free ADP and H^+, both of which are products of ATP hydrolysis, promotes breakdown of PCr. Aerobic energy production through an increase in free ADP will therefore, through the creatine kinase equilibrium, result in a breakdown of PCr. Thus, depletion of PCr is not necessarily a sign of anaerobiosis but may reflect increased energy turnover and activation of aerobic metabolism.

In addition to ADP, signals of major importance for the control of the energetic processes are intracellular concentrations of Ca^{2+}, AMP, P_i, and the mitochondrial redox state. Increases in Ca^{2+}, ADP, AMP, and P_i are linked to the contraction process and the energy demand and ensure that the rate of ATP formation equals the rate of ATP utilization. Further control of the different pathways is achieved through substrate activation, feedback inhibition, and allosteric regulation. At low metabolic rates,

the rate of glycolysis is balanced by an equal rate of pyruvate oxidation, and there is no accumulation of pyruvate or lactate in the tissues despite a large increase in the rate of glycolysis. At higher metabolic rates, when either the availability of O_2 is limited or the maximal aerobic capacity of the tissue is approached, formation of pyruvate exceeds pyruvate oxidation and lactate accumulates. The metabolic signals to turn on pyruvate formation (glycogenolysis and glycolysis) and pyruvate oxidation (citric acid cycle and mitochondrial respiration) are similar: increases in ADP, P_i, and Ca^{2+}. An imbalance between these processes shown by lactate formation at higher exercise intensity or during hypoxia may be related to a change in the oxidation-reduction state of the NAD^+/NADH couple, which regulates pyruvate entry into the citric acid cycle.

As lactate formation and PCr breakdown during exercise are not necessarily related to anaerobiosis, the term *anaerobic threshold* is misleading. The term *lactate threshold* better describes the condition related to work intensity, when ATP synthesis occurs to a greater extent through glycolysis. Therefore, the lactate threshold does indicate an important functional point in metabolism. Experimental evidence suggests that a decrease in tissue O_2 availability has metabolic consequences (e.g., PCr breakdown and enhanced glycolysis) before cellular respiration is limited by hypoxia. These metabolic changes reflect the adaptation of the tissue to an increased metabolic rate relative to the availability of O_2.

Cellular Respiration and the Mitochondrion

As noted in the previous section, the primary role of cellular respiration is to produce ATP from O_2 consumption during the process of oxidative phosphorylation (Fig. 28). This fundamental process and its regulation occur within the mitochondria. In mitochondria, various nutrients are converted by intermediary metabolism to CO_2 and NADH for oxidation. This oxidation provides the energy to establish an electrochemical proton gradient (Dp) across the mitochondrial inner membrane. The Dp drives the influx of precursors for substrate oxidation, synthesis of ATP, export of products, and maintenance of osmotic stability. The cell depends on mitochondrial provision of ATP because glycolysis, the only other metabolic process to produce significant amounts of ATP, yields just four ATP molecules, compared with 26 from oxidative phosphorylation.

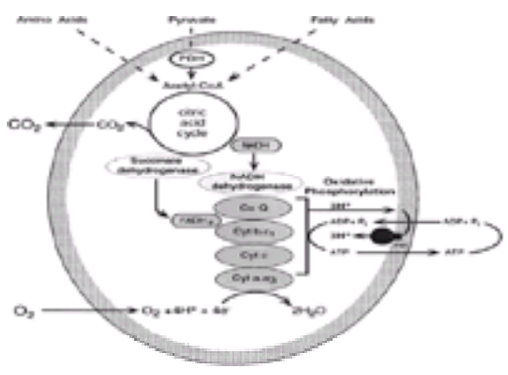

FIG. 28. Schematic drawing of mitochondrial respiration. CO_2 is produced from the oxidation of carboxylic acids in the citric acid cycle. Reducing equivalents in the form of NADH and $FADH_2$ are generated and supplied to the respiratory chain from the citric acid cycle. Molecular O_2 is reduced by cytochrome *c* oxidase as NADH and $FADH_2$ are reoxidized for use in the citric acid cycle. Energy in the form of ATP is generated from ADP by oxidative phosphorylation.

Supply of Oxidizable Substrates

Most of the substrates for cellular energy production are supplied by dietary fats, proteins, and carbohydrates. Carbohydrates and some amino acids are converted to three-carbon acids (e.g., pyruvate), whereas fats and other amino acids are converted to two-carbon acetyl compounds. Mitochondria convert pyruvate and hydrocarbon chains to acetyl-CoA and oxidize acetyl-CoA to CO_2. The systems involved in these processes directly supply the reducing equivalents (electrons) to the mitochondrial electron transport chain and are essential for mitochondrial ATP production.

Oxidation of acetyl-CoA to CO_2 is catalyzed by the enzymes of the citric acid cycle. The electrons from this oxidation are handled by three dehydrogenases that reduce NAD^+ to NADH, and one that reduces ubiquinone to ubiquinol. The enzymes involved in the production of NADH are isocitrate, a-ketoglutarate, and malate dehydrogenases. Succinate dehydrogenase contains a flavin coenzyme (FAD) and does not require NAD^+. Several other dehydrogenases transfer electrons to the electron transport chain through NADH and ubiquinone; however, these reactions contribute little relative to the citric acid cycle. The most important factors affecting turnover in the citric acid cycle are the availability of NAD^+, the rate of acetyl-CoA production, mitochondrial ADP concentration, and loss of tricarboxylic acid for other biosynthetic function. Under some conditions, the rate of flux through the cycle is limited by formation of citrate by condensation of acetyl-CoA and oxaloacetate. Because oxidation of NADH and ubiquinol are coupled to synthesis of ATP, regulation of respiration also occurs at the level of the dehydrogenases.

Mitochondrial Electron Transport

The electrons from NADH formed in the reactions of the citric acid cycle are transported to O_2 through a series of respiratory complexes in the mitochondrial inner membrane. These complexes catalyze three successive redox reactions in which the mobile carrier ubiquinone and cytochrome *c* catalytically oxidize NADH to NAD^+, culminating in the four-electron reduction of molecular O_2 to water. Each of the respiratory complexes also transports protons out of the mitochondrial matrix in response to the flow of electrons, thereby capturing the energy available from the oxidation-reduction process in the form of the electrochemical proton gradient (Dp) across the inner membrane. This Dp provides the energy to drive ATP synthesis from ADP and P_i by coupling the reaction to the movement of protons.

The electrochemical proton gradient has two components: a chemical gradient (DpH) and an electrical potential (Dy). The chemical gradient is the difference in the concentration of protons between the matrix space and the cytoplasm. The concentration of protons is expressed as pH, so that the chemical gradient is given as DpH. The matrix pH is about 7.6, whereas the cytoplasmic pH is approximately 7.0. The energy available from DpH is insufficient to drive ATP synthesis under normal conditions in the cell. Multiple transport systems enable the energy available from oxidation to maintain a large electrical potential across the inner membrane. This potential is about –160 mV inside the mitochondrion. It drives positively charged molecules into the matrix and supplies much of the energy needed for ATP synthesis.

ATP Synthesis

The synthesis of ATP from ADP and P_i during oxidative phosphorylation is catalyzed by an ATP synthase. This enzyme is an electrogenic proton transporter that utilizes energy from the Dp. Under most conditions, the Dp formed by electron transport is sufficient to support ATP synthesis. Without electron transport, as occurs during anoxia and with mitochondrial inhibitors, the ATPase can generate Dp by hydrolyzing ATP from glycolysis. The ATPase also can hydrolyze ATP when the membrane cannot maintain the pH gradient, as occurs in the presence of uncouplers of oxidative phosphorylation. The physiologic significance of the latter two modes of operation of the enzyme is unknown.

Mitochondrial Metabolite and Ion Transport Systems

Compartmentation of metabolites and ions across the inner mitochondrial membrane is tightly regulated and plays an integral part in respiratory control. The entry of carbon substrates into the mitochondrial compartment, along with extrusion of products (e.g., ATP) is achieved by specific transporter systems driven by components of the Dp. Electroneutral DpH-dependent transport systems for pyruvate and Pi effect the accumulation of pyruvate and P_i in the matrix according to the DpH across the inner membrane. The dicarboxylate and tricarboxylate carriers catalyze electroneutral exchange of P_i for citric acid cycle intermediates. Hence, the mitochondrial distribution of these anions depends indirectly on DpH. Some mitochondrial systems catalyze transport that is dependent on Dy and results in a net charge movement across the inner membrane. These systems can establish a potential (electrogenic movement) or can move charged species according to an existing potential (electrophoretic movement). The adenine nucleotide transporter catalyzes the exchange of matrix ATP^{4-} for cytosolic ADP^{3-}, allowing electrophoretic movement of a negative charge out of the matrix. This is the major mechanism for supplying ADP to the ATP synthase, and subsequently ATP to the cytoplasm.

Heterogeneity of Mitochondrial Distribution and Function

Although aerobic respiration occurs in all mammalian tissues, the maximal O_2 consumption rate, respiratory control characteristics, mitochondrial morphology, and mitochondrial distribution vary among tissues. In most cell types, the need for a continuous supply of energy to support function is met by specific associations of mitochondria with energy-requiring systems. Because energy demand varies with workload, there is no “normal” O_2 consumption rate; instead, cellular function determines the O_2 consumption rate. Changes in function can markedly alter the relative contributions of different tissues to the total O_2 consumption by the body.

Variations in energy needs and other functional demands are associated with differences in mitochondrial respiratory components and their regulation. In muscle, cycles of contraction require cyclical changes in mitochondrial shape and cellular oxygenation. Myocytes have features to accommodate these demands. Muscle mitochondria are found as networks, or reticula, and myocytes contain myoglobin to facilitate cellular transfer. Other types of cells also have highly specialized adaptations to function.

Mitochondria from various tissues also differ in protein composition. The contents of some enzymes and transporters vary qualitatively, whereas indispensable enzymes and transporters vary quantitatively. Molecular studies show that tissue-specific isoenzymes exist for essential components such as the adenine nucleotide transporter, cytochrome *c,* and cytochrome *c* oxidase. Mitochondrial function may be optimized by regulation of enzyme contents and activities per volume of mitochondria, volume percent of mitochondria in cells, and spatial distribution of mitochondria in cells. In various cells, the distribution of mitochondria is different at the morphologic level. The volume of mitochondria per cell (volume density) also varies up to 100-fold in different human tissues. Furthermore, mitochondria differ between tissues in size and shape, inner membrane folding, and buoyant density. Differences in mitochondrial structure and composition also occur in different cells of the same cell type.

Regulation of mitochondrial function occurs at several sites, especially those involving generation and utilization of Dp and volume regulation. Regulation of Dp involves control of electron flow into the electron transport complexes at the NAD^+-linked dehydrogenases and at cytochrome *c* oxidase. Several of the important NAD^+-linked dehydrogenases are regulated by Ca^{2+}, and cytochrome *c* oxidase contains regulatory subunits. Electrophoretic transport systems, including the adenine nucleotide transporter, also regulate the Dp. Variations at different sites could result in significant differences in regulation of respiratory function without changes in overall mitochondrial structure.

Adaptive changes in mitochondria can occur in response to physiologic challenges. These mitochondrial changes serve to adapt function to the prevailing conditions, and they include changes in volume density, adjustment of enzymatic and transport activities per unit mass, and spatial distribution of the organelles within cells. Changes in volume density are associated with altered aerobic work capacity; greater mitochondrial density provides a greater maximal ATP production under these conditions. This principle does not hold in disease, as impaired mitochondrial function can necessitate increased density to maintain function. Change in mitochondrial volume density also occurs in response to development and differentiation, exercise, conditioning, starvation, chronic hypoxia, changes in diet, and pharmacologic agents.

Altered expression of enzyme and transport activities per unit of mitochondrial volume occurs with adaptation to different physiologic states. For instance, thyroxine administration and recovery from hyperthyroidism result in changes in cytochrome *c* oxidase and citrate synthase. Urea cycle enzymes are increased by high-protein diets and by starvation. Chronic hypoxia causes a decrease in mitochondrial enzymes, whereas physical conditioning increases the concentrations of these enzymes. Thus, alterations in the composition of enzymes and transport systems provide another mechanism for cells to optimize ATP production.

At the cellular level, mitochondrial density and distribution are important determinants of the O_2 concentration required to maintain cellular ATP production. The distribution of mitochondria appears to represent a balance between the need to have a high capacity for ATP production at sites of high ATP demand and the need to oxygenate the cells adequately at physiologic blood PO_2. Most cells and tissues have a functional reserve that allows enhanced activity under physiologic or pathologic challenge. For tissues with high energy requirements, the metabolic demand is met by high volume density of mitochondria and, in some tissues, by clustering of mitochondria. The higher volume density and clustering can increase the O_2 concentrations required for function. Tissues with high mitochondrial volume density and clustering are inherently more susceptible to O_2 deficiency, and this susceptibility is increased by higher metabolic needs.

The effects of hypoxia on mitochondrial function indicate that different metabolic pathways are selectively vulnerable to tissue hypoxia. The apparent K_m of cytochrome *c* oxidase in many adult mammalian cells occurs at a PO_2 10 to 160 times greater than the isolated oxidase, which has a K_m of less than 0.1 mmHg. This means that failure of mitochondrial function can occur at a relatively high O_2 concentration compared with that of isolated mitochondria. Many reactions that depend indirectly on O_2 (i.e., those dependent on ATP) are vulnerable over the same O_2 concentration range. Studies of activities of different ATP-requiring systems in cells show that some are much more sensitive to ATP depletion, and hence to tissue hypoxia, than others. The order of these sensitivities is determined both by the K_m values of the enzymes for ATP and by the location of the enzymes in the cell relative to the mitochondria. Depending on whether changes in enzymatic activities cause irreversible injury, the different sensitivities of the O_2- and ATP-dependent enzymes to O_2 availability can affect cell viability directly.

All mammalian cells can survive some period of severe O_2 deficiency without irreversible injury. Such nonlethal hypoxic periods occur when cells function with reduced metabolic and respiratory capacity. These conditions are distinct from both normal and irreversible hypoxic or anoxic states. During brief anoxia, the mitochondrial Dp is maintained despite substantial decreases in cellular ATP concentrations. The energy required for maintenance of Dp is made available when specific ion transport systems are inhibited that drive ATP synthase activity. Such selective inhibition of ion transport allows cells to preserve the mitochondrial milieu and facilitates their recovery on reoxygenation. Similar metabolic suppression may occur in other tissues, such as the kidneys, where inhibition of transport functions protects against anoxic injury. The myocardium exhibits a response termed *stunning,* in which an ischemic episode results in inhibition of mitochondrial respiratory functions and reversible cessation of contractile activity. Suppression of synaptic function (*idling*) protects neurons from anoxic injury, and postanoxic suppression of cellular respiratory rate in the brain also may be the consequence of an endogenous mechanism to preserve viability. Whether such conditions occur in critically ill patients during ARDS, sepsis, or other shock states is unknown. The precise mechanisms regulating respiratory function in these diseases also are not clear, but the existence of such mechanisms clearly would influence cellular O_2 demand and the amount of O_2 that must be delivered to the tissues by the circulation.

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CHAPTER

4 Respiratory Mechanics

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INTRODUCTION

For effective respiration, air must be drawn through the airways and distributed among approximately 400,000,000 alveolar compartments within the lung parenchyma. Respiratory mechanics is the study of the forces involved in this task and how these forces govern the volumes and flows of gases, blood, and interstitial fluids in the lung. Abnormalities of respiratory mechanics are central to the pathophysiology of most disorders of the respiratory system. An understanding of respiratory mechanics is essential for the rational assessment and treatment of these disorders, and the purpose of this chapter is to provide a basis for such understanding.

We emphasize the mechanical properties of the lung and passive chest wall. Intersecting topics, such as the function of the respiratory muscles, gas exchange with the pulmonary circulation, and the control of ventilation, are developed in detail in other chapters. We start by describing the passive respiratory system as a simple *viscoelastic* system, which means that the forces developed can be resolved into those in phase with flow (viscous forces) and those in phase with volume (elastic forces). This approach is useful, because these viscoelastic properties and their derangements in disease can be clearly assigned to specific structures (e.g., lung versus chest wall, airway caliber, loss of surfactant) and easily evaluated. We then turn to a very different mechanical phenomenon—namely, expiratory flow limitation. This operates only at high rates of ventilation in normal subjects but is responsible for the ventilatory disability of patients with obstructive lung diseases. Next, we discuss the mechanical basis governing the distributions of volume and ventilation among the gas-exchanging air spaces of the lung. In health, there is a degree of nonuniformity of volume and of ventilation that is ordinarily of little physiologic consequence. In disease, however, there may be sufficient nonuniformity to impair gas exchange. We also discuss the impact of lung mechanics on blood flow and interstitial fluid balance in the lung. This becomes particularly important during mechanical ventilation. Finally, we deal with the energetics of breathing, describing the mechanical loads placed on the respiratory muscles in terms of work of breathing, and the physiologic costs incurred in terms of oxygen consumption by the respiratory muscles.

MECHANICAL PROPERTIES OF THE PASSIVE RESPIRATORY SYSTEM

The mechanical loads that the muscles of respiration must overcome to ventilate the lungs are imposed by the passive components of the respiratory system—the airways, lungs, and chest wall. To assess these passive loads, measurements must be made with the muscles relaxed; the assumption is made that the properties of the passive components remain the same in the presence or absence of respiratory muscle activity.

Respiratory mechanics deals primarily with the *flows, velocities, volumes,* and *pressures* developed by the respiratory system and the gas contained within it. Flow is a measurement of the volume of gas per unit time (e.g., peak expiratory flow of 10 L/s). It is different from velocity, which is a measurement of the distance per unit time (e.g., a mean of 15 m/s, for a peak flow of 10 L/s in a trachea with a cross-sectional area of 6.7 cm^2). Volume generally refers to the gas contained in a space (e.g., a volume of gas in the lung at ordinary end-expiration, or functional residual capacity, of 3.5 L). Pressure is the force per unit area applied perpendicularly to a surface (i.e., no shear force). Generally, the absolute pressure (e.g., ambient pressure of 1000 cm H_2O) is of no interest in respiratory mechanics, and the pressure in a given location is reported relative to the ambient air pressure (e.g., a pleural pressure of –5 implies a pressure 5 cm H_2O below the ambient pressure). More often than not, the pressure *difference* across the wall of a structure (transmural pressure) is of more importance than the absolute pressures, because it is the pressure differences that have mechanical effects. For example, the pressure difference between the alveolar gas and the pleural space is the same at a given lung volume during a maximal inspiratory effort against a closed glottis (Müller's maneuver) as it is during a maximal expiratory effort against a closed glottis (Valsalva's maneuver), because that difference depends only on the elastic tensions in the lung parenchyma, which in turn depend on lung volume.

Viscoelastic Properties

Viscoelastic Model

Elasticity is the property of matter that causes it to return to its resting shape after deformation by an external force. The passive components of the respiratory system exhibit elastic properties, storing energy during inspiration as would a steel spring. That stored energy is the source of the pressure difference across the relaxed respiratory system. It is available to return the respiratory system to its original volume when the inspiratory muscles relax during expiration. *Viscosity* is the frictional property of fluids (gaseous or liquid). It is the major source of the flow-related pressure differences across the respiratory system.

In quiet breathing, the passive respiratory system behaves very much like a simple viscoelastic structure. The viscoelastic properties of the respiratory system may be modeled by two passive elements arranged in series, so that the airways contribute the pressure difference between the airway opening and the alveolar gas, $P_{ao} - P_{alv}$, and the alveolar parenchyma and passive chest wall contribute the pressure difference between the alveolar gas and the body surface, $P_{alv} - P_{bs}$. Their sum, measured during relaxation of the respiratory muscles, is the pressure difference across the passive respiratory system:

$$P_{rel,rs} = P_{ao} - P_{bs} = (P_{ao} - P_{alv}) + (P_{alv} - P_{bs}) \quad \textbf{(1)}$$

The first term in parentheses is the viscous, flow-related pressure difference, and the second mostly represents the elastic, volume-related pressure difference. The behavior of such a model during a volume excursion can be described by the equation of motion:

$$P_{rel,rs} = P_{rel,rs,o} + (1/C_{rs})\,\Delta V + R_{rs}\,\dot{V} \quad \textbf{(2)}$$

where $P_{rel,rs,o}$ is the initial passive transrespiratory system pressure, DV is the volume excursion, $\dot{V}$ is instantaneous flow, and C_{rs} and R_{rs} are characteristic moduli of the elastic (compliance) and viscous (resistance) components, respectively. This behavior can be displayed as a plot of passive transrespiratory system pressure against lung volume (Fig. 1). When the volume is cycled very slowly to minimize the viscous contribution, the plot describes a narrow loop (*solid tracing*). The overall slope of this loop reflects the elastic properties, $1/C_{rs}$. When volume is cycled more rapidly, the loop widens (*interrupted tracings*). The width of the loop divided by the difference of flow reflects the viscous properties, R_{rs}. In addition to the elastic and viscous contributions to the transrespiratory system pressure equation, an additional pressure component is sometimes added to represent the inertial effects of the gas and chest wall structures as they accelerate and decelerate. At ordinary breathing frequencies, however, inertial factors are small and are usually ignored.

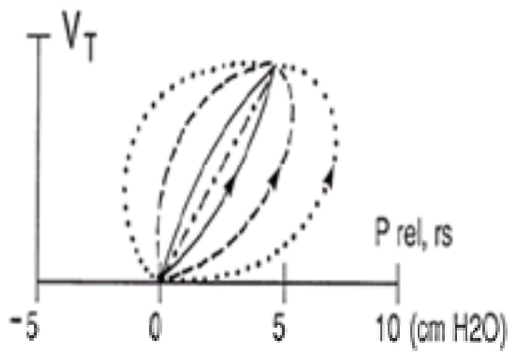

FIG. 1. Idealized viscoelastic behavior during passive ventilation in a normal subject, showing the pressure difference across the relaxed respiratory system, $P_{rel,rs}$, as a function of tidal volume, V_T, during very slow flow (*solid curve*) and sequentially higher flows (*dashed and dotted curves*). The viscoelastic model envisions an elastic component, represented by the *thin line* drawn between the points of no flow, with a slope of $1/C_{rs}$, and a viscous component, represented by the flow-related departures from the thin line, adding to the elastic pressure during inflation and subtracting from it during deflation, and accounting for the counterclockwise looping.

Elastic Recoil Properties of the Respiratory System

Typical elastic properties of the relaxed respiratory system are shown in Fig. 2. Over the range of about 20%–80% of the vital capacity (VC), the curve is reasonably linear, and the elastic properties can be characterized simply by specifying the recoil pressure and slope at a specified volume. In the example illustrated, the curve crosses the zero pressure axis at about 3 L of lung gas volume and has a slope (elastance or its inverse, compliance) of about 100 mL for every 1 cm H_2O. Away from this volume in either direction, the elastic forces act to return the respiratory system toward this zero pressure point. Thus, a normal subject at rest expires passively to this zero elastic recoil position by the end of each breath, and under these conditions, the end-expiratory lung volume, or functional residual capacity (FRC), is elastically determined.

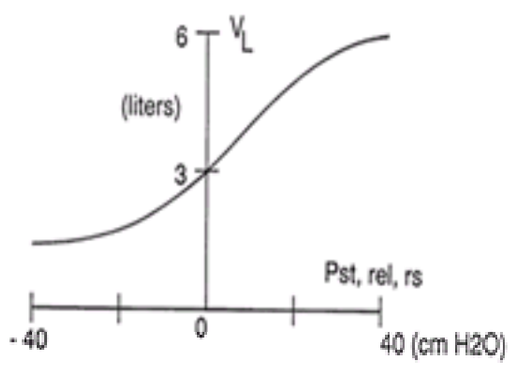

FIG. 2. Idealized elastic behavior of the respiratory system, as shown by the pressure at the airway opening measured statically (no flow) in the relaxed subject, $P_{st,rel,rs}$, as a function of lung gas volume.

The pressure at any given volume on the passive curve indicates the elastic load, that is, the inspiratory or expiratory forces that would be required to hold the respiratory system at that volume. The elastic load increases as volume increases, reaching about 40 cm H_2O at total lung capacity (TLC) in the example shown. Note that the slope of the curve decreases at high and low lung volumes, that is, the positive and negative elastic loads increase sharply. At these extremes of volume, the strength that the muscles can apply with a maximal inspiratory or expiratory effort also wanes sharply. The volume at which the elastic load and the maximal inspiratory strength available to overcome that load converge is the limit to further inspiration (e.g., TLC). For this reason, a decrease of TLC (restriction) signifies an increase in elastic recoil, a decrease in the effective strength of the inspiratory muscles, or both. The converse mechanism sets the limit to expiration in healthy young subjects, the residual volume (RV). (The dynamic mechanism that sets RV in older subjects and patients with obstructive airways disease is discussed later.)

The separate contributions of the lung and chest wall to the elastic properties of the respiratory system can be readily distinguished. That of the lung is the pressure difference across the visceral pleura, $P_{alv} - P_{pl}$, and that of the relaxed chest wall is the pressure difference between the parietal pleura and the external surface of the body, $P_{pl} - P_{bs}$. Although direct measurements of alveolar and pleural pressures are difficult, they can be inferred from relatively noninvasive measurements. P_{alv} is the same as P_{ao} when measured statically, and P_{pl} is the same as esophageal pressure, P_{es}, which is easily measured with a thin-walled balloon introduced *per nares.* Thus, a plot of lung volume versus the static transpulmonary pressure difference ($P_{st,L} = P_{ao} - P_{es}$) characterizes the elastic properties of the lung (*dashed curve,* Fig. 3), and a plot versus the pressure difference across the relaxed chest wall ($P_{rel,cw} = P_{es} - P_{bs}$) characterizes the elastic properties of the chest wall (*dotted curve*). The latter measurement requires complete relaxation of the respiratory muscles, which is difficult to ensure in the awake subject. Surface electromyograms have been helpful by providing a feedback reference for adequacy of voluntary relaxation, and reliable data have been obtained in subjects who are anesthetized and paralyzed.

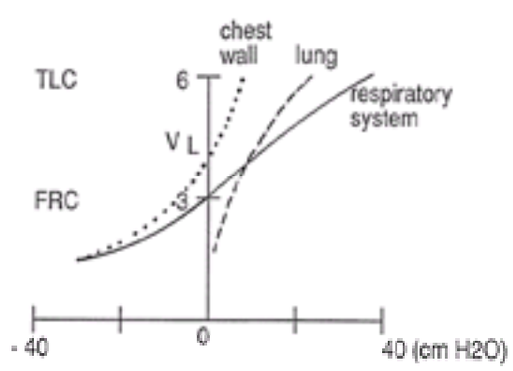

FIG. 3. Similar display to Fig. 2, showing the elastic contributions of the lung, P_L (*dashed curve*), and of the relaxed chest wall, $P_{rel,cw}$ (*dotted curve*). Note that the curves sum to the transrespiratory system pressure, $P_{rel,rs}$.

Elastic Properties of the Lung

A typical normal curve is shown in Fig. 3. Elastic recoil is about 4 cm H_2O at FRC, and compliance, C_L, is about 200 mL/cm H_2O over most of the volume range, but elastic recoil increases and compliance decreases markedly near TLC. The recoil pressure is positive over the full range of attainable volumes, reflecting the remarkable fact that the lung is under tension, inflated above its resting volume, for its entire life.

Elastic tensions in the lung are borne mainly by two components: (1) the fibrous network of collagen and elastin that supports the alveolar septa, airways, and pleura, and (2) the air-liquid interface of the alveolar septa. Elastin fibers have the requisite extensibility to sustain tensile force, F, over the full range of operating lung volumes. The elastic fiber network of the lung elastically increases tension when the network is stretched during inflation. Collagen fibers, by contrast, are very stiff and produce large increases in tension when stretched by only a small amount. The collagenous component of the fibrous network has been thought to serve as a safety

net against overdistension, coming under tension at high lung volume and accounting for the pronounced stiffening (decrease in C_L) seen near TLC. The complex anatomic relationship of collagen fibers with elastin fibers suggests that collagen also participates at lower volumes. The energy stored as a result of elastic work during inspiration by the increase in length of the fibrous components, dl, under tension, F, is the integral $\int F\,dl$ and is equal to the area under the inspiratory limb of the static volume-pressure curve.

Surface or interfacial tension, t, provides a second force that contributes to the elastic recoil of the lung. Evidence for this is the substantial reduction of recoil that occurs when the air-liquid interface is obliterated by filling the lung with saline solution. The physical basis for interfacial tension is the attraction between the molecules of the liquid phase, which far exceeds the attraction between the liquid and gas molecules. As a result, the forces acting on each liquid molecule at the interface are unbalanced, with a net force directed into the liquid phase, away from the gas phase. With every such molecule being pulled down out of the interface, the favored, least-energy configuration is that with the smallest surface area—that is, the surface is always "trying" to get smaller. For this reason, fine drops of water, as in a fog, are nearly spherical, the shape with the smallest surface area for a given volume. The elastic energy stored by the increase in area, dA, of the interface under tension, t, is the integral $\int t\,dA$. In the lung, interfacial tension is substantially reduced by the presence at the interface of pulmonary surfactant, produced by the type II alveolar cells. (The biology and biochemistry of pulmonary surfactant are treated in detail in Chapter 17; only its mechanical effects are dealt with here.)

The manner in which these tension-bearing structures interact with each other can be inferred from their anatomic relationships. First, the pseudoplanar alveolar septum connects along most of its edges to other alveolar septa, forming a continuously interconnected network, suggesting that septal elastic tension is directly transmitted from one septum to the next throughout the alveolar parenchyma. The alveolar parenchyma attaches to the inner aspect of the visceral pleura, so that its elastic tensions pull inward on the visceral pleura, lowering pleural pressure, P_{pl}, relative to alveolar gas pressure, P_{alv}, and accounting for the measurable $P_{st,L}$. Second, the alveolar septum is constructed like a sandwich, with a pseudoplanar fibrous network placed between two air-liquid interfaces. The mechanical consequence of this parallel physical arrangement is that the elastic tensions of the fibrous network and air-liquid interfaces are additive, so that elimination of the two air-liquid interfaces when the lung is filled with saline solution eliminates a substantial portion of lung recoil.

On the other hand, a series relationship exists at the point where alveoli open onto alveolar ducts. Here, tensions are transmitted directly from the septum to a structure of very different composition, the curved "cables" of the alveolar entrance rings, composed of relatively heavy, elastin-rich connective tissue and smooth muscle. The mechanical consequence of such a series relationship is that although the tensions in the two components must be in equilibrium, changes in the mechanical state of either structure cause distortion. For example, constriction of the smooth muscle of the entrance ring narrows the duct and pulls the radial septa inward toward the lumen of the duct. Conversely, increased tension in the septum, as with a deficiency of surfactant, draws the radial septa away from the center of the duct, dilating it. Despite the very different shapes and compositions of the duct and its surrounding alveolar tissues, their elastic properties are relatively well-matched, such that they expand and contract nearly proportionally with inflation and deflation.

Third, peribronchial and perivascular pressures, $P_{p\text{-}br}$ and $P_{p\text{-}vasc}$, can be considered to be nearly the same as pleural pressure, because the elastic elements of the alveolar parenchyma surround the bronchovascular structures, and elastic recoil at that site lowers $P_{p\text{-}br}$ and $P_{p\text{-}vasc}$ relative to P_{alv}, just as it lowers P_{pl} relative to P_{alv} at the visceral pleura.

The effects of disease on these tension-bearing components have predictable functional effects. Emphysema, by damaging the elastin fibers and destroying alveolar septa, reduces lung recoil, shifting the volume-pressure curves of the lung and respiratory system to the left and increasing compliance. This reduction of elastic recoil permits inspiration to higher volumes, accounting in part for the increase in TLC seen in emphysema. It also reduces the tethering forces applied to the airways, which causes them to be narrower at a given lung volume. This results in increased resistance and allows them to obstruct more readily at low lung volumes, thereby leading to a markedly decreased expiratory flow limit (see below). Conversely, the increase of collagenous fibers seen in pulmonary fibrosis restricts the lung by increasing lung recoil. This reduces TLC and FRC and tends to keep the airways open, thereby decreasing airways resistance and allowing them to remain open at lower lung volumes. Most significantly, the increase in elastic recoil increases the elastic load on the inspiratory muscles.

Reduced levels of surfactant or surfactant with an abnormal composition has similar "restrictive" effects, increasing lung recoil. The most significant functional consequences, however, are a decrease in end-expiratory lung volume (FRC) and a marked increase in the tendency of regions of the parenchyma to collapse at low lung volumes. This mechanism is responsible for the microatelectasis found in the adult respiratory distress syndrome (ARDS) and the respiratory distress syndrome of premature neonates.

There are two important additional mechanical effects of impaired surfactant, both a consequence of the pressure difference across the curved air-liquid interface. The first is the effect on the "critical opening pressure" of collapsed portions of lung. When portions of lung deflate during expiration to the point that the airways serving them close, gas is trapped in the distal alveolar regions; a plug of liquid may be found in the lumen of the closed airway. At both ends of the plug are air-liquid interfaces, concave to the air phase. Surface tension in these interfaces lowers the pressure in the fluid of the plug relative to that in the gas, and this pressure difference is described by the Laplace relationship:

$$P_{alv} - P_{liq} = \tau/r_1 + \tau/r_2 \qquad \textbf{(3)}$$

where r_1 and r_2 are the radii of curvature of the surface. This negative pressure holds the airway walls together until distending pressure is applied at a level great enough to open the airway (critical opening pressure). As long as the airway remains shut, the compliance of the region is zero. This mechanism operates where and when distending pressures are low: at end-expiration at the bases of lungs of elderly subjects, in obese subjects, or in patients with diaphragmatic paralysis in the supine position. Critical opening pressures may be increased further in areas of the lung in which the distal air spaces are gas-free (e.g. microatelectasis of ARDS). In such cases, airway opening pressures may be as high as 10 to 20 cm H_2O.

The second effect is on lung fluid balance. Although the air-liquid interface is relatively flat over much of the surface of the alveolar septum, it is concave in the corners of the alveolus, and consequently the pressure in the liquid phase in the corner is lower than that in the gas phase. Interfacial tension, then, becomes important in determining the Starling equilibrium governing fluid balance in the lung. High t favors pulmonary edema, drawing liquid from the capillaries into the interstitial space and into the alveolar spaces. Conversely, pulmonary surfactant, by reducing t, permits the alveoli to remain dry despite their small size.

Elastic Properties of the Chest Wall

A typical chest wall volume-pressure curve is shown in Fig. 3. The recoil pressure of the relaxed chest wall is about –4 cm H_2O at FRC. The curve for the chest wall, like that of the lung, is quite linear over most of the range of lung volumes, and it has a similar compliance, $C_{rel,cw}$, of about 200 mL/cm H_2O. In contrast to the lung, which stiffens near TLC, the chest wall stiffens near RV.

Elastic energy is stored in and released from the passive chest wall by bending, stretching, and raising the abdominal wall, diaphragm, rib cage, and spine during inspiration and expiration. In particular, the marked stiffening of the chest wall near RV is caused by inward bending of the ribs and stretching of the diaphragm up into the thoracic cavity.

The elastic properties of the chest wall may be adversely affected by specific disease processes. The chest wall may be restricted by skeletal changes, such as ankylosing spondylitis or kyphoscoliosis, or by abdominal changes, as in massive ascites, pregnancy, or morbid obesity. Each of these conditions increases the recoil pressure of the passive chest wall, displacing the volume-pressure curves of the passive chest wall and respiratory system to the left, increasing the passive load on the inspiratory muscles, and decreasing the maximal end-inspiratory lung volume, TLC, and the relaxed end-expiratory lung volume, FRC.

Viscous Properties of the Respiratory System

The major source of the pressure differences in phase with flow is frictional pressure losses along the conducting airways. These losses produce a pressure difference between the airway opening and the alveolus, $P_{ao} - P_{alv}$, that depends on the dimensions of the airways, the physical properties of the gas, the flow rate itself, and the flow regime or velocity profile (streamlines) of gas movement. In quiet breathing, the streamlines are parallel and straight (*laminar flow*). The physics of this flow regime is expressed by Poiseuille's Law, which relates the pressure loss between the inlet, P_i, and outlet, P_o, of a cylindrical tube to its length, l, its radius, r, the viscosity of the gas, μ, and the flow rate, $\dot{V}$:

$$P_i - P_o = (8/\pi)\,\mu\,l\,r^{-4}\,\dot{V} \qquad \textbf{(4)}$$

With laminar flow, then, the pressure loss increases directly with the flow rate (Eq. 4 and the *solid portion of the curve* in Fig. 4). Under these conditions, the ratio of the

frictional pressure loss to the flow rate, $(P_i - P_o)/\dot{V}$, is a constant, the *flow resistance,* R. This ratio is often expressed as its reciprocal, the *conductance,* G.

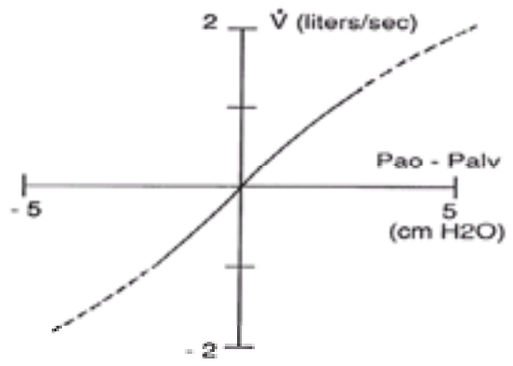

FIG. 4. Expiratory flow as a function of the pressure difference between the airway opening, P_{ao}, and the alveolar gas, P_{alv}, for a given volume. The resistance at a given point on the curve is the inverse slope of a line drawn between the origin and that point. The *solid portion of the curve* is linear, indicating constant airways resistance, consistent with laminar flow, but bends over, indicating higher resistance, at higher inspiratory or expiratory flow rates as turbulent flow begins.

When flows are increased, as during exercise, or when the airways are much narrowed, the streamlines do not remain straight and parallel. Eddies develop; laminar flow becomes *turbulent flow.* The velocity at which this changeover occurs can be predicted by the ratio of the inertial forces to the viscous forces, Reynold's number:

$$N_R = (2\ \rho\ u^2)/(\mu\ u\ r^{-1}) \quad \textbf{(5)}$$

where r is gas density, u is mean velocity, and μ is gas viscosity. The conditions that lead to turbulent flow (N_R 2000) generally do not occur in the distal airways, where the velocity of gas, u, is relatively low. In the proximal airways, however, where u is higher, conditions for a high Reynold's number occur more readily, and flow becomes turbulent when ventilatory rates are high. The pressure loss under a turbulent flow regime is as follows:

$$P_i - P_o = (1/\pi^2)\ f\ l\ r^{-5}\ \dot{V}^2 \quad \textbf{(6)}$$

where f is a friction factor that depends on wall roughness and N_R.

A critical insight from Eq. 4 and Eq. 6 is the importance (fourth and fifth powers!) of airway caliber. This is the basis for the increases in airways resistance seen when the airways are narrowed by mucus, smooth-muscle constriction, or remodeling in asthma, or by reduced tethering of the airways resulting from reduced elastic recoil in emphysema. A second critical insight is the dependence of turbulent flow on the density of the gas, r, rather than on its viscosity, μ, as in laminar flow. This is the basis for the sometimes dramatic clinical reduction in upper airway obstruction caused by local narrowing (tracheal tumor) observed when the low-density gas helium ("heliox") is substituted for the nitrogen in inspired gas.

Resistance in turbulent and orifice flow is higher than in laminar flow and is not constant, but increases with increasing flow and is characterized by curvilinearity of the overall pressure-flow relationship at higher flows (*dashed portion,* Fig. 4). This relationship may be approximated by the empiric Rohrer equation:

$$P_{ao} - P_{alv} = K_1\ \dot{V} + K_2\ \dot{V}^2 \quad \textbf{(7)}$$

where the constant K_1 reflects primarily the behavior under low flow and laminar conditions, and K_2 the additional costs of turbulent flow.

To measure the viscous pressure losses down the airways, it is necessary to know the gas pressure in the alveoli, P_{alv}. This cannot be measured directly in the intact chest, but it can be inferred by body plethysmography. The difference between P_{ao} and P_{alv} divided by the flow rate recorded with a pneumotachograph during a panting maneuver (to open the glottis as much as possible) yields airway resistance, R_{aw}. Another approach is to analyze volume-pressure loops (Fig. 1) and simultaneously measure flow rates; R may be obtained by dividing the width of the loop at a given volume by the difference in flow rates at that volume. A third approach, which may be used to estimate airway resistance in an intubated patient on a mechanical ventilator, takes advantage of the abrupt equilibration of the pressure at the mouth (P_{ao}) with the alveolar gas pressure (P_{alv}) when the distal end of the breathing circuit is briefly occluded at the end of inspiration. The abrupt decrement in pressure observed when the circuit is occluded may be attributed to the flow-related pressure drop along the airways. This observed pressure drop, divided by the preocclusion flow rate, gives R_{aw}.

At the distal end of the conducting airway tree, individual airways are very small and therefore each has a high resistance. Nevertheless, the flow through any one airway is very small because of the very large number of airways arranged in parallel, and consequently, the pressure drop across any one of these airways is quite small. Indeed, the greatest part of the total airway frictional pressure loss is incurred in the upper airways (nose, pharynx, and larynx); the loss is smaller in the trachea and proximal bronchi, and least in the distal airways. The overall airways resistance decreases with increasing lung volume because of the effect of lung recoil on airway caliber. Because their lengths and radii vary nearly as $V_L^{1/3}$, airways resistance, as can be derived after inserting such values in Eq. 4, is inversely related to lung volume. For this reason, R_{aw} is often multiplied by lung volume to obtain *specific airways resistance,* SR_{aw}, a parameter that is nearly independent of the lung volume at which it is measured. Its reciprocal is the *specific airways conductance,* SG_{aw}.

Frictional Pressure Differences Across the Lung Tissues

The solid structures of the respiratory system also incur frictional energy loss during breathing. This is the source of the openness of the very slow loop in Fig. 1. In contrast to the energy loss associated with gas flow in the airways, however, the frictional energy loss across the lung tissue is relatively independent of flow rate. Instead, it is a nearly constant fraction, h, of the tidal volume, V_T, multiplied by the overall tidal pressure excursion, V_T^2/ C_L. The mechanism for this behavior has not as yet been worked out, but there is some appeal in relating the observed energy losses to a parameter h, that is relatively constant, rather than to resistance, a parameter that is an inverse function of frequency and compliance. These tissue frictional losses are small. Nonetheless, in quiet breathing the airway pressure losses are also small, and the tissue frictional losses then represent a large fraction of the total.

Expiratory Flow Limitation

A very different phenomenon supersedes viscoelastic behavior at high rates of ventilation in normal subjects, or at lower rates of ventilation and even at resting ventilation in subjects with obstructive lung disorders. This phenomenon is expiratory flow limitation. Up to a certain relatively modest expiratory effort, flow increases linearly with increasing effort (*solid portion of the lines,* Fig. 4 and Fig. 5). Beyond this effort, however, flow is *effort-independent,* and for a given lung volume, flow does not increase even if more effort is applied (*dashed lines,* Fig. 5).

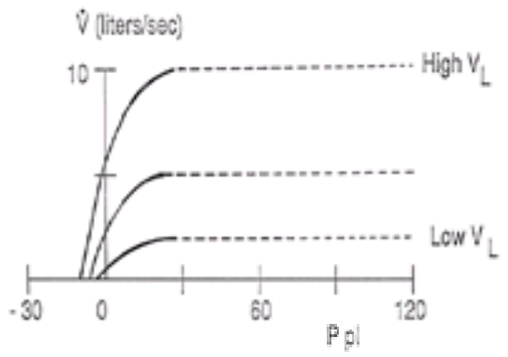

FIG. 5. Expiratory flow as a function of transpulmonary pressure for three different lung volumes. At each lung volume, the relationship is linear at low driving pressures, as in Fig. 4 (*solid portion of each curve*). At relatively modest expiratory efforts, however, flow reaches an absolute maximum; in other words, maximal flow is *effort-independent.* The maximal flow, however, is very much lower at lower lung volumes, showing that maximal flow is *volume-dependent.*

Maximal expiratory flow is also *volume-dependent.* This is readily seen by comparing the three curves in Fig. 5, each of which shows the flow-pressure relationship for a given lung volume. The limiting flow is higher for the higher volumes. This positive volume-dependence is directly demonstrated when maximal expiratory flow is plotted against lung volume (maximal expiratory flow-volume curve, or MEFVC) (Fig. 6).

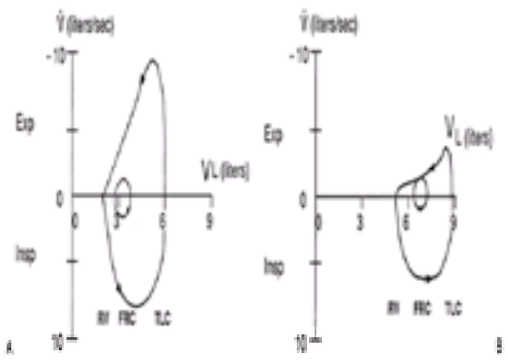

FIG. 6. A: Flow as a function of volume in a normal subject. The *outer loop* shows a forced expiration followed by a forced inspiration. The maneuver starts from a maximal inspiratory position, TLC. The expiratory flow rate peaks when about 20% of the VC has been expired and through the rest of expiration falls inexorably toward zero at maximal expiration, RV. Over this lower 80% of the forced expiratory VC, the curve is effort-independent and is extraordinarily reproducible in an individual *unless* there is a change in airway caliber (e.g., asthma) or lung recoil (e.g., emphysema). Flow during forced inspiration depends on airways resistance and the force/length/velocity properties of the inspiratory muscles. The *inner loop* shows quiet breathing, well within the outer (limiting) loop. As ventilation is increased, the loop increases its vertical dimensions (higher inspiratory and expiratory flows) and usually its horizontal dimensions (increased tidal volume) as well. At high levels of ventilation, however, the loop encounters the expiratory flow limit. Higher flows are then possible only if the curve moves to the right (to higher operating volumes), where the flow limit is higher. **B:** Similar plots in a subject with severe emphysema. Maximal expiratory flow at all volumes is severely decreased. This dynamically increases RV. Furthermore, the loop representing quiet breathing has been forced by the slope of the flow-limiting curve to move to the right. This increases FRC (hyperinflation). TLC is increased mainly because of the loss of elastic recoil. The increase of TLC is typically less than the increase of RV, and therefore the difference between TLC and RV (the VC) is decreased. Maximal *inspiratory* flow is decreased because of higher airways resistance and impaired inspiratory function at high chest wall volumes, but is less pronounced than is the decrease of maximal *expiratory* flow.

The example shown is of a normal subject performing a maximal forced expiratory maneuver followed by a maximal inspiratory maneuver. Having first inspired as deeply as possible, the subject makes a vigorous, sustained expiratory effort. The initial, rising portion of the MEFVC (roughly the first 20% of the VC) varies somewhat with effort, but the rest of expiration is flow-limited (i.e., effort-independent). In this flow-limited region, flow falls progressively during expiration and approaches zero flow at RV. This maximal forced expiratory maneuver has been dubbed an “unnatural act,” because it is not performed except in the laboratory and in certain individuals with severe obstructive lung disease during normal breathing. The concept of flow limitation and its indices, derived from the MEFVC, are useful in understanding and assessing ventilatory limitation and failure in obstructive airways disease.

In obstructive lung disease, maximal expiratory flow is reduced at all lung volumes (Fig. 6B). One consequence ABof this is an increase in the RV. A young, healthy subject can expire down to a statically determined volume at which the elastic recoil of the respiratory system and the available strength of the expiratory muscles are matched but oppositely directed (see above), but in obstructive lung disease the maximal expiratory flow is reduced, preventing the subject from expiring down to the statically determined RV; RV becomes dynamically determined.

With more severe disease, flow limitation may also increase FRC (“hyperinflation”). In the normal subject, quiet breathing follows a small inspiratory-expiratory flow-volume loop contained within the maximal loop. In obstructive lung disease, however, expiratory flow may encounter the flow limit even at rest. Passive expiration then may be interrupted by the next inspiration before the pressure difference across the passive respiratory system reaches zero (Fig. 2). FRC then also becomes dynamically increased above the elastically determined volume. The increase in volume may permit the ventilatory needs to be met, because of the positive volume-dependence of maximal expiratory flow.

One consequence of hyperinflation is elevation of end-expiratory alveolar gas pressure, as can be predicted from Fig. 2. This is readily measured in intubated patients when the airway is momentarily occluded at the end of passive expiration, and it provides a useful indication (“auto-PEEP”) of hyperinflation. With very severe disease, the expiratory flow limitation may be so extreme that resting FRC may end up higher than the premorbid TLC (Fig. 6B)! For hyperinflated patients to increase their ventilation above resting levels, they must breathe at even higher volumes. Although this increase in operating volumes permits a higher level of ventilation, it also impairs inspiratory muscle function by requiring the muscles to operate at shorter lengths and with less favorable mechanical purchase on the chest wall (e.g., flat diaphragm). Ironically, *expiratory* limitation burdens the *inspiratory* muscles! This mechanism (*expiratory* flow limitation ® *increased* operating volumes ® decreased *inspiratory* muscle reserve) is in fact the main cause of exercise limitation, fatigue, and ventilatory failure in acute and chronic obstructive lung diseases. Note that ventilatory capacity in obstructive lung disease is improved by improvement of inspiratory function (e.g., the ability of the chronically hyperinflated patient to inspire to very high lung volumes), and not by strengthening of the expiratory muscles.

It is not useful to think of expiratory flow limitation in terms of a flow resistance. Resistance is the inverse slope of the chord connecting a particular point on the expiratory flow/P_{pl} curve to the zero flow point (Fig. 5). R, as we have seen, is a very useful parameter at lower flows, predicting how much flow can be achieved for a given effort and explaining that prediction in terms of structure and physical properties. All of that significance is lost, however, when excess expiratory pressure is applied to the respiratory system (*dashed portions of the curves,* Fig. 5), and the slope of the chord, R, then varies with the expiratory effort.

The mechanism of expiratory flow limitation involves an interplay between the mechanical properties of the airways, the lung parenchyma, and the characteristics of the respired gas. Consider that in the absence of flow, the airways are effectively distended by lung recoil, $P_{alv} – P_{pl}$. The pressure difference across their walls is the intra-airway pressure, P_{aw}, less the peribronchial pressure, $P_{p\text{-}br}$. P_{aw} is the same as P_{alv} in the absence of flow, and $P_{p\text{-}br}$ is approximately the same as P_{pl}. In expiration, however, P_{aw} is lower than P_{alv} because of frictional viscous losses and the Bernoulli effect. The Bernoulli effect is the lowering of pressure associated with an increase of velocity, and it becomes important in the proximal airways because of convective acceleration, resulting from a substantial increase in the velocity (Dv) of the expired gas as it enters the much smaller net cross-sectional area of the large airways and trachea. A lower intrabronchial pressure produces a lower bronchial transmural pressure difference, which in turn produces a narrower airway, which in turn requires a higher velocity because of convective acceleration, which in turn produces a lower intrabronchial pressure because of the Bernoulli effect. And so on. This cycle of effects has an equilibrium at low expiratory flows solution at all points in the airway. But at some particular higher expiratory flow rate, the cycle of effects reaches the point at some location along the airways at which any higher flow rate would be impossible because it would be incompatible with the airway remaining open! This location is called the aerodynamic “choke point,” and the flow at which it develops is the maximal expiratory flow rate. This maximal flow depends (positively) on three conditions: (1) cross-sectional area and stiffness of the airway at the choke point, (2) elastic recoil (because it provides the driving pressure for flow in the airways upstream of the choke point and because its tethering action increases the

cross-sectional area and stiffness of the airway), and (3) low resistance of the airways upstream of the choke point. The features of expiratory flow limits in health and disease can be understood in this framework. None of these three conditions depends on expiratory effort—hence the *effort-independence* of maximal expiratory flow. The second and third conditions are increased by higher lung volumes—hence the positive *volume-dependence* of maximal flow. Asthma lowers maximal expiratory flow by reducing the caliber of the airways (the first and third mechanisms), and emphysema largely by reducing lung elastic recoil (the second mechanism).

The principles of flow limitation are also relevant to cough. Immediately upstream of the choke point, the airways are dynamically compressed during a cough and the velocity of the air stream is high. As the kinetic energy of the air stream is proportional to the square of its velocity, the energy available to shear mucus from the airway walls is markedly enhanced by this dynamic compression. The choke point moves peripherally as lung volume decreases, and for this reason serial coughs at lower volumes clear progressively more peripheral airways.

DISTRIBUTIONS OF VOLUME AND VENTILATION

The lung parenchyma, consisting largely of interconnected alveolar septa, divides the gas in the human lung into an estimated 400,000,000 gas-exchanging alveolar spaces. What governs the distribution of gas volume within the parenchyma? What mechanisms ensure that inspired gas distributes itself so that there is a reasonable turnover of the resident gas throughout the parenchyma?

Distribution of Volume

The alveolar septa and the alveoli exhibit a degree of variability in size and shape but generally appear to be made of the same structural components. There is no evidence of nonuniformity of elastic properties at a scale larger than about 0.5 cm. Furthermore, at a local level the parenchyma is stable in the sense that one small region is constrained from enlarging or shrinking at the expense of its neighbors. This stability, “mechanical interdependence,” is an inherent property of a network constructed of elastic elements with positive length-tension compliances.

At a regional level, however, there is significant nonuniformity of inflation, primarily because of gravity. The weight of the lung tissue (including blood) makes it sag. As a result, the alveoli in the upper regions are relatively inflated and those in the dependent regions relatively deflated. In the upright position, this gradient of inflation applies from apex to base. In the left lateral decubitus position, it applies from right to left. A vertical gradient of inflation reflects a vertical gradient of elastic tensions, the septal tensions being greater in the upper region from which the lung is “hung” and lesser in the dependent region on which the lung is “sitting.” Although the details of the distribution of pleural pressure remain somewhat controversial, a reasonable starting assumption is that pleural pressure and the associated elastic tensions within the parenchyma maintain a vertical gradient (in centimeters of water per centimeter of vertical distance) equal to lung density (in grams per cubic centimeter), such that the difference in lung recoil between the apex and base of a lung 30 cm in height might be on the order of 6 cm H_2O.

Distribution of Ventilation

In the healthy lung, there is both local and regional nonuniformity of ventilation. At a scale of about 0.5 cm, the nonuniformity of ventilation is modest. At FRC, the variability of the distribution of ventilation has been quantitatively estimated (in terms of the variability of the volume of regions as fractions of their volumes at full expansion) as being on the order of 0.013. The source of the variability presumably is local nonuniformity of elastic tensions. A much greater nonuniformity, however, results from the systematic vertical gradient of ventilation. With quiet breathing in a sitting position, the ventilation of the dependent regions of the lung is about twice that of the apical regions. The generally accepted mechanism for this is that the more distended apical regions of the lung are less compliant than the less distended basilar regions.

Figure 7 shows the specific compliance to be a decreasing function of elastic recoil. Specific compliance is the inverse slope of the $V/P_{el,L}$ curve *divided by V.* It represents the volume change for a given volume of gas rather than for a given anatomic entity, such as an alveolus, and is useful for calculating the fractional turnover of resident gas. Given the assumption that the amplitudes of the pressure swings during the breathing cycle are reasonably uniform, the specific compliance predicts that the turnover of resident alveolar gas volume will be less where the distending pressure is greater, at the apices in the vertical lung, and greater where the distending pressure is very low, in the more dependent regions. An additional nonuniformity of ventilation is seen when portions of lung deflate so far during the breathing cycle that the airways serving them close, trapping gas in the alveolar regions they serve, until a deep inspiration increases the local inflating pressures above the critical opening pressures of the regions.

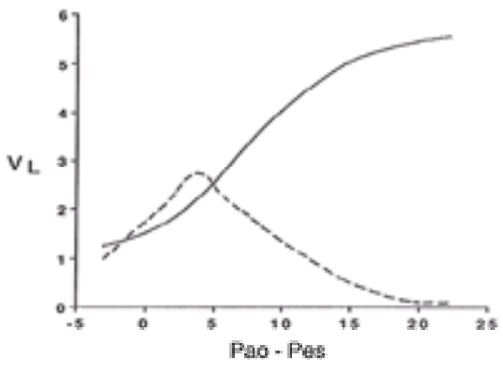

FIG. 7. Regional ventilation depends on regional specific compliance. Lung volume (V_L) (*solid curve*) and specific compliance (SC_L) (*dashed curve*) as functions of lung recoil pressure ($P_{ao} – P_{es}$) obtained during a slow expiration. In the upright chest, the recoil pressure is greater at the apex of the lung ($P_{ao} – P_{es} \sim 8$) than at the base ($P_{ao} – P_{es} \sim 2$). Because SC_L is less at 8 than at 2, the apical region is correspondingly less ventilated.

Finally, viscous properties may cause nonuniformity of ventilation at higher levels of ventilation or with narrowing of the airways. Consider a model in which a number of viscoelastic units ventilate in parallel (e.g., lobes, lobules, or smaller units). Each ventilating unit consists of a flow-resistive element (airway) and an elastic element (distensible parenchyma) in series. The passive emptying of such a unit follows an exponential time course:

$$V = e^{-t/(RC)} \quad \textbf{(8)}$$

where t is the time from the onset of the passive expiration, R is the flow-resistance of the airway of the unit, and C is its compliance. The product, RC, is the *time constant* of the exponential decay and is the time when emptying is 1/e, or about half completed. When regional time constants are short compared with the time of expiration, as they are in the healthy lung during quiet breathing, all units expire to their elastically determined volume. However, when breathing is rapid, and particularly when time constants are longer (higher airway resistance, higher compliance, or both), passive emptying is not completed in all lung units; those units with higher time constants lag behind those with lower time constants. Units with lower time constant are preferentially ventilated.

In disease states, volumes may be very unevenly distributed because of local changes in elastic properties, either from altered connective tissue properties or impaired surfactant. Ventilation may also become unevenly distributed because of uneven time constants, as in asthma, in which the R of small airways is (unevenly) increased, and in emphysema, in which both the R and the C (because of the loss of elastic structure) are increased.

Different patterns of respiratory muscle recruitment may also result in uneven distribution of ventilation, although the effect is small relative to that produced by inequalities of unit time constants. Inhalations deriving from contractions of rib rather diaphragmatic muscle result in preferential distribution of ventilation to the upper lung units, as does active expiration to RV followed by a passive inspiration.

LUNG MECHANICS AND PULMONARY HEMODYNAMICS

Respiratory mechanics directly affect the right ventricular preload, the right ventricular afterload, the left ventricular afterload, and the volume of the intrapulmonary extracapillary vessels. These effects become particularly important during mechanical ventilation.

Lung mechanics affect pulmonary hemodynamics by three distinct mechanisms.

The first mechanism is a consequence of the effects of intrathoracic pressure on right ventricular preload and left ventricular afterload. Intrathoracic pressure varies during spontaneous breathing, voluntary inspiratory or expiratory efforts, and mechanical ventilation. Such changes alter the relationships between the intrathoracic and extrathoracic vascular pressures; in particular, the intravascular pressure gradients at the thoracic inlet and at the level of the diaphragm may be affected. For example, during normal breathing, inspiration *decreases* all intrathoracic pressures relative to extrathoracic pressures. The fall of pressure in the intrathoracic vena cava relative to that in the extrathoracic great veins momentarily aids return of venous blood from the abdomen, head, and limbs. Similarly, the fall of blood pressure in the thoracic aorta relative to that in the arteries of the upper extremities, neck, and abdomen momentarily impedes arterial outflow. A spontaneous inspiration, then, has the effects of momentarily *increasing* right ventricular preload and left ventricular afterload.

Opposite effects occur when the inspiration is passively delivered by mechanical ventilation, because it passively *increases* all intrathoracic pressures relative to extrathoracic pressures. This impedes filling of the right side of the heart and aids emptying of the left side of the heart (i.e., it momentarily *decreases* both the right ventricular preload and the left ventricular afterload). Greater effects are seen when pressure changes affect the full breathing cycle, as in continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP). The increase in intrathoracic pressure under these circumstances is predictably the increase of chest wall volume achieved by the CPAP or PEEP divided by the compliance of the passive chest wall (Fig. 3). Although the changes of pressure may be small, the effects on right ventricular preload may be large, because the right ventricle in diastole is highly compliant. This reduction of right ventricular preload and left ventricular afterload explains the immediate benefit of CPAP or PEEP in acute pulmonary edema, and also the reduction of cardiac output that may ensue when CPAP or PEEP is applied in patients whose intravascular volumes are low or applied pressures are high.

No hemodynamic effects are *directly* attributable to changes of intrathoracic pressure on structures that lie completely *within* the thorax. Consider, as an example, the rise in pulmonary capillary wedge pressure, PCWP, seen when PEEP or CPAP is applied to the airway. The PCWP tracing provides an estimate of left atrial pressure and, in the absence of mitral disease, of left ventricular end-diastolic pressure. The increases of these pressures associated with PEEP or CPAP, however, do not quantitatively reflect increases in the transmural pressure differences across the atrium or ventricle (the measurements with functional meaning because they indicate the degree of filling of the chambers and their compliance) except in the unlikely event that the intrathoracic pressure is unchanged. Fortunately, the relevant transmural pressure differences can be estimated from PCWP – P_{es}.

The second mechanism operates through effects of lung elastic recoil, $P_{alv} - P_{pl}$, on right ventricular afterload. Consider the relationships among the pressures in the alveoli, P_{alv}, the pleural space, P_{pl}, the pericardial space, P_{pc}, and the cavity of the right ventricle, P_{RV}. The contractile tension of the right ventricular myocardium during systole creates a transmural pressure difference between the right ventricular cavity and its pericardial (equivalent of pleural) surface, $P_{RV} - P_{pl}$. Pressure in the right ventricle exceeds that in the pulmonary capillary because of frictional losses, $P_{RV} - P_{pc}$. The distending pressure of the pulmonary capillary must be positive for it to remain open, $P_{pc} - P_{alv}$. Pressure in the alveolus exceeds pleural pressure because of lung elastic recoil, $P_{alv} - P_{pl}$. These serial pressure differences can be related in the algebraic identity as follows:

$$(P_{RV} - P_{pl}) = (P_{RV} - P_{pc}) + (P_{pc} - P_{alv}) + (P_{alv} - P_{pl}) \quad \textbf{(9)}$$

which shows that the right ventricular transmural pressure difference equals the sum of the frictional pressure drop in the pulmonary arteries, the distending pressure of the capillaries, and lung recoil. The latter is generally the largest of the three, and it becomes particularly important when high inflating pressures are imposed by mechanical ventilation.

A third mechanism, probably of little clinical significance other than that it contributes to tamponade physiology, links lung distention to the blood volumes of the intrapulmonary, extra-alveolar arteries and veins. Lung distention *per se* distends all but the smallest intrapulmonary arteries and veins, as was demonstrated in the l920s by C. C. Macklin, who found that positive-pressure inflation of an excised lung paradoxically sucked fluid into these vessels! The explanation of this phenomenon is that these vessels, lying within the bronchovascular compartments, exhibit “mechanical interdependence” with the elastic structure of the surrounding lung. The result of this mechanism is that the volumes of both vascular compartments increase and decrease cyclically as the lung inflates and deflates.

ENERGETICS: WORK RATE AND COSTS OF BREATHING

Spontaneous ventilation reaches its limit and respiratory failure may ensue when respiratory muscles, usually the muscles of inspiration, are overloaded. Up to this point, we have characterized only the *pressure* loads presented by the passive respiratory system. The ability of the muscles to accomplish a given ventilatory task, however, depends not only on the forces they must develop to overcome the pressure loads of the task, but also on the required *velocity* of shortening, on the *duration* of activation, and, most importantly, on their *operating lengths.* These factors may be linked through consideration of the energetics of breathing, first by calculating the *viscoelastic work rate,* which is the rate of *physical* energy required by the passive respiratory system to carry out a given ventilatory task in a given time, and second by measuring the *oxygen consumption,* which is the *chemical* energy actually expended by the muscles in carrying out the task. As the inspiratory muscles are far more critical to ventilation than are the expiratory muscles, we focus on the *inspiratory* work load.

Viscoelastic Work of Breathing

The physical work, W, performed by a muscle in carrying out a given task is the integral of force it develops, F, times the incremental distance it shortens, dl—that is, $\int F\,dl$, or equivalently the integral of pressure times the incremental volume displaced, $\int P\,dV$. The mean inspiratory work *rate,* $\dot{W}_{insp}$, is the work of a single inspiration times the frequency, f. The integral can be depicted graphically (Fig. 8), so that the work performed on the passive respiratory system in a single inspiration is the area between the $V_L/P_{rel,rs}$ curve and the volume axis.

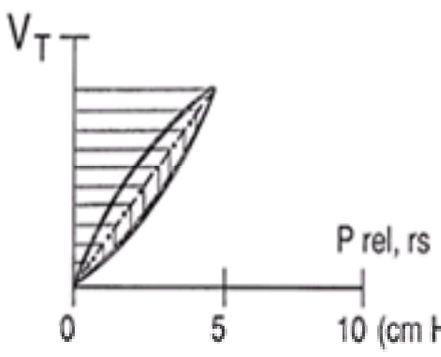

FIG. 8. The pressure difference across the passive respiratory system, $P_{rel,rs}$, as a function of displaced volume, as in Fig. 1. The work of a single inspiration is the integral $\int P_{rel,rs}\,dV$ and can be partitioned into elastic (*horizontal shading*) and viscous (*vertical shading*) work with the assumption of linearity of elastic recoil between end-inspiration and end-expiration.

Work performed on the respiratory system can be partitioned into two components. That expended on the lung can be distinguished from that expended on the chest wall by integrating the transpulmonary pressure difference, $P_L = P_{ao} - P_{es}$ (lung component), and the pressure difference across the chest wall, $P_{rel,cw} = P_{es} - P_{bs}$ (chest wall component). Work can be further partitioned between elastic and viscous sources based on the assumption that the elastic component (Fig. 9) is linear between the end-inspiratory and end-expiratory points. A line drawn between these two points separates the work expended to overcome elastic forces (*horizontal shading*) from that expended to overcome the viscous forces (*vertical shading*).

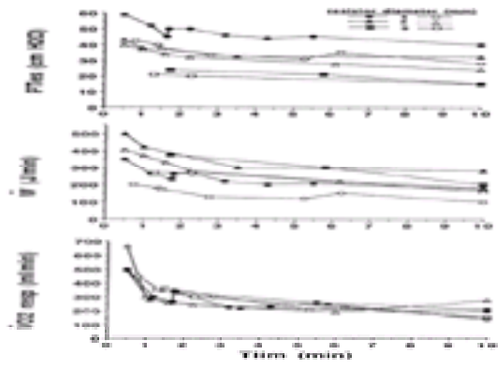

FIG. 9. Endurance in a variety of strenuous ventilatory tasks. A normal subject was assigned a variety of tasks, each of which entailed breathing an assigned tidal volume at an assigned frequency from spontaneous or increased FRC (*closed and open symbols*), through a range of inspiratory resistors (*circles, triangles, squares*), until he could no longer maintain the task. **A:** Plot of the esophageal pressure-time product, PT_{es}, against time to task failure, T_{lim}. **B:** Data replotted to show the work rate, $\dot{W}$. **C:** Data replotted to show the incremental oxygen consumption incurred in carrying out the assigned task. The ability of the inspiratory muscles to sustain a specific ventilatory task is reduced as the pressure, flow, duty cycle, or lung volume is increased. There are trade-offs among the four variables such that, for example, the same time to task failure, T_{lim}, is seen in high-pressure, low-flow tasks and low-pressure, high-flow tasks. Neither pressure nor work rate of an imposed breathing task predicts endurance well when volume or flow is varied. The incremental oxygen cost of the task is the best predictor.

The effects of increasing ventilation, of changing the pattern of breathing, or of changes in the mechanical properties of the respiratory system can be analyzed graphically or mathematically. Graphically, the elastic work of a single inspiration (area) is increased when tidal volume, V_T, is increased (extending the line representing the elastic component), when compliance, C_{rs}, is decreased (lowering the slope of the V/P_L curve), or when there is hyperinflation (sliding the operating volumes up the elastic line), and the elastic work rate is that area times the frequency, f. Mathematically, these relationships can be expressed in the following equation:

$$\dot{W}_{el} = (V_T/C_{rs})\,(V_T/2 + \Delta FRC)\,f \qquad \textbf{(10)}$$

where DFRC is the increment above FRC determined elastically, and $\dot{W}_{el}$ is the rate of elastic work performed.

Graphically, the viscous work is increased when the volume-pressure loop is widened by increase of inspiratory flow, $\dot{V}$, or resistance, R_{rs}. Mathematically, these effects on viscous work rate can be seen from the following relationship:

$$\dot{W}_{res} = (\pi^2/4)\,R_{rs}\,V_T^2\,f^2 \qquad \textbf{(11)}$$

where $\dot{W}_{res}$ is the rate of resistive work performed.

Note the interactions between frequency, tidal volume, and ventilation. For example, at a given ventilation, an increase in frequency requires a decrease in tidal volume. These changes have opposing effects on work rate. More rapid, shallower breaths increase overall ventilation for a given alveolar ventilation, increasing the inspiratory flow rates, $\dot{V}$, and therefore the viscous load, but decreasing the elastic load. The net effect on $\dot{W}$ is relatively small over the usual breathing rates, but the effect may become significant at very high or very low frequencies. Usually with increases in ventilation, both frequency and tidal volume increase and $\dot{W}$ increases on both counts. Finally, the work of decompressing intrathoracic gas during inspiration against airway resistance can also be calculated; it can become significant when inspiratory resistance is high, as in asthma.

Energy Costs of Breathing

More relevant to the ability of the respiratory muscles to accomplish a given ventilatory task is the (metabolic) energy cost of that task, and this may differ substantially from the energy actually converted into viscoelastic work. First, it is possible for metabolic costs to be considerable even when no viscoelastic work is accomplished, as during inspiratory effort against a closed glottis, in which chemical energy (adenosine triphosphate) is expended but no work is done. Second, the purpose of muscular contraction is to displace the chest wall against a pressure load, accomplished by shortening of the muscle against a force load. However, the displacement and pressure effected by a given muscle depend on its mechanical coupling to the respiratory system and on the coordination of its contraction with the contraction of the other respiratory muscles. For these reasons, the viscoelastic work of a particular breathing task may be a very misleading index of the difficulty of actually accomplishing the task. Furthermore, the ability of a muscle to develop force depends on its length. For this reason, inspiratory muscles are weak at high lung volumes and cannot perform as they can at lower lung volumes. These three conditions (expenditure of energy without accomplishing work, operating at unfavorable mechanical advantage or with suboptimal coordination, and operating at unfavorable sarcomere lengths) particularly impair inspiratory muscle function at high lung volumes.

The energy costs of a breathing task turn out to be a much better predictor of the ability of the respiratory muscles to perform a task than is the viscoelastic work. Time to task failure has been studied for a variety of sustained tasks. It is shortened by tasks in which inspiration is elastically loaded, resistively loaded, or performed at increased lung volumes. The incremental energy cost (oxygen consumption) is not simply related to the physical work accomplished (viscoelastic work rate in the loaded breathing task); the efficiency of the system is variable among different tasks. Oxygen consumption has been found to be the parameter that best predicts the time to task failure (Fig. 9). This suggests that the limit to sustainable performance of the respiratory muscles is the rate at which they can aerobically generate adenosine triphosphate. This in turn depends on the pattern of pressure and flow loads rather than the external work accomplished. More critically, it depends on the operating lung volume, which is so critical to respiratory failure and to the ability of a hyperinflated patient to be weaned from mechanical ventilation.

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CHAPTER

5 Nonrespiratory Functions of the Lung

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INTRODUCTION

The human respiratory tract is a complex organ system specialized for exchange of gases between environmental air and blood circulating through the pulmonary vascular bed. The respiratory system also performs a spectrum of important nonrespiratory functions (Table 1). Certain of these lung functions, such as speech, heat and water conservation, host defense, and filtration of systemic blood, are a consequence of unique anatomic features of the respiratory system. Functional diversity of the lungs also arises from a heterogeneous population of constituent cells that participate in water and electrolyte transfer, air space defense, local neuroendocrine regulation, xenobiotic metabolism, and excretion of volatile substances. This chapter reviews the nonrespiratory functions of human respiratory tract cell populations as they relate to morphologic organization within functionally distinct compartments, including the conducting airways, alveolar region, and vascular structures. The important role of the lung in host defense is reviewed elsewhere in this volume; therefore, only a summary table of lung host defenses is provided for reference (Table 2).

Speech
Heat and water conservation
Electrolyte transport
Host defense
Neuroendocrine secretion
Xenobiotic metabolism
Surfactant synthesis and turnover
Antioxidant defense
Excretion of volatile substances
Filtration
Hemofluidity

TABLE 1. *Nonrespiratory functions of the lung*

Irritant reflexes
Cough
Sneeze
Bronchoconstriction
Mechanical barriers
Nasal vibrissae
Nasal turbinates
Nasopharyngeal and oropharyngeal walls
Airway carinae
Lymphoid tissues
Waldeyer's tonsillar ring surrounding orifice to lower airways
Bronchus-associated lymphoid tissue (BALT)
Mucociliary escalator
Humoral immunity
IgA—predominant in upper airways
IgG—predominant in lower airways
IgM and IgE also present
Cellular defenses
Lymphocytes—individual or aggregates
Natural killer cells
Macrophages—intravascular, interstitial, or alveolar
Polymorphonuclear leukocytes

TABLE 2. *Lung host defense*

FUNCTIONS RELATED TO CONDUCTING AIRWAYS

Speech

Speech and language are uniquely human characteristics generated by coordinated activity of the cerebral cortex, the brain stem respiratory drive center, and structural components of the upper airway. Phonation, or creation of sound, results from purposeful expiration of air through the vocal cords located within the larynx. Changes in the pitch of sound emitted by the larynx are achieved by stretching or relaxing the vocal cords and by altering the shape and mass of vocal cord edges. Resonance is added by several structures, including the mouth, nose and paranasal sinuses, pharynx, and chest cavity. Final articulation of sound into language is accomplished with the lips, tongue, and soft palate.

Heat and Water Conservation

During normal spontaneous respiration, inspired air is fully saturated with water vapor at body temperature (Fig. 1). Incoming ambient air is warmed by conduction and convection as it passes through the nasopharynx and tracheobronchial tree. As inspired air is warmed, it is also humidified by evaporation of water from the airway lining. Evaporation of water from the mucosal surface during inspiration transfers thermal energy to the passing air stream and results in net cooling of the airway surface.

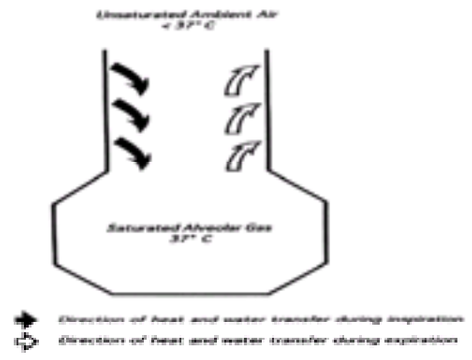

FIG. 1. Countercurrent heat and water exchange in conducting airways.

During expiration, temperature and vapor pressure gradients are reversed, and air loses thermal energy to the cooler airway surface. As air cools during expiration, its ability to hold water decreases, and water condenses along the airway surface. Countercurrent exchange of heat and water during normal tidal respiration allows conditioning of inspired air while thermal energy and water are conserved during expiration. Under normal circumstances, tidal respiration results in a net loss of only about 250 mL of water and 350 kcal of heat from the airways in a 24-hr period.

Countercurrent heat and water exchange is influenced by environmental factors and air flow velocity. Net transfer of heat and water depend on temperature and vapor pressure gradients between the airway surface and passing air stream. Low environmental temperatures increase convective cooling of the airway surface; low humidity enhances evaporative cooling of the airways. The additional heat and water required to condition inspired air raise caloric requirements in cold climates.

Transfer of heat and water from the mucosal surface to inspired air is also related to linear velocity of air flow. Higher flow velocities are associated with lower rates of heat and water transfer to the air stream during inspiration and reduced condensation during expiration. Increases in ventilation during physical activity or other stresses thereby augment the net loss of heat and water from the mucosal surface.

Temperature of the internal milieu can also affect net heat and water transfer. The reduction in temperature gradient between air leaving the lungs and the mucosal surface that occurs at elevated body temperatures facilitates water loss. Net water loss in the setting of fever or physical exertion may actually serve as a mechanism for temperature regulation. The respiratory tract has a major role in temperature control in fur-bearing animals; however, it is not thought to affect core temperature regulation significantly in humans under normal circumstances.

Airway heat and water exchange may have important clinical implications in asthmatic patients, in whom airway cooling caused by low ambient temperatures or increased minute ventilation may provoke bronchospasm. Bronchoconstriction in cooler environments may result from acute stimulation of thermally sensitive body surface and mucosal receptors; however, airway constriction in some asthmatic patients may outlast the duration of thermal receptor stimulation. In this setting, bronchoconstriction is thought to relate to enhanced heat and water loss from the mucosal surface. Ambient temperature-induced bronchoconstriction may be mimicked in asthmatic subjects by increasing minute ventilation at any level of ambient temperature and humidity.

Heat and water exchange in the conducting airways may affect the mucociliary transport mechanism. Effective ciliary action depends on the volume and composition of the overlying mucus layer. Although characteristics of this fluid layer are largely determined by active ion transport across the epithelium and by autonomic control of submucosal gland secretion, evaporative losses and thermally regulated secretion and reabsorption may also contribute to fluid characteristics at the mucosal surface.

Electrolyte Transport

Airway epithelial cells actively transport electrolytes between the airway lumen and the interstitial compartment of the alveolar wall (Fig. 2). Water absorption passively follows net Na^+ transfer from the mucosal surface to the interstitial compartment. In contrast, net fluid secretion is a function of active epithelial cell Cl^- transport from the interstitium to the airway lumen; water passively follows Cl^- movement into the lumen. The balance between Na^+ absorption and Cl^- secretion, and hence net water movement, depends on airway region, pharmacologic intervention, and neurohumoral influences.

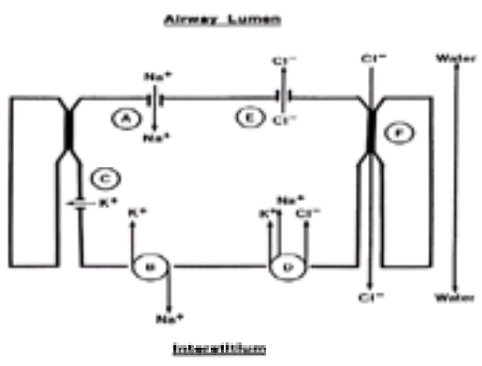

FIG. 2. Electrolyte transport by lung epithelial cells. Na^+ moves passively from the airway lumen into the epithelial cell through a selective Na^+ channel (**A**) down an electrochemical gradient. Na^+, K^+-ATPase (**B**) located in basolateral membranes actively pumps Na^+ from the cell into the interstitium in exchange for K^+, thereby maintaining an intracellular Na^+ concentration that favors passive Na^+ diffusion from the lumen. The accumulation of K^+ within the cell creates an electrochemical disequilibrium that favors passive movement of K^+ out of the cell through basolateral K^+ channels (**C**). Movement of K^+ into the interstitial compartment maintains an intracellular electrochemical gradient that is favorable for Na^+ entry and Cl^- secretion. Cl^- enters the cell from the interstitial space on the Cl^--Na^+-K^+ cotransporter (**D**). Cl^- is then secreted by passive movement down an electrochemical gradient through selective apical membrane Cl^- channels (**E**). Under normal basal conditions, Na^+ is absorbed from the lumen down its electrochemical gradient. Cl^- and water are passively absorbed through a permeable paracellular pathway (**F**) secondary to net Na^+ movement toward the interstitium. Water secretion occurs when the electrochemical gradient favors Cl^- movement into the airway lumen. Cl^- secretion requires activation of apical Cl^- channels.

The predominant direction of fluid movement under basal conditions is from airway lumen to interstitium. Fluid accumulates in the proximal airways as secretions converge from distal regions of greater cross-sectional area via mucociliary transport. Fluid homeostasis is maintained primarily by absorption of Na^+ from the airway lumen down an electrochemical gradient. Cl^- and water follow Na^+ through permeable paracellular pathways. Net Cl^- secretion by epithelial cells is unusual under basal circumstances. However, inhibition of Na^+ absorption, with amiloride, for example, may shift the electrochemical gradient in favor of Cl^- secretion. Furthermore, Cl^- secretion may be stimulated by several neurohumoral agents. Prostaglandins E_2 and F_{2a}, b-adrenergic agents, leukotrienes, adenosine, vasoactive intestinal peptide (VIP), and bradykinin stimulate epithelial Cl^- and water secretion; these mediators activate intracellular second messengers (cAMP, diacylglycerol, Ca^{2+}) that in turn activate apical Cl^- channels and lead to net water secretion.

As previously noted, effective mucociliary clearance depends on mucosal epithelial cell electrolyte and fluid transport. Mucociliary transport forms an important defense against foreign material that comes in contact with the mucosal surface of the airway. The fluid component of the mucociliary transport system is produced by secretory epithelial cells and submucosal glands. Two layers of fluid cover the airway mucosa (Fig. 3). A thin, watery sol layer of low viscosity is in direct contact with epithelial cells and allows free movement of cilia. A slightly thicker and more viscous gel layer rests above the sol layer and traps particulate matter for removal by rhythmic ciliary beating. The sol layer is produced by secretory epithelial cells, whereas the more viscous gel layer arises from submucosal glands.

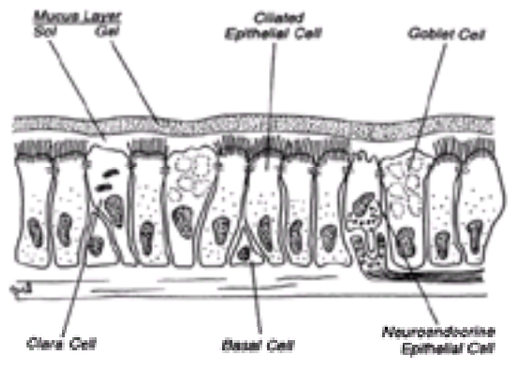

FIG. 3. Histology of conducting airway epithelium.

Epithelial secretory cells of the conducting airways are generally of three varieties. Goblet cells produce a complex mixture of glycoprotein, lipid, immunoglobulin, salt, and water. Serous epithelial cells contribute neutral glycoproteins, lysozyme, and an epithelial transport component of IgA to the sol layer. Clara cells are nonciliated epithelial cells found in highest density in the bronchioles. These cells demonstrate secretory granules containing lipid, protein, and neutral glycoprotein. It has been suggested that Clara cells secrete the hypophase of the surfactant layer.

The clinical impact of epithelial secretory function is demonstrated in cystic fibrosis. In cystic fibrosis, abnormally increased epithelial Na^+ absorption and decreased Cl^- secretion result in relatively dehydrated mucus and defective mucociliary transport. As a result, individuals with cystic fibrosis frequently have severe respiratory infections.

Metabolism

Epithelial cells of the conducting airways are generally metabolically active cells engaged in production of mucoid secretions, electrolyte transport, and xenobiotic metabolism. Synthesis and release of soluble mediators, such as the eicosanoids prostacyclin (PGI_2) and PGE_2, have been reported. Lung epithelial cells demonstrate antioxidant defense mechanisms against free radical oxygen species that may arise from endogenous oxidative metabolism; high concentrations of inspired oxygen, ozone, or airborne chemicals; and circulating xenobiotic compounds.

Xenobiotic Metabolism

Xenobiotic metabolism is largely a function of the liver; however, the presence of xenobiotic metabolizing enzymes in the human lung is well documented. These pathways generally involve both metabolic (phase I) and conjugative (phase II) reactions. Phase I reactions include oxidation, reduction, or hydrolysis; they generate metabolites that may or may not retain pharmacologic activity of the original xenobiotic. Oxidative reactions most often involve metabolism via the cytochrome P_{450} enzyme system. Phase II reactions involve glucuronidation, sulfation, acetylation, or conjugation with glutathione or amino acids. These reactions render the parent xenobiotic, or its metabolite, water-soluble and devoid of pharmacologic activity.

Relatively low concentrations of several xenobiotic deactivating enzymes have been identified in the lung (Table 3). The fact that the distribution of xenobiotic metabolizing enzymes is limited to Clara cells and type II alveolar epithelial cells may account for the relatively low levels of these enzymes in the lung as a whole. Cytochrome P_{450} mono-oxygenase activity has been localized within Clara cells of the conducting airways. Other phase I enzymes, including ethoxycoumarin-*O*-de-ethylase, a microsomal enzyme that catalyzes *O*-demethylation, and epoxide hydrolase, which catalyzes hydrolysis of epoxides arising from oxidative metabolism, have been identified in the lung. Their cellular distribution is less well defined. Activity of several conjugative enzymes has also been demonstrated in the lung; these enzymes include glutathione-*S*-transferases, acetyltransferase, and sulfotransferases.

	Lung	Liver	Intestine	Kidney
Phase I activity				
ECOD	1.0	20.6	0.5	1.2
mEH	0.1	2.1	<0.1	<0.1
Phase II activity				
GST	0.1	0.2	0.1	0.2
AT	0.1	0.7	0.3	0.2
P-ST	<0.1	0.1	<0.1	<0.1

ECOD, ethoxycoumarin-*O*-de-ethylase; mEH, microsomal epoxide hydrolase; GST, glutathione-*S*-transferases; AT, acetyltransferases; P-ST, phenol sulfotransferases.

[a] The table shows relative activities of five enzymes in lung, liver, intestine, and kidney. All activities, which are expressed relative to ECOD in lung, were derived from data presented by Krishna and Klotz.

TABLE 3. *Relative activities of deactivating enzymes in major organ systems*[a]

Many circulating basic lipophilic amines undergo first-pass retention in the lung as a result of endothelial metabolism. Significant first-pass removal has been demonstrated for propranolol, meperidine, fentanyl, and sufentanil, as examples. Retention and extraction of drugs is a function of diffusion or active transport of the substance into the intracellular compartment, followed by enzymatic modification. First-pass retention appears to be a partially saturable phenomenon, whereas overall extraction occurs independently of substance concentration.

Antioxidant Defense

By virtue of its large surface area that is continuously exposed to environmental air, the respiratory epithelium is at risk for damage caused by free radical oxygen metabolites. Generation of free radicals from exogenous sources may be achieved by direct interaction between inhaled agents and epithelial cells, and indirectly via activation of airway inflammatory cells that generate large quantities of reactive oxygen species. Endogenous oxidative metabolism also generates oxygen-derived free radical species that may interact with cell membrane phospholipid moieties and glycoproteins and thereby disrupt their structural integrity. Reaction of oxygen-derived free radicals with cellular components is thought to contribute to the pathogenesis of many disease processes, including bronchopulmonary dysplasia, asthma, emphysema, pulmonary fibrosis, and ARDS (adult respiratory disease syndrome).

The most biologically active oxygen species include superoxide, hydrogen peroxide, hydroxyl radical, and nitric oxide, although several other species have been identified. Superoxide is generated as a by-product of mitochondrial respiration or by interaction of microsomal and nuclear membrane cytochromes with oxygen; it subsequently spontaneously dismutates or is scavenged by superoxide dismutase. Hydrogen peroxide is formed indirectly from enzymatic and nonenzymatic dismutation of superoxide or directly by a cytoplasmic reaction catalyzed by xanthine oxidase. Hydrogen peroxide decomposes into water and oxygen in the presence of catalase. Hydrogen peroxide and alkylhydroperoxides are also scavenged by glutathione redox reactions. Superoxide and hydrogen peroxide react to generate hydroxyl radicals. Hydroxyl radicals also arise from Haber-Weiss and Fenton reactions, which are catalyzed by trace levels of transition metals such as Fe^{2+}. Nitric oxide is formed from the terminal guanidine nitrogen atom of L-arginine by NADPH-dependent oxidation; the reaction is catalyzed by nitric oxide synthase. Although nitric oxide has become well-known for its favorable vasodilatory properties, it can react with superoxide to form peroxynitrite, which degenerates into other very potent mediators of oxidant injury. Free radicals may be released into the extracellular environment if they are produced in quantities that exceed intracellular scavenging mechanisms.

Lung antioxidant defense mechanisms protect airway epithelial and other cell types from harmful effects of reactive oxygen species generated by endogenous metabolism and inhaled chemicals. The major intracellular defense mechanisms against reactive oxygen species include superoxide dismutase, catalase, and glutathione redox enzymes. Different cell populations within the lung vary in their resistance to oxidative injury. Although knowledge of antioxidant enzyme distribution in the human respiratory tract is limited, most antioxidant enzymes in the respiratory tract appear to be localized in the airways. Lower relative concentrations of mitochondrial superoxide dismutase and catalase are present in the bronchial epithelium. Extracellular superoxide dismutase is found in high concentrations in areas

rich in type I collagen, in connective tissues surrounding smooth muscle, and in the junctions between epithelial cells. Antioxidant enzymes that have been identified in other cell populations of the lung are discussed below with other functions involving those cell types.

Neuroendocrine Function

Cells with neuroendocrine characteristics have been identified in the respiratory tract of humans and several other animals. Sensitive immunocytochemical and radiolabeling techniques have localized a wide variety of peptide mediators in the lung (Table 4). Although many of these mediators have been localized in association with autonomic nerve fibers, the present discussion is limited to their association with neuroendocrine epithelial cells and pulmonary vascular endothelial cells.

Peptides associated with parasympathetic nerves
Vasoactive intestinal peptide (VIP)
Peptide histidine isoleucine (PHI)
Galanin
Peptides associated with sympathetic nerves
Neuropeptide Y (NPY)
Peptides associated with sensory nerves
Calcitonin gene-related peptide (CGRP)
Substance P
Peptides associated with endocrine cells
Calcitonin gene-related peptide
Calcitonin
Gastrin-releasing peptide or bombesin (GRP)
Endothelin
Enkephalin
Serotonin (5-HT)
Somatostatin
Cholecystokinin
Substance P
Human chorionic gonadotropin (HCG)
Pancreatic secretory trypsin inhibitor
Pituitary adenylate cyclase-activating peptide
Peptides associated with pulmonary endothelium
Prostacyclin
Endothelial-derived relaxant factor (EDRF/nitric oxide)
Acetylcholine
Endothelin
Peptide associated with large pulmonary vessels
Atrial natriuretic peptide (ANP)

TABLE 4. *Peptide mediators identified within the lung*

Neuroendocrine Epithelial Cells

Epithelial cells that produce peptide mediators have been identified throughout the tracheobronchial tree. These neuroendocrine epithelial cells are demonstrated with silver impregnation staining or antibodies to general endocrine markers, such as chromogranin. Neuroendocrine epithelial cells of the airways share many characteristics with APUD (amine precursor uptake and decarboxylation) cells of the diffuse neuroendocrine system. In humans, pulmonary neuroendocrine epithelial cells are identified by expression of peptide mediators, such as gastrin-releasing peptide (bombesin) and serotonin. In human fetal bronchi, neuroendocrine epithelial cells appear as early as at 8 weeks' gestation and may be involved in regulation of normal lung development. Peptides are expressed in a differential pattern during human airway development. Gastrin-releasing peptide is the primary peptide produced during early human fetal development, whereas calcitonin predominates later in development.

Limited evidence suggests that tracheobronchial neuroendocrine epithelial cells communicate with nonadrenergic, noncholinergic neurons located within the airways. The significance of this communication is unclear. Large numbers of neuroendocrine epithelial cells develop in the airways of animals subjected to experimental hypoxia and in humans who live at high altitudes. From these observations, it has been postulated that neuroendocrine epithelial cells serve a chemosensitive function and relay information about air oxygen content to the central nervous system.

FUNCTIONS RELATED TO THE ALVEOLAR SPACE

Metabolism

The alveolar surface is lined by two distinct populations of epithelial cells (Fig. 4). Type I alveolar epithelial cells are thin, flattened cells that cover approximately 95% of the alveolar surface; they are thought to be relatively quiescent metabolically and form the epithelial surface of the gas diffusion barrier. Type II alveolar cells, in contrast, are cuboidal, metabolically active epithelial cells that cover the remainder of the alveolar surface.

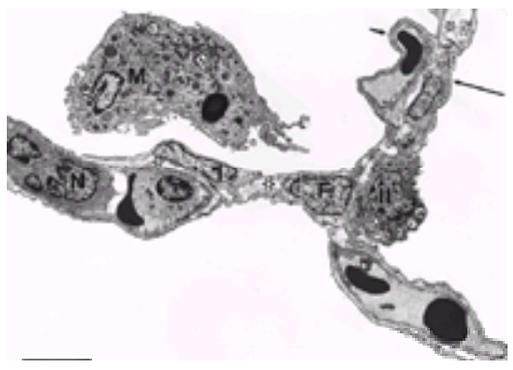

FIG. 4. Morphology of alveolar septum from a normal human lung. *M,* macrophage; *I,* type I alveolar epithelial cell; *II,* type II alveolar epithelial cell; *F,* interstitial fibroblast; *N,* intravascular neutrophil. *Bar* = 5 µm. Note the relatively thin air-blood barrier (*short arrow*) along at least one side of most capillaries. In the region of the *small arrow,* the thickness of the air-blood barrier is less than 0.5 µm. The diameter of the alveolar capillaries is less than 5 µm in most regions. The thick portions of the alveolar septal blood-gas barrier (*long arrow*) commonly range from 3 to 5 µm in thickness and contain connective tissues (*asterisk*) and fibroblasts within the interstitium.

Type II alveolar epithelial cells are the source of pulmonary surfactant, as discussed below. They also demonstrate a capacity for xenobiotic metabolism, as well as enzyme activities that protect against oxidant stress. Type II cells secrete soluble factors that act locally to modulate functions of other lung cells, such as fibroblasts. These regulatory mediators may be important in the coordination of normal lung development, as well as in repair of a damaged alveolar region. Among soluble factors produced by type II cells are several eicosanoids (PGI_2, PGE_2, TXB_2, LTB_4, and LTC_4). The functions of type II cell-derived eicosanoids are poorly defined but may be important in regulation of regional blood flow and ventilation-perfusion matching.

Several investigators have shown that type II alveolar cells synthesize and secrete extracellular matrix components in vitro. Moreover, cultured type II cells participate in the turnover of their underlying substratum. It has been postulated that type II cell matrix synthesis and turnover may be important in repairing damaged substratum such that it will support restoration of differentiated alveolar epithelial cell function.

Surfactant Turnover

Pulmonary surfactant is a complex lipoprotein substance forming a thin fluid film over the alveolar surface. Surfactant is a heterogeneous substance composed of lipid (primarily phospholipid) and specific surfactant-associated proteins (SP-A, SP-B, SP-C, and SP-D). Surfactant is best known for its role in lowering surface tension at the alveolar air-liquid interface; more recent evidence suggests that surfactant is also important in host defense against invading organisms, and that it contains antioxidant enzyme activity.

Type II alveolar epithelial cells synthesize and secrete the lipid and apoprotein components (SP-A, SP-B, SP-C, and SP-D), as demonstrated schematically in Fig. 5. Surfactant is stored in cytoplasmic lamellar bodies that fuse with the cell membrane to release surfactant components into the alveolar space by exocytosis. Surfactant secretion is regulated by soluble mediators, such as glucocorticoids and b-adrenergic agonists, as well as by intracellular second messenger signals generated by mechanical strain in the type II cell.

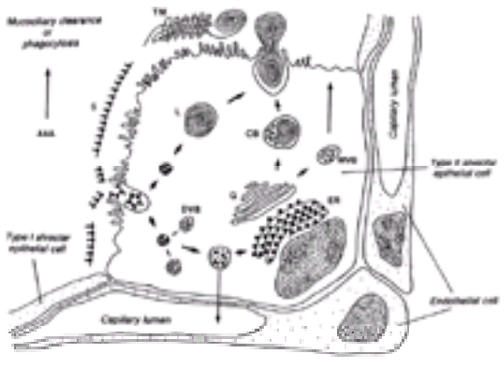

FIG. 5. Pathways of blood coagulation. Surfactant phospholipid and apoproteins are synthesized in the endoplasmic reticulum (*ER*). Phospholipid components are released from the Golgi (*G*) as lamellar bodies (*L*) or combination bodies (*CB*) containing both phospholipid and apoprotein moieties. Surfactant apoproteins may also be released from the Golgi packaged as multivesicular bodies (*MVB*). Lamellar bodies are secreted from the type II alveolar epithelial cell by exocytosis. Surfactant apoproteins A, B, and C are thought to be secreted with lamellar body phospholipids; it has also been suggested that surfactant apoprotein A may be secreted directly from multivesicular bodies. Following exocytosis, the lamellar body uncoils into a lattice structure designated as tubular myelin (*TM*), which subsequently forms the phospholipid-rich surfactant monolayer (*S*) at the air-liquid interface. Surfactant components are cleared from the alveolar space by several mechanisms. A small amount of surfactant may be removed by mucociliary clearance or alveolar macrophage phagocytosis. The type II cell actively clears surfactant components by endocytosis. Some surfactant that has undergone endocytosis is recycled directly into lamellar bodies and resecreted; other surfactant components are metabolized by enzymes contained within dense microvesicular bodies (*DVB*). Metabolized surfactant components may then be recycled for synthesis of new surfactant or released into the circulation for elimination.

Following secretion, surfactant components transform into a three-dimensional, latticelike structure, tubular myelin. Tubular myelin is thought to be a precursor to the surface tension-lowering film of dipalmitoylphosphatidylcholine. Alveolar surfactant is in a constant state of flux; it turns over every 5 to 10 hrs. The quantity of surfactant in the alveolar space is adjusted with changes in alveolar volume, so that an adequate reduction in surface tension is provided at all times. Adjustments in the surfactant pool occur rapidly; alveolar surfactant can increase by 60% during exercise and quickly return to pre-exercise levels with rest.

Clearance of surfactant from the alveolus may involve uptake and resecretion, degradation and incorporation into new surfactant, or complete removal from the surfactant pool. Turnover studies *in vivo* demonstrate that surfactant components are internalized by type II cells and resecreted. Other investigations suggest that surfactant is degraded by type II cells, alveolar macrophages, or within the surfactant fluid layer, and its degradation products are incorporated into newly synthesized surfactant components. Removal of surfactant from the lung may also occur by movement up the mucociliary escalator and swallowing, transfer across the alveolar endothelial-epithelial barrier into the lymph and blood, or degradation and transfer of breakdown products to other organs.

Excretion of Volatile Substances

The importance of human lung in excretion is readily demonstrated by its ability to eliminate the equivalent of more than 10,000 mEq of carbonic acid each day. Details of this important respiratory function have been discussed elsewhere in this volume. Several nonrespiratory metabolites that are volatile at body temperature are also excreted from the alveolar surface. A large number of volatile compounds arise from normal endogenous metabolism; they may also arise from pathologic metabolic pathways characteristic of certain disease states. Measurement of volatile substances in expired air can provide useful diagnostic information relating to abnormal metabolic processes or ingestion of toxic substances. Measurement of breath alcohol concentration, for instance, is used commonly to determine the degree of intoxication.

More than 300 volatile organic compounds have been detected in exhaled air from humans. Most of these substances are hydrocarbons that are either aliphatic (alkanes, alkenes, alkynes) or aromatic (benzene) in nature. The source of exhaled hydrocarbons is often uncertain. A significant number of aliphatic and aromatic hydrocarbons are detectable in expired air by virtue of their prevalence in ambient air. Cigarette smoking is a source of hydrocarbons such as ethene, propene, and propane. A variety of normal and pathophysiologic metabolic processes give rise to volatile carbohydrates that may be excreted from the lung. Hydrocarbons are primarily eliminated by cytochrome P_{450} metabolism in the liver; a smaller number are excreted as volatile gas from the alveolar surface. Lung hydrocarbon excretion assumes a more important role in conditions associated with decreased hepatic cytochrome P_{450} activity.

Certain volatile constituents of exhaled air reflect specific underlying disorders of metabolism. For instance, elevated breath levels of isoprene have been reported in hypercholesterolemia. Isoprene is a breakdown product of dimethylallylpyrophosphate and thereby is linked to the synthesis of the cholesterol precursor, mevalonic acid. The presence of acetone in exhaled breath during ketoacidosis is a well-known phenomenon. Limited glucose availability in conditions such as diabetes mellitus and starvation results in increased mobilization and oxidation of fatty acids. In turn, the production of acetoacetate, acetone, and/or b-hydroxybutyrate increases, and consequently acetone can be detected in urine and exhaled breath. Methylmercaptan, a derivative of methionine metabolism, is excreted from the alveolar surface in hepatic failure and imparts a distinctive odor (fetor hepatis) to exhaled air.

Measurement of breath hydrogen concentration has been employed as an indicator of carbohydrate malabsorption; bacterial breakdown of unabsorbed carbohydrate in the intestine releases hydrogen. Methane is also released by bacterial metabolism in the intestine in some individuals. Furthermore, bacteria in the intestinal tract of methane excretors may convert hydrogen to methane. Combined measurement of breath hydrogen and methane levels has been advocated as a useful indicator of carbohydrate malabsorption in methane excretors.

A large group of volatile hydrocarbons is generated by oxygen radical-induced peroxidation of cellular lipids and proteins. Free radicals generated by ionizing radiation, chemical exposure, physical stress, and other factors may overwhelm endogenous antioxidant defenses and react with polyunsaturated fatty acids and cell glycoproteins to disrupt cell membranes and other structures. The major end products of lipid peroxidation in humans are ethane (arising from degradation of the 3-carbon family of polyunsaturated fatty acids, e.g., linolenic acid) and pentane (arising from degradation of the 6-carbon family of polyunsaturated fatty acids, e.g., linoleic acid and arachidonic acid). Aldehydes and ketones (acetaldehyde, propanal, pentanal, hexanal, and acetone among others) also arise from n-3 and n-6 polyunsaturated fatty acid metabolism and are detectable in human breath. Several investigations have produced data that suggest measurement of breath ethane and pentane concentrations is a useful noninvasive means of evaluating lipid peroxidation in humans.

Lipid peroxidation has been implicated in the pathobiology of aging and a multitude of other pathophysiologic processes. Measurement of breath hydrocarbon levels may have diagnostic potential in disease processes that involve lipid peroxidation. In fact, elevated breath levels of hydrocarbons have been reported after acute myocardial infarction, in relation to lung malignancy, in cirrhosis, and in neurologic illnesses, including multiple sclerosis and schizophrenia.

FUNCTIONS RELATED TO THE VASCULAR COMPARTMENT

Filtration

The pulmonary capillary bed serves as a filter that detains formed blood elements and particulate matter larger than the average capillary diameter of 8 to 10 µm. Pulmonary arterioles may remove larger particles as they taper distally into the capillary network. Filtration in the lung protects other, more sensitive organs, such as the brain and heart, from disabling, or even fatal, effects of particulate embolism.

The lungs commonly remove thrombi that migrate from the peripheral venous circulation. Most of these thrombi are small and do not significantly compromise gas exchange function of the lung. Pulmonary thromboembolism has been identified in as many as two thirds of consecutive patients undergoing autopsy. These observations may provide an underestimate of the true incidence of pulmonary thromboembolism, as intrinsic thrombolysis may remove clot in many instances.

Filtration of cellular elements in the lung may provide a mechanism for modifying the cellular composition of circulating blood. Studies of venous and arterial blood demonstrate higher numbers of megakaryocytes in venous blood and greater numbers of platelets in arterial blood. These findings suggest that megakaryocytes released from the bone marrow are detained and fragmented in the pulmonary circulation. Autopsy observations confirm the presence of significant numbers of megakaryocytes within the lung.

Both white and red blood cells are removed from circulating blood as it traverses the lungs. Lymphocytes and leukocytes may be detained in the pulmonary vascular bed. Limited evidence from transfusion of leukemic blood suggests that the lungs may serve to maintain a preset level of circulating leukocytes. The lung also removes

damaged or lysed erythrocytes.

The lung traps a number of other physiologic emboli, including air, fat, bone marrow, and fragments of placental tissue or amniotic fluid during pregnancy. Malignant cells that have migrated from other tissues may be captured by the lung and establish pulmonary metastases. Infectious organisms can also migrate from other sites and establish infection in the lung. Pulmonary complications of infectious emboli most commonly result from tricuspid or pulmonic valve endocarditis. Foreign materials, such as talc, may be filtered from the venous circulation in intravenous drug users.

Although gas exchange can be disrupted by detention of certain blood particulates, embolic events are often physiologically insignificant or completely reversible if limited to the lung. Enzymatic destruction or phagocytosis of particulate material in lung may prevent fatal embolic events in more sensitive organs, such as the brain.

Metabolism

The pulmonary vascular endothelium forms an expansive blood-tissue barrier that is exposed to the entire volume of cardiac output and, thereby, is uniquely positioned for metabolic functions. Products of endothelial metabolism can be released directly into the circulation; moreover, a number of circulating peptide mediators, lipids, and nucleotides undergo processing by pulmonary endothelial cells (Table 5).

Substances metabolized after endothelial uptake
Serotonin
Prostaglandins E and F
Leukotrienes
Norepinephrine
Substances metabolized at the endothelial surface
Bradykinin
Angiotensin
Adenine nucleotides

TABLE 5. *Vascular endothelial metabolism in the lung*

Several peptide mediators arise from pulmonary vascular structures. Atrial natriuretic peptide (ANP) is produced, stored, and released from specialized myocardial cells that extend into the pulmonary veins. ANP mediates pulmonary blood vessel and airway smooth muscle relaxation. Pulmonary vascular endothelium produces a number of vasoactive and bronchoactive mediators. Prostacyclin and endothelial-derived relaxant factor (EDRF/nitric oxide) have vasodilator properties, whereas endothelin produces vasoconstriction and bronchoconstriction. Endothelin has been shown to have trophic effects on smooth muscle cells and fibroblasts that may be important in repair of damaged lung.

Some circulating substances are processed by lung endothelial cells after being transported from the circulation to the intracellular compartment. The best-known example of intracellular metabolism of circulating compounds is serotonin. Serotonin, or 5-hydroxytryptamine (5-HT), is primarily synthesized from tryptophan in endocrine cells of the gastrointestinal tract. 5-HT serves as a central nervous system neurotransmitter; its release from circulating platelets promotes platelet aggregation. After secretion by the gastrointestinal tract, 5-HT is taken up and stored by nerve endings and platelets, or removed from the circulation by liver and lung.

The lungs remove serotonin from the circulation by a sodium-dependent, carrier-mediated process. After 5-HT is taken up by endothelial cells, it is rapidly metabolized by monoamine oxidase and aldehyde dehydrogenase to physiologically inactive 5-hydroxyindole acetic acid (5-HIAA). Elevated urinary excretion of 5-HIAA is noted in patients with carcinoid syndrome, a neoplasm of endocrine argentaffin cells (APUD cells) characterized by oversecretion of 5-HT. Pulmonary endothelial cells also remove norepinephrine and prostaglandins of the E and F series from the circulation via an active transport process.

Metabolic processing of other substances occurs at the cell surface without intracellular uptake. Perhaps the best-known example of a substance that undergoes metabolism at the cell surface is angiotensin. Angiotensin-converting enzyme, a carboxypeptidase, activates the vasoconstrictor, angiotensin II, from a decapeptide precursor molecule, angiotensin I. Angiotensin I is produced by the enzymatic action of renin on circulating angiotensinogen secreted by the liver. Bradykinin and adenine nucleotides also are inactivated at the pulmonary endothelial cell surface.

Hemofluidity

Normal respiratory functions of the lung depend on continuous blood flow through the pulmonary vascular bed. The entire cardiac output passes through the pulmonary vascular system, making these vessels vulnerable to damage by circulating organisms, toxins, and embolic material. Whereas injured pulmonary vessels may provide a nidus for bleeding or clot formation, intrinsic mechanisms that determine hemostasis and anticoagulation are modulated by the pulmonary vascular endothelium.

Clotting results from the generation of thrombin by either intrinsic or extrinsic pathways of coagulation (Fig. 6). The intrinsic pathway is initiated by interaction between clotting factors and injured vessel wall or platelets; activation of the extrinsic pathway requires release of lipoprotein activity (tissue factor) from damaged tissue. Coagulation by either pathway involves controlled interaction of several clotting factors that converge with the activation of factor X. Activated factor X catalyzes the conversion of prothrombin to thrombin; thrombin in turn cleaves soluble fibrinogen to create a meshwork of insoluble fibrin strands. Platelets and red cells are trapped among the fibrin strands to form a stable clot. In addition to cleaving fibrinogen to fibrin, thrombin also cleaves factor XIII to stabilize the fibrin clot.

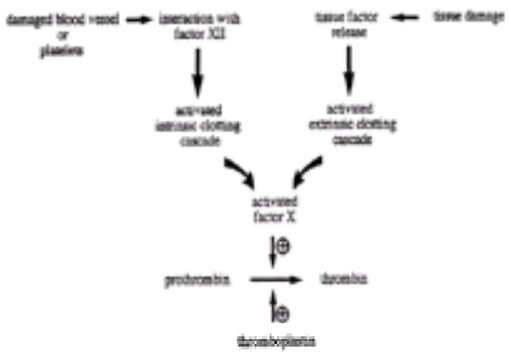

FIG. 6. Schematic representation of surfactant turnover.

Generation of thrombin in the lung is also mediated by thromboplastin. Thromboplastin is a phosphatide-protein complex, found in abundance in the lung, that augments conversion of prothrombin to thrombin.

Thrombin is involved in limitation, as well as initiation, of clot formation (Fig. 7). Thrombin interacts with the endothelium via thrombomodulin to activate protein C, which inhibits clotting factors V and VIII and activates fibrinolysis. In addition to activating protein C, thrombin also initiates release of plasminogen activator from endothelial cells. Plasminogen activator in turn cleaves circulating plasminogen to plasmin, which digests fibrin. The vascular endothelium can also bind and inactivate thrombin; furthermore, it can modify coagulation by releasing the vasodilator prostacyclin in response to thrombin.

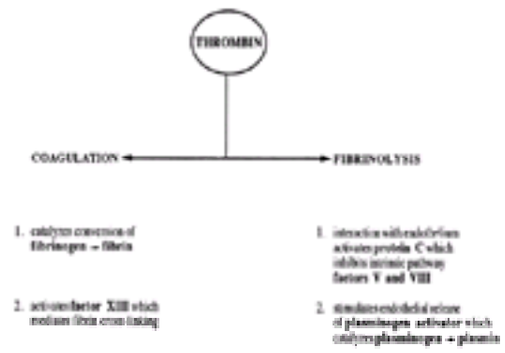

FIG. 7. Modulation of clotting and fibrinolysis by thrombin-dependent mechanisms.

CONCLUSION

Although the respiratory system is specialized for gas exchange, it also performs many important nonrespiratory functions. The functional diversity of the lung arises from its unique organization of heterogeneous constituent cells into branching airways ending in an expansive gas exchange surface intimately surrounded by an extensive capillary network through which the entire cardiac output flows. Structural features of the conducting airway system provide important functions in nonrespiratory activities such as speech, heat and water conservation, and host defense against inhaled foreign material or organisms. Cells of the conducting airways, alveolar region, and pulmonary vascular system participate in many nonrespiratory functions, including electrolyte and water transport, xenobiotic metabolism, antioxidant defense, surfactant production and turnover, neuroendocrine secretion, excretion of volatile substances, and maintenance of hemofluidity. Many nonrespiratory activities of the lung serve to maintain the gas exchange integrity of the respiratory system. Other nonrespiratory activities are important in maintaining physiologic homeostasis overall.

ACKNOWLEDGMENTS

The authors thank Dr. David Phelps for advice in the preparation of Fig. 5 and Dr. James Crapo for providing Fig. 4. We also acknowledge research support from grants HL-20344 and HL-31560 from the National Institutes of Health, as well as from the American Lung Association of Central Pennsylvania.

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CHAPTER

6 The Respiratory Muscles

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INTRODUCTION

The worldwide poliomyelitis epidemic in the 1950s affected millions of people. The polio virus targeted many motor neuron pools, amongst which were those in charge of ventilation control causing, in many cases, clinical ventilatory failure. An ingenious, albeit palliative, answer to this type of ventilatory failure was the development of the iron lung, an external negative pressure ventilator that saved the lives of countless patients infected during the epidemic. The purpose of assisted ventilation was not to restore the function of the motor neurons, but to take over the work of the failing muscles. Even though polio is now very infrequent in the developed parts of the world, the use of ventilators has increased and the machines have evolved in sophistication and capability. Close to half of all patients admitted to intensive care units require mechanically assisted ventilatory support. Almost all the ventilatory support currently provided uses positive rather than negative pressure, but the overall aims and principles remain the same: to replace the flailing chest. This book has several chapters devoted to mechanical ventilation. In this introduction we point out how, under a variety of clinical conditions, the ventilatory control lapses, and muscles fail to ventilate the lungs, whose final result is ventilatory failure with hypoxia and, frequently, hypercapnia.

Basically, ventilation depends upon the ability of the respiratory pump to move air in and out of the gas exchange portion of the lung. The respiratory muscles serve as the vital link between the different components of the pump: the respiratory centers, the conducting nerves and, ultimately, the lung itself.

The respiratory muscles contract during the breathing cycle, thereby changing the anatomical configurations of the chest wall by displacing its components, so that air can move in and out of the lungs. This chapter systematically analyzes the overall anatomical and physiological arrangements of the respiratory muscles. It specifically addresses the clinical application of these concepts, and familiarizes the reader with the different clinical conditions that are described in other portions of this textbook.

ANATOMICAL CONSIDERATIONS

There are many muscles that participate in ventilation, and they can be divided into those that are inspiratory in action and those that, by their anatomical arrangement, are predominantly expiratory in function. In turn, the inspiratory muscles are divided into ones that actively contribute to inspiratory pressure generation during regular tidal breathing (the so-called primary muscles of respiration) and the accessory muscles, which are activated to participate in ventilation under conditions of increased ventilatory demands.

There are also muscles that participate in breathing whose function is not primarily to displace the ribcage or abdomen. These muscles, located in the upper airways, act to prevent the collapse of the conduits and, in this way, facilitate airflow. The pharyngeal constrictor muscles, genioglossus, and neck strap muscles all increase patency of the pharynx, while the laryngeal abductor muscles open the vocal cords. The activation of these muscles must be synchronized, and actually precede the contraction of the inspiratory muscles.

The diaphragm is the most important muscle of inspiration. As shown in Figure 1, it has a central noncontractile tendon, from which muscles fibers radiate down and outwards to fit into the lower ribcage, and in the first 3 lumbar vertebrae. During contraction, it assists lung inflation through three mechanisms. The diaphragm uses the abdomen as a fulcrum against which it leans, thereby expanding the rib cage. During contraction, the diaphragm also helps inflation because of the cephalocaudal orientation of its fibers, and the curvature of its shape. This anatomical arrangement will expand the ribcage as the fibers shorten. The curvature of the diaphragm approximates the shape of a hemisphere with a radius r. Laplace's law for a sphere states that P = 2T/r, where P is the pressure inside the sphere, and T is the tension in the wall. If T is maintained constant and the diaphragm flattens, its curvature will decrease, r will increase and, by definition, P must decrease. Finally, the diaphragm transmits the increase in abdominal pressure during contraction to the rib cage, through its zone of apposition. This action also has an expansive action on the ribcage.

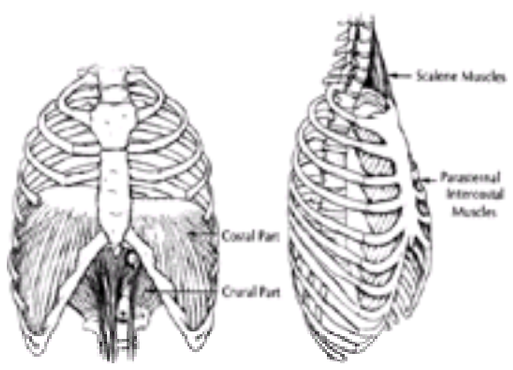

FIG. 1. The left panel shows the human diaphragm in situ at the full expiratory position. Notice the non-contractile central tendon, the radical cephalocaudal orientation of its fibers, and how it is opposed the inner aspect of the lower ribcage. The right panel shows the parasternal intercostal and scalene muscles. Only the left scalene muscles are shown, to illustrate their origin on the spine and their insertion on the first rib.

Patients with COPD characteristically develop lung hyperinflation, causing an increase in the resting volume of the ribcage. It is believed that hyperinflation reduces diaphragmatic strength by shortening of the diaphragmatic fibers, which places the muscle at a suboptimal point on its length tension curve. However, recent studies have demonstrated that when diaphragmatic fibers are experimentally shortened, the muscles adapt by dropping sarcomeres and achieving a new optimal length, so that each bundle is capable of generating its maximal tension for that new length. It can therefore be implied that the decreased diaphragmatic pressure generating capacity in COPD patients is either due to anatomical and mechanical derangement, or to contractile dysfunction, and not to simple length-tension changes.

The other primary inspiratory muscles (some of them also shown in Fig. 1) are the external intercostals, the parasternal part of the internal intercostals, the triangularis sterni and the scalene. They are activated during tidal breathing in normal individuals, but significantly increase their participation in ventilation during increased ventilatory demand. They play a particularly important role in diseases characterized by hyperinflation such as in COPD because they undergo less anatomic shortening, and therefore operate at a lesser mechanical disadvantage than the diaphragm. On the other hand, the true “accessory muscles”, i.e. the sternomastoid, subclavian, pectoralis minor and major, serratus anterior, upper and lower trapezius, and latissimus dorsi, which are usually inactive during normal breathing may

become increasingly important under special circumstances, like in strenuous exercise and in cases of severe ventilatory load. They are also active in patients with severe COPD.

There are other muscles that are not thought to be respiratory in nature such as the muscles of the shoulder girdle. These muscles have dual actions that include fixing the upper ribcage, partaking in upper torso positioning and elevating the upper extremity. They may also exert a pulling action on the rib cage, when they contract and are fixed at their extrathoracic anchoring point. Because of this, patients with severe COPD will often find relief to their dyspnea when they lean on a surface and fix their shoulder girdle.

The respiratory muscles have functions other than breathing. They also participate in very complex functions, like speaking and singing. This requires the simultaneous activation of the inspiratory and expiratory muscles. In other instances synchronous expulsive maneuvers will be needed to achieve other functions such as sneezing, vomiting, and defecating. They may also need to act in concert to facilitate parturition and micturition. A unique aspect of to the respiratory system is the sneezing and coughing reflex. These maneuvers require an initial deep inspiratory effort, followed by the closure of the glottis and a forceful contraction of the diaphragm and the abdominal muscles. When the upper airways are suddenly opened, the increased intra-abdominal pressure results in an explosive expiratory effort. This sudden increase in peak flow helps clear airways, and is very important for the management of secretions. Conditions that result in impaired coughing frequently results in the accumulation of secretions in the lungs, leading to development of atelectasis.

Physiologic Principles

There are two basic principles that control the behavior of muscles when subjected to physiologic stimuli. They are applicable to muscles in general and also include the respiratory muscles. The first is the relationship between the length of a muscle and its capacity to generate force (Fig. 2). The muscle generates more force as it lengthens until it reaches an optimal length. Stretching the muscle beyond that point is associated with decreased strength, until the muscle fibre brakes. More importantly, as the resting length of a muscle shortens (which occurs in diseases that cause lung hyperinflation) the force generating capacity for a given electrical stimuli decreases. In the case of the respiratory muscles, if a similar pressure is required to maintain ventilation then the only possible compensatory mechanism is the recruitment of more muscle fibers, i.e. increasing the motor output of the central nervous system, and then increase the firing rate to the muscle.

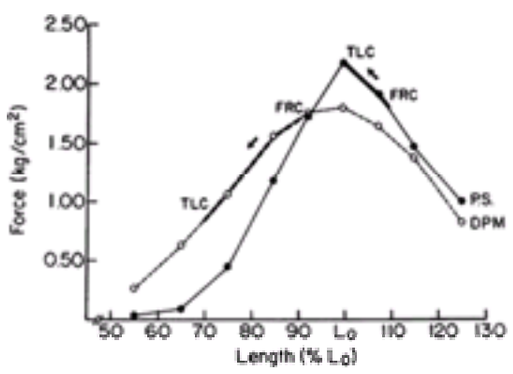

FIG. 2. The relationship between contractile force(kg/cm2) and resting length (%lo) for isolated, perfused strips of canine diaphragm (DPM) and parasternal (PS). Contractile force of both muscles is greatest at optimum resting length(LO). In situ, at functional residual capacity (FRC), the diaphragm is shorter and the parasternal muscles are longer than Lo, and loses force generating capacity. In contrast, the parasternal muscles shorten less. Towards their Lo, and gain force generating capacity. (Reproduced from Farkas G et al. J Appl Physiol 1985;59:528).

The second principle is that of the inverse relationship between the velocity of muscle contraction, and force generation capacity (Fig. 3). As the velocity of contraction increases (as in increased respiratory rate), the capacity to generate forces decreases. Although of limited clinical importance because of the usually relatively low speed of contraction of the respiratory muscles, it may become important at very fast breathing rates, or in patients whose respiratory ailment is associated with very short inspiratory times. Under resting breathing conditions the velocity of contraction and the inspiratory muscle force generated is about 5% of their maximal capacity. Up to 50% of maximal force or velocity can be sustained for prolonged periods of time (hrs).

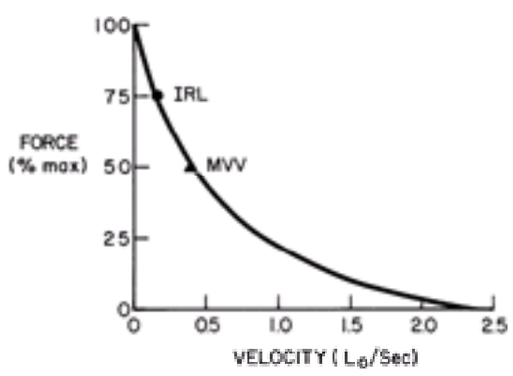

FIG. 3. Idealized representation of the relationship between contractile force(% of maximum) and velocity of shortening (Lo/s) of the human diaphragm. Maximum shortening velocity, measured in vitro, is about 2.5 Lo/s. The points identified as IRL and MVV are estimates of the shortening velocity when measured through a resistance (IRL) and during unencumbered maximal voluntary ventilation (MVV). As shortening velocity increase, force output falls. Force output during the MVV maneuver is estimated to be half that during the maximal static contraction of the diaphragm (Reproduced from Fishman A (ED), Update: Pulmonary diseases and disorders. New York : McGraw-Hill, 1992:88).

Skeletal Muscle Cell Types

Skeletal muscles are composed of different types of muscle fibers. Based upon histochemical staining they have been divided into types I, IIa, and IIb. Type I fibers have a high oxidative capacity and a low concentration of glycolytic enzymes. When activated, they develop a slow rise in force. Physiologically, they are the first to be recruited during muscle activation, because they generate low levels of force and are fatigue resistant. Type IIb fibers which have a low oxidative capacity and a high concentration of glycolytic enzymes, are the last to be recruited, and generate the optimal level of force quickly and may also fatigue rapidly. Type IIa has moderate enzyme concentrations, and is intermediate with respect to fatigability. The diaphragm is composed of approximately 50% Type I and 50% type II fibers, enabling it to withstand the enduring work it has to perform over an individual's lifetime. These properties of the skeletal muscle bear an important relevance to their response to training. In the case of the respiratory muscles, an increasing number of motor units are recruited with increased ventilatory loads, with the type I, IIa, and IIb fibers being recruited in a sequential fashion.

The effects of training on fiber composition vary, depending on the method of training utilized. Endurance training increases the myoglobin content, the capillary density, the mitochondrial density, and the oxidative enzyme capacity of type I fibers. In contrast, strength training increases fiber size (i.e. muscle hypertrophy); with little or no effect on enzyme concentration. Animal studies using biopsy specimens of the ventilatory muscles before and after different forms of training have shown the aforementioned training effects of the diaphragm and other inspiratory muscles. It is now becoming evident that these are a continuum on the fiber composition of type II cells, rather than two distant groups.

METABOLIC AND ENERGY DEMANDS OF THE RESPIRATORY MUSCLES

The concept that muscles behave in the same way as mechanical devices do by consuming energy and producing work, both of which are measurable, was developed in the early part of the twentieth century. Skeletal muscle efficiency was, in fact, reported to be about 25%, while respiratory muscle efficiency was noted to vary from 2% to 24%. The idea that a lack of energy supply, manifested in the form of insufficient oxygen and substrate, result in muscle failure is also well established. Because of these assertions, the role of blood perfusion has been widely explored; hyperpnea is equated to an increase in the blood flow of the diaphragm, as well as other

respiratory muscles. Blood flow to the diaphragm, increases by up to 260 mL/100gr min in maximally exercised ponies. This value which is similar to other skeletal muscles, is achieved by dilatation of the diaphragm vasculature.

Blood flow to the diaphragm has been studied during phrenic nerve stimulation. As opposed to limb muscles, where the duty cycle is relatively constant, the respiratory muscle's duty cycle can vary. The duty cycle is considered to be important because during contraction, the blood flow is either partially or completely interrupted, with flow restitution occurring during the relaxation phase. The first comprehensive study quantifying the relationship between diaphragmatic blood flow (Qdi) and the duty cycle was published by Bellemare et. al. In that study perfusion was related to the product of Pdi multiplied by the duty cycle. The mathematical product was called the tension (or pressure) time index, and has been very useful for defining the physiological behavior of the loaded diaphragm. The authors described a parabolic relation between TTdi and Qdi. Diaphragmatic perfusion rises up to a TTdi value of .20, then declines. Post contraction hyperpnea begins to increase, which is suggestive of blood flow limitation (Fig. 4). Earlier studies have, in fact, shown that the endurance time of the diaphragm when breathing against resistance was also related to the product of force developed and the duty cycle, and that time to task failure was predictable. If breathing was held at a TTdi of .20 or lower, that time is about one hour. In contrast, time to task failure will be about 15 min at TTdi of 0.30. Interestingly, a much higher Pdi (70% of Pdi max) can be also be sustained for 1h, provided that the duty cycle in decreased to .30, which gives more perfusion time (TTdi remains at 0.21). The effect of high tension is offset by the shorter duty cycle. The concept of a pressure threshold is, in reality, valid only if Ti/Ttot is 0.40 -0.45. A duty cycle of 0.30 is common among severe COPD patients. The concept of a threshold TTdi, below which task failure does not develop, and above which it will eventually occur, was proposed by Bellemare and Grassino and is graphically shown in Fig. 5. It should be noted that these results apply to the prevailing experimental conditions from which the data was obtained (constant perfusion pressure and square pressure wave). Regardless of the conditions, the results emphasize the relevance of blood perfusion to the maintenance of diaphragm contractility.

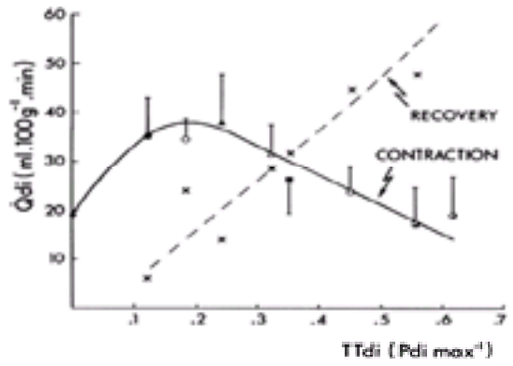

FIG. 4. Relationship between the diaphragmatic blood flow (Qdi) and the Tension Time index (Ttdi). Resting breathing values are the first point to the left. All subsequent data points were obtained with higher inspiratory resistances until a steady state was reached; bilateral phrenic stimulation was used. Peak values of Qdi were obtained at a Ttdi of .15 to .20. Higher Ttdi resulted in decreased flows. The dashed line represents the values of a post-stimulation Qdi. It increases linearly with the amount of Ttdi achieved by stimulation. This is an expression of O2 debt incurred.

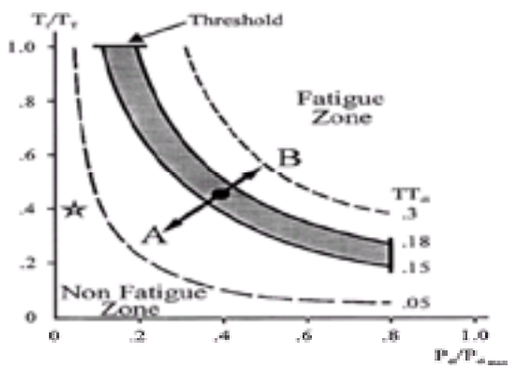

FIG. 5. The Tension Time (or Pressure Time) Index. It is the product of the inspiratory time expressed as a percentage of the total duration of the breathing cycle (Ti/Ttot), multiplied by the Pdi/Pdi max. (Mean trandiaphragmatic pressure developed expressed as a percentage of the Pdi maximal). Each point on the diagram defines a unique breathing pattern. Threshold: all breathing patterns in this zone can be sustained for 45 min or longer in normal human subjects breathing against inspiratory levels (Ttdi of .15 to .20). Fatigue zone: breathing patterns in this zone will result in a failure to sustain the pressure in less than 45 minutes. Muscle fatigue was the main cause of failure in the well motivated subjects. The main mechanism was insufficient blood flow as shown in fig. A. The fatigue threshold can be achieved at smaller Ttdi (arrow A) if the mean blood pressure is lower than normal. The threshold can be higher (B0 if the tension is higher (hyperfusion). The star in this figure is the Ttdi of a normal subject breathing at rest. The Ttdi in normal subjects exercising at 80% of their VO2 max is about .15, but the mechanisms of fatigue may be more complex than in resistive breathing.

Respiratory muscle endurance can be shorter or longer (for a given TTdi), depending on perfusion pressure. If perfusion pressure is increased, endurance is prolonged. In shock, TTdi task failure develops at a TTdi lower than 0.15 to 0.20. Respiratory rate can also affect respiratory muscle perfusion. Faster frequencies increase Qdi for a given TTdi, since Qdi is linearly related to the respiratory muscle's oxygen consumption in normal humans. Other conditions may also influence diaphragmatic perfusion. For example, hypoxemia also increases blood to the diaphragm. The aforementioned mechanisms seem to be adaptive in COPD, where both a fast respiratory rate and a lower tidal volume (faster, shallow breathing) may help preserve muscle performance.

The cellular mechanisms through which blood flow regulates muscle contractibility are not only related to the delivery of oxygen and other substrates, but also to the washout of the catabolites. Limitations of the aerobic metabolism lead to a dependence on creatinine kinase and myokinase for ATP synthesis from ADP only, with the accumulations of Pi and H^+, both of which are deleterious to muscle contractibility.

NEURAL CONTROL AND COORDINATION

The diaphragm and the other respiratory muscles are controlled by central motor neurons which normally maintain rhythmic breathing. The muscles of the upper airways are innervated by lower cranial nerves (ninth, tenth, eleventh and twelfth). The innervation of the other muscles depend on their anatomical location, and in descending order include: the sternocleidomastoid supplied by the spinal accessory nerve (eleventh cranial nerve) with roots from cervical 1 and 2 levels, the diaphragm, supplied by the phrenic nerves with roots from C3 to C5, the parasternal intercostal, supplied by the intercostal nerves. The abdominal muscles, which are mainly expiratory in action, are supplied by motorneurons arising from T8 to L2 levels.

It is evident that given the wide array of neurons that may participate in ventilation, a great degree of coordination is needed to maintain efficient and appropriate ventilation. Unique to the respiratory system is the fact that the natural rhythmic automatic breathing can be voluntarily overridden by the cortex. The system usually functions smoothly, because during quiet breathing we use primarily the diaphragm, the scalene, and some intercostals. With increased ventilatory loads, “accessory muscles” increase their participation in ventilation. Apart from their potential role in respiration, some of these muscles participate in other functions. For example, the upper torso and shoulder girdle muscles assist in positioning the upper extremities, abdominal muscles help with speech, defecation and parturition. Therefore, in situations where these muscles are being used for nonventilatory work, it is important that they maintain a high degree of coordination. When incoordination occurs, either because of an increased load or because of competing control integration, the resulting dysfunction can compromise the patient with underlying lung disease. It has been shown that when patients with severe COPD perform unsupported arm exercise, they develop early thoracoabdominal dyscoordination and fatigue. This type of exercise causes dyssynchrony between the rib cage the and diaphragm-abdomen, because of the competing output of the centers controlling respiratory and tonic activities of the accessory ventilatory muscles and the diaphragm.

Clinical evaluation of Respiratory Muscle Function

The most frequent symptom of respiratory muscle dysfunction is dyspnea. This symptom can be described with different degrees of exercise in many different conditions, including heart conditions. Indeed, dyspnea, which is caused by respiratory muscle dysfunction, is frequently confused with heart ailments. Characteristically, patients with diaphragmatic dysfunction will complain of dyspnea when supine (like cardiac patients), and sometimes have extensive workup

including catheterization, before the exact nature of the problem is elucidated. Patients with bilateral diaphragmatic paralysis report an immediate onset of dyspnea when supine as opposed to patients with heart failure who will complain of dyspnea after a variable time in the supine position. A physical exam can help sort out the nature of the problem. Measurement of the breathing frequency is helpful, because patients with respiratory muscle dysfunction will breathe at a faster rate. Similarly, the patients will adopt a shallow breathing pattern, irrespective of the reason of the muscle dysfunction. Close observation may reveal use of the accessory muscle, and paradoxical inward retraction of the abdomen during inspiration, because the diaphragm is unable to generate pressure to displace the abdominal wall.

Under certain circumstances special considerations apply. In patients with central nervous depression (drug overdoses), the breathing pattern tends to be shallow and slow irrespective of the degree of ventilatory failure. Likewise, patients with hypothyroidism can develop slow shallow breathing which will reverse with thyroid replacement. Patients with severe COPD will not develop the very fast rate seen in patients with interstitial lung disease because of the expiratory obstruction to airflow which tends to prolong the expiratory phase. On the other hand those patients will ineffectively contract the diaphragm and this will retract the lower ribcage (Hoover's sign). They will also contract the abdominal muscles during expiration. This pattern can be easily detected on the physical exam in the most severe cases but not be quite so visible in the milder stages.

During the evaluation, it may be helpful to induce coughing as patients with global respiratory muscle weakness will not be able to generate effective cough. A summary symptoms and signs, and their correlates to disease states and mechanisms is shown in Table 1.

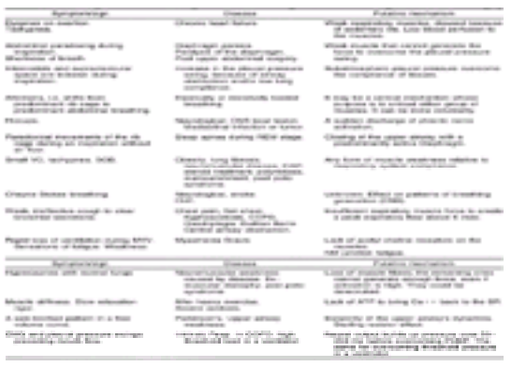

TABLE 1. *Clinical evaluation of respiratory muscle dysfunction*

Laboratory Evaluation of Respiratory Muscle Function

The most accurate source of information on respiratory muscle function is provided by measuring muscle specific physiological properties, like their level of neural activation, force generation, operational length, velocity of shortening, electrophysiological properties, and pattern of recruitment.

In practice, evaluation of the collective function of all the inspiratory and expiratory muscles is the most convenient way for their clinical assessment. It is remarkable that the lung volume-intrathoracic pressure relationship of all the muscles forming the chest wall strongly resembles the force-length characteristic function of a single skeletal muscle fiber. It is, in fact, near functional residual capacity that all inspiratory muscles combined are at their optimal length, and provide the highest intrathoracic inspiratory force. In contrast, all the expiratory muscles develop their maximal force near total lung capacity, where their length is optimal. Their force decreases as lung volume decreases.

The causes of respiratory muscle dysfunction can be found within the neuromuscular activation pathway, as shown in Fig. 6. Upon nerve stimulation, acetylcholine (Ach) is liberated at the neuromuscular junction, where it binds to Ach receptors postsynaptically, thereby causing changes in the muscle fiber membrane potential, and leading to the propagation of membrane depolarization along the surface of the fiber, a signal that is clinically measurable as the electromyogram (EMG). This depolarization also travels towards the center of the muscle fiber via the transversal tubules, which triggers the release of Ca^{++} ions from the sarcoplasmic reticulum into the cytoplasm. In the presence of ATP, CA^{++} links to troponin and triggers the sliding of myosin on actin, thereby generating force (clinically measured as intrathoracic pressure) and velocity of shortening (estimated by mouth flow). The magnitude of intrathoracic pressure developed depends on the initial degree of overlapping between thick and thin filaments within the muscle sarcomere. The magnitude of the shortening depends on the load the muscle encounters, as well as on the number of muscle fibers recruited, and the motorneurones firing rate. The overall degree of muscle activation can be estimated from the recorded EMG signal. Appropriate analysis of the signal, such as the root mean square value (RMS), can be used to quantify muscle activation.

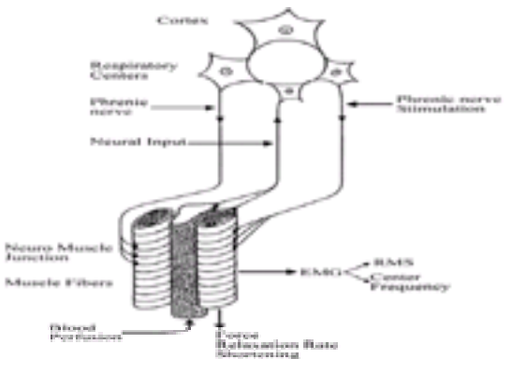

FIG. 6. The diagram shows the different levels of central control of breathing, the afferent and efferent neural pathways. Muscle failure or fatigue can happen A) at the central level (i.e. derecruitment) because of nerve lesions. B) At the nuero muscular junction (transmission failure) C) at the fiber level, being caused by insufficient perfusion, leading to excitation failure or contraction failure . On the right side, there are indications about how to test failure, a maximal phrenic stimulation, which can increase the max. Voluntary force, is an indication of Central Fatigue . EMG Centroid Frequency is an indicator of the muscle membranes conduction velocity. EMG Root Mean Square is an indicator of activation levels reached at the muscle cell. Force is the final mechanical output. Relaxation rate is an index of sarcomere function. Spontaneous shortening is an index of the respiratory center output and muscle force for a given breath.

The ultimate consequence of respiratory muscle dysfunction is ventilatory failure. There are several pathways that can lead to ventilatory failure. One is a lack of central drive (usually due to an overdose of neural depressants such as barbiturates or opiates). This results in lack of muscle activation, and overall hypoventilation. Another path is an alteration in the natural inactivation of acetylcholine or its rate of liberation. This also leads to hypoventilation due, to failure at the neuro muscular junction (myasthenia gravis, curare or curare like muscle relaxants). If respiratory muscle activation occurs, the muscle may still fail to generate adequate pressure through failure of the excitation contraction coupling mechanism. This is a complex step. Dysfunction can happen when the membrane Na^{+}/K^{+} channels are blocked, when lactic acid or inorganic phosphates accumulate in muscle fibers, or when CA^{++} does not recycle fast enough in and out of the sarcoplasmic reticulum.
Excitation-contraction coupling failure leads to loss of muscle force in spite of neuronal activation. This step can be assessed in several ways:

1)Loss of force upon maximal stimulation of the phrenic nerve, which then reverses with muscle rest (fatigue),
2)a slowing down of the relaxation rate of the diaphragm (measured as the rate of decay of transdiaphragmatic pressure), and
3)a change in the central frequency of the power spectrum of the EMG signal.

This is an indicator of the membrane's reduction in the velocity of conduction of myopotentials. A final pathway relates to phenomena independent of adequate intrinsic muscle function. It may be that the activation and contraction are normal, but the muscles are highly preloaded (COPD, obesity, ribcage deformity, interstitial lung disease), so an inordinate amount of muscle force is used to overcome the load before air actually moves onto the lung. Clinical observation of how the chest wall moves, measurements of ribcage and abdomen movements or relative changes in the simultaneously determined pleural (esophageal) and abdominal (gastric) pressures swings may help define the degree of respiratory muscle dysfunction.

Respiratory Muscle Strength

The oldest, simplest and most useful test of respiratory muscle strength is the maximal inspiratory (PI max) and expiratory (PEmax) pressures. There is a significant literature reporting values in normal subjects, patients with COPD, lung fibrosis, and obesity. There are acceptable instruments and techniques adaptable to clinical practice. The pressures are measured during maximal static efforts against a partially closed airway. A small airleak is created during the efforts, in order to avoid the suction effect of the mouth muscles if the glottis is allowed to close. The test has also been expanded to determine mouth pressure over a range of lung volumes over the vital capacity. Like many tests in pulmonary research, the maximal PI and PE are dependent on subject's cooperation, and the value obtained may underestimate the true strength of the respiratory muscles. Nevertheless, there are several practical uses for the measurement of PI max. Its serial evaluation over time can provide insight as to the progression or regression of muscle weakness (as in Guillain-Landry-Barrett syndrome, and weaning from mechanical ventilation) or fatigue. Patients with a maximal inspiratory force of <25 cmH_2O are at high risk of developing ventilatory failure. Similarly, maximal expiratory force of <30 cmH_2O at FRC is seen in patients with ineffective cough, which forecasts an accumulation of bronchial secretions and possible atelectasis, pneumonia and ventilatory failure.

Knowledge of the pressure swing required to sustain ventilation and the value of maximal inspiratory pressure (PImax) allows the calculation of the “force reserve” (Fig. 7). Pressure swings of higher than 50% of maximal inspiratory pressure are associated with rapid (within 15 min) fatigue and task failure. This may occur during some clinical conditions, and could be a reason for ventilatory failure.

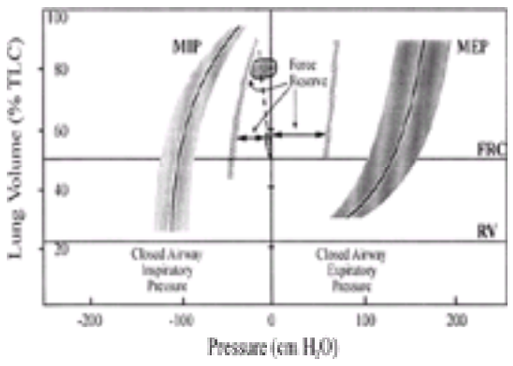

FIG. 7. Force reserve: the values of the MIP (Maximal Inspiratory Pressure) or PI max measured at the mouth against an occluded airway and MEP (pressure at the mouth during a maximal expiratory effort) or PE max. On the ordinate is lung volume, expressed as a percentage of total lung capacity. Predicted MIP-MEP values are shown in the shade areas. The dotted area represents pressures of about 40% of max, levels beyond which a sustains breathing pattern will result in failure. The dashed line is the elastic recoil of the lungs. The loop at FRC is the plural pressure swing required during resting breathing. Notice the margin of force reserve . The upper loop simulated the COPD patient. Hyperinflation and COPD result in lower forces and higher resistances decreasing considerably the force reserve margin.

The direct measurement of PI and PE max can be complemented by the determination of the force exerted by the elastic recoil of the lungs and the chest wall. At FRC, the outward recoil of the chest wall and the inward recoil of the lung are balanced, so the PI and PE max represent the true force of the respiratory muscles. At total lung capacity and residual volume, the values of PI are under or overestimated by about 25%. At TLC, PI max at the mouth is in fact 0, because the muscles have to overcome the elastic recoil of the lungs and the chest wall, which is approximately 30 cmH_2O. Intrathoracic pressure measured with an esophageal balloon would provides the correct value of the respiratory muscle force.

Maximal Transdiaphragmatic Pressure (Pdi)

This test requires the simultaneous measurement of esophageal (to represent pleural) and gastric (to represent abdominal) pressure, using balloon catheters placed in the mid-esophagus and in the stomach, respectively. Pdi is calculated as the difference between Pga and Pes, measured at isotime during a maximal voluntary effort. Pdi can also be estimated by using the difference between Pga and occluded mouth pressure (P mouth). The pressure needed to overcome elastic recoil of the lungs is added to mouth pressure (–5 cms H_2O at FRC and –25 cmH_2O at TLC in normals). The measurement of PdI max is performed while maintaining a small air leak, whose purpose is to help keep the glottis open. With all its caveats, Pdi max is the best index of intramuscular tension and the pressure developed across the diaphragm. There should be a negative pressure in the thorax with simultaneous positive pressure in the abdomen. Pdi should be recorded at known lung volume, keeping the chest wall configuration constant. Values from normal subjects and patients with different lung diseases, as well as details about the technique, have been published. There is considerable variability in the Pdi values obtained in humans, depending on the technique and the subject's capacity to complete the maneuvers. At Pdi values higher than 50% of maximum, blood flow is interrupted altogether. Blood flow is, however, partially reestablished during expiration. This physiological phenomenon is the basis for the explanation about how fatigue develops while breathing against high inspiratory resistance. A Pdi max value higher than 100 cmH_2O is not associated with muscle weakness, and cannot be the cause of ventilatory failure. A low Pdi max value can, however, be the consequence of many different factors, such as a lack of muscle mass, malnutrition, neurological disorder, neuromuscular junction disorder, and intrinsic muscle disease.

Another method of measuring the pressure generating capacity of the diaphragm is the so-called Sniff Test. This test is done by having the person perform a brisk maximal voluntary inspiratory effort through one of the nostrils. The pressure is measured at the nostril or the mouth. The major advantage of this test is that it can be successfully completed by most people with very little training, and it can be easier to perform than a Pdi max maneuver. Its main disadvantage is that it is a dynamic maneuver, where force is affected by the velocity and degree of muscle shortening. This tends to underestimate the value of the force, with respect to those obtained during static maneuvers. A sniff pressure value higher than 80 cmH_2O is likely to represent a good force, and respiratory muscle weakness is unlikely to be present. Low sniff pressure values provide less certainty regarding the presence of weakness. This test is being perfected and, as more experience is gained, it might be better standardized.

Phrenic Nerve Stimulation Techniques

This consists of supramaximal bilateral stimulation of the phrenic nerves at the neck using surface electrodes, resulting in a single brisk diaphragmatic contraction (twitch) pressure. Esophageal and gastric pressures are measured simultaneously with the double balloon technique. This allows the determination of Pdi. Adequate stimulation can be achieved with the use of an electric current, or through magnetic depolarization coils. The former stimulates the phrenic nerves specifically, while the latter is more likely to stimulate several nerve groups as the coils are relatively large. This problem may be solved with the development of smaller coils. Magnetic phrenic nerve stimulation can be done in either the sitting or supine position, and does not require abdominal binding. Cervical magnetic stimulation allows for prospective studies of the respiratory muscles of supine patients. It is nevertheless important to note that magnetic stimulation can interfere with the function of pacemakers and should never be used in patients with these devices in place.

Electrical stimulation should be done in the sitting position, with control of the diaphragm's compound muscle action potential, in order to achieve “supramaximal” nerve stimulus. Changes in the distance between the electrode and the nerve can change the stimulating current intensity, and thereby influence the test's outcome. In some instances, wires have been implanted close to the nerve and left in place to repeat the test, as well as document the changes in force as a function of time. Cutaneous stimulation can be painful, can cause ballistic movement of the arm and is difficult to perform in obese persons. There are numerous studies that provide comparative values from normals and patients with lung disease. The electrically induced twitch pressure values range from 25 to 35 cmH_2O, whereas they range from 30 to 35 cmH_2O for magnetic stimulation. Measurement of the time interval from nerve stimulation until the beginning of the action potential (CMAP) provides the phrenic nerve velocity of conduction. Absence of CMAP indicates phrenic nerve transection, or neuro muscle junction failure.

Respiratory Muscle Endurance

These are important and relevant tests of respiratory muscle function. This should provide more relevant information than tests of respiratory muscle force. There are a few techniques that have both broad acceptance and recognized clinical value; these results are shown in Fig. 8. The first one is the measurement of endurance while breathing at high levels of ventilation. Under these conditions, the respiratory muscles develop high velocity of shortening at relatively low forces, as seen in bicycle exercise. Maximal voluntary ventilation (MVV) is sustainable for about 10 to 15 sec by a normal subject. At this point ventilation decreases, because tidal volume and breathing frequency cannot be sustained. This is fatigue of the respiratory muscles. Maximal voluntary sustainable ventilation is about 50% to 60% of the MVV in normal subjects. It is also the level of VE observed during heavy aerobic exercise (competitive cross country skiing, and marathon running). Maximal sustainable ventilation for 1 to 2 hrs is not a practical clinical test, but has been used in research. Shorter versions using step increases of 10% in the VE every three minutes,

starting at 20% of maximum MVV, and going on until the subject cannot sustain the load, have proven to be useful. In patients with airflow limitations, the load increase is limited by the airflow limitation and progressive hyperinflation, which leads to chest wall configuration changes and muscle shortening. Similarly, its applicability for other patients with different respiratory diseases is limited.

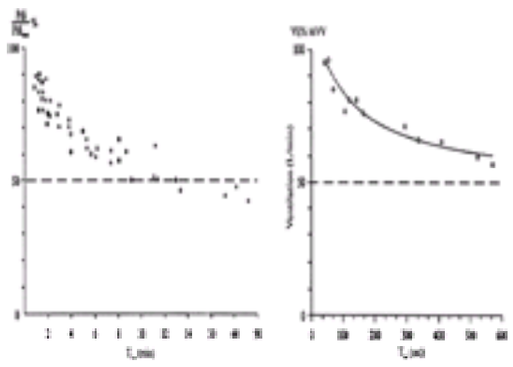

FIG. 8. Left Panel: Time to task failure (time limit) of the inspiratory muscle during resistive breathing in normal subjects. A Pdi of about 50% of max. Can be sustained for about 1h. Right Panel: Time to task failure (Time limit) of the various levels of voluntary ventilation (expressed as a percentage of maximal voluntary ventilation). Ventilation of about 55% max can be sustained for about 10 min or longer. This test was extended to 1 h. In subsequent studies. Sustainable ventilation value is about 50-60% of MVV.

Evaluation of Endurance While Breathing Against Inspiratory Loads

Under these conditions, the respiratory muscles develop high force and slow velocity of shortening. In essence, the subject tested has to breathe against an inspiratory threshold load, which must be overcome before air can flow into the lungs. Mouth flow can be maintained at comparable value, despite the range of load. The load is increased periodically (i.e: every 3 minutes), until the subject cannot overcome it, and consequentially has to stop the test. The highest load value tolerated for a total period (3 minutes, in this case) is then recorded. This test has gained some acceptance, but requires some learning before it yields reproducible results. In the initial reported tests, the breathing pattern was controlled. Subsequent tests conducted in COPD patients resulted in varying breathing patterns, because the patients adopted different breathing strategies when faced with the load. To avoid the influence of force and timing, the pressure time index, or breathing pattern, can be monitored during the test.

One of the most widely accepted methods of measuring respiratory muscle endurance consists of letting the subjects or patients breathe at a level that is a known fraction of the maximal force (PI max). For example, beginning at 30% of PI max, while keeping the CO2 constant. The load is then increased every 2 minutes by 10%, until the person can no longer sustain the pressure for a full period (2 minutes, in this case). The value of the load causing task failure or the tension time index value achieved at that time, can be used to quantify endurance.

Electrophysiological Evaluation of Respiratory Muscles

The EMG is the electrical signal recorded during muscle activation. The muscle is activated by the depolarization and repolarization of the muscle membrane, caused by neural stimulation at a rate of 5 to 50 pulses/sec. If the phrenic nerve is electrically stimulated with a short pulse (0.2 msc), it induces a biphasic muscle action potential on the diaphragm. This can be measured at the surface of the thorax with two electrodes placed along the diaphragm. This is called the compound muscle action potential. During voluntary contractions, motor units are recruited and the firing rate increases resulting, in increasing force production. The spatial and temporal summation of individual motor unit action potentials generate the interference pattern signal. As mentioned previously, the signal can be analyzed by calculating the root mean square (RMS or time domain analysis), which is then expressed as a percentage of a maximal RMS value previously obtained by sustaining an active TLC. Either the RMS peak value (at the end of each inspiration), or the average RMS during a breath is reported. This signal is proportional to the number of fibers recruited, as well as the frequency of motor unit firing rate. RMS is also proportional to muscle force for any given muscle length.

Another form of EMG analysis is to calculate the power spectrum in the frequency domain. This EMG domain is measured in periods (windows) of 20 to 200 msc, where heart PQRST signals are excluded (gated). The index Pdi/RMSdi is an expression of diaphragm effectiveness, because it provides an indirect indication of the ability of the muscle to convert an electrical signal into force. This index is low at FRC (lengthened muscle), and high at TLC (shortened muscle). The power spectrum can be quantified by calculating its moments, one of which is the center frequency. Values of center frequency have been shown to be related to the velocity of propagation of the potential along the membrane. When the EMG of the crural diaphragm is measured with a 10 mm bipolar esophageal electrode, the normal value for CF is 100 ± 4 Hz. During fatigue, CF progressively decreases to values around 60 Hz, at which point it tends to stabilize. A decrease of 15% to 20% of the resting CF is thought to represent a value associated with the development of fatigue. Center frequency returns to baseline values within 5 min after withdrawing the load. Experimental evidence obtained in animals shows that fatiguing loads sustained for periods close to 2 hrs considerably prolongs the recovery time of the center frequency, which can now take several hours. Under these conditions, there is evidence of membrane injury and sarcomere disruption. Whether this occurs in humans is unknown, but is theoretically possible. Muscle injury can explain the prolonged recovery of force observed in some cases of respiratory muscle fatigue.

Electromyographic quality recording of the diaphragm has recently been standardized by Sinderby et. al. It is expected that the standardization of methods and automatization of data recording and analysis will allow for a wider applicability of this important signal. Fig. 9 shows an example of uncoordinated EMG RMS (the patient's neural drive) while ventilated in the assist mode.

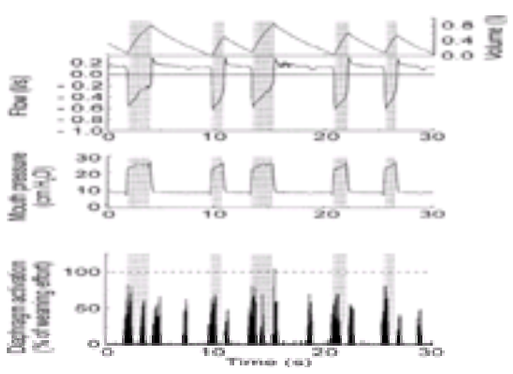

FIG. 9. Neuro mechanical coupling: The panels show 30 seconds of breathing in a patient ventilated on the demand mode. The top panel shows tidal volume and flow, indices of mechanical performance. The lower panel shows the firing of the diaphragm (EMG s RMS from the crural portion). Notice the discrepancy in breathing frequency between the ventilator (10 / min) and patient (30 / min). A considerable number of inspiratory efforts are out of phase with the ventilator. The middle panel shows the simultaneously monitored airway pressure.

Evaluation of Respiratory Muscle Coordination

The use of respiratory inductance plethysmography bands or magnetometers on the ribcage and abdomen, is a noninvasive tool that allows simultaneous recording of the volume displacement of each of the two compartments. Plotting each signal against the other (Konno-Mead plots) provides qualitative and quantitative evaluation of respiratory muscle coordination. Normally, inspiration increases the diameter of both the ribcage and abdomen. Simultaneous calibration against a known lung volume (spirometer) allows for the continuous noninvasive evaluation of tidal volume, and course of breathing. It is very useful because it can help monitor occurrence of apnea, hyperpnea, irregular, and rapid shallow patterns of breathing. Dyssynchronous and paradoxical thoracoabdominal movements can be identified under a variety of experimental and clinical conditions as shown in Figure 10. When well calibrated, tidal volume and minute ventilation can be measured within 5% to 10% of the values obtained via measurements at the mouth. Time based recording of EMG, pressure swings, thoracoabdominal displacements, and airflow allows inferences about the time course of muscle recruitment and their interaction. Application of these techniques to real clinical situations will provide us with a better understanding of

the respiratory system, and its behavior during different conditions, such as patient ventilator interaction, prediction of weaning failure, and the complex interrelation between sleep and respiration.

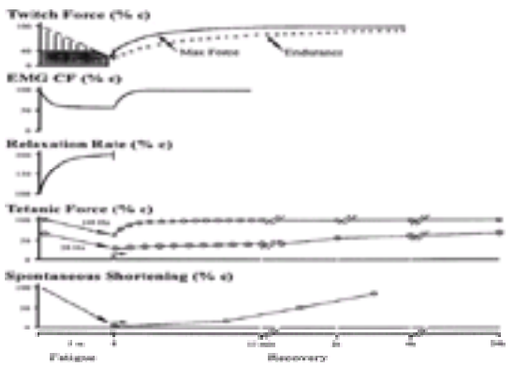

FIG. 10. Time course of various parameters during an isometric contractions held at 40% of maximal force (task) until failure. Panel from the top: Maximal force: voluntary contraction is held at 40% of the force obtained during maximal voluntary effort or during maximal electrical supramaximal pulses of the nerve. The vertical lines are pressure swings obtained by electrical stimulation, showing a progressive loss of maximal force. Task failure occurs when maximal force is equal to task force. The time elapsed from the start until task failure is known as the time limit, or endurance. The exercise is defined as a fatiguing task, because there was loss of maximal force. Regaining the ability to develop maximal force takes a few minutes. Regaining the ability to perform the same task again, however, takes hours. This panel shows the time course of the central frequency (CF) of the EMG obtained via surface electrodes and Fast Fourier transforms in the same exercise. Decay of CF is fast, and is a forewarning of task failure. This parameter is an expression of membrane potential conduction velocity. Relaxation rate shows the time course of relaxation time (if the contraction if interrupted). Control values are the same as in a rested muscle. This parameter is linked to a failure at the sarcomere level, mainly related to calcium coupling and release from troponin. Tetanic force shows the decrease in force during an electrical stimulation at 100Hz or 20Hz, and its ensuing rate of recovery. Recovery from fatigue is faster when the muscle is probed with 100Hz than with 20Hz; the former is proposed to be caused by conduction mechanisms, while the latter is done by contraction mechanisms. Spontaneous shortening of the diaphragm before (100%) and after task failure, and time of recovery.

Respiratory Muscle Fatigue

Definitions

It is now widely accepted that sustained muscular activity causes a reduction in the maximal force (or velocity of shortening of the muscle). The causes are many, and can concurrently develop from the motor cortex to the sarcomere microfibers. Loss of the capacity to generate maximal force due to exertion, recoverable during rest, is defined as *muscle fatigue.* Since the concept of fatigue is a temporary loss of force, maximal force must be measured two or more times during the trial period. *Task failure* is defined as the inability of the muscle to continue to perform a given prefixed target (work, force, tidal volume, ventilation). Although fatigue precedes task failure, task failure does not necessarily follow fatigue. Task failure of the respiratory muscles occurs when they lose the capacity to generate the force required to sustain normal alveolar ventilation. Muscle injury can be defined as a structural change in the sarcolemma or sarcoplasm, and is usually induced by fatiguing contractions, sustained for long periods of time (several hours), as may happen to the respiratory muscles during airway obstruction. Recovery from injury takes several days, giving place to muscular remodeling where, in addition to muscle repair, there are changes in the quality of the muscle's structural or contractile proteins. Muscle weakness is a permanent loss of force, regardless of its origin.

Mechanisms of Respiratory Muscle Fatigue and the Rationale for Diagnostic Tests

Breathing tasks that are “sustainable” will be held mainly by recruitment of fatigue resistant fibers (type I), requiring oxygen to generate ATP. By themselves, type I fibers will not generate more than 30% of the maximal force, but will be able to sustain force for prolonged periods of time. High force (about 40%–50% of max) limits muscle perfusion and may deprive all cells of adequate oxygen supplies and catabolite removal. Low force will allow adequate perfusion of type I fibers, which are fatigue resistant and sustain breathing for life. The chemical composition of the muscles' interstitial space (e.g. K^+ concentration, low pH) provides neural feedback to the respiratory center.

Fatigue, which can be thought of as a regulatory mechanism through which a temporary hypoventilation is allowed to avoid muscle injury, may happen at the central level by derecruitment of fibers, at the neuro muscular junction (failure of transmission), and at the muscle levels (failure of the membrane to conduct potentials, or sarcomere to shorten or relax). Muscle force is the conventional parameter used to determine the level of muscle activity, and is dependent on length and the velocity of shortening. We can now measure parameters other than force that are known to change as fatigue develops. The challenge is to determine how they contribute or how they are related to force, and how they can be used as diagnostic tools for muscle dysfunction.

Figure 10 shows the parameters that help evaluate neuro muscular function and the techniques available for measuring fatigue. A nerve stimulation test can be performed by giving short pulses (.2 msec) of electrical or magnetic currents applied to the nerves during contraction (upper pannel). The resulting twitch force produces a maximal muscle force output. A decrease in twitch force is an indication of muscle fatigue. Presence of twitch force while the muscle is developing maximal voluntary effort is an indication of “central” fatigue or submaximal activation. Techniques for stimulating abdominal muscles through percutaneous low dorsal nerve stimulation is now under development.

Partial mechanisms of muscle fiber function relevant to fatigue can be monitored by several other techniques Membrane excitability due to changes in the sarcolemma polarity induced by nerve stimulation can be measured using the EMG. When the index force/RMS decreases during sustained contractions at constant length, it is an indication of failure of the muscle contraction mechanism, relative to the neural command (fatigue). The frequency domain analysis of EMG provides information about the velocity of propagation of potentials along the fibers, through calculation of the frequency power spectrum. Fatiguing muscle fibers while exerting high force shows a shift towards an increased power in the low frequency component of the spectrum. Membrane excitation is a relevant function because it is the key mechanism to liberate Ca^{++} from the sarcoplasmic reticulum, which is necessary to induce contraction of the sarcomere.

Shifts in the frequency power spectrum occur early in a fatiguing contraction (within a minute of loading), and may serve as a marker for the prediction of task failure (second panel). Fatigue is not, however, the only factor that changes the velocity of propagation of potentials. An alternative to measuring EMG generated by voluntary contraction is to measure the compound muscle action potential resulting from a single .2ms electrical stimulation given to the nerve of a relaxed muscle. Here, all fibers are recruited at once resulting in a biphasic potential, the length and shape of which permits to distinguish neuro muscular abnormalities and/or fatigue.

Velocity of muscle contraction. Once the muscle contracts, its velocity of shortening and velocity of relaxation have been used as an expression of the sarcomere function. Inadequate Ca^{++} binding to and release from troponin (mainly due to lack of ATP) results in a slowing of the sarcomere velocity of relaxation (the muscle becomes stiffer during fatigue). The relaxation rate of the diaphragm during fatiguing contractions is slower than in the fresh diaphragms of normal subjects. When the muscle is subjected to fatiguing contractions, changes in relaxation rates are seen well before task failure occurs, and so the test can be used to herald task failure. Figure 10 also shows the time course of recovery of after low and high frequency stimulation.

Muscle Metabolism

Muscle biopsies and nuclear magnetic resonance spectroscopy (NMR) are the techniques most frequently used to monitor metabolic changes in the contracting muscle. While these techniques have been of great value to study limb muscles, their use in respiratory muscles is much more limited. Phosphorous was the earliest and most frequently used atom to measure high energy phosphates (ATP, ADP, P2r or Ph). The carbon atom (CMRS) has been used to label substrates such as glucose, acetate and pyruvate.

The use of atoms of sodium and potassium (Na^+ and K^+ MRS) permits the monitoring of the intracellular ionic compositions, both of which have great significance in the propagation of membrane potential, and intracellular and extracellular water movement in muscle tissue. Cine MRI is a recent technological development, which has been applied to visualize dynamic internal events such as the beating of the heart or displacement of the diaphragm. Intense muscle exercise results in an accumulation of Pi and an increase in H^+, both affecting pH and the enzyme's capacity to generate ATP. Metabolic changes leading to muscle fatigue may soon be amenable to *in vivo* measurements.

Documentation of Respiratory Muscle Fatigue in Human Subjects. Some of the experimental studies of respiratory muscle fatigue were, in reality, measurements of the total duration during which a given force could be sustained, i.e. time to task failure, or endurance. Once task failure is established, we can assert that fatigue preceded (fatiguing contraction pattern). The evolution of maximal force as a function of time has been well documented in fatiguing contractions. Two major types of tasks have been used to elicit fatigue of the respiratory muscles: a) breathing against high inspiratory (or expiratory) resistance, and b) performing maximal voluntary ventilation under isocapnic conditions (Fig. 7). The resistive breathing protocol consists of setting a target Pdi, duty cycle, and frequency of breathing, or mouth pressure. The target is held until failure; with PaCO2 remaining at a normal level. Fewer studies offered breathing resistance without instructions about how to breathe (i.e. the subject chooses his/her own pattern of breathing). Under these conditions, PaCO2 tended to increase or decrease; in general, it increases considerably when resistances are high, and decreased when resistances were low. Overall, the results of resistive breathing experiments have shown that a pressure swing of about 50% of maximum force sustained at a duty cycle of .4 could be endured for one hour or longer. A few studies have evaluated fatigue in accessory respiratory muscles or abdominal muscles. Task failure was well documented, and we can therefore infer that fatigue did occur. In resistive breathing, the pattern of contraction consists of slow velocity, high force, small shortening, and high intramuscular pressure. Presence of muscle fatigue has been documented by measuring the force frequency curves in the diaphragm before and after task failure. All have shown decreases in maximal pressure following resistive breathing which ended in task failure. It is possible to conclude that fatigue of the respiratory muscles in human subjects does happen during experimental loaded breathing.

The model of fatigue caused by inspiratory resistance breathing may apply to some clinical conditions like heavy snoring or sleep apnea, where peak plural pressures of 40 to 60 cm H_2O have been reported. Such conditions are, however, prevalent for short periods (minutes), followed by unloading (airway opening), and are not expected to cause fatigue.

Expiratory resistive breathing was shown to result in fatigue of abdominal muscles, and can happen in severe expiratory airway disease. Patients with COPD represent a unique situation. Their mean Pdi swing is in the range of 10 to 15cm H_2O (rest), and can increase to 20 cm during exercise; these values are close to 50% of their maximum. It is well documented that high intramuscular tension limits muscle blood perfusion leading to failure. In COPD it is likely that the relatively low Pdi measured may underestimate the intramuscular tension, since the flat diaphragm is far less effective in developing intrathoracic pressure, due to a defective coupling with the rib cage. It is not known if diaphragm perfusion is impaired in COPD. There are, in fact, studies that report a lack of increase in diaphragm perfusion in animals whose lungs were hyperinflated via PEEP: despite a threefold increase in work of breathing and pressure time index. It is known that the degree of activation of the diaphragm in COPD during resting breathing is about three times higher than in normal subjects. Recent studies show that activation of the diaphragm in COPD can rise to 85% of maximal during moderate exercise, and support the hypothesis of a high intramuscular tension in the diaphragm, which is not evident from Pdi measurements.

The second method used to induce respiratory muscle fatigue is to ask normal subjects to sustain the maximal voluntary ventilation (MVV) as long as they can, which is usually a very short period of time (about 30 sec.). Normal subjects can sustain a VE of about 55%-60% of their MVV for periods of 20 min or longer. Such levels of ventilation are seen in aerobic sports such as the marathon, skiing, and biking. During MVV the muscles contract at high speed, relatively low force, and undergo large changes in length with every breath.

In order to measure fatigue of the diaphragm at high levels of minute ventilation, the Pdi generated has been measured by applying a single electrical pulse and short trend stimulations of 10 and 20 Hz. to the phrenic nerves of normal subjects before and after exercise at 85% or 95% of their VO2 max (ventilation in the range of 80 and 120 L/min, respectively). A decrease in the value of the Pdi twitch, volitional Pdi max, and a reduction in the relaxation rate was observed during the test exercising at 95% of VO2 max. No difference was found after exercising at 85% VO2 max. Studies of Pdi max following a marathon run resulted in decreases in volitional Pdi max. It is therefore reasonable to assume that fatigue of the diaphragm develops when VE is held at 50% to 60% levels of MVV or higher. This is of relevance in sports medicine, where the limitations of body performance can be attributed to limitations in ventilation. Fatigue of the respiratory muscle in aerobic exercise may be a more relevant issue in well trained athletes than in sedentary people.

In summary, the loss of force of the respiratory muscles leading to fatigue does happen in human subjects. This becomes evident when subjects are sustaining either 50% of their maximal force or 50% of their maximal voluntary ventilation. Losses in force at lower rates have not been well documented. The monitoring of parameters showing more subtle evidence of muscle dysfunction than a loss of maximal force during loading in both normal and diseased subjects remains an exiting challenge.

Respiratory Muscles Training

In patients with COPD, as the diaphragm becomes functionally impaired, the accessory muscle contribution to ventilation progressively increases. Patients with symptomatic lung disease like COPD are limited in their capacity to exercise, because of dyspnea. Evidence suggests that the dyspnea relates more to respiratory control and muscle function than to airflow obstruction. As the ratio between the pressure needed to ventilate and the maximal pressure that the muscles can generate (Pdi/Pdimax or PI/PImax) increases, there is a proportional increase in dyspnea. Dyspnea also increases with increases in the duration of the contraction (Ti/Ttot) cycle and respiratory frequency. Because these factors have been shown to correlate with EMG evidence of respiratory muscle fatigue, changes in any of them may help explain the observed increase or decrease in exercise performance after training.

Based upon these principles one may postulate the following treatment goals:

1)Decrease in inspiratory force,
2)Shortening of inspiratory time,
3)Increases in maximal inspiratory pressures,
4)Decrease in respiratory frequency, and
5)Improved coordination among the different respiratory muscles.

Data suggests that it is primarily through the last three mechanisms that systematic training in COPD may result in improved exercise endurance.

Exercise Conditioning

Lower Extremity Exercise

Patients with underlying lung disease are restricted in their ability to perform exercise. This leads to a progressive reduction in their physical activity. This, in turn, deconditions the muscles further, perpetuating physical inactivity and a sedentary lifestyle. This is depicted as the downward spiral of patients with COPD. A major goal of exercise training in pulmonary rehabilitation is to interrupt the downward spiral by enabling patients to tolerate a higher level of activity. It is clear that exercise conditioning improves exercise endurance.

In the mostly uncontrolled studies that have evaluated the effect of rehabilitation on exercise performance, the results are clear. Most patients included had moderate to severe airway obstruction with hypoxemia, without carbon dioxide retention. In most studies, the subjects exercised an average of 3 days per week for a total duration of 6 weeks. Walking, with or without treadmill and bicycle ergometry, were the more commonly used exercise modalities. Irrespective of the training mode, exercise endurance increased, without measurable changes in pulmonary function. In none of these studies were ventilatory muscles adequately studied, but the lack of change in vital capacity or lung volume suggest minimal if any effect of general exercise on respiratory muscle function.

Data obtained from several randomized studies with control groups in patients with underlying COPD is now available. The results revealed a significant increase in the 12-minute walking test and peak oxygen uptake with important decreases in the perception of dyspnea and improvement in health related qality of life. Based upon a review of the existing literature, increased VO_2 following exercise training as demonstrated in a few studies, can be interpreted as an enhanced physiological response to exercise. Some studies have demonstrated a decrease in the heart rate, VCO_2, and VE following exercise training. Recent data suggest that the changes are due to true physiological changes, because there have been documented increases in the enzyme content of the mitochondria of peripheral muscle biopsy in trained patients. On the other hand, most evidence indicate that ventilatory muscle function per se is not significantly affected by aerobic leg exercise, although this hypothesis has not been well studied.

Arm Exercise Conditioning

It has been demonstrated that eight weeks of 3 times weekly unsupported arm exercise results in a significant decrease in VE, VO_2 and VCO_2 for simple arm elevation. Several studies have looked at both arm and leg training, and have demonstrated improved task specific performance. Although theoretically possible, arm training has not resulted in significant changes in respiratory muscle function. Its beneficial effects are probably related to the decreased ventilatory demands, because the “efficiency” of the shoulder girdle and arm muscles improve with the training.

Methods of Specific Respiratory Muscle Training

As discussed above, whole body exercise fails to improve ventilatory muscle endurance in patients with COPD, whereas normal subjects and patients with cystic fibrosis may increase ventilatory muscle strength with intense aerobic exercise. It is possible that the levels of ventilation achieved during exercise in COPD is inadequate to generate the appropriate increase in ventilatory endurance. Since reduced inspiratory muscle strength is evident in patients with COPD, considerable efforts have been made to define the role of respiratory muscle training in these patients.

Training has been achieved using two different strategies: strength training and endurance training.

Strength Training. This is achieved through the application of a high intensity low frequency stimulus. This is done by performing repeated inspiratory effort maneuvers against a closed glottis or shutter. Studies have determined an increase in PImax with respiratory muscle strength training. In one study, the Pi max increased by 53% in patients with COPD after 5 weeks of training. Another demonstrated a 50% increase in PImax in 9 patients after 4 weeks of training. The extent to which strength training contributes to clinical improvement is debatable, but it is not unreasonable to assume that some of the observed benefits reported after respiratory muscle endurance training may relate to the increased strength achieved.

Endurance Training. Achieved through the application of low intensity, high frequency stimulus, the following three methodologies have been explored: flow resistive loading, threshold loading and ventilatory isocapnic hyperpnea.

Flow Resistive Loading: The goal is achieved by having the patient breathe through orifices of progressively smaller diameters. Although it is tempting to attribute the ability to breathe through smaller orifices as improved endurance, this may very well just represent an adaptive breathing strategy. It has, indeed, been shown in patients that just by changing the breathing pattern to one of slow long breaths, there was an improvement in resistive breathing endurance, despite the use of a smaller orifice.

In studies where attention was given to the breathing pattern, the results have been encouraging. One first group demonstrated improved ventilatory muscle strength, endurance and exercise capacity in COPD patients who underwent ventilatory muscle training in addition to rehabilitation versus rehabilitation alone. Another study demonstrated improved respiratory muscle strength and endurance in a treated group, as compared to controls. The treatment group reached progressively higher target pressures, whereas the control group breathed through an unloaded system. It is of interest that a significant reduction of dyspnea was observed in the treatment group.

Threshold Loading: The principle of this training mode is to ensure an adequate inspired pressure to ensure training independent of inspiratory flow rate. The results of the controlled studies that have evaluated threashold load training, have shown an increase in respiratory muscle strength, increased endurance to a ventilatory load and a decrease in dyspnea during this maneuver. Those studies which evaluated other important outcomes, such as health related quality of life and exercise capacity, unfortunately demonstrated only minimal improvements. In conclusion, although threshold loading improves ventilatory muscle strength and endurance for resistive breathing; it also seems to decrease dyspnea with exercise, there are minimal systemic benefits from these changes. Other outcomes have not been examined, and require further studies.

Ventilatory Isocapnic Hyperpnea: In this form of training, the patient maintains a high level of minute ventilation for 10 to 15 minutes 2 or 3 times daily while CO_2 is kept constant. This concept simulates whole body exercise such as running, by subjecting the diaphragm and other inspiratory muscles to low tension, high levels of repetitive activity. The level of hyperpnea is measured as the maximum sustained ventilatory capacity (MSVC), defined as the maximum level of ventilation that can be sustained under isocapnic conditions for 15 minutes. The few studies that used this training mode showed that muscle endurance improved in the range of 20% to 50%. Controlled studies by 2 groups have demonstrated that although MSVC improves in COPD patients trained for 6 weeks, exercise endurance is no better than the control groups. Because it is difficult to implement and with no demonstrable change in outcomes other than the improved respiratory muscle endurance, isocapneic hyperventilation is not used as a from of ventilatory muscle training.

Breathing Retraining. There are other less conventional forms of training that are open to critical review, but are conceptually solid and may offer new avenues of treatment. Patients with COPD manifest a higher ventilatory drive than normal patients. In fact, patients on mechanical ventilation who cannot wean have a higher ventilatory drive than those patients who successfully wean. If we could decrease this drive, it would become possible to decrease the consequences of such a high drive: increased work of breathing, respiratory rate and perhaps dyspnea. Although it is scant, there is some available data that supports the study and application of these therapeutic tools.

Feedback: In a recent study, 40 patients were evaluated after at least 7 days of mechanical ventilation. They were randomized to conventional weaning or weaning with the use of electromyographic feedback training using the frontalis signal as an indication of tension and to induce relaxation. They also used the surface EMG of intercostals and diaphragm as indicators of respiratory muscle activity. Using feedback signals to encourage relaxation and larger tidal volumes, there were differences between treated and untreated patients. The results indicate a reduction in mean ventilator days for the biofeedback group. Tidal volume and mean inspiratory flow increased significantly for this group. The increase was also significant when corrected by diaphragmatic EMG amplitude. This was interpreted as improved diaphragmatic efficiency. The authors concluded that breathing retraining resulted in a more efficient breathing pattern which, in turn, decreased dyspnea and anxiety, and allowed for quicker weaning time in the treated patients.

Postural Changes: It is known that musculoskeletal tone and contraction may be determined by habitual positioning. Over the last few years, increasing attention has been given to the voluntary inhibition of those patterns. This has been particularly useful for artists. A recent study demonstrated improved peak expiratory flow rate, maximal voluntary ventilation and maximal inspiratory and expiratory pressures in normal subjects who underwent lessons in proprioceptive musculoskeletal education, compared to controls. This method has not, per-se, been systematically evaluated in patients with lung disease, but breathing retraining (pursed lip breathing and diaphragmatic breathing) constitutes a form of therapy that resembles the above discussed techniques.

Pursed Lip Breathing: Indeed, pursed lip breathing results in a slowing of the breathing rate with increases in tidal volume. PLB will result in a shift in the pattern of recruitment of the ventilatory muscles from one that is predominantly diaphragmatic to one that recruits more the accessory muscles of the ribcage and abdominal muscles of exhalation. Perhaps this shift may contribute to the relief dyspnea that has been reported by patients when this breathing technique is adopted. Patients on ventilators cannot purse lip breath, but it has been shown that the administration of respiratory retard, or PEEP, improves oxygenation, decreases respiratory rate, augments ventilation, and improves work of breathing in weaning patients. Pursed lip prevalence in COPD is related to the degree of airway obstruction.

CONCLUSION

Over the last two decades, numerous studies of ventilatory muscle training on patients with chronic airflow limitations have been reported. Uniformly, they indicate that VMT results in either increased strength or endurance for the specific task for which they were trained. Several questions have been answered regarding the acceptable methods of training. However, based upon the existing literature, we still cannot recommend routine ventilatory muscle training to all patients with COPD, since there is limited evidence that it improves outcomes such as quality of life, or activities of daily living. Future research will attempt to evaluate the role of VMT as an adjunct to other well proven training strategies, such as aerobic leg training. The scientific evaluation of less accepted techniques, such as breathing retraining, yoga, and biofeedback deserve interest and efforts.

Surgery and Respiratory Muscle Function

By removing the most abnormal emphysematous lung and decreasing resting lung volume, lung pneumoplasty allows the respiratory muscles and especifically the diaphragm to regain length and/or mechanical coupling advantage. Recent data shows improved respiratory muscle performance at rest and during exercise and decreased dyspnea. The latter may happen because of a reduction in the neural drive, as overall mechanics and impedance improve after LVR. As more experience is gained with this procedure, it will become a therapeutic option for selected patients with severe COPD.

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CHAPTER

7 Molecular Biology of Lung Disease

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INTRODUCTION

In the past two decades, the techniques of molecular biology have been used increasingly, not only in basic science but also in clinical research. Today, clinicians, including specialists in pulmonary medicine, are confronted frequently with reports of studies in which the techniques of molecular biology are employed. This chapter is intended to help readers understand the information and techniques that are the basis of molecular biology. The concepts of genomic deoxyribonucleic acid (DNA), primary messenger ribonucleic acid (pre-mRNA) processing, including alternative splicing, and translation of mRNA into protein are introduced first. The common techniques of molecular biology are presented next, followed by examples of recent advances in pulmonary research in which these techniques have been used.

BASIC CONCEPTS

Genomic DNA

The nucleus of each normal human somatic cell contains 46 chromosomes—44 somatic chromosomes and two sex chromosomes, which are either XX in a female or XY in a male. Each chromosome contains a single, linear, compacted, double-stranded DNA molecule, which is the genetic material, plus associated proteins, such as histones. The structure of DNA consists of two long complementary polynucleotide chains that wind around each other to form a double helix. The basic building block of the polynucleotide chain is a mononucleotide, comprised of a phosphate group, a sugar ring (deoxyribose), and a base moiety, either a purine (adenine, *A,* or guanine, *G*) or a pyrimidine (cytosine, *C,* or thymine, *T*). The backbone of the helix consists of deoxyribose-phosphate groups. Except at the 5' end of the DNA strand, each phosphate group forms a 5'-3' phosphodiester bond between the fifth carbon of one deoxyribose ring and the third carbon of the adjacent deoxyribose ring. The nucleotide base (G, A, T, or C) attached to each deoxyribose moiety is in the center of helix, oriented perpendicularly to its axis. The two strands of the DNA helix are held together by hydrogen bonds between complementary base pairs (two bonds between adenine and thymine, three between guanine and cytosine). The strands are antiparallel, one running in the 5' to 3' direction and the other in the 3' to 5' direction. Because adenine pairs only with thymine and guanine only with cytosine, the sequence of nucleotides in one strand of the double helix determines the sequence of the other.

The complete DNA sequence, comprising the total genetic information carried on all chromosomes in a cell, is called *genomic DNA.* It is estimated that haploid human genomic DNA contains 3 x 10^9 base pairs (bp), representing 100,000 to 500,000 genes. A gene, which consists of the entire DNA sequence necessary for the synthesis of a functional polypeptide or RNA molecule, such as transfer RNA (tRNA) or ribosomal RNA (rRNA), is the smallest functional physical unit of inheritance. A gene contains not only the nucleotides that encode the amino acids of a protein (coding sequences) or the sequence of a functional RNA, but also all the other DNA sequences needed to produce the primary RNA transcript (Fig. 1). In the eukaryotic genome, critical noncoding sequences include (1) transcription regulatory sequences with promoter, promoter-proximal elements, and enhancers, (2) a sequence at the 3' end of a gene that signals the position for 3' cleavage and polyadenylation, and (3) intervening sequences (introns) that are later removed by splicing of primary RNA transcripts.

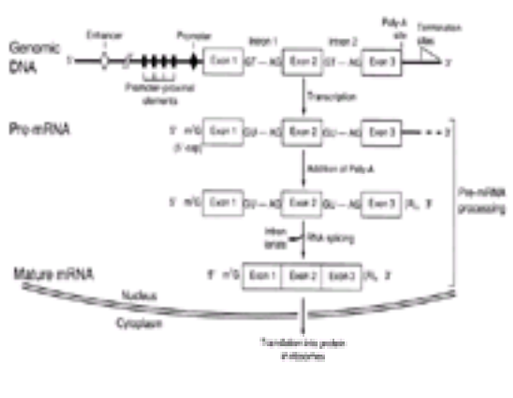

FIG. 1. Gene expression in mammals. Shown at the top is the basic structure of a gene in genomic DNA. Exons (sequences preserved in the mature mRNA), introns (intervening noncoding sequences), and important elements of gene regulation, including the promoter, promoter-proximal elements, enhancer, poly(A) site, and the universally conserved dinucleotides (GU and AG) at the 5' and 3' ends of each intron, are indicated. The gene is first transcribed into pre-mRNA transcripts. After several steps of pre-mRNA processing, including 5' capping with 7-methylguanylate (m^7G), polyadenylation at the 3' end, and RNA splicing to excise introns and ligate exons, mature mRNA is ready to be transported to the cytoplasm for translation into protein in ribosomes. See text for details.

The promoter contains a sequence that determines the site of transcription initiation by an RNA polymerase. Promoter-proximal elements, usually adjacent to the promoter, bind specific factors (transcription factors) to regulate the rate of transcription of the gene into pre-mRNA. An enhancer consists of sequence, located either upstream or downstream at a distance from the transcription initiation site, that can increase or decrease the rate of transcription of the gene by binding to a specific factor(s).

Primary Messenger RNA Processing and Alternative Splicing

Although the genetic information is stored in DNA in the nucleus, the protein (gene product) is synthesized on ribosomes in the cytoplasm. The mRNA, an edited copy of the gene, carries the genetic information from the nucleus to the cytoplasm. The structure of RNA is slightly different from that of DNA, in that uracil replaces thymine

and ribose replaces deoxyribose.

As the first step in transferring genetic information from DNA to protein in eukaryotic cells, a protein-encoding gene is transcribed by RNA polymerase II into pre-mRNA (Fig. 1). The pre-mRNA includes exons (sequences preserved in the mature mRNA) and introns (intervening sequences). RNA polymerase II initiates transcription at the first nucleotide of the first exon (the transcription initiation site) of a gene and stops at any one of multiple sites 0.5 to 2 kilobases (kb) downstream from the 3' end of the last exon (termination sites). To yield a functional mature mRNA, the pre-mRNA undergoes several processing steps in the nucleus, including capping at the 5' end, cleavage and polyadenylation at the 3' end, and ligation of exons with concomitant excision of introns (RNA splicing). Shortly after transcription of pre-mRNA begins, the 5' end of the newly formed RNA is capped with 7-methylguanylate. In addition, in vertebrate cells, the 2' hydroxyls of the ribose of the first and second nucleotides at the 5' end are methylated. This 5' cap facilitates ribosome binding to RNA and increases the efficiency of translation of mRNA into protein. At the 3' end, an endonuclease cleaves the pre-mRNA at the 3' end of the last exon [poly(A) site], usually 10 to 30 bp downstream from the poly(A) signal, which often includes an AAUAAA sequence. Then, a sequence of 100 to 250 adenylate residues [poly(A) tail] is added by a polymerase. Finally, introns are excised by RNA splicing before the mature mRNA is transported to the cytoplasm, where it can be translated.

Pre-mRNA splicing is a tightly regulated process in which introns must be accurately and efficiently removed and exons spliced together to yield mature mRNA. In each mammalian intron, the nucleotides GT are at the 5' end and AG at the 3' end. Important *cis*-acting elements are required for accurate and efficient splicing, including highly conserved consensus sequences at the 5' and 3' splice sites. In addition, many *trans*-acting elements are involved in forming the complex spliceosome for pre-mRNA splicing. These include small nuclear ribonucleoproteins (snRNPs) U1, U2, U4, U5, and U6, and many non-snRNP factors. During pre-mRNA splicing, the 5' splice junction is cleaved first, and the most 5' nucleotide of the intron (G) is joined in a 2'-5' phosphodiester bond to a specific point nucleotide (A) to generate a lariat intermediate. Then, cleavage at the 3' splice junction releases the lariat intron and the two exons are ligated. Mature mRNA is formed in this manner, ready to be transported to the cytoplasm for translation.

Different exons in a given pre-mRNA can be included in the final mature mRNA. This is termed *alternative splicing,* which greatly increases the diversity of proteins that can be derived from a single pre-mRNA. Alternative splicing usually is regulated in a tissue- or development-specific manner. For example, fibronectin (a large extracellular matrix protein) mRNA in fibroblasts contains EIIIA and EIIIB exons, whereas the fibronectin mRNA in hepatocytes does not. Alternative splicing can occur because of differences in sequences at critical splice sites. For example, there is a variable in-frame skipping of exon 9 in cystic fibrosis transmembrane conductance regulator (CFTR) mRNA transcripts. From 0%–92% of CFTR mRNA transcripts in the respiratory epithelium may have a deletion of exon 9 sequences (exon 9^-). This is mainly because of differences among individuals in the length of a polythymidine tract close to the 3' splice site of exon 9. An inverse relationship exists between the length of the polythymidine tract (5T, 7T, or 9T) and the proportion of exon 9^- CFTR mRNA transcripts in respiratory epithelium.

Protein Synthesis: Translation of mRNA into Protein

In the cytoplasm, protein synthesis occurs on ribosomes, where the nucleic acid sequence of mRNA (A, U, G, C) is translated into an amino acid sequence to form a polypeptide by the combined action of tRNAs and ribosomes. From the starting point of translation of mRNA, each triplet of bases forms a “codon” that specifies which amino acid is to be incorporated into the growing polypeptide chain by interaction with a specific tRNA, which contains a unique complementary three-base “anticodon.” There are 64 (4^3) possible codons. Of these, 61 are used to specify 20 different amino acids, and three are stop signals to indicate the end of a polypeptide chain. With the exception of methionine and tryptophan, each amino acid is encoded by more than one codon. Remarkably, every cell of every organism, from bacteria to humans, uses the same three-base genetic code to designate the amino acid that is to be incorporated into the growing polypeptide chain. Ribosomes consisting of rRNAs and many associated ribosomal proteins provide binding sites for all the accessory molecules of protein synthesis. Ribosomes and bound tRNAs move along an mRNA transcript to translate its genetic information into a protein.

COMMON TECHNIQUES OF MOLECULAR BIOLOGY

Isolation of Samples

The lung provides the molecular biologist with a relatively convenient source of samples for evaluation of gene expression and function. Whereas obtaining tissue samples from most organs may require a surgical procedure, the lung is readily accessible via fiberoptic bronchoscopy, which is a less invasive procedure. During bronchoscopy, sampling of respiratory epithelium is performed by brushing with a cytology brush, whereas bronchoalveolar lavage (BAL) allows sampling of the epithelial lining fluid and inflammatory cells in the bronchoalveolar space. Evaluation of sputum or cells from the lining of the nasal passages may be accomplished without bronchoscopy.

Sputum

Sputum can yield information about the cellular and biochemical composition of the lung. Expectorated sputum can be collected easily and analyzed repeatedly. Induction of sputum by inhalation of hypertonic saline aerosol has been used successfully to diagnose lung infections (e.g., *Pneumocystis carinii* pneumonia in patients infected with HIV). Analysis of the cellular constituents of sputum has been used as a less invasive method than bronchoscopy to evaluate and monitor airway inflammation in asthmatic patients. Sputum consists of soluble (SSP) and gel (SGP) phases, which can be separated by centrifugation. Like BAL fluid, SSP can be analyzed to give information about exudation of plasma protein into the airway lumen of patients with lung disease. The amount of protein in SSP is reported to be elevated in several lung diseases, including asthma, chronic bronchitis, and cystic fibrosis (CF), and is reduced by therapy. To assess proteins in SGP, it is necessary to solubilize the SGP with dithiothreitol, a reducing agent that cleaves disulfide bridges in the mucin molecules. Analysis of proteins in sputum with specific antibodies is a valuable tool for studying inflammatory processes in the lung. Analysis of sputum from patients with CF revealed the presence of excess DNA from desquamated epithelial cells, neutrophils, and eosinophils, resulting in increased viscosity and impaired clearance and thereby playing a significant role in airway disease in these patients. This finding led to the development of a specific therapy using recombinant human deoxyribonuclease I, an enzyme that acts as a “molecular scissors” to cleave DNA in purulent lung secretions, making them easier to expectorate.

Bronchoalveolar Lavage

BAL is an invaluable means of evaluating inflammatory and immune processes in the lung. Lavage recovers cells resident in the bronchoalveolar space; these can be used for a variety of morphologic and functional studies after separation from fluid by simple centrifugation. A sample of cells is evaluated by light microscopy for total cell number, differential cell count, cell morphology, and the presence of any abnormal substances (e.g., asbestos bodies). In normal subjects, lavage yields macrophages (90%), lymphocytes (10%), and <1% neutrophils, eosinophils, and/or basophils. A high lymphocyte count is frequently found in hypersensitivity pneumonitis and sarcoidosis. Elevated numbers of neutrophils are common in CF, idiopathic pulmonary fibrosis (IPF), connective tissue disorders, and adult respiratory distress syndrome.

Depending on the cells needed, an array of techniques can be used to isolate specific types of cells from lavage fluids for further characterization. These techniques include the following: adherence to plastic, band-density-gradient centrifugation, and the use of cell-specific antibodies immobilized on the surface of superparamagnetic microspheres (Dynabeads). Dynabeads coated with a specific ligand can be added to a heterogeneous suspension to bind the desired target molecule, forming a complex that is removed from the suspension using a magnet. This technology allows for further subdivision of cell populations (e.g., separation of lymphocytes into B cells and T cells and further categorization of T cells into $CD4^+$ and $CD8^+$ populations). In sarcoidosis, for instance, the lymphocytes in BAL fluid are predominantly $CD4^+$, whereas $CD8^+$ T lymphocytes predominate in hypersensitivity pneumonitis.

Inflammatory cells from BAL fluid can also be evaluated for gene expression at the mRNA or protein level or for the presence of a specific DNA sequence. As gene expression can be altered when cells are removed from the body, it is important that they be processed promptly. When the cells are lysed, released RNases and proteases degrade RNA and proteins, respectively. Cells should be lysed, therefore, in a “protective buffer” appropriate for their intended use. Cells destined for RNA analysis should be handled in an RNase-free environment and lysed in a buffer containing guanidium thiocyanate, a powerful inactivator of RNases. Cells processed for protein analysis need to be lysed in the presence of antiproteases. An alternative approach is to freeze cells as a pellet to be thawed in a specific buffer, depending on the intended use. The latter approach, however, carries a risk for degradation if samples are accidentally thawed.

It may be important to define changes in gene expression in cells after their removal to an *ex vivo* environment. This can be done by maintaining the isolated cells in culture while the desired studies are performed. For instance, one may ask whether bronchial epithelial cells continue to express high levels of inducible nitric oxide synthase after their removal from the lung.

Evaluation of proteins, cytokines, and other mediators in BAL fluid can yield useful information regarding the inflammatory status of the lung. Results of analysis of BAL fluid are usually expressed relative to the volume of epithelial lining fluid. The latter is estimated by comparing concentrations of urea in samples of lavage fluid and plasma obtained simultaneously.

Brushing Techniques

Brushing of the nose and/or main bronchi is useful to obtain samples of respiratory epithelium. Nasal epithelial cells are obtained from the inferior turbinate under direct visualization using a cytology brush. Bronchial epithelial cells are obtained from the trachea and main bronchi during bronchoscopy using a cytology brush. Samples obtained by brushing can be processed in a fashion similar to that described for lavage cells.

Blood

Genomic DNA, purified from blood cells, can be used to correlate pulmonary findings with genetic information (e.g., polymorphism in a specific gene to be related to airway hyperreactivity). It is often useful to compare levels of a component in sputum or lavage fluid with systemic levels in plasma or serum. In addition, estimation of quantities of epithelial lining fluid requires that levels of urea in BAL fluid be compared with levels of urea simultaneously measured in plasma.

Polymerase Chain Reaction

The polymerase chain reaction (PCR) has revolutionized molecular genetic analysis by allowing the exponential amplification of DNA. PCR can produce an enormous number of copies of a single DNA molecule, enough DNA for most molecular biology procedures. DNA polymerase, the enzyme that normally is responsible for DNA replication, is used to synthesize a complementary strand of DNA with the four nucleotides as substrates and a single DNA strand as a template. Because DNA polymerase is not able to initiate DNA synthesis *de novo,* PCR requires a short piece of complementary polynucleotide that acts as a primer. PCR, therefore, mimics the in vivo process of DNA replication.

The particular sequence of DNA to be amplified is defined by a specific pair of DNA primers. The latter are added, in excess, to a tube that contains a mixture of all four deoxynucleotide precursors, the DNA to be amplified, and DNA polymerase. The mixture is heated to 95°C to denature the template DNA (denaturing step). At this temperature, double-stranded DNA molecules separate, forming single strands that become templates for the production of copies with the primers and DNA polymerase. The temperature is then lowered to allow primers to anneal to the complementary sequences in the DNA molecules (annealing step), generating the primed templates for DNA polymerase. This annealing temperature is a key variable in determining the specificity of the PCR and differs depending on the sequence of the primers. The temperature is then raised to 72°C, the optimal temperature for activity of heat-stable *Taq* DNA polymerase, which was isolated from bacteria that live in thermal springs. The temperature is held at 72°C, allowing DNA synthesis to proceed (extension step). At the end of this period, the temperature is raised again to 95°C, so that double-stranded DNA (the original strand and the newly synthesized complementary strand) separates. These single strands become templates for another round of DNA synthesis, and the cycle of denaturation, annealing of primers, and synthesis of new strands by DNA polymerase is repeated for 20 to 50 cycles. PCR does not require a highly purified DNA as a template and can therefore be performed directly on cell lysates from virtually any source.

"RNA" Polymerase Chain Reaction (Reverse Transcription-Polymerase Chain Reaction)

The adaptation of PCR for the analysis of specific mRNA molecules provided a breakthrough. In this technique, short oligonucleotides are annealed to mRNA to act as primers for reverse transcriptase. This enzyme, isolated from certain RNA viruses, uses RNA as a template to synthesize a complementary DNA (cDNA) strand, which then becomes a template for PCR amplification. The exquisite sensitivity of this simple modification of PCR makes possible the detection and sequence analysis of mRNAs that are extremely rare. Because RNA must be reverse transcribed to cDNA before amplification can take place, this technique has become widely known as *reverse transcription-polymerase chain reaction* (*RT-PCR*). Given the proclivity of enzymatic amplification to reveal rare molecules, one must consider whether the amplified products arise from RNA or from contaminating DNA. Whenever possible, PCR primers should be chosen from different exons. Inadvertent amplification of DNA can then be recognized by the size of the products resulting from amplification of the intervening introns. It may be avoided by enzymatic treatment of samples with DNase before RT-PCR. DNA amplification may also be detected by amplification of a control sample without prior reverse transcriptase treatment.

"Hot-Start" Polymerase Chain Reaction

The specificity of PCR can be further enhanced using the "hot-start" technique, which minimizes nonspecific binding of primer to template during preparation of PCR reactions at room temperature. All reagents except one (usually DNA polymerase) are mixed and kept at 70° to 95°C. Just before cycling, the missing component is added to initiate the reaction at the elevated temperature. The method can be automated by interposing a physical barrier of wax between the reaction mixture and the component to be added last. Mixing occurs only at high temperature, when the wax melts. A recent innovation is the use of a neutralizing monoclonal antibody to block DNA polymerase activity during the mixing of PCR components. When the temperature is raised above 70°C during the first PCR cycle, the enzyme-antibody complex dissociates, the antibody is inactivated, and the DNA polymerase becomes active. Typical applications of hot-start PCR include reactions involving complex genomic or cDNA templates, very-low-copy-number targets, "multiplex" PCR (i.e., multiple primer pairs in the same tube), and "long" PCR (see below).

"Touchdown" Polymerase Chain Reaction

"Touchdown" PCR involves gradually decreasing the annealing temperature (e.g., by 1°C every other cycle) to a "touchdown" annealing temperature, which is then used for approximately 10 cycles. The approach takes advantage of the exponential nature of PCR to favor products resulting from correct matches between primers and template rather than incorrect intermediates. In the above example, a difference of 1°C between specific and spurious annealing temperatures will give a twofold difference in favor of the specific product per cycle.

"High-Fidelity" Polymerase Chain Reaction

DNA replication in vivo is extraordinarily accurate. Most bacterial DNA polymerases possess an exonucleolytic activity that scrutinizes DNA synthesis and removes mismatched nucleotides. *Taq* polymerase, however, does not have this "proofreading" capability and incorporates one incorrect nucleotide per approximately every 2 x 10^4 nucleotides. When an exact sequence is required, such as when PCR is being used for cloning, high-fidelity enzymes with "proofreading" exonuclease activity are required (e.g., *Pfu* polymerase, which has an error rate of one per approximately 2 x 10^6 nucleotides).

"Long" Polymerase Chain Reaction

This is one of the most important recent advances in PCR technology and is likely to have revolutionary effects on molecular biology. Until recently, it has been difficult to amplify more than 5 kb of DNA, probably because of premature termination of synthesis at sites of mismatched base pairs. Although DNA polymerases with "proofreading" exonuclease activity can remove mismatches and extend the chain, they can not overcome this length limitation, probably because their exonuclease activity eventually degrades the PCR primers. The solution was to use a mixture of *Taq* polymerase and a small amount of polymerase that possesses a "proofreading" exonuclease activity. Evidently, very little exonuclease activity is sufficient for removal of the mismatches, permitting the predominant polymerase activity to complete strand synthesis. The capability of "long" PCR to amplify DNA sequences of up to 42 kb will make it possible for the speed and simplicity of PCR to facilitate and complement many techniques in molecular genetics.

Rapid Amplification of cDNA Ends

Conventional approaches to the characterization and sequencing of mRNA rely on the preparation and screening of a cDNA library. Frequent problems, however, include loss of rare messages during library preparation and failure to produce complete cDNA molecules because of premature termination of reverse transcription. Rapid amplification of cDNA ends (RACE) offers an opportunity to isolate a message of interest directly by amplification of full-length mRNA. Unlike conventional PCR, which requires knowledge of the sequences flanking the region of interest to design PCR primers, an anchored PCR can be performed when only a small amount of sequence information is available (40 to 50 nucleotides). Amplification is carried out between a defined site (known sequence) and unknown sequences at either the 3' or 5' end of the mRNA. 3' RACE takes advantage of the natural poly(A)$^+$ tail present in virtually every mRNA. In this procedure, mRNAs are converted to cDNA using reverse transcriptase with an oligo(dT) adapter primer. Specific cDNA is then directly amplified by PCR using a gene-specific primer that anneals to the region of known sequence and an adapter primer that targets the poly(A) tail region. 5' RACE uses a sequence-specific primer to initiate the synthesis of the cDNA strand. By means of terminal transferase, cDNA is modified by the addition of a poly(A) tail to flank the 5' end. PCR amplification is then carried out with a sequence-specific primer and an oligo(dT) primer complementary to the newly synthesized tail. Reamplification using a second, internal (nested) sequence-specific primer greatly reduces spurious amplification products. It is advisable to monitor PCR products by Southern blot hybridization using a specific oligomer, to confirm that the desired product has been amplified. After amplification, 5' and 3' RACE products can be combined by ligation to produce an intact, full-length cDNA that can be sequenced directly or cloned into an appropriate vector for further analysis.

Limitations of Polymerase Chain Reaction

The great sensitivity of PCR, although a major advantage, is also its major limitation. Because of the enormous amplification attainable by PCR, small amounts of DNA contamination, either from previous PCR amplification, positive control templates, or samples with large amounts of DNA, can result in product formation even in the absence of added template DNA. Aerosol droplets from a pipette tip may contain amplifiable molecules after prior handling of a positive sample. The use of dedicated equipment and pipette tips with hydrophobic filters is recommended to minimize the incidence of false-positives. All reaction mixtures should be prepared in an area separate from that where PCR products are analyzed. Irradiation of PCR solutions with ultraviolet (254 nm) light before adding DNA template "sterilizes" or renders nonamplifiable any contaminant DNA by causing thymine dimers to form. Another approach is to use uridine triphosphate (UTP) instead of deoxythymidine in the PCR reaction mixture and include the enzyme uracil-*N*-glycosylase (UNG). UNG will degrade any DNA from a former PCR because it contains UTP. UNG is then inactivated by the high temperature initiating the new PCR, so that desired products of the amplification can accumulate.

A second limitation that poses a major hurdle to the concept of quantitative PCR stems from the nonlinear nature of the amplification process. Because of the exponential nature of PCR, an early error can be amplified exponentially and in an unpredictable manner, preventing accurate quantitative results. Two approaches can circumvent this problem: (1) During reverse transcription of mRNA, a known quantity of synthetic mRNA, which can be easily differentiated from the endogenous message, is added, and the two cDNAs are amplified simultaneously in the same reaction mixture with the same sets of primers. The amplified unknown is then compared with the amplified standards. (2) During PCR amplification, a known amount of modified cDNA is added to the PCR medium to compete with the target sequence for the same primers. If the competitor were present at the same concentration as the unknown, both DNAs would be amplified to the same extent. By using several different percentages of the competing DNA, the amount of endogenous DNA can be estimated.

Differential Gene Expression

Paramount to understanding the molecular biology of lung disease is a knowledge of genes that are differentially expressed during physiologic and pathologic processes. Differentially expressed genes can be identified by detecting differences in levels of mRNAs in different types of cells or under different conditions in the same cell. This may be important, for example, to an investigator who would like to identify genes involved in the pathogenesis of IPF. After a group of patients fitting the diagnostic criteria and a group of normal subjects to be used as controls have been screened, and with the knowledge that the alveolar macrophage is important in the pathogenesis of this disease, samples may be obtained by BAL from both groups. Differential cDNA library screening, subtracted cDNA libraries, or PCR-based differential display can be used to identify genes expressed differently in alveolar macrophages from the two groups.

Differential Screening

Differential screening allows a gene-by-gene comparison of mRNA populations in the two samples. For this purpose, a cDNA library is prepared using mRNA isolated from the alveolar macrophages of patients with IPF, plated on agar, and transferred to duplicate sets of filters. Filter A is hybridized to a cDNA probe prepared from alveolar macrophage mRNA of normal subjects. Filter B is hybridized to a cDNA probe prepared in a similar fashion from alveolar macrophage mRNA of patients with IPF. Unlike Southern or Northern hybridization, differential screening must be performed under conditions of limiting (rather than excess) probe to detect differences in the concentrations of mRNA from the two populations. cDNA clones (as plaques) that demonstrate different levels of hybridization with the two probes represent mRNAs that are differentially expressed and can be isolated and screened to confirm their differential expression. This method is straightforward and works well for genes that are highly expressed. It is difficult, however, to isolate mRNAs of low abundance, because of variable signal intensity and relatively high background. The use of subtracted libraries and/or subtracted probes improves the chances of cloning rare cDNAs (see below).

Subtractive Hybridization

Subtractive cloning can be used to construct a cDNA library that is enriched in transcripts of genes specifically expressed in cells of patients with IPF. Single-stranded cDNA is synthesized using mRNA from these cells and then hybridized to an excess of biotinylated mRNA from cells of normal subjects. The cDNA sequences representing mRNAs expressed in normal cells will hybridize, whereas those unique to the cells of patients with IPF will remain single-stranded. By adding streptavidin, a protein that binds to biotin, the biotinylated sequences and cDNA hybridized to them can be removed. Nonbiotinylated single-stranded cDNAs from patients with IPF remaining in the solution can then be used to create a subtracted cDNA library enriched in clones that are unique to patients with IPF. This library is then screened using a probe made from RNA of normal subjects. To enhance specificity, a subtracted probe can be used. Subtracted cDNA probes can be prepared using the same principle as for subtracted cDNA libraries. A major problem with subtracted libraries is the very small number of colonies sometimes obtained, in part as a result of the loss of mRNA during the two or more rounds of hybridization that may be needed to remove shared sequences. This can be overcome by using PCR amplification of both the original and the subtracted DNAs. With very limited amounts of starting RNA, multiple rounds of subtraction and amplification may be needed.

Differential Display Reverse Transcription-Polymerase Chain Reaction

Differential display combines the power of PCR amplification and the high resolution of polyacrylamide gel electrophoresis. Each RNA is transcribed to a cDNA by means of a set of four oligo(dT) primers that anneals to the poly(A) tails, each with an anchored two bases at the 3' end, $T_{12}XA$, $T_{12}XC$, $T_{12}XG$ and $T_{12}XT$ (where X is a degenerate mixture of A, G, and C). Each degenerate anchored oligo(dT) primer will, in theory, reverse transcribe one fourth of the total mRNA population. In combination with a set of 5' random 10-mer oligonucleotide primers, which should anneal to arbitrary subsets of mRNA present in the cell, the cDNA population is amplified by PCR. Each of the random 10-mers anneals to a complementary sequence located at a different distance from the 3' terminus, yielding PCR products of different sizes. By varying primer combinations, most of the RNA species in a cell can be represented. PCR reaction products (labeled with a radioactive isotope, such as sulfur 35 or phosphorus 33, or fluorescein) are separated by electrophoresis in a polyacrylamide gel for side-by-side comparison of RNA samples from different cells, allowing recognition of differentially expressed genes. Differential expression is detected by inspection of autoradiograms to identify bands present in only one group, such as patients with IPF. Fluorescent products can be analyzed using an automated DNA sequencer. Although band intensity may correlate with mRNA abundance, the method is not believed to be quantitative.

Further analysis of differentially displayed sequences requires excision of the band from the gel and elution of the DNA, followed by repeated amplification and gel purification. The DNA is then subcloned, so that it can be sequenced and used to make probes for analysis of Northern blots. High-efficiency cloning can be carried out by taking advantage of the single additional A residues at the 3' ends of PCR products; single T residues are added at the 3' ends of a vector to facilitate ligation to the PCR product (TA cloning). The chosen DNA is then directly used as a probe in Northern blot analysis, utilizing the pools of mRNA from the two groups to confirm differential expression and provide information about the molecular weight of the identified transcripts. Once differential expression of a band is confirmed and sequence is known, it should be determined whether the sequence is part of a true open reading frame (i.e., encodes a protein sequence). The identified sequence can be compared with a gene database to determine if it is part of a novel gene and if it bears sequence similarities to other gene families, which may provide clues to function. The same cDNA can then be used to obtain a full-length clone of the novel gene by screening a cDNA library.

Although differential display provides a rather simple and rapid way of identifying differentially expressed genes, several problems are inherent to the technique. Because of its great sensitivity, it can potentially detect a very large number of genes. Screening and confirmation of differential expression of all these could be very time-consuming. Differential amplification, display, and confirmation should therefore be carried out with multiple identical samples before proceeding. Every experiment requires appropriate controls (e.g., samples without reverse transcriptase paired with reverse transcribed PCR samples to detect amplification of products from contaminating DNA not removed by DNase treatment of RNA samples), as well as confirmation of differential expression by Northern analysis before further cloning or sequencing procedures.

Screening for Members of Common Family Genes

The methods considered above illustrate a rather random approach to identifying novel genes. This may not always be the best strategy. When looking for related genes, which presumes prior knowledge of amino acid sequence of the proteins analogous to the one that is sought, degenerate pools of oligonucleotide primers can be designed for PCR amplification, usually performed at a low annealing temperature to permit several possible mismatches. This, however, can result in an enormous number of irrelevant PCR products. If enough sequence is known, it is advisable to screen PCR products by hybridization with a specific probe before further analysis. An alternative approach is to use a degenerate oligonucleotide probe to screen a cDNA library for the desired gene. For instance, a conserved sequence of seven or more contiguous amino acids provides enough information to design a degenerate oligonucleotide probe to select and clone cDNAs encoding related proteins. If the sequence of another conserved region of the desired gene is known, screening can be simplified by using a second probe to evaluate clones positive on initial screening.

Screening for a Specific Protein or Specific Function

If the nucleotide sequence is not known, functional assays or specific antibodies that recognize the desired gene product can be used. This is accomplished by constructing and screening an expression library of cDNAs with an open reading frame that encodes the desired protein fused to a bacterial protein inserted adjacent to bacterial promoters. Fusion proteins may be more stable than native proteins in bacteria and are therefore likely to yield more product. The cDNA library is screened by incubation with an antibody specific for the protein of interest (primary antibody); then, following removal of unbound antibody, a second antibody is added to react with

the primary antibody. The second antibody can be labeled with radioactive isotope, coupled to biotin, or conjugated with an enzyme such as alkaline phosphatase; each provides a means to detect the clone expressing the desired protein. The clone is then isolated and the cDNA sequence determined. Similar principles apply in screening with a functional assay (e.g., ADP-ribosyltransferase activity) instead of antibodies.

Identifying a Protein by Western Blotting

Western blotting is a simple, sensitive, and powerful method for immunologic detection of particular proteins of interest in a complex mixture of proteins. This commonly used technique combines the resolving power of gel electrophoresis, the specificity of antibodies, and the sensitivity of enzyme assays. Proteins are first denatured in the presence of sodium dodecyl sulfate and separated according to molecular weight by polyacrylamide gel electrophoresis. Then, an electric field is applied to drive the separated protein molecules out of the gel and onto a paper-thin nitrocellulose membrane or its equivalent, where they are immobilized. In the second step, the specific protein of interest is identified by soaking the membrane in a solution containing an antibody (primary antibody) specific for that protein (antigen). Then, the antibody bound to the antigen is reacted with a second antibody, which is covalently linked to alkaline phosphatase or horseradish peroxidase. After washing the membrane, the enzyme linked to the second antibody is detected by reaction with a chromogenic substrate to yield a visible product or with a substrate that yields a luminescent product, which can be detected by autoradiography. Alternatively, the antigen-antibody complex can be detected using protein A labeled with iodine 125, which binds to the antibody.

RECENT ADVANCES IN PULMONARY RESEARCH

Polymerase Chain Reaction in the Diagnosis of Pulmonary Infections

Standard diagnostic procedures for pulmonary infections are based on the ability to grow organisms in culture or to detect their presence in serum using antibodies. These tests can be relatively insensitive and time-consuming. Because of its high sensitivity, PCR may facilitate the early diagnosis of many infectious diseases.

Mycobacterium tuberculosis *Infection*

The diagnosis of *M. tuberculosis* infection requires growth of organisms in culture, a procedure that takes several weeks. More rapid diagnosis of pulmonary tuberculosis can be made by detection of acid-fast organisms in sputum smears. The results of smears are positive, however, in only 50%–75% of cases. Prompt and sensitive diagnosis by PCR is feasible using specific primers for a sequence within a gene that is highly conserved in all mycobacterial species. The amplified fragment is then hybridized with species-specific oligonucleotide probes to identify the specific strain. As few as 10 bacilli in 10^6 cells can be detected by PCR, which has also been used to identify *M. tuberculosis* in blood samples. With the inherent potential for false-positives owing to its great sensitivity, positive PCR results must be interpreted in conjunction with clinical information. In contrast, a negative PCR result rules out the diagnosis. Although at present PCR has not totally replaced established procedures for the diagnosis of *M. tuberculosis* infection, it may be particularly useful in certain categories of patients. In a patient with negative smear results and positive culture results, PCR could provide an early diagnosis on which to base initial therapy. In addition, by the amplification of bacterial DNA sequences that contain mutations associated with antibiotic resistance, PCR may play an important role in the rapid identification of multidrug-resistant strains of *M. tuberculosis.* PCR may be used to diagnose primary tuberculosis in children, which is sometimes difficult to diagnose by conventional means. The results of direct examination of sputum or gastric aspirates are usually negative, and the results of culture are positive in only 20% of cases. Tuberculin skin tests are difficult to interpret in children who are immunosuppressed or have received Calmette-Guérin vaccination. *M. tuberculosis* has been detected by PCR in gastric aspirates from many children with primary tuberculosis and cultures negative for bacteria.

Cytomegalovirus Pneumonitis

The diagnosis of cytomegalovirus (CMV) pneumonitis in immunocompromised patients may be difficult, because of its clinical similarity to diffuse lung injury of other causes. Immunofluorescent staining of alveolar macrophages and epithelial cells for CMV antigens with specific monoclonal antibodies has been used, in combination with clinical findings, to make the diagnosis. PCR provides a very sensitive assay for the detection of CMV in bronchoalveolar lavage fluid. For rapid diagnosis of CMV infection, the combination of PCR and immunofluorescence is an optimal strategy that provides almost 100% sensitivity and specificity. PCR is also useful as a rapid assay to exclude the diagnosis of CMV pneumonitis. In addition, detection of CMV in blood by PCR has been used to predict in which patients CMV pneumonitis is likely to develop or, after completion of initial therapy, which patients are likely to relapse.

Pneumocystis carinii *Pneumonia*

PCR is a highly sensitive technique for the identification of *P. carinii* in BAL fluid or induced sputum; it detects the gene that encodes the mitochondrial rRNA of *P. carinii.* Diagnostic PCR is more sensitive for detecting *P. carinii* than are traditional silver staining and immunofluorescent procedures. The specificity of PCR detection can be enhanced by hybridizing PCR products to specific oligonucleotide probes on Southern blots. Detection by PCR of *P. carinii* in serum has been proposed as a simple test for the diagnosis of disseminated pneumocystosis.

Other Pulmonary Infections

Candida albicans, Mycoplasma pneumoniae, Bordetella pertussis, Aspergillus fumigatus, Legionella pneumophila, respiratory syncytial virus, and influenza virus are examples of other organisms that have been identified using PCR.

Latent Infections

In several studies, the results of PCR in diagnosis of *Mycoplasma* infections were discordant with serologic findings, consistent with the observation that *Mycoplasma* can persist in tissues long after clinical disease has resolved. Although PCR can be useful for detection of persisting sequences of an infectious agent, the clinical interpretation of the finding depends on establishing whether it represents continuing or latent infection. There are situations, however, in which the mere presence of the sequences in a host may have important clinical implications, as in the case of gene therapy protocols utilizing adenovirus (AV) vectors in the lung. In this approach, the normal gene is directly delivered to the respiratory epithelium using AV vectors that have been rendered replication-defective by deletion of a region, E1a, that is critical for viral replication. There is the possibility, however, of a replication-defective AV vector replicating as a result of recombination or complementation with viral E1a sequences present in the host cells from prior infections. Using specific primers to amplify E1a by PCR and evaluating PCR products with a probe specific for that region, it is possible to identify individuals who harbor that viral sequence in their cells. Special precautions in these individuals may be warranted, such as frequent monitoring for evidence of viral replication.

Gene Therapy

Gene therapy is a medical intervention designed to alter the genetic program of cells with therapeutic intent. The goal is to modify specific cells to express, temporarily or permanently, a specific set of new genetic information in a fashion that will be beneficial in the treatment of hereditary or acquired disease. There are two basic strategies of gene therapy. First, cells may be genetically modified ex vivo for subsequent implantation in the host target tissue or organ. This can be carried out using either autologous cells derived from the intended recipient of the therapy or cells from other individuals or species. Alternatively, cells may be modified in vivo. Viral or nonviral vectors can be used for gene therapy (Table 1).

Method	Applicability		Integration
	In vivo	Ex vivo	
Viral			
Retrovirus	+	+++	yes
Adenovirus	+++	+	no
Adeno-associated virus	+++	++	yes
Herpes virus	+++	+	no
Other viruses (e.g., vaccinia)	+++	+	no
Nonviral			
Naked plasmid	+++	+	no
Liposome-plasmid complex	+++	+	no
Ligand-plasmid complex	+++	+	no
Particle bombardment	++	++	?
Combination system			
Co-internalization	+++	+	no

+++, High applicability; ++, medium applicability; +, low applicability; ?, integration results not definitive.

TABLE 1. *Methods of gene transfer to mammalian cells*

Vectors

Retrovirus (RV) is an RNA virus that enters the cell through specific viral receptors on the cell surface. Once inside the cell, RNA is converted to DNA by the reverse transcriptase activity of the virus itself. The double-stranded DNA provirus is then randomly integrated into the host genome, if the cell is actively dividing. In most RV vectors, the *gag, pol,* and *env* genes are replaced with the gene of interest, so that vectors are capable of entering cells and inserting the new genes into the genomes but cannot direct cells to produce infectious RVs. Theoretically, the newly integrated exogenous gene will be passed on to progeny of the cell when it divides. RV is, thus far, the most widely used vector in gene transfer protocols approved by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health. A major disadvantage of RV as a vector for use in vivo, however, is that it cannot be used to express genes in nondividing cells.

The AV vector is more efficient than RV for in vivo gene therapy. AV is a double-stranded DNA virus that provides several major advantages. Replication of host cells is not required for expression of a gene transferred by AV, and there is no known association of human malignancies with AV infection despite its high incidence. In most AV vectors currently used, the E1 region, which is important for viral replication, is deleted. Disadvantages of the AV vector are that (1) many AV genes included in the presently used vectors induce an immune reaction, and (2) gene expression is not stable, as the vector does not integrate into the host genome.

Adeno-associated virus (AAV) is a 4.7-kb, single-stranded DNA virus of the parvovirus family. The AAV genome consists of two genes, *rep* and *cap,* flanked by inverted terminal repeats that serve as signals for origin of DNA replication and packaging. AAV is nonpathogenic and appears not to alter the clinical course of AV infection. AAV cannot naturally replicate and requires coinfection with AV or herpesvirus, which provide helper functions. AAV has the ability to integrate into the DNA of nondividing cells. In the absence of helper virus, AAV infection results in high-frequency, stable DNA integration, usually into a specific site on human chromosome 19 at q13.4. In AAV vectors, the *rep* and *env* genes are usually deleted and replaced with the gene of interest to minimize the possibility of inducing immunity by the expression of viral genes. AAV can be produced to titers of $>10^{10}$ plaque-forming units (pfu) per milliliter. All these features make AAV vectors attractive for human gene therapy. Their disadvantages, however, include the inability to accommodate large genes (packaging limit of 4.5 kb) and the potential risk for contamination by helper viruses, as production of AAV vector requires coinfection with AV or herpesvirus.

Liposomes

Liposome-plasmid complexes are the most frequently used nonviral vectors for human gene therapy. Liposomes are lipid model membranes that can form a complex with DNA and facilitate its transfer into cells, probably through nonspecific fusion of the liposome-plasmid complex with cell membranes.

Gene Transfer Protocols

To date, >100 human gene transfer protocols have been approved by RAC. Of these, 18 are aimed at treating individuals with lung diseases: 13 for CF, one for a_1-antitrypsin deficiency, and four for primary lung cancer (Table 2).

Disease	Gene	Vector	Tissue transduced	Number[b]
Hereditary				
Cystic fibrosis	CFTR	Adenovirus	Nasal and respiratory epithelium	4
	CFTR	Adenovirus	Nasal epithelium and/or maxillary sinus	3
	CFTR	Adenovirus	Respiratory epithelium	2
	CFTR	Adeno-associated virus	Nasal and respiratory epithelium	1
	CFTR	Adeno-associated virus	Maxillary sinus	1
	CFTR	Liposome-plasmid complex	Nasal epithelium	2
a_1-Antitrypsin deficiency	a_1-AT	Liposome-plasmid complex	Nasal and respiratory epithelium	1
Lung cancer				
Non–small-cell lung cancer	p53	Retrovirus	Tumor	1
	K-*ras* (AS)			
	p53	Adenovirus	Tumor	1
Small-cell lung cancer	IL-2	Liposome-plasmid complex	Skin	1
Adenocarcinoma	CEA	Vaccinia virus	Skin	1

CFTR, cystic fibrosis transmembrane conductance regulator; a_1-AT, a_1-antitrypsin; p53, p53 tumor suppressor gene; K-*ras* (AS), antisense sequence of K-*ras* oncogene; IL-2, interleukin-2; CEA, carcinoembryonic antigen.
[a]Only protocols approved by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health by December 1995 are included.
[b]Number of protocols approved.

TABLE 2. *Summary of approved protocols for gene therapy of human lung diseases*[a]

For CF, AV vectors are used in nine protocols, AAV vectors in two, and liposome-plasmid complexes in two. In five protocols, vectors are delivered to both nasal epithelium and lung respiratory epithelium, in two to respiratory epithelium only, and in six to nasal and/or maxillary sinus epithelium. In twelve protocols, the vector is instilled in the lung via bronchoscopy or delivered to the nasal and/or maxillary sinus epithelium through a rhinoscope or catheter under direct visualization. In one protocol, the AV vector is administered by aerosol to the lung.

It has been observed that about 30% of adenocarcinomas of the lung have a mutated K-*ras* oncogene, and 50% of non–small-cell lung cancers have mutations or deletions of the p53 tumor-suppressor gene. In two protocols for lung cancer, an RV or AV vector containing wild-type p53 cDNA (for tumors with mutated or deleted p53) or antisense K-*ras* (for tumors with mutated K-*ras*) is injected into a residual endobronchial lesion of non–small-cell lung cancer. Immunotherapy was proposed in two other protocols. In one protocol, intradermal injection of recombinant carcinoembryonic antigen (CEA) vaccinia virus is followed by subcutaneous injection of CEA peptide to induce a host immune response. In the other, autologous tumor cells, irradiated to prevent proliferation, are transduced ex vivo with a liposome-plasmid complex containing an interleukin-2 cDNA and then injected subcutaneously.

Of protocols for gene therapy of human lung diseases, data from four studies of patients with CF have been reported in detail. An AV vector was used in three and a liposome-plasmid complex in one. In all studies, successful gene transfer to a small fraction (<1%–14%) of nasal or respiratory epithelial cells was demonstrated, and CFTR protein or mRNA was detected for at least 9 days. In three studies, two with AV vectors and one with a liposome-plasmid complex, partial correction of abnormalities of potential difference across nasal epithelium was noted. One controlled study using an AV vector, however, failed to demonstrate correction of functional defects in nasal epithelium. In one study, the AV vector caused the level of interleukin-6 in serum to increase, and pneumonia developed in one person who received 2×10^9 pfu of AV vector into a large airway. Parameters of pulmonary function and chest roentgenographic and computed tomographic findings in this patient returned to baseline after 1 month.

Although the technologies are still far from ideal, data relevant to human gene therapy are encouraging; after further refinement, it seems likely that gene therapy will become an increasingly useful therapeutic option.

Transgenic Mouse Model

Transgenic mice have recently been used as models for the study of many human diseases, not only because mice are relatively closely related to the human species but also because their genetic manipulation and propagation are relatively rapid.

Transgenic mice are produced by the permanent alteration of a small part of the genome, which is achieved by at least two different strategies. In the first, a cloned DNA construct is delivered into the male pronucleus of the newly fertilized mouse egg by microinjection. The introduced foreign DNA randomly integrates into the mouse genome, without preference for a particular chromosomal location, and the injected eggs are implanted into a foster mother. Of the 10%–30% of those that develop to term, up to 40% may contain integrated foreign DNA. They are heterozygous and can be bred to homozygosity. Mice that carry the foreign gene are termed *transgenic,* and the integrated DNA is the transgene. Because the foreign DNA is randomly integrated into the mouse genome, there are several potential problems, such as insertion of the transgene into an essential gene or differential expression of the transgene resulting from differences in sites of integration or differences in the number of gene copies introduced.

In contrast to random integration of transgenes, the second strategy modifies a selected gene at a precise location within the genome of a mouse embryonic stem (ES) cell by homologous recombination. Mouse ES cells are derived from the inner cell mass, which corresponds to the future embryo, of a mouse blastocyst. Under suitable culture conditions, the ES cells can proliferate in vitro, remain undifferentiated, and be subcultured repeatedly. Usually, ES cells are grown on a monolayer of fibroblasts that have been treated so that they cannot divide. A cloned DNA construct is then delivered into the ES cells by electroporation. The foreign DNA becomes integrated into the homologous gene locus of the mouse genome by homologous recombination and disrupts or mutates the endogenous gene. ES cells with integrated

foreign DNA can be identified by PCR and/or Southern analysis. They can be positively and/or negatively selected, taking advantage of properties of specific, simultaneously introduced genes. Recombinant ES cells are then microinjected into blastocysts derived from mice with a coat color different from that of the donor of ES cells and implanted in a foster mother. From the coat color of the chimeric offspring, the contribution of recombinant ES cells can be easily evaluated.

Examples of transgenic mouse models for human pulmonary diseases are described below.

Idiopathic Pulmonary Fibrosis

Tumor necrosis factor-a (TNF-a) produces both fibrogenic and inflammatory effects. Expresssion of TNF-a mRNA and protein is increased in type II pneumocytes of individuals with IPF. Surfactant protein C (SP-C) is synthesized and secreted by type II pneumocytes. By microinjecting a construct containing a mouse TNF-a gene, including the entire 3' untranslated region directed by a 3.7-kb fragment of the 5'-flanking region of the human SP-C gene (SP-C/TNF-a), into the male pronucleus of mouse fertilized eggs, Miyazaki et al. generated transgenic mice with elevated expression of TNF-a in alveolar epithelium, mainly in type II pneumocytes. Five of thirteen founder mice died at birth or after 1 month with severe lung lesions. Surviving mice transmitted a pulmonary disease to their offspring, the severity of which was correlated with levels of TNF-a mRNA in the lung. At 1 to 2 months of age, leukocytic alveolitis, with a predominance of T lymphocytes, was extensive within the interlobular septa, beneath the pleurae, and around extra-alveolar small vessels. The extent of fibrosis was minimal at this stage. However, at 6 months of age, the alveolar septa were markedly thickened, resulting in large part from the accumulation of desmin-containing fibroblasts. Alveolar spaces were enlarged and contained desquamated epithelial cells. Alveolar surfaces were lined by hyperplastic type II pneumocytes. Increased levels of vascular cell adhesion molecule-1 (VCAM-1) mRNA, enlargement of the endothelial cytoplasm, and increased platelet trapping in alveolar capillaries were also observed. In general, the numerous pulmonary lesions in the SP-C/TNF-a mice were very similar to those in individuals with IPF.

Transgenic mice in which human transforming growth factor-a (hTGF-a) was expressed under the control of a 3.7-kb fragment of the 5'-flanking region of the human SP-C gene also exhibited pulmonary fibrosis. The fibrosis was prominent in subpleural, peribronchiolar, peribronchial, and perihilar regions. There was, however, no apparent fibrosis or thickening of the alveolar interstitium. The severity of fibrosis differed with the founder line and the abundance of transgene product in the lungs. In addition, greater than normal mitotic activity and numbers of epidermal growth factor (EGF) receptors in the interstitial cells of the fibrotic lesions were observed. These findings support the hypothesis that hTGF-a produced by respiratory epithelial cells stimulates the growth of mesenchymal components of the lung.

These kinds of transgenic mice provide valuable models for evaluating the molecular mechanisms that contribute to the pathogenesis of pulmonary fibrosis and for testing therapeutic strategies in vivo.

Pulmonary Alveolar Proteinosis

Granulocyte-macrophage colony-stimulating factor (GM-CSF), a 23-kd (kilodalton) glycoprotein, stimulates the proliferation of hematopoietic progenitor cells, as well as their differentiation to monocytes/macrophages, neutrophils, and eosinophils. To delineate the *in vivo* function of GM-CSF, Dranoff et al. generated mice carrying a null allele of the GM-CSF gene by homologous recombination in embryonic stem cells. Unexpectedly, the homozygous transgenic mice had normal numbers of peripheral bloods cells, bone marrow progenitors, and tissue hematopoietic populations, including splenic dendritic cells. However, in all homozygous mutant mice, but not in heterozygous or wild-type mice, a progressive accumulation of surfactant lipids and proteins developed in the alveolar space, characteristic of human pulmonary alveolar proteinosis. In mutant mice, levels of surfactant proteins SP-A, SP-B, and SP-C were markedly increased in BAL fluid, although the abundance of surfactant mRNA was indistinguishable from that in wild-type mice. Moreover, the alveolar macrophages of mice deficient in GM-CSF were filled with surfactant protein and lipid, although no accumulation of SP-A was observed in type II pneumocytes. It appeared that alveolar macrophages were defective in processing pulmonary surfactants, as a result of the absence of GM-CSF in the mutant mice, leading to pulmonary alveolar proteinosis. In addition, extensive pulmonary lymphoid hyperplasia surrounding the airways and veins, developed in mutant mice, which could have been the result of an excessive response to otherwise innocuous inhaled antigens.

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CHAPTER

8 Pulmonary Imaging

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INTRODUCTION

Despite the introduction of many technologically advanced imaging modalities, a conventional chest radiograph remains the initial, and sometimes only, diagnostic image necessary to evaluate patients with suspected chest abnormalities. Typically, observations derived from chest radiography, in combination with the clinical history, suggest at least a differential, if not a definitive, diagnosis. Only after complete characterization and assessment of a chest radiographic abnormality are additional diagnostic imaging studies indicated; these can range from low-technology examinations, such as decubitus chest radiographs, to sophisticated technologic examinations, such as computed tomography (CT), magnetic resonance imaging (MRI), nuclear imaging, pulmonary and bronchial artery angiography, and ultrasonography. At this time, the most important of these additional diagnostic imaging studies is CT of the chest. Chest CT has done more to revolutionize the radiologic evaluation and subsequent care of patients with thoracic abnormalities than any other radiographic technique since the invention of conventional chest x-ray imaging.

In addition to conventional radiography and CT, three other broad categories of radiographic examinations can potentially be used to evaluate chest abnormalities. These include angiography, nuclear imaging, and MRI. Although much less frequently performed than chest radiography or CT, these other examinations listed are essential tools in the diagnosis and management of patients with specific medical problems, such as hemoptysis, pulmonary embolus, or brachial plexus involvement by neoplasm. It is now routine practice to use images for accurate staging of a thoracic neoplasm, percutaneous biopsy of a mediastinal mass, drainage of a collection of fluid, or quick assessment of the response of a chest abnormality to therapy. The older imaging techniques (plain tomography and bronchography) have generally been supplanted by one of these newer techniques that in conjunction with other procedures, such as fiberoptic bronchoscopy, provide more reliable anatomic and physiologic information with less patient discomfort. Ideally, the pulmonologist and the radiologist should work together to plan a cost-effective diagnostic and therapeutic imaging workup.

In this chapter, the relevant technical principles of common radiologic examinations are described, and the clinical indications, advantages, and limitations of each examination type are reviewed. A comprehensive review of the myriad diagnostic and interpretative findings found on routine chest radiography or the more specialized examinations is beyond the scope of this chapter; however, clinically pertinent signs are illustrated. A systematic, simplified approach to interpreting any imaging study and organizing a relevant differential diagnosis is presented at the conclusion of the chapter.

STANDARD PLANE CHEST RADIOGRAPHY

Radiographic Technique

Two distinct radiographic techniques are used to obtain a conventional chest radiograph (posteranterior and lateral); the high-kilovoltage (>100 kV) and low-kilovoltage (<90 kV) techniques. The principal advantage of the high-kilovoltage technique is better display of the lung parenchyma without interference from overlying ribs, clavicles, or heart. The principal advantage of the low-kilovoltage technique is the enhancement of the contrast between pulmonary vessels and parenchyma and the identification of calcium. Pulmonary nodules are more easily detected on high-kilovoltage films (100 to 130 kV).

The standard chest radiograph is taken at full inspiration with the patient approximately 72 inches from the plane of the x-ray film. This minimizes geometric magnification of the heart and enhances visualization of the pulmonary vasculature. The optimal density of a conventional posteroanterior or lateral chest x-ray film is a matter of individual preference. In general, the mediastinal structures should be easily discernible from the lung parenchyma and the bones. The intervertebral disk spaces and ribs should be identifiable on a routine posteroanterior film, but not at the expense of an optimal view of the lung parenchyma.

After conventional chest radiographs, portable chest radiographs are the next most frequently used radiographic examination of the chest. No commonly accepted standards or techniques are available for performing portable chest radiographs, as they are for standard posteroanterior and lateral chest radiographs. Further, these films are obtained in the anteroposterior direction, so that magnification artifacts occur. Consequently, the quality and reproducibility of a portable chest x-ray film is extremely variable. The rates for repeated portable chest radiographs are two to four times greater than those for repeated conventional radiographs. Portable chest x-ray films are often obtained in the sickest and most unstable patients. The variabilities of exposure, penetration, and positioning make interpretation of these films more problematic. Standard protocols that maximize consistent and reproducible high-quality portable films should be used.

The most commonly employed portable chest x-ray technique uses manually selected low kilovoltages and exposure times, without a grid. This technique results in portable films of relatively high contrast that are often degraded by scatter radiation. The mediastinal structures or lung parenchyma may not be optimally visualized because the films are either underexposed or overexposed. Overexposure may be done intentionally, to improve visualization of a monitoring line or tube. However, this is an unnecessary practice that contributes to poor overall film quality.

Portable chest x-ray films should be obtained using a fixed high-kilovoltage technique (approximately 110 kV) with a grid and phototiming. Phototiming devices are unavailable in many hospitals, and manually selected exposure times are then required. The high-kilovoltage technique is preferred because portable films can be produced that consistently approximate the quality of a conventional chest x-ray film. An important added benefit is decreased radiation exposure to the patient and hospital personnel. The decrease in exposure time more than compensates for the higher kilovoltage used.

Indications

The American College of Radiology Thoracic Expert Panel has developed a set of indications for chest films that includes signs and symptoms referable to the pulmonary or cardiovascular systems, suspicion of pulmonary or cardiovascular involvement by systemic or extrathoracic diseases, and monitoring of progression or regression of previously identified thoracic abnormalities. Chest radiographs are generally indicated in individuals presenting with the following symptoms: hoarseness, dyspnea, productive or nonproductive cough, hemoptysis, or pleuritic pain (Fig. 1). These symptoms suggest abnormalities in the following anatomic structures: trachea and small and large airways (Fig. 2); lung parenchyma; pleural space; mediastinum, including the heart; and the bony thorax. All these structures may be visualized on a high-quality chest radiograph.

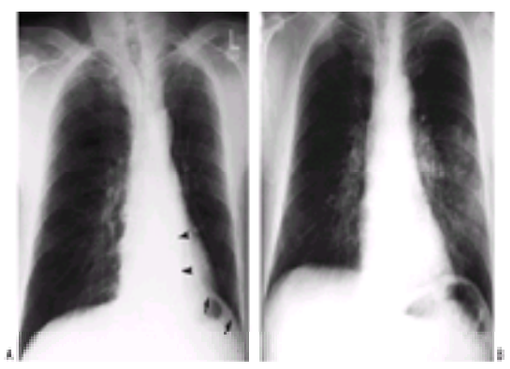

FIG. 1. A: Classic radiographic findings of left lower lobe collapse. These include volume loss (demonstrated by a shift of the mediastinum, heart, and trachea to the left), a triangular opacity in a retrocardiac location (*black arrowheads*), and silhouetting of the medial portions of the left hemidiaphragm. Only the lateral portion of the hemidiaphragm (*black arrows*) is delineated. **B:** In a radiograph obtained after chest physical therapy, the left lower lobe collapse has resolved. The shift of the mediastinum and the triangular retrocardiac opacity are no longer present. The left hemidiaphragm is identified medially.

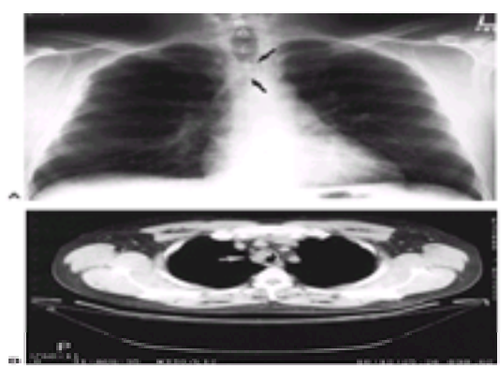

FIG. 2. A: Chest radiograph demonstrating a subtle mass (*black arrows*) projecting into the tracheal air column. **B:** Chest CT confirms the presence of a large fungating mass (*white arrowhead*) within the trachea. The vast majority of tracheal neoplasms are either of squamous cell or minor salivary gland origin. The pathologic specimen revealed adenoid cystic carcinoma.

Routine/Screening Radiography

The utility of chest radiography in routine, periodic, or screening situations (e.g., routine, daily portable chest radiographs in the intensive care unit setting, periodic screening chest films in asymptomatic ambulatory patients, and screening chest radiographs in asymptomatic HIV-infected adults) remains controversial. Routine/screening radiography may be indicated in high-risk populations, but they have not been found to be of use even in the prospective evaluation of persons who smoke, who have a higher risk for the development of lung carcinoma. Chest radiographs that were formerly taken routinely in various clinical situations but are no longer indicated include routine prenatal chest radiographs, routine admission chest radiographs of asymptomatic individuals, routine chest radiographs of geriatric patients in long-term facilities or of patients in psychiatric facilities, periodic examinations unrelated to occupational exposures, mandated chest radiographs for detection of tuberculosis as a condition of initial or continuing employment, and routine preoperative radiographs of patients under the age of 20. Lateral projections should be eliminated from the routine screening examination in patients between the ages of 20 and 39 years.

Portable Radiography

Portable chest radiographs should be routinely obtained in critically ill patients in the intensive care unit setting, as they have been shown to demonstrate unexpected findings or provide an indication for altering therapy in 37%–65% of a population of intubated patients. The American College of Radiology Expert Panel agrees with this opinion and has stated that daily, portable chest radiographs are indicated in patients who are receiving mechanical ventilation, who have acute cardiopulmonary problems to assess lung water, or in whom a new monitoring device or tube has been placed (Fig. 3). Portable chest radiography is indicated only during the initial evaluation of patients who receive just cardiac monitoring.

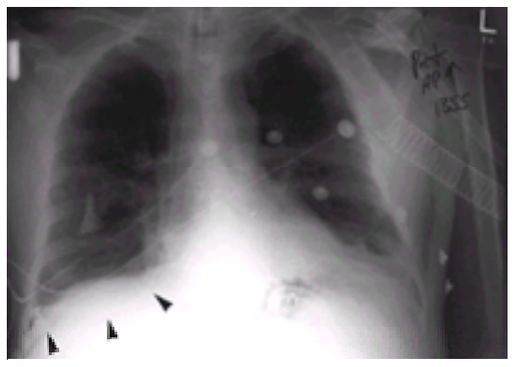

FIG. 3. A portable chest film demonstrating abnormal placement of a nasogastric tube (*black arrowheads*) into the right costophrenic angle. Feeding tubes are much more likely than nasogastric tubes to be inappropriately placed, because they are smaller in diameter and composed of more pliable material.

In settings other than the intensive care unit, the most frequent indications for portable chest radiographs include assessment of a nonambulatory patient for pneumonia or congestive heart failure, or following placement of a monitoring device (Fig. 3). Because of the limitations of the portable technique, it may be difficult to identify or distinguish between atelectasis, pneumonia, adult respiratory distress syndrome (ARDS), pleural effusions, and typical or atypical cardiogenic or noncardiogenic edema.

Utility of the Baseline (Old) Chest Radiograph

A baseline or old chest x-ray film is one of the most important resources in the diagnostic process for two reasons. First, it serves as a baseline examination with which comparisons may be made, so that detection of changes is possible. Second, with the aid of an old film, an assessment of the relative acuity or chronicity of an

observation is possible; this is an invaluable aid in the development of a differential diagnosis. Old films should be obtained for comparison whenever possible. Costs are minimized because the need for additional imaging is reduced, and quality of care is improved because the evaluation is expedited.

Decubitus and Oblique Films

On occasion, decubitus and oblique chest views may be indicated to answer or clarify specific diagnostic questions raised by interpretation of the initial chest radiograph. Decubitus views can delineate the presence and quantity of a free-flowing pleural effusion before performance of a diagnostic or therapeutic thoracentesis. Views are obtained with the patient lying in a recumbent position; each hemithorax should be alternatively visualized in the dependent position. An important advantage of obtaining bilateral decubitus views is that as fluid shifts, the underlying lung parenchyma can more adequately be evaluated for potential abnormalities that may have been hidden by the pleural fluid. In unusual circumstances, a decubitus view of the chest can demonstrate a tiny pneumothorax not necessarily seen on an expiratory upright chest film.

Oblique films of the chest, obtained by rotating the patient with respect to the film, are used to ascertain whether an opacity in the lung represents a parenchymal abnormality versus an overlap of bronchial vascular markings or an abnormality originating in the ribs. These views are usually requested by a radiologist when the level of suspicion is not particularly high that an abnormality seen on a chest x-ray film represents a true parenchymal abnormality or when the availability of CT scanning is limited. Oblique chest radiographs have been used to improve the identification, documentation, and characterization of pleural abnormalities, such as pleural plaques; these functions have now largely been replaced by CT scanning, diagnostic ultrasonography, and MRI.

Rib films, also obtained with the patient positioned obliquely with respect to the film, differ from oblique chest films in that the radiographic techniques used for a rib series are designed to improve the identification of bone abnormalities, such as fractures and metastatic disease, at the expense of visualization of lung parenchyma.

Apical Lordotic Films

Apical lordotic views, obtained with patient standing erect and the x-ray film angled 15° cephalad to the chest, are of limited utility. These views, along with apical kyphotic views, were previously used to improve visualization of the lung apices, thoracic inlet, and superior mediastinum. However, these views rarely provide sufficient additional information to make a diagnosis unequivocal. Questionable parenchymal, thoracic inlet, or mediastinal abnormalities that previously were evaluated by apical lordotic views should now be imaged with chest CT or MRI.

Chest Fluoroscopy

The utilization of chest fluoroscopy has declined in the evaluation of thoracic abnormalities with the advent of chest CT. Unlike routine chest radiography, fluoroscopy of the chest is usually performed at about 70 kV. The low-kilovoltage technique enhances the ability to detect calcium within a thoracic lesion. Current indications for chest fluoroscopy include diagnosis of diaphragmatic paralysis; discrimation between a possible rib or pleural abnormality and a parenchymal lung abnormality (pleural plaques versus a pleura-associated small parenchymal lung nodule); guidance of needle placement during percutaneous needle biopsies of lung, pleural, rib, and mediastinal masses and during percutaneous drainage of fluid collections within the chest; and guidance of bronchoscope and needle placement and confirmation of correct positioning before transbronchoscopic biopsy.

Digital Chest Radiography

The ability to acquire and display radiographs, including chest films, in a digital format should improve efficiency and decrease radiation exposure to patients and medical personnel. This technique is now becoming widely available.

COMPUTED TOMOGRAPHY

CT scans of the chest have two very significant advantages over routine chest radiographs: superior contrast sensitivity, which aids in differentiating fat, water, air, and calcium; and the ability to display cross-sectional anatomy, thereby eliminating superimposition of adjacent anatomic structures. Although images are usually obtained and displayed in a transverse fashion, multiplanar displays now allow sagittal and/or coronal reconstructions. With the advent of spiral CT scans, three-dimensional displays and holographic images may be obtained. All reconstructed display formats are designed to aid in the presentation of complex anatomic relationships. Decreased spatial resolution is the one significant disadvantage of CT in comparison with conventional chest radiography. The identification of small pulmonary nodules is easier on a chest CT scan, not because spatial resolution is enhanced, but rather because contrast sensitivity is enhanced between essentially black normal lung parenchyma and the soft-tissue density characteristic of pulmonary nodules, and also because relevant anatomy is displayed without superimposition of normal structures.

Technique

CT scans are usually obtained at end-inspiration with the patient lying supine. Two basic designs of commercial CT scanners are currently available. In one design, the x-ray tube and detectors rotate simultaneously around the patient, and in the other, the detector wing is stationary and the x-ray tube rotates. Either design produces high-quality images. Routine scanning of the chest is usually done in 8- to 10-mm-thick slices obtained contiguously from the lung apex to base through the diaphragm; the adrenal glands are often imaged as well. This basic scanning protocol may be modified depending on the specific clinical problem.

In general, the use of intravenous contrast material should be limited to evaluations in which vascular lesions (pulmonary arteriovenous malformation, pseudoaneurysm) are suspected, or in which precise vascular anatomy is needed (invasion of a pulmonary artery by a lung neoplasm). Intravenous contrast material can also be used to resolve a central lung mass from associated lung collapse or to identify a pleural effusion as transudative or exudative.

Indications

A compete list of indications for chest CT are too numerous to review here. Some of the more common indications are staging of common primary malignancies of the thorax (bronchogenic carcinoma, esophageal carcinoma); staging of intrathoracic lymphoma; evaluation of suspected vascular abnormalities (arteriovenous malformation, venous varices, pseudoaneurysms, aneurysms with or without dissection); and evaluation or staging of extrapulmonary processes, which include the following:

1. Pleural lesions (mesothelioma) (Fig. 4)

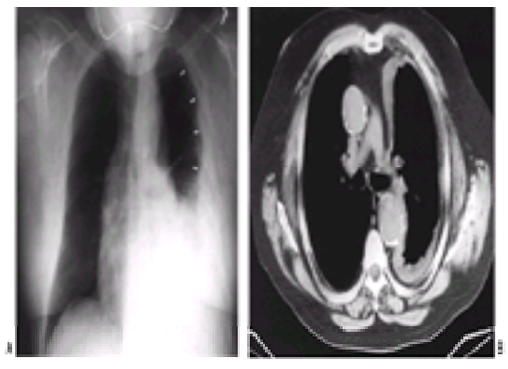

FIG. 4. A: A chest radiograph reveals a blunted costophrenic angle with a lobular configuration (*white arrowheads*) along the lateral pleural surface. This is atypical for a simple transudative pleural effusion, which would exhibit a smooth interface between the lung and pleura and not surround the entire lung. The chest radiographic appearance is very suggestive of a mesothelioma, which was confirmed on chest CT. **B:** A single image from a chest CT scan shows an encased left lung with associated contraction of the hemithorax.

2. Rib lesions (primary bone tumor, Ewing's sarcoma)
3. Pleural space processes (empyema)
4. Lesions of the chest wall

5. Diaphragmatic lesions (diaphragmatic hernias, congenital or posttraumatic)
6. Abnormalities arising from hilar and mediastinal structures, including thymic neoplasms (thymolipoma, thymoma); esophageal abnormalities (duplication cysts); pericardial or cardiac abnormalities (pericardial effusions, pericardial cysts); tracheal neoplasms (primary squamous cell carcinoma, salivary gland tumors); mediastinal or hilar adenopathy; and neoplasms originating in or invading the mediastinum (germ cell tumors, goiter)
7. Malignant neoplasms with a propensity to metastasize to the lung (melanoma, renal cell carcinoma)

Chest CT may also be indicated to characterize more completely an abnormality of uncertain etiology detected on a chest radiograph (Fig. 5).

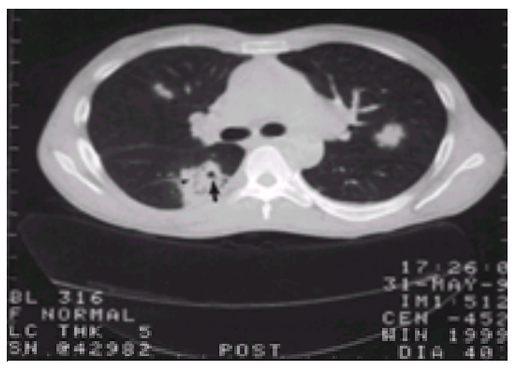

FIG. 5. Chest CT reveals three poorly defined nodular infiltrates. In one of the nodular opacities, air bronchograms (*black arrowhead*) and cavitation (*black arrow*) are visible. The differential diagnosis is broad and includes a diverse clinical conditions such as non-Hodgkins lymphoma, bronchoalveolar cell carcinoma, and Wegner's granulomatosis. With an appropriate clinical history (e.g., a patient with fever and a new systolic murmur), the differential diagnosis is narrowed to septic emboli.

High-resolution chest CT scans employ a modification of the standard acquisition and display protocol to produce thin-section (1.0 to 1.5 mm) cuts that enhance the spatial resolution of lung parenchyma. Edges are sharper and scan times are shorter with this technique. High-resolution CT can detect abnormal lung when the findings on chest x-ray film and conventional CT scan are normal. This modality is used in the evaluation of early interstitial lung disease; active disease is characterized by ground-glass opacities and interstitial or air space nodules, and inactive disease is characterized by scarring. Biopsy specimens can be obtained from areas of lung that appear active on high-resolution CT, or such areas can be followed during therapy.

In the appropriate clinical setting, certain specific diagnoses may be made by high-resolution CT without need of lung biopsy. The entities most confidently diagnosed by high-resolution CT include lymphangiomyomatosis, histiocytosis X, lymphangitic carcinomatosis, sarcoidosis, silicosis, and idiopathic pulmonary fibrosis.

Helical CT scanning is an important recent technologic innovation in which the patient is continuously fed through the scanner gantry as the x-ray images are being taken. This technique generates volumetric information that can be displayed in a conventional axial plane or in a variety of orthogonal planes. Helical CT offers three significant advantages over conventional scans. First, scan times are reduced to 30 to 60 seconds, which increases productivity. Second, less intravenous contrast is required to achieve high-quality scans, and misregistration artifacts are significantly reduced. Third, multiplanar reformation is possible with less degradation of the image. Clinically, helical CT scanning enhances detection and quantification of suspected pulmonary nodules in comparison with conventional CT scans. Vascular imaging is vastly improved, so that helical CT can replace angiography in the evaluation of aortic dissection and trauma and may eventually replace coronary angiography and pulmonary arteriography. Multiplanar reformatting has been used to display complex mediastinal and tracheobronchial anatomy.

NUCLEAR IMAGING OF THE THORAX

Nuclear imaging of the thorax is performed for a variety of clinical indications. The most common and important use of nuclear imaging is in the workup of suspected pulmonary embolus (ventilation-perfusion scans).

Technique

Technetium 99m is the most commonly used radionuclide in diagnostic imaging because it has no particulate emission, has a relatively short half-life (6 hours), and emits almost entirely 40-keV (kiloelectron volt) photons. This makes it a relatively ideal nuclear imaging agent. After intravenous administration, the relevant organ or organs are imaged with a gamma camera. The gamma camera measures the number of photons emitted by the radionuclide and displays these counts as dots; the intensity of the display (number of dots) is proportional to the amount of activity.

The choice of the particular radionuclide or radiopharmaceutical to be used for a particular study is guided by pharmacologic considerations. For example, the radionuclide xenon 133 gas is used almost exclusively for lung ventilation studies because it is not soluble in blood, whereas the radiopharmaceutical agent Tc 99 microaggregated albumin (MAA) is used for multiple indications, but primarily to detect pulmonary emboli or right-to-left shunting. It is extremely soluble in blood and does not appear in exhaled gas.

Pulmonary Embolus

Both ventilation and perfusion nuclear scans are required to assess the likelihood of pulmonary embolism. For these studies, to assess pulmonary ventilation and perfusion simultaneously, a radionuclide is inhaled (xenon 133 gas) and a radiopharmaceutical agent (Tc 99 MAA) is injected intravenously. Images obtained during inhalation, steady-state breathing, and exhalation provide information about regional and overall ventilatory dynamics. Radiolabeled aerosols are sometimes used instead of radioactive gases. Studies using these radioactive aerosols are technically more difficult to perform and may not detect small ventilation defects, but they do provide the important advantage of providing images in views corresponding to the perfusion abnormalities.

The majority of Tc 99 MAA particles injected to assess perfusion are in the 10- to 30-µm range; they mix in the right atrium and ventricle. The particles then enter the pulmonary circulation and become trapped in the pulmonary capillary vascular bed. Because of the relatively small numbers of particles compared with the number of pulmonary capillaries, further vascular obstruction does not occur. Nevertheless, in patients with known pulmonary hypertension or suspected right-to-left shunts, the quantity of Tc 99 MAA injected is usually reduced.

At this time, ventilation and perfusion images are interpreted using criteria and guidelines developed from the Prospective Investigation of Pulmonary Embolus Diagnosis (PIOPED) study. Small but important modifications and refinements to the criteria have been recently made. The size and number of matched and mismatched defects, relative to the concurrent chest x-ray image, are assessed to determine the relative probability of pulmonary embolus. Scans are rated as highly probable for the diagnosis, of intermediate, low, or very low probability, or normal. In the revised PIOPED criteria, four categories have been arbitrarily assigned numeric values: high (80%–100%, probable for the diagnosis), intermediate (20%–79%), low (<19%), and normal. A normal ventilation-perfusion scan essentially rules out the diagnosis of pulmonary embolus.

The classic nuclear imaging characteristics of pulmonary embolus are a high-probability ventilation-perfusion scan, defined as a normal ventilation scan with multiple peripheral perfusion defects corresponding to lobar or segmental anatomy, and a normal chest radiograph. High-probability ventilation-perfusion scans have a specificity for pulmonary embolus of approximately 97%, but a low sensitivity. Only about 41% of the patients demonstrated to have pulmonary embolus by angiography also have a high-probability ventilation-perfusion scan. Angiography studies have shown that a clinically high index of suspicion for pulmonary embolus and a high-probability ventilation-perfusion scan strongly correlate with the presence of pulmonary embolus, and likewise a clinically low index of suspicion for pulmonary embolus and a low-probability ventilation-perfusion scan correlate strongly with the absence of pulmonary embolus.

Other Indications

Perfusion lung scans are also used preoperatively to estimate the amount of lung function that will remain in patients with poor lung function after lobectomy or pneumonectomy (Chapter 13) and to detect and quantify right-to-left shunting (hepatopulmonary syndrome). To document right-to-left shunting, images of the brain or kidney are usually obtained to identify the abnormal location of radioactivity and document the arteriovenous shunt. By measuring the amount of activity in these organs and comparing it with the amount of activity in the lungs, the percentage of shunting can be calculated.

Nuclear imaging may also be used to evaluate occult or suspected pulmonary infection, to assess hilar and mediastinal adenopathy secondary to metastatic disease or lymphoma, and to detect inflammation in the lung parenchyma secondary to adverse drug reactions or alveolitis. Gallium 67 can detect lung injury caused by drugs such as bleomycin before any abnormality can be visualized on chest x-ray films; it can also detect occult lymphoma in mediastinal lymph nodes that appear to be of normal size on CT and occult infections of the interstitium, such as *Pneumocystis* infection. Gallium 67 scanning has been used in conjunction with determination of angiotensin-converting enzyme (ACE) levels to estimate the degree of activity of pulmonary sarcoidosis.

Gallium 67 and thallium 201 scans in combination have been shown to be extremely useful in distinguishing between Kaposi's sarcoma, mycobacterial infection, and lymphoma. This is a common problem in patients with the acquired immune deficiency syndrome (AIDS). Matched patterns of uptake on gallium 67 and thallium 201 scans are suggestive of non-Hodgkin's lymphoma, whereas a gallium-negative and thallium-positive pattern indicates Kaposi's sarcoma. Finally, a gallium-positive and thallium-negative scan is highly suggestive of mycobacterial infection, although other granulomatous infections, such as cryptococcosis, histoplasmosis, or coccidioidomycosis, cannot be completely ruled out by this technique.

PULMONARY ANGIOGRAPHY

Angiography is the least frequently used radiographic study to investigate chest abnormalities. Nevertheless, it is an important diagnostic and potentially therapeutic tool used in the evaluation of specific pulmonary abnormalities.

Technique

Access to the arterial or venous system is gained by catheterization through the groin or upper extremity using the Seldinger technique or one of its variations. Contrast material is injected into the vascular system and rapid-sequence films are obtained. Angiography is associated with low rates of complications, which may be categorized as systemic, local, or catheter-related occurrences.

Systemic complications include the development of contrast-induced nephropathy or severe allergic reaction with cardiovascular collapse. Examples of local complications related to the puncture site are development of a groin hematoma or a pseudoaneurysm. Examples of catheter-related complications are distal embolization or intimal dissection. Before any interventional procedure is undertaken, the relative benefits versus risks need to be understood clearly by the radiologist, referring clinician, and patient. To prevent complications and assess risk, a complete history should be taken (diabetes, contrast allergy, previous bleeding diathesis), and the coagulation status (platelet count, prothrombin time, partial thromboplastin time) and serum creatinine level should be determined before the procedure is performed.

Indications

Pulmonary arteriography is the most common angiographic procedure involving the thorax and is usually performed to rule out pulmonary embolus. Pulmonary angiography is also indicated in the assessment of chronic thromboembolic disease as a suspected cause of pulmonary hypertension, and as part of the evaluation of small pulmonary arteriovenous malformations. Large malformations are more easily diagnosed using contrast-enhanced chest CT.

In the workup of pulmonary embolus, pulmonary arteriography is almost always preceded by ventilationperfusion scanning. Abnormal findings on the scan can be used to guide the subsequent catheterization of the pulmonary arteries. If the ventilation-perfusion scan demonstrates a segmental defect in the left lower lobe, then the left lower lobe pulmonary artery is catheterized first so as to expedite the diagnosis and obviate the need for additional angiographic runs. However, negative results from the study of the left lower lobe pulmonary artery do not in turn obviate the need to image the entire pulmonary arterial system, as pulmonary emboli do not necessarily correspond to defects observed on a ventilation-perfusion scan.

The classic angiographic findings of pulmonary embolic disease include intraluminal filling defects and abrupt arterial cutoffs (Fig. 6). Because intraluminal clot begins to dissolve after 24 hours and 80% of the clot has lysed by 7 days, pulmonary arteriography should be performed as close in time to the suspected clinical event as possible.

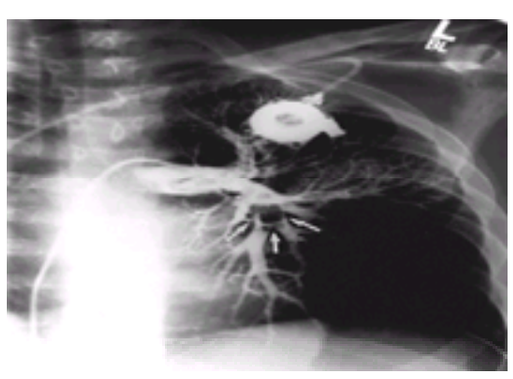

FIG. 6. Pulmonary arteriogram illustrating multiple pulmonary emboli. A large filling defect (*white arrows*), clot, is depicted in the left lower lobe pulmonary artery. Anticoagulation therapy does not immediately take effect to prevent the formation of additional emboli. The indications for fibrinolytic therapy are limited in the treatment of pulmonary embolus.

Elevated pulmonary arterial pressure and left bundle branch block are relative contraindications for pulmonary arteriography. An increase in mortality (<0.5%) is associated with right ventricular end-diastolic pressures of >20 mm Hg, and a left bundle branch block may progress to complete heart block during the procedure. These relative contraindications can be addressed by modifying the angiographic technique and placing a temporary transvenous pacing wire.

Angiography is also used to evaluate the systemic circulation, the thoracic aorta (thoracic aortography), and the bronchial circulation (Fig. 7). The indications for thoracic aortography vary from institution to institution, but generally the procedure is performed to evaluate the possibility of thoracic aortic aneurysm, thoracic aortic dissection, and traumatic injury to the thoracic aorta. At the present time, CT and MRI have begun to replace thoracic aortography for these indications, as they are noninvasive, less labor-intensive, and more cost-effective than angiography. Bronchial arterial arteriography is usually performed to identify the site of bronchial arterial bleeding in patients with life-threatening hemoptysis of known cause who cannot undergo surgical resection (Fig. 8). After identification of the site of bleeding, embolization of the vessel may be performed to reduce hemorrhage. Bronchiectasis, aspergillosis, or cystic fibrosis are the most frequent causes of this type of hemoptysis.

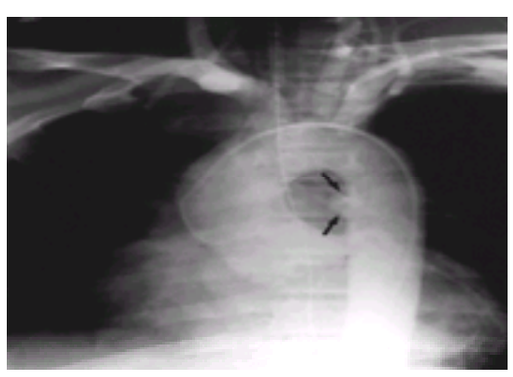

FIG. 7. Thoracic aortogram demonstrating an abnormal collection of contrast (*black arrows*) outside the normal wall of the descending thoracic aorta at the level of the ligament of the ductus arteriosus, diagnostic of an aortic laceration. Aortic lacerations are almost always associated with a deceleration injury, especially in automobile accidents.

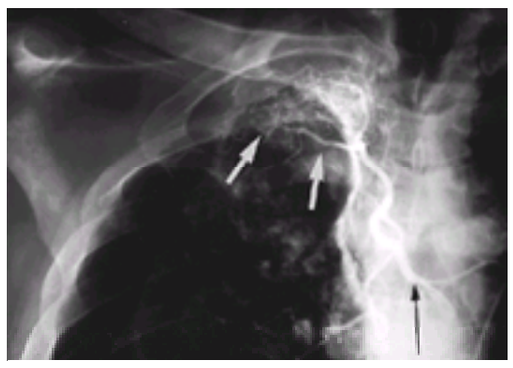

FIG. 8. Bronchial arteriogram in a patient with a known mycetoma who presented with severe recurrent hemoptysis. A bronchial artery is cannulated by a catheter (*black arrow*) before embolization. The abnormal vascularity associated with the mycetoma is visualized in the apex of the right lung (*white arrow*).

Venography of the central veins in the chest, such as the superior vena cava, left and right innominate veins, and the azygos vein, is performed rarely. Thrombosis of these vessels, which may be caused by mediastinal neoplasm, mediastinitis, or iatrogenic instrumentation, is more easily investigated noninvasively with either CT or MRI, or an ultrasonographic examination. Occasionally, vascular stents have been deployed in the treatment of superior vena cava syndrome.

MAGNETIC RESONANCE IMAGING

Principle

MRI is a relatively new imaging technique that produces images without the use of ionizing radiation. In an MR image, each voxel is a gray scale representation of the relative intensity of a radio wave signal emanating from tissue that has been perturbed by a characteristic radio frequency (RF pulse). The radio wave signal emanating from each tissue depends on several factors, the most important of which is time. T_1 and T_2 relaxation times originate from this principle. Cardiac gating and suppression of respiratory motion are essential to produce chest images of diagnostic quality. At the time of this writing, poor spatial resolution, respiratory motion, and the lack of sufficient hydrogen protons in lung make MRI of the lung parenchyma impractical for most indications.

Whereas the information in CT scans is acquired in a transverse plane through the chest, MRI is capable of imaging the chest in any plane. Another advantage of MRI in comparison with CT is its ability to identify vascular structures without the use of intravenous iodinated contrast. If contrast is necessary, gadolinium-based contrast agents have a better safety profile than iodinated contrast and can be used to delineate vascular structures. Although neither CT nor MRI can detect neoplastic invasion of tissues at the microscopic level, the superior contrast resolution of MRI offers an advantage in the diagnosis of subtle invasion of fat or soft tissues by tumor.

Current applications of MRI include evaluation of both the central venous and central pulmonary vasculature. Suspected superior vena cava syndrome, resulting from either malignancy or mediastinitis, may be diagnosed using MRI, as can invasion of pulmonary arteries or even the heart by a large central mass. Thoracic aneurysms and pseudoaneurysms, as well as aortic dissections, are readily identified by MRI (Fig. 9). Mediastinal masses, originating from any compartment, may be imaged.

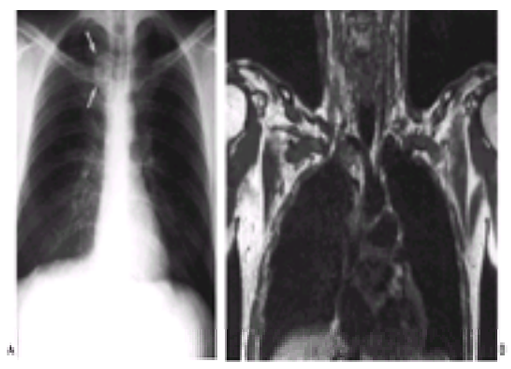

FIG. 9. A: Chest radiograph demonstrating a 2-cm peripherally calcified mass in a right paratracheal location. A vascular origin should be suspected in any chest lesion with peripheral curvilinear calcification. **B:** A coronal MRI displaying a pseudoaneurysm of the right subclavian artery in a patient with a remote history of a penetrating knife wound.

The ability to study anatomic structures in sagittal or coronal planes and the excellent contrast resolution make MRI the modality of choice in the investigation of abnormalities related to the diaphragm, lung apex, chest wall, and mediastinum (Fig. 10). Diaphragmatic abnormalities, such as posttraumatic or congenital hernias, are displayed to advantage. Similarly, abnormalities originating within the lung apex, such as a superior sulcus neoplasm, are optimally staged with MRI as either confined to the thorax or invading the brachial plexus. Chest-wall or mediastinal masses originating in any lung compartment may also be imaged.

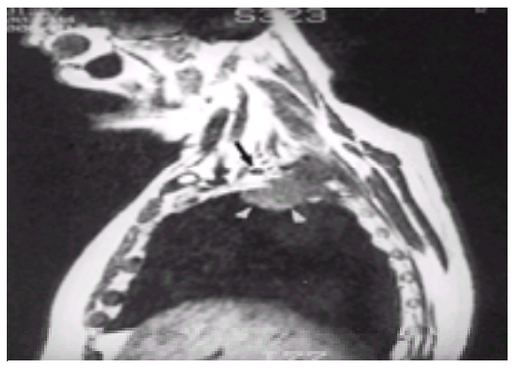

FIG. 10. A superior sulcus neoplasm (*white arrowheads*) extending through the parietal pleura into the supraclavicular fossa is depicted on a sagittal MRI. The cancer spares the subclavian artery (*black arrow*) and brachial plexus, immediately cephalad to the artery.

MRI is also extremely useful in evaluating perihilar and pericardial abnormalities. However, MRI is presently used only as an adjunct to CT in the evaluation of nonvascular abnormalities of the mediastinum and hilar regions, primarily because of expense. Unfortunately, MR signal characteristics cannot reliably distinguish between benign and malignant adenopathy in patients with lung carcinoma. However, residual fibrosis can be distinguished from active neoplastic disease following radiation therapy for lymphoma. Likewise, MRI is capable of distinguishing between rebound thymic hyperplasia and recurrent disease.

INTERVENTIONAL PROCEDURES

Nonangiographic interventional procedures of the chest that require imaging guidance fall into two general categories: percutaneous biopsy (parenchymal lesions, mediastinal masses, or pleural abnormalities) in which either a skinny or cutting needle is used, and percutaneous aspirations and/or drainage of fluid collections located within the pleural space or lung parenchyma and the mediastinum. Imaging guidance for interventional procedures is provided by fluoroscopy, CT, or ultrasonography. The choice of imaging guidance depends on the availability of equipment and the expertise and experience of the operator.

Significant intrathoracic hemorrhage is an avoidable complication associated with interventional procedures. If the number of adequately functioning platelets is >75,000/mm^3 and the INR (International Normalized Ratio) is normal, then the risk for significant hemorrhage is greatly reduced. Patients with known bleeding disorders or abnormal coagulation parameters require a detailed hemostatic evaluation to avoid morbidity associated with these procedures. Also, the needle route should be chosen to avoid larger vessels, such as the internal mammary, intercostal, central hilar, and mediastinal vessels. Significant morbidity has occurred when these vessels have been punctured.

Pneumothorax is the most common complication of percutaneous biopsy of the chest, with a reported rate of 5%–60% of all biopsies (average rate, ~25%–30%). The risk for pneumothorax is related to several factors: the extent of underlying lung disease, especially when adjacent to the lesion from which biopsy samples are being taken (emphysema), and the number of needle passes, especially when passes are made through multiple pleural surfaces or cross a fissure or lung parenchyma during biopsy of the mediastinum.

The percutaneous biopsy route should therefore be planned to avoid crossing multiple pleural surfaces. Up to half the patients who experience a pneumothorax as a result of a percutaneous biopsy require chest tube drainage. A small pneumothorax that does not affect hemodynamics or respiration may be treated with a small catheter and Heimlich valve. If the pneumothorax is large and affects hemodynamics and/or respiration, a large-bore chest tube should be placed.

Frank hemoptysis is almost always self-limiting.

Percutaneous Lung Biosy

Percutaneous lung biopsy has a relatively high safety profile and is usually performed with needles under 19 gauge, although larger needles are required for core biopsies. The diagnostic yield for malignant lesions is approximately 95%. The diagnostic yield is not as high for nonmalignant lesions. The appropriate handling of a specimen is crucial to ensure an accurate diagnosis and requires cooperation between the radiology, laboratory, and clinical services. For example, malignant cytologies are more likely to be obtained from a percutaneous biopsy specimen directly prepared by the cytopathologist or pathologist. Some specimens require special handling (flow cytometry), which necessitates special preparation of the aspirate.

Percutaneous Drainage of Fluid Collections

Although large pleural effusions are usually managed without image-guided drainage procedures, percutaneous drainage of smaller pleural, parenchymal, or mediastinal fluid collections requires imaging for optimal placement of drainage catheters. Small and loculated pleural effusions are most conveniently aspirated under ultrasonic guidance. Uncomplicated empyema is characterized by early clinical presentation, lack of loculations, relatively nonviscous purulent material, and the absence of a thick pleural peel, and may be drained successfully with a percutaneously placed catheter. Postoperative or loculated empyema, or empyema associated with bronchopleural fistula, is less likely to be drained successfully by the percutaneous technique. Fibrinolytic agents have been introduced into the pleural space to aid in the drainage of loculated empyemas. Percutaneous drainage of lung abscesses and mediastinal abscesses has a limited role.

APPROACH TO INTERPRETATION OF RADIOGRAPHIC STUDIES

There are many approaches to the interpretation of a radiographic study. Some approaches are unique to a particular diagnostic imaging modality, and others are unique to a specific clinical problem. The approach to the interpretation of radiographic studies discussed here utilizes a series of simple but informative questions applicable to simple and sophisticated radiologic techniques and most clinical problems. The answers to these questions assist in characterizing an abnormality identified on a radiographic examination and thereby help to build a differential diagnosis. After a radiologic differential diagnosis has been constructed, a clinical decision can be made as to further diagnostic workup.

In the interpretative process, the answers to a set of specific questions that more clearly define the radiologic abnormality can aid in forming a diagnosis. The order in which these questions are asked is not necessarily critical. Although each individual question may seem simple and not likely to elicit important information, the combination of questions and their subsequent answers are extremely enlightening.

An accurate clinical history is a critical component in the diagnostic process of identifying and characterizing an observed radiologic abnormality and developing a differential diagnosis. Whereas a clinical history aids in the interpretation of an examination, the radiologic history (previous film) is also an important tool that improves and contributes to the accuracy of observations. For example, a clinical history of dyspnea, cough, wheezing, pedal edema, and jugular venous distension would suggest the likelihood of finding signs of congestive heart failure on a chest radiograph. Or, a prominent hilum that might otherwise be dismissed as a normal variant would be re-evaluated as a probable mass in the light of an old film showing a normal hilum.

The *temporal history* of the abnormality should be assessed. A widened mediastinum on a chest radiograph has a large differential diagnosis, but knowing the chronicity or acuity of the finding limits the differential diagnosis. A chronically widened superior mediastinum unchanged over many years suggests a benign etiology, such as mediastinal lipomatosis. A newly widened superior mediastinum suggests a more acute process, such as lymphoma or metastatic adenopathy. An acutely widened mediastinum indicates a probable mediastinal hematoma, especially with the confirmatory clinical history of a recent line placement or an automobile accident.

Is the abnormality *solitary, multifocal,* or *diffuse?* For example, a solitary pulmonary nodule on a chest x-ray film has a vast differential diagnosis, but in a specific clinical situation (e.g., in a patient with a long smoking history and occupational exposure to asbestos), a primary lung carcinoma is very likely. However, if subsequent chest CT shows this solitary pulmonary opacity to be one of three pulmonary nodules, the differential diagnosis now suggests metastatic disease to the lung. Similarly, if a follow-up chest radiograph in 3 days demonstrates multiple nodular opacities and cavitation, the differential diagnosis would change again to include multiple septic emboli or granulomatous disease with cavitation.

What is the *density* (composition) of an abnormality? Although the internal composition of a lesion can sometimes be determined on a chest radiograph, chest CT or MRI can accomplish this task more accurately and is therefore indicated for this purpose. Five important internal tissue types may be easily identified on CT or MR scans:

1. Gas (cavitation)
2. Low-density material (lipid) (Fig. 11)

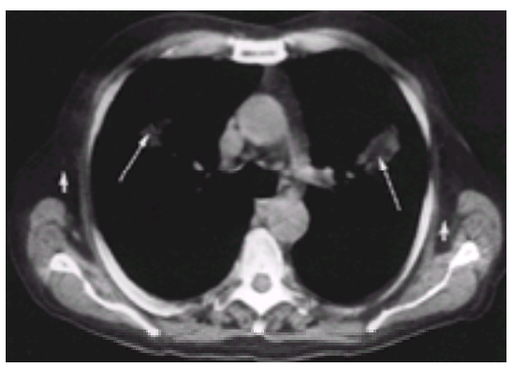

FIG. 11. Chest CT in a patient whose chest radiograph demonstrated multiple, poorly defined nodular opacities that waxed and waned shows bilateral opacities (*long white arrows*) with internal attenuation, similar to that of subcutaneous fat (*short white arrows*). A diagnosis of lipid pneumonia was made.

3. High-density material (hemorrhage)
4. Intermediate-density material (soft tissue)

5. Calcification

A lesion that exhibits *cavitation* may represent a lung abscess, a carcinoma with cavitation, or mycetoma. A lesion that is calcified might represent a calcified granuloma, if located centrally, or a lung carcinoma engulfing an adjacent calcified granuloma, if located eccentrically. A solitary lesion containing material of several types of density by CT suggests a hamartoma.

What are the *shape, size,* and *margins* of the lesion? For example, a defect that conforms to the shape of a segment of lung on a perfusion scan has considerably more significance than a perfusion defect with a shape that is either subsegmental or round in appearance. An earlier principle (solitary vs. multiple) is combined with the principle of shape and size, and the presence of multiple segmental defects on a perfusion lung scan without corresponding matches on a ventilation scan then changes the interpretation of the examination to a high probability for pulmonary embolus.

Similarly, the differential diagnosis for multiple bilateral rounded opacities is vastly different depending on the size of the opacities. When the radiologic differential diagnosis is broad, the clinical history becomes very important. A fine nodular pattern on a chest radiograph in a febrile patient suggests a differential diagnosis that includes fungal, tuberculous, nocardial, and viral infection, whereas in an afebrile patient the differential diagnosis includes sarcoidosis, inhalational disease, metastasis, and less common entities, such as eosinophilic pneumonia (Fig. 12).

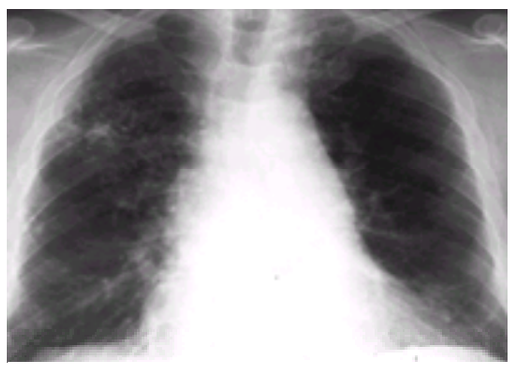

FIG. 12. A chest radiograph demonstrating innumerable pulmonary nodules <1 cm in diameter. Some of the nodules are calcified, and in the right upper lobe the nodules are more confluent. This area represents a developing conglomerate mass in a patient with silicosis.

It is also important to determine whether the margins of a lesion are sharply or poorly demarcated. A sharply demarcated lesion suggests encapsulation, whereas indistinct and fuzzy margins suggest a lesion that may be infiltrating into adjacent structures (Fig. 13). For example, multiple bilateral rounded opacities with poorly defined margins on a chest x-ray film suggest a differential diagnosis that includes inflammatory, neoplastic, connective tissue, vascular, occupational, iatrogenic, and idiopathic entities. Additional information, such as whether the opacities wax and wane, occasionally show cavitation, or are associated with febrile episodes, restricts the differential diagnosis to etiologies such as Wegener's or lymphomatoid granulomatosis (Fig. 14). Violation of anatomic boundaries usually suggests an aggressive process, although not necessarily a neoplasm. An abnormality located in the periphery of the lung with evidence of pleural reaction and rib destruction might be caused by actinomycosis rather than carcinoma of the lung.

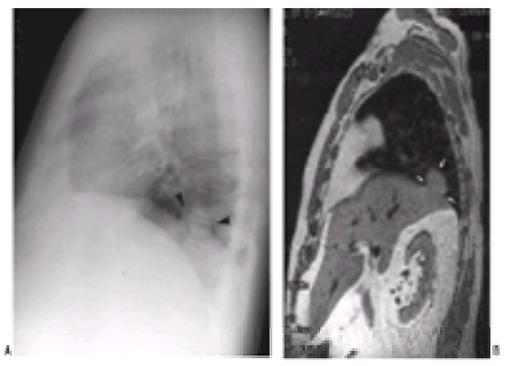

FIG. 13. A: A lateral chest radiograph demonstrating an approximately 2-cm rounded opacity (*black arrowheads*) adjacent to the right hemidiaphragm. Because the inferior margin of the lesion was silhouetted by the diaphragm, it was suspected that the abnormality originated from or below the diaphragm. **B:** A sagittal MRI of the chest shows the liver (*white arrowheads*) herniating through the diaphragm.

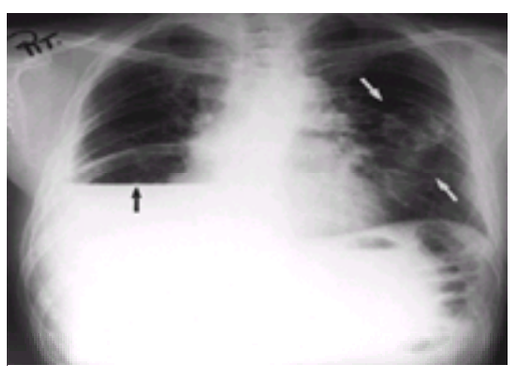

FIG. 14. A postoperative chest radiograph demonstrates an air-fluid level (*black arrow*) in the right pleural space following an open lung biopsy. In the left lung, two cavitary masses (*white arrows*) are identified. The masses, which waxed and waned during a period of months, were pathologically proved to be Wegner's granulomatosis.

From what tissue does the abnormality originate? Specifically, does the lesion arise from the rib or pleura, or from the lung parenchyma, or from within a mediastinal structure? The characteristics of the margin of the lesion also yield important information. For example, a peripherally situated mass forming acute angles with the pleural surface suggests that the mass originates within the lung parenchyma, whereas the same mass forming obtuse angles suggests an origin in the pleura or chest wall.

Sometimes the anatomic location of an abnormality is easily determined from the chest radiograph, as in the case of rib destruction (implying that the abnormality is located in part in the pleural space and also in the chest wall). CT or MRI is usually required to obtain such information (Fig. 15).

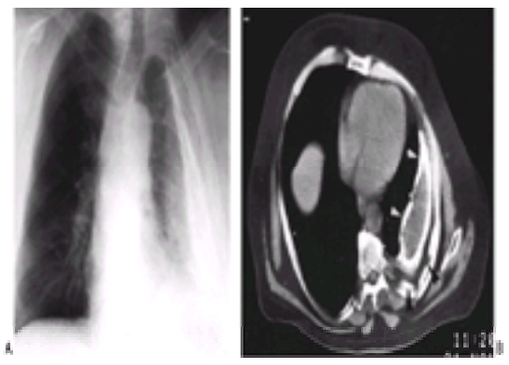

FIG. 15. A: A chest radiograph depicts a relatively small left hemithorax, pleural thickening, and extensive pleural calcification. **B:** Subsequent chest CT reveals calcification of the visceral (*white arrowheads*) and parietal pleura surrounding a high-density pleural effusion. The apparent pleural thickening on the chest radiograph is shown to be extensive subpleural fat (*black arrowheads*). Increased asymmetric subpleural fat associated with a pleural effusion is almost always indicative of an empyema, in this case a tuberculous empyema.

Localizing an abnormality within a specific anatomic compartment is also extremely valuable when constructing a differential diagnosis. For example, if a mediastinal mass can be localized to the posterior mediastinum, or if interstitial lung disease is confined to the lung bases, then the differential diagnosis is further narrowed.

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CHAPTER

9 Pulmonary Function Testing

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INTRODUCTION

Pulmonary function tests are widely used to provide objective measures of lung function for (1) detecting and quantifying pulmonary impairment in cardiopulmonary diseases; (2) following the evolution of diseases and monitoring response to therapy; (3) monitoring the effects of environmental, occupational, and drug exposures associated with lung injury; (4) assessing preoperative risk; and (5) assessing disability and impairment. This chapter focuses on the practical pulmonary function tests that are of most use in day-to-day clinical medicine.

The steps in gas exchange from ambient air to cell (Table 1) help put pulmonary function testing in perspective. As respiratory gases move by passive diffusion, optimal concentrations of oxygen (O_2) and carbon dioxide (CO_2) in alveolar gas are necessary to transfer them to and from pulmonary capillary blood. The alveolar environment for gas transfer is established by alveolar ventilation, a function of the bellows action of the lung. Many lung function tests (static lung volumes, spirometry, airways resistance, and respiratory muscle function) characterize the mechanical aspects of the air pump. By themselves, they do not prove that gas exchange is either normal or abnormal. The second step in gas exchange, gas transfer from the alveolar air to blood, is traditionally assessed with carbon monoxide (CO) diffusing capacity (transfer factor) and arterial blood gas measurements. Diffusing capacity is an indirect test, whereas arterial blood gases allow a more direct assessment of O_2 loading and CO_2 removal from blood. Assessing gas transport and gas transfer from blood to cells involves evaluation of arterial and mixed venous blood gases, cardiac output, and end-organ function (usually brain and kidney function). These aspects of gas transfer are usually the focus of the intensive care unit and are not directly assessed in traditional pulmonary function laboratories.

Step	Purpose	Structure(s)	Tests to characterize structure or function
Ventilation	Maintain normal alveolar O_2 and CO_2 pressures (PAO_2 and $PACO_2$)	Air pump (lungs, chest wall, and neuromuscular apparatus)	$PaCO_2$, spirometry, lung volumes, airways resistance, respiratory muscle strength
Gas transfer (lungs)	Transfer of gases between alveolar air and pulmonary capillary blood	Alveolar capillary membrane	Arterial blood gases (PaO_2 and $PaCO_2$), alveolar-arterial PO_2 gradient [$P(A-a)O_2$], oxygen content, carbon monoxide diffusing capacity
Circulation	Delivery of O_2 from the lungs to the systemic capillaries and CO_2 from the systemic capillaries to the lungs	Blood pump (heart and blood)	Heart function (e.g., cardiac output, oxygen content, oxygen delivery)
Gas transfer (periphery)	Transfer of gases between systemic capillaries and metabolizing cells	Systemic capillary membranes and metabolizing cells	Difficult to assess. Tests of end-organ function (e.g., central nervous system and renal function) provide regional information and are the least clinical indicators. Lactic acidosis may occur with tissue hypoxemia but is not a definite indicator of its presence.

TABLE 1. *Gas exchange between the atmosphere and body cells: gas transport system steps*

Control of breathing can be assessed by measuring the ventilatory response to progressive hypercarbia or hypoxemia, but these tests are uncommonly used in clinical practice. The final element in practical lung function testing is measuring cardiac and respiratory responses to exercise. Because exercise stresses the entire heart, lung, and blood system, exercise testing provides an opportunity to tease out the factors leading to dyspnea and impaired exercise capacity. Exercise testing is covered in Chapter 10. Reference sources for exercise are also included in this chapter's reference list.

Lung function tests are different from most other medical tests in that many of them require patients to participate actively and vigorously. Test quality depends on coaching every patient to an acceptable, vigorous effort. My own experience in evaluating pulmonary function laboratories suggests that it is not uncommon to find poor test quality in more than half of the studies at an initial evaluation. It is also not uncommon to see dramatic improvement in test quality after the staff has been trained to recognize quality tests and encouraged to coach more vigorous effort. Even when test quality is carefully controlled, some patients are unable to perform the tests. In a general population study, in which test quality was carefully controlled, Hankinson and colleagues found about 85% of more than 6000 spirometry studies met American Thoracic Society (ATS) standards of quality. Individual pulmonary laboratories can institute quality control measures and, with modest effort, bring their test quality to these standards.

STATIC LUNG VOLUMES

The static lung volume subdivisions, illustrated in Fig. 1, are grouped into volumes and capacities. Volumes, the primary subdivisions, cannot be subdivided. Capacities contain two or more volumes and, therefore, can be subdivided. Total lung capacity (TLC), the volume of air in the lungs at the end of a maximal inspiration, is attained when maximal inspiratory muscle force is counterbalanced by the recoil forces of the lung and chest wall. The maximal volume of air that can be exhaled after a maximal inhalation is vital capacity (VC). Vital capacity can be measured with either an inspiratory or an expiratory maneuver and with either an unforced, slow exhalation (SVC) or a nearly maximally forced maneuver (FVC). The volume of air remaining in the lungs after a maximal exhalation is residual volume (RV). RV is determined by the balance of the forces tending to reduce lung volume (maximal expiratory muscle force and inward lung recoil) against the force tending to increase lung volume (outward recoil of the chest wall). Tidal volume (V_T) is the volume of air moved with each breath during normal breathing. Functional residual capacity (FRC) is usually defined as the volume of air in the lungs at the end of a quiet, relaxed exhalation, although it is sometimes used to indicate the volume of air in the lungs at the end of a tidal breath regardless of whether exhalation is active or passive. Inspiratory capacity (IC) is the maximal volume of air that can be inhaled from

FRC. Expiratory reserve volume (ERV) is the maximal volume of air that can be exhaled from FRC. IC and ERV have little role in diagnostic testing, although ERV is the most commonly reduced lung volume in the morbidly obese.

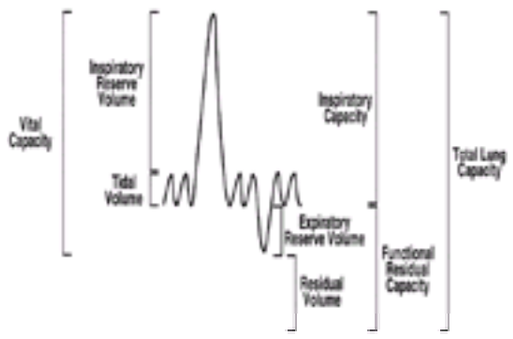

FIG. 1. Lung volumes and capacities. Volumes cannot be subdivided. Capacities contain two or more volumes. (Reproduced with permission from Aldose MD. Practical aspects of pulmonary function testing. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* Boston: Little, Brown; 1993.)

The displaceable lung volumes—those that can be inhaled and exhaled from the mouth—are measured with a spirometer. Two types of spirometer are schematically illustrated and described in Fig. 2. The parameters measurable with a spirometer are vital capacity, tidal volume, inspiratory capacity, and expiratory reserve volume (Fig. 1). The remaining volumes and capacities contain residual volume, which cannot be measured with a spirometer. Plethysmographic, gas dilution, and radiographic techniques each measure one of the capacities that contains residual volume. Once measured, this capacity can be combined with the appropriate displaceable volumes to calculate all the remaining lung volumes and capacities. The following descriptions are brief overviews. The reader is directed to the reference list for more detailed descriptions of the tests and how they are performed.

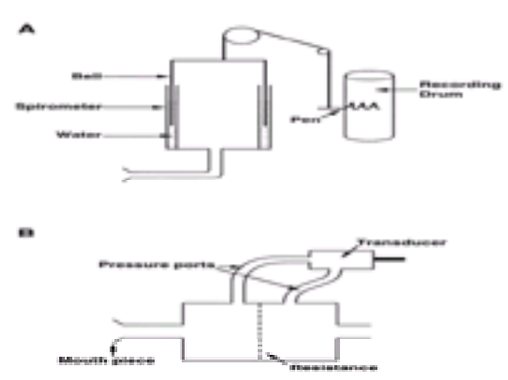

FIG. 2. Two types of spirometers. **A:** Volume-based spirometer that uses water as a seal. Air blown into the spirometer causes the bell to rise, inscribing the height of a cylinder and, therefore, volume. Time is also recorded to allow measurement of volumes as a function of time. As volume is the primary measurement, flows are derived by differentiating the volume-time information. **B:** Flow-based spirometer. Air is blown across a resistor; differential pressures measured across the resistor are related to flow. As flow (volume/time) is the primary measurement, it must be integrated to get volumes. (Reproduced with permission from Aldose MD. Practical aspects of pulmonary function testing. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* Boston: Little, Brown; 1993.)

Gas Dilution Techniques

Gas dilution techniques measure the gas volume in the lungs that communicates via the airways. Although the techniques vary in details, all use a mass balance approach to calculate lung volume. The most common approach is schematically illustrated in Fig. 3. The patient is allowed to breathe from a known volume and concentration of a relatively insoluble and inert tracer gas [e.g., helium (He)]. Mixing is allowed to occur for a variable length of time, and the final mixed concentration of tracer gas is measured. A mass balance equation uses the initial volume and tracer gas concentration and the final tracer gas concentration to calculate the volume present in the patient's lungs at the moment tracer gas breathing began. The assumptions that the tracer gas is relatively insoluble and inert and is well mixed in lung air are critical. Use of a relatively soluble gas would cause lung volumes to be overestimated; incomplete gas mixing would cause them to be underestimated. In the case of the He rebreathing method, the patient quietly rebreathes from the test circuit for 4 to 7 min, with occasional deep breaths, until gas measurements demonstrate the concentration of He in the circuit is stable, indicating complete mixing in lung air. The long rebreathing time (up to 7 min) allows complete mixing of He in the circuit, but it also means that CO_2 has to be removed from and O_2 added to the circuit to ensure patient safety and comfort.

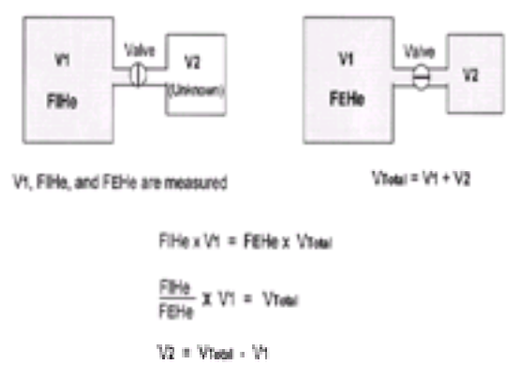

FIG. 3. Schematic illustration of the basic theory of gas dilution measurement of lung volume. Air in a subject's lungs is allowed to come into equilibrium with a known mass of a relatively insoluble and inert gas, such as He. Initial volume (V_1) and He concentration (F_IHe) are known. The diluted, final He concentration (F_EHe) is used to calculate the unknown volume (V_2).

A gas dilution measurement of TLC (usually reported as alveolar volume, or V_A) accompanies every measurement of the single-breath CO diffusing capacity test. In this test, subjects inhale a VC-sized volume of gas that contains about 10% He, 0.3% CO, and 17%–21% O_2, hold their breath for 10 sec, and then exhale. An alveolar gas sample is analyzed to get the diluted alveolar He concentration. The assumption that He is completely mixed during the 10-sec breath-hold is reasonably acceptable in healthy individuals; for healthy people, TLC is only minimally underestimated compared with the multibreath technique. In patients with airway obstruction, mixing becomes less complete as obstruction worsens, and TLC is progressively underestimated. Therefore, in patients with airway obstruction, the single-breath technique has little utility as a technique for measuring TLC.

Nitrogen (N_2) washout techniques also use a mass balance approach to estimate TLC. In the multibreath N_2 washout method, the subject begins breathing 100% O_2 at FRC. O_2 is breathed until N_2 is displaced from the lungs, and the mass of displaced N_2 is measured. FRC is calculated assuming (1) that the mass of displaced N_2 is equal to the mass of N_2 in the lungs at the beginning of the test, and (2) that the initial concentration of N_2 in the lungs was 80%. TLC is estimated as FRC + IC (Fig. 1). N_2 washout techniques also underestimate TLC when airway obstruction is present.

Plethysmography

Plethysmography is used to measure lung volumes and airway resistances. For lung volumes, plethysmography measures the compressible gas volume in the chest using Boyle's Law: the product of gas volume and pressure is a constant ($V_1 \times P_1 = k$) when temperature is held constant. The test is performed by having the patient sit in a sealed box and pant gently against a closed shutter located at the mouth. During the inspiratory phase of the panting maneuver, the thoracic volume increases, slightly decompressing the volume of air in the lungs while compressing the air in the box. In the expiratory phase of the panting maneuver, thoracic gas volume decreases slightly, compressing the air in the lungs and decompressing box air. By Boyle's Law,

$$V_1 \times P_1 = V_2 \times P_2$$

The initial pressure and volume at FRC (the beginning volume before panting) are P_1 and V_1. Pressure and volume at the end of the inspiratory phase of the pant are P_2 and V_2, which can be rewritten as $(P_1 + DP) \times (V_1 + DV)$. P_1 and DP are measured at the mouth, assuming that mouth pressure is equal to alveolar pressure, and DV is measured using the change in box pressure. The equation can then be solved for V_1.

Body plethysmography is still considered the “gold standard” of techniques used to measure static lung volumes. It is, however, sensitive to technical and procedural errors and, like all other lung volume techniques, requires exquisite attention to quality control. For example, the assumption that mouth pressure equals box pressures tends to fail when panting frequency exceeds one pant/sec, because there is inadequate time for the pressure changes at the mouth to equilibrate with alveolar pressure. This is a particular problem in patients with airway obstruction, in whom rapid panting causes a significant overestimation of TLC.

When plethysmographic and single-breath gas dilution measurements of TLC are made during the same test session, the difference between the two ($TLC_{PL} – TLC_{GAS}$) can be used as an estimate of the poorly ventilated gas volume in the lungs, commonly referred to as trapped gas. The volume of trapped gas is increased in the presence of airway obstruction.

Radiographic Total Lung Capacity

TLC can also be estimated from standard posteroanterior and lateral chest radiographs. A radiographic TLC measurement starts with a calculation of total intrathoracic gas volume, from which estimated volumes for the mediastinum, heart, blood, and diaphragm are subtracted. Several studies show excellent correlation between radiographic TLC and plethysmographic TLC in healthy individuals and those with airway obstruction. The advantages of radiographic measurement of TLC are that the methodology is simple, requires no special equipment, and takes little time. However, chest radiographs solely for measuring TLC cannot be justified, even though the radiation exposure is small. Luckily, chest radiographs are often available because they are commonly included in evaluations for respiratory diseases. In addition, the radiographic method can be used to re-create a history of TLC. Old chest radiographs often provide the only source of lung volume information from a patient's past. They can provide evidence of change in a patient whose loss of lung volume would otherwise not have been detectable. This advantage is being compromised by the current trend to destroy radiographs earlier.

The radiographic TLC method has not yet been proved accurate in patients with interstitial lung diseases, and test variability is larger than for other methods. Chest structures are magnified slightly on chest radiographs. Published methods usually use a magnification factor based on a target-film distance of 72 inches (183 cm). For other target-film distances, the magnification factors differ and must be computed by the reader.

Pathophysiologic Correlates with Lung Volumes

The three basic patterns of lung volumes illustrated in Fig. 4 are normal, overinflation (too large), and restriction (too small). In the normal pattern, TLC, VC, and RV fall within a reference range based on healthy people. RV in the young constitutes about 25% of TLC, and FRC about 40%. With aging, lung recoil decreases causing a slight shift in the pattern of air flow toward one of obstruction. With aging, TLC remains essentially unchanged, RV increases, and FRC either increases slightly or does not change. RV increases with aging primarily because the slight shift toward an obstructive pattern makes it impossible for a true expiratory plateau to be reached and RV becomes a dynamic measurement, dependent on expiratory time.

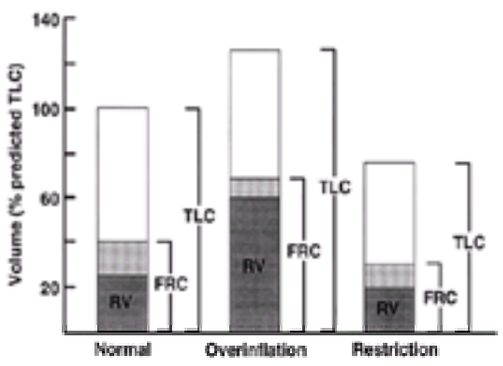

FIG. 4. The three basic lung volume patterns: normal, overinflation (too large), and restriction (too small). (Reproduced with permission from Aldose MD. Practical aspects of pulmonary function testing. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* Boston: Little, Brown; 1993.)

Diseases that alter the elastic properties of either the chest wall or lungs may alter lung volumes. Diseases such as emphysema reduce lung recoil and may cause TLC, FRC, and RV to be increased, even when minimal airflow obstruction is present. In emphysema, airway obstruction commonly accompanies decreased lung recoil, and both contribute to overinflation. Mechanically, airway obstruction leads to the initiation of inspiration before expiration is complete; overinflation follows. The process is exacerbated when respiratory rate increases, causing expiratory time to be shortened. Asthma is a classic illustration of a disease with overinflation secondary to airflow obstruction. There is also evidence in asthma that inspiratory muscle activity persists throughout expiration, contributing to overinflation.

Overinflation is primarily determined by an elevated TLC. Other patterns may be used to suggest the presence of overinflation, but one should be cautious in calling overinflation when TLC is within the normal range. The suggestive patterns are an elevated RV or the presence of significant gas trapping.

Lung volumes may be reduced (restriction) in any disease process that increases lung recoil (e.g., pulmonary fibrosis), compresses the lungs (pleural effusion), decreases chest wall compliance (kyphoscoliosis, morbid obesity), alters the shape of the chest (kyphoscoliosis), or decreases respiratory muscle function (neuromuscular diseases, diaphragmatic paralysis).

TLC is also the primary variable used to determine the presence of restriction. Technically, the presence of restriction can be determined only by a reduction in TLC. From a practical standpoint, however, a reduced VC in the absence of airway obstruction has proved to be an excellent predictor of restriction and is an inexpensive, simple parameter to monitor change in patients with restrictive diseases. When both TLC and VC are measured and one is low and the other normal, decisions to classify the presence of restriction should default to TLC. The default to TLC assumes there is no evidence that TLC is underestimated because of technical problems.

DYNAMIC TESTS OF LUNG FUNCTION

Spirometry

Spirometry, which can include both quiet and forced VC maneuvers, is the most common and useful of the lung function tests. Its clinical utility has been proved extensively, it is the least expensive test to perform, and it should be the test most widely available in doctors' offices, clinics, and hospitals. The FVC test is performed by having a patient inhale to TLC and then make a maximally forced exhalation into a spirometer. Classically, exhaled volume is measured as a function of time. Flow may also be measured and displayed as a function of exhaled volume. The three primary spirometric indices in the forced test are FVC, forced expiratory volume in 1 second (FEV_1), and their ratio, FEV_1/FVC. Numerous other spirometric measures are available, but their clinical utility is less well established. Typical volume-time and

flow-volume spirographic displays for a healthy individual are shown in Fig. 5.

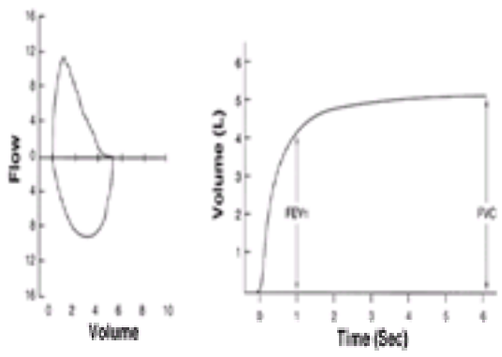

FIG. 5. Spirogram of acceptable quality in a healthy 54-year-old man. In the flow-volume display, markers of good quality include a quick start with a rapid rise in expiratory flow, a well-defined peak flow, the absence of a cough or hesitation in the early portion of the spirogram, and an exhalation that exceeds 6 seconds. The slight tail at the end of exhalation and the continued increase in volume even after 6 seconds of exhalation (volume-time tracing) reflect normal age-related changes.

Test quality depends on achieving a maximal inhalation, a nearly maximal effort during the initial few seconds of exhalation, and a complete exhalation. A complete exhalation is indicated by a plateau in the volume-time tracing; a minimum expiratory time of 6 sec is recommended. A plateau is rarely reached in individuals with airflow obstruction or in healthy older people who have reduced airflow at low lung volumes because of the normal age-related loss of lung recoil. Because expiratory flow never truly reaches a plateau in these individuals, VC increases and FEV_1/VC falls with increased expiratory time. The effect of expiratory time on the FEV_1/VC ratio is minimized if expiratory time lasts at least 10 seconds or if SVC is used rather than FVC.

Syncope may occur, even in healthy subjects, when maximal expiratory force is exerted throughout the entire maneuver. Recent evidence suggests that spirogram quality is not be altered if patients are allowed to reduce their expiratory effort after about 3 seconds and continue to exhale without squeezing hard.

Detailed standards for quality control published by the ATS and the European Respiratory Society (ERS) are outlined in Fig. 6. The first step is to acquire a spirometer that has been demonstrated to meet accuracy standards. Although this statement seems flagrantly obvious, a study of more than 50 instruments on the market in the early 1980s found that only about half met ATS accuracy standards. The problems have largely been corrected, and most but not all commercially marketed spirometers now meet accuracy standards. Care should still be taken to be certain of the accuracy of a spirometer before purchase. Once in use, spirometers need regular quality control checks to ensure proper performance. Such checks are especially important after an instrument has been serviced or upgraded.

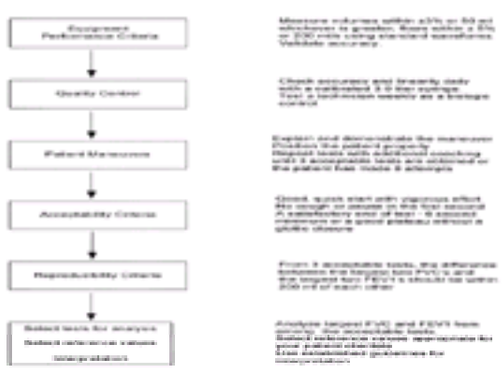

FIG. 6. Summary of ATS recommended steps to assure good-quality spirometric measurements. The same steps can be modified slightly to ensure good quality of all other pulmonary function tests. (Modified and reproduced with permission from Crapo RO, Chair. Standardization of spirometry: 1994 update. Official statement of the ATS. *Am J Respir Crit Care Med* 1995;152:1107–1136).

As instrumentation has improved, the major quality issues now have to do with how the tests are performed. Test quality includes acceptability criteria for each effort and reproducibility criteria for the series of tests performed (Fig. 6). Current standards require that at least three acceptable quality spirograms be obtained. The reproducibility criteria are then applied to the acceptable spirograms to ensure that the data are representative of the patient (Fig. 6). If spirograms of acceptable quality do not meet reproducibility criteria, the patient should be asked to perform the test again. If both the acceptability and reproducibility criteria are not met in eight tries, it is unlikely that they will be with further tests, and the study may be terminated. Efforts to improve the procedural aspects of spirometry include immediate computerized analysis of each test waveform with feedback to the technician about test quality, often with a statement about how to correct problems. Computer displays have also been created to help motivate patients to make good efforts.

Acceptability and reproducibility criteria are ideal targets for the quality of test performance. Even suboptimal tests may provide some useful information, and patient data should not be discarded only because of failure to meet acceptability and reproducibility criteria. The best data available should be submitted for interpretation, and the interpretation should deal with the limitations. Often, partial information can be gleaned from a less-than-optimal test. For example, a test with completely inadequate initial effort still may yield a VC if a reasonable end of test is achieved. Failure to meet acceptability criteria in an individual test occurs for a variety of reasons, including inability or unwillingness of a patient to perform the test, even with vigorous coaching. Failure to meet reproducibility criteria in an individual test may also indicate the presence of hyperreactive airways. Frequent test failures in a laboratory indicate the presence of quality control problems.

Most quality issues are the responsibility of the laboratory and its director, but clinicians who use pulmonary function tests in their medical practice should be able to recognize good-quality tests as well as various disease patterns. Spirograms should be analyzed for quality by visually inspecting both flow-volume and volume-time displays. Typical good-quality spirograms along with several faulty spirogram patterns are illustrated in Fig. 5, Fig. 7, and Fig. 8.

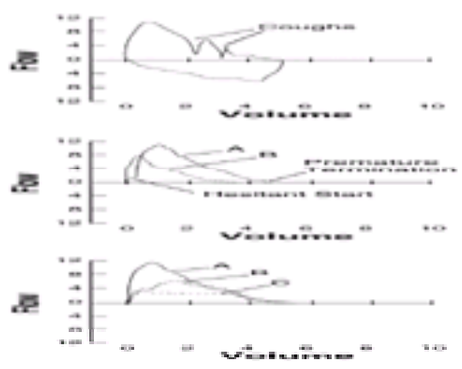

FIG. 7. Several types of faulty spirograms. **Top panel:** Multiple coughs begin early in exhalation (before 1 second). Coughs are characterized by sudden falls in flow followed by quick restoration of flow. Early coughs may cause FEV_1 to be underestimated. **Middle panel:** A hesitant start (waveform A) could cause FEV_1 to be overestimated, and a premature termination of exhalation would cause FVC to be underestimated. Waveform B, from the same patient, illustrates an inadequate inhalation followed by a good expiratory effort. Alone, the curve would be graded acceptable; it is unacceptable when compared with waveform A. **Bottom panel:** Nonreproducible tracings. Waveform A is an acceptable tracing. Waveforms B and C show two different but submaximal initial efforts. FEV_1 may be underestimated with the submaximal efforts; FVC may be acceptable in all tracings depending on the presence of an adequate inhalation and end of test.

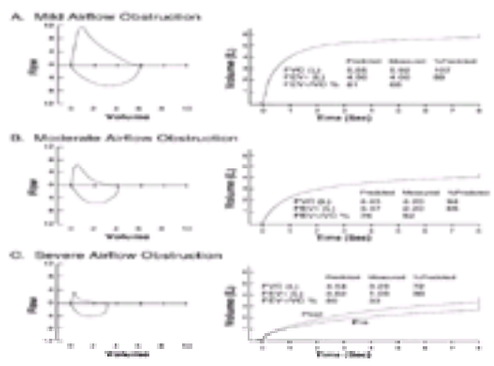

FIG. 8. Typical spirograms for mild, moderate, and severe airway obstruction. Note that with increasing obstruction, the flow-volume tracings show increasing concavity toward the horizontal axis. The *bottom panel* contains prebronchodilator and postbronchodilator tracings, illustrating a good response to administration of an inhaled bronchodilator.

Full spirometry should include both FVC (forced) and SVC (unforced) maneuvers. SVC is often larger than FVC, especially in older persons and those with airway obstruction, in whom the forced maneuver effectively causes some air trapping. If the unforced maneuver is excessively slow, VC will be underestimated. The largest VC found during testing, whether from the forced or the unforced maneuver, should be used to calculate the FEV_1/VC ratio.

For studies that meet acceptability and reproducibility standards, the next question is choosing which measurements to use for interpretation. In general, selecting only from acceptable tests, the largest FVC, FEV_1, and peak flow are used for interpretative purposes; they need not come from the same trial. If midflows (e.g., $FEF_{25\%-75\%}$) or instantaneous flows (e.g., $V_{max50\%}$) are used for interpretation, they should be selected from the single, acceptable-quality spirogram that has the largest sum of FVC and FEV_1. Average ($FEF_{25\%-75\%}$) and instantaneous flow ($V_{max50\%}$) variables should be used only to assist in decision making when the primary indices (FVC, FEV_1, FEV_1/VC) are close to the lower limits of their normal ranges. Average and instantaneous flows have limited clinical utility and are not discussed further here.

Pathophysiologic Correlations with Spirometry

From a diagnostic standpoint, spirometry is used only to classify patients as having one of three patterns: normal, airflow obstruction, and restriction. Specific diagnoses cannot be made with spirometry alone; spirometry patterns must be interpreted according to the clinical questions being asked. The interpretation of spirometry is discussed in detail in the section below on interpretation.

Maximum Voluntary Ventilation

Maximum voluntary ventilation (MVV) is the maximum amount of air that a person can exhale while breathing as fast and deep as possible with vigorous coaching. It is measured over 12 to 15 sec and expressed as L/min at BTPS (body temperature, ambient pressure, and saturated with water vapor) conditions. Test duration is short, because people cannot sustain the MVV maneuver much beyond 15 sec. It is often estimated rather than measured by multiplying the FEV_1 by 35 or the $FEV_{0.75}$ by 40. An optimal test is somewhat hard to describe, because V_T decreases as respiratory rate increases. As a general rule, the peak MVV in healthy subjects occurs at a respiratory rate close to 100 breaths/min with a V_T about 35% of VC. There is, however, not much variation in MVV for respiratory frequencies from 70 to 120/min.

The MVV is a nonspecific test. Reductions in MVV occur in the presence of airway obstruction and chest restriction associated with neuromuscular diseases, loss of coordination, and diminished cognitive function. It may also be reduced because the subject is unwilling to work maximally during the test, as may occur in elderly patients, those with chronic illness, and individuals for whom a poor test result promises secondary gain. Because it is so nonspecific, the clinical utility of MVV is limited. One could, however, argue that the nonspecific nature of the test might also be an advantage in some instances. Reductions in MVV correlate well with postoperative risks for respiratory complications and with dyspnea from any cause. If measured MVV is significantly below calculated MVV, one can tentatively speculate that nonpulmonary factors are involved in the reduction.

The MVV is often used in exercise studies to estimate ventilatory reserve. The common practice of using an estimated MVV for this purpose is problematic, because the normal between-individual variation in measured MVV is large and because there are so many variables besides FEV_1 that affect MVV.

Peak Expiratory Flow and Peak Flow Meters

Peak expiratory flow (PEF) is the maximum flow achieved during an FVC maneuver. It occurs very early in the FVC maneuver (usually within the first 0.2 sec if the maneuver is well performed). This places the measurement in the most effort-dependent portion of the FVC maneuver. Thus, PEF is significantly more effort-dependent than FEV_1, and of less clinical utility from that aspect. The value of PEF in clinical medicine derives from the availability of small, easily portable, highly reproducible, inexpensive peak flow meters. The meters are acceptably accurate but are less accurate than good spirometers. Reproducibility is excellent for individual PEF meters, but there is less reproducibility between meters and there can be marked differences among different PEF meter models. The low cost and reproducibility of PEF meters makes them a practical monitoring device for patients with asthma. Because asthma symptoms and physical findings are imperfect indicators of the severity of asthma, the addition of a relatively inexpensive, objective assessment of lung function is attractive. Monitoring information from PEF meters is of two basic types: (1) trending over days to months, and (2) trending across a day. Increased variability across a day (>20%) indicates airway hyperreactivity and may be an indication of diminished asthma control or a reaction to a provocative stimulus (asthma trigger). At the present time, PEF meters should not be used diagnostically to define normal or abnormal function, because there are no reference values that are applicable to all PEF meter models.

Peak flow meters can be used to track response to medication, monitor the course of asthma, and quantify the effects of exposures to potential triggers or other environmental factors. In numerous national and international guidelines, peak flow meters are used to structure individualized asthma management plans. In the midst of all the enthusiasm for PEF meters, a small note of caution must be sounded. At present, the role of PEF meters in the management of asthma is largely based on reasonable suppositions; there is little science to document exactly what their benefits are and who should be using them.

Bronchodilator Administration and Testing

In patients with airway obstruction, it is common practice to perform spirometry before and after the administration of an inhaled, rapidly acting b_2-selective agonist. The test is performed by obtaining baseline spirometry, administering the bronchodilator medication, waiting a brief period (usually about 15 min), and then repeating the spirometry. The 15-min wait is conservative; some studies suggest 5 min is enough. The test is best performed with a spirometer but can be done with a peak flow meter. An improvement in FEV_1 of 12% and 200 mL is considered an unequivocally positive response. There is, however, some controversy on how to calculate the percentage of change. The ATS statement calculates it as percentage of change from the baseline study, and the ERS publication as a percentage of the reference value for FEV_1. An increase in peak flow of 60 L/min is considered a positive response.

A positive response is considered strong evidence that the patient will benefit from bronchodilator therapy. The converse, however, is not true. The absence of a bronchodilator response in a single laboratory setting does not predict whether bronchodilator therapy will benefit an individual patient. The laboratory outcome can be affected by several technical issues, including the dose and method of administration of the bronchodilator, the wait time, and the quality of the spirogram efforts. In addition, patient response is variable from one day to the next and may vary with the choice of b-adrenergic agonist. Finally, the obstructive effect of mucous plugging and mucosal edema might be large enough to mask a smooth muscle response to bronchodilator medication. Often, a several-week trial of regular bronchodilator therapy is required to decide whether a patient is benefitting or not. The decision to use bronchodilator medication in a patient is therefore a clinical decision. Bronchodilator response in a laboratory setting contributes to the decision but should not be the sole determinant.

Bronchial Reactivity Testing

Airway hyperresponsiveness, an index of the degree of airway narrowing on exposure to provocative stimuli, is one of the primary characteristics of asthma. On average, the airways of asthmatic patients are far more sensitive to provocative stimuli than those of nonasthmatic subjects. Airway hyperreactivity can usually be

suggested by simple tests, such as documenting a response to a bronchodilator or documenting excessive variation in peak flow during a day (most nonasthmatic subjects have a within-day variation in peak flow of <20%). Specific tests measuring response to provocative stimuli are, however, sometimes needed to document the presence of airway hyperresponsiveness.

Two broad categories of stimuli are used to provoke airway narrowing: (1) exposure to aeroallergens like ragweed antigen or chemicals like toluene diisocyanate (specific stimuli), or (2) exposure to methacholine, histamine, exercise, hyperventilation, or cold dry air (nonspecific stimuli). However, the bronchoconstrictive response will vary with the individual stimulus regardless of category.

The most common nonspecific bronchoprovocation test uses methacholine, a parasympathomimetic analogue of acetylcholine, as the bronchoconstricting agent. Methacholine chloride is prepared in several dilutions and administered as a nebulized aerosol in progressively increasing doses. The test begins with baseline measurements of FEV_1 and/or airway resistance. If airway resistance is measured, changes are usually expressed as specific conductance (1/resistance/thoracic gas volume). A second set of measurements follows administration of the diluent alone. Each methacholine dose is followed, after a brief wait, by measurement of FEV_1. A response is considered positive if a sustained 20% fall (calculated from the postdiluent value) in FEV_1 is observed within the prescribed dosage schedule (Fig. 9). The dose of methacholine that elicits a 20% fall in FEV_1 is designated as the PC_{20}, the provocative concentration that causes a 20% fall in FEV_1. As the study is performed in steps, the PC_{20} is calculated either mathematically or graphically from the stepwise changes in FEV_1 (Fig. 9). The response is a continuum; the lower the PC_{20}, the more reactive the airways. Most asthmatic patients have a PC_{20} of £8 mg/mL. If specific conductance is used as the measure of response, a positive response is indicated by a 35% fall (PC_{35}) during the test. Methacholine challenge testing deals with complex issues and requires rigid standardization to ensure that proper doses of active drug are administered on a proper schedule, that timing of spirometry relative to the dose is controlled, and that spirometry quality and patient safety are properly addressed. Details of these issues and protocols are provided in articles in the reference list. Standard protocols for methacholine challenge that include seven dosage steps are time-consuming; abbreviated protocols with fewer steps have been found to produce acceptable results for clinical testing.

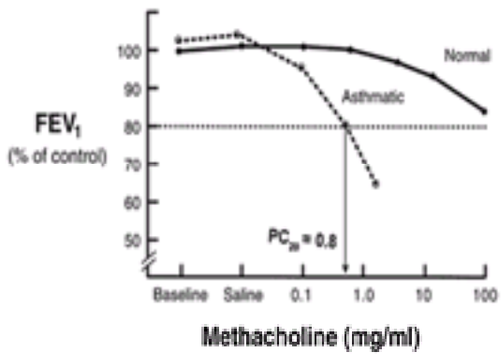

FIG. 9. Graphic display of normal and asthmatic responses to a methacholine challenge test. FEV_1 expressed as a percentage of the control (diluent value) is graphed against the methacholine dose. The point at which the fall in FEV_1 exceeds 20% is used to calculate the provocative concentration, PC_{20}. (Figure courtesy of Charles Irvin, Ph.D.)

Methacholine challenge studies are common in research protocols involving asthma because they allow bronchial hyperreactivity to be quantified and monitored. In most clinical settings, it is not necessary to document or quantify airway hyperreactivity with formal challenge tests. However, when the diagnosis of asthma is uncertain, bronchoprovocation studies may be clinically useful, as in a patient who has normal spirometry results but also has chest symptoms, such as cough or chest tightness, that suggest asthma. A positive methacholine challenge test result in this setting is highly suggestive of asthma. Clinical monitoring airway hyperreactivity during therapy as a means of quantifying response to treatment is controversial. Currently, such monitoring would be indicated only in selected patients under special circumstances.

Methacholine challenge testing is a safe procedure, but when methacholine is administered in large doses to asthmatic patients it can provoke severe attacks. Excessive salivation, abdominal cramping, diarrhea, and sweating can occur if the systemic dose is excessive. Atropine is a specific antidote. Contraindications and precautions are well described in standard references. Bronchoprovocation with sensitizing agents like antigens or occupational sensitizers is associated with higher risks, and more caution is warranted. Testing with sensitizing agents should be limited to laboratories specializing in such studies.

Exercise Bronchoprovocation

Exercise provokes bronchospasm in 60%–90% of asthmatics. The level of ventilation obtained during exercise is probably the most important determinant of this response to exercise. For testing outside a laboratory, a fall in FEV_1 of 15% or more in response to modest amounts of exercise (achieving ventilation at 40%–50% of predicted MVV) is considered a positive test result. With formal testing in a laboratory, a 10% fall in FEV_1 with exercise may be significant. Standardized protocols are available.

DIFFUSION

After arterial blood gas measurement, the most common test of gas transfer across the lungs is the CO diffusing capacity (D_LCO), also called *transfer factor* (T_LCO). The test measures the rate of transfer of CO from the lungs to the blood. Units of measurement are expressed in two ways. In North America, D_LCO is expressed as mL CO/min/mmHg driving pressure; in Europe, T_LCO is expressed as mmol CO/min/kPa. CO, rather than O_2, is used as the gas of interest because in the lungs it behaves similarly to O_2, with the advantage that D_LCO can be measured, whereas D_LO_2 cannot. The pathway for the movement of CO or O_2 from alveolus to hemoglobin (Hb) molecule is illustrated in Fig. 10. Diffusion across the alveolar-capillary membrane is only a small portion of the pathway. In fact, accumulating evidence suggests that mixing within the red cell and the chemical reaction rate are far more important limiting factors in healthy individuals than is diffusion across the alveolar-capillary membrane. This supports the European community's decision to describe the test as transfer factor rather than diffusing capacity.

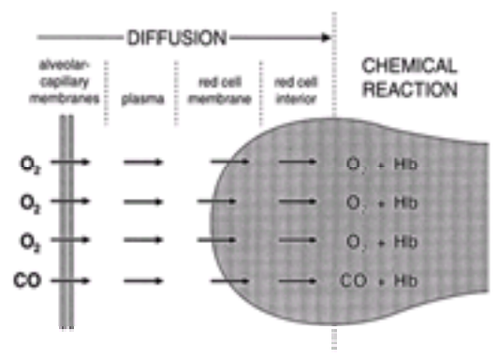

FIG. 10. The diffusion pathway for O_2. Pathway lengths in this figure do not reflect true pathway distances. The pathway is identical for CO, the gas used in the diffusing capacity test. O_2 and CO move across the alveolar-capillary membrane, traverse a very thin plasma layer, cross the red cell membrane, diffuse within the red cell interior, and chemically react, binding with Hb. O_2 and CO compete for the same binding sites on the Hb molecule (Reproduced with permission from Forster RE, DuBois AB, Brisco WA, Fisher AB. *The Lung: Physiologic Basis of Pulmonary Function Tests.* 3rd ed. Chicago: Year Book; 1986).

Diffusing capacity can be measured with single-breath, steady-state, and rebreathing techniques. The single-breath technique is by far the most common, best-standardized, and readily available technique. It also is the method on which most of our clinical information relating D_LCO to disease states is based. The

single-breath test is performed as follows: The patient exhales to RV, a valve is opened, and the patient inhales to full VC the test gas, which in addition to N_2 contains 0.3% CO, an inert, insoluble tracer gas (e.g., He), and 18%–21% O_2. The patient relaxes into a breath-hold at TLC for 10 sec and then exhales rapidly. An alveolar sample is collected for analysis after anatomic and mechanical dead space is flushed out by exhaled air. The test is safe and easy to perform. Details of the technique and the computations involved are well described in current ATS and ERS standards documents.

Several important technical and physiologic issues must be considered to avoid interpretive errors. The first is that the selection of reference values for D_LCO is confounded by the fact that in early studies, D_LCO measured in the same person in different laboratories could vary by as much as 90%. These differences occur because test results are affected by variations in procedural and computational techniques. Although recent testing has demonstrated that standardizing the performance and calculation procedures reduces this large interlaboratory variability, there are still differences of 15%–20% between well-standardized laboratories. Thus, reference data must be carefully selected, or interpretative errors will be frequent.

The remaining issues center on physiologic variables that can influence D_LCO without indicating the presence of an abnormality in lung function. CO competes with O_2 for the same Hb sites, and the number of binding sites available influences D_LCO. Anemia decreases and polycythemia increases D_LCO. Interpreting D_LCO in patients without knowing their Hb concentration is potentially misleading, especially in settings in which Hb is likely to be altered. In patients being monitored for pulmonary injury while receiving chemotherapy, for example, a fall in D_LCO could reflect lung injury, the development of anemia, or both. If carboxyhemoglobin (CoHb) is elevated, as in smokers, the COHb effectively reduces the available binding sites while at the same time creating a small CO back pressure in the plasma. These effects combine to lower D_LCO artifactually about 1% for each 1% increase in COHb. The best (although, not the easiest) method of avoiding problems with COHb is to have patients refrain from smoking overnight before testing. An optimal procedure is to also measure Hb and COHb once during each D_LCO testing session and adjust measured D_LCO accordingly. The small back pressure created by CO is another factor to keep in mind during testing. The test gas itself will raise the COHb level about 0.5% for each trial.

Because CO and O_2 compete for the same Hb binding site, changes in O_2 pressure that give one or the other a competitive advantage also artifactually alter D_LCO. For example, administration of supplemental O_2 increases the inspired O_2 concentration (F_IO_2), gives the advantage to O_2, and lowers D_LCO. As individuals move from sea level to higher altitudes, the decreased barometric pressure lowers F_IO_2 and gives the advantage to CO, causing D_LCO to increase about 0.35% for each decrease of 1 mmHg in alveolar partial pressure of O_2 (P_AO_2). Using a correction factor in the computation or simulating the F_IO_2 at sea level (150 mmHg) by adding O_2 to the test gas mixture will compensate for the effect of altitude.

Pathophysiologic Correlations

Diseases associated with decreased D_LCO include those that (1) reduce lung surface area (emphysema and pulmonary fibrosis), (2) thicken or alter the structural components of the alveolar-capillary membrane (pulmonary fibrosis), or (3) obstruct or obliterate pulmonary capillaries (pulmonary embolism, fibrosis, emphysema, pulmonary hypertension). Although the combination of airway obstruction, overinflation, and a reduced D_LCO are the best physiologic markers for emphysema, this entire constellation of findings does not usually occur until later stages of the disease. Isolated reductions in D_LCO have been reported to be early indicators of the presence of both emphysema and interstitial fibrosis. For example, in one report of patients with dyspnea, normal chest radiographs, and pathologically demonstrated pulmonary fibrosis, a reduced D_LCO was the among the most common functional abnormalities. However, the sensitivity and specificity of an isolated reduction in D_LCO, even in the presence of dyspnea, are still unknown.

Reductions in D_LCO are thought to predict exercise-associated arterial O_2 desaturation. In patients with chronic obstructive lung disease and restrictive lung diseases, D_LCO values that are <50% of predicted have been shown to correlate with exercise hypoxemia. Reports are not entirely consistent, however. One should view the 50% threshold with some suspicion because of the known large interlaboratory variability in percentage of predicted values for D_LCO.

Increases in D_LCO are not commonly encountered clinically. They occur in the presence of polycythemia and with intrapulmonary hemorrhage (e.g., Goodpasture's syndrome). They may also represent a technical problem, as D_LCO can be dramatically increased when an individual continues to try to inhale during the breath-hold part of the test (Mueller maneuver).

RESPIRATORY MUSCLE STRENGTH

Routine pulmonary function tests may be useful in suggesting the presence of respiratory muscle dysfunction. Typically, individuals who cannot generate normal respiratory muscle force have a reduced VC. In patients with bilateral diaphragmatic paralysis, VC is usually smaller in a supine than in an upright position. VC may also be a useful tool to follow patients with respiratory muscle dysfunction. MVV is commonly reduced in the presence of respiratory muscle dysfunction, but its use is limited because so many different factors reduce it.

Overall respiratory muscle strength is usually assessed by measurement of maximum inspiratory (MIP) and expiratory (MEP) pressures at the mouth. These pressures can be easily measured with portable pressure meters in most clinical settings. MIP is usually measured from RV, and MEP from TLC. Patients should be coached to make the maneuver from their lungs and not use their cheek muscles, which can generate falsely high pressures. The measurements are made against a closed valve; a small, 1-mm fixed air leak is introduced to reduce the effect of using the cheek muscles to generate pressure. Mouth pressures well within a normal range (MIP >80 cm H_2O) can be used to exclude clinically significant respiratory muscle weakness. Lower values are more problematic, because they can represent disease or inadequate effort.

In patients for whom measurements of MIP and MEP do not resolve the question being asked, more sophisticated assessment of respiratory muscle function can be performed with measurement of transdiaphragmatic pressures and with nerve stimulation tests. These tests have the disadvantage that they are more technically demanding and therefore are usually limited to specialty laboratories.

Tests of respiratory muscle strength are useful when neurogenic and myopathic processes are known or suspected. They are also useful when diaphragmatic weakness, fatigue, or paralysis are suspected. Diaphragmatic weakness, when severe, can cause dyspnea and tachypnea and can, even when mild, contribute to dyspnea resulting from other disease processes.

TESTS OF ELASTIC PROPERTIES

These tests are used to characterize the elastic properties of the lung and chest wall. They require the measurement of transmural pressures across the lung (lung elastic recoil pressure, or P_{el}) and across the chest wall (chest wall elastic recoil pressure, or P_{th}). The chest wall includes the abdomen. Measurement of these transmural pressures requires estimates of pleural pressure (P_{pl}) and alveolar pressure (P_{alv}). A small esophageal balloon is inserted into the lower third of the esophagus; esophageal pressure is used to approximate pleural pressure. Mouth pressure under static conditions (no air flow in a relaxed patient with an open glottis) is used to approximate alveolar pressure. Under static conditions, esophageal and mouth pressures are measured at several lung volumes between TLC and RV. Curves relating transmural pressures to lung volume (pressure-volume curves) are calculated separately for the lungs and chest wall and for the respiratory system (lung and chest wall combined). Compliance is calculated as change in lung volume divided by change in pressure (DV/DP).

Normal aging and diseases like pulmonary emphysema, which involve disruption of the alveolar walls, are associated with decreased lung recoil pressures for a given lung volume and, consequently, increased lung compliance. Diseases like pulmonary fibrosis increase lung elastic recoil pressures and reduce lung compliance. Aging and chest wall disorders are associated with decreased chest wall compliance.

Although these tests are critical for clarifying the pathophysiology of lung function in various diseases, their clinical utility in routine patient care has never been proved. Interested readers should consult pulmonary physiology texts for further information.

ARTERIAL BLOOD GASES

Thus far, the discussion has been concerned with tests of the mechanical properties of the lung—the bellows action that moves air into and out of the lungs. The mechanical studies, including spirometry, lung volumes, and respiratory muscle testing, characterize the function of the lung but do not provide any estimate of how adequately the lung is performing its primary function. Measurement of arterial blood gases provides direct evidence about the adequacy of gas transfer across the lungs.

It is important to understand both what information is provided by arterial blood gases and what is not. Arterial blood gases define how well the lung is loading O_2 into and removing CO_2 from blood. However, they characterize only the initial steps in the gas transport system (Table 1). They do not allow an overall assessment of the

adequacy of delivery of O_2 to cells or of the adequacy of cellular function.

Blood gas technology is advancing rapidly. Blood gas machines are now highly automated. They calibrate and monitor themselves for errors. They wash and rinse themselves and provide numerous alert messages when conditions are not properly controlled. They measure temperature and barometric pressure and compensate for electrode nonlinearity with empirically derived mathematical algorithms. Because they do so much and the technician needs to do so little, laboratory physicians and technicians may become less knowledgeable about the details of blood gas analysis. The increased accuracy of modern blood gas machines partially compensates for this lack of knowledge while at the same time exacerbating it.

The field of noninvasive monitoring of blood gas parameters is also advancing rapidly. Pulse oximeters are widely used, and other techniques for continuously monitoring blood gas parameters are being developed. In the managed care environment, blood gas analysis, along with most other laboratory measurements, is under increasing scrutiny. Documentation for the efficacy of these measurements is being required.

Details of blood gas measurement and interpretation are available in several of the references listed. Briefly, analysis of arterial blood gases involves three separate issues: (1) acid-base status, (2) ventilation status, and (3) oxygenation status. The importance of the lungs in maintaining acid-base balance is illustrated by the fact that the lungs excrete approximately 13,000 mEq of CO_2 per day. In contrast, the kidneys excrete 40 to 80 mEq of fixed acid per day. In a blood gas report, pH and $PaCO_2$ are the two measured elements relating to acid-base balance. The pH and arterial pressure of CO_2 ($PaCO_2$) are used to calculate bicarbonate concentration using the Henderson-Hasselbalch equation. Calculated bicarbonate may provide quick insight into the metabolic component of acid-base derangements.

The adequacy of ventilation is assessed with the $PaCO_2$, according to Eq. 1:

$$PaCO_2 \propto \frac{\dot{V}CO_2}{\dot{V}_A} \propto \frac{\dot{V}CO_2}{\dot{V}_E - \dot{V}_D} \quad \textbf{(1)}$$

where $\dot{V}CO_2$ is CO_2 production, $\dot{V}_A$ is alveolar ventilation, $\dot{V}_E$ is minute ventilation, and $\dot{V}_D$ is dead space ventilation.

Equation 1 illustrates that $PaCO_2$ is determined by the matching of $\dot{V}_A$ to $\dot{V}CO_2$. An elevated $PaCO_2$ indicates hypoventilation; that is, $\dot{V}_A$ is inadequate relative to $\dot{V}CO_2$. Inadequate $\dot{V}_A$ can occur because $\dot{V}_E$ is reduced and/or $\dot{V}_D$ is increased. If $PaCO_2$ is low, hyperventilation is present. A normal $PaCO_2$ implies adequate matching of $\dot{V}_A$ to $\dot{V}CO_2$, but it is not the sole determinate of the efficiency of ventilation. Efficiency of ventilation must be interpreted in light of the clinical setting, including breathing parameters and $\dot{V}CO_2$. Problems with $\dot{V}CO_2$ can usually be diagnosed simply by looking for markers associated with increased $\dot{V}CO_2$ that may be driving the metabolic processes. In the intensive care unit, these markers include fever and overfeeding with parenteral nutrition. Increases in $\dot{V}CO_2$ are rarely reflected directly as increases in $PaCO_2$ because the ventilatory reserve is so large.

Evaluation of oxygenation parameters includes assessment of the PaO_2 and arterial O_2 content. The PaO_2 provides a valuable—but incomplete—estimate of the adequacy of O_2 loading in the pulmonary capillary blood. It is useful to think of PaO_2 as an intensive rather than a quantitative variable. Although very useful, PaO_2 by itself gives no information about the volume of O_2 contained in the blood (O_2 content). Analyzing both PaO_2 and O_2 content enhances blood gas information.

CO-oximeters are available for accurate measurement of Hb concentration, arterial O_2 saturation (SaO_2), COHb concentration, and methemoglobin (Met-Hb) concentration. Their availability improves the accuracy of estimations of SaO_2 and simplifies the diagnosis of CO poisoning. Blood gas reports should now routinely include a calculation of arterial O_2 content (CaO_2) using CO-oximeter measurements (Eq. 2). Its components include Hb concentration, SaO_2, and the volume of O_2 dissolved in plasma, calculated as $0.0031 \times PaO_2$. The amount of O_2 dissolved in the plasma is trivial compared with the amount bound to Hb in most clinical settings.

$$CaO_2 = 1.39\ Hb \times SaO_2 + 0.0031\ PaO_2 \quad \textbf{(2)}$$

Calculation of the alveolar-to-arterial pressure gradient for O_2, or $P(A\text{-}a)O_2$, when the patient is breathing room air can be useful in separating the physiologic causes of hypoxemia. The method of calculating $P(A\text{-}a)O_2$ is shown in Eq. 3:

$$P(A\text{-}a)O_2 = FIO_2(PB\text{-}47) - PaCO_2\left(FIO_2 + \frac{1\text{-}FIO_2}{R}\right) - PaO_2 \quad \textbf{(3)}$$

where $P(A\text{-}a)O_2$ is the alveolar-to-arterial pressure gradient for O_2, FIO_2 is the inspired O_2 concentration, ($PB - 47$) is the barometric pressure minus water vapor pressure at 37°C, and R is the respiratory quotient (usually assumed to be 0.8). For blood gases obtained at sea level with a patient breathing room air, Eq. 3 can be reduced for rapid clinical use as follows:

$$P(A\text{-}a)O_2 = 150 - 1.2 \times PaCO_2 - PaO_2$$

It is clinically useful to categorize the physiologic causes of hypoxemia. Physiologic causes of hypoxemia are summarized in Table 2, along with corresponding alveolar-to-arterial gradients when appropriate.

Cause	$P(A\text{-}a)O_2$
Low PaO_2	
• Low inspired PO_2, FIO_2 is low Barometric pressure is low	• Normal If inspired PO_2 is incorrectly assumed to be 21%, the A-a gradient may be elevated.
• Hypoventilation (Elevated $PaCO_2$)	• Normal
• V/Q mismatching	• Elevated
• Diffusion impairment	• Elevated Rarely a cause of hypoxemia
• Right-to-left shunting	• Elevated With large shunt, response to oxygen poor
Low oxygen content (CaO_2)	
• Anemia	
• Low SaO_2 Presence of other hemoglobin species, such as COHb or Met-Hb Shift of oxyhemoglobin curve to right	

COHb, carboxyhemoglobin; Met-Hb, methemoglobin; CaO_2, arterial oxygen content; FIO_2, fraction of inspired oxygen; PO_2, partial pressure for oxygen; PaO_2, arterial partial pressure for oxygen; $P(A\text{-}a)O_2$, alveolar-arterial gradient for oxygen; $PaCO_2$, arterial partial pressure for carbon dioxide; V/Q, ventilation/perfusion.

TABLE 2. *Physiologic causes of hypoxemia*

The most common noninvasive measurement of oxygenation status is made by pulse oximetry. Pulse oximeters do not directly measure SaO_2 but relate light absorption across the finger to arterial blood gas data from volunteers in whom arterial blood gases and pulse oximeter light absorption are simultaneously obtained. One side of a pulse oximeter probe contains two light-emitting diodes, each emitting light at a different wavelength (one at about 660 nm and one at about 940 nm). The other side contains a photocell to measure light intensity after light has passed through a finger or ear lobe. A clever variation of Beer's Law (the light absorbed by a solute in a solution is related to the concentration of the solute) is used to estimate SaO_2. Light is absorbed in a pulsatile fashion, increasing with each heartbeat. The assumption is that the increased absorption is caused by arterial blood.

It is important to keep in mind the limitations of pulse oximetry. These include the margin of error, the fact that pulse oximetry does not differentiate between different Hb species, and the effect of substances in the body that may affect light absorption. As a general rule, a single isolated measurement of SaO_2 by pulse oximetry will be within ±4% of the saturation measured in blood directly. Therefore, a pulse oximeter reading of 90% could actually be between 86% and 94%. If the device is being

used to monitor SaO_2 in a single individual, a 2% change is considered significant. As pulse oximetry only uses two wavelengths of light, it cannot distinguish either COHb or Met-Hb. Pulse oximeters measure COHb as if it were oxyhemoglobin. In a patient with CO poisoning, therefore, the low SaO_2 would not show up on a pulse oximeter reading.

Other conditions that may result in misleading readings include presence of dyes (methylene blue), elevated bilirubin, states of low perfusion, anemia, and presence of strong external light sources, which may interfere with absorbance measurement. On occasion, the assumption that the pulsatile waveform marks arterial blood does not hold. For example, in a patient with tricuspid regurgitation and strong venous pulsations, the pulse oximeter cannot separate arterial from venous pulsations, and an erroneous reading may occur.

REFERENCE VALUES AND INTERPRETATION

Background

The first step in interpreting pulmonary function tests is selecting the best possible reference values. For many tests, the selection is made by a laboratory physician, but as equipment moves into offices and clinics, individual clinicians will be called on more and more often to make that choice. Guidelines for selecting reference values are widely available. For pulmonary function tests, the ATS and ERS provide access to appropriate reference values.

Medical decisions are made after comparing clinical observations with one or more sets of reference data. This is not as simple as defining a normal range. Results of clinical tests that fall within a normal range often imply absence or low risk of disease. This may not be correct when the typical representative comparison is made. For example, a cholesterol value may fall well within an average range from a general population sample but indicate increased risk for coronary disease when compared with reference data based on total risk assessment. In pulmonary function testing, the assumption may also be incorrect. For example, an individual who starts out with an FEV_1 that is 110% of the predicted value could suffer a reduction of 25% or more in FEV_1 and still have a value within the normal range. The loss—and thus the underlying disease process—would not be detected by routine lung function testing.

Interpreting lung function tests may also be based on comparisons of observed values with reference value information, including comparisons with recognized disease patterns or values previously measured in the same patient. Using historical lung function data from the same patient neatly eliminates all the between-individual variability that exists in the representative group comparison; changes as small as 5% can be detected. However, it is not practical to perform baseline studies in every patient against the unlikely chance that a pulmonary disease will develop. It is practical, however, to track individual lung function in at-risk populations, such as those in occupations with a known tendency to cause lung injury.

The issues involved in reference value selection and comparison have been the subject of many expert panels and are well described by Solberg (1989) and Grasbeck (1990). The general rules, modified slightly for pulmonary applications, are as follows: (1) The reference population must be clearly defined and described. (2) The patient being examined must resemble the reference study subjects as much as possible in regard to the biologic factors known to contribute to lung function variability. For lung function, these factors are sex, age, height, weight, ethnic group, past and present health, socioeconomic status, and environmental exposures, including cigarette smoke, air pollution, and occupational exposures (Fig. 11). (3) Clinical and reference value measurements should be made with adequately standardized methods and appropriate quality control. Technical variability is reduced when a clinical laboratory makes measurements with the same standardized methods as those used in a reference value study. This last issue is the basis for the development of equipment and procedural standards that have been published by many different respiratory societies.

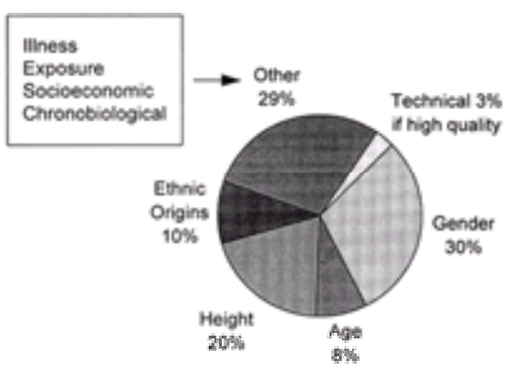

FIG. 11. Schematic illustration of the sources of variability in lung function tests. These sources of variability must be dealt with as part of the performance and interpretation of lung function tests or else the noise encountered in the testing will overwhelm the signal of interest, which in a clinical setting is usually change in lung function with disease. Note that the 3% technical variability assumes high-quality tests. Substandard tests can cause technical variability to exceed all other sources of variability. (Created from data contained in Becklake MR, White N. Sources of variation in spirometric measurements. *Occup Med State of the Art Rev* 1993; 8:241–264.)

Reference data vary depending on the population being sampled, the method of sampling the population, and the methods of analyzing the data. The data may be gathered from a subset of a population sample in a larger epidemiologic study, or it may come from a study specifically designed as a reference value study. Although the optimal method of sampling a population is random sampling, volunteer samples are less expensive and easier to perform and thus more frequently used. Sample size is important. In general, lung function reference studies are better if they include at least 10 subjects of each sex for each decade. The method of analysis also influences reference ranges. In some pulmonary function reference studies, only linear relationships are considered; in others, complex models are used.

Lower Limits for Reference Ranges (Lower Limits of Normal)

Once reference values have been selected, a reference range defines the limits for comparisons. In pulmonary function testing, three sets of limits are commonly used. The most common is also the least desirable. It defines the normal range for FEV_1/VC as >70% or >75% and the normal range for everything else as the predicted value ±20%. This method is popular because of its simplicity, but it is statistically incorrect and should be abandoned. The FEV_1/VC ratio falls with aging, so a fixed ratio to define normal is inappropriate. Using ±20 to define a reference range causes false-negative results in younger and taller patients and false-positive tests in shorter, older patients. It causes large numbers of false-positive errors in the interpretation of midflows and instantaneous flow variables, for which statistically appropriate lower limits of normal approach 50% of the predicted value.

Two statistically acceptable approaches to lower limits of normal are available. One, based on an assumption that the data distribution is Gaussian, uses 95% confidence intervals, usually calculated as 1.645 times the standard error of the estimate in a linear regression equation. The other is based on a calculated lower (or upper) 5th percentile. The percentile calculation is usually based on data expressed as a percentage of the predicted value. Calculation of percentiles avoids the Gaussian distribution assumption. Both are probably acceptable for basic pulmonary function tests that involve FVC and FEV_1. The instantaneous and midflow variables are more likely to have skewed distributions; reference ranges defined with percentiles are preferable for these variables.

Lower limits of normal are variable and should not be treated as arbitrary demarcations. Measured values that lie well within or outside the normal range can be interpreted with confidence. Those that lie close to lower or upper limits should be interpreted with caution. In these borderline cases, clinical information is the best guide to categorizing a test result.

Restricting the Number of Tests Used in an Interpretation

More than 30 parameters can be obtained from spirometry, lung volumes, and diffusing capacity. By chance alone, more than 25% of healthy subjects would have an abnormal result in one or more tests if all 30 were used. The chances for a false-positive test decrease when one is selective about the number of results analyzed. For spirometry, the interpretation should focus on three variables: VC, FEV_1, and FEV_1/VC. For static lung volumes, the interpretation should focus on TLC, and for diffusing capacity, on D_LCO. The other results reported may help make decisions in borderline cases, but clinical data are even more useful in those borderline situations.

General Interpretative Guidelines

Spirometry

A simple algorithm for interpreting spirometry using three variables is outlined in Fig. 12. Obstructive lung diseases are characterized by decreased expiratory flows compared with healthy persons. Early airway obstruction, which begins in the small airways, tends to reduce flows at lower lung volumes. Numerous tests for small-airways disease have been studied. Tests, including closing volume, $V_{max50\%}$, and $FEF_{25\%-75\%}$, tend to correlate well with small-airways disease in groups, but there is still no convincing evidence they can be effectively used in a clinical setting to diagnose the presence of small-airways disease in a given individual. The pattern of reduced air flow at lower lung volumes is also seen as part of normal aging, reflecting the loss of elastic recoil of the lungs with age.

FIG. 12. Simple algorithm for interpretation of spirometry. For simplicity, the severity of restriction based on VC is not diagrammed. Severity of restriction here would use percentage of predicted VC and use a scale similar to that for obstruction. (Adapted from information contained in Becklake MR, Crapo RO, co-chairs. Lung function testing: selection of reference values and interpretative strategies. Official statement of the American Thoracic Society. *Am Rev Respir Dis* 1991;144:1202–1218.)

As airway obstruction worsens, air flow is reduced at higher lung volumes. The flow-volume display shows progressively more concavity toward the horizontal axis; the volume-time curve shows a slowly rising volume even after 6 to 10 sec. The primary marker for the presence of airway obstruction is the FEV_1/VC ratio. Once airway obstruction has been diagnosed on the basis of FEV_1/VC, severity is classified using the FEV_1% (FEV_1 as a percentage of the predicted value) (Fig. 12). The characteristic patterns of severe airway obstruction are illustrated in Fig. 8. All expiratory flows are reduced. With good effort, a well-defined but reduced peak flow is seen, followed by a rapid fall in flow to a very low level. At that point flow decreases almost linearly, and the patient never achieves a true expiratory plateau.

Central airway obstruction has a characteristic pattern, depending on the location of the obstruction (Fig. 13). The classic pattern is not seen, however, until the obstruction is rather advanced. The pattern of central airway obstruction can be replicated by submaximal inspiratory and expiratory efforts. Therefore, vigorous patient effort is especially important when central airway obstruction is suspected.

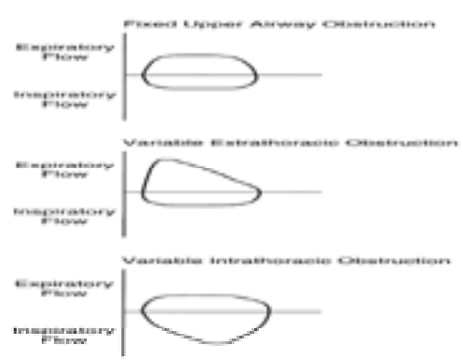

FIG. 13. Central airway obstruction patterns. Three basic forced expiratory flow-volume patterns seen in the presence of at least moderate upper airway obstruction are schematically illustrated. The basic pattern of airflow obstruction in central airways is constant flow over a significant portion of the inhaled and/or exhaled volumes. In fixed central airway obstruction, the pattern does not vary with inspiration or expiration. Variable extrathoracic obstruction is associated with a relatively normal pattern during expiration, as extrathoracic airways widen during exhalation and narrow during inspiration. Conversely, variable intrathoracic obstruction tends to have a more normal pattern during inspiration, as intrathoracic airways tend to widen during inspiration and narrow during expiration. The patterns may also be seen with submaximal effort. The patterns are present to some degree in patients with milder degrees of obstruction but may be more subtle.

Restrictive patterns in spirometry are characterized by a reduced VC in the absence of airway obstruction (FEV_1/VC is normal). Flows taken from a spirogram are typically reduced when restriction is present because of the smaller absolute lung volume, and by themselves they do not indicate the presence of combined obstruction and restriction. Small VCs commonly occur in the presence of obstruction because expiratory time is relatively short. If airway obstruction is present and VC is low, no certain determination of restriction can be made on the basis of spirometry alone. If it is clinically indicated, a measurement of TLC is necessary to confirm the presence of a combined obstructive and restrictive pattern. The presence of restriction can also be determined in most patients who have airway obstruction by simply reviewing the chest radiograph obtained for other clinical reasons.

Static Lung Volumes

The static lung volume variables used for interpretation should be limited to TLC to avoid excessive numbers of false-positive results. Statistically based lower limits of normal should be used. In the classification of restriction, occasionally TLC and VC findings will conflict. If there are no obvious technical problems, TLC should determine the estimation of restriction. The classic pattern of overinflation includes elevations in TLC, FRC, and RV. Increases in FRC and RV may precede increases in TLC, but one should be cautious in using them to diagnose overinflation, because they also increase the risk for false-positive calls. Overinflation can also be recognized in chest radiographs when classic signs are present.

Diffusing Capacity

The primary variable used for interpretation is D_LCO. There is increasing hesitancy to use D_L/V_A in interpretative schemes, largely because it frequently conflicts with D_LCO and the clinical situation. A laboratory can usually categorize D_LCO only as within or outside the reference range. The one pattern of findings that suggests a clinical diagnosis is the combination of airway obstruction, evidence of overinflation, and a low D_LCO (suggesting emphysema). Further interpretation of alterations in D_LCO requires knowledge of the clinical question being asked. A common pattern is to find a reduced D_LCO as the only abnormality in a battery of pulmonary function tests. In the absence of other clinical or functional information, an isolated reduction in D_LCO does not have clinical significance and need not be pursued further.

Changes in Lung Function Measurements with Time

It is difficult to define precisely a significant change with time. A consistent trend in lung function revealed with multiple measurements will define significant change earlier than will two or three measurements. For changes in VC and FEV_1 occurring within a few weeks, a 12% change in healthy subjects and 20% in subjects with obstruction is likely to be significant. Through years, a 15% change (adjusting for age) is probably significant for both. For D_LCO and TLC, within-test and between-test variability are increased, and criteria defining change with time are largely absent. When no trending information is available, I tend to consider changes of >15% as

significant, but do so with some discomfort.

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CHAPTER

10 Exercise Testing

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THE INTEGRATIVE CARDIORESPIRATORY EXERCISE TEST

The essence of clinical integrative cardiorespiratory exercise testing is the ability to assess oxygen uptake ($\dot{V}O_2$) from measurements of ventilation and respired gas concentrations. When considered together, these parameters (ventilation, gas exchange, $\dot{V}O_2$, and others) allow for extended conclusions to be made regarding diverse cardiovascular, respiratory, and metabolic adaptations to the stress of exercise. Normal peak O_2 uptake indicates adequate (although not necessarily optimal) gas transport from the atmosphere to the mitochondria of muscle and effective utilization of molecular O_2 by the cellular enzymatic machinery. Fick's relationship portrays the factors governing O_2 consumption:

$$\dot{V}O_2 = \dot{Q} \times C(a\text{-}\bar{v})O_2 \quad (1)$$

where $\dot{Q}$ is cardiac output, C is content, a denotes arterial blood, and $\bar{v}$ denotes mixed venous blood. The determinants of O_2 uptake, as delineated by Fick's relationship, are presented in Table 1. O_2 utilization depends on a synchronized response of many supporting systems to the metabolic load. However, normal values for peak $\dot{V}O_2$ do not ensure that each element of the O_2 transport chain is normal, as not all are rate-limiting. Exercise capacity can be normal for age despite certain loss of heart, lung, or hemoglobin structure and/or function. On the other hand, when peak $\dot{V}O_2$ is reduced (if this is not caused by poor effort), one (or more) of the components of the O_2 transport/utilization chain is evidently abnormal.

Variable	Determinants
Cardiac output	Heart function, normality of peripheral and pulmonary vascular beds, volume status, blood viscosity, and drugs
Arterial O_2 content	Hemoglobin concentration, P_{50}, poisonous gases (CO), lung function, pulmonary vascular bed, central ventilatory control, and inspired O_2 pressure
Mixed venous O_2 content	Cardiac output, status of peripheral vascular bed and oxidative cellular machinery, including poisonous gases (CO)

P_{50}, oxygen half-saturation pressure of hemoglobin; CO, carbon monoxide.

TABLE 1. *Determinants of O_2 uptake, as described by Fick's relationship*

When exercise capacity is restricted, it is a challenge for the clinical physiologist to identify the organ(s) or system(s) whose malfunction is causing the limitation. This goal is approached by a thorough analysis of the response to exercise, including symptoms, electrocardiographic pattern, blood pressure, ventilation, gas exchange, O_2 uptake, partial pressure of arterial blood gases, and blood pH and lactic acid concentrations. These are assessed at submaximal and/or at the highest tolerable work rate. More than one protocol may be used for exercise testing. In this review, we concentrate (unless otherwise stated) on data collected during incremental maximal studies (on a cycle ergometer or a treadmill). Various aspects of exercise physiology are addressed only briefly, and the reader is referred to recent editions of comprehensive textbooks and review articles for the details of physiology, muscle fiber type, bioenergetics, cardiovascular and ventilatory control issues, and clinical applications. As is discussed later, it is usually possible to differentiate between ventilatory and cardiovascular mechanisms leading to exercise limitation. However, discrimination among potentially limiting constituents within the O_2 transport chain (mainly cardiovascular factors) and between cardiovascular limitation and poor fitness is more subtle (poor fitness may be considered a reversible form of cardiovascular dysfunction).

WHY PERFORM AN INTEGRATIVE EXERCISE STUDY?

Metabolic exercise challenge is not performed to arrive at a specific pathophysiologic diagnosis, even though, on occasion, such diagnosis is feasible (i.e., myocardial ischemia or asthma induced by exercise). Exercise is performed to evaluate how an individual (with normal or diseased organs) adapts to physical stress, and/or to answer specific, quantitative physiologic questions. Examples of such questions are shown in Table 2. They are often difficult or impossible to settle based on resting pulmonary functions or resting hemodynamic data. Marked discrepancy often exists between resting measurements and the actual peak exercise O_2 uptake. For example, in patients with severe heart or lung disease, such as a left ventricular ejection fraction of <20%, or a forced expiratory volume in 1 sec (FEV_1) of <1 L, exercise capacity varies; it may be nearly normal or severely reduced.

1. Is exercise capacity reduced, and if yes, to what extent?
2. Which supporting system is limiting exercise or causing exertional dyspnea?
3. Are gas exchange and arterial blood gases normal during exercise, and if not, what is the extent of the abnormality?
4. What is the metabolic cost ($\dot{V}O_2$) of performing a given work rate task?
5. What is the ventilatory requirement for performing a given work rate task?
6. Is there a clue that suggests the presence of metabolic abnormality or myopathy?
7. Does the exercise intolerance represent a behavioral abnormality or an apparent intolerance is being fabricated for a secondary gain?
8. What is the metabolic level ($\dot{V}O_2$) that a subject can sustain?

TABLE 2. *Examples of questions that can be answered by an integrative cardiorespiratory exercise test*

The pattern of response to the exercise challenge should direct any subsequent diagnostic workup (if needed). At that stage, workup should be targeted to arrive at a specific diagnosis (e.g., pulmonary angiography for an apparent pulmonary embolic disease, or specific muscle enzyme assay for an apparent metabolic myopathy). The algorithms used for interpretation of the exercise data are based on recognition of distinctive patterns. These algorithms are founded on known physiologic principles, but their predictive power in some specific disease categories needs further clarification.

NORMAL AND ABNORMAL CARDIOVASCULAR, VENTILATORY, AND GAS EXCHANGE RESPONSES TO AN INCREMENTAL WORK RATE EXERCISE TEST

Cardiovascular Response

Stroke Volume and Heart Rate

Cardiac output ($\dot{Q}$) increases during exercise as a linear function of the metabolic rate at all levels of fitness. However, heart rate (HR) and stroke volume (SV) react differently. The SV rapidly reaches its highest level at a work rate that is about one third of the maximal. This SV is maintained throughout the range of work rates. In contrast, HR increases linearly with $\dot{V}O_2$ throughout exercise. From rest to peak exercise, SV may double in fit subjects, and HR rises even more.

In heart disease or in unfit subjects (3 weeks of bed rest is sufficient to induce a state of unfitness), SV augmentation during exercise is limited, and SV often actually falls below resting level. In these patients, augmentation of cardiac output is mostly or solely dependent on HR, which is high at rest and rises steeply during exercise. If the chronotropic effect is also depressed, the rise in cardiac output is further limited.

In trained subjects, at rest and at any given work rate, SV is higher, HR is slower, and the slope of the HR response is more shallow. In addition, with training, as $\dot{V}O_2$ rises, the O_2 content of the venous blood ($\bar{v}O_2$) becomes progressively smaller, but maximal HR does not rise. In sedentary subjects, the lowest $\bar{v}O_2$ content, at peak exercise, is 3 to 4 mL/100 mL [$C(a\text{-}\bar{v})O_2$ = 16 to 17 mL/100 mL], whereas in athletes, values for $\bar{v}O_2$ can be lower. SV is augmented as a result of higher venous return during exercise (Starling's effect) and of the inotropic, sympathetic effect. The change in HR is brought about by loss of parasympathetic tone at the low range of work rates and by sympathetic stimulation at the higher range of work rates. If the normal response is inhibited by a negative chronotropic process, a pharmacologic agent (e.g., a beta blocker), or by actual denervation (e.g., heart transplantation), the cardiac output response is delayed or limited.

Augmentation of O_2 consumption during physical activity is supported by a rise of O_2 flux ($\dot{Q}$), but also by augmented extraction of the O_2 stored in the arterial blood, which increases the $C(a\text{-}\bar{v})O_2$. By using Fick's equation and assigning an estimate to these parameters during exercise, we can calculate peak $\dot{V}O_2$ in a subject. Assuming a peak $\dot{Q}$ of 20 L/min and arterial and mixed venous O_2 concentrations of 20 and 2 mL/100 mL, peak $\dot{V}O_2$ = 20 L/min × 0.18 = 3.6 L/min. This level is characteristic for a relatively fit subject.

Peripheral and Pulmonary Vascular Resistance and Blood Pressure

The elevated O_2 flux during exercise is directed preferentially to the muscles (up to 70%–80% at peak exercise) secondary to a marked fall in peripheral vascular resistance in the vascular bed of the active muscles. Local accumulation of active metabolites (including endothelium-derived relaxing factors, i.e., nitric oxide) contribute to selective vasodilation at the metabolically active tissues. Generalized sympathetic stimulation causes vasoconstriction in nonactive vascular beds. If vascular resistance is relatively fixed, as in peripheral vascular disease, the capacity of the muscle to sustain generation of force will be limited. In systemic hypertension, peripheral vascular resistance at rest is elevated and the fall during exercise is also limited. These factors contribute to exercise limitation in hypertensive patients. Pulmonary vascular resistance also falls considerably during exercise. This is brought about by marked recruitment of capillary bed not perfused at rest. However, even in normal subjects, the increment in blood flow exceeds the capacity of the peripheral resistance to fall, and as a result, systemic blood pressure normally rises during exercise. The systolic pressure rises linearly with exercise intensity, but the peak value and the slope increase with age. A level of 200 mmHg is considered normal for systolic pressure at peak exercise. Diastolic pressure rises to a lesser extent, with a maximum of about 90 mmHg. Despite equal augmentation of flow in the two circuits, the mean pulmonary arterial pressure rises during exercise to an absolute value of 15 mmHg, whereas the mean systemic arterial pressure rises 50 mmHg above the resting level. The rise of the pulmonary pressure during exercise becomes marked if pathologic processes affect the pulmonary vascular bed.

Ventilatory Response

Whereas cardiac output for a given $\dot{V}O_2$ is mostly predictable, ventilation can vary markedly, even at similar metabolic rates. Unfortunately, disease processes affecting the lungs or heart are commonly associated with a higher ventilatory demand, thus placing affected patients at further disadvantage.

Factors Affecting Exercise Ventilation

Ventilation is determined by factors described by the following equation:

$$\dot{V}_E = K \times \dot{V}CO_2/PaCO_2 + \dot{V}_D \quad \textbf{(2)}$$

where $\dot{V}_E$ is ventilation, K is a constant, $\dot{V}CO_2$ is CO_2 production, and $\dot{V}_D$ is dead space volume flow (V_D × respiratory rate). The linkage of $\dot{V}CO_2$ and $\dot{V}_D$ to ventilatory demand is clear. These factors represent the metabolic rate and the fraction of wasted ventilation. Ventilation is tightly linked to $\dot{V}CO_2$ rather than to $\dot{V}O_2$. This linkage facilitates the regulation of arterial pH (which changes with fluctuating $PaCO_2$) rather than the regulation of alveolar PO_2 (PAO_2). As the slope of the hemoglobin dissociation curve at nearly normal PaO_2 is shallow, the effect of larger PAO_2 fluctuations on arterial hemoglobin saturation is modest.

The contribution of the third factor, $PaCO_2$, to the ventilatory demand is less clear. For a given metabolic rate, ventilation is higher if resting $PaCO_2$ is lower. This results from the fact that when the concentration of CO_2 in the arterial blood, $PaCO_2$, and hence in the alveolar air, is lower, any ventilated volume eliminates less CO_2 than when CO_2 concentration in the alveolar air is higher. This set-point effect is advantageous to patients with chronic obstructive pulmonary disease (COPD) which is associated with abnormally elevated $PaCO_2$, because the high $PaCO_2$ leads to a reduced ventilatory demand at any given $\dot{V}CO_2$. However, this same set-point effect imposes a larger ventilatory response in healthy or COPD subjects when $PaCO_2$ is low or needs to be lowered, as in chronic metabolic acidosis. As shown by the above relationship (Eq. 2), $\dot{V}_E$ is directly proportional to $\dot{V}CO_2$. Therefore, the higher the $\dot{V}CO_2$, the larger the $\dot{V}_E$ increment for any given decrement of $PaCO_2$. As a result, trained subjects, operating at high metabolic levels, require a progressively larger ventilatory response to compensate for the lactic acidosis produced during

exercise.

The integrated effect of these three factors governing exercise ventilation is illustrated in the four-quadrant graph of Fig. 1. It is shown that ventilation in response to exercise at $\dot{V}O_2$ of 1 L/min can vary markedly. This variation is related to the respiratory exchange ratio (R), the CO_2 set point, and the ratio of dead space to tidal volume (V_D/V_T). It can be as low as 20 L/min or as high as 60 L/min. This relationship illustrates why the ventilatory response during exercise may be markedly increased, even in the absence of intrinsic lung disease. With the exception of V_D/V_T, the factors governing ventilation, $\dot{V}CO_2$ and $PaCO_2$, can be abnormal as a result of metabolic causes, such as metabolic acidosis. Even V_D/V_T can vary without any apparent lung disease, as a consequence of the breathing pattern.

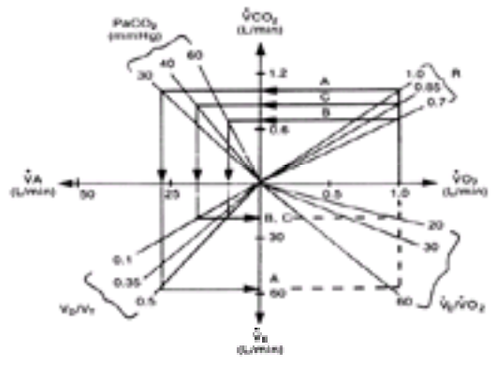

FIG. 1. Schematic representation of the effect of the respiratory exchange ratio (R), the $PaCO_2$ set point, and the dead space fraction of the breath (V_D/V_T) on the ventilatory response to exercise ($\dot{V}_E$) at a metabolic rate of O_2 uptake ($\dot{V}O_2$) of 1.0 L/min. If values for all three determinants are normal [*line B;* the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$)) will be 20], the $\dot{V}_E$ will be 20 L/min. However, if R is elevated, the $PaCO_2$ set point is low (such as if the load is above the subject's anaerobic threshold), and the V_D/V_T is high (*line A*), the ventilatory response will be 60 L/min. [Modified with permission from Whipp BJ. The bioenergetics and gas exchange basis of exercise testing. In: Weisman IM, Zeballos RJ, eds. *Clinical Exercise Testing.* Philadelphia: WB Saunders; 1994 (*Clin Chest Med;* vol 15).]

In addition to these three factors, ventilation is affected by various other stimuli, such as PaO_2, pH, and temperature, and it can be modified voluntarily.

Periodic Breathing in Heart Failure

In patients with advanced failure of the left side of the heart (and rarely in otherwise healthy subjects), breathing is oscillatory, with alternating phases of hyperventilation and hypoventilation; each cycle (peak to peak) lasts up to 1 min. This pattern is more distinct during exercise of low to moderate intensity and is attenuated at high intensity. The oscillations are associated with simultaneous oscillations of O_2 uptake. However, as shown in Fig. 2, the $\dot{V}O_2$ oscillations exceed (in amplitude) and precede (in phase) the ventilatory oscillations. True $\dot{V}O_2$ oscillations must result from oscillatory blood flow, not from oscillatory breathing. Therefore, the coexistence of $\dot{V}O_2$ and $\dot{V}_E$ fluctuations suggests that circulatory oscillations (represented by $\dot{V}O_2$ oscillations) play an important or even a primary role in the induction of ventilatory oscillations.

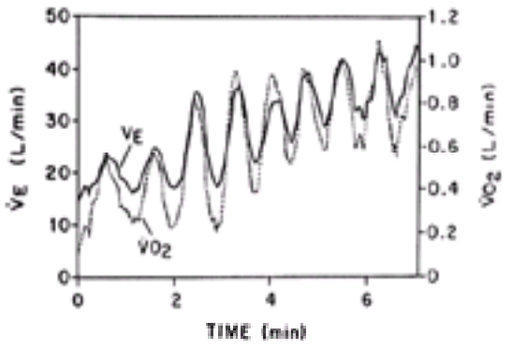

FIG. 2. Ventilation ($\dot{V}_E$) and O_2 uptake ($\dot{V}O_2$) in a subject with heart failure during 2 minutes of rest (time 0 to 2 minutes) and during incremental exercise. Oscillations are present at rest and are augmented as exercise starts. $\dot{V}O_2$ oscillations exceed (in amplitude) and precede (in phase) the $\dot{V}_E$ oscillation. Because hemoglobin is fully saturated, the $\dot{V}_E$ oscillations cannot induce these $\dot{V}O_2$ oscillations. Therefore, pulmonary blood flow must be oscillatory. (Modified with permission from Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. *Am Rev Respir Dis* 1992;145:776–781.)

Pattern of Breathing During Exercise

The ventilatory response is brought about by increasing both the tidal volume (V_T) and the respiratory rate. Normally, at low work rates, the change in V_T predominates. V_T reaches its maximal exercise value, which is about 60% of the vital capacity (VC), and this ratio is unchanged across age groups. V_T at peak exercise is, however, 70% of the inspiratory capacity (IC). Respiratory rate, which rises minimally at low work rates, is the predominant variable at the higher range of work rates above the anaerobic threshold (AT)] and does not reach a plateau during exercise. In disease states, such as COPD, interstitial lung disease, and congestive heart failure, the pattern is similar. However, the contribution of V_T to ventilation is smaller and that of the respiratory rate is larger. In these disease states, the 60% ratio of V_T to VC is maintained, but the ratio of V_T to IC, especially in interstitial lung disease, approaches 100%. The normal and abnormal relationships between V_T, VC, IC, and maximal voluntary ventilation (MVV) in healthy subjects and patients with obstructive and restrictive lung disease are schematically illustrated in Fig. 3.

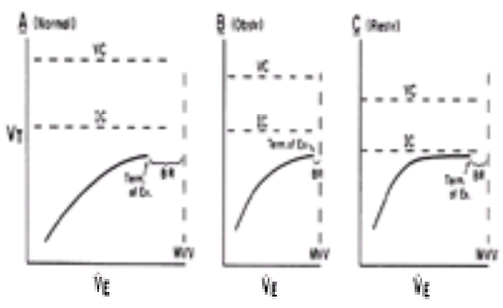

FIG. 3. Tidal volume (V_T) related to the vital capacity (VC), inspiratory capacity (IC), and maximal voluntary ventilation (MVV; *vertical dashed line*), as a function of minute ventilation ($\dot{V}E$), during an incremental exercise. The normal response (**A**), the pattern in obstructive lung disease (**B;** *Obstr*), and the response in restrictive disease (**C;** *Restr*) are shown. V_T as a fraction of the VC is not different. However, in restrictive diseases it approaches the IC at an early stage of exercise. Breathing reserve (BR; MVV minus end-exercise $\dot{V}_E$) is low in B and C. (Modified with permission from Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R, eds. *Principles of Exercise Testing and Interpretation.* 2nd ed. Philadelphia: Lea & Febiger; 1994.)

When breathing is periodic, as in congestive heart failure, the fluctuations are brought about predominantly by oscillations of the VT. Fluctuations in respiratory rate are smaller in magnitude and are opposite in phase to the fluctuations of VT. Therefore, the respiratory rate fluctuations, if anything, attenuate the amplitude of the $\dot{V}_E$ oscillations.

Gas Exchange During Exercise

Oxygen Cost for Performing Work: Work Efficiency

The O_2 cost for a given increment in work rate is constant. Small, true variations depend on the specific substrate being utilized, and false variations result from differences in motor skills when various tasks are performed. This O_2 cost, which is 10.2 ± 1 mL/min per watt (W) for upright cycling, holds true irrespective of a subject's age, sex, or training status. At high-intensity exercise (above the AT), the contribution of anaerobic metabolism increases. Theoretically therefore, $D\dot{V}O_2$/Dwork rate is expected to be lower. However, it has been found that if the work rate increments are between 10 and 25 W/min, the normal ratio is sustained. Analysis of the position and shape of the $\dot{V}O_2$-work rate relationship is of clinical importance. Upward displacement of the curve is characteristic of situations of high metabolic cost, such as obesity or thyrotoxicosis. The slope of the relationship is apparently normal in these situations, although small differences in the slope (within the normal range) have been suggested, at least in hyperthyroidism (Fig. 4). Flattening of the slope is characteristic of low O_2 availability or utilization. The normal value of 10.2 mL/min/watt translates to muscular work efficiency (for that task) of approximately 30%--that is, the caloric equivalent of the work generated is 30% of the caloric equivalent of the energy consumed, as shown in Eq. 3:

$$\text{Efficiency} = \text{Work Done} \times 100/\text{Energy Cost} \qquad \textbf{(3)}$$

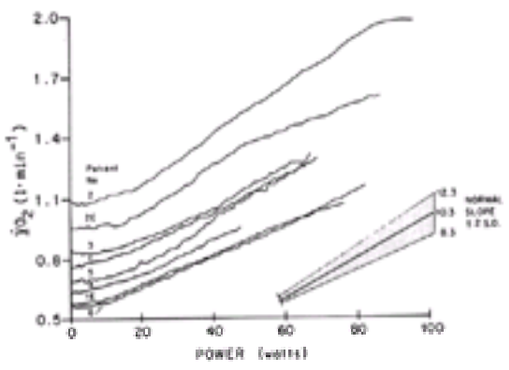

FIG. 4. Relationship of work rate and O_2 uptake in six patients (*1–6*) with hyperthyroidism during an incremental exercise test. Patients 1 and 2 repeated the test at the euthyroid state (*1E* and *2E*). Despite high O_2 uptake during pedaling at 0 W (consistent with hyperthyroidism), the relationship fell within the normal range. The normal range of the slope, 10.2 ± 1 mL/W, is shown by the *dashed area.* In the euthyroid state (*1E* and *2E*), the curves, as expected, are displaced downward. However, the slope is also more shallow relative to the hyperthyroid state (*1* and *2*). This suggests a mild change of work efficiency in hyperthyroidism. (Modified with permission from Ben-Dov I, Sietsema KE, Wasserman K. Oxygen uptake in hyperthyroidism during constant work rate and incremental exercise. *Eur J Appl Physiol* 1991;62:261–267.)

The work done per unit of time is the work rate in watts. Energy cost for that change in watts is actually measured or calculated by multiplying change in watts (above 0 W) by 10 mL of O_2 per minute per watt. To convert the denominator to calories, the caloric value of 1 mL of O_2/min is 5 cal/min. In the numerator, each 4.186 W = 1 cal/sec [1 cal = 4.186 J (joules)], and 1 W is defined as 1 J/sec, so that 1 W = 14 cal/min. For example, if $D\dot{V}O_2$ from 0 to 100 W = 1000 mL of O_2/min, the efficiency can be calculated as follows:

$$\text{Efficiency} = 100 \times \frac{100\ \text{W} \times 14\ \text{cal/min}}{1000\ \text{mL} \times 5\ \text{cal/min}} =$$

$$100 \times \frac{1400}{5000} = 28\%$$

Anaerobic (Lactate) Threshold

At a certain work intensity, usually about 50% of the individual $\dot{V}O_{2max}$, lactic acid starts to accumulate in the muscles and in the blood at a faster rate, and this metabolic level can be detected from measurements of gas exchange. The first gas exchange criterion used for the detection of accumulation of lactic acid is the respiratory exchange ratio (R). This accumulation of lactic acid represents a larger contribution of anaerobic metabolism to the energy utilized, as shown in Fig. 5. The metabolic rate ($\dot{V}O_2$) at which this shift occurs is defined as the anaerobic threshold (AT). The lactic acidosis of exercise is crucial for performing at high work intensities. Acid pH facilitates O_2 dissociation from hemoglobin at low capillary PO_2. This is achieved by inducing a shift to the right of the hemoglobin dissociation curve, thereby allowing higher capillary PO_2 (high driving pressure for diffusion) despite lower O_2 content. The shift towards a larger contribution by anaerobic metabolism could result from a limited O_2 supply to the muscle mitochondria at the AT. However, some authors dispute this. In any case, the accumulation of lactic acid is clearly linked to O_2 supply. Situations in which O_2 supply to the muscles rises (such as breathing a high concentration of O_2 and perhaps training) increase the AT, whereas situations in which O_2 supply falls (anemia, heart failure, low inspired O_2, carboxyhemoglobinemia) reduce the AT.

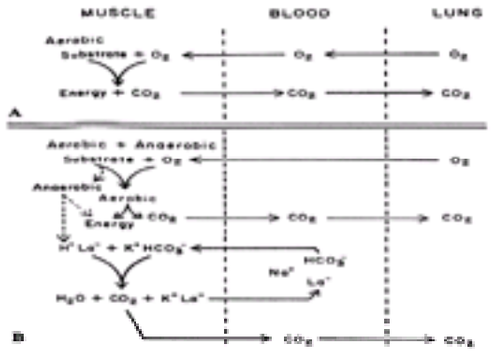

FIG. 5. Aerobic (**A**) and aerobic plus anaerobic (**B**) pathways for energy generation from substrates and molecular O_2. The aerobic pathway produces CO_2 and ATP. The anaerobic pathway produces lactic acid and ATP. The acid is buffered by intracellular bicarbonate ions, a reaction that produces additional CO_2, which is eliminated by ventilation. As lactate accumulates in the cell, part diffuses to the extracellular space and to the blood in exchange for a bicarbonate ion. If the substrate is glucose, 36 ATP molecules are produced by aerobic metabolism, whereas only two ATP molecules are produced by the anaerobic pathway. (Modified with permission from Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R, eds. *Principles of Exercise Testing and Interpretation.* 2nd ed. Philadelphia: Lea & Febiger; 1994.)

Besides O_2 shortage, other mechanisms have been proposed as explanations for the accumulation of lactic acid. Two alternative mechanisms may account for the lactic acidosis of exercise. The first is the possible role of shifting at the AT to the activation of more glycolytic, type II muscle fibers with lower oxidative capacity. The other is the possible role of rate-limiting mitochondrial oxidative enzymes. There is no evidence, however, that either of these mechanisms is operative. Irrespective of its mechanism, the AT is physiologically important as a metabolic level. It represents the highest work intensity that an individual can endure; higher levels provoke lactic acidosis and rapid fatigue. It also represents the metabolic level above which, even with a constant work rate effort, a steady state for $\dot{V}O_2$ (and for other gas exchange variables) is delayed or not attained.

The AT can reproducibly be determined noninvasively from gas exchange parameters. The criteria used for determination of the AT from an incremental test are summarized in Table 3 and demonstrated in Fig. 6. It has been found that in healthy subjects and in disease states the noninvasive AT corresponds or is close to the AT determined invasively by measuring lactate concentration, lactate-to-pyruvate ratio, blood pH, or blood bicarbonate concentration. If a low normal value for the AT is chosen (e.g., <40% of predicted peak $\dot{V}O_2$), the AT becomes a sensitive index to distinguish normality from various kinds of cardiovascular dysfunction. However, low AT is also found when O_2 flow is reduced, in severe ventilatory diseases, and in deconditioning.

Definition of criterion	Explanations and critique
Slope is steeper for $\dot{V}_E$ and for $\dot{V}CO_2$ response curves.	Reflects excess $\dot{V}CO_2$ and $\dot{V}_E$. The initial small change of the slopes is often obscured. $\dot{V}_E$ is often irregular.
$P_{ET}O_2$ rises while $P_{ET}CO_2$ remains unchanged.	Reflects excess breathing relative to $\dot{V}O_2$. This point is often obscured because of small absolute change of $P_{ET}O_2$ and relatively shallow slope of $P_{ET}CO_2$.
$\dot{V}_E/\dot{V}O_2$ rises while $\dot{V}_E/\dot{V}CO_2$ remains stable.	Ratios between these changes. Using the ratios highlights the turning point.
R ($\dot{V}CO_2/\dot{V}O_2$) rises, usually to > 1. CO_2 approaches the value of $\dot{V}O_2$.	Reflects the excess $\dot{V}CO_2$, but practically often obscured by fluctuations resulting from an irregular $\dot{V}_E$.
V-slope, $\dot{V}CO_2$ starts to accelerate faster relative to $\dot{V}O_2$.	Reflects the excess $\dot{V}CO_2$ above $\dot{V}O_2$. Eliminates the dependency on normal ventilatory response to the acid load (normal ventilatory control and mechanics are not required).

$\dot{V}_E$, minute ventilation; $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 production; $P_{ET}O_2$ and $P_{ET}CO_2$, end-tidal pressure of O_2 and CO_2, respectively.

TABLE 3. *Gas exchange criteria for determination of the anaerobic threshold from incremental exercise testing*

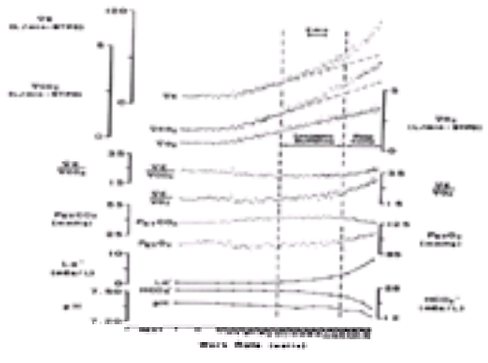

FIG. 6. Parameters used to determine the anaerobic threshold. Gas exchange parameters, lactic acid and bicarbonate concentrations, and blood pH are recorded at rest, during unloaded pedaling, and during an incremental period. The *left vertical dashed line* represents the anaerobic threshold. At this metabolic level, the slopes of the following curves accelerate: lactic acid, $P_{ET}O_2$, ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$), O_2 uptake ($\dot{V}O_2$), ventilation ($\dot{V}_E$), and the respiratory exchange ratio (R; not shown). The slopes of the following curves show a fall: pH and bicarbonate. The slopes of the $P_{ET}CO_2$ and the $\dot{V}_E/\dot{V}CO_2$ remain stable at the threshold and change only at a later stage, when respiratory compensation starts. (Modified with permission from Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R, eds. Principles of Exercise Testing and Interpretation. 2nd ed. Philadelphia: Lea & Febiger; 1994.)

The AT can be determined noninvasively in most normal subjects and in many patients with cardiovascular disease. However, in some normal subjects the data are not discriminative. In moderate to severe COPD, the AT is attained (and can be detected) in approximately two thirds of patients. In general, because of higher noise-to-signal ratio, the lower the peak $\dot{V}O_2$, the less likely it is that a distinct value for the AT can be determined from gas exchange parameters. When the respiratory response is erratic or irregular, as in periodic breathing, it is difficult to discern the AT. However, even in these latter situations, the V-slope method, in which $\dot{V}O_2$ is plotted against $\dot{V}CO_2$, using an appropriate scale (Fig. 7), is often helpful. By this method, determination of the AT is not dependent on ventilation (control or mechanics). In situations in which the AT cannot be detected from gas exchange data, it can be discerned by invasive measurements after plotting $\dot{V}O_2$ against lactate, bicarbonate, or the lactate-to-pyruvate ratio. In rare situations, when an even more sensitive method is needed, O_2 should be plotted against lactate levels using a log scale for both axes. This method enables discrimination between the early and late slopes of lactic acid accumulation, below and above the AT.

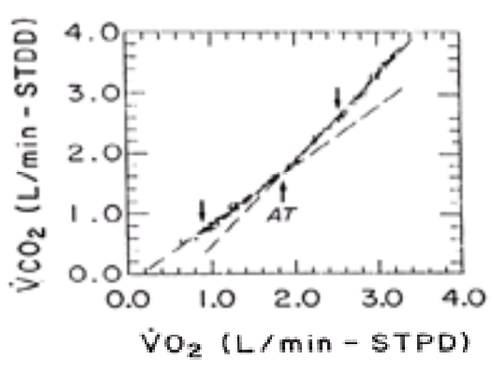

FIG. 7. V-slope method for determination of the anaerobic threshold (AT) from incremental exercise data of a healthy subject. $\dot{V}O_2$ is plotted against $\dot{V}CO_2$. The initial slope of the relationship is linear; at $\dot{V}O_2$ of 1.9 L/min, the slope becomes steeper. The point of deviation of the slope indicates the AT. The *dashed lines* represent the initial and late slopes of the relationship. Determination of AT by this method eliminates dependency on the normality of the ventilatory response. (Modified with permission from Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60:2020–2027.)

The kinetics of lactic acid accumulation and wash out at the transition from rest to exercise and during recovery is shown for a representative subject in Fig. 8. If a single blood sample is drawn for peak exercise lactic acid, bicarbonate, or pH change, the levels at 2 to 3 min after exercise are representative of the peak exercise values.

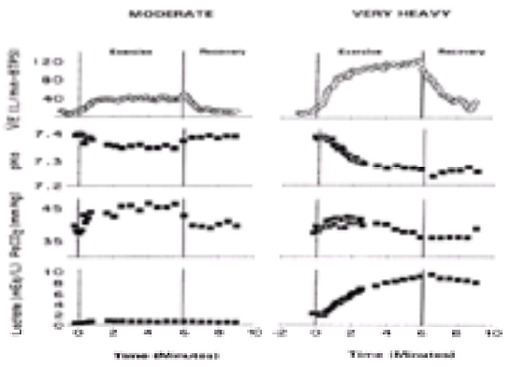

FIG. 8. Ventilation ($\dot{V}_E$), arterial Ph (pHa), arterial PCO2 ($PaCO_2$), and blood lactate in a subject exercising at a constant work rate of moderate intensity (below the anaerobic threshold) and at a constant work rate of very high intensity (close to the highest tolerable level). During the test at moderate intensity, a steady state for $\dot{V}O_2$ during exercise was attained, and lactic acid remained at the resting level. During the test at high intensity, no steady state was attained for the $\dot{V}O_2$ and lactic acid. At the recovery phase, despite a rapid fall of $\dot{V}O_2$, the concentration of lactic acid and the pHa remained at peak exercise levels for at least 2 to 3 minutes. (Modified with permission from Stringer W, Casaburi R, Wasserman K. Acid-base regulation during exercise and recovery in humans. *J Appl Physiol* 1992;72:954–961.)

The AT can be estimated if needed from a constant work rate test, but this demands repetition of the test at several work rates. At a below-AT intensity, a steady-state $\dot{V}O_2$ is maintained. At an intensity above the threshold, a steady state is delayed or not attained. Therefore, if $\dot{V}O_2$ at minute 3 of a constant work rate exercise is subtracted from $\dot{V}O_2$ at minute 6 ($D\dot{V}O_2$), the proximity to the AT can be estimated (Fig. 9). The larger the difference, the farther the metabolic level is above the AT. If the difference is 0, the metabolic level is below (or at) the individual AT. This method of calculating the AT from a constant work rate test is useful in patients with severe exercise limitation or for whom maximal exercise is considered too risky.

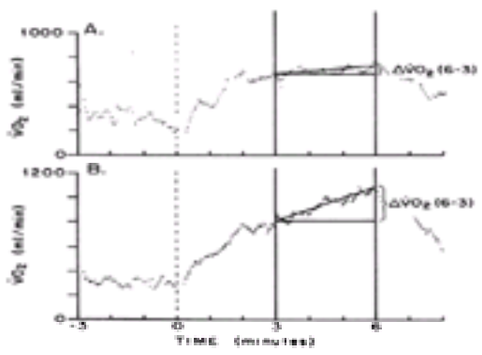

FIG. 9. $\dot{V}O_2$ response to a constant work rate exercise at 25 W (**A**) and 75 W (**B**) of a patient with heart failure. Exercise starts at time 0. The $D\dot{V}O_2$ is calculated from a linear regression of $\dot{V}O_2$ between minutes 3 and 6 of the exercise. In B, the difference is 300 mL. The departure from a steady state for O_2 uptake indicates that this metabolic rate is well above the patient's anaerobic threshold. In A, the difference is 50 mL, indicating that the metabolic rate is just above (or at) the patient's anaerobic threshold. This patient will probably be able to sustain a 25-W task (walking) for long period but will become exhausted after few minutes at a 75-W task. (Modified with permission from Zhang YY, et al. O_2 uptake kinetics in response to exercise: a measure of tissue anaerobiosis in heart failure. *Chest* 1993;103:735–741.)

PARAMETERS USED FOR INTERPRETATION OF EXERCISE DATA

Maximal or Peak O_2 Uptake

Maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$) should be related to the mode of exercise—namely, to the mass of the exercising muscles. $\dot{V}O_{2max}$ is different for running on a treadmill or cycling with the legs than for cycling with the upper extremities. Predicted maximum should be based on ideal body weight for a given height. Otherwise, overweight patients will be expected to achieve unusually high values. In underweight individuals, the height may overestimate muscle mass, and therefore the predicted $\dot{V}O_{2max}$. The maximal $\dot{V}O_2$ is ideally defined as the $\dot{V}O_2$ plateau level (stable $\dot{V}O_2$ despite rising work rate). Our experience has been that true plateau is more often not attained, especially in patients with heart disease. A false plateau is noted when a subject slows the pedaling rate at peak exercise, so that the desired work rate is not maintained. In this situation, the $\dot{V}CO_2$ curve is also relatively flat. If a plateau is not demonstrable, peak $\dot{V}O_2$ rather than $\dot{V}O_{2max}$ should be reported. Peak $\dot{V}O_2$ is meaningful if the patient effort is judged to be adequate and if gas exchange measurements indicate proximity to peak tolerable level (i.e., R >1.2), provided no noncardiovascular mechanism (ventilatory or skeletal) leads to termination of exercise.

Peak Heart Rate and Heart Rate Reserve

HR rises linearly with $\dot{V}O_2$. In heart disease, the rise of cardiac output is more dependent on HR. Therefore, the relation of HR to work rate shows upward displacement and/or a steeper slope. However, these characteristics of the curve cannot distinguish between heart disease and situations of low O_2 availability and/or deconditioning.

There are limitations to reliance on the HR response. The maximal HR, even in healthy subjects, can deviate markedly from the predicted mean maximum. Furthermore, in patients with heart failure, the predicted maximal HR is typically not attained, and the deviation from the predicted peak value is larger for the more disabled, as shown in Fig. 10. Likewise, HR response can be attenuated by chronotropic dysfunction (ischemia) or by commonly used medications.

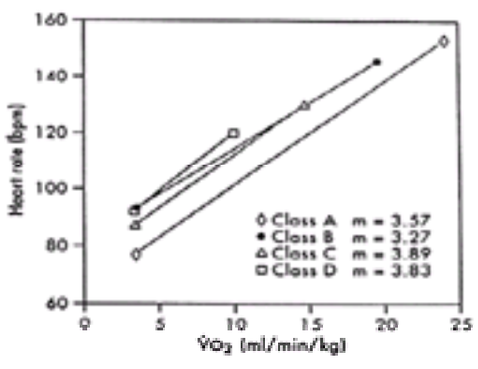

FIG. 10. The response of heart rate (mean) as a function of O_2 uptake ($\dot{V}O_2$) for patients with heart failure of the four functional classes. The higher the functional class, the higher the heart rate at peak exercise. The ability of the sicker patients to increase heart rate (and cardiac output) is more limited. (Modified with permission from Weber KT, et al. *Cardiopulmonary Exercise Testing: Physiological Principles and Clinical Applications.* Philadelphia: WB Saunders; 1986.)

Oxygen Pulse

O_2 pulse, the volume of O_2 extracted (or loaded) during one heart beat, is calculated from Fick's relationship ($\dot{V}O_2 = \dot{Q} \times C(a\text{-}\bar{v})O_2$; Eq. 1) by dividing both sides of the equation by HR:

$$\dot{V}O_2/HR = O_2\ Pulse = SV \times C(a\text{-}\bar{v})O_2 \quad \textbf{(4)}$$

where SV is stroke volume.

The O_2 pulse depends on the product of SV and the $C(a\text{-}\bar{v})O_2$. Therefore, quantitative assessment of each of these from the O_2 pulse is possible only when the other variable is of a relatively constant value. SV is relatively constant at high levels of exercise or during exercise in the supine position, whereas $\bar{v}O_2$ is temporarily relatively constant (if $\dot{V}O_2$ is measured breath by breath) early in the transition from rest to exercise, when the venous effluent from the exercising muscles has not reached the lung. During this phase, most of the change of pulmonary arterial hemoglobin O_2 saturation is caused by the rise in pulmonary blood flow. Close to peak exercise, when O_2 extraction is near the maximum, $\bar{v}O_2$ is also relatively constant.

O_2 pulse can be reduced in any situation in which $\dot{V}O_2$ is reduced—heart disease, peripheral vascular disease, anemia, and other situations leading to reduced O_2 content or reduced O_2 utilization (including deconditioning).

Ventilatory Equivalents for Oxygen and Carbon Dioxide and the Dead Space-Tidal Volume Ratio

The ventilatory equivalents can be considered as markers of ventilatory efficiency, because they represent the ventilatory demand at a given metabolic rate. Relative to rest, the values of the ventilatory equivalents decline at low- to moderate-intensity exercise, probably because of more optimal matching of ventilation to perfusion. The lowest values are reached around the AT. Above this metabolic rate, the ventilatory equivalents for O_2 and CO_2 diverge. Initially, when excess CO_2 is produced from buffered, newly formed lactic acid, the ventilatory equivalent for O_2 rises. Later, after a short isocapnic period, the ventilatory equivalent for CO_2 also rises, as a result of compensatory hyperventilation (Fig. 6).

The values of the ventilatory equivalents depend on various factors linking ventilation to its metabolic regulators (Eq. 2). The equivalents can also change in response to hyperventilation, either voluntary or secondary to anxiety or discomfort. When the ventilatory equivalents at a given exercise intensity are abnormally elevated, the simultaneous presence of a high $PaCO_2$ indicates (and a high $P_{ET}CO_2$ may suggest) that the abnormality is the result of intrinsic lung disease (poor distribution of ventilation, high $\dot{V}/\dot{Q}$ areas, or an increased dead space). The pattern of change of the ventilatory equivalents during incremental exercise in healthy subjects and in patients with obstructive and restrictive lung disease is schematically shown in Fig. 11. The ventilatory equivalents therefore contribute to our understanding of the ventilatory requirement. However, these parameters do not accurately reflect the dead space volume of the lung, calculation of which should be based on measurement of arterial PCO_2. The V_D/V_T is calculated as shown in Eq. 5.

$$V_D/V_T = (PaCO_2 - P_{ET}CO_2)/PaCO_2 - V_{DV}/V_T \quad \textbf{(5)}$$

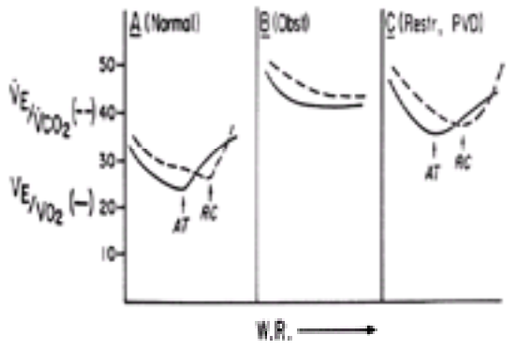

FIG. 11. A: Schematic illustration of the ventilatory equivalents for O_2 ($\dot{V}_E/\dot{V}O_2$) and CO_2 ($\dot{V}_E/\dot{V}CO_2$) as a function of work rate in a normal subject, in obstructive ventilatory (**B**) (*Obst*), restrictive ventilatory (**C**) (*Restr*), and pulmonary vascular disease (*PVD*) states. The anaerobic threshold (AT) at the lowest level of $\dot{V}_E/\dot{V}O_2$ and the respiratory compensation point (RC) at the lowest level of $\dot{V}_E/\dot{V}CO_2$ are marked. The values for the ventilatory equivalents normally fall during light to moderate exercise and rise again when lactic acidosis occurs. **B:** Because of mechanical restraint, the anaerobic threshold is often not attained and/or the respiratory compensation is limited, so that the late rise is not seen. **C:** Pattern is similar, but the absolute values are abnormally elevated. (Modified with permission from Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R, eds. *Principles of Exercise Testing and Interpretation.* 2nd ed. Philadelphia: Lea & Febiger; 1994.)

where $P_{ET}CO_2$ is end-tidal partial pressure of CO_2 and V_{DV}/V_T is the dead space volume of the breathing valve apparatus. As noted, the breathing valve volume should be taken into account in this calculation.

The specificity of the ventilatory equivalents as markers of certain diagnoses is low, as high values are seen in lung disease, heart disease, pulmonary vascular disease, and metabolic acidosis. The calculated ratio of dead space to tidal volume (V_D/V_T) is more predictive of an intrinsic lung abnormality. However, the V_D/V_T is high when breathing frequency is high, and its sensitivity is limited even in relatively advanced pulmonary vascular disease, which contradicts previous belief that a lack of fall in V_D/V_T during exercise is sensitive and often the sole detectable abnormality in early pulmonary vascular disease, even at a stage in which it cannot be detected by other clinical modes.

PaO_2 and $P(A\text{-}a)O_2$ Difference

PaO_2 in healthy subjects is normal or increased during exercise, but the $P(A\text{-}a)O_2$ difference usually widens. This behavior is also characteristic of situations of low O_2 carrying capacity that are not caused by lung disease, such as anemia, neuromuscular weakness, and unfitness. In obesity, PaO_2 rises and $P(A\text{-}a)O_2$ narrows early during exercise; subsequently, behavior of the parameters is similar to the normal response. Exceptions to these rules occur in the early phase of exercise, when ventilation lags behind $\dot{V}O_2$ rise, and in trained athletes at peak exercise, when PaO_2 can fall. Interestingly, in uncomplicated heart failure, PaO_2 also remains relatively unchanged throughout exercise.

In patients with COPD, exercise PaO_2 may remain unchanged, slightly improve, or fall. In interstitial and pulmonary vascular disease, an exercise-induced fall (often profound) of PaO_2 is more characteristic, and this fall progresses as exercise intensity increases. Exercise desaturation is a consistent finding in the presence of right-to-left intracardiac shunt, and the degree of desaturation is probably proportional to the magnitude of the shunt. The degree of exercise desaturation cannot be accurately predicted from resting data, such as diffusion capacity for carbon monoxide (D_LCO), and needs to be measured directly.

$PaCO_2$ and $P(a\text{-}ET)CO_2$ Difference

In normal subjects exercising at low to moderate intensity, $PaCO_2$ remains at or near the resting level. At higher intensities, $PaCO_2$ progressively falls, as a result of ventilatory compensation for lactic acidosis.

In COPD, $PaCO_2$ may rise slightly during exercise, even in patients in whom the resting value is normal. In interstitial lung disease, $PaCO_2$ is usually normal or slightly reduced.

At rest, the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) is lower by 2 to 3 mm/Hg than $PaCO_2$, so that the $P(a\text{-}_{ET})CO_2$ is positive. However, during exercise this difference becomes negative. $PaCO_2$ is an average value, measured across several breathing cycles. In contrast, end-tidal partial pressure is obtained during a late stage of a single expiration. During this phase of the breathing cycle, the alveolar partial pressure of CO_2 (P_ACO_2) rises progressively as a result of the CO_2-rich venous blood reaching the lung. As $\dot{V}CO_2$ rises during exercise, P_ACO_2 during expiration rises at a faster rate, allowing the $P_{ET}CO_2$ to surpass the mean $PaCO_2$. In situations in which units of high ventilation-perfusion ratio ($\dot{V}/\dot{Q}$) predominate in the lung (as in pulmonary vascular disease), CO_2 is not being added to the end-tidal gas at a fast rate, and $P(a\text{-}_{ET})CO_2$ remains positive. In the presence of right-to-left shunt, as venous CO_2 is diverted to the arterial side, even less CO_2 is being added to the alveolar gas, and therefore this difference is consistently positive. The magnitude of the difference is proportional to the fraction of shunted blood.

SYSTEMS LIMITING EXERCISE CAPACITY

The concept of the presence of a supporting system that limits exercise needs clarification. Obviously, the output of every system is restricted, and when a system fails to increase its output to a level required to perform a given task, this system restricts the ability to accomplish that task. However, at peak output of a supporting system (i.e., heart or lung), if the neural stimulus to an exercising muscle to generate force persists, the muscle can respond in two ways. It can either maintain (at least temporarily) the peak or close-to-peak output, or it can cease to generate force (i.e., electromechanical dissociation). If in response to inability of the heart to increase the O_2 flux the muscle ceases to generate force, then the heart obviously limits exercise capacity. However, if despite inadequate O_2 flux the muscle maintains (temporarily) maximal or nearly maximal contractions, then the heart does not directly limit exercise capacity. In this latter situation, the restricted function of the heart induces a deviation from homeostasis (i.e., lactic acidosis), which is perceived as a sensation that cannot be endured.

When a certain intensity of this sensation is reached, it leads to voluntary cessation of muscle contraction. In most situations encountered during clinical exercise testing, there is probably no global failure of force generation, but rather a distasteful sensation, resulting from stimuli such as the ventilatory load or acidosis. According to this description, exercise starts and probably ceases voluntarily. Therefore, the question about a system limiting exercise should be modified. The challenge is to identify the system(s) whose capacity is inferior relative to the load, therefore creating discomfort. To avoid such discomfort, the individual prefers to terminate the effort.

A striking demonstration of the role of intensity of symptoms as a determinant of exercise tolerance is provided by a comparison of responses to work between healthy subjects and patients with moderate to severe COPD. In both groups, the median intensity of dyspnea and of perceived leg exertion at peak exercise were similar (approximately 70% of the maximal intensity on the scales used). This intensity of sensation obviously occurred at a lower work intensity in the patients with COPD.

A partial list of disorders that may limit exercise capacity, including pathophysiology and discriminative findings, is shown in Table 4.

TABLE 4. *Pathophysiology and discriminating measurements of some disorders limiting exercise performance(reduced maximum $\dot{V}O_2$)*

Ventilatory Limitation of Exercise

Ventilatory limitation of exercise is defined on the basis of a limited exercise breathing reserve. The maximal output of the respiratory system is the maximal voluntary ventilation (MVV). It is assumed that the maximal output can be accurately measured or estimated. The 10-sec resting MVV maneuver is the favored method. The estimated MVV is obtained by multiplying the measured forced expiratory volume in 1 second (FEV_1) by a factor of between 35 and 40 (estimated MVV = $FEV_1 \times 40$). It is also assumed that this maximal resting ventilation volume is valid for exercise (a disputable assumption). The actual peak exercise ventilation ($\dot{V}_{Emax}$) is then subtracted from the MVV. The closer the $\dot{V}_{Emax}$ is to the MVV, the closer the subject is to the ventilatory limit. A difference of <15 L/min between MVV and $\dot{V}_{Emax}$ (MVV – $\dot{V}_{Emax}$), or a $\dot{V}_{Emax}$-to-MVV ratio of >80% ($\dot{V}_{Emax}$/MVV) has been considered diagnostic for the presence of ventilatory limitation to exercise (Fig. 12).

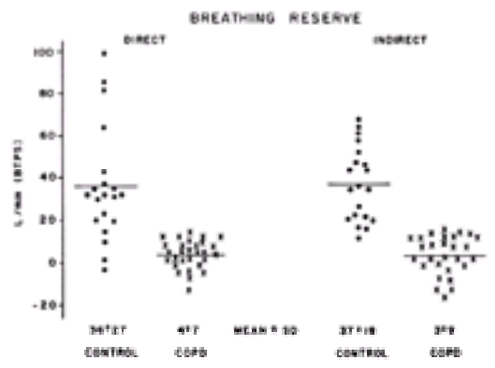

FIG. 12. Breathing reserve (MVV – $\dot{V}_{Emax}$) in patients with COPD and in control subjects. On the *left side,* the MVV was calculated from directly measured MVV. On the *right side,* the MVV was empirically estimated (MVV = $FEV_1 \times 40$). The estimated MVV is slightly higher. In the patients with COPD, the reserve is close to 0, indicating the proximity to the limit of ventilation. Interestingly, the calculated reserve in some patients has a negative value, indicating that breathing during exercise exceeds the resting MVV. (Modified with permission from Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R, eds. *Principles of Exercise Testing and Interpretation*. 2nd ed. Philadelphia: Lea & Febiger; 1994.)

The same principle of breathing reserve can be applied to every tidal breath during exercise (Fig. 13). If the flow rates during exercise approach (or surpass) the boundary of the maximal resting flow volume loop, then a subject is at or close to the ventilatory limit. If the ratio between peak exercise V_T and IC approaches 1 during exercise, this also represents ventilatory limitation (Fig. 3).

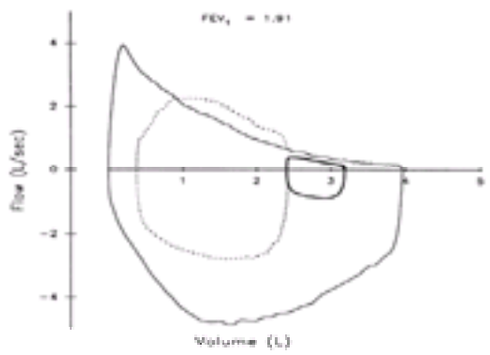

FIG. 13. Schematic representation of resting inspiratory and expiratory maximal flow volume loop (*outer solid line*), resting tidal breathing (*inner solid line*), and breathing at peak exercise (*dashed line*) in a patient with COPD. During exercise (but not at rest), the flow rates surpass the boundary of the resting maximal expiratory curve. In addition, the end-expiratory lung volume has increased about 0.75 L (left shift) during exercise relative to rest. This patient is probably close to or at his ventilatory limit during exercise. [Modified with permission from Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. In: Weisman IM, Zeballos RJ, eds. *Clinical Exercise Testing.* Philadelphia: WB Saunders; 1994 (*Clin Chest Med;* vol 15).]

Maximal breathing capacity during exercise, however, is not necessarily the same as the resting MVV. There is evidence, at least in COPD, that breathing capacity during exercise often exceeds the resting MVV (Fig. 12), and the calculated reserve may become (absurdly) a negative value. It is likely that in other diseases, such as certain neuromyopathies, and in heart failure, maximal breathing capacity during exercise may be lower than the resting level. Furthermore, when the ventilatory load is profound, subjects often stop exercise because of dyspnea, even before a true physiologic limit has been attained. Factors such as acidosis or hypoxemia enhance the sensation of dyspnea and exaggerate the cessation of effort at a ventilatory level that is lower relative to the resting MVV.

Cardiovascular Limitation to Exercise

In contrast to ventilatory limitation, determination of cardiovascular limitation on the basis of the concept of “cardiac exercise reserve” is difficult to achieve. Measurement (or estimation) of the maximal attainable cardiac output and/or the actual cardiac output at peak exercise is a demanding task. Using the HR reserve (predicted peak exercise HR minus actual peak exercise HR) as a substitute for cardiac output reserve is not practical. Peak HR is highly variable, and many patients with heart disease do not attain the age-predicted maximal HR, as shown in Fig. 10. Therefore, the diagnosis of cardiovascular limitation (in contrast to diagnosis of ventilatory limitation) is indirect and based on the presence of a combination of gas exchange and other criteria that indicate an exhausted O_2 transport/utilization capacity. These criteria are summarized in Table 5. The criteria are not specific for a distinctive type of cardiovascular dysfunction, but they reveal an exhausted O_2 transport capacity. Therefore, situations such as anemia, certain hemoglobinopathies, carbon monoxide poisoning, or even severe arterial hypoxia, produce similar gas exchange abnormalities.

(a)
Chest pain, claudication leg pain or syncope
Ischemic electrocardiographic changes or exercise-induced arrhythmia
Blood pressure fall
High respiratory exchange ratio (R ≥ 1), in the presence of low $\dot{V}O_2$max, especially when $\dot{V}O_2$-WR relationship becomes shallow
Low and flat O_2-pulse-WR relationship
Low HR reserve
Lack of ventilatory limitation (normal or high breathing reserve)
(b)
Tachycardia, steep HR-$\dot{V}O_2$ relationship
Low and relatively shallow O_2-pulse-WR relationship, with rise after exercise
Low $\Delta\dot{V}O_2/\Delta$WR ratio
Early lactic acidosis, low anaerobic threshold
Periodic breathing
Low $\dot{V}O_2$max while breathing reserve is normal or high
Abnormally high blood pressure or limited rise of blood pressure during exercise
Limited HR response

TABLE 5. *Indications that a cardiovascular (or O_2 flow) limitation to exercise (a) is present, or that a cardiovascular abnormality (b) is present*

Different Categories of Cardiovascular Processes Affecting Exercise Capacity

Although many of the gas exchange criteria listed in Table 5 are present in cardiovascular disease of any type (central cardiac, peripheral vascular, or pulmonary vascular disease), certain alterations are more likely to occur with specific abnormalities. For example, exercise desaturation and elevated dead space volume are more likely in pulmonary than in peripheral vascular disease. Elevated ventilatory equivalents are present in failure of the left side of the heart and in pulmonary vascular disease, but are less likely to occur in isolated peripheral vascular disease or anemia. These associated findings are useful to distinguish the specific segment within the cardiovascular circuit that limits exercise.

Clinical Symptoms at Peak Exercise

It is tempting to believe that the subjective complaint at peak exercise is specific for the system leading to exercise limitation. Chest pain, leg pain, fatigue, and lightheadness are suggestive of cardiovascular limitation, whereas shortness of breath suggests ventilatory limitation. However, these symptoms lack specificity and are of low diagnostic value, as the perception of stressful stimuli at peak exercise varies among individuals.

INDICATIONS FOR AN INTEGRATIVE CARDIORESPIRATORY EXERCISE TEST

Exercise study is done primarily to quantitate functional capacity and magnitude of gas exchange abnormalities, and to identify the supporting system(s) limiting exercise. A detailed list of situations in which exercise testing has been recommended, or is potentially valuable, is shown in Table 6. This list includes firmly established indications and also situations in which an exercise test is potentially beneficial, even if its role in these situations has not been systematically evaluated. For exercise to be a useful clinical tool, it should provide sensitive and specific criteria for the diagnosis of diseases, and these should have a high predictive value. However, more remains to be learned concerning the relative merit of various exercise-derived parameters and their combinations. For example, the predictive value of parameters such as low AT or low breathing reserve during exercise (how low is low?) for specific diagnoses (i.e., cardiac or ventilatory limitations) is difficult to ascertain. Because of the lack of widely accepted and easily obtainable measurements (a “gold standard”) for classifying patients according to whether they are limited by cardiac or ventilatory factors, a stringent sensitivity analysis cannot be applied to these exercise-derived gas exchange criteria.

TABLE 6. *Indications for the integrative cardiorespiratory exercise test, and situations in which the testis potentially valuable*

DATA ANALYSIS

Most commercial exercise systems provide options for data averaging and plotting. For general clinical use, eight breaths, or 15- to 30-second averaging, are acceptable. Despite averaging, however, the data are often obscured by oscillatory noise. Unusually deep or shallow breaths, especially when functional residual capacity (FRC) is oscillating or the breathing pattern is periodic, will predictably obscure the real data. Values are chosen from these averaged time plots or from the tabular report after ensuring that no spurious estimates are selected.

Values for $\dot{V}O_2$, HR, O_2 pulse, respiratory exchange ratio, $\dot{V}_E$, work rate, and other parameters are measured at peak exercise. Various parameters, such as the ventilatory equivalents and AT, are determined at certain submaximal exercise levels. The lowest value should preferably be reported for the ventilatory equivalents. Some parameters, such as V_D/V_T and blood gases, are recorded repeatedly during exercise, and others, such as $D\dot{V}O_2$/Dwork rate, are calculated from continuous exercise data. The obtained values are compared with the normal reference values, which should be applicable to the specific population studied, and the percentage deviations from normal means are calculated.

Framework for Interpretation of Cardiorespiratory Exercise Test

Algorithms for interpretation have been published (see Wasserman et al.).

The interpreter should be present during the test. Attention should be paid to patient cooperation—motivation, coordination, and maintenance of the pedaling rate—especially close to peak exercise. Data regarding the course of the test, including symptoms at peak exercise and a note on special events, should be available. Not rarely, a subject stops exercise for a trivial cause (e.g., dry oral mucosa), a situation that does not allow conclusions to be reached regarding the true physiologic maximum. To determine if the measurements are acceptable, it is prudent to allude to the measured metabolic values at rest and during unloaded cycling. Resting $\dot{V}O_2$ should be 200 to 300 mL/min, and R should be 0.8 to 0.9. At unloaded pedaling, $\dot{V}O_2$ roughly doubles (depending on the body weight). $\dot{V}O_2$ at any work rate can be estimated by the following equation:

$$\dot{V}O_2\ (\text{mL/min}) = 5.8 \times \text{weight (kg)} + 10.2 \times \text{work rate (W)} + 151 \quad \textbf{[6]}$$

If a value deviates markedly from the expected, the validity of the data should be questioned. After completion of the test, the following steps are required for data analysis:

1. Assess if exercise capacity, as determined by the $\dot{V}O_{2max}$, is normal. A normal $\dot{V}O_{2max}$ does not in itself indicate normality of either the cardiovascular or ventilatory system. Each or both systems (and others) may be abnormal and yet have sufficient reserve to allow for the age-predicted $\dot{V}O_{2max}$ to be attained. For previously trained subjects, attaining the age-predicted level may actually represent deterioration. Therefore, even if $\dot{V}O_{2max}$ is within the normal range, the cardiovascular and respiratory responses need to be carefully analyzed to prove the normality of the supporting systems.
2. If $\dot{V}O_{2max}$ is reduced, optimal patient cooperation and satisfactory performance of the study should first be ascertained. On occasion, the requested power output is not achieved because of slowing of the pedaling rate at high exercise intensity. This predictably leads to spurious lowering or flattening of the slope of physiologic functions, such as $\dot{V}O_2$ or O_2 pulse. (In this situation, as opposed to true flattening, both $\dot{V}CO_2$ and $\dot{V}O_2$ are level.) The next step is to determine which organ system is limiting exercise, is closer to its maximal capacity, or is inducing the intolerable symptom(s) that are leading to cessation of effort. At first, broad categories, such as respiratory, cardiovascular, metabolic, musculoskeletal, or motivational limitations, should be sought. If breathing reserve is reduced, ventilatory limitation is present. Cardiovascular limitation is suggested by a combination of findings reflecting reduced or exhausted O_2 transport capacity (Table 5). Among these findings, the normality or abnormality of the AT is fundamental. If one system is limiting exercise capacity, it does not mean that the other systems are normal, or even that the other systems are not concomitantly limiting. Cardiovascular and respiratory limitations often coexist at the same metabolic load. On the other hand, when one system is limiting, other supporting systems are not being challenged to their maximal capacity, so that their normality cannot always be ascertained.
3. If exercise capacity is reduced and the major limiting system can be found, the pathophysiology leading to the exercise limitation should be specified. This includes classification according to obstructive versus restrictive lung disease, myocardial (ischemic, valvular, or conductive) versus peripheral or pulmonary vascular disease, or metabolic causes, such as anemia or acidosis. Other contributing factors (especially those that are potentially treatable) to the limitation should be looked for, such as pharmacologic or metabolic causes. This goal is achieved by a detailed analysis of multiple subjective and objective characteristics of the responses, and their comparison with resting subjective and objective data.
4. It should be determined whether information obtained from the exercise test advances understanding of the patient's symptoms, functional capacity, essential diagnostic workup, and treatment plan. The required complementary diagnostic workup or modes of therapy should be arranged for the patient.

After implementation of this sequential analysis, most patients can be assigned either to a normal exercise tolerance group or to one of the broad diagnostic groups of abnormal exercise tolerance. A certain number of patients remain enigmatic. In our experience, a common dilemma is that of the patient with reduced exercise capacity who, by the cited criteria, is classified with the cardiovascular group but for whom static measurements (e.g., echocardiogram) show no resting cardiovascular abnormality. In some of these individuals, the cause is poor fitness. In others, we believe that heart function, even if normal at rest, may be abnormal during exercise. In some patients, especially hypertensive subjects, diastolic dysfunction may be an important cause of exercise limitation. Another problematic group is comprised of patients with known, often advanced, cardiac and/or ventilatory disease who stop exercise before breathing reserve is exhausted or before significant lactic acidosis (a true physiologic limit) is attained. Some of these patients may be restricted by peripheral causes, such as peripheral and/or respiratory muscle weakness.

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CHAPTER

11 Diagnostic Procedures Not Involving the Pleura

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SPUTUM

The examination of sputum for cytologic and microbiologic diagnoses continues to be useful despite well-documented shortcomings. Contamination of sputum with oral contents is problematic for the interpretation of bacteriologic findings. However, it is less of a problem for the diagnosis of endobronchial malignancy or infection with organisms, such as *Pneumocystis carinii,* that are not colonizers of the oropharyngeal mucosa.

For cytologic examination, sputum is best collected early in the morning. There are a number of methods for handling sputum before staining for cytologic diagnosis, but in general, the diagnostic yield of the cytologic examination of sputum ranges from 50%–90%. The diagnostic yield for sputum can be increased by examining multiple specimens; improved recovery rates have been demonstrated for up to five samples. The collection of sputum for examination has the advantage of being noninvasive, and adequate samples can be readily obtained on an outpatient basis with a minimal amount of patient instruction. However, obtaining a positive diagnosis from sputum does not always obviate the need for bronchoscopy. In the case of tumors other than the small-cell type, bronchoscopy is often essential for adequate staging when a patient is being considered for surgery. False-positive results from cytologic examination of the sputum are low, ranging from 1%–3% in most series, and tend to occur when acute inflammation is present.

Cytologic examination of sputum in noninfectious, benign disorders is rarely fruitful. Exceptions include the findings of lipid-laden macrophages, suggestive of aspiration, lipoid pneumonia, or fat embolism, or hemosiderin-laden macrophages, suggestive of intrapulmonary hemorrhage associated with Goodpasture's syndrome, idiopathic pulmonary hemorrhage, or diffuse alveolar hemorrhage as a complication of high-dose chemotherapy.

In infectious diseases, attention to detail in sputum collection is essential. The patient must be encouraged to produce secretions from the tracheobronchial tree rather than saliva. Sputum can be induced by inhalation of an aerosolized solution of saline solution, distilled water, propylene glycol, or sulfur dioxide. In any case, observation by trained personnel can greatly aid in the collection of an adequate specimen. Once the sputum specimen has been obtained from the patient, it should be delivered promptly to the microbiology laboratory if bacterial, mycotic, or viral diseases are suspected. Interpretation of sputum Gram stains requires attention to the clinical presentation. Amplification of DNA by polymerase chain reaction can extend the sensitivity of sputum analysis and has been applied in the detection of tuberculosis and infection with *Chlamydia trachomatis* and HIV-1. For the detection of mycobacteria, three fresh, early-morning specimens give the best yield. Because of the hardiness of these organisms, 24- to 72-hr collections of sputum are useful, especially when sputum production is scant and sputum induction is either not available or ineffective.

Cytologic examination of sputum for offending organisms is most clearly diagnostic when organisms are identified that portend significant lung disease in the clinical setting. Thus, isolation of *P. carinii* in patients with AIDS or *Aspergillus fumigatus* in patients with leukemia are indications for specific therapy. In hosts who are not immunocompromised, sputum findings can be diagnostic of pneumonia when the Gram stain demonstrates predominance of a single organism or cultures yield a pure growth of a pathogen. The utility of sputum cytology for diagnosis of pneumonia is maximized by the use of special stains, such as the Grocott-Gomori silver stain for fungi or *P. carinii,* and the use of immunologic and molecular biologic techniques, such as the direct fluorescent antibody stain or polymerase chain reaction for *Legionella.*

TRANSTRACHEAL ASPIRATION

A major limitation of examination of sputum in infectious diseases is contamination by the oropharyngeal contents. Transtracheal aspiration was introduced as a method for bypassing the oropharynx during collection of tracheobronchial secretions. In this technique, the cricothyroid membrane and overlying skin are anesthetized and a large-bore (14-gauge) needle is passed into the trachea with gentle aspiration of air confirming proper placement. A plastic catheter is threaded caudally, and once it is in place, the needle is withdrawn. A small amount of saline solution is infused through the catheter, causing cough, and the secretions that are produced are aspirated into the catheter. False-negative results in transtracheal aspiration are rare, estimated to be <1%. However, false-positive results, resulting from colonization of the lower respiratory tract in association with chronic bronchitis, cigarette smoking, and chronic diseases, are not uncommon, with estimates of a false-positive rate up to 27%. Even in a young, healthy population, Gram stain of a transtracheal aspirate offers no advantage over sputum Gram stain in the initial management of acute pneumonia. Because of these limitations and rare but severe complications, which include mediastinal and subcutaneous emphysema, hypoxemia with complicating cardiac arrhythmias, and hemorrhage (rarely associated with fatality), transtracheal aspiration is not as widely performed as previously. The development of other diagnostic procedures, including bronchoalveolar lavage (BAL), protected specimen brush catheters, and, when more invasive procedures are clinically justified, transthoracic needle aspiration or video-assisted thorascopic lung biopsy, has provided alternatives to transtracheal aspiration that are safer or yield more useful information.

FLEXIBLE FIBEROPTIC BRONCHOSCOPY

Flexible fiberoptic bronchoscopy was introduced by Dr. Ikeda in the late 1960s. By the mid-1970s, the flexible fiberoptic bronchoscope was widely utilized in the United States, and its clinical applications have continued to expand even as limitations of flexible fiberoptic bronchoscopy have become more fully appreciated.

Flexible fiberoptic bronchoscopy can be readily performed in sedated, spontaneously breathing patients following anesthesia of the upper airway mucosa with topically

applied agents. The tip of the bronchoscope can be passed through the nose or mouth with the patient sitting or supine. Alternatively, bronchoscopy can be performed in previously intubated patients, or intubation can be performed over the bronchoscope. In intubated patients, a size 7.5-French or larger endotracheal tube assures adequate air flow. Instillation of lidocaine through the bronchoscope effectively suppresses cough. Cough and bronchospasm are minimized by pretreatment with inhaled b-agonists. Atropine is also routinely administered before flexible fiberoptic bronchoscopy to diminish airway secretions and prevent vasovagal reactions. To help ensure safety, patients should have intravenous access established before bronchoscopy. Vital signs should be checked on a regular schedule, cardiac rhythm monitored via electrocardiography, and oxygen saturation monitored continuously.

Flexible fiberoptic bronchoscopy is relatively contraindicated in patients with uncorrected coagulopathies, severe airway obstruction, hypoxia or hypercarbia, or cardiac arrhythmias. It is also contraindicated in patients who are uncooperative. Complications of flexible fiberoptic bronchoscopy are rare but potentially include drug reactions, cardiac arrhythmia, hemorrhage, pneumothorax, pneumonia, and exacerbation of airway diseases.

Flexible fiberoptic bronchoscopy has proved to be an invaluable diagnostic technique for endobronchial lesions. The bronchoscope can be used to visualize the airways directly down to the fourth or fifth generation, allowing for precise localization of endobronchial lesions and visual identification of neoplasms, aspirated foreign bodies, and sites of trauma to the airways, such as tracheal lesions caused by prolonged endotracheal intubation or bronchial wall erosions caused by broncholiths.

In the evaluation of hemoptysis, flexible fiberoptic bronchoscopy has been used to localize anatomic sites of bleeding from peripheral lesions and to visualize directly bleeding from lesions in the central airways.

Direct visualization of the airways by flexible fiberoptic bronchoscopy enables identification of characteristic changes associated with acute inflammation, such as mucosal edema, erythema, friability, and secretion of mucus; thus, it can be used to confirm diagnoses associated with acute inflammation, such as pneumonia or acute bronchitis. Likewise, changes typical of chronic bronchitis may be identified, including hyperemia, thinning and striations of the mucosa, and mucosal pits that represent orifices of enlarged submucosal glands.

Direct visualization of endobronchial lesions is very useful for the staging of lung cancer. The extension of a tumor mass into the trachea, onto the carina or within 2 cm of the carina, implies that the tumor cannot be resected without special techniques to reconstruct the trachea.

Flexible fiberoptic bronchoscopy can also be used for follow-up of chemotherapy or radiation therapy of endobronchial lesions. The ability to sample pulmonary lesions, both endobronchial and extrabronchial, via the flexible fiberoptic bronchoscope greatly extends its clinical utility.

ENDOBRONCHIAL BIOPSY

Endobronchial biopsies are performed with forceps introduced through the suction port of a flexible fiberoptic bronchoscope. A number of instruments can be used for endobronchial biopsy. Biopsy forceps are available in various configurations, all of which can provide adequate samples. Preference for forceps configuration is primarily a function of operator training and experience. If the surface of the endobronchial lesion is smooth and firm, the biopsy forceps may, at times, slide off the lesion. This can be prevented by using a “spear” forceps, in which a small knife emerges from the base of the forceps and is encompassed by the forceps. This knife can be plunged into the tumor, anchoring the forceps and allowing biopsy to proceed. If the endobronchial lesion involves an airway wall parallel to the orientation of the bronchoscope, there may not be an adequate surface for the forceps to grab and hold. In this case, a curette designed to flex to 90° can be used to scrape the lesion to obtain a sample for cytologic examination.

The partial occlusion of the suctioning channel by the introduction of the biopsy forceps may limit suctioning of airway secretions, thereby compromising the field of view and increasing the technical difficulty of the biopsy. This problem can be avoided by using a smaller-sized forceps and a larger-sized suctioning channel, or by employing a bronchoscope with two suctioning channels.

Endobronchial biopsies are generally performed following the instillation of lidocaine directly onto the mucosal surface to be sampled. The procedure is typically complicated by small (<5 mL) amounts of bleeding, but with highly vascular lesions, especially endobronchial carcinoid tumors, the resulting bleeding can be massive and life-threatening. Highly vascular endobronchial carcinoid tumors can be recognized by their cherry-red appearance. A flexible fiberoptic bronchoscope should not be used to obtain specimens from endobronchial lesions with this presentation; rather, such lesions should be approached with a rigid bronchoscope and appropriate surgical support.

Endobronchial biopsies have been associated with pneumothorax. However, the incidence of pneumothorax following endobronchial biopsy is exceedingly low and does not justify routine chest roentgenograms following the procedure.

The greatest utility of endobronchial biopsy is in the diagnosis of cancer. Typically, endobronchial malignancies represent bronchogenic carcinoma. However, endobronchial metastases can occur, most frequently from carcinoma of the breast, malignant melanoma, and tumors of the kidney or colon.

Cytologic brushes provide another tool for collection of endobronchial material. Vigorous brushing of the mucosal surface with a stiff brush exfoliates cells that are ideal for cytologic examination. The cytologic brush samples a larger surface area than an endobronchial biopsy forceps. The brush can be used to obtain samples from airways distal to the visual field of the bronchoscope, so that the complications associated with transbronchial biopsy can be avoided (see below). Hemorrhage is rare, but brushing with cytologic brushes is routinely associated with more bleeding than is obtaining samples with a forceps alone. This is especially true if the mucosa is friable, as is often the case when airways inflammation complicates an endobronchial lesion.

The diagnostic yield of direct forceps biopsy of endobronchial lesions is very high. Reported diagnostic yields range from 70%–100%, with most investigators reporting yields of up to 95%. Lesions associated with false-negative results include large necrotic masses from which nondiagnostic, necrotic material is obtained and lesions that are physically difficult to sample because of their shape, surface characteristics, or location.

Brushings also have a high diagnostic yield of up to 93% for directly visualized lesions. However, they do not appear to add significantly to the diagnostic yield of endobronchial forceps biopsy if the lesion is readily visualized. Similarly, cytologic examination of washings gathered through the bronchoscope during the course of the bronchoscopy or expectorated sputum gathered after bronchoscopy has been utilized, but neither of these specimens adds to the diagnostic yield of forceps biopsy.

TRANSBRONCHIAL BIOPSY

Transbronchial biopsy extends the utility of flexible fiberoptic bronchoscopy to include sampling of peripheral masses and pulmonary parenchyma suspected of being diseased or infected. Transbronchial biopsies are performed by extending the biopsy forceps beyond the visual range of the bronchoscope. Patient cooperation is essential. The forceps are opened during deep inhalation and closed during exhalation. This enfolds lung parenchyma into the forceps, increasing the amount of lung parenchyma that is sampled.

The procedure is generally performed under biplanar fluoroscopy to localize sampling of discrete lesions accurately and to prevent extreme peripheral placement of the forceps, which may result in perforation of the lung pleura. Unintentional biopsy of small muscular arteries can lead to bleeding. Instillation of 1 mL of 1:20,000 epinephrine before performing the biopsy and keeping the bronchoscope wedged into the airway at the site of sampling generally controls the bleeding. Thus, it is imperative that the bronchoscope be maintained in a wedged position until hemostasis is ensured. Transbronchial biopsies are also associated with an incidence of pneumothorax as high as 5%. Most of these cases are not serious, but occasionally placement of a chest tube is required.

The diagnostic yield of transbronchial biopsy varies according to the character of the lung lesion being assessed. For peripheral masses, diagnostic yields range from 30%–90%, with a mean of about 60%. Yields have been improved by the use of bronchography to plan the bronchoscopic approach to the peripheral lesion and by the use of bedside cytology with repeated sampling after the procedure. In interstitial lung diseases, transbronchial biopsy can validate clinical diagnoses of sarcoidosis, pulmonary alveolar proteinosis, eosinophilic granuloma, hypersensitivity pneumonitis, and lymphangioleiomyomatosis. Transbronchial biopsies can be diagnostic in each of these diseases because of their distinctive pathologic features. In contrast, transbronchial biopsy is not felt to be diagnostic for idiopathic pulmonary fibrosis or other interstitial pneumonitides. The diagnostic yield for interstitial lung disease has been most extensively studied for sarcoidosis. Sampling errors are minimized by repeated biopsies; for sarcoidosis, four biopsies have been found to produce up to a 90% yield.

Transbronchial biopsy has also been used for the diagnosis of infectious diseases. In most infectious diseases, sampling is best done by BAL (see below), but there are exceptions. The yield of BAL is low in fungal infections, particularly invasive aspergillosis, and such cases should be approached with transbronchial biopsy or transthoracic needle aspiration if clinically feasible. Prophylactic treatment for *P. carinii* in patients with AIDS leads to lower yields with BAL in the diagnosis of *P. carinii*

pneumonia. Yields are increased from 60%–80% by the addition of transbronchial biopsy.

TRANSBRONCHIAL NEEDLE ASPIRATION

A variety of needles have been developed for needle aspiration of lesions via the flexible fiberoptic bronchoscope. The choice depends on operator preference and biopsy site. Steel needles are preferred for transbronchial and transtracheal biopsies, whereas flexible plastic needles are better suited for apical biopsies. Needle aspiration is especially useful for the diagnosis of lesions that lie beyond the visual field of the bronchoscope. The technique has been used to sample paratracheal nodes, mediastinal nodes (especially subcarinal nodes), submucosal lesions, extrabronchial lesions, and peripheral masses. Transbronchial needle aspiration can be used to approach peripheral lesions that are, because of airway anatomy, inaccessible to the transbronchial biopsy forceps.

To sample areas contiguous to the large airways, the needle is advanced under direct visualization to the suspected area and pushed through the airway wall, and suction is then applied to aspirate a specimen for cytologic examination. Following withdrawal of the needle from the bronchoscope, a small amount of saline solution is used to flush the specimen from the needle. To sample peripheral lesions, the needle is advanced under fluoroscopic guidance and plunged transbronchially directly into the lesion. Complications resulting from needle aspiration, which are rare, include pneumothorax and pneumomediastinum with reported rates of <1%.

The diagnostic yield for aspiration of paratracheal and hilar adenopathy, as visualized on chest roentgenograms, is quite high, with a sensitivity of 50% and specificity of 96% in one study. Investigations have suggested that the yield for needle aspiration can be improved by the use of computed tomographic (CT) guidance. The yield for transbronchial needle aspiration of peripheral masses depends on the size of the lesion. The recovery rate is 33% for lesions <2 cm in diameter and 80% for lesions ^{3}2 cm in diameter. Transbronchial needle aspiration may compliment transbronchial biopsy. In cases in which the transbronchial forceps cannot reach the lesion because of anatomic distortion of the airways, a transbronchial needle can be used to penetrate directly into the lesion through the distorted airway. Transbronchial needle aspiration has not been associated with significant complications.

BRONCHOALVEOLAR LAVAGE

Technique

The lower respiratory tract can also be sampled with the technique of BAL. In this method, a sterile isotonic solution is infused through the biopsy port of the bronchoscope. This fluid fills the intraluminal space of the conducting airways and the alveoli, and it can then be recovered by aspiration. Because the fluid mixes with the intraluminal contents, the resulting lavage fluid effectively samples the intraluminal space of the lower respiratory tract.

A large number of variations of the technique have been developed. In general, however, the procedure is done after wedging the bronchoscope in a segmental or subsegmental bronchus. The wedged position allows the lavage fluid to be infused distally in a controlled manner into a single region of the lung, and more or less prevents the fluid from spreading proximally into other lung regions. The fluid most commonly used is sterile normal saline solution. Warming the fluid to body temperature is felt to reduce cough.

The fluid initially infused reaches the intraluminal space of the more proximal conducting airways more effectively than it reaches the more distal alveolar spaces. As a result, the use of small volumes of fluid can provide a sample enriched for bronchial contents. To have an adequate sampling of alveolar contents, a total volume of at least 100 mL is generally recommended. The fluid is infused in aliquots varying in volume from 20 to 60 mL. Reduced volumes have been successfully used in children. Most bronchoscopists aspirate the fluid immediately after infusion, but some investigators allow the fluid to remain for a period of dwell time. The procedure can be repeated in several subsegments if desired.

Complications

Apart from the procedure of flexible fiberoptic bronchoscopy, BAL itself has some associated risks. The most common complication is fever. The syndrome of post-BAL fever typically develops 4 to 6 hours after the procedure, characterized by the sudden onset of rigors, fever, and malaise. Symptoms generally respond promptly to intravenous meperidine (Demerol) and often to oral acetaminophen. The syndrome is self-limited and generally resolves within 24 hrs. Fever after bronchoscopy is not thought to be caused by infection, but rather by the release of endogenous pyrogens. The occurrence of this complication appears to increase with the volume of fluid used. With a 300-mL lavage, the frequency is felt to be 20%–30%.

Infiltrates on chest roentgenogram are also common, occurring in the majority of individuals studied immediately after the procedure. These infiltrates, which presumably represent retained fluid and atelectasis, generally spontaneously resolve within 24 hrs. True infections may also occur following BAL with a frequency of 1/1000 or less. Patients generally have fever, cough, and often pleuritic chest pain 1 to 3 days following the bronchoscopy. Bleeding, pneumothorax, and bronchospasm have been reported but are rare.

Transient declines in both vital capacity and FEV_1 (forced expiratory volume in 1 second) are frequent, and these can be associated with hypoxemia. They generally are limited to about 10% declines in predicted values. Interestingly, BAL in patients with mild asthma appears to be associated with no statistically significant increased risk for decline in lung function in comparison with normal controls, although bronchospasm has been reported as a complication. These transient declines in lung function are not clinically significant in individuals with normal lung function. However, in individuals with severely compromised lung function, BAL can lead to retention of carbon dioxide or precipitate respiratory failure. Should such individuals require BAL, however, the procedure can still be performed. It is recommended that before BAL is performed, such patients undergo intubation with or without the initiation of mechanical ventilation to support ventilation and gas exchange.

Processing Bronchoalveolar Lavage Specimens

The techniques for handling and processing BAL fluids are varied. It is important that each center have a standardized technique to allow valid interpretation of results from lavage performed by different personnel. Close cooperation between clinicians and pathologists is obviously required.

Indications for Bronchoalveolar Lavage

BAL is often the diagnostic modality of choice in evaluating immunocompromised individuals with suspected pneumonia. Because the lavage fluid effectively samples the peripheral intraluminal space, peripheral intraluminal infections can be diagnosed with a high degree of reliability. For example, the diagnostic yield for *P. carinii* pneumonia in untreated patients is felt to be >95%. Viral infections can also be diagnosed reliably. For cytomegalovirus and herpesvirus, pathognomonic cytopathic changes can be recognized cytologically. The sensitivity for detecting viral material can be increased with the use of special techniques, including monoclonal antibodies, cDNA probes, and the polymerase chain reaction. Samples obtained by BAL can also be cultured for viruses, and the cultures can be analyzed using a variety of diagnostic techniques. Monoclonal antibodies can be used to assist in the diagnosis of other infections, including *Legionella* infection, but the yield is greater when this technique is combined with culture methods. The recent introduction of the analysis of BAL fluid with the polymerase chain reaction provides a very sensitive method for the detection of *Legionella, Mycobacterium, Pneumocystis, Chlamydia, Mycoplasma* organisms, and for an increasing number of viruses.

BAL fluid can also be used for the diagnosis of fungal infection, both cytologically and by culture. Because some fungi, particularly *Mucor-Absidia* and to some extent *Aspergillus,* preferentially invade the vascular spaces, the intraluminal sampling technique of BAL may not be as effective. For this reason, the diagnostic yield of BAL in cases of invasive aspergillosis may only be 50%. Negative results, therefore, must be interpreted with caution.

The sensitivity of BAL for the detection of some micro-organisms that are not inevitably associated with disease (e.g., cytomegalovirus and *candida*) creates the problem of distinguishing between infection and colonization. Asymptomatic colonization may precede clinically significant infection in some situations. Thus, although BAL can provide diagnostic information, this information must be used in an appropriate clinical context.

BAL can also provide diagnostic information in individuals who are not immunosuppressed but are suspected of having infections. Not only can unusual organisms be detected, but quantitative cultures can help to confirm the presence of pneumonia when other causes of lower respiratory tract abnormalities are also present. The presence of $>10^5$ organisms on a quantitative BAL culture has a specificity approaching 100% for the diagnosis of bacterial pneumonia. This technique also permits the identification of multiple pathogens, which appear quite frequently in hospital-acquired cases of pneumonia. Quantitative cultures combined with protected BAL, in which a special catheter is used, or with culture of only the last aliquot of fluid infused during BAL appears to have improved specificity. In direct comparisons, the specificity and sensitivity of quantitative BAL appear to be similar to those of the more complex protected brush and protected BAL procedures.

Cytologic examination of BAL fluid for pulmonary malignancy can be performed. Primary and metastatic solid tumors and hematologic malignancies can be readily detected by standard and specialized cytologic techniques. BAL appears to be particularly effective in the diagnosis of lymphangitic carcinomatosis. This is probably because in such cases the tumor involves not only the pulmonary interstitium but also the intraluminal spaces. The diagnostic yield for primary lung cancer by BAL

depends on several factors. Most importantly, the appropriate segment must be washed. Diagnostic yields >50% have been reported. In one large series, BAL was felt to have a superior diagnostic yield when compared with transbronchial biopsy for the diagnosis of peripheral lesions not visualized at bronchoscopy. BAL has also been suggested as one means to follow the effectiveness of chemotherapeutic intervention in patients with lung cancer.

Both routine and special cytologic techniques can be used to diagnose pulmonary malignancies in material obtained by BAL. For example, monoclonal antibodies for specific tumor-associated antigens may be helpful in detecting rare cells and determining the type of malignancy. When routine cytologic analysis is used, however, it is essential that material be interpreted by a skilled cytologist and that appropriate clinical correlations be made. In a number of nonmalignant conditions, abnormal cells can be observed that are confused easily with cancer. Infection, cytotoxic therapy, and severe inflammation may all be associated with a range of atypical cells having an appearance that can vary from mildly metaplastic to closely resembling malignancy. Thus, the diagnosis of pulmonary malignancy based on cytologic material obtained by BAL should be made only in an appropriate clinical setting.

It is possible to use BAL to assess inflammatory processes in the lower respiratory tract, such as interstitial lung diseases and lower airways diseases. The BAL findings are not pathognomonic of any particular interstitial disease, but they may be suggestive. For example, increased numbers of neutrophils in BAL fluid are often seen in idiopathic pulmonary fibrosis, whereas increased numbers of T-helper cells are found in pulmonary sarcoidosis and of T-suppressor cells in hypersensitivity pneumonitis. Thus, the analysis of inflammatory cells obtained by BAL, although not specific, can often be helpful in suggesting a diagnosis.

The intensity of alveolitis, as suggested by BAL, may be helpful in making clinical decisions, such as when to proceed to definitive biopsy procedures or when to initiate or change therapy.

Eosinophilia and increased numbers of mast cells, together with increased levels of eosinophil- and mast cell-derived mediators, are commonly found in the airways of patients with asthma. The presence of these cells and their mediators correlates with hyperresponsiveness and clinical symptoms. Increased airways neutrophilia has been reported by some investigators in asthma and has also been reported in chronic bronchitis. Although patients with airways disease have been studied by BAL, at present this technique should be regarded primarily as a research procedure rather than as a clinical tool.

BAL has also been used to obtain material for the analysis of a large number of chemical components present in the lower respiratory tract. These measurements are mainly research activities without current clinical use.

SCALENE NODE BIOPSY

Pulmonary malignancies as well as inflammatory diseases of the lung spread in a somewhat predictable pattern, based on the lymphatic drainage system. The lymphatics of all the lobes of the right lung drain initially into the lymphatic sump of Borrie, a collection of intrapulmonary lymph nodes lying between the upper lobe bronchus and the bronchus medius. From there, the upper lobe drainage enters the lower paratracheal area in the region of the azygos vein. The middle and lower lobes drain to the subcarinal, pulmonary ligament, and paraesophageal nodes. From these locations, all lobes of the right lung drain to the right scalene area. Both lobes of the left lung drain to the lymphatic sump between the upper and lower lobe bronchi and hence to the subcarinal, pulmonary ligament, and paraesophageal nodes. The upper lobe also drains to nodes in the aortopulmonary window, left paratracheal area, and anterior mediastinum. Approximately 25% of left lower lobe drainage crosses over to the right side, whereas 90% of the left upper lobe drainage stays on the left, eventually reaching the left scalene nodes. However, it is important to remember that these drainage patterns are not absolute, and crossover metastases from either side may occur, probably as a result of obstructed lymphatics.

The procedure of scalene node biopsy is well established and is almost always carried out with local anesthesia. A 5-cm transverse incision is made over the lateral border of the sternocleidomastoid muscle, 2 cm superior and parallel to the clavicle. The fat pad containing lymph nodes, located in the space posterior to the sternocleidomastoid muscle and anterior to the anterior scalene muscle, is removed for microscopic study. The most important structures encountered are the subclavian vein inferiorly, the internal jugular vein and carotid artery medially, and the phrenic nerve lying on the anterior surface of the anterior scalene muscle and on the left side the thoracic duct. The operating time for this procedure is short, and postoperative patient discomfort is minimal.

In patients with lung cancer, biopsy of palpable scalene nodes has a positive diagnostic rate of about 80%. In patients with lung cancer but nonpalpable scalene nodes, the positive diagnostic rate is only about 20%. Scalene node biopsy has been used in nonmalignant disease as well. The biopsy of nonpalpable scalene nodes may offer a positive diagnosis in as many as 80% of patients with sarcoidosis and other granulomatous diseases.

Complications of scalene node biopsy include hematoma, seroma, pneumothorax, infection, air embolism, lymph fistula, hoarseness, phrenic nerve palsy, chylothorax, or a Horner's syndrome. These complications are rare, with a total prevalence of all complications of only 1%–2% and a mortality rate of 0.1%. Prior radiation therapy incorporating the scalene nodes in the field of radiation is a relative contraindication, as the resulting fibrosis complicates surgical dissection and healing and may lower the likelihood of a positive biopsy result.

For suspected malignant intrathoracic disease, most authors would recommend that scalene node biopsy be performed first whenever palpable nodes are present. Scalene nodes positive for malignancy are N3 nodes, indicating a stage of IIIB for lung cancer, considered by most to be beyond curative resection. Routine biopsy of nonpalpable scalene nodes in patients with lung cancer has a low diagnostic yield, especially with peripheral lesions and tumors <3 cm in diameter. Although the matter is controversial, most surgeons would forego scalene node biopsy in these patients and proceed with staging using radiologic imaging and mediastinoscopy when indicated. Used judiciously, scalene node biopsy is a simple, valuable procedure that may obviate the need for more invasive staging or even thoracotomy.

MEDIASTINOSCOPY

Technique and Complications

Mediastinoscopy is a surgical procedure performed under general anesthesia with the neck hyperextended and the head turned to the left. A short (4-cm) transverse incision is made centered just above the suprasternal notch. Once the pretracheal fascia is reached, blunt finger dissection is used to open the relatively bloodless plane of loose areolar tissue just anterior to the trachea. The rigid mediastinoscope is introduced into this plane and is advanced down as far as the carina. In this way, right and left paratracheal nodes, anterior subcarinal nodes, and some proximal right hilar nodes may be visualized and sampled. Access to the left hilum is limited by the aortic arch. In performing this procedure, the surgeon has only monocular vision without depth perception. Expertise is essential, because the pretracheal space entered by the mediastinoscope contains a number of vital structures, including the aortic arch, superior vena cava, brachiocephalic artery, and left atrium. This procedure is relatively brief, and patients require only an overnight hospital stay. Mediastinoscopy requires pliable tissue planes free of adhesions to allow blunt dissection, so that prior mediastinoscopy, other mediastinal surgery, or mediastinal radiation therapy are relative contraindications to this procedure. Prior open heart surgery may fix the mediastinal structures and make mediastinoscopy much more difficult. Superior vena caval obstruction usually causes mediastinal venous engorgement and elevates the risk for bleeding, but it is not an absolute contraindication for mediastinoscopy.

Because the nodes draining the left upper and lower lobes may drain to the subaortic nodes or the anterior mediastinum, they may not be readily accessible to standard cervical mediastinoscopy. To approach these nodes, an extended cervical mediastinoscopy has been described. With this technique, the anterior mediastinum can also be explored through the same neck incision, but this method has not become popular because of its perceived difficulty and higher risks.

Despite the vital structures surrounding the area explored with the mediastinoscope and the limited surgical field, complications from standard cervical mediastinoscopy are infrequent in the hands of an experienced surgeon. The principle risk is hemorrhage from laceration or inadvertent sampling of a blood vessel. Pneumothorax, recurrent laryngeal nerve paralysis, tracheal injury, or wound infection also may occur. The prevalence of all complications is low (1.7%–2.3%), and the rate of emergency thoracotomies required to control serious complications is 0.3%. In two recent clinical series with a combined total of 2259 patients undergoing mediastinoscopy, there were no deaths. A mortality of £1% has been reported in most series.

Indications for Cervical Mediastinoscopy

Cervical mediastinoscopy is primarily indicated to evaluate the status of mediastinal lymph nodes in patients with potentially resectable lung cancer who do not have palpable supraclavicular nodes. The technique also provides a tissue diagnosis for any patient whose primary lesion is not accessible or who is not a candidate for resection because of poor pulmonary function or other medical reasons. The diagnostic yield depends largely on patient selection. When routine mediastinoscopy is performed in all patients with presumed operable carcinoma of the lung, 27%–30% of patients have metastatic disease in the excised nodes. The highest yields have been seen in patients with tumors of the right lung, larger central tumors, and small-cell tumors or adenocarcinomas.

An area of considerable interest has been the role of CT of the chest in staging mediastinal metastases in patients with lung carcinoma. Based on studies of CT scans in normal patients and cadavers, nodes up to 1 cm in diameter are generally considered to be normal. Nodes with a diameter of ³1.5 cm are abnormal, and nodes between 1 and 1.5 cm in diameter are indeterminate or suspect. With these criteria, the sensitivity of CT ranges from as low as 61% up to 95%, and specificity from

50%–94%. Magnetic resonance imaging of the chest has not offered any advantages over CT in the assessment of mediastinal nodes.

Recent studies including exhaustive lymph node dissections and meticulous correlation with CT findings have demonstrated that the sensitivity of CT may not be as high as previously thought. Mediastinal metastases were found involving lymph nodes of <1 cm in diameter in as many as 33% of patients. These nodes would have been classified as normal using the CT criterion for normal size of £1 cm in diameter. Nevertheless, patients with mediastinal micrometastases or minimal N2 disease discovered at the time of thoracotomy have 5-year survival rates of as much as 34% after resection of the tumor and mediastinal metastases followed by postoperative radiation therapy.

CT may be useful in screening for macroscopic metastatic disease indicated by enlarged nodes (>15 mm) or indeterminate nodes (10 to 15 mm) that need to be verified by mediastinoscopy. If CT shows no mediastinal abnormalities and especially if there is a small peripheral lesion, then mediastinoscopy can be bypassed as a surgical staging procedure, and the surgeon can proceed directly to thoracotomy. At thoracotomy, a thorough mediastinal node dissection must be performed in all patients with negative findings at mediastinoscopy or in patients in whom this procedure has not been performed, so as to make an accurate determination of the surgical stage. Meticulous sampling of mediastinal nodes at thoracotomy is also important in all patients with tumors of the left lung, as metastases to some nodal groups may be inaccessible by mediastinoscopy. Thus, a policy of routine mediastinoscopy for all patients is not a reasonable, cost-effective approach in lung cancer.

Mediastinoscopy is also indicated to verify the diagnosis of nonpulmonary malignancies, such as lymphoma, and of granulomatous diseases, such as sarcoidosis, histoplasmosis, and occasionally tuberculosis. The diagnostic yield is high, particularly with CT evidence of mediastinal or hilar adenopathy. Mediastinoscopy is practically 100% accurate in the diagnosis of sarcoidosis in the presence of appropriate CT abnormalities and has become the preferred invasive diagnostic procedure with this disease whenever transbronchoscopic biopsy is unsuccessful and other, more accessible sites are not involved.

Parasternal Anterior Mediastinotomy

Anterior mediastinotomy requires general anesthesia with endotracheal intubation. A short, transverse (“hockey stick”) incision is made over the second or third costal cartilage just adjacent to the sternum on the appropriate side. A segment of cartilage is removed, and through the bed of the resected cartilage an extrapleural plane is bluntly developed toward the hilum of the lung. Use of a headlight and careful retraction allows evaluation of nodes in the anterior mediastinum lying in front of the great vessels, right paratracheal nodes, subaortic nodes on the left, and tracheobronchial angle nodes. Vigorous retraction occasionally permits sampling of paraesophageal nodes, posterior-inferior tracheobronchial nodes, or posterior subcarinal nodes. Entry into the pleural cavity (often done inadvertently) permits direct exposure of hilar masses for biopsy. When the pleura has been entered, a small chest tube is inserted through a separate wound and is left on suction for a short time after wound closure and recovery. Depending on the number of frozen sections obtained and the extent of dissection necessary, most procedures can be completed in a reasonably brief period of time. The in-hospital recovery time is generally 1 to 2 days, depending on whether a chest tube is used or not. Postoperative discomfort is mild but usually greater than that experienced after mediastinoscopy.

Few complications occur with anterior mediastinotomy, although it is more invasive and has a slightly higher complication rate than mediastinoscopy. Bleeding is usually controlled by pressure or suture; if bleeding is severe, the incision can be extended into an anterior thoracotomy for repair of the site of bleeding. Wound infection, pneumothorax from unsuspected pleural entry, pleural effusion, pneumonia, and phrenic nerve damage also have been described. The total rate of all complications is reported at 6.7%–9%, and the mortality rate is 1% or less. Relative contraindications to this procedure include a history of prior median sternotomy or radiation therapy, as adhesions and lack of pliable tissue planes make dissection hazardous through the small mediastinotomy incision.

The indications for anterior mediastinotomy are generally the same as for mediastinoscopy. In patients with nonpalpable supraclavicular nodes who have suspected pulmonary malignancies and evidence of mediastinal adenopathy, anterior mediastinotomy is a good staging alternative to mediastinoscopy. It permits access to nodal areas such as the anterior mediastinum and aortopulmonary window, which are common sites of left lung metastases but are inaccessible by mediastinoscopy. Mediastinotomy is preferred in patients with the superior vena caval syndrome, prior mediastinal radiation therapy, or prior mediastinoscopy. In cases of nonpulmonary neoplasms and inflammatory diseases, mediastinotomy offers the potential for biopsy of enlarged mediastinal nodes seen on CT, and also allows an open lung biopsy to be performed through the same incision should the mediastinal nodes prove nondiagnostic.

Some surgeons prefer anterior mediastinotomy because it provides an open, more accessible surgical field, compared with the limited field provided by mediastinoscopy. However, mediastinoscopy is associated with less morbidity and mortality, a shorter operating time, and less postoperative pain than anterior mediastinotomy. Mediastinotomy and mediastinoscopy can be viewed as complementary rather than competing procedures that have equivalent results in properly selected patients. The procedure to be used is best chosen based on CT and individual patient evaluation, with the goals of minimizing morbidity and maximizing the likelihood of a diagnosis.

PERCUTANEOUS TRANSTHORACIC NEEDLE BIOPSY

Transthoracic needle aspiration or biopsy has several indications, which include the following: (1) diagnosis of parenchymal lung nodules, particularly peripheral lesions, whether solitary or multiple; (2) classification and staging of suspected pulmonary or mediastinal metastasis; (3) diagnosis of suspected infectious diseases (nodules or infiltrates); (4) diagnosis of mediastinal, hilar, and pleural masses; and (5) evaluation of lesions for which bronchoscopic evaluation has failed to provide a definitive diagnosis.

Contraindications include anticoagulation, bleeding dyscrasia, and thrombocytopenia (platelet count <50,000). It is essential that the patient be able to cooperate fully with the procedure. If not, the complication rate rises and adequate specimens may not be obtained. If clinically indicated, coagulation defects can be temporarily corrected, reducing the risk for hemorrhage. Severe chronic obstructive pulmonary disease (COPD) is a relative contraindication. COPD is associated with an increased risk for pneumothorax from percutaneous needle aspiration or biopsy, and such patients are less able to tolerate the effects of a pneumothorax. Other relative contraindications to transthoracic needle aspiration include pulmonary hypertension, positive-pressure mechanical ventilation, and suspected vascular lesions, such as arteriovenous malformations.

Sensitivity of transthoracic needle biopsy ranges from 60%–97%. Diagnostic yield is optimal when adequate samples are provided, and both an experienced surgeon to perform the biopsy and an experienced cytopathologist to interpret the results are required. Transthoracic biopsy of malignant mediastinal and hilar lesions provides an accurate diagnosis in approximately 90% of cases. The positive yield for metastatic pulmonary and mediastinal disease is >80%. Correlation between cytologic and histopathologic diagnoses varies from 77%–82% and depends on sampling error, intraobserver variability in interpretation, and tumor pleomorphism.

Tools and Technique

Several types of needles are available for percutaneous sampling of the lung. These fall into two basic types: aspiration or fine needles and biopsy needles. Aspiration needles for the lung and mediastinum usually range in size from 18 to 23 gauge and are primarily used to aspirate cells for cytologic examination, but they may provide small fragments of tissue for histology as well. Probably the most familiar of the aspiration needles is the Chiba needle, which has a beveled tip angled at 24° and an inner removable stylet. Spinal needles can also be utilized as aspiration needles for the lung and mediastinum. They have a greater bevel angle, possess thicker walls, and hence are stiffer than the Chiba needle.

Biopsy needles also are of two general types: small-gauge biopsy needles and cutting biopsy needles. Small-gauge biopsy needles (e.g., Greene, Turner, Westcott, or Haaga needles) are modified aspiration needles designed to acquire small samples of tissue for histologic examination and preparation of cell blocks. The fine needles are commonly employed for transthoracic needle biopsy of the lung and mediastinum and are superior for obtaining cells for cell block analysis. Cutting needles are designed to obtain adequate amounts of tissue for histology. The sample provided by needle biopsy augments cytologic diagnosis of malignancy, confirming the diagnosis of a specific cell type or supporting a negative cytologic result. However, there is controversy regarding whether histologic sections of tissue obtained with thin needles significantly often lead to a positive diagnostic result when needle cytology specimens have given a negative result. Cutting needles are recommended for the biopsy of an unknown primary or a possible second primary; evaluation of suspected benign disease, especially in the anterior and posterior mediastinum; and for cases in which several passes or prior attempts with an aspiration needle have not revealed a positive cytologic diagnosis. Concerning the question of increased risk for hemorrhage, a recent prospective study demonstrated that the use of large-bore, true-cut needles was not associated with a significantly greater rate of complications than fine-needle aspiration in the evaluation of mediastinal masses, even those situated near major vessels.

Imaging Guidance

Fluoroscopy, CT, and ultrasonography have all proved to be effective guides for transthoracic needle biopsy. Fluoroscopy has the advantages of low cost and relative ease of operation. Lesions that are at least 1.5 to 2 cm in diameter can be adequately visualized by fluoroscopy. Biplanar fluoroscopy is the most precise fluoroscopic technique. CT of the chest should probably be obtained before fluoroscopically guided needle biopsy to ensure that the suspected lesion is not vascular and to localize the lesion in relation to other vital structures, thus helping to design the optimal pathway for the aspiration or biopsy needle. CT-guided transthoracic needle biopsy should be considered for lung and mediastinal lesions that are not well visualized by fluoroscopy because of small size or other reasons. CT-guided imaging is

suggested for lesions between 0.5 and 1.5 cm in diameter that are contiguous to major vascular structures or blebs. CT-guided needle biopsy is limited by the higher cost and longer duration of the procedure.

Complications

The most common complication following transthoracic needle aspiration or biopsy is pneumothorax. The frequency of pneumothorax in most studies ranges from 10%–35% following fluoroscopically guided procedures, and is approximately 37% when CT is the imaging method employed. The increased incidence of pneumothorax in CT-guided needle biopsies is most likely a consequence of the use of this imaging method for more difficult lesions requiring longer biopsy time and multiple passes with the needle. Thoracostomy tubes are required in fewer than half of cases of needle biopsy pneumothorax. In one series of 2421 transthoracic, fine-needle biopsies, a pneumothorax developed in 34% of patients, but only 7.8% required insertion of a thoracostomy tube. Indications for thoracostomy tube treatment of a pneumothorax following biopsy include dyspnea, a pneumothorax >30% in size, or an interval increase in the size of the pneumothorax on repeated x-ray imaging of the chest. A 7-French chest tube with a Heimlich valve is frequently sufficient to treat a pneumothorax following biopsy. Needle size does not appear to affect the incidence of pneumothorax. Factors that do predispose to biopsy-induced pneumothorax include increased number of needle passes, increased depth of the lesion, cavitary lesions, increasing patient age, and the presence of COPD.

Other mild complications include hemoptysis, which occurs in approximately 10% of cases, and subcutaneous emphysema.

Procedure

Transthoracic needle aspiration biopsy is usually an outpatient procedure. Patients who are very anxious may benefit from premedication with short-acting sedatives or benzodiazepines. Atropine has been used to reduce vagal tone and help prevent the possibility of vasovagal reactions. An intravenous line is routinely inserted, and electrocardiogram, arterial saturation, and blood pressure are routinely monitored during and after the procedure. The lesion to be sampled is localized, usually with fluoroscopy, and prior CT radiographs are examined for visualization of the lesion and its relation to vital structures. The patient is placed in the supine, prone, oblique, or lateral decubitus position according to the location of the lesion. The approach for mediastinal and hilar lesions depends on the size and proximity of the lesion to cardiovascular structures. In general, for anterior mediastinal masses, the anterior or parasternal approach is preferred, whereas for posterior mediastinal lesions, a paravertebral approach is often chosen. For biopsy of hilar masses, an anterior or posterior approach is employed, depending on whether the lesion is anterior or posterior to hilar vessels on contrast-enhanced CT of the thorax. Lidocaine (Xylocaine) is used for local anesthesia of the skin, subcutaneous tissue, and parietal pleura. Whenever possible, the needle is advanced over the superior margin of a rib to avoid injury of the intercostal neurovascular bundle. The actual passage of the needle into the lesion should be accomplished during breath-holding at end-expiration. This is particularly important in the biopsy of small nodules.

Techniques have been described that allow for multiple passes of the needle into a suspect lesion without repeated penetration of the pleura. In one method, the coaxial technique, an inner, smaller-gauge needle is used to aspirate samples repeatedly through an outer, larger needle passed just to the outer margin of the lesion. This method can be used with small-gauge biopsy needles and cutting biopsy needles, thereby allowing for histologic as well as cytologic examination. Following the biopsy, some choose to inject 5 to 10 mL of an autologous blood clot to patch the tract of the outer needle. In the second technique (the tandem needle approach), one needle is passed into the lesion to localize or mark the site while the second needle is employed for aspiration and biopsy in tandem to the path of the marker needle. Rapid cytologic processing of the samples can be used both to minimize the number of passes made and to ensure that diagnostic material is obtained. Gram-stained smears and cultures of aspirated materials should be done if indicated. If cores of tissue are obtained, these should be submitted in formalin for histopathologic examination.

A chest radiograph is routinely performed immediately after the procedure, and then 2 to 4 hours later, to detect the presence of a pneumothorax. The patient's vital signs should be monitored after the procedure, and the patient should be observed for symptoms of chest pain, dyspnea, hemoptysis, and cardiovascular instability.

Interpretation and Clinical Application of Results

Difficult clinical decisions must be made when a biopsy result is negative or benign, which occurs in 5%–25% of all transthoracic needle biopsies. Biopsy should be repeated if findings are nonspecific (e.g., inflammation, necrosis, or hemorrhage), as a negative result does not exclude malignancy. Repetition of the procedure with a biopsy needle should be considered if tissue for histology was not obtained, or the surgeon should proceed directly to thoracotomy for a histologic diagnosis. A specifically benign diagnosis, such as hamartoma, granuloma, or infection, is usually reliable. However, if the clinical presentation or radiologic features strongly suggest malignancy, then a thoracotomy should be performed despite specifically benign findings. When the clinical presentation and radiographic features are more consistent with benign disease, the patient can be carefully followed with regular x-ray imaging every 3 months for the first year, then every 4 to 6 months for the second year, and annually thereafter. Subsequent growth of the lesion revealed on chest x-ray films warrants prompt re-evaluation. Conversely, an interval reduction in the size of the suspect lesion lends support to a benign diagnosis, and further observation of the lesion is appropriate.

OPEN LUNG BIOPSY

Technique

When less invasive diagnostic methods fail, or the clinical situation dictates the need for a very rapid definitive diagnosis, open lung biopsy remains the most reliable approach.

Open lung biopsy is performed under general anesthesia with endotracheal intubation. For most diffuse infiltrative or nodular lung disease, a small, 5- to 7-cm incision is made over the fourth or fifth intercostal space anteriorly. The pleural cavity is exposed with a small rib spreader. A portion of the lingula, the anterior portion of the right or left lower lobe, or the right middle lobe is allowed to herniate through the wound. In the inflated state, a transverse or wedge biopsy of lung is excised using lung staplers and is sent fresh for pathologic and bacteriologic examinations. Most importantly, the portion of lung obtained should include adequate amounts of both normal and abnormal tissue. If appropriate, several samples from two lobes may be obtained through the same incision. Lateral and posterior portions of either lung are usually not accessible for biopsy through this anterior incision. A chest tube is left in place in the pleural cavity, usually for 24 to 48 hours. The entire surgical procedure is brief, with minimal blood loss. The small, anterior thoracotomy incision usually does not significantly compromise the mechanics of breathing in a group of patients who usually have serious underlying systemic disease. Localized nodular disease or peripheral nodules, especially in the apical, posterior, and lateral areas of the lung, generally require a more extensive, full posterolateral thoracotomy for access.

Complications

The reported complications from a small diagnostic anterior thoracotomy include bleeding, wound infections, persistent air leak, pneumonia, or any systemic complication of general anesthesia. In a review of 15 clinical series with a total of 2290 open lung biopsies, the overall complication rate was 7.0% and the mortality was 1.8%, usually related to a patient's underlying disease. The yield of specific diagnoses in this large group was 94%. Relative contraindications to open lung biopsy include patient instability, which can usually be improved by judicious medical management, and coagulopathies, which may be corrected in most cases with blood component therapy.

To minimize the morbidity of an open lung biopsy for diffuse infiltrative disease, the lingula or middle lobe is frequently sampled, as these areas allow for the smallest incision and shortest operating times. The question of the representative accuracy of this approach has been answered by a prospective study, which found a 100% histologic correlation of lingular biopsies with open biopsies of other lung segments obtained at the same thoracotomy. Thus, it appears that lingular biopsies are extremely accurate and representative of the pathologic process occurring in diffuse infiltrative lung disease.

Indications

The indications for an open lung biopsy and its sequence in the diagnostic algorithm depend on the pulmonary process and the patient's systemic condition. Of all patients with chronic infiltrative lung disease, transbronchial biopsy can be expected to provide a definitive diagnosis in only approximately 40%. In contrast, open lung biopsy yields a specific diagnosis in approximately 90%. Transbronchial biopsy findings of interstitial pneumonia, chronic inflammation, nonspecific reaction, and fibrosis are generally regarded as nondiagnostic and should lead to open lung biopsy.

In immunosuppressed patients with pulmonary infiltrates, considerable differences of opinion exist regarding the risk-benefit ratio of an open lung biopsy. In some series, open lung biopsy had a very high (97.5%) diagnostic accuracy rate and determined therapy in 45% of patients. However, the mortality in patients whose biopsy findings dictated a change in treatment was not significantly different from that in patients in whom no chae was indicated.

There is much controversy concerning the indications for open lung biopsy in patients with AIDS who have pulmonary infiltrates. In one series, a 70% diagnostic

accuracy rate was found in patients in whom transbronchial biopsy was nondiagnostic. In a later, prospective study of AIDS patients with interstitial infiltrates, combined transbronchial lung biopsy and alveolar lavage gave a diagnostic yield of 85% for infections, comparable with that of open lung biopsy (88%), thereby indicating a minimized need for open lung biopsies. An exception to this is an expected diagnosis of Kaposi's sarcoma, for which open biopsy is more frequently diagnostic.

In general, open lung biopsy is accompanied by low morbidity and low mortality with a high diagnostic yield. In properly selected patients, it should not be unduly delayed to perform other, less productive diagnostic techniques when a definitive tissue diagnosis can be readily and safely obtained. Of critical importance is maximal use of the biopsy specimen, including microbiologic examinations in addition to pathologic study and also including chemical and physical examinations when indicated.

VIDEO-ASSISTED THORACOSCOPIC SURGERY

Thoracoscopy has generated a large amount of interest as a newer approach to lung biopsy. When performed with a rigid scope, classic thoracoscopy was a limited procedure that provided the surgeon with poor visualization and access to intrathoracic structures. Application of video-endoscopic technology and percutaneous methods of dissection and exposure developed for abdominal surgery has resulted in a major advance in the diagnosis and treatment of intrathoracic disease.

Technique

Video-assisted thoracic surgery is performed under general anesthesia using a double-lumen endotracheal tube. The patient is positioned in the lateral decubitus position and the skin is antiseptically prepared and draped as for a standard posterolateral thoracotomy. The ipsilateral lung is collapsed and a 2-cm incision is made in the midaxillary line in the seventh intercostal space. After digital entry and palpation of the pleura surrounding the incision to avoid tearing adhesions, a 10-mm operating port is inserted. The video-telescope is inserted through the port to inspect the intrathoracic contents, and images are projected onto a high-resolution video monitor. One to three operating ports are then inserted through small, separate incisions in the anterior and posterior axillary lines, preferably along a line that can be used for a thoracotomy incision should the need arise. The entrance ports need not be sealed, as in laparoscopy, because carbon dioxide insufflation is not required to maintain an operating field. Through the operating ports the surgeon and assistant may dissect, retract, staple, excise, and digitally palpate the lung and intrathoracic structures. Application of the electrocautery and argon beam electrocoagulator is significant with this method. At the completion of the procedure, one or two small chest tubes are tunneled into the chest and the small thoracoscopy incisions are closed.

The primary reason for the development of thoracoscopy, and now video-assisted thoracic surgical techniques, is to permit invasive intrathoracic diagnostic and therapeutic procedures to be performed with minimal pain and morbidity. Complications of this procedure vary with the actual surgery performed. Pneumothorax, air embolism, bleeding, and inadvertent lung injury are the most common intraoperative complications of the procedure, but these can be controlled easily in most instances with current instrumentation. The results of a large series suggest an overall complication rate of 14% and mortality ranging from 1.5%–9.8%, depending on the underlying clinical condition, indications, and the video-assisted thorascopic surgical procedure performed. Intraoperative complications may lead to urgent thoracotomy in 1%–3% of cases, and patients are draped and prepared for open thoracotomy at the onset of the procedure.

Contraindications to video-assisted thoracic surgery are generally based on limitation of visualization of the intrathoracic space. Absolute contraindications include an obliterated pleural space, an inability to tolerate one-lung anesthesia, the need for high positive-pressure ventilation, and severe chronic or acute respiratory insufficiency, all of which would not allow collapse of the ipsilateral lung for exposure. Thus, when a patient being maintained on a ventilator in the intensive care unit requires open lung biopsy, the standard approach of anterior thoracotomy is generally used. Additionally, the procedure may be ill-advised for patients who have previously undergone thoracoscopy or even tube thoracostomy because of excessive adhesions in the pleural space. The clotting parameters of patients who are receiving anticoagulant medication or who have a coagulopathy must be normalized before video-assisted surgery can be performed.

Indications

The most traditional indication for thoracoscopy is evaluation of pleural effusions and other pleural pathology by visual exploration and directed biopsy. In a series of 102 patients with recurrent pleural effusion in whom all prior studies were nondiagnostic, a definitive diagnosis was obtained in 80.3% with thoracoscopy; there was no procedure-related mortality and a 2% complication rate.

Open lung biopsy an ideal indication for video-assisted surgery. Unlike traditional small anterior thoracotomy and classic lung biopsy, in which sampling is limited, with video-assisted biopsy any segment of any lobe of the lung in which disease has been identified can easily be sampled to make a definitive diagnosis. Small peripheral subpleural lung nodules up to approximately 2 cm in diameter can be resected for diagnosis by means of video-assisted surgery. The expected diagnostic yield with video-assisted open lung biopsy should equal or even exceed that of the standard open procedure. Other specific diagnostic and therapeutic applications of video-assisted thoracic surgery include biopsy of aortopulmonary and other mediastinal nodes; excisional biopsy of a variety of benign and malignant masses of the lung, chest wall, and mediastinum; biopsy and excision of bronchial, pericardial, and mediastinal cysts; evaluation and treatment of recurrent pneumothorax; thoracic sympathectomy; pericardial biopsy and excision; and even lobectomies in selected cases.

Despite the fact that video-assisted thoracic surgery is somewhat more difficult and tedious to perform than surgery done through a traditional open thoracotomy incision, the benefits of lessened postoperative pain, a shortened hospital stay, and quicker recovery have led to increasing use of the technique. As the technology advances, one can expect that the future will bring new diagnostic and therapeutic indications for video-assisted thoracic surgical techniques.

PULMONARY ANGIOSCOPY

Pulmonary vascular diseases present diagnostic dilemmas for which diagnostic and treatment modalities are limited. Direct visualization of vascular structures has been investigated and shows promise for expanding diagnostic capabilities.

The equipment is based on traditional endoscopic designs, except that the fiber bundle is narrow (outer diameter of 2.8 mm) and long (120 cm). Although blood in the peripheral vascular bed and in the very small coronary arterial bed can be flushed from the field of view intraoperatively, visualization in the much larger pulmonary arterial bed is best achieved using an inflatable balloon over the lens to displace blood mechanically from the area to be viewed.

The procedure is very similar to catheterization of the right side of the heart. The angioscope is passed through an introducing catheter, usually in the internal jugular vein, and directed into the right side of the heart and pulmonary arteries using direct visualization and fluoroscopy. The balloon can be inflated or deflated as needed, and distal tip deflection facilitates accurate movement of the angioscope into areas of interest.

Animal studies have established the diagnostic accuracy of angioscopy in detecting acute pulmonary emboli and the hemodynamic safety of the procedure. Safety has been confirmed in subsequent human trials.

To date, angioscopy has been applied to the diagnosis of chronic pulmonary hypertension, particularly to distinguish chronic thromboembolic pulmonary hypertension from other causes of chronic vascular obstruction and hypertension. Chronic thromboembolic pulmonary hypertension was chosen as the initial area of investigation because of significant problems with standard techniques, such as angiography, in establishing the diagnosis or determining operability.

Distinctive endoscopic features of chronic pulmonary emboli can be identified by angioscopy. These include roughening of the intimal lining, presence of bands and webs, irregular vessel contour, vascular obstruction by fibrotic masses of organized emboli, and partial recanalization. Abnormalities associated with other diseases can also be identified, such as atherosclerotic plaques, extrinsic vessel compression, and tumor. Perhaps most importantly, angioscopy has proved useful in determining the proximal extent of the chronic thromboembolic process and is therefore useful in assessing operability, a key issue in this patient population.

With this foundation established in an unusual disease entity, future clinical trials may focus on the more common problem of acute pulmonary emboli, to evaluate the role of angioscopy in relation to lung scanning and angiography. Applications in valvular heart disease will also be an area for future exploration.

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CHAPTER

12 Pleural Anatomy, Physiology, and Diagnostic Procedures

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ANATOMY

The pleural space is real, approximately 10 to 20 μm in width and situated between the mesothelium of the parietal and visceral pleurae. The parietal and visceral pleurae are continuous at the hilum, where they are penetrated by the pulmonary and bronchial vessels and the two main bronchi with their accompanying nerves and lymphatic vessels. The areas of the two pleural surfaces are approximately equal (2000 cm^2 in a person weighing 70 kg) if the interlobar fissures of the visceral pleura and the costophrenic recesses of the parietal pleura are included. Both the visceral and parietal pleurae consist of a single layer of pleomorphic mesothelial cells, a basement membrane, and layers of collagen and elastic tissue in addition to the microvessels and lymphatics.

The mesothelial cells vary in shape from flattened with an elongated nucleus and minimally discernible cytoplasm to cuboidal or columnar with a round nucleus and an indistinct luminal surface. Despite differences in morphology, mesothelial cells remain a single layer at all sites. Mesothelial cells vary in thickness from 1 to 4 μm and in surface diameter from 16 to 40 μm. Mesothelial cells contain surface microvilli that are approximately 0.1 μm in diameter and up to 3 μm in length. The density of microvilli is higher on the visceral than on the parietal mesothelial cells, possibly to trap hyaluronic acid-rich glycoprotein, particularly in the lower portion of the thorax, to decrease friction between the lung and chest wall.

Openings between mesothelial cells, called *stomata,* range in size from 2 to 12 μm and are found only on the parietal pleural surface by scanning electron microscopy. These stomata communicate directly with lymphatic lacunae, the roofs of which contain bundles of collagen. Stomata are the usual exit point for pleural liquid, protein, and cells that are removed from the pleural space.

In humans, the visceral pleura is supplied by branches of the bronchial circulation. The venous return from the subpleural capillaries drains largely into the pulmonary veins. The human parietal pleura is supplied by branches of the arteries that flow to the adjacent chest wall. The costal pleura is supplied by branches of the intercostal and internal mammary arteries; the mediastinal parietal pleura by branches of the bronchial and upper diaphragmatic, internal mammary, and mediastinal arteries; and the apical pleura by branches of the subclavian artery. The venous system of the parietal pleura drains into the bronchial veins. The diaphragmatic pleura is supplied by branches of the internal mammary artery, thoracic and abdominal aorta, and celiac arteries; drainage is into the inferior vena cava and brachiocephalic trunk.

The lymph drainage of the pleural space has a major impact on the accumulation of pleural fluid in normal and disease states. Lymphatic drainage of the pleural space begins at the stomata that are located mainly in the mediastinum caudally and on the intercostal and diaphragmatic pleurae. The stomata connect with lymphatic lacunae situated immediately below the mesothelial layer and appear to be closed at their end by the endothelium of lymphatics to form valves. The lymphatic lacunae drain into larger lymphatic channels that course along the intercostal space and drain into the mediastinum. The origin of lymphatic vessels in the parietal pleura determines the node into which the fluid drains. The pleura of the anterior thoracic wall and anterior portion of the diaphragm drains to the sternal lymph nodes; the middle portion of the diaphragmatic pleura drains to the middle mediastinal lymph nodes; the anterior portion of the diaphragmatic and mediastinal pleura drains into the anterior mediastinal lymph nodes; the posterior portion of the diaphragmatic pleura drains to the posterior mediastinal lymph nodes; and the costal parietal pleura drains to the intercostal lymph nodes. The majority of the visceral pleura drains to the middle mediastinal lymph nodes, whereas the visceral pleural drainage of the lower lobes flows into the posterior mediastinal lymph nodes.

PHYSIOLOGY

Most of what is known about normal pleural fluid turnover is derived from noninvasive studies of pleural fluid formation in the sheep, an animal with a pleural anatomy similar to that of humans. The assumption is made that in the steady-state condition, pleural fluid absorption is equivalent to pleural fluid formation. The normal pleural fluid-to-plasma protein ratio is approximately 0.15, and the pleural fluid volume is about 0.1 to 0.2 mL/kg. Studies from sheep show that pleural fluid is formed at an hourly rate of 0.01 mL/kg, the equivalent of 0.6 mL/h in a 60-kg person.

Pleural fluid is essentially an ultrafiltrate of the systemic pleural microvessels. Because the parietal pleural microvessels are closer to the pleural space than are the visceral pleural microvessels, the interstitial fluid in the parietal pleura moves between mesothelial cells into the pleural space along a pressure gradient; most or all of the interstitial liquid that moves out of the visceral pleural microvessels is removed by lung lymphatics because the fluid would have to travel a greater distance to enter the pleural space. Therefore, in normal humans, the parietal pleura is responsible for most or all pleural fluid formation. Pleural fluid exits the pleural space via the lymphatic stomata of the parietal pleura. Most pleural fluid exits the pleural space by bulk flow, not by diffusion. In addition to the pleural liquid being removed through the stomata, cells and protein exit by this route. The lymphatic flow from the pleural space is influenced by both the contractility of the lymph vessels and respiratory movements. The circulation of fluid in the pleural space enabling liquid to move into stomata may be driven by respiratory movements.

The lymphatic drainage of the pleural space appears to have a large reserve, so that when an abnormal amount of pleural fluid accumulates in disease states, it must represent increased formation, decreased absorption, or both. Most probably both mechanisms contribute to pleural fluid formation. An increase in pleural fluid formation is unlikely to cause a pleural effusion clinically, as the pleural lymphatics have an extensive reserve to handle excess fluid formation. Furthermore, a decrease in pleural fluid absorption is unlikely to cause a pleural effusion clinically because the normal entry rate is slow.

Mechanisms of increased formation of pleural fluid include the following: (1) an increase in microvascular pressure (as occurs in congestive heart failure); (2) a decrease in pleural pressure (as in atelectasis), which decreases the pressure surrounding the nearby microvessels and increases the gradient of pressures driving fluid across the microvascular barrier; and (3) a decrease in plasma oncotic pressure (as in hypoalbuminemia), which increases the forces for filtration until the balance is restored.

When the lymphatic system is involved by disease at any point from the stomata of the parietal pleura to the mediastinal lymph nodes, a decrease in absorption rate can occur. Factors that may affect lymphatic flow include the following: (1) inhibition of lymphatic contractility during infiltration by malignancy or anatomic abnormalities (as in yellow nail syndrome); (2) limitation of respiratory movement (as in lung collapse); (3) blockage of lymphatic stoma by malignancy or fibrin; (4) acute increases in systemic venous pressure; and (5) decreased fluid availability to the stoma after pneumothorax.

Pleural fluid can form when fluid moves across the diaphragm from the peritoneal cavity, either because of congenital diaphragmatic defects or by convection across the two mesothelial layers. Inflammation may also be a factor, as in acute pancreatitis and increased pleural capillary filtration. There is no evidence for the existence of direct lymphatic channels connecting the peritoneal and pleural spaces across the diaphragm. Lastly, mediastinal inflammation, as seen in esophageal sclerotherapy and esophageal perforation, can lead to a pleural effusion. When fluid from a pancreatic pseudocyst or rupture of the thoracic duct (chyle) collects in the mediastinum, a pleural effusion can form when the mediastinal pleura ruptures.

DIAGNOSTIC PROCEDURES

Thoracentesis

Diagnostic Yield

The discovery of a pleural effusion provides an opportunity for the clinician to verify the disease, procedure, or drug that has caused the effusion. With a simple bedside procedure, thoracentesis, the fluid can be rapidly sampled and observed, its constituents observed microscopically, and its contents quantified. A comprehensive and systematic approach to analysis of pleural fluid in conjunction with the clinical presentation should allow the clinician to diagnose the cause of a pleural effusion in 75% of cases. A definitive diagnosis, such as the finding of malignant cells or specific organisms in pleural fluid, can be established in only one of four patients; however, a presumptive diagnosis, based on a clinical impression before thoracentesis, can be substantiated by pleural fluid analysis in an additional 50% of patients. Even with a nondiagnostic thoracentesis, pleural fluid analysis can be useful in excluding other possible causes of a pleural effusion, such as infection. Therefore, in three of four patients the cause of an effusion can be “diagnosed,” and in >90% of patients information relevant to clinical decision making can be gained by pleural fluid analysis.

Indications and Contraindications

When a pleural effusion is suspected on physical examination and confirmed radiographically, a diagnostic thoracentesis should be performed in an attempt to establish the cause of the effusion. If the clinical diagnosis (e.g., uncomplicated congestive heart failure) is secure, it is reasonable to observe the patient's response to therapy and proceed with thoracentesis only when the clinical response is not appropriate. There are no absolute contraindications to diagnostic thoracentesis. Relative contraindications include a bleeding diathesis, anticoagulation, a small volume of pleural fluid, and mechanical ventilation. The needle should never be passed through an area of active skin infection. The patient on mechanical ventilation is not at increased risk for pneumothorax when undergoing thoracentesis, but tension pneumothorax is more likely to develop if the lung is punctured.

Technique

Diagnostic thoracentesis should be a simple and rapid procedure for the operator and impose minimal discomfort on the patient. Patient anxiety can be minimized greatly if the procedure is explained completely at the time informed consent is obtained. It is rarely necessary to administer atropine, narcotics, or sedative drugs for a diagnostic thoracentesis.

The selection of the site for thoracentesis is critical to a successful outcome. A chest radiograph should be available in the procedure room for review before site selection. The physical examination should dictate the precise placement of needle insertion. The site should be one to two interspaces below the level where the percussion note becomes flat and tactile fremitus decreases. With a free-flowing effusion, an area midway between the spine and the posterior axillary line should be selected, as the ribs are easily palpated in this location. When the interspace is selected, the needle should be passed over the superior surface of the rib to avoid possible laceration of the neurovascular bundle, which courses near the inferior rib margin. This is especially applicable in elderly patients, who tend to have tortuous intercostal arteries that may impinge on the intercostal space, so that the risk for laceration is increased. If the fluid is loculated or small, as demonstrated by decubitus radiographs, thoracentesis should be done under ultrasonic guidance. Thoracentesis should be performed with the patient positioned exactly as during ultrasonography.

Good technique minimizes complications. The operator should maintain appropriate sterile technique and clean a wide area around the site selected for needle puncture. A 10% povidone-iodine solution decreases the usual cutaneous bacterial population by 85% for about 1 hour. The quaternary ammonium compounds, such as benzalkonium chloride, have a rapid onset of action, but their activity is antagonized by soaps and tissue constituents, and when these compounds are applied to the skin, they tend to form a film under which bacteria may remain viable. Furthermore, these compounds do not kill spores and require more than 5 minutes to decrease the bacterial population by 50%. The normal pleural space appears to have effective mechanisms for clearing bacteria; however, patients with severe pleural injury or immunosuppression probably are at increased risk for iatrogenic empyema if careful aseptic technique is not maintained.

If the skin, periosteum of the rib, and parietal pleura are properly injected with lidocaine, the patient should have minimal pain, similar to the discomfort associated with venipuncture. When pleural fluid is obtained by aspirating with the syringe containing lidocaine, the syringe and needle should be withdrawn and a 22-gauge needle, 1 1/2 inches long and attached to a 50-mL syringe, should be used along the same tract to obtain fluid for diagnostic evaluation. One milliliter of heparin (1:1000) should be added to prevent clotting of the fluid.

Occasionally the thoracentesis will be “dry.” This may result from the absence of pleural fluid, incorrect needle placement, or a needle of inappropriate length. If air is obtained in the syringe, the lung has been punctured because the needle was placed superiorly to the effusion. If no air, or possibly blood, is obtained, the needle may have been inserted too inferiorly or been too short for an obese patient. If there are no adverse consequences of this misadventure, then appropriate adjustment of the technique usually results in a successful procedure. A longer needle should be used in a patient who is markedly obese.

Fifty milliliters of fluid is all that is necessary for complete pleural fluid analysis. The tests requested should be based on the clinical presentation. It is not clinically efficacious or cost-effective to request an entire battery of pleural fluid tests. It is probably cost-effective and clinically efficacious to order the following tests for all patients who undergo a diagnostic thoracentesis: total protein, lactate dehydrogenase (LDH), nucleated cell count and differential, and either a glucose or pH determination. Concomitant serum protein, LDH, and glucose levels should be measured; arterial pH should be measured if the pleural fluid pH is below 7.30 and acidemia is suspected. The aforementioned tests provide information that allows characterization of the fluid as a transudate or an exudate, narrows the differential diagnosis of an exudate, and indicates the degree of pleural inflammation and the acuteness of pleural injury. Gram, acid-fast bacilli (AFB), and potassium hydroxide (KOH) stains should be performed and pleural fluid cultured when infection is suspected. Pleural fluid cytology should be requested when malignancy is suspected or if an exudate is undiagnosed; lipid studies should be ordered when the fluid is milky, and immunologic studies should be performed if rheumatoid or lupus pleuritis is suspected. Amylase concentration should be measured when pancreatitis, pancreatic pseudocyst, esophageal rupture, or malignancy is considered.

Complications

Complications of diagnostic thoracentesis include pain at the needle insertion site, bleeding (local, intrapleural, or intra-abdominal), pneumothorax, empyema, and spleen or liver puncture. Pneumothorax is the most common clinically important complication of diagnostic thoracentesis and has been reported to occur in up to 10% of patients. The rate of pneumothorax correlates indirectly with operator experience. However, the pneumothorax usually is small and often can be treated expectantly. Liver or spleen puncture tends to occur when the patient is not sitting absolutely upright, because movement toward a recumbent position causes cephalad migration of the abdominal viscera. However, even if the liver or spleen is punctured with a small-bore needle, generally the outcome is favorable if the patient is not receiving anticoagulants and does not have a bleeding diathesis.

Pleural Fluid Analysis

Definitive Diagnosis

There are only a select number of diagnoses or causes of the effusion that can be established definitively by thoracentesis. These include malignancy, empyema, tuberculous pleurisy, fungal infection of the pleural space, lupus pleuritis, chylothorax, urinothorax, esophageal rupture, hemothorax, peritoneal dialysis, and extravascular migration of a central venous catheter (Table 1). Confirming the diagnosis of chylothorax does not establish the cause but provides evidence that the thoracic duct has been violated; lymphoma is the cause in >50% of cases. Esophageal rupture is the single entity associated with a pleural fluid having a high amylase concentration and a pH of <7.00. A pancreatic pleural effusion is associated with a high amylase concentration but the pH is virtually always >7.30. Some malignant pleural effusions have high amylase concentrations and the pH is >7.30 in two thirds of these patients; when the pH is low in malignant effusions, it rarely is <7.05. Empyema, tuberculous pleurisy, rheumatoid disease, and lupus pleuritis can all be associated with a low pleural fluid pH (<7.30), but the pleural fluid amylase concentration is less than the concomitant serum value. With extravascular migration of a central venous catheter, the resultant pleural effusion can be similar to the infusate and may be hemorrhagic and neutrophil-predominant because of trauma and inflammation. The pleural fluid-to-serum glucose ratio is >1.0; however, the pleural fluid glucose level is usually lower than that of the infusate, as glucose is transported rapidly from the pleural space.

Disease	Diagnostic pleural fluid tests
Empyema	Observation (pus, putrid odor); culture
Malignancy	Positive cytology
Lupus pleuritis	LE cells present
Tuberculous pleurisy	Positive AFB stain, culture
Esophageal rupture	High level of salivary amylase; pleural fluid acidosis (pH < 7.00)
Fungal pleurisy	Positive KOH stain, culture
Chylothorax	Triglycerides (>110 mg/dL); lipoprotein electrophoresis positive for chylomicrons
Hemothorax	Hematocrit (pleural fluid/blood ratio >0.5)
Urinothorax	Creatinine (pleural fluid/serum ratio >1.0)
Peritoneal dialysis	Protein (<1 g/dL); glucose (300–400 mg/dL)
Extravascular migration of a central venous catheter	Observation (milky if lipids are infused); glucose pleural fluid/serum >1.0
Rheumatoid pleurisy	Characteristic cytology; pH 7.00; glucose <30 mg/dL; LDH > 1000 IU/L

TABLE 1. *Diagnoses or causes that can be established definitively by pleural fluid analysis*

Diagnostic Clues at the Bedside

Diagnostic clues can be obtained by gross inspection of the pleural fluid as it is being aspirated from the patient's chest (Table 2). A straw-colored fluid is typical of all transudates and minimally inflammatory exudative effusions, such as those seen in early malignancy, tuberculous pleurisy, and yellow nail syndrome. A bloody fluid in the absence of trauma suggests either malignancy, benign asbestos pleural effusion (BAPE), postcardiac injury syndrome (PCIS), or pulmonary infarction. A milky effusion suggests chylothorax but can be caused by a chyliform effusion (a lipid effusion that is not chyle with or without a high cholesterol level) or an empyema. Chylothorax signifies leakage of chyle from the thoracic duct, and the pleural fluid virtually always has a triglyceride concentration of >110 mg/dL; a triglyceride concentration of <50 mg/dL virtually excludes chylothorax. A chyliform effusion occurs in chronic pleural disease and is usually associated with a trapped lung, rheumatoid pleurisy, or tuberculous pleurisy, or is the result of pneumothorax therapy for tuberculosis. The diagnosis of a chyliform (cholesterol) effusion can be established by identifying cholesterol crystals on smears of the sediment; these rhomboid-shaped structures impart a lustrous sheen to the pleural fluid. Some chyliform effusions have high triglyceride levels; to differentiate between a chylothorax and a chyliform effusion that does not demonstrate cholesterol crystals, or if the triglyceride concentration is between 50 and 110 mg/dL, a lipoprotein electrophoresis should be performed to evaluate for the presence of chylomicrons, which are diagnostic for chylothorax.

Feature	Suggested diagnosis
Color	
Pale yellow (straw)	Transudate, some exudates
Red (bloody)	Malignancy, BAPE, PCIS, pulmonary infarction, trauma
White (milky)	Chylothorax or cholesterol effusion
Brown	Long-standing bloody effusion; rupture of amebic liver abscess
Black	Aspergillus
Yellow-green	Rheumatoid pleurisy
Color of enteral tube feeding	Feeding tube has entered pleural space
Color of central venous line infusate	Extravascular catheter migration
Character	
Pus	Empyema
Viscous	Mesothelioma
Debris	Rheumatoid pleurisy
Turbid	Inflammatory exudate or lipid effusion
"Anchovy paste"	Ruptured amebic liver abscess
Odor	
Putrid	Anaerobic empyema
Ammonia	Urinothorax

BAPE, benign asbestos pleural effusion; PCIS, postcardiac injury syndrome.

TABLE 2. *Diagnoses suggested by observations of pleural fluid*

When an amebic liver abscess ruptures into the pleural space, it produces an “anchovy paste”–like pleural aspirate that is a mixture of liver tissue that has undergone cytolysis, small pieces of liver parenchyma, and blood. The effusion is almost always right-sided. Amebae can be demonstrated in pleural fluid in <10% of patients. In patients with rheumatoid pleurisy, the fluid may have a yellowish-green tint or may appear to contain debris that results from exfoliation of necrotic visceral pleural rheumatoid nodules.

When fluid the color of the enteral feeding is aspirated from the pleural space, it confirms that a narrow-bore enteral feeding tube has passed through the tracheobronchial tree and into the pleural space. When the pleural fluid is similar to the infusate in a central venous line, extravascular catheter migration, which is most commonly associated with left-sided catheter placements through the jugular veins, has occurred. A viscous effusion suggests malignant mesothelioma because of the high levels of hyaluronic acid. A putrid odor is diagnostic of an anaerobic empyema, and the smell of ammonia suggests ipsilateral obstruction uropathy producing a urinothorax.

Transudates and Exudates

The characterization of pleural fluid as a transudate or an exudate is the next deductive step in pleural fluid analysis following observation of the aspirate. Transudates, largely because of imbalances in hydrostatic and oncotic pressures in the chest, can also result from movement of fluid from the peritoneal (cirrhosis) or retroperitoneal (urinothorax) spaces, or from iatrogenic causes, such as crystalloid infusion into a central line that has migrated extravascularly. Nevertheless, the diagnostic possibilities with a transudate are limited, and the diagnosis can usually be easily determined from the clinical presentation (Table 3).

Cause	Comment
Effusion virtually always transudative	
Congestive heart failure	Acute diuresis can result in pseudoexudate
Cirrhosis	Rare without clinical ascites
Nephrotic syndrome	Usually subpulmonic and bilateral
Peritoneal dialysis	Massive effusion develops within 48 hours of initiating dialysis
Hypoalbuminemia	Edema fluid rarely isolated to pleural space
Urinothorax	Caused by ipsilateral obstructive uropathy
Atelectasis	Caused by increased intrapleural negative pressure; common in ICU setting
Constrictive pericarditis	Bilateral effusions
Trapped lung	Result of remote inflammation
Superior vena caval obstruction	Caused by acute systemic venous hypertension or acute blockage of thoracic lymph flow
"Classic exudates" that can be transudates	
Malignancy	Caused by early lymphatic obstruction, obstructive atelectasis, or concomitant disease
Pulmonary embolism	Incidence of 23%; caused by atelectasis
Sarcoidosis	Stage II and III disease
Hypothyroid pleural effusion	Transudates secondary to hypothyroid heart disease

TABLE 3. *Causes of transudative pleural effusions*

In contrast, exudative effusions can be caused by a variety of diseases and present more of a diagnostic dilemma. Exudates result primarily from pleural and lung inflammation (pneumonia) or impaired lymphatic drainage of the pleural space (malignancy), and these in turn represent a capillary protein leak or decreased protein removal from the pleural space, respectively. Exudates can also result from the movement of fluid from the peritoneal space, as seen in acute or chronic pancreatis, chylous ascites, and peritoneal carcinomatosis. Disease in virtually any organ can cause exudative pleural effusions through a variety of mechanisms, including infection, malignancy, immunologic responses, lymphatic abnormalities, noninfectious inflammation, iatrogenic causes, and movement from below the diaphragm (Table 4).

TABLE 4. *Causes of exudative pleural effusions*

The most practical method of distinguishing between transudates and exudates is measurement of serum and pleural fluid protein and LDH concentrations. If at least one of the following criteria is met, the fluid is virtually always an exudate, and if none is met, the fluid is virtually always a transudate: (1) pleural fluid protein-to-serum protein ratio of >0.5; (2) pleural fluid LDH-to-serum LDH ratio of >0.6; and (3) pleural fluid LDH >67% of the upper limits of normal for the serum LDH. Recent data using receiver operating characteristics (ROC) analysis suggest that an LDH concentration of 160 IU/L is the ideal cutoff point to separate transudates and exudates. Pleural fluid cholesterol appears to be a relatively good differentiating marker, with a level of 60 mg/dL as a cutoff; virtually all effusions with cholesterol levels of <60 mg/dL are transudative, and up to 10% of exudates have cholesterol levels of <60 mg/dL.

Transudates have characteristic, but not diagnostic, cellular and biochemical characteristics that support their noninflammatory pathogenesis. These effusions are usually straw-colored, nonviscous, and odorless. In approximately 80% of cases, the nucleated cell count is <1000/μL; it is rare to find a transudative effusion with a nucleated cell count of >10,000/μL. Eighty-five percent of transudative effusions have red blood cell counts of up to 10,000/μL, so the clinician cannot conclude that a serosanguinous effusion is not a transudate. Furthermore, serosanguinous transudative effusions do not become pseudoexudates by LDH criteria, possibly because extensive pleural space hemolysis would be required to affect pleural fluid LDH. Transudative effusions, because of their noninflammatory nature, are mononuclear-predominant and composed of lymphocytes, mesothelial cells, and monocytes-macrophages; it is extremely unusual for classic transudates to be neutrophil-predominant, and if found, this should suggest dual diagnoses. A low pleural fluid glucose level is not found in transudative effusions, and the pleural fluid pH is alkaline (with the exception of urinothorax) and exceeds the simultaneously obtained blood pH, usually in the range of 7.45 to 7.55.

In the acute stages of an exudate, the inflammatory response produces pleural fluid with high nucleated cell counts and a predominance of neutrophils. In the subacute or chronic stages, the exudative effusions may have low cell counts of <5000/μL with a predominance of mononuclear cells, usually lymphocytes.

Pleural Fluid Cells

The nucleated cell count in pleural fluid is virtually never diagnostic; however, counts of >50,000/μL usually are found only in parapneumonic effusions, usually empyema. Transudates generally are associated with nucleated cell counts of <1000/μL, and chronic exudates, as in malignancy and tuberculosis, with counts of <5000/μL. Patients with pleural fluid nucleated cell counts of >10,000/μL generally have substantial pleural inflammation, as can occur with pneumonia, pancreatitis, PCIS, and pulmonary infarction. When pleural fluid is grossly purulent, the nucleated cell count often is less than anticipated, because lysis of neutrophils has occurred and the debris from these cells, in addition to fibrin and collagen, causes turbidity and purulence of the fluid.

The timing of thoracentesis in relation to the acute pleural injury determines the predominant cell in the exudate. Acute exudative pleural effusions are neutrophil-predominant. As the time from the acute insult to performance of thoracentesis lengthens, the effusion becomes mononuclear-predominant if pleural injury is not persistent. Diseases in which the patient is examined soon after the onset of symptoms, such as pneumonia, pulmonary embolism, and pancreatitis, usually are associated with neutrophil-predominant effusions.

Pleural fluid lymphocytosis, particularly lymphocyte counts of 85%–90%, suggests tuberculous pleurisy. However, lymphoma, sarcoidosis, and chronic rheumatoid pleurisy should be considered in the proper clinical setting. Carcinomatous pleural effusions have >50% lymphocytes in two thirds of cases. As the aforementioned diseases can be diagnosed by closed pleural biopsy, the presence of an unknown exudate and lymphocytosis is the prime indication for pleural biopsy. Approximately a third of patients with transudative pleural effusions have a predominance of lymphocytes; however, this finding is of no clinical relevance and does not indicate the need for pleural biopsy.

Pleural fluid eosinophilia (>10% of total nucleated cells are eosinophils) suggests a benign, self-limited pleural effusion associated with air or blood in the pleural space. Therefore, it is commonly seen following pleural space hemorrhage, pulmonary infarction, pneumothorax, or BAPE, or after thoracentesis. Pleural fluid eosinophilia is rare but not unknown in tuberculous pleurisy and is unusual with a malignant pleural effusion despite the high incidence of pleural space hemorrhage. When air or blood is not present with pleural fluid eosinophilia, parasitic disease (paragonimiasis, hydatid disease), fungal infection (histoplasmosis), and drugs (dantrolene, nitrofurantoin) should be considered. Approximately one third of eosinophilic pleural effusions are idiopathic; many of these effusions are probably caused by occult pulmonary embolism or BAPE, as these effusions are frequently bloody. Pleural fluid basophilia (>10% of total nucleated cells are basophils) is rare and suggests leukemic involvement of the pleura.

Mesothelial cells are predominant in transudative pleural effusions and are found to a variable degree in exudates. The presence of mesothelial cells in exudates is important, because if >5% of cells are mesothelial cells, tuberculous pleurisy is virtually excluded, and they may be confused with malignant cells. Mesothelial cells are scarce in the pleural space when there is diffuse pleural injury or fibrosis inhibiting exfoliation; this has been noted with empyema, rheumatoid pleurisy, after pleurodesis, and in chronic malignant effusions.

The pleural fluid macrophage has its origin in the circulating blood monocyte. The macrophage appears to modulate pleural injury and is called to the pleural space by pleural fluid neutrophil chemotaxins. The presence of macrophages is of no diagnostic value, but it is important not to confuse these cells with mesothelial cells, as the presence of macrophages does not exclude tuberculous pleurisy.

Finding a large number of plasma cells in pleural fluid suggests multiple myeloma with pleural involvement. A small number of plasma cells is nondiagnostic and has been observed in a spectrum of diseases ranging from congestive heart failure to malignancy.

The presence of blood-tinged pleural fluid is of minimal diagnostic value, as only a few drops of blood in 500 mL of fluid will result in hemorrhagic fluid. Up to 50% of exudates and 10%–15% of transudates may be sanguineous. The finding of more than 100,000 red blood cells per microliter suggests that the exudate is caused by trauma, malignancy, pulmonary embolism, PCIS, or BAPE. In the absence of trauma, malignancy is the most common cause of a frankly bloody pleural effusion. Determining whether the bloody effusion is real or caused by a traumatic thoracentesis frequently poses a dilemma. A traumatic thoracentesis is suggested by nonuniform color during aspiration, clotting of the fluid within several minutes, and the absence of hemosiderin-laden macrophages.

Pleural Fluid Chemistries

A low pleural fluid glucose concentration (<60 mg/dL, or pleural fluid-to-serum ratio of <0.5) narrows the differential diagnosis of the exudate to rheumatoid pleurisy, empyema, malignant effusions, tuberculous pleurisy, lupus pleuritis, and esophageal rupture. The mechanisms responsible for a low pleural fluid glucose concentration include decreased transport of glucose from blood to pleural fluid (malignancy, rheumatoid pleurisy) and increased glucose utilization by constituents of pleural fluid (empyema, malignancy). The lowest glucose concentrations are found in empyema and rheumatoid pleural effusions, with glucose being undetectable at times. In tuberculous pleurisy, lupus pleuritis, and malignancy, the glucose concentration when low is generally in the range of 30 to 55 mg/dL.

A pleural fluid pH of <7.30 with a normal blood pH is found in the same conditions associated with a low pleural fluid glucose concentration. Pleural fluid acidosis has been found with esophageal rupture (pH of 6.00), empyema (5.50–7.29), rheumatoid pleurisy (7.00), malignancy (7.05–7.29), and lupus pleuritis (7.05–7.29). The mechanisms responsible for pleural fluid acidosis are increased acid production by pleural fluid cells and bacteria (empyema), and decreased acid efflux from the pleural space because of pleuritis or pleural fibrosis (malignancy and rheumatoid pleurisy). A low pleural fluid pH has diagnostic, prognostic, and therapeutic implications in malignancy and parapneumonic effusions. In parapneumonic effusions, a pleural fluid pH of <7.10 suggests the need for chest tube drainage. In malignant pleural effusions, a pH value of <7.30 predicts a short survival time, an increased yield on pleural biopsy and cytology, and a poor response to pleurodesis.

An increased pleural fluid amylase concentration (above the upper limits of normal for serum, or a pleural fluid-to-serum ratio of >1.0) indicates one of four diagnostic

possibilities: (1) acute pancreatitis, (2) pancreatic pseudocyst, (3) esophageal rupture, and (4) malignancy.

In addition to fulfilling one of the criteria defining an exudate, a high LDH level (>1000 IU/L) suggests empyema, rheumatoid pleurisy, or paragonimiasis involving the pleural space.

Immunologic Studies

A pleural fluid rheumatoid factor titer of 1:320 or higher is suggestive but not diagnostic of rheumatoid pleurisy. The finding of LE cells in pleural fluid is virtually diagnostic of lupus pleuritis. The likelihood of demonstrating LE cells in pleural fluid appears to be enhanced if the fluid is allowed to remain at room temperature for several hours before it is examined with Wright stain. An antinuclear antibody (ANA) titer of 1:160 or higher or a pleural fluid-to-serum ANA ratio of 1.0 or greater is suggestive but not diagnostic of lupus pleuritis. Pleural fluid complement levels are low in most patients with lupus pleuritis and rheumatoid pleurisy; this is true whether total hemolytic complement or complement components are measured.

Cytology

Cytology is a more sensitive test for the diagnosis of malignant pleural effusions than is percutaneous pleural biopsy, because pleural metastases tend to be focal and the latter is a blind sampling procedure. The yield of cytology increases as the disease becomes more advanced. With improved techniques, the yield from exfoliative cytology now approaches 90%–95%. If the clinician suspects a malignant effusion, several hundred milliliters of fluid should be removed at the initial diagnostic thoracentesis. This maneuver will not improve the yield on the initial study, but if the results are negative, a repeated procedure several days later may provide fluid with fewer degenerative cells and freshly exfoliated malignant cells. If the results of a second cytologic examination several days after the first are negative, a third examination soon after usually is nondiagnostic. Reasons for a true negative cytologic examination include improper handling of the specimen, variance of tumor type, and lack of interest and expertise of the cytopathologist.

Pleural Biopsy

Several techniques for percutaneous pleural biopsy have been available since the 1920s, but not until the 1950s, with the popularization of the Cope and Abrams needles, did routine bedside pleural biopsy become available to the clinician.

Percutaneous pleural biopsy is a simple bedside or outpatient procedure whose main indication is the evaluation of exudative effusions of unknown cause. The two diagnoses most commonly established by pleural biopsy are malignancy and tuberculosis. The diagnosis of rheumatoid pleurisy, fungal pleurisy (coccidioidomycosis, blastomycosis), sarcoidosis, and parasitic diseases, such as echinococcosis) also can be confirmed by pleural biopsy. Culturing *Coccidioides* from pleural tissue appears to be an excellent method of establishing the diagnosis of acute coccidioidal pleural effusion.

Demonstration of free-flowing fluid in the pleural space is imperative if complications are to be minimized. If doubt exists, confirmation before biopsy of fluid location by ultrasonography is recommended. The presence of pleural fluid is not a prerequisite for percutaneous pleural biopsy; if pleural symphysis does not exist, allowing air to enter the pleural space will separate the lung from the chest wall and allow the biopsy to be performed safely. If loculated pleural fluid is present, the biopsy should be done under ultrasonic guidance.

Contraindications to pleural biopsy include (1) pleural symphysis; (2) an uncooperative patient; (3) anticoagulation; (4) a bleeding diathesis, including moderate to severe azotemia, when a normal bleeding time cannot be ensured; (5) empyema; and (6) local cutaneous lesions (herpes zoster, pyoderma).

Technique

Proper positioning of the patient is important for any invasive procedure but particularly for pleural biopsy. The patient should be seated leaning backward in a chair with arms resting against the backrest or on a table to allow optimal patient comfort and ease of access of the operator to the posterior chest wall. Vasovagal episodes during pleural sampling are not uncommon in anxious patients; proper preparation of the patient, adequate local anesthesia, and preoperative administration of atropine virtually eliminate this complication.

A biopsy site should be chosen one to two intercostal spaces below the fluid level demonstrated on physical examination. Appropriate anesthesia of the parietal pleura and periosteum of the rib provides maximal patient comfort and cooperation. A skin incision parallel to the ribs with a No. 11 blade facilitates entrance to the pleural space of the 11-gauge outer cannula just above the superior border of the rib. When the outer cannula enters the pleural space, a characteristic pop is felt. After fluid is aspirated through the trocar, pressure is applied in the direction of the cutting needle, allowing the parietal pleura to be snagged. Several biopsy specimens should be obtained by rotating the trocar and cutting needle to different locations, with care taken to avoid the intercostal neurovascular bundle, which is more likely to be encountered with extreme cephalic or caudal angulation. The tissue is cut from the parietal pleura by advancing with a twisting motion (Cope needle) or rotating the inner cutting needle (Abrams needle). Three to five specimens should be taken from a single site. The pleural tissue should be placed in 10% formaldehyde for histologic examination and in sterile nonbacteriostatic saline solution for culture. If malignancy is the suspected diagnosis, only a single specimen needs to be cultured. If tuberculosis is likely, the specimen should be divided evenly between histology and culture.

Diagnostic Yield

The literature reports a wide range of diagnostic yields, from 30%–70% in patients with malignancy and 60%–95% in patients with tuberculous pleurisy. Patient population, biopsy technique, and the expertise of the operator, pathologist, and microbiology laboratory account for some of the variability. In a compilation of 14 series from the literature inclusive of 2893 pleural biopsies, 51% were nondiagnostic, 245 (75%) of 325 were positive for a confirmed diagnosis of tuberculous pleurisy, and 618 (57%) of 1080 were positive with a known diagnosis of carcinoma.

Sampling error has led to controversy as to the number, location, and sites for percutaneous pleural biopsy. A paucity of data exists regarding an adequate number of individual biopsy specimens to be taken at a single site, yet there is a suggestion that four or more improve the diagnostic yield. The sampling location usually is directed by the fluid level as determined on radiologic and physical examination. Thoracoscopy has demonstrated the nonuniform location of pleural metastasis. The highest yield would be expected from specimens obtained close to the diaphragm and midline, as pleural metastases tend to begin in the former location and spread toward the costal pleura and cephalad. Increasing the number of biopsy sites at one sitting does not appear to increase the diagnostic yield in either tuberculous pleurisy or malignancy. The stage of the malignancy at the time of pleural biopsy appears to be related to the diagnostic yield; more studies are positive in patients with far-advanced disease. The diagnostic yield is also high in patients with malignancy and a low pleural fluid pH (<7.30), as in advanced disease hydrogen ion efflux from the pleural space is impaired by increased tumor bulk and pleural fibrosis.

The primary indication for percutaneous pleural biopsy today is tuberculous pleurisy, as this test provides the highest diagnostic yield. With improvement in cytologic techniques, the yield of pleural fluid exfoliated cytology approaches 95% when the pleura is involved with malignancy; therefore, pleural biopsy rarely adds to the diagnosis. However, there are instances in which results of the cytologic examination are negative and the pleural biopsy findings are positive. Therefore, if findings of the first cytologic examination are negative and malignancy is suspected, a second procedure should include repeated cytologic examination with a single-site percutaneous pleural biopsy.

Complications

Potential complications of closed-chest pleural biopsy cover a spectrum ranging from pain at the needle insertion site to empyema; however, complications are unusual and generally of minimal clinical consequence. Pneumothorax, the most common and potentially important clinical complication, usually is small and is caused by the entrance of air through the needle into the pleural space, not by lung puncture. Small pneumothoraces have been reported in up to 15% of biopsies and usually can be treated expectantly. Site pain (reported incidence of 1%–15%) can be minimized with good technique and local anesthesia. Vasovagal reaction, reported in 1%–5% of patients, can virtually be eliminated with the use of atropine. The remaining complications, including hemothorax, transient fever, tumor seeding, site hematoma, subcutaneous emphysema, air embolism, biopsy of extrapleural tissue (liver and spleen), and empyema, occur in <1% of patients.

Thoracoscopy

Jacobaeus first described an endoscopic approach to serous cavities more than 80 years ago and published his experience in lysing pleural adhesions in the treatment of tuberculosis and the diagnosis of tumors based in pleura. The previously mentioned procedures were the major indications for thoracoscopy during the next two decades. Interest in thoracoscopy waned with the development of percutaneous needles for pleural biopsy. Recently, there has been a renewed interest in thoracoscopy because of better endoscopic optic systems, improved technology of the instrument itself, and interest in less invasive procedures. Today, thoracoscopy

is used predominantly in the diagnostic evaluation of pleural effusions of unknown cause and for talc pleurodesis. Most procedures are performed using rigid thoracoscopes because of their superior optical systems, large working channels, and ease of maneuverability.

Usually, diagnostic thoracoscopy is performed under local anesthesia with small incremental doses of narcotics and a benzodiazepine. A chest tube is required after thoracoscopy. In diagnostic cases in which only the parietal pleura is sampled, a small chest tube can be used (16 to 20 French). With talc pleurodesis, a larger chest tube is placed and should remain in place until the pleural fluid drainage is <150 mL/d.

The diagnostic accuracy of thoracoscopy in pleural effusions of unknown cause varies depending on the duration of follow-up and the diagnostic methods employed, with the diagnostic accuracy in reported series ranging from 69%–96%. Although thoracoscopy is less invasive than formal thoracotomy and in certain circumstances is a better alternative than observation, it should not replace percutaneous needle biopsy. Although thoracoscopy is excellent for the diagnosis of metastatic cancer or mesothelioma, it should be unnecessary in the diagnosis of tuberculous pleurisy, as pleural biopsy culture and histology and pleural fluid culture will yield a diagnosis in the vast majority of patients. Furthermore, it is usually not helpful in the diagnosis of nonmalignant pleural disease, except to reveal the following: benign asbestos pleural plaques, which are large, white lesions that may resemble teeth; white patchy lesions of the visceral pleura with diffuse telangiectasia, seen in radiation pleuritis; a granular appearance on the pleural surface in rheumatoid pleurisy; and visceral and parietal pleural adhesions and gray-white plaques in tuberculous pleurisy.

Talc by poudrage is a highly effective method of pleurodesis for both malignant and nonmalignant pleural effusions. Talc slurry through a chest tube appears to have similar efficacy to talc poudrage and is less expensive, as the cost of thoracoscopy is avoided.

The mortality from diagnostic thoracoscopy in >4000 cases is <0.1%, comparable with the mortality of bronchoscopy with transbronchial biopsy. The potential complications, which are rare, include postoperative air leak, hemorrhage, hypotension, hypoxemia, subcutaneous emphysema, vagal syncope, and metastatic invasion of the access tract.

The only absolute contraindication is pleural symphysis. Cough, hypoxemia, severe cardiac disease, and coagulopathy are relative contraindications.

Open Pleural Biopsy

Although formal thoracotomy provides excellent visualization of the pleura and the opportunity to obtain the largest biopsy specimens, thoracoscopy has virtually replaced open pleural biopsy for the diagnosis of unknown pleural disease. However, in certain instances, as when attempting to establish definitively the diagnosis of malignant mesothelioma, which often requires a large amount of tissue, open pleural biopsy may be necessary. However, some clinicians have reported high diagnostic yields for malignant mesothelioma with thoracoscopy. Neither open pleural biopsy nor thoracoscopy always provides a diagnosis in unknown pleural disease, particularly with nonmalignant causes. At times, a malignancy is not discovered for months following open pleural biopsy; in these cases, the effusion was probably paramalignant at the time of the procedure.

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CHAPTER

13 Preoperative Evaluation and Relation to Postoperative Complications

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INTRODUCTION

This chapter is designed to inform internists and surgeons, including pulmonologists and thoracic surgeons, of the pulmonary dysfunctions and complications that increase morbidity and mortality in patients undergoing surgical procedures, and to suggest a cost-effective method of assessing patients preoperatively. These pulmonary complications are especially likely to occur in patients who are older, obese, or smokers, who undergo thoracic or abdominal surgery, or who have lung or other organ system diseases or undergo lung resection.

PATHOPHYSIOLOGIC FEATURES OF MAJOR POSTOPERATIVE PULMONARY COMPLICATIONS

Atelectasis and Shunting with Hypoxemia

Lung volumes change quickly during anesthesia and surgery. In Fig. 1, the declines in both vital capacity (VC) and forced expiratory volume in 1 second (FEV_1) in the week after abdominal or thoracic surgery are striking and persistent, even though no lung was resected. Concurrently, alveolar-arterial differences in partial pressure of oxygen [$P(A\text{-}a)O_2$] increased. During surgery with general anesthesia, increases in $P(A\text{-}a)O_2$ and $P(A\text{-}a)CO_2$ (alveolar-arterial difference in partial pressure of carbon dioxide) could be attributed to decreases in lung compliance, increased shunting, increased pulmonary dead space, or decreased efficiency of ventilation secondary to ventilation and perfusion mismatching—that is, mechanisms causing increases in venous admixture.

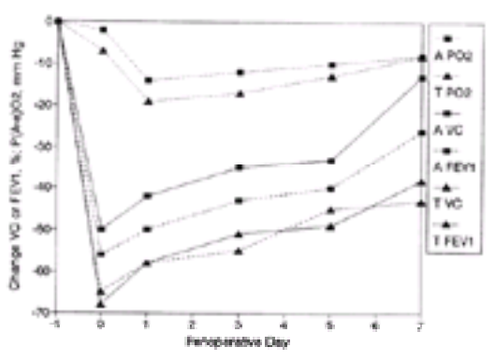

FIG. 1. Average change in spirometric values (%) and $P(A\text{-}a)O_2$ (mmHg) after thoracic (*T*) or abdominal (*A*) surgical procedures in 34 patients. (Modified with permission from Bryant LR, et al. Lung perfusion scanning for estimation of postoperative pulmonary function. *Arch Surg* 1972;104:52.)

Altered mechanics of the chest wall and diaphragm, however, with a decrease in functional residual capacity (FRC), are the primary cause of the development of areas of atelectasis and secondary hypoxemia. Ventilation during anesthesia with gas mixtures low in nitrogen (N_2) may also accelerate air space collapse. Patients undergoing upper abdominal surgery who have the greatest reduction in FRC postoperatively also have the highest incidence of pulmonary complications. If patchy atelectasis is sought, it can nearly always be demonstrated roentgenographically during general anesthesia for upper abdominal surgery. The appearance of these areas of atelectasis during anesthesia in normal individuals correlates positively with the magnitude of shunting and can usually be cleared by application of positive end-expiratory pressure (PEEP) at 10 cm H_2O. Apparently, inhalation anesthetics inhibit hypoxic pulmonary vasoconstriction more than do intravenous anesthetics, thus tending to cause more overperfusion of poorly ventilated air spaces and greater hypoxemia.

Rarely in patients undergoing cardiac transplantation or in patients with severe lung disease who are undergoing resection, sufficient pulmonary hypertension develops to open a potentially patent foramen ovale and cause shunting from the right to left atrium, with very severe widening of the $P(A\text{-}a)O_2$. The diagnosis of a patent foramen ovale can be made by having the patient breath 100% O_2. Because of the resulting high alveolar and end-pulmonary capillary PO_2 and complete saturation of hemoglobin at these high pressures, the venous admixture resulting from the development of a right-to-left shunt reduces the measured PaO_2 in an almost linear

fashion proportional to the size of the shunt.

Factors Predisposing to Postoperative Pneumonia

Impaired Transport of Mucus

Transport of mucus from the lower lobes and trachea is impaired for several days after upper abdominal surgery under general anesthesia, but only minimally after surgery of a lower extremity. It is well assessed by insufflation of the airways with tantalum. This transport deficiency, also associated with visible atelectasis, is probably related more to immobilization, diaphragmatic dysfunction, and ineffective coughing than to endotracheal intubation.

Aspiration

Aspiration of oral and gastric contents occurs occasionally in normal individuals during sleep. In the perioperative period, such aspiration of gastric or oropharyngeal contents into the tracheobronchial tree may cause pulmonary dysfunction resulting from acid burns, mechanical obstruction, or bacterial pathogens. Aspiration can easily occur during induction of anesthesia (if the stomach is not empty or emptied) whenever the endotracheal cuff is not properly inflated, or postoperatively if extubation is premature (before the gag reflex returns). Postoperatively, the use of a nasogastric tube may increase pulmonary aspiration.

Pre-existing Lung Infection

Both clinically evident and subclinical respiratory tract infection are associated with an increased risk for pneumonia. Carrel and colleagues found that pneumonia frequently developed in cardiac patients in whom immediate postsurgical tracheal aspirates were positive for micro-organisms despite perioperative antibiotic therapy (8 of 26), but rarely in those with negative aspirates (1 of 72).

Impaired Coughing

Coughing to clear secretions in the postoperative period is especially difficult in the presence of postoperative chest and abdominal pain. Coughing is less effective in patients with obstructive lung disease and low expiratory flow rates.

Respiratory Failure

Postoperative respiratory failure commonly occurs in patients with severe obstructive lung disease undergoing thoracic or upper abdominal surgery. Preoperative CO_2 retention, obesity, sepsis, and shock all increase the probability of postoperative respiratory failure. Maede and colleagues showed that the ratio of abdominal to transdiaphragmatic pressure decreased postoperatively, indicating diaphragmatic weakness, and that the greatest reductions occurred in the 4 of their 20 patients who required mechanical ventilation for 2 to 6 days. The decrease in lung volumes and flow rates during the several days following chest or upper abdominal surgery, especially when combined with pain, weakness, and sedation, necessarily reduces the drive and ability of postoperative patients to ventilate and remove metabolically produced CO_2. The elimination of CO_2 rarely is a problem except in patients with significant lung disease. In these patients, the ability to ventilate may be not only seriously reduced but also inefficient, the latter attributable to an increase in the ratio of physiologic dead space to tidal volume (V_D/V_T). Postoperative infection with fever and increased metabolism (causing high CO_2 production) and the intraoperative insufflation of CO_2 during an abdominal endoscopic procedure are additional causes of acute respiratory acidosis and respiratory failure.

The degree of V_D/V_T abnormality can be calculated from the patient's estimated or measured CO_2 output and measurement of the arterial CO_2 and minute ventilation. In patients whose ability to ventilate is compromised, repeated assessments with changes in ventilator settings and body position may be necessary to reduce the V_D/V_T and optimize CO_2 removal. With anemia, heart failure, shock, or infection, ventilation with high O_2 or high ventilatory pressures can lead to further lung damage and failure.

Pulmonary Embolism

Pulmonary emboli are common sequelae of venous thrombosis in the deep veins of the leg. In one study, the incidence of deep venous thromboses in three groups of hospitalized patients was as follows: (1) 11% in those without any of the risk factors of advanced age, obesity, malignancy, recent surgery, or history of deep venous thromboses; (2) 50% in those with three risk factors; and (3) 100% in those with four or more risk factors. Another expert group estimates the incidence of deep venous thrombosis as follows: (1) approximately 10%–20% (high risk) in patients older than 40 years with a recent history of venous thrombosis, or those undergoing extensive abdominal or pelvic surgery for malignancy, or those undergoing major orthopedic surgery of a lower extremity; (2) approximately 2%–10% (moderate risk) in patients undergoing general surgery of >30 minutes' duration (risk increases progressively with advancing age, malignancy, congestive failure, obesity, varicose veins, prolonged immobilization, and paralysis); and (3) <1% (low risk) in patients having uncomplicated or minor surgery of <30 minutes' duration. In these three groups, the risk for fatal pulmonary embolism is approximately 1%–5%, 0.1%–1%, and <0.01%, respectively, with an overall risk for general surgery of approximately 1%. Despite this known high incidence, even now in a well-known academic medical center with a major interest in thromboembolic disease, a correct diagnosis was established before autopsy in only 30% of patients who had a fatal pulmonary embolism. Wheeler and Anderson further noted a low incidence of thromboembolic prophylaxis even in high-risk patients, ranging from 9%–56% in different New England hospitals.

RISK FACTORS

The following are some of the recognized risk factors contributing to an increase in pulmonary complications postoperatively.

Age

The maximal flow rates, FEV_1, VC, FEV_1/VC, and maximum voluntary ventilation (MVV) all decline with age, so that normal individuals have less ventilatory reserve and less ability to clear secretions by coughing as they age. Additionally, and probably related to the decrease in elastic recoil and resultant increase in residual volume (RV), the $P(A\text{-}a)O_2$ increases each year on average by approximately 0.4 mmHg. Thus, even without pulmonary, neuromuscular, or other organ disease processes, there is a gradual reduction in PaO_2 with aging and less reserve for the increased ventilatory requirements that may be needed postoperatively. Postoperative hypoxemia increases with advancing age. Of course, the more frequent occurrence of other systemic diseases with advancing age necessarily adds to the likelihood of postoperative problems.

Obesity

Obesity is a major cause of postoperative complications. At least two studies found that after upper abdominal surgery, obesity was the most important risk factor associated with clinically significant atelectasis. The incidence of both preoperative and postoperative hypoxemia increases strikingly with obesity and age and is worse in the supine position (Fig. 2). Such hypoxemia is primarily a consequence of the high proportion of regions with decreased ventilation without compensatory reduction in perfusion (low $\dot{V}_A/\dot{Q}$) at the lung bases, but it may be aggravated by reduced ventilatory drive associated with CO_2 retention or metabolic alkalosis. With moderate thoracic and abdominal obesity, the VC may remain within normal limits, but the expiratory reserve volume (ERV) inevitably declines, indicating that the resting position of the diaphragm is elevated. With extreme obesity, the VC and MVV may become significantly decreased below predicted values in the absence of intrinsic lung disease and despite normal general muscle strength. Thus, hypoxemia, hypercapnia, somnolence, sleep apnea, and pulmonary hypertension are common complications of even moderate obesity. As hypoxemia and atelectasis are common postoperative occurrences even in patients who are not obese, and ventilatory work is increased with truncal obesity, obese patients have multiple handicaps in the postoperative period. Additional disadvantages for obese patients are the requirements for larger doses of many anesthetics because of their high solubility in fatty tissue, the longer time needed to eliminate anesthetics from the body, the longer time necessary to complete the surgical procedure, the increased acidity of gastric juice, and the increased frequency of aspiration of gastric contents. To this list can be added the higher incidence of diabetes mellitus and cardiovascular and thromboembolic diseases and the difficulties involved in postoperative ambulation and nursing care.

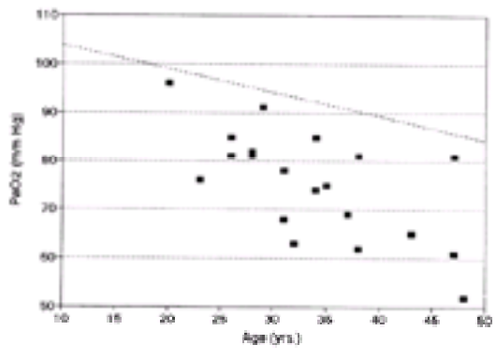

FIG. 2. Effect of age on PaO_2 in morbidly obese, awake, supine patients. The *dotted line* is regressed from data of Sorbini and colleagues for normal adults, with a standard deviation of 4 mmHg. (Modified with permission from Vaughan RW, et al. Postoperative hypoxemia in obese patients. *Ann Surg* 1974;180:877.)

Surgical and Incisional Site

Evidence is overwhelming that the incidence of postoperative morbidity and mortality is closely linked to the site of surgical intervention. It should be recalled that with upper abdominal surgery or thoracic surgery without lung resection, the FEV_1 and VC are strikingly reduced as soon as they can be measured postoperatively and do not usually return to preoperative levels within 1 week. When possible, it is desirable to choose an incisional site in thoracic surgery associated with lesser postoperative discomfort. A higher rate of atelectasis and hypoxemia occurs with vertical than with horizontal laparotomies. The overall incidence of postoperative cardiopulmonary complications becomes progressively lower in patients undergoing lower abdominal, pelvic, and extremity surgery. However, the incidence of venous thromboses and pulmonary emboli is very high in patients undergoing hip and knee surgery.

Lung Disease

Although postoperative morbidity and mortality cannot be accurately predicted for every patient, patients with significant lung disease undergoing thoracic or abdominal surgery are at high risk. Both obstructive and restrictive lung diseases are handicaps. However, the former carries a greater postoperative risk than the latter. In 1956, Miller and associates introduced a four-quadrant diagram based on the $FEV_{0.5}$ and VC, later modified by others, to categorize disturbed respiratory mechanics. This diagram graphically identifies relative postoperative risk in patients with obstructive, restrictive, and combined lung disorders (Fig. 3). All other things being equal, it can be noted in this diagram that the risk for postoperative ventilatory failure might be (1) slightly better than marginal in a patient with an FEV_1/VC of 50% and a VC or total lung capacity (TLC) that is 50% of predicted (i.e., moderate obstruction and moderate restriction); (2) prohibitive in a patient with an FEV_1/VC of 35% and VC or TLC that is 80% of predicted (i.e., severe obstruction and mild restriction); but (3) satisfactory in a patient with an FEV_1/VC of 70% and a VC or TLC that is 45% of predicted (mild obstruction and severe restriction). These differences in risk are logically related to the difficulty encountered by patients with obstructive disease in clearing airway secretions in the postoperative period.

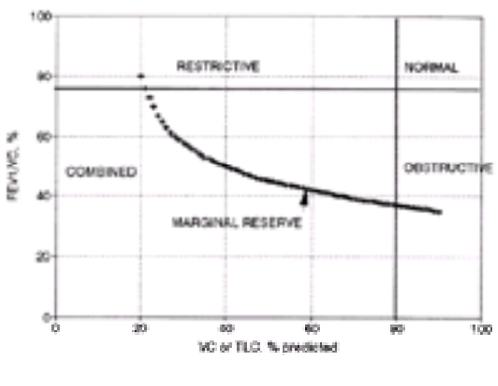

FIG. 3. Four-quadrant diagram for estimation of the relative risk of surgery in patients with lung disease. The *upper fourth* of the graph includes patients who are normal or have only restrictive lung disease; the *lower three fourths* includes patients with obstructive disease with or without restrictive lung disease. As a broad generalization, all patients below the marginal reserve line can be expected to require ventilatory support postoperatively. (Modified with permission from Hodgkin JE. Evaluation before thoracotomy. *West J Med* 1975; 122:104.)

Stein and colleagues noted that a reduced maximal expiratory flow rate ($FEF_{200-1200}$) was a potent predictor of postoperative pulmonary complications. Even patients with severe restrictive lung disease often have increased lung elastic recoil, can maintain satisfactory peak flow measurements, and can clear secretions adequately. On the other hand, patients with severe obstructive lung disease often have a very low $FEF_{200-1200}$ or peak flow readings and an ineffective cough. When either restrictive or obstructive lung disease has progressed to the stage at which CO_2 retention has occurred, the risk of surgery increases markedly. To oversimplify, the "blue bloater" chronic bronchitic patient is likely to be at greater risk than the "pink puffer" for the same severity of airways obstruction. The risk for complications in the asthmatic patient is inversely related to the adequacy of control of the asthma before the time of surgery.

Resection of Lung Tissue

It is logical to expect that morbidity and mortality would be directly related to the amount of lung tissue resected. In many series, this expectation is obscured by patient selection, because those who are not expected to survive often do not have lung resected. More important than the amount of lung tissue removed is the ability of the remaining lung tissue to transfer O_2 and CO_2 between blood and environment through the processes of ventilation, diffusion, and perfusion. Thus, in those patients undergoing resection of a significant amount of lung tissue, it is wise to quantify the total lung function.

Smoking

It may be difficult to confirm statistically significant abnormalities in cardiovascular or pulmonary function in many smokers, even those who have smoked for long periods. Nevertheless, several studies do confirm that smokers, even those without demonstrable pulmonary or cardiovascular disease, are at increased risk for postoperative complications. For example, Wightman found a 15% incidence of postoperative complications (fever, productive cough, and abnormal chest findings) after abdominal surgery in smokers, compared with a 6% incidence in nonsmokers. Laszlo and colleagues found a 53% incidence of postoperative complications in smokers, versus a 22% incidence in nonsmokers. Carrel and coworkers prospectively evaluated 100 patients undergoing cardiac surgery and found that the development of postoperative pneumonia was highly correlated with smoking, abnormal spirometry, and positive tracheal aspirates at the time of intubation. Poor oral hygiene, chronic cough, reduced ciliary function in the airways, likelihood of larger numbers of pulmonary bacterial pathogens, elevated carboxyhemoglobin levels, and the effects of nicotine on the cardiovascular system all contribute to the increased morbidity in smokers.

Cardiovascular, Neuromuscular, and Other Organ Disease

Patients with heart failure, recent myocardial infarction, or arrhythmia are at increased risk for postoperative cardiopulmonary complications, but moderate systemic hypertension is not a risk factor. Understandably, a recent stroke, psychosis or severe neurosis, degenerative neurologic processes, acute or chronic infections, damage to the upper airways or rib cage, compromised immunologic status, chronic drug or alcohol abuse, difficulty with mastication or swallowing, and chronic toxic or metabolic disorders all increase the likelihood of pulmonary morbidity.

Type and Duration of Anesthesia

Because of the many variables that influence selection of anesthetics and postoperative morbidity, it is difficult to compare different types or routes of anesthesia for the same operation. In two series of patients with severe obstructive lung disease, there was no difference in arterial oxygenation when general was compared with regional anesthesia for lower abdominal surgery. Clearly, the following are desirable: a smooth induction, adequate control of the airway and ventilation, adequate oxygenation without sudden shifts in acid-base status, reduction in atelectasis during and after surgery, adequate blood and fluid replacement, avoidance of other organ toxicity, and quick recovery from the anesthetic and muscle relaxant agents. There is consensus that the duration of the surgical procedure is much more significant than the type or route of administration of anesthesia.

PREOPERATIVE EVALUATION OF PATIENTS NOT UNDERGOING LUNG RESECTION

History and Physical Examination

It is trite but true that a good history and physical examination are extremely cost-effective and essential if unexpected morbidity and mortality are to be avoided. The history should include specific questions regarding duration and frequency of smoking; other drug history; dyspnea; activity level; cough frequency and characteristics; quantity and type of sputum production; intermittent wheezes or noisy breathing; chest pain, tightness, or distress; possible recent infections; toxic exposure; weight change; immobility; and venous insufficiency. Other major organ systems should not be ignored. For example, there is no significant cost associated with identifying patients with a high susceptibility to pulmonary embolism, who should receive appropriate prophylaxis. Likewise, Gracey and associates found that daily production of 2 oz or more of sputum was a valuable predictor of postoperative complications.

In the physical examination, poor oral hygiene, chest asymmetry, signs of airway disease, the duration (in seconds) of a complete forced expiration, body habitus, and evidence of clubbing, edema, or venous disease should be specifically noted. If the patient's subjective assessment seems inappropriate for objective physical findings, further evaluation is necessary. Wise physicians weigh their assessment of the patient's daily activity, exercise, and symptom status (or lack thereof) against the expected stress of surgery. We have all seen patients whose daily activity level is so low that they do not complain of dyspnea despite advanced heart or lung disease, and we regard highly those surgeons who walk or climb stairs with their patients before major surgery!

Roentgenography, Electrocardiography, and Other Laboratory Tests

A recent posteroanterior chest roentgenogram and electrocardiogram (ECG) should be obtained for anyone undergoing a significant surgical procedure. The necessity for other laboratory measures, including a hemogram, urinalysis, blood chemistries, and smears or cultures of body fluids, depends on the surgery contemplated and the findings elicited or suspicions aroused during the history and physical examination.

Arterial Blood Gas Analysis

An arterial blood gas analysis is indicated for obese patients, patients with neuromuscular disease, and those with symptoms or signs suggestive of recent or current respiratory disease. An elevated $PaCO_2$, regardless of the cause, is a significant finding associated with high postoperative risk. A PaO_2 significantly below that predicted for the patient's age and body habitus indicates the need for further evaluation. Unexpected acid-base disturbances may also be detected from analysis of arterial blood gases and pH.

Spirometry

In general, we recommend simple spirometry for patients undergoing upper abdominal or thoracic surgery who are moderately to severely obese or who have a history of heavy smoking or symptoms or signs suggesting lung disease or heart failure. Spirometry is probably not cost-effective in asymptomatic patients or in mildly symptomatic patients undergoing surgery of an extremity. The important measures are FEV_1, VC, $FEF_{200–1200}$ or peak flow rate, and the directly measured MVV for 10 to 15 seconds. Except for body weight, visualization of the tracings, calculation of the FEV_1/VC, division of the VC into the inspiratory capacity and the ERV, and other measurements or calculations add little. It is especially important to measure the MVV directly in a patient who appears to be infirm or who is undergoing thoracic or upper abdominal surgery; inability to perform the MVV maneuver adequately gives warning that the patient may not be able to cooperate, coordinate, learn, or perform the necessary postoperative ventilatory maneuvers.

If airway obstruction is present, spirometry should be repeated after inhalation of a bronchodilator.

A review by Zibrak and associates criticized the methodology of earlier studies and concluded (in part) that “in upper abdominal surgery, spirometry and arterial blood gas analysis did *not* consistently have measurable benefit in identifying patients at increased risk for postoperative pneumonia, prolonged hospitalization, and death.” This report went on to suggest that further critical investigation was required to reach a consensus regarding the role of preoperative pulmonary function tests in patients not undergoing lung resection.

We disagree. There is already significant evidence that preoperative spirometry is valuable in identifying patients at increased risk. Three decades ago, Stein and coworkers prospectively selected, at random, 100 ward patients admitted for surgical procedures. Of these, 32 did not have surgery because of lack of surgical indication and 5 were not operated on because of the severity of their cardiac or pulmonary disease. The 63 remaining patients were divided into two groups on the basis of their respiratory function. Group 1 patients had essentially normal lung function: $FEF_{200–1200}$ was >200 L/min (3.3 L/s) in 30 and was unmeasured in 3 patients; the single-breath O_2 test measured £2.5% in 30 and was unmeasured in 3; and the estimated $PaCO_2$ was £41 mmHg in 28 and was unmeasured in 5. Group 2 patients had abnormal lung function: $FEF_{200–1200}$ was <200 L/min in 30 patients; the single-breath O_2 test measured ³2.0% in 18, £2.5% in 8, and was unmeasured in 4; and the estimated $PaCO_2$ was ³42 mmHg in 9, £41 mmHg in 18, and unmeasured in 3. Respiratory complications occurred in only one patient in group 1 and in 21 patients in group 2. In group 2, 7 of 9 patients undergoing thoracotomy and 11 of 12 undergoing abdominal surgery experienced complications.

The positive evidence from four more recent studies should be considered. First, Gracey and colleagues in a prospective study found that 6 of 35 patients with a midexpiratory flow rate ($FEF_{25–75}$) below 50% of predicted and forced vital capacity (FVC) below 75% of predicted (group A) required prolonged mechanical ventilation, whereas only 1 of 122 patients with values exceeding these (group B) required such ventilation after several types of surgery. Four of these 7 patients died. The total number of complications also differed significantly. Complications occurred in 12 of 35 patients (34%) in group A versus 15 of 122 patients (12%) in group B.

Poe and associates prospectively examined 209 patients undergoing elective cholecystectomy and postoperatively identified 21 with atelectasis, 8 with purulent bronchitis, and 2 with pneumonia. These 31 patients were hospitalized an average of 1.5 days longer than the others. Abnormal peak flow and the single-breath O_2 test were significant predictors of postoperative pulmonary complications, whereas reduced FVC was a significant predictor of prolonged hospitalization.

Vodinh and coworkers prospectively studied 153 patients undergoing nonurgent vascular surgery. In comparing 24 clinical and laboratory factors, they found postoperative respiratory complications were significantly higher only in those with a clinical chest abnormality, recent bronchitis, aortic surgery, longer duration of surgery, low FEV_1/VC, and low PaO_2. They concluded that spirometry and blood gas analysis were helpful in assessing risk.

Finally, Carrel and colleagues, in a prospective study of patients undergoing cardiac surgery, also demonstrated that incidence of postoperative pneumonia was correlated with abnormal results of preoperative lung function studies.

It is unlikely that any test can ever clearly distinguish between those who will or will not survive, or between those who will or will not have a specific complication. We suggest that spirometry and blood gas analyses should not be performed in everyone undergoing abdominal or thoracic surgery without lung resection, but that these tests are usually indicated for patients with asthma, chronic cough, sputum production, dyspnea, wheezing, poor exercise tolerance, congestive failure, weakness, or morbid obesity.

Gas Transfer and Lung Volume

Unless lung resection is contemplated or the patient has significant spirometric abnormalities, measurement of gas transfer (D_LCO) and RV add cost and only infrequently provide additional information regarding operative risk.

Exercise Testing

If the patient has heart or lung disease or both, and the severity of the exercise limitation is uncertain, exercise testing with metabolic, ventilatory, gas exchange, blood pressure, and ECG measures may add information helpful in further assessing operative risk. Gerson and coworkers prospectively studied 177 geriatric patients undergoing abdominal and noncardiac thoracic surgery and included supine exercise testing in their multivariate analysis. They found that a patient's inability to perform 2 minutes of such exercise and raise the heart rate above 99 beats per minute (bpm) was the best single predictor of cardiac (14%), pulmonary (14%), or combined (22%) complications. There were 10 complications (9%) and 1 death (1%) in the group of 108 patients who could increase their heart rate to >99 bpm, and 29 complications (42%) and 5 deaths (7%) in the group of 69 patients who were unable to do so.

Because of the high perioperative mortality in elderly patients undergoing elective colorectal surgery or abdominal surgery for aortic aneurysm, Older and his colleagues successfully used noninvasive cardiopulmonary exercise testing with gas exchange measurements to screen 187 of 191 such patients over the age of 60. Forty-four had ECG tracings during exercise showing changes attributable to myocardial ischemia. Surgery was performed in the 187 screened patients, with an overall in-hospital mortality of 7.5%, 5.9% from cardiovascular causes. Mortality from cardiovascular causes was 18% in the 55 patients with an anaerobic threshold $\dot{V}O_2$ of <11 mL/min per kilogram, but was only 0.8% in the 132 patients with an anaerobic threshold that was ³11 mL/min per kilogram. The association of an anaerobic threshold $\dot{V}O_2$ of <11 mL/min per kilogram and preoperative ischemia resulted in a mortality of 42%, whereas those with preoperative ischemia and a higher anaerobic threshold had a mortality of only 4%. In addition to recommending exercise testing with gas exchange measurements for major abdominal surgery in the elderly, they suggest that all patients with demonstrated preoperative myocardial ischemia or an anaerobic threshold of <11 mL/min per kilogram be admitted preoperatively for stabilization. The use of these policies has measurably reduced perioperative mortality.

Conclusions

Williams-Russo has commented that “preventing cardiac morbidity may be the best approach to reducing pulmonary morbidity.” From the viewpoint of the patient, surgeon, and internist, we may unwisely evaluate the risks for morbidity and death by segregating the causes as “cardiovascular” or “pulmonary,” as these systems are so clearly interrelated in real life.

In the individual patient, the risk of operative intervention needs to be weighed against the risk of other therapies or nontreatment of the patient's disorder. It is wise to delay surgery when the likely morbidity and mortality of thoracic or upper abdominal surgery can be reduced by active intervention (e.g., through weight loss, anticoagulation, antibiotic or corticosteroid therapy, or intensive bronchodilator therapy). If such delay significantly decreases the patient's chances for recovery or cure of the primary disorder, then only very brief interventions before a decision regarding surgery are warranted. Table 1 gives some broad guidelines suggestive of high morbidity and mortality in thoracic or upper abdominal surgery.

Factor or test	Upper abdominal surgery	Lung resection[a]
Age >70 y	+	+
Abnormal ECG	+	+
FEV_1 <40% predicted	+	++
FEV_1/VC <40%	++	++
$FEF_{200-1200}$ <2 L/s	++	++
MVV <50% predicted	+	+++
D,CO <, 50% predicted	+	++
$PaCO_2$	++	+++
PaO_2 <60 mmHg	+	±
VO_2max <15 mL/min/kg	++	+++

± indicates possible increase in mortality; +, some increase in mortality; ++, considerable increase in mortality; +++, very high increase in mortality.

[a] None of these factors or values should be used as absolute contraindications to surgery.

[b] Preoperative quantitative perfusion scans with preoperative FEV_1, MVV, DLCO, and VO_2max tests values are helpful in predicting same test values postoperatively after lung resection.

TABLE 1. *Some factors associatedwith high surgical mortality*[a]

PREOPERATIVE EVALUATION OF PATIENTS UNDERGOING LUNG RESECTION

Initial Preoperative Assessment

All the evaluations considered for patients in whom lung resection is not planned, including DLCO and lung volume measurements, are useful also in the patient being evaluated for lung resection. Commonly, lung resection is performed in malignant states, but similar evaluation is indicated for patients with decreased lung function resulting from inflammatory, traumatic, hereditary, or other disorders. Roentgenographic examinations will always be more complete, and endoscopy results may be available. Bronchodilator responsiveness becomes very important if ventilatory function is significantly reduced, and DLCO should certainly be measured. If maximal inspiratory and expiratory pressures are low, preoperative pulmonary rehabilitation may reduce the incidence of postoperative complications.

In the earliest of several retrospective studies, Gaensler and coworkers found that the MVV was an important predictor of survival in patients undergoing lung resection for tuberculosis; if the preoperative MVV was <50% of predicted, 50% of the patients died, whereas if the MVV was >50% of predicted, only 1% of the patients died. Boushy and associates found that advanced age, severity of dyspnea, high RV, low gas transfer per lung volume (DLCO/VA), reduced FEV_1, and reduced MVV were all significant predictors of high morbidity and mortality. Confirming the value of the MVV, Didolkar and associates, in a retrospective study of resection for lung cancer, found that mortality from cardiopulmonary complications was much higher in those with an MVV that was <60% of predicted. There were no postoperative deaths in the nine patients older than 70 years who had a normal ECG and an MVV that was >60% of predicted.

Ferguson and coworkers retrospectively reviewed their results for lung resection in 237 patients (cancer in 203 and benign disease in 34). They took into account 38 different preoperative and operative risk factors and found, by logistic regression analysis, that the DLCO was the most important predictor of postoperative survival and the sole predictor of pulmonary complications. For DLCO values that were <60%, 61%–80%, 81%–100%, and >100% of predicted, postoperative mortality was 25%, 8%, 5%, and 0%, respectively, and pulmonary complications were 45%, 33%, 13%, and 11%, respectively.

Several investigators have utilized measures of pulmonary arterial pressure, pulmonary vascular resistance, and right ventricular injection fraction preoperatively and intraoperatively after pulmonary arterial clamping. These invasive measures are generally less useful than noninvasive exercise testing and quantitative scans in estimating postoperative morbidity and mortality.

Predicting Postoperative Function

When resting preoperative lung function, as measured by spirometry and DLCO, is significantly impaired, or when large portions of lung may be removed surgically, it is worthwhile to predict postoperative lung function to assess postoperative survival or quality of life. Bronchospirometry and the lateral position tests, introduced in the 1950s and 1960s, were of some assistance in predicting postoperative function, but they have now been supplanted by newer techniques.

Quantitative radioisotopic ventilation and perfusion scans are now commonly and effectively used to predict postoperative FEV_1, DLCO, and peak $\dot{V}O_2$ (Fig. 4 and Fig. 5). In each case, the expected postoperative FEV_1, DLCO, or peak $\dot{V}O_2$ is calculated by multiplying each preoperative value by the measured ratio of expected postoperative lung activity to preoperative total lung activity. For example, if 40% of the quantitatively measured perfusion scan activity occurs in the lung that is to be resected, the calculated postoperative DLCO or peak $\dot{V}O_2$ will be 60% of the preoperative DLCO or peak $\dot{V}O_2$. Ventilation scans or quantitative computed tomography (CT) can be similarly used to predict postoperative FEV_1 values. Using the ratio of the number of expected postoperative lung segments to the total number of preoperative segments tends to give an underestimate of postoperative function, because lung segments differ in size and because the removed segments are likely to be worse than those retained.

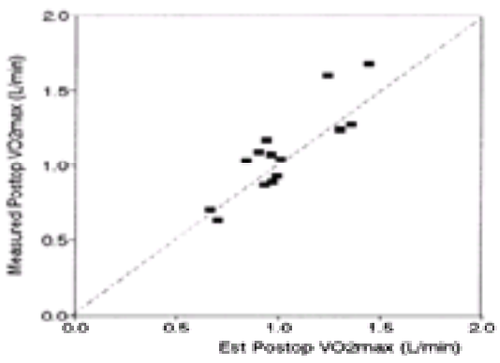

FIG. 4. Comparison of measured postoperative FEV_1 and estimated postoperative FEV_1 in 28 patients undergoing pneumonectomy. Estimated postoperative FEV_1 was calculated from preoperative FEV_1 and quantitative technetium Tc 99m perfusion scans. (Modified with permission from Corris PA, et al. Use of radionuclide scanning in the preoperative estimation of pulmonary function after pneumonectomy. *Thorax* 1987;42:285.)

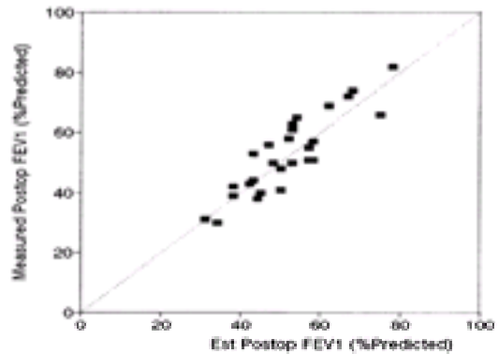

FIG. 5. Comparison of measured postoperative $\dot{V}O_{2max}$ and estimated postoperative $\dot{V}O_{2max}$ in 14 patients undergoing pneumonectomy. Estimated postoperative $\dot{V}O_{2max}$ was calculated from preoperative $\dot{V}O_{2max}$ and quantitative technetium Tc 99m perfusion scans. (Modified with permission from Corris PA, et al. Use of radionuclide scanning in the preoperative estimation of pulmonary function after pneumonectomy. *Thorax* 1987;42:285.)

Markos and coworkers prospectively studied by lung function tests and scintigraphy 55 consecutive candidates for lung cancer resection. Fifty-three underwent thoracotomy, with pneumonectomy in 18, lobectomy in 29, and no resection in 6. Postoperative FEV_1 and D_LCO were well predicted from preoperative measures. There were only 3 deaths, all occurring in the 6 candidates who had a predicted postoperative FEV_1 of 40% or less. Wahi and associates reviewed 197 consecutive cancer patients undergoing pneumonectomy. Of the 14 perioperative deaths, 13 occurred in patients undergoing right pneumonectomy. Those with a predicted postoperative FEV_1 exceeding 1.65 L had lower mortality.

Pierce and colleagues found that the predicted postoperative product, which is the predicted postoperative FEV_1 times predicted postoperative D_LCO, was the best predictor of surgical mortality in 54 consecutive patients with bronchogenic carcinoma. The mean values of their population were as follows: age, 67; FEV_1, 76% of predicted; D_LCO, 85% of predicted; and peak $\dot{V}O_2$, 18.4 mL/min per kilogram. Pneumonectomy was performed in 11, lobectomy in 29, and lesser resection in 14. There were 48 survivors. Although peak $\dot{V}O_2$ values did not predict outcome, 2 of the 3 patients with peak $\dot{V}O_2$ values that were <14 mL/min per kilogram died in the perioperative period. In 331 candidates, Kearney and associates found that the primary predictor of resectional outcome was the absolute predicted postoperative FEV_1, but they did not analyze D_LCO or peak $\dot{V}O_2$ values.

Exercise Testing

Two early studies showed the value of preoperative exercise testing in patients undergoing lung resection. Eugene and colleagues found that among 19 patients, death occurred in 3 of 4 patients with a peak $\dot{V}O_2$ of <1 L/min. In 22 patients, Smith and coworkers found no deaths and 10% morbidity if peak $\dot{V}O_2$ exceeded 20 mL/min per kilogram; 17% deaths and 67% morbidity with peak $\dot{V}O_2$ of 15 to 20 mL/min per kilogram; and 17% deaths and 100% morbidity if peak $\dot{V}O_2$ was <15 mL/min per kilogram.

Bechard and Wetstein prospectively evaluated 50 consecutive patients undergoing lung resection with the surgeon blinded to the preoperative peak $\dot{V}O_2$ values. Candidates for resection were required to have an FEV_1 of >1.7 L for pneumonectomy (10), 1.2 L for lobectomy (28), or 0.9 L for wedge resection (12). Mortality was 4% and other morbidity 12%. Both peak $\dot{V}O_2$ and anaerobic threshold measures predicted mortality and morbidity, but age, FVC, FEV_1, and MVV did not. Maurice and colleagues found 8 of 37 high-risk patients to have a peak $\dot{V}O_2$ of >15 mL/min per kilogram. All survived resectional surgery.

Walsh and colleagues prospectively evaluated 66 patients with potentially resectable non–small-cell lung cancer, considered to be high risks on the basis of preoperative FEV_1 that was <40% of predicted, predicted postoperative FEV_1 that was <33% of predicted, resting $PaCO_2$ exceeeding 45 mmHg, or at least two criteria indicating cardiac disease. In 20 patients with a peak $\dot{V}O_2$ of >15 mL/min per kilogram, there were no perioperative deaths and 40% complications. Among five patients with a peak $\dot{V}O_2$ of <15 mL/min per kilogram, there was one death. In this population, only surgical versus medical treatment and peak $\dot{V}O_2$ exceeding 15 mL/min per kilogram significantly predicted survival; age, FEV_1, $PaCO_2$, clinical stage, and T status did not. Bollinger and coworkers operated on 25 high-risk patients, with only three deaths. Lower preoperative or predicted postoperative peak $\dot{V}O_2$ values correlated with higher morbidity and mortality.

Conclusions

Physicians and surgeons are obligated to share information and expectations with patients before making final decisions on therapy. Assigning an exact risk to a major surgical procedure in the individual cancer patient is difficult, but multiple high-risk factors and common sense can dictate against surgical treatment. Debility and cardiovascular disease add to risk. Smoking cessation, vigorous bronchodilator therapy, and rehabilitating exercise therapy may help. Despite recent advances in therapy, I am not as optimistic as Olsen in believing that “almost no one” is inoperable. In a high-risk patient, measures of D_LCO, quantitative perfusion scan, and gas exchange exercise testing are all clearly useful in assessing risk. Because of differences in patient sex, size, and age, both absolute and percent predicted values should be considered.

PREVENTION OF COMPLICATIONS

Preoperative Considerations

The more severe the risk of complications, the more important it is to take effective action preoperatively. Patients should stop smoking as soon as it is realized that surgery is likely, even if the patient has normal findings on pulmonary function tests. Cessation for even a few days is advantageous. Advantages of smoking cessation include an expected reduction in cough, improvement in ciliary function and mouth hygiene, reduction in lower airway pathogens, and reduction in carboxyhemoglobin levels. Warner and colleagues, in a blinded prospective study of patients undergoing coronary bypass surgery, found that postoperative pulmonary complications developed in approximately 1 of 3 of the current smokers, 5 of 9 of those who stopped smoking for less than 2 months, 1 of 7 of those who stopped smoking for more

than 2 months, 1 of 9 of those who stopped smoking for 6 months or more, and 1 of 9 of those who had never smoked.

If the patient is obese and surgery can be delayed, weight reduction is advisable, especially if the surgery involves the thorax or upper abdomen. In those with hypoventilation and CO_2 retention, a weight loss of 10 to 20 kg may bring improvement. However, caloric and fluid intake should be adequate during the days immediately preceding major surgery.

We recommend intensive bronchodilator therapy for any patient with obstructive lung disease who shows evidence, either clinically or in the pulmonary physiology laboratory, of improvement with such treatment. Asthma should be cleared with steroids if necessary.

There is little evidence that routine antibiotic prophylaxis is beneficial, but recognized pulmonary infections should be aggressively diagnosed (smear and culture) and treated for several days preoperatively if feasible.

Several studies show that preoperative training in deep-breathing respiratory maneuvers reduces postoperative complications and is cost-effective in patients who undergo thoracic or upper abdominal surgery. Bartlett and coworkers emphasized that frequent inspiratory rather than expiratory maneuvers were essential. In a prospective study of 343 cholecystectomy patients, Thoren found roentgenographic atelectasis in 12% of those who performed preoperative and postoperative breathing exercise, 27% of those who performed postoperative breathing exercise only, and 42% of the control group. In patients undergoing abdominal surgery, Celli and associates found that clinical complications and duration of hospital stay were much diminished in patients who had respiratory treatment started 1 day before surgery and continued postoperatively than in a randomly selected control group. Roukema and colleagues prospectively randomized patients with noncompromised pulmonary status undergoing abdominal surgery into two groups. Group 1 consisted of 84 patients with no breathing exercises, whereas group 2 consisted of 69 patients treated with preoperative and postoperative exercises. Pulmonary complications occurred in 60% of group 1 versus 19% of group 2.

Stein and Cassara compared three groups of patients undergoing abdominal and thoracic surgery: (1) those considered to be of normal risk; (2) those considered, on the basis of pulmonary function tests, to be high-risk and who were not treated; and (3) those considered to be high-risk and who were treated intensively preoperatively with smoking cessation, bronchodilator drugs, inhalation of humidified gases, chest physiotherapy, and antibiotics when indicated. Postoperative pulmonary complications occurred in 1 of 17 patients in group 1, 14 of 20 patients in group 2, and 5 of 22 patients in group 3. We have often seen patients who were considered to be prohibitive risks for lung resection become acceptable risks after several weeks of intensive therapy.

Cardiovascular disease should be treated aggressively to minimize pulmonary edema, congestive failure, myocardial ischemia, arrhythmias, significant systemic or pulmonary hypertension, hypercoagulability, and the likelihood of postoperative thromboembolic disorders. Primary prophylaxis (i.e., the prevention of deep vein thromboses by drugs or physical methods) is cost-effective, may be life-saving, and should be used whenever possible in patients with high to moderate risk for thromboembolism. Primary prophylaxis consists of anticoagulation with low-dose heparin (5000 units subcutaneously 2 hours preoperatively, and then every 8 to 12 hours postoperatively without monitoring), adjusted-dose heparin (preoperative and postoperative dosage dependent on activated partial thromboplastin time), low-molecular-weight heparin, or oral anticoagulants. Alternatively, primary prophylaxis can consist of reduction in venous stasis with dihydroergotamine, intermittent pneumatic leg compression, or graduated compression stockings. The selection of specific primary prophylaxis depends on the site and type of surgery performed and the patient's other medical problems.

If aspiration occurs or is likely to occur, as in the obese patient, antacid therapy tends to minimize the expected pulmonary complications.

Intraoperative Considerations

To the best of our knowledge, there is no evidence that the route or type of anesthetic used affects the likelihood of postoperative pulmonary complications. Usually the anesthesiologist (on the basis of skill, training, and experience) selects the most appropriate agents and route for the specific problem at hand. There is no clear evidence that spinal anesthesia is superior to general anesthesia in maintaining intraoperative and postoperative oxygenation, even in patients with severe obstructive lung disease, perhaps because of better control of the airways with general anesthesia. Among other things, the anesthesiologist attempts to maintain adequate cardiac output, oxygenation, CO_2 removal, and stable fluid and acid-base status; minimize arrhythmias, pooling of blood in extremities, and microatelectasis and macroatelectasis; and prevent aspiration of oral and gastric contents into the lung.

During laparoscopic cholecystectomy in which CO_2 is used for insufflation, a significant respiratory acidosis may develop in patients with cardiac or pulmonary disease. Because end-tidal CO_2 pressures may be misleading during such insufflation, arterial PCO_2 and pH should be monitored.

Postoperative Considerations

Ventilator support after recovery from anesthesia may be brief or prolonged. Continuous positive airway pressure (CPAP) or PEEP is usually helpful in improving oxygenation and CO_2 removal by decreasing atelectasis, improving $\dot{V}_A/\dot{Q}$, and reducing barotrauma to the lung.

Hypoxemia can be reduced and ventilation of the lung bases improved by keeping the patient, especially if obese, in a sitting or semirecumbent position rather than in a supine position (Fig. 6).

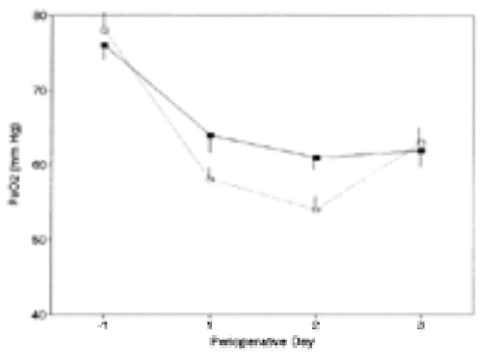

FIG. 6. Effect of body position on PaO_2 after abdominal surgery in 22 markedly obese patients. *Solid symbols* and *solid line* indicate semirecumbent position; *hollow symbols* and *dotted line* indicate supine position. (Modified with permission from Vaughan RW, Wise L. Postoperative arterial blood gas measurements in obese patients. Effects of position on gas exchange. *Ann Surg* 1975;182:705.)

Aggressive respiratory therapy to minimize atelectasis, increase FRC, improve oxygenation, and clear secretions is valuable and cost-effective. Previously, expiratory resistance and intermittent positive-pressure breathing were used frequently, but these have generally been discarded because of ineffectiveness, high cost, or barotrauma. Bronchodilator aerosol therapy alone is insufficient to improve lung volumes and oxygenation maximally after thoracic or upper abdominal surgery. There are many reports that compare the effectiveness of the following currently recommended modalities: (1) coughing and deep breathing (CDB) exercises; (2) sustained maximal inspiration or incentive spirometry (IS), using one of several available devices; (3) breathing with inspiratory resistance (IR); and (4) CPAP or PEEP by face mask. The major disadvantages of CDB, IS, and IR are the necessity for patient cooperation and the likely attendant increase in pain. PEEP or CPAP may be costlier and slightly increase the possibility of barotrauma or aspiration, but they hasten improvement in FRC and PaO_2 postoperatively in patients in whom atelectasis tends to develop. They may be detrimental to patients with severe emphysema, who are already hyperinflated because of highly compliant lung units.

Nearly all authors stress the necessity for frequent and vigilant respiratory care in the high-risk population. Because of postoperative pain, analgesics may be necessary to improve coughing and deep breathing. With severe thoracic or abdominal pain, selective and repeated nerve blocks may help the patient's performance of ventilatory maneuvers.

It is important to reduce the likelihood of aspiration with good endotracheal tube and cuff care and good technique when giving nutritional support. If a nasogastric tube is used, it should be of small caliber. Overdistention of the stomach should be avoided.

Secondary prophylaxis for thromboembolism is more costly than primary prophylaxis but is still cost-effective and life-preserving. It consists of screening high-risk patients postoperatively with tests specific for venous thromboses (e.g., fibrinogen uptake, Doppler ultrasonography, impedance plethysmography, and venography), followed by full-dose anticoagulant therapy when test results are positive. Secondary prophylaxis should be used when prophylactic anticoagulation is desired but contraindicated (e.g., urgency of surgery, neurosurgery, spinal anesthesia) or when supplementation of primary prophylaxis is required in very high-risk patients.

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CHAPTER

14 Approach to the Clinical and Radiographic Evaluation of Patients with Common Pulmonary Syndromes

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INTRODUCTION

The invention of the stethoscope by Laennec early in the nineteenth century represented a quantum leap in the power of physicians to diagnose pulmonary diseases. The advent of radiographic imaging of the chest early in the twentieth century was an advance of equal importance; its full potential has not yet been realized, even with the invention of computed tomography (CT) about 25 years ago. The past four decades have seen the development and dissemination of other powerful tools: clinical pulmonary function testing, flexible fiberoptic bronchoscopy, ultrasonography, radionuclide scintiscanning, and improved laboratory evaluation of body fluids.

Despite the enormous advances these techniques have brought to our understanding of pulmonary diseases and the accuracy with which we can diagnose them, the physician's role in diagnosis remains undiminished. The medical history continues to be the single most powerful tool in the physician's armamentarium. It is the physician, using skills carefully honed during years of study, who separates the important from the unimportant data in the history, formulates a differential diagnosis, puts the laboratory studies into proper perspective with the history, and establishes the diagnosis. In this chapter, we present an approach to history taking and physical examination and briefly discuss the clinical and radiographic presentation of common pulmonary syndromes.

HISTORY

Patients with pulmonary disease most commonly seek medical attention because they are troubled by symptoms. Less often, they are referred to a physician because of an abnormal laboratory test result, such as a positive tuberculin test, or abnormal findings on a screening chest radiogram. Sometimes, patients are referred because of the presence of an extrapulmonary lesion known to be frequently associated with pulmonary disease, such as sarcoidosis involving the skin or eyes. The medical interview always begins with the patient's chief complaint.

Chief Complaint

The chief complaint should generally be recorded in the patient's own words; patient satisfaction is greater and the risk of the physician missing the patient's chief complaint is less if the patient is permitted to express major concerns fully and freely instead of simply responding to the physician's closed-ended questions. Each chief complaint is explored in detail. Questions should not be leading and should be expressed in words the patient can easily understand. The purpose is to permit the physician to evaluate the significance of the complaint; gathering of data and interpretation of the history proceed in parallel.

Patient's Assessment of Symptoms

It is important to involve patients in the diagnostic and therapeutic decisions that will affect their welfare. Is a symptom troubling the patient enough to justify ordering an expensive, perhaps invasive diagnostic test, or is the patient content with the physician's reassurance that a serious, potentially disabling or life-threatening condition is not present? What is the principle underlying the treatment plan? What is to be expected from the various drugs that have been prescribed, and are the expected effects immediate or delayed? What are the possible side effects of the drugs—immediate and delayed? If drugs are being used for symptom relief, as in the management of severe asthma, what options may the patient exercise as symptoms vary in severity? What changes of lifestyle are in order? Involving patients directly in their care (cooperative self-management) is an important ingredient in patient satisfaction and therapeutic success.

Pulmonary Symptoms

The number of pulmonary symptoms is limited: cough, expectoration of sputum, hemoptysis, chest pain, dyspnea, and wheezing. The precise manner of presentation of symptoms, the sequence in which they appear, the factors that worsen and alleviate them, and their response to treatment may be of value in suggesting the nature of the underlying disease process. For example, a cough with coryza and purulent sputum that abates with antibiotic treatment is compatible with an infectious bronchitis; a chronic cough with blood-streaked sputum in a cigarette smoker raises the suspicion of bronchogenic carcinoma.

Cough

Mechanisms

Cough may be defined as a forced expulsion of air associated with the generation of a harsh noise. Physiologically, cough is a reflex, forced expiratory event that comprises a rapid inspiration followed by an expiratory effort against a closed glottis, with rapid generation of a high intrapulmonary pressure. Sudden opening of the glottis is followed by an explosive expiration, which has the effect of moving excessive secretions or particulate material toward the mouth.

Cough may be initiated voluntarily or involuntarily. Irritant receptors located in the external auditory canal, larynx, trachea and large bronchi, pleurae, and stomach give rise to afferent stimuli that course centrally over the vagal nerves. The sensitivity of irritant receptors is greatest at the glottis and the main bronchial carina and diminishes rapidly after about the fourth-order bronchi. Thus, large amounts of secretion can pool in the distal airways without initiating a cough. Stimuli from the nose and paranasal sinuses travel centrally over the trigeminal nerve and from the pharynx over the glossopharyngeal nerve. Stimuli from the pericardium and the diaphragm may initiate cough by afferent impulses coursing over the phrenic nerve. Efferent pathways include the vagus, phrenic, trigeminal, facial, hypoglossal, and accessory nerves as well as the intercostal and lumbar nerves innervating the intrinsic and accessory muscles of respiration.

Normally, secretions from the lungs and airways are removed by ciliary motion, which activates the mucociliary escalator and moves secretions toward the pharynx, where they are swallowed or expectorated. When this mechanism fails or is overwhelmed, cough takes over the critical role of maintaining the clearance function of the airways. The expiratory effort against a closed glottis, which is the first phase of a cough and lasts about 0.2 second, raises the intrapleural pressure to about 100 cm

H_2O, although values as high as 300 cm H_2O may be reached. Opening of the glottis is followed by highvelocity, turbulent flow. As expiration proceeds, lung volume diminishes and dynamic compression of intrathoracic airways occurs. For a given flow, the linear velocity of gas is higher in an airway narrowed by dynamic compression than in one in which the normal geometry is maintained. If narrowing also occurs as a result of secretion in the airway, a pressure gradient is created that moves secretions toward the pharynx. These high linear velocities also set the secretions and bronchopulmonary tissues into vibration, creating the characteristic sound of a cough.

The effectiveness of cough may be impaired if any phase of the process is abnormal. The cough reflex may be suppressed by changes in irritant receptor function caused by narcotics, local or systemic anesthetics, or mucosal disease, as in bronchiectasis with severe destructive changes. Neurologic disease may affect any portion of the reflex pathways. Chest wall pain or asthenia resulting from age, illness, or neuromuscular disease may decrease the inspiratory effort preceding cough, thus decreasing the lengthening of expiratory muscle fibers required to develop a high intrapleural pressure against the closed glottis. Inspiratory as well as expiratory muscular dysfunction may result in a weak cough. Obstruction of air flow, as in asthma or emphysema, impairs the effectiveness of cough by decreasing the velocity of the flow of air available for moving secretions. Glottic closure is helpful but not essential for effective coughing; the pressure developed when the glottis is closed is 50%–100% greater than when a forced expiratory maneuver is carried out with the glottis open. Tracheotomized patients learn to carry out forced expiratory maneuvers that are effective in mobilizing their secretions, and persons with an intact glottis may elect to carry out forced, expiratory, coughlike maneuvers through a partially open glottis to minimize the pain induced by a forceful cough in the presence of acute tracheitis or chest wall pain.

The maximal expiratory pressure (MEP) is useful for assessing cough strength in patients with impaired muscle strength, and is likely a more accurate measure of cough strength than forced vital capacity. Patients with MEP values of 60 cm H_2O or more are able to generate sufficient peak flow to produce an effective cough.

Diagnostic Features

Cough of Recent Onset. Normal persons cough infrequently when they are well. The most common reason for the development of cough in a normal person is a viral respiratory infection. Such infections may be sporadic but more often occur in community epidemics or household or workplace clusters. One or more of coryza, sore throat, fever, chills, sweats, malaise, backache, retrobulbar pain, and postnasal discharge may accompany the cough. Cough may be nonproductive or productive, and an acute tracheitis may be accompanied by a tearing or burning substernal pain. The usual duration of cough resulting from an acute respiratory infection is 2 to 3 weeks, but occasionally the cough lingers much longer and is accompanied by wheezing that worsens after exercise or breathing cold air. Such patients show evidence of airways hyperreactivity on challenge with methacholine or cold air.

The history and physical findings of rhinopharyngitis, with or without middle ear disease, establish the diagnosis of cough resulting from an acute upper respiratory infection. A chest radiogram is not necessary to exclude pneumonia unless abnormalities are found on chest examination, or prostration is severe and persistent. Wheezing with cough of recent onset suggests air flow obstruction, possibly from asthma. Stridor indicates involvement of the upper airway.

Chronic cough. Cough that has persisted for more than 3 weeks may be considered to be chronic. However, it is not always easy to know whether chronic cough has been present; patients who have a mild repetitive cough (e.g., on arising) may either be unaware of it or misinterpret it as a natural phenomenon. The symptom will not be elicited unless the patient is asked whether cough occurs on arising, and sometimes it will come to light only after a family member has been questioned. It may also be helpful to determine whether cough described as of recent onset is really new or represents an exacerbation of a chronic condition. Finally, the recent cessation of a longstanding productive cough may indicate retention of bronchial secretions; this is observed occasionally in respiratory failure complicating chronic obstructive airways disease. Weakness, fatigability, fever, and night sweats suggest the presence of tuberculosis, other chronic infection, or malignancy. Physical examination, a chest radiogram, and simple laboratory studies are usually sufficient to establish these diagnoses.

The pioneering work of Irwin has established a diagnostic protocol, based on the locations of the afferent limb of the cough reflex, for investigating chronic cough that is not of obvious etiology. Some causes of chronic cough are listed in Table 1. Chronic bronchitis is the most common cause of chronic cough, occurring in up to 30% of cigarette smokers. The postnasal discharge syndrome is next most frequent. This syndrome is diagnosed when the patient describes a sensation of secretion dripping from the back of the nose into the throat, often with the need for frequent clearing of the throat. Physical examination reveals a cobblestone appearance of the oropharyngeal mucosa, sometimes with overlying mucoid or mucopurulent secretion.

Frequent
Chronic bronchitis (occurs in 30% of smokers)
Postnasal drip syndrome (caused by rhinitis ± sinusitis)
Asthma (may be variant, without wheezing)
Gastroesophageal reflux
Congestive heart failure
Cystic fibrosis
Chronic infections (tuberculosis, deep mycotic infections)
Infrequent
Occupational factors
Bronchiectasis
Psychogenic cough (may occur with stridor; is rarely nocturnal)
Interstitial lung disease
Bronchogenic carcinoma
Angiotensin-converting enzyme inhibitors
Pulmonary vascular disease
Tracheal compression (neck or mediastinal mass)
Recurrent aspiration (observed in the elderly and persons with swallowing disorders caused by neuromuscular disease; often accompanied by recurrent pneumonia)
Aspirated foreign body (rare in adults except with mental illness, mental retardation, or coma)

TABLE 1. *Some causes of chronic cough*

Asthma is easy enough to diagnose when the patient describes episodic wheezing and shortness of breath. However, it must be remembered that asthma may present as only cough, with minimal expectoration and no wheezing. The cough is frequently precipitated by exposure to cold air or exercise and is often dry. An increase of >20% in FEV_1 (forced expiratory volume in 1 second) after administration of a sympathomimetic agonist aerosol, a positive result on a cold air or methacholine challenge test, or a therapeutic response to aerosol treatment with a b-adrenergic agonist support the diagnosis (Chapter 40).

Gastroesophageal reflux (GER) as a cause of chronic cough, with or without wheezing, is controversial. There is no question that some patients have chronic cough secondary to GER. Heartburn or regurgitation of acid material into the mouth may be caused by GER or a Zenker's diverticulum. These patients tend to cough more when lying down at night and respond promptly to treatment of the GER.

Troublesome cough may complicate the treatment of hypertension with angiotensin-converting enzyme inhibitors. Congestive heart failure is a common cause of chronic cough, and this is usually easily diagnosed from the history of heart disease, orthopnea, paroxysmal nocturnal dyspnea, exertional dyspnea, and the physical examination. The presence of chronic productive cough with purulent sputum, often in a nonsmoker, with or without evidence of patchy, persistent pneumonic disease on physical examination and chest radiography, should raise the possibility of cystic fibrosis, which is the most common genetic defect of Caucasians. The disease may present in adults with minimal or no gastrointestinal symptoms of pancreatic involvement (Chapter 73). Chronic cough is a frequent symptom in patients with bronchogenic carcinoma. Tracheal compression, sometimes in the neck, as by a goiter (Fig. 1), but more often in the region of the carina, may also give rise to a dry cough.

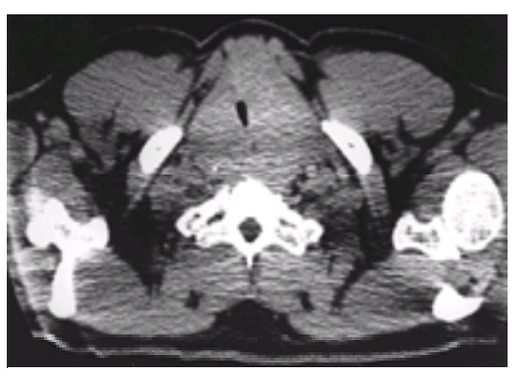

FIG. 1. Enlargement of the thyroid gland usually does not compress the trachea, which is supported by stiff cartilaginous rings. However, when a goiter becomes

extremely large, as demonstrated here, the shape of the tracheal cross-section can be distorted and diminished.

Occasionally, patients are observed with psychogenic cough. Such patients are usually young. The cough is frequent, sometimes with accompanying aphonia or stridor and a rather characteristic barking or brassy quality. The cough rarely disturbs sleep, although it may make work or attendance at school impossible. Psychologic abnormalities are not necessarily obvious, although they are usually detectable. The diagnosis is usually evident from the nature of the cough. An investigation to exclude organic disease is necessary, but clinical judgment must be exercised to keep the workup within reasonable bounds.

Complications of Cough. Cough syncope occurs mainly in middle-aged men who have chronic obstructive pulmonary disease (COPD). Fainting follows within 10 to 20 seconds of a paroxysmal cough that cannot be controlled by the patient. The mechanism is obscure; the fainting appears to be related to impairment of venous return and fall in cardiac output as a result of elevated intrathoracic pressure; at the same time, intracranial pressure is elevated by the transmitted intrathoracic pressure. The result is diminution of cerebral blood flow. Consciousness is usually promptly regained, and fatalities caused by this syndrome are rare.

Persistent cough may produce hoarseness. Large increases in muscular forces during severe cough may result in tearing of muscle fibers or rib fracture; the latter occurs most often in the posterior axillary line. Paroxysmal cough may cause headache and back pain. Chronic cough may contribute to recurrent inguinal hernia in men and to urinary incontinence in women. Persistent chronic cough seriously disrupts daily life and may be disabling.

Sputum

Mechanisms

A normal person produces between 10 and 40 mL of tracheobronchial secretion per day. The secretion, consisting primarily of an aqueous solution of mucous glycoprotein, is produced by the airways submucosal glands and goblet cells and is carried to the oropharynx by the mucociliary escalator. Increased amounts of secretion may be noted after eating, especially of highly seasoned food. The mechanism is most likely overflow vagal stimulation of the respiratory glands from intense gastric stimulation. Secretion may be stimulated in response to inhaled gaseous or particulate irritant substances. Inflammation of the respiratory tract also results in an increase in secretory activity, but the characteristics of the secretion are changed by the addition of pus cells, plasma proteins, and other inflammatory products, coming either from the bronchial walls or from the alveoli.

Differential Diagnostic Features

The quantity and quality of expectorated material are important features in bronchopulmonary diseases. The volume is usually best expressed by patients in some household unit of measurement, such as ounces, teaspoons, or tablespoons. Description of the secretions as clear and colorless (like egg white) indicates uninfected secretions; a yellow or green color indicates a purulent exudate. Purulence is most often the consequence of infection and the presence of neutrophilic leukocytes. However, large numbers of eosinophils can make sputum appear purulent. A fetid odor suggests anaerobic infection, as in aspiration lung abscess or necrotizing pneumonia. Rusty or brownish-red sputum is indicates the mixing of blood with the secretions, usually in an acute infectious process such as pneumococcal pneumonia.

In coal miners, the sputum may be black because of the presence of large amounts of anthracotic pigment; black sputum may sometimes occur long after work in the mines has ceased. Cigarette smokers may describe brownish sputum. A three-layered sputum with an uppermost frothy layer, a central mucous layer, and a thick bottom layer is said to be characteristic of bronchiectasis, but this nonspecific appearance may be seen in any bronchitic process with a large volume of secretions. Large amounts of mucoid sputum, up to a liter per day, are an unusual manifestation of alveolar cell carcinoma. Mucoid bronchorrhea may also be seen occasionally with chronic bronchitis. Fibrinous casts may be expectorated in the very rare plastic bronchitis syndrome, and “pearls” or wormlike structures comprised of bronchiolar casts are frequently expectorated in asthma. The latter are made up of eosinophils, desquamated bronchial epithelium, and Curschmann's spirals—spiral structures that consist of eosinophils and Charcot-Leyden crystals, which are eosinophil-derived. Brownish bronchiolar plugs may be observed in allergic bronchopulmonary aspergillosis.

The descriptions of sputum provided by patients are often inaccurate, and the physician should make every effort to look at secretions during the examination. Patients with chronic disease should be taught to differentiate between purulent and mucous secretions.

Hemoptysis

Mechanisms

Hemoptysis is defined as the expectoration of blood. The quantity of blood may vary from a few streaks mixed with bronchial secretions to an exsanguinating hemorrhage. The site of bleeding may be anywhere in the respiratory tract, including the nose or the mouth, and the mechanisms of bleeding are varied. The bronchial mucosa may bleed because of congestion from inflammation, often with accompanying superficial erosion of the overlying epithelium. Passively engorged blood vessels, as in mitral stenosis, may also bleed readily, either without evident cause or as a result of mucosal ulceration accompanying minor respiratory infections. Bleeding may result from ulceration of a tumor, such as a bronchial carcinoid or a bronchogenic carcinoma (Fig. 2). Indeed, hemoptysis may occur as the bronchial wall is penetrated by an eroding structure, such as an infectious or noninfectious granuloma, a calcified lymph node, or an aortic aneurysm, which may be atherosclerotic, luetic, or dissecting. Rarely, in empyema, a ventricular-bronchial communication may cause massive hemoptysis. In bronchiectasis, the bronchial arteries undergo enlargement and extensive anastomosis with the pulmonary arteries; erosion into a bronchial artery with its systemic level of blood pressure may give rise to massive hemoptysis.

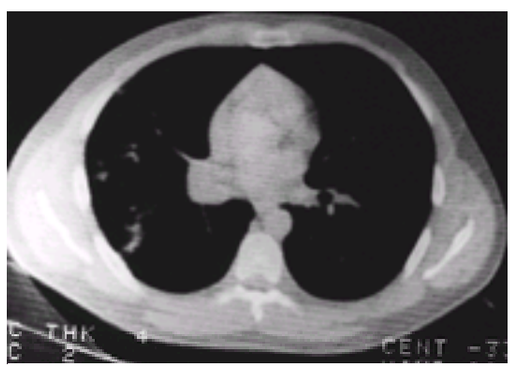

FIG. 2. This patient presented with dyspnea on severe effort; the findings on plain chest x-ray film were normal. On CT, the right hilum appeared to be enlarged. On bronchoscopy, this appearance was shown to be the result of complete occlusion of the bronchus intermedius by a bronchial carcinoid. Only minimal postobstructive parenchymal disease is present because of effective collateral air flow.

Blood may come from the pulmonary parenchyma, as from the vascular granulation tissue lining an anaerobic abscess (Fig. 3), a tuberculous abscess, an abscess of gram-negative bacillary or staphylococcal origin, or a mycetoma. If a blood vessel wall in an abscess is left unsupported by parenchyma, and especially if the blood vessel wall is eroded by the infectious process, hemorrhage may be massive and even exsanguinating. Hemorrhage commonly arises more simply from congested pulmonary parenchyma, as in pneumococcal pneumonia, or from engorged and necrotic parenchyma in pulmonary infarction (Fig. 4).

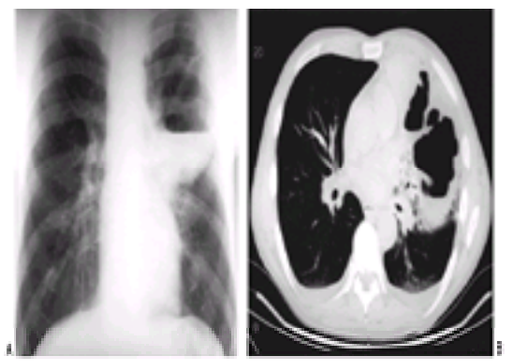

FIG. 3. A: Anaerobic lung abscess. On chest x-ray film, a large abscess cavity with an air-fluid level fills nearly the entire left upper lobe. Note that some streaky remnants of lung tissue remain visible, as do several smaller air-fluid levels. An area of pneumonia, seen here in the left infrahilar region, is commonly noted, reflecting infected but not yet necrotic lung adjacent to the abscess. **B:** On CT, the multilocular nature of the lung abscess is apparent. Small, air-containing structures in a region of perihilar pneumonia represent bronchiectasis and early foci of necrosis. Note the shaggy interior cavity wall, typical of lung abscess.

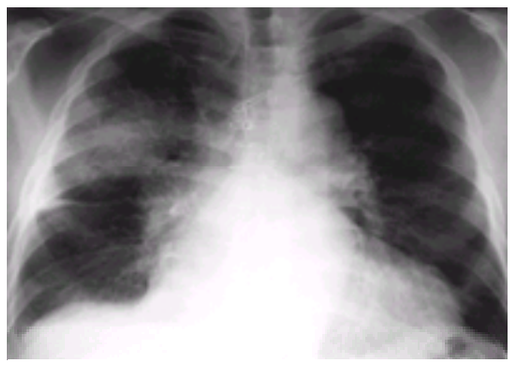

FIG. 4. This patient, with a cardiac valve replacement not clearly seen here, received excessive anticoagulant therapy with warfarin and presented with hemoptysis. In the right upper lobe, there is a dense opacification consisting of intraparenchymal hemorrhage. Unlike consolidations caused by infection, parenchymal hemorrhage tends to clear rapidly.

Differential Diagnostic Features

Patients describe hemoptysis in various ways. Pulmonary parenchymal or bronchial bleeding may be perceived as a bubbling sensation in the tracheobronchial tree, followed by the expectoration of blood. When underlying infection has been present, the patient may not be aware of any change in the quantity of secretion but may note blood mixed with mucus or replacing it. When bleeding is profuse, clots may be expectorated.

Bronchopulmonary bleeding may sometimes be manifested as vomiting of blood. Bleeding occurs during the night, and the blood reaches the oropharynx and is swallowed without the patient waking. The swallowed blood acts as an irritant and produces vomiting in the early morning hours. Roentgenographic and physical examination of the chest are therefore mandatory in the investigation of every patient with hematemesis. Hematemesis rarely masquerades as hemoptysis; the presence of gastrointestinal symptoms such as nausea and vomiting and a history of alcoholism or cirrhosis, sometimes with a past history of hematemesis, usually point to the correct diagnosis. The presence of food in a specimen of the bloody fluid and an acid pH suggest gastric origin. If the chest radiogram is negative, the presence of blood or “coffee grounds” material in the gastric aspirate settles the issue.

A history of epistaxis must be sought in patients with hemoptysis, because blood from the nasopharynx can be aspirated during the night and coughed up in the early morning. The nasopharynx should be examined in all patients with hemoptysis who have a negative chest radiogram.

Small stones or gravel may be expectorated with blood in broncholithiasis, a condition in which calcium in granulomatous lymph nodes erodes through the bronchial wall, or a foreign body aspirated years earlier becomes calcified (Fig. 5). In the extremely rare catamenial hemoptysis, resulting from endometrial implants in the bronchial wall, the expectoration of blood occurs concomitantly with menstruation.

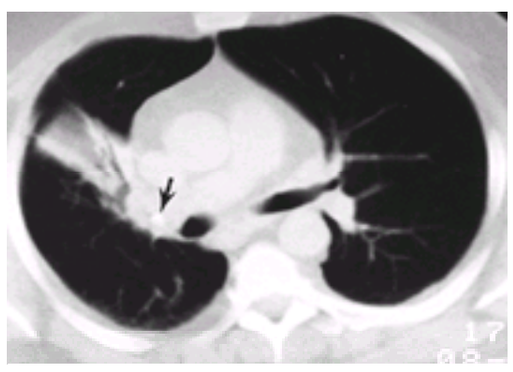

FIG. 5. CT demonstrates partial middle lobe collapse. Some patent bronchi are visible. A focus of calcification (*arrow*) is seen centrally near the origin of the middle lobe bronchus. At bronchoscopy, a broncholith composed of calcified and encrusted aspirated vegetable material was removed.

Table 2 provides a partial list of the more than 100 disease entities that can cause hemoptysis. Tuberculosis and bronchiectasis used to be the most common causes of hemoptysis. Erosive bronchitis in smokers with chronic bronchitis is now the most frequent cause of expectoration of blood, accounting for 40%–50% of all cases of hemoptysis. Bronchogenic carcinoma is the second most frequent cause of hemoptysis, underlying 20%–25% of all cases. Blood-streaked bronchitic sputum may be the only hint that a bronchogenic carcinoma has developed in a long-time smoker.

Frequent
Chronic bronchitis
Bronchogenic carcinoma*

Infrequent
Bronchiectasis*
Tuberculosis
  Active*
  Inactive (post tuberculous bronchiectasis)
Pulmonary contusion
Pulmonary abscess*
Bronchoarterial fistula*
Cardiogenic (mitral stenosis, pulmonary edema—pink sputum)
Aspergilloma*
Coagulopathy*
Pulmonary infarction
Idiopathic pulmonary hemosiderosis
Goodpasture's syndrome
Pulmonary telangiectasis*
Amyloidosis
Bronchectasis*
Bronchiolithiasis
Sjögren's syndrome
Deep mycotic infection*
Bronchial adenoma
Metastatic carcinoma
Foreign body
Wegener's granulomatosis
Pseudohemoptysis (epistaxis, hematemesis, bleeding gums, malingering)

* Most frequent cause of massive hemoptysis.

TABLE 2. *Some causes of hemoptysis*

Massive hemoptysis, of which the most common causes are identified in Table 2, may be defined as expectoration of 600 mL or more of blood in 24 hrs. Hemoptysis of this magnitude is life-threatening and requires close monitoring and often urgent diagnostic and therapeutic intervention.

Chest Pain

Mechanisms

Pain in the chest may be derived from the chest wall (dermatomes T1-12), pleurae, trachea and main airways, mediastinum (including the heart and esophagus), and abdominal viscera. The parietal pleura is supplied with pain receptors; the visceral pleura is free of them. Pleuritic pain may be referred to the area of skin supplied by the same sensory roots that supply the area from which pain is arising. Thus, the pleurisy accompanying a right lower lobe pneumonia and involving dermatome T-11 may mimic the pain of acute appendicitis. The sensory fibers of the central tendon of the diaphragm run with the phrenic nerve (C3-4), and the pain of diaphragmatic pleurisy may be referred to the tip of the shoulder. Cardiac pain (T1-4) may radiate down the ulnar aspects of the arms, more often the left, and may radiate up into the jaws. Visceral pain from the gallbladder, pancreas, or hepatic or splenic flexures of the colon may be referred to the epigastrium, substernal area, or lower thorax, as may the pain of upper abdominal peritonitis. A variety of other reactions may accompany severe chest pain. Autonomic reactions such as tachycardia and sweating may be observed; parasympathetic reactions include bradycardia, nausea, and vomiting. Skeletal muscle splinting may accompany severe pleuritic pain of any cause, and was present in the patient with malignant mesothelioma shown in Fig. 6.

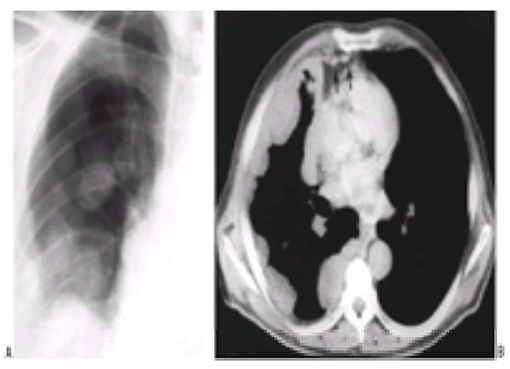

FIG. 6. A: Malignant mesothelioma presenting as multiple, large, rounded masses apparent in this right hemithorax. Some of the more centrally located lesions have the appearance of well-demarcated intraparenchymal lesions. However, others, which demonstrate broad, smooth margins merging with the chest wall, clearly have a pleural origin. **B:** It is evident on the corresponding CT image that there are no intraparenchymal lesions; rather, all the abnormalities are based in the pleura. Mesothelioma typically forms large, rounded lobules along the entire pleural surface. Microscopic invasion of the chest wall is poorly assessed on CT. Gross extension to other mesothelial surfaces, such as the contralateral pleura or peritoneum, can often be detected on CT. In this case, there is direct invasion (*arrow*) of pericardial fat immediately posterior to the sternum.

Pain, like other sensory phenomena, is poorly understood, but it begins with a noxious stimulus generated mechanically or chemically as a result of tissue injury and inflammation. The chemical mediators released from inflamed tissues that initiate pain are beginning to be understood. Tissue receptors are activated and pain stimuli are transmitted via the peripheral afferent nervous system. Visceral pain is transmitted centrally via lowvelocity, unmyelinated C-fibers; cutaneous and chest wall pain are transmitted by high-velocity, myelinated A-fibers.

The pain stimuli are processed in complex, incompletely understood ways by the central nervous system. This processing accounts for a variable dissociation of the central perception of pain from the magnitude of the peripheral stimulus. Many factors, such as emotion, depression, and competing stimuli, may influence the perception of pain. Visceral pain tends to be dull and poorly localized, whereas chest wall pain tends to be sharper and better localized.

Differential Diagnostic Features

History taking is the key to evaluating chest pain. There is only a weak relationship between the severity of chest pain and the importance of its underlying cause; accordingly, all chest pain must be taken seriously. The precise cause of chest pain cannot always be determined by taking a history and doing a physical examination, but it is generally possible to make a judgment as to whether the origin of the pain is the pleura, the chest wall, or the viscera, and to develop a diagnostic plan. Table 3 provides a partial list of causes of chest pain.

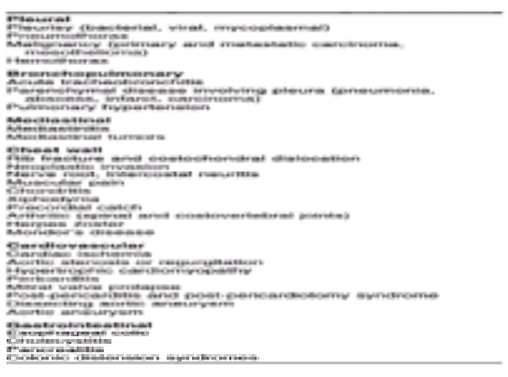

TABLE 3. *Some causes of chest pain*

Pleural Pain. Chest pain that tends to be sharply localized, worsens during coughing, deep breathing, or motion of the trunk, and is relieved by maneuvers limiting the expansion of a particular part of the chest is very likely to be pleuritic in origin. The pain, which occurs more often at the lung bases than in the upper lung zones, may range in severity from mild and aching to excruciating. Worsening during respiratory motions is its hallmark. Pleuritic pain is caused by stretching of the inflamed parietal pleura. However, in chronic pleuritis, pain endings may no longer be stimulated despite roughening of the pleural surfaces, which continue to give rise to a loud rub.

The rapidity of onset of the pain varies with its cause. Pleuritic pain accompanying a spontaneous pneumothorax or pulmonary infarct is usually sudden in onset. Pleurisy of viral origin or associated with pneumonia may be more gradual in onset and occurs in the context of an acute febrile, prostrating illness. Infection with coxsackievirus B produces a syndrome known as pleurodynia (Bornholm syndrome); this is characterized by fever, malaise, sore throat, debility, and anorexia and is followed by the sudden onset of muscular and pleuritic pain, with abdominal pain and muscle spasm in about half the cases. The disease runs its course in 3 to 7 days and may be complicated by a small pleural effusion. Tuberculous pleural effusion may be initially manifested by pleuritic pain and cough that subside rapidly. Parenchymal tuberculosis with overlying pleural disease, often occurring in the context of chronic systemic illness, may cause aching of the chest wall without a clear relation to respiration.

Pain Caused by Bronchopulmonary and Mediastinal Disorders. The lung parenchyma has no pain receptors. However, acute pulmonary diseases that involve the overlying pleura, such as pneumonia, lung abscess, and pulmonary infarction, cause pleuritic pain. Acute tracheobronchitis may give rise to substernal discomfort, with

a tearing, rasping, sharp substernal pain on coughing. Mediastinitis causes a retrosternal, aching, oppressive sensation that can occasionally be severe. Chronic disorders of the large airways, such as tracheal or bronchial tumors, chondritis, or ulcers, do not cause pain. Mediastinal tumors are usually asymptomatic but can cause chest pain if they compress or invade mediastinal structures or chest wall.

Pain Caused by Malignancy. The pain of a carcinoma invading the spine or ribs is generally well localized and of a severe, unremitting character (Fig. 7). With mesothelioma (Fig. 6) or metastatic carcinoma, as from a primary breast tumor, the pain may be more diffuse. Involvement of chest wall and nerve roots results in local, gnawing chest wall pain and radiation of the pain to the affected dermatomes. Thus, in Pancoast's syndrome, in which the brachial plexus is involved by an invasive primary lung tumor located peripherally in the extreme apex of the lung, there is pain in the shoulder, the scapular region, or the medial aspect of the arm and hand. The pain of this tumor sometimes masquerades as subacromial bursitis. The pain of vertebral metastases tends to be in the midline, often with girdle radiation, and may be associated with tenderness over the affected area. Intercostal neuropathy, which may result from irritation of an intercostal nerve by a costal metastasis or some other factor, may result in severe, lancinating, burning pain that is unilateral and segmental in distribution. There may be sensory loss or hyperesthesia over the affected dermatomes. Intercostal neuropathy is one cause of the post-thoracotomy pain syndrome; traumatic neuroma in the thoracotomy scar and recurrent tumor are other causes.

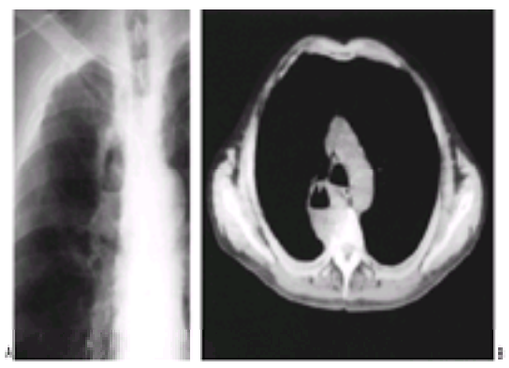

FIG. 7. A: A large mass is present in the right paramediastinal area. An air-fluid level is present within the central cavitary portion of the lesion, defining its approximate inner and outer margins. A small projection into the cavity from the lateral wall suggests the possibility of necrotizing tumor. The diagnosis of squamous cell carcinoma was confirmed by bronchoscopy. **B:** On CT, the entire anterolateral aspect of the adjacent vertebral body has been eroded. Chest wall invasion may be readily apparent or completely undetectable on CT.

Pain Originating in the Chest Wall. Fracture of a rib, either during trauma or spontaneously during cough, causes local pain in the affected area. The pain is severe, worsened by respiratory and trunk motion, and may be accompanied by a grating sensation during breathing. Local tenderness develops early, and a callus may be felt as the fracture heals. Costochondral dislocation, occurring from muscular effort or less frequently trauma, causes less severe, anterolateral chest pain.

The rare occurrence of subacute chondritis causes a dull, aching pain of the anterior chest wall that is not affected by breathing. The second, third, and fourth cartilages are most frequently involved, but the process can involve any costal cartilage or the xiphoid process. Disease of the thoracic spine may be associated with involvement of the costovertebral joints and cause discomfort or pain in the chest wall. Chest wall pain may be caused by damage to muscle fibers secondary to the severe muscular effort associated with coughing during an acute respiratory infection or with unusually severe exercise. Herpes zoster is often heralded by several days of neuritic pain in the affected dermatomes; the pain persists during the cutaneous phase of the disease, and postherpetic neuralgia with its burning and paroxysmal lancinating pain may persist for long periods.

A rare cause of superficial chest wall pain is thrombosis of the superficial vein of the thoracic wall (Mondor's disease). The process is of unknown etiology but is self-limited. It may last several weeks; an initial acute phase is followed by an indolent phase, and a palpable subcutaneous cord over the lateral chest wall is its only sign.

Precordial catch is a pricking, precordial (left parasternal) pain, usually occurring at rest and often associated with emotional stress. The pain is variably worsened by deep inspiration, is not precipitated by effort, and tends to be transient and stabbing in character. It occurs more often in men than in women and is infrequently observed after the third decade. The pain is not caused by heart or lung disease and is probably of chest wall origin. The diagnosis is made by the characteristic history, negative physical findings, and appropriate laboratory tests performed to exclude visceral disease.

Cardiovascular Pain. The pain of cardiac ischemia results from an imbalance between the supply and demand of oxygen in the myocardium, and most often results from atherosclerotic coronary arteries. The pain of angina pectoris is induced by exercise, especially after a heavy meal or in cold or windy conditions. The chest pain is vague, diffuse, and ill-defined—that is, it is visceral in nature. Generally located substernally or in the anterior midline, it is described as constricting or squeezing, or as a weight on the chest. The pain may radiate down the medial aspect of the left arm (less often the right) or into the neck or mandible. Angina is relieved by rest or sublingual nitroglycerin. The pain of myocardial infarction is usually more persistent, lasting longer than 20 minutes, and is often accompanied by sweating, nausea, hypotension, dyspnea, and arrhythmias. Unstable angina occurs episodically at rest or with little provocation, and it may herald an impending myocardial infarction.

Cardiomyopathy may cause anginal chest pain, as may aortic stenosis and, to a lesser degree, aortic regurgitation. Mitral valve prolapse may be associated with sharp, stabbing chest pain not provoked by exertion; it is more frequent in female patients.

The pain of pericarditis is in the midline but not as distinctly substernal as the typical pain of myocardial ischemia. Because of the intimate association of the pericardium and the mediastinal pleura, pericardial pain often exhibits characteristics suggesting pleural involvement—it is worsened by inspiration and coughing. When the central tendon of the diaphragm is involved, the pain is referred to the trapezius ridge. Pericardial may be so severe that it mimics myocardial infarction, or be so mild and pleuritic in nature that acute pleurisy or pulmonary infarction become diagnostic considerations. The pain is often relieved by sitting up and leaning forward or by lying on the right side. Spontaneous pneumomediastinum may also give rise to pain that has the characteristics of pericarditis.

Pain associated with acute pulmonary hypertension is similar to the pain of myocardial infarction, but the electrocardiographic and laboratory features of that disease are absent. The pain may be associated with multiple or massive pulmonary emboli or with an infectious process in a patient having a restricted pulmonary vascular bed or mitral stenosis. Its mechanism is unknown; it may be caused by the sudden distension of the main pulmonary artery and stimulation of mechanoreceptors.

Chest pain, usually excruciating and starting in an anterior substernal location, is the predominant presenting symptom in dissecting aneurysm of the aorta (Fig. 8). Unlike the pain of myocardial infarction, which waxes and wanes, this pain is usually maximal at onset. It is common for the pain to migrate posteriorly as the dissection propagates distally. Nondissecting aneurysm can produce continuous aching or lancinating pain in the chest, shoulder, and back by compressing the thoracic spinal nerves; bone erosion causes boring, intractable back pain.

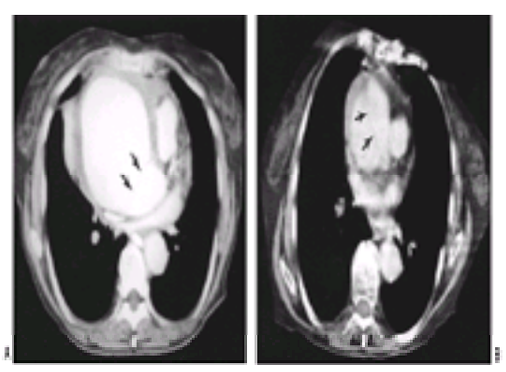

FIG. 8. A: In many cases, dissection of the aorta is easily seen on contrast-enhanced CT, as demonstrated in this example. Here, a large saccular component of the aneurysm at the root of the aorta bulges anteriorly and to the right into the sinus of Valsalva. The intimal flap is visible as a thin, dark, obliquely oriented line (*arrows*) at the posterior aspect of the large, contrast-enhanced aortic root. Note that the attenuation of the region immediately surrounding the aorta is higher than that of fat and normal soft tissue and is caused by leakage of blood into the pericardial sac, a portion of which encompasses the aortic root. **B:** In another patient with aortic

dissection, the dilatation of the aorta is not as extensive. Some intrapericardial hemorrhage is seen anterior to the aortic root. The intimal flap (*arrows*) can again be seen, in this case oriented anteroposteriorly. Note in both cases the gentle curvature of the intimal flap toward one lumen or the other, a common appearance.

Chest Pain Related to Gastrointestinal Disease. Recurrent noncardiac chest pain is a common clinical condition that is often frustrating to the physician. Such patients often have undergone angiography demonstrating normal or near-normal coronary arteries, but they continue to have angina-like chest pain that prompts repeated visits to the physician's office or emergency department. They have a low risk for myocardial infarction or cardiac death.

Spasm of the esophagus or esophageal colic is one important cause of such chest pain. The pain may mimic cardiac pain perfectly. It ranges from mild to severe and may last from 5 or 10 minutes to many hours. The pain is usually substernal and may radiate down one or both arms, and into the neck, jaws, teeth, or epigastric area. Radiation through to the back suggests an esophageal origin, as does the association of heartburn and relief of pain by the ingestion of alkali or by changing from a recumbent to an upright position.

Proving that chest pain is of esophageal origin is often difficult. Different types of esophageal motility disorders have been described in association with chest pain: achalasia, diffuse esophageal spasm, “nutcracker” esophagus, and nonspecific motility disorder. However, the precise relation between these abnormal contractions and chest pain is far from clear; chest pain is frequently not present when motility disorders are being demonstrated in the laboratory, and motility disorders are often not associated with impaired esophageal function. Katz et al., reviewing the records of 910 patients studied manometrically for noncardiac chest pain, found abnormal motility in 28% during baseline manometry; diffuse spasm and achalasia were present in only 10% and 2% of subjects, respectively. Nutcracker esophagus and nonspecific motility disorders were most common, in 48% and 36%, respectively. Ambulatory pressure monitoring and monitoring of pH have also been widely studied to evaluate chest pain, as have provocative tests such as acid infusion and intravenous edrophonium.

Distension of the splenic flexure may cause left lower chest pain; the pain is usually relieved by passing flatus and is not related to breathing or trunk motion. Gallbladder disease may also give rise to epigastric and midline chest pain mimicking angina as well as to right upper quadrant abdominal pain. The history of gastrointestinal symptoms and the atypical nature of the chest pain are helpful in differential diagnosis.

Dyspnea

Dyspnea may be defined as discomfort associated with breathing and is a symptom of both pulmonary and cardiac disease. In taking the history, it is important to determine whether dyspnea occurs only on exercise or also at rest; if the symptom occurs only on exercise, what has been the time course of its development? If dyspnea occurs at rest, how is the symptom related to the time of day, eating, and body position? A partial listing of the causes of dyspnea is given in Table 4, and a simple categorization of the severity of dyspnea is given in Table 5. The flowing section briefly summarizes our knowledge of the mechanisms of dyspnea, including the contributions of the relatively new field of respiratory psychophysics.

Acute
Upper airway obstruction (laryngospasm, aspirated foreign body, neoplasm)
Asthma
Chest trauma (rib fracture, pneumothorax, lung contusion, vascular rupture, bronchial rupture)
Pneumonia (pleural effusion may contribute)
Pulmonary embolism
Acute interstitial lung disease (hemorrhage, adult respiratory distress syndrome)
Cardiogenic pulmonary edema
Spontaneous pneumothorax
Chronic
Chronic obstructive pulmonary disease
Cystic fibrosis
Interstitial lung diseases
Pleural effusion
Fibrothorax
Chest wall abnormalities (kyphoscoliosis, neuromuscular disease, diaphragmatic paralysis)
Pulmonary vascular disease (primary pulmonary hypertension, organizing pulmonary emboli, veno-occlusive disease, vascular malformations)
Cardiovascular disease
Severe anemia
Psychogenic dyspnea

TABLE 4. *Some causes of dyspnea*

Grade	Degree	Defining clinical characteristics
0	None	Not troubled with breathlessness except with strenuous exercise
1	Slight	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Moderate	Walks more slowly than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Severe	Stops for breath after walking about 100 yards or after a few minutes on the level
4	Very severe	Too breathless to leave the house or breathless when dressing or undressing

TABLE 5. *American Thoracic Society dyspnea scale*

Mechanisms

Dyspnea may be accounted for by a decrease in ventilatory capacity, an increase in ventilatory demand during exercise, or by the perception of increased breathing as being uncomfortable. Put somewhat differently, the symptom varies directly with the demand for ventilation and inversely with ventilatory capacity. The symptom is related to the patient's perception of whether ventilation is appropriate to a particular level of activity. Thus, the expected increase in ventilation while climbing a flight of stairs quickly is not perceived as dyspnea; a similar level of ventilation while climbing three or four stairs would be perceived as dyspnea by an observant patient. An increase in the effort required to produce a given level of ventilation, as in asthma, might also be perceived as dyspnea.

Decreased ability to move air in neuromuscular, obstructive airways, or cardiac diseases may cause dyspnea. Cardiopulmonary disease may increase ventilatory demand in many different ways, thereby causing dyspnea: hypoxemia, hypercapnia, increased hydrogen ion concentration, and increased reflex activity from the lungs, muscles, or central blood vessels. For example, ventilatory capacity is relatively well maintained in diffuse interstitial disease, but there is an increase in ventilatory demand and elastic work of breathing during exercise that gives rise to dyspnea. Dyspnea occurs in COPD primarily because of the decrease in ventilatory capacity and the increase in resistive work of breathing. However, none of these physiologic correlates of dyspnea provides an understanding of the sensory basis of dyspnea.

Differential Diagnostic Features

The duration of dyspnea, whether it is of gradual or rapid onset, whether it is episodic or continuous, and its relation to effort should all be determined. For example, gradual onset of dyspnea suggests slowly progressive disease of the heart, lungs, or musculoskeletal system. Rapid onset of dyspnea suggests an acute respiratory infection; sudden worsening of air flow obstruction, as in asthma; or a sudden event, such as a pulmonary embolus. Dyspnea produced by a level of exercise not previously causing discomfort suggests slowly progressive heart or lung disease or anemia. Dyspnea occurring only during exercise suggests slowly progressive disease; dyspnea occurring also at rest suggests heart failure of fluctuating severity or variable air flow obstruction. Breathlessness may be similar to that experienced during normal exercise, suggesting that air flow obstruction is not present, or breathlessness may be associated with labored breathing (difficulty in moving air into or out of the chest), suggesting that airflow obstruction is present. The presence of air-flow obstruction is confirmed if the dyspnea is associated with wheezing (whistling or musical noises in the chest). Sudden chest pain occurring with dyspnea suggests a pulmonary infarction, spontaneous pneumothorax, or myocardial infarction. An episode of aspiration may precede dyspnea associated with pneumonia. Hemoptysis occurring with the dyspnea may signal diffuse interstitial lung diseases, as in Goodpasture's syndrome or pulmonary hemosiderosis. Expectoration of frothy pink sputum and orthopnea suggest pulmonary edema. Coryza, malaise, cough,

expectoration, and chest pain suggest an acute upper or lower respiratory infection.

Severe dyspnea in a patient without airflow obstruction or heart disease should suggest the possibility of a diffuse interstitial parenchymal process, pulmonary embolism, or primary pulmonary hypertension (Fig. 9). The presence of fine crackles on auscultation suggests interstitial lung disease; the signs of pulmonary hypertension should be carefully sought in the absence of crackles. Paroxysmal nocturnal dyspnea can occur with either left ventricular failure or obstructive airways disease. Obstructive airways disease is not usually accompanied by orthopnea, whereas left ventricular failure and bilateral diaphragmatic paralysis virtually always are.

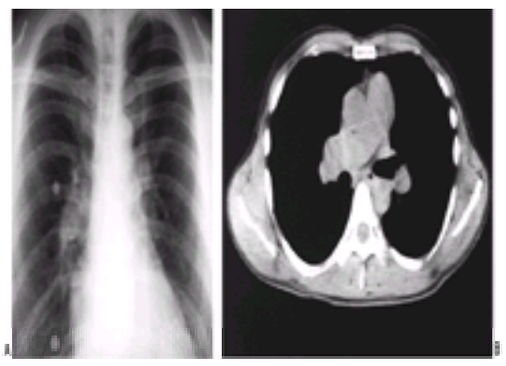

FIG. 9. A: On posteroanterior view of the chest in pulmonary hypertension, the central pulmonary arteries are enlarged and the peripheral arteries appear diminutive in size. On a lateral view, a hypertrophied right ventricle may be encroaching on the retrosternal air space. **B:** The diameters of the main and right pulmonary arteries are easily seen to be greater than the diameter of the adjacent aorta on CT of the mediastinum.

Trepopnea, or dyspnea in one lateral position but not in the other, may be produced by unilateral lung disease, unilateral pleural effusion, or unilateral airway obstruction. Platypnea, or dyspnea in the upright position relieved by recumbency, may be produced by intracardiac shunts or vascular shunts in the lungs. Differentiation of dyspnea of cardiac origin from that of pulmonary origin usually depends on demonstrating whether cardiac or pulmonary disease is present. Sophisticated tests of cardiac and pulmonary function and exercise testing may at times be necessary to settle the question, or to determine the relative contributions of heart and lung disease when both are present.

Psychogenic dyspnea occurs in several forms. The syndrome usually presents as breathlessness unrelated to exertion, occurring in women more often than in men, usually in the third or fourth decades of life. If the patient is hyperventilating (i.e., breathing in excess of metabolic needs), the partial pressure of arterial carbon dioxide ($PaCO_2$) decreases, with a resultant decrease in cerebral blood flow. Lightheadedness, faintness, visual disturbances, numbness, and tingling of the fingers and perioral areas may be noted. Patients are often disproportionately anxious.

Another form of hyperventilation is sighing dyspnea. This occurs equally often in both sexes, may occur at any age, and is not usually accompanied by symptoms of hypocapnia or severe anxiety. The symptom may appear in patients with known heart or lung disease. The patient usually complains of not being able to get enough air at rest. Effort dyspnea is not present unless associated heart or lung disease is present, and then the effort dyspnea is different from the resting breathlessness. The patient usually describes how the expected deep visceral sensation of comfort or satisfaction in the epigastrium is not felt after a sighing inspiration. Consequently, the patient repeats a series of deep inspirations to attempt to produce this normal sensation. Because normally this sensation decreases and then disappears with successive sighs, the deep breaths do not have the desired effects, and the patient complains of being unable to “fill the chest with air satisfactorily.” A precipitating event can rarely be identified. A negative chest radiogram and electrocardiogram added to the negative findings on physical examination and a careful explanation of the nature of the symptoms are usually sufficient to produce relief.

Wheezing

Some patients with obstructive airflow disease may be aware of wheezing, but most are not and rather describe difficult breathing or a sense of tightness in the chest. Sounds generated by breathing may be heard only by family members. Wheezing may be audible only during recumbency. This symptom may suggest the possibility of asthma as the underlying cause in a patient with cough or dyspnea of obscure origin.

Stridor

Stridor is a harsh, blowing noise resulting from obstruction of the trachea or larynx by tumor (Fig. 10), bilateral vocal cord paralysis, other forms of vocal cord dysfunction, tracheal compression, edema associated with inflammation, or the impaction of a foreign body. The airway must be narrowed to about 5 mm in an adult before stridor is produced. Stridor is mainly inspiratory, because air flow is more rapid during this respiratory phase. It has a characteristic crowing or musical sound. However, when upper respiratory tract obstruction is very severe and alveolar hypoventilation has occurred, stridor may be absent. Stridor may also be hysterical in origin.

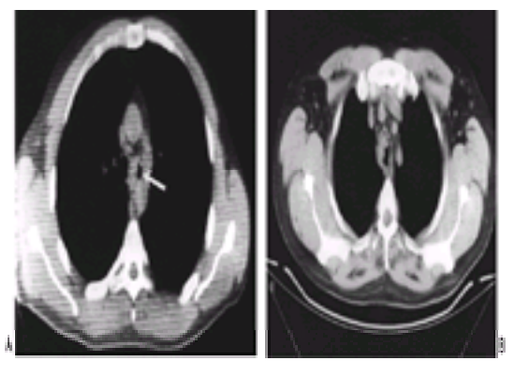

FIG. 10. A: This tracheal squamous papilloma originated near the carina. On inspiratory CT, it can be seen partially occluding the left main bronchus (*arrow*). On expiratory chest x-ray films and CT, there was significant air trapping in the left lung as the lesion created a ball valve effect. The partial obstruction also caused the patient to wheeze. **B:** This tracheal cylindroma demonstrates a lobular, intraluminal mass of soft-tissue density on CT. The affected portion of the tracheal wall is obscured by the neoplasm itself. Often, the bulk of a tracheal tumor is intraluminal rather than extraluminal.

Obstructive Sleep Apnea

Disorders of breathing associated with sleep have been reported with increasing frequency during the last four decades. Obstructive sleep apnea (OSA) is a condition in which 10 or more episodes of upper airway obstruction, each lasting 10 seconds or longer, are detected per hour of sleep. The resultant hypoxemia and impaired quality of sleep result in daytime hypersomnolence, a variety of cardiovascular abnormalities (arrhythmias, cor pulmonale), and neuropsychologic complications. The prevalence of OSA is not known, but it is estimated to affect 1%–2% of the population.

OSA should be suspected whenever excessive daytime sleepiness and snoring coexist. Obesity and alcohol abuse are well-known aggravating factors but need not be present. Nocturnal restlessness, choking spells, frequent urination at night, enuresis, and loss of libido are common. Morning headache and falling asleep during the day while working, engaging in conversation, or driving an automobile are all well-known features of this syndrome. An increased frequency of accidents at home, at work, or while driving is common. It is essential to question the spouse or dwelling partner of the patient regarding these symptoms as well as snoring and apneic episodes during sleep, as the patient may be unable to give an account of them.

The presence of systemic hypertension, plethora associated with polycythemia, and evidence of pulmonary hypertension and cor pulmonale suggest OSA. Obesity, hypothyroidism, acromegaly, and maxillofacial or oropharyngeal abnormalities are predisposing factors, but none of these risk factors, including obesity, need be present. The diagnosis is established by polysomnography.

Systems Review and Social History

After the history of present illness has been completed, a careful review should be made of the function of other body systems. Joint pain with or without skin abnormalities may indicate the presence of a systemic disease, such as rheumatoid disease or sarcoidosis. Raynaud's phenomenon with thickening of the skin of the hands or face, possibly with dysphagia, suggests the possibility of progressive systemic sclerosis. A chronic skin ulcer may be evidence of systemic spread of a pulmonary fungal infection. Late afternoon fatigue, denoting a chronic inflammatory process in the body such as tuberculosis or a deep mycotic infection, may have been so insidious in onset as not to have reached the patient's awareness until the question is carefully put.

Tobacco-Smoking History

The tobacco-smoking history should be taken in a standard manner (Table 6). Patients should be asked if they currently smoke cigarettes. If the response is in the negative, the patient should be asked, “Did you ever smoke?” It is not rare for a patient with pulmonary disease, who has stopped smoking recently because of an alarming symptom such as hemoptysis, to answer negatively when asked, “Do you smoke tobacco?” The age when regular smoking began should be determined. The risk for lung cancer is inversely proportional to the age at which smoking was begun. The total number of years smoked should be calculated. If the patient has stopped smoking, the age at cessation of smoking should be recorded. For former smokers, the number of years of abstinence should be calculated; the risk for lung cancer drops with the duration of abstinence, approaching that of nonsmokers after 10 years, although some risk is nonreversible. The average amount of tobacco smoked per day (packs of cigarettes, number of cigars, ounces of pipe tobacco) during the patient's smoking lifetime should be noted, as it provides a rough estimate of whether a patient is a light, medium, or heavy smoker.

Age when started
• How old was the patient when regular smoking began?
Duration of smoking
• Were there periods when the patient stopped smoking?
• Is the patient currently smoking?
• At what age did the patient stop smoking?
Amount of tobacco smoked
• What is the average lifetime number of cigarettes smoked per day?
• What is the average lifetime number of cigars smoked per day?
• What is the average lifetime amount of pipe tobacco smoked per day?
• Pack-years of cigarettes smoked (average packs per day times number of years smoked) may be calculated, but as the only data recorded, this provides insufficient information.

TABLE 6. *The smoking history*

Alcohol Use, Illicit Drugs, Sexual Preference

A detailed review of the use of alcoholic beverages should be routine because of the association of alcohol abuse and anaerobic, gram-negative, and other pulmonary infections (Fig. 11), as well as tuberculosis. Inquiry regarding the use of illicit drugs is essential; intravenous drug use is associated with septic pulmonary emboli, bacterial endocarditis, and human immunodeficiency virus (HIV) infection. A sexual history should be obtained. Male homosexuality, frequent use of prostitutes, anal intercourse by women, and heterosexual intercourse with intravenous drug users are risk factors for HIV infection and AIDS, with its panoply of unusual lung diseases (Fig. 12).

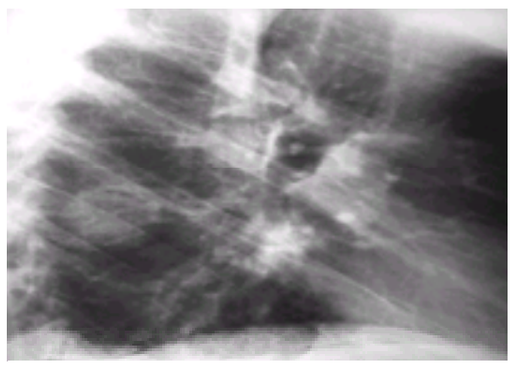

FIG. 11. In this lateral projection from an intravenous drug abuser, an abscess with a small air-fluid level is observed in the posterior segment of the lower lobe; additional parenchymal abscesses were seen elsewhere on other views. Lung abscesses associated with intravenous drug abuse or indwelling catheters tend to be smaller than those seen with underlying pneumonias; they also tend to be multiple and form cavities. In addition, abscesses in intravenous drugs abusers tend to demonstrate relatively rapid growth and cavitation.

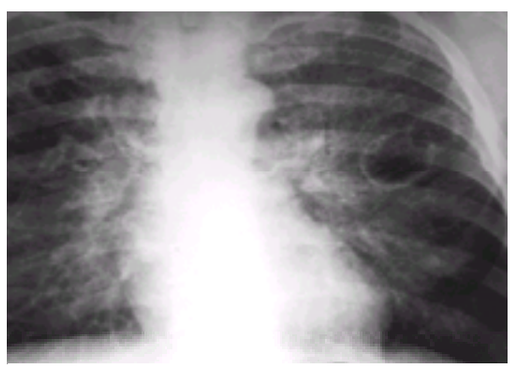

FIG. 12. The classic radiographic appearance of *Pneumocystis carinii* infection in an immunocompromised patient is that of hazy perihilar infiltrates, although the range is broad, from normal-appearing lungs to lobar consolidation. Parenchymal cystic and thin-walled cavitary changes have been associated with *Pneumocystis* infections, typically in the upper lobes. Two such cysts are evident in the left upper lobe of this AIDS patient with *P. carinii* infection.

Medical Drug Use

A detailed record should be made of all drugs that have been taken for medical use, whether purchased over-the-counter or prescribed by a physician. The patient's history of allergic or toxic reactions to drugs should be noted. A large number of drug-induced lung diseases have been reported, and these have been summarized in recent reviews and are discussed in Chapter 22. Table 7 provides a list of the most common drug-induced pulmonary diseases.

Parenchymal reactions
Pulmonary edema
Aspirin, heroin, methadone, propoxyphen
Interstitial pneumonia
Nitrofurantoin, gold salts, sulfasalazine
Cytotoxic agents
Alkylating agents: busulfan, cyclophosphamide, chlorambucil, melphalan
Antibiotics: bleomycin, mitomycin
Antimetabolites: methotrexate, azathioprine
Nitrosoureas: BCNU (bischloroethylnitrosourea)
Pulmonary infiltrates with eosinophilia
Nitrofurantoin, methotrexate, penicillin, and many others
Diffuse interstitial lipidosis
Amiodarone
Airways reactions
Chronic cough
Angiotensin-converting enzyme inhibitors
Asthma
Aspirin, nonsteroidal anti-inflammatory agents, β-adrenergic antagonists
Obliterative bronchiolitis
D-penicillamine (treatment of rheumatoid disease and neutrophilic fascitis)
Pleural reactions
Drug-induced systemic lupus erythematosus
Hydralazine, procainamide, isoniazid, phenytoin, D-penicillamine, and many others
Pleural effusion
Dantrolene, and in association with parenchymal disease, busulfan, nitrofurantoin, amiodarone, and many others
Opportunistic infections
Corticosteroids, cytotoxic agents

[a] A partial listing.

TABLE 7. *Drug-induced pulmonary diseases*[a]

Occupational History

The relationship of lung disease to occupation is not always clear. Current symptoms may be work-related. The patient may suggest the relationship or may answer affirmatively when asked the simple question of whether respiratory symptoms are worse at work. Support for the suspected relationship is provided if other workers at the same workplace have similar symptoms. Some disorders, like byssinosis (Chapter 35), are worse on the day of return to work after a weekend at home. Other disorders, such as air flow obstruction caused by diisocyanates, improve during weekends or vacations. The connection between occupational exposure and lung disease is much less evident when there is a long latent period between the onset of exposure and the appearance of symptoms (Fig. 13 and Fig. 14). The only way of knowing whether to consider seriously the diagnosis of an occupational pulmonary disease is to obtain an occupational history in systematic fashion.

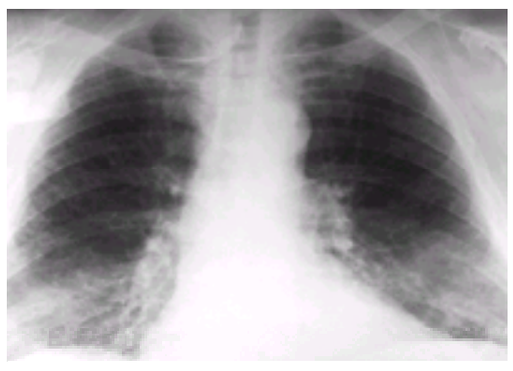

FIG. 13. The fine reticular pattern of asbestosis almost invariably tends to involve the lower lobes bilaterally. As the disease progresses, silhouetting of the diaphragm or cardiac borders by the interstitial lung disease may occur, and the appearance may be indistinguishable from that of idiopathic pulmonary fibrosis (Fig. 24). It is common to see either parenchymal asbestosis or asbestos-related pleural plaques; less commonly, both may be seen in the same patient.

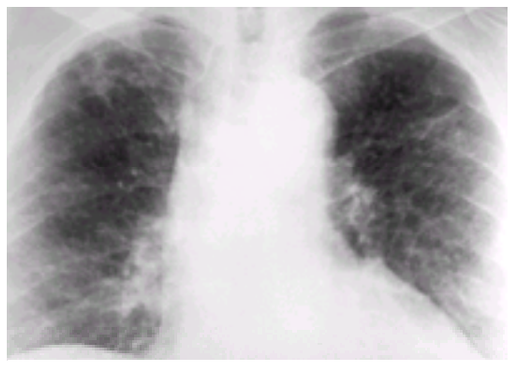

FIG. 14. Characteristic findings of silicosis are demonstrated throughout both lungs of this sandblaster: diffuse, small, scattered nodules, some calcified, with a slightly greater density in the upper lobes. In addition, a dense opacity has formed in the right upper lobe, representing a cicatrized conglomerate of multiple individual nodules. Secondary distortion and irregular contours of the hila are apparent.

All jobs (part-time and full-time) should be listed chronologically, with exact dates recorded if possible. Exactly what jobs were performed and what activity each entailed should be determined exactly—not just the name given to the job. Materials used should be identified, with the appropriate government agency called if necessary to determine the constituents of a substance with a brand name. The physician should obtain general estimates of the intensity of exposure and calculate a rough duration of exposure, should ask whether protective measures were used or recommended, and should inquire about ventilation in the plant. The interval between the start of the job and the beginning of symptoms should be determined. The physician should ask about examinations offered by the industry, such as chest radiograms. The environmental history should be completed with questions about exposures during hobbies or home activities, the presence of pets, use of humidifiers, and the geographic history.

PHYSICAL EXAMINATION

Inspection

Inspection is performed while the history is taken. It will be evident whether the patient is debilitated and chronically ill or presents the appearance of good health. It will also be evident whether the patient is dyspneic at rest, is cyanotic, or has a gross chest wall deformity. It is easy to see whether respirations are shallow or deep, slow or fast, but it is notoriously difficult to assess the effects of an altered breathing pattern on the adequacy of alveolar ventilation. The patient with rapid, shallow respirations may appear to be overbreathing when in fact dead space ventilation is excessive and alveolar ventilation is inadequate. Shallow respirations may be seen with myxedema or raised intracranial pressure; deep respirations are a characteristic feature of metabolic acidosis, as in diabetic ketoacidosis or renal failure.

Flaring of the alae nasi may accompany the rapid respiratory pattern in patients with severe pneumonia. Widespread and severe obstruction of the airways is signaled by noisy breathing and labored expiration, often with pursed-lip breathing and use of accessory muscles of respiration; retraction of the lower interspaces and supraclavicular fossae may be evident during inspiration. Supraclavicular retraction and use of accessory muscles is especially prominent with stridor. Periodic respiration, with intervals of regularly recurring apnea, occurs in cardiac failure, in narcotic and sedative drug overdose, and with increased intracranial pressure. The facial grimacing and sudden cessation of inspiration accompanying pleuritic pain may be dramatic.

Cyanosis

Cyanosis, or blueness of the skin and mucous membranes, is observed when more than 5 g of reduced hemoglobin is present per 100 mL of capillary blood in tissues. Thus, cyanosis may not occur during severe hypoxemia in the presence of anemia and is more evident with erythrocytosis than with a normal level of hemoglobin. Cyanosis may also be associated with methemoglobinemia or sulfhemoglobinemia. Interobserver variability in detecting cyanosis is high unless the arterial oxygen saturation is <85%; thus, cyanosis is an insensitive tool for detecting hypoxemia. To avoid confusion with cyanosis resulting from venous stasis in cold fingers or toes, it is best to detect cyanosis by observing the tongue and oral mucous membranes. Sweating, coarse tremor, twitching, asterixis, drowsiness, and coma may accompany

the hypercapnia that often complicates severe hypoxemia.

Digital Clubbing and Hypertrophic Osteoarthropathy

Digital clubbing may be defined as a focal enlargement of the subcutaneous tissue in the terminal phalanges of the digits, especially the dorsal surfaces; the mechanism is unknown. With rare exceptions, the process is bilateral; the toes as well as the fingers may be involved. Clubbing of the digits, although a most important finding in lung disease, is not specific for pulmonary disease and may be seen in inflammatory bowel disease, hepatic cirrhosis, congenital cyanotic heart disease, and bacterial endocarditis, and as a familial occurrence. Clubbing in pulmonary disease is most frequently found in association with neoplasms, particularly bronchogenic carcinoma, but may also be seen with mesothelioma and Hodgkin's disease. Clubbing can develop rapidly with suppurative lung disease, such as lung abscess; it is common with bronchiectasis and in cystic fibrosis of the pancreas. Clubbing is observed in about 15% of patients with interstitial lung disease and in patients with arteriovenous fistula of the lung. Among the pneumoconioses, clubbing is particularly prevalent in asbestosis.

Digital clubbing is almost never seen in tuberculosis unless the disease is complicated by suppurative bronchiectasis or is a complication of cyanotic congenital heart disease. Clubbing is not observed with chronic bronchitis and emphysema, and its occurrence with either condition should raise the possibility of complicating bronchogenic carcinoma.

In hypertrophic osteoarthropathy (HOA), periosteal new bone forms over the bones of the distal arms and legs, sometimes accompanied by symmetric arthritic changes involving the ankles, knees, wrists, and elbows. There may be thickening of the skin of the distal third of the arms and legs and, rarely, facial thickening. Digital clubbing is almost invariably also present, and there may be neurovascular changes of the hands and feet. The mechanism of HOA, like that of clubbing, is unknown. HOA is always associated with some underlying disease, most often an intrathoracic neoplasm, especially bronchogenic carcinoma; it may be seen with suppurative lung diseases. When joint involvement is prominent, a mistaken diagnosis of arthritis may be made.

The diagnosis of clubbing is made entirely from physical examination. The soft tissues at the base of the nail are spongier than normal. The hyponychial angle, the angle between the dorsum of the distal phalanx and a line connecting the cuticle and the hyponychium, is greater than the normal 195º. Mild clubbing may be difficult to recognize. As the process increases in severity, the shape of the distal digit is changed, with dorsal-palmar or side-to-side thickening. It is important not to confuse filbert nails (increased supero-inferior curvature of the nails) with clubbing. The absence of a spongy nail bed and a normal hyponychial angle are the clues to correct diagnosis. Radiographs of the distal bones of the leg and arm may reveal periosteal formation of new bone that is characteristic of HOA (Fig. 15).

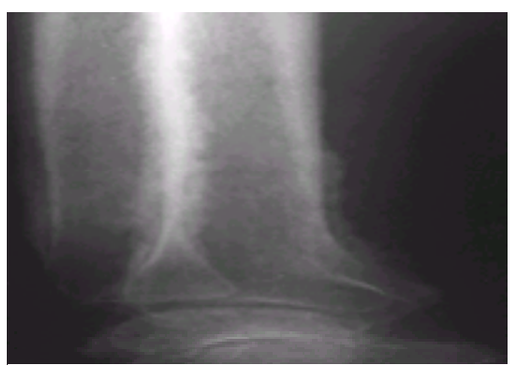

FIG. 15. Hypertrophic pulmonary osteoarthropathy typically involves the diaphyses and metaphyses of tubular bones of the extremities, often in a symmetric manner. In this patient with lung cancer, extensive periosteal new bone is evident along the cortical margins of the distal tibia and fibula.

Thorax

Inspection of the thorax is best carried out during the early part of the physical examination, with the patient sitting or standing, although the recumbent position is just as satisfactory for studying the patient's anterior aspect. Minor asymmetry of the thorax is common. In the defect known as *pectus excavatum,* the lower two thirds of the sternum is markedly depressed behind the frontal plane of the thorax. Other variants of this condition are horizontal grooves in the lower anterior thorax on one or both sides; similar horizontal grooves may remain after rickets in childhood. With pigeon breast (pectus carinatum), there is abnormal protrusion of the sternum anteriorly, especially in its upper part. This deformity may be idiopathic or may be acquired during childhood, most commonly as a result of chronic pulmonary overdistension in asthma or of severe cardiomegaly (Fig. 16).

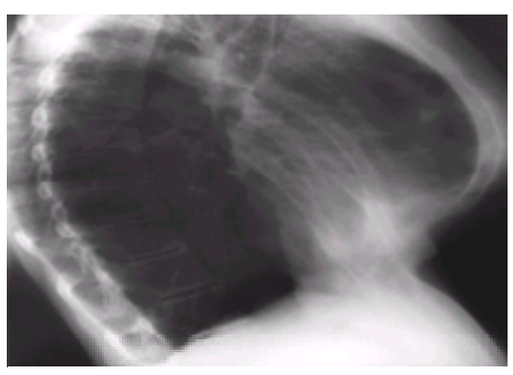

FIG. 16. In this lateral view of a patient with severe pectus excavatum, the heart is displaced posteriorly and superiorly by the lower sternum and xiphoid process. This deformity can cause silhouetting of the heart borders on the corresponding posteroanterior view, and it should not be mistaken for middle lobe or lingular disease. The normal downward slope of the ribs is accentuated as they bend toward their articulations with the sternum.

The presence of thoracic kyphosis or kyphoscoliosis and swellings of the chest wall may be observed. These may denote the presence of an inflammatory process, such as a cold abscess, a tumor of the subcutaneous tissue or chest wall, or a necessitating empyema. Patients with an increase in anteroposterior diameter (e.g., with thoracic kyphosis) need not have air flow obstruction. The increase in anteroposterior diameter often observed in emphysema is caused by an increase in functional residual capacity and total lung capacity.

As the chest is observed during respiration, a decrease or lag in motion on one side of the thorax may indicate the presence of underlying disease. Similarly, a flattening or drawing in of the chest, normally best observed in the supraclavicular fossae, may indicate the presence of an underlying fibrosing process. Differences in the two pectoral muscles (the right pectoral muscle may be larger in right-handed people) should be recognized and should not be confused with disease in the underlying lung. A completely immobile thorax is seen in ankylosing spondylitis with fusion of the costovertebral joints, or, rarely, in patients with severe bilateral pleural disease. The scars of an empyema drainage or thoracotomy should be noted. Engorged veins over the thorax and neck may be present in patients with superior vena caval obstruction. It should be remembered that expiratory filling of the neck veins is often seen in expiratory airways obstruction.

Palpation

Asymmetry or a decrease in movements that is suspected during inspiration may be confirmed by palpation of the thorax. The location and nature of the apical cardiac impulse should be determined; lateral shifts of the apical impulse along with lateral displacement of the trachea are the main physical signs of a shift of the mediastinum from its usual midline position. The finding of a right ventricular lift at the end of systole, felt in the left parasternal area, denotes the presence of right ventricular hypertrophy. Palpable pulmonic valve closure should be looked for as an additional sign of pulmonary hypertension.

The transmission of the vibrations of the spoken voice to the chest wall (vocal fremitus) may be palpated. The intensity of vibration is increased with an increase in the

loudness of the voice and a decrease in the pitch of the syllables used; hence, the common command to the patient to say “99” in a loud voice. As these vibrations are generally bilaterally asymmetric, being more intense over the right hemithorax than the left, it may be difficult to assess the significance of slight increases or decreases in vocal fremitus. However, it is usually easy to be certain of the complete absence of vibration. This denotes the presence of non-air-containing material in the thorax, such as fluid, that is totally absorbing the vibrations. Some degree of fremitus often persists with air in the pleural space, except when the pneumothorax is complete.

Percussion

The sound produced by percussion is determined by the combination of the sound made as the striking finger hits the pleximeter finger and the vibrations coming from the chest wall and the structures underlying it. Percussion over normally aerated lung produces vibrations that are maximal in the range of the natural frequency of the thorax (about 140 Hz in the average young adult man). When the lung is consolidated or the pleural space is filled with fluid, the percussion note is impaired. Relatively few added vibrations come from the underlying solid material, and the low-intensity, relatively high-pitched percussion note is predominantly caused by the sound of impact. A similar percussion note is generated by percussing over the liver. Percussion over an air-containing structure, such as a gas-filled stomach, tends to produce a louder note with a more musical quality (about 180 Hz with a harmonic at 360 Hz) than that produced by percussing over an aerated lung. Such a note is referred to as *tympanitic.*

Percussion is also useful for identifying the interface between the lung and solid structures. The interface between lung and liver, the outer margins of cardiac dullness, and the positions of the diaphragm may be readily determined. In identifying such an interface, a light, rapid percussion stroke should be used, and the pleximeter finger should be moved back and forth rapidly until the interface between normal and decreased percussion notes is accurately identified.

The exact characteristics of the percussion note vary over different parts of the thorax, depending on whether percussion is being carried out over chest wall covered only by subcutaneous tissue and skin, or whether muscles also cover the area. It should be recognized that even with the most vigorous percussion blow, vibrations do not come from a depth of more than 5 cm beneath the surface. It is not possible from percussion alone to differentiate between pleural fibrosis, pleural fluid, and pulmonary consolidation. When percussing over lung, it is generally sufficient to describe the percussion note as normal, dull, or absent. Hyperresonance may be found over a tension pneumothorax.

Auscultation

Careful clinical observations coupled with knowledge of lung physiology and the application of modern electronic technology have resulted in the development of new information regarding the genesis of the normal and adventitious sounds coming from the lungs. Recent reviews summarize much of this new information.

Sound Generation

The spectrum of normal hearing is 16 to 16,000 Hz, and most chest sounds are in the lower range of this spectrum (<1000 Hz), where the sensitivity of hearing is low. The intensity of a sound is determined by the amplitude of the vibrations, the distance the sound must travel, the medium through which the sound travels, and the amount of sound absorbed during the transit. The quality or timbre of a sound is determined by its harmonics or overtones and depends on the sound generator; we have no difficulty identifying whether the same note is played on an oboe, a violin, or a piano.

Sounds generated by the vibrations of gas bubbles in a liquid stream are termed *cavitation noise;* this mechanism may be involved in production of crackles. Sounds are also generated by complex turbulence when gas flows past a pole or a wire, through a tube into a cavity, or exits from a narrow nozzle. Flow visualization in models and casts of airways suggests that sounds are generated as gas develops turbulent flow just distal to the spurs or carinae of bifurcations in large and small airways.

The intensity of the sound generated in the airways, vibrations set up in airway walls, the direction of transmission of the sound, the nature of the material through which the sound is transmitted, the selective absorption of some sound frequencies but not others, and the reflection of sound from air-fluid interfaces all influence the characteristics of the sound detected through the stethoscope on the surface of the chest. The rate of sound transmission through lung tissue is 30 to 60 m/s, compared with 1530 m/s through soft tissue and 1600 to 1800 m/s through bone.

Breath Sounds

Auscultation over the normal lung (Fig. 17) reveals sounds having a murmuring quality; these vesicular or normal breath sounds contain a spectrum of frequencies between 100 and 500 Hz, with maximal intensity below 200 Hz. The sounds increase rapidly in intensity during inspiration, with no pause as expiratory sound begins. A rapid fall-off in intensity occurs during expiration, with little sound heard during the latter two thirds of expiration.

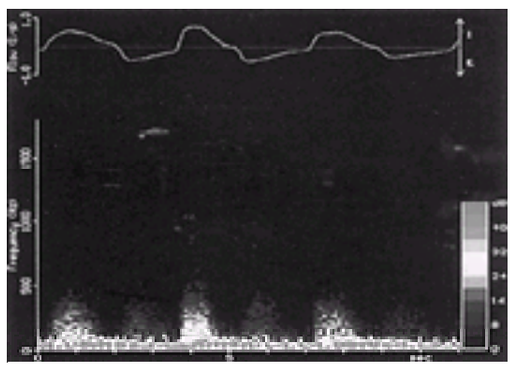

FIG. 17. Normal vesicular breath sounds. Sound spectrogram with simultaneous pneumotachogram (*top*); sound frequency in hertz (Hz) is represented on the ordinate, time (s) on the abscissa; colors designate sound intensity in decibels (dB) on the scale (*lower right*). Recorded over the left posterior lung base in a 13-year-old boy with cystic fibrosis. Note that inspiratory breath sounds are louder than expiratory sounds and that there is no pause between the respiratory phases. The frequencies are virtually all below 500 Hz and are most intense below 250 Hz. Contributions of low-frequency muscle and cardiovascular sound are visible. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) *See color plate 4.*

Auscultation over the trachea (Fig. 18) reveals a harsh, strident sound with almost equal intensity throughout inspiration and expiration, but with a distinct pause between the inspiratory and expiratory phase. Tracheal sounds contain frequencies up to about 1200 Hz, with loudest components below 900 Hz. Bronchovesicular breath sounds have features of tracheal and vesicular breath sounds; the sounds generated are harsher than vesicular sounds, are heard throughout expiration, and are similar in quality during the two phases of respiration. These sounds are normally heard only in the right infraclavicular region and posteriorly between the scapulae. There is much individual variation in the character of normal breath sounds, although they are constant in any one individual. The bronchial component is generally more evident in thin people.

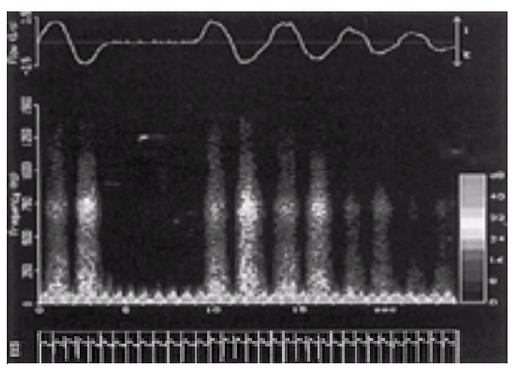

FIG. 18. Normal tracheal breath sounds. Sound spectrogram as described in Fig. 17, but with simultaneously recorded electrocardiogram (*bottom*). Recorded over the

trachea at the suprasternal notch in a healthy, 26-year-old, male nonsmoker. The typical features of normal tracheal sounds are evident, with a broad frequency distribution, extending close to 1500 Hz during both inspiration and expiration, a slightly louder expiration, and a clear break (absence of respiratory sound) between the respiratory phases. During 5 seconds of breath holding and zero air flow, the contribution of low-frequency cardiovascular sounds becomes evident. The electrocardiogram helps to identify the high-intensity, low-frequency heart sounds. The dependence of sound intensity on air flow is obvious during the latter parts of this observation, when the subject was breathing more shallowly. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) *See color plate 6.*

Calculations based on the size of the peripheral airways and the physics of gas flow in tubes show that air flow is laminar in the airways beyond the terminal bronchioles. Laminar air flow in small tubes does not produce sound. A widely accepted formulation is that the sounds heard over the periphery of the lungs are generated by turbulent air flow in the trachea and large bronchi. The sound travels at first through the gas contained in the large bronchi, but as the sound passes peripherally, airway caliber becomes too small for its transmission, and the sound energy is transmitted through lung tissue. The lung behaves as a band-pass filter, with a steep roll-off of frequencies above 200 Hz. Put differently, tracheal sounds are relatively rich in high frequencies. High-frequency absorption is characteristic of lung parenchyma; vesicular sounds that have passed through the most parenchyma have the smallest high-frequency component.

Consolidation of lung tissue (Fig. 19) with continued patency of the main bronchi results in the transmission of sounds from the large airways to the periphery with little change in their character. The sounds are similar to those heard over the cervical trachea and are termed *tubular* or *bronchial.*

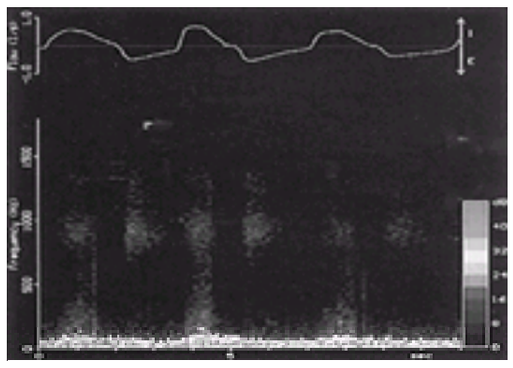

FIG. 19. Bronchial breath sounds. Sound spectrogram as described in Fig. 17, simultaneously recorded over the corresponding site on the right posterior lung base in the same patient as in Fig. 17. Pneumonia and consolidation of the right lower lobe were present, and bronchial breathing is evident. In comparison with the left side (Fig. 17), there is a decrease in intensity of breath sounds but an increase in high-frequency components extending above 1000 Hz. This is most evident during expiration; in contrast to the normal left side (Fig. 17), expiratory breath sounds are louder than inspiratory breath sounds. Contributions of low-frequency muscle and cardiovascular sound are visible. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) *See color plate 5.*

Fluid, air, or scar tissue in the pleural space forms a sound barrier that diminishes the transmission of breath sounds, either because of altered absorption of sound, reflection at the lung pleural interface, or, in the case of pneumothorax, increasing acoustic mismatching of chest wall and underlying air. If the layer of fluid or scar tissue is thick enough, the sounds are absent. Some transmission of breath sounds through a pneumothorax persists except when the collection of air is large. Sounds of higher frequencies may pass through a thin layer of fluid, which gives the breath sounds at the upper borders of a large pleural effusion a bronchovesicular quality. Consolidation of lung tissue with accompanying occlusion of the segmental or lobar bronchi also results in a complete sound barrier, with obliteration of normal breath sounds. Similar principles govern the transmission of the whispered and spoken voice to the surface of the chest.

Spoken Voice

Recordings of the spoken vowels *E* and *A* over the periphery of the chest disclose that *E* results in lower-pitched vibrations reaching the periphery than is true for *A.* Sound recordings over consolidated lung tissue or over a thin layer of fluid reveal selective transmission of the vibrations from the *E,* with attenuation of the lower harmonics and increased transmission of the higher harmonics. The transmitted sound has both the recorded and spoken characteristics of an *A,* a phenomenon referred to as *E-to-A change* or *egophony.*

Whispered Voice

A similar phenomenon gives rise to increased transmission of the whispered voice, a finding termed *whispered pectoriloquy.* The whispered words “one, two, three” are normally heard over the periphery of the normal lung as three ill-defined murmuring or rushing sounds. However, the syllables are clearly identifiable when the transmitted whispered voice is heard over consolidated lung with patent bronchi. Recordings show a marked increase in the intensity of sound transmitted between 200 and 600 Hz over consolidated lung, in contradistinction to the sharp cutoff of frequencies above 200 Hz in recordings made over a normal lung.

Adventitious Sounds

The adjective *adventitious* is reserved for sounds heard only in disease states. In recent years, a consensus has been reached that adventitious sounds arising from the lungs can be classified into continuous and discontinuous sounds. Continuous sounds are usually louder than the accompanying breath sounds, with a duration longer than 250 ms. Discontinuous sounds are explosive sounds, with a duration shorter than 20 ms. First described by Laennec, these sounds have been given a plethora of confusing names through the years by various authors. In the 1970s, the American Thoracic Society agreed on the terminology shown in Table 8.

Acoustic characteristics	American Thoracic Society nomenclature	Common synonyms
Discontinuous, interrupted sounds; loud, low in pitch	Coarse crackle	Coarse rale
Discontinuous, explosive sounds; less loud, shorter in duration, and higher in pitch than coarse crackle	Fine crackle	Fine rale
Continuous sounds longer than 250 ms; high-pitched; dominant frequency 400 Hz or more; a hissing or musical sound	Wheeze	Sibilant rhonchus
Continuous sounds longer than 250 ms; low-pitched; dominant frequency about 200 Hz or less; a snoring sound	Rhonchus	Sonorous rhonchus

TABLE 8. *Classification of common lung sounds*

Wheezes and Rhonchi

Wheezes and rhonchi are sounds whose duration is 250 ms or more. Wheezes have a hissing or less often a musical character. Their dominant frequency is 400 Hz; when wheezes are musical, harmonics of a relatively constant frequency of up to about 1000 Hz are generated. Rhonchi are lower-pitched, with frequencies predominantly below 200 Hz (Fig. 20 and Fig. 21).

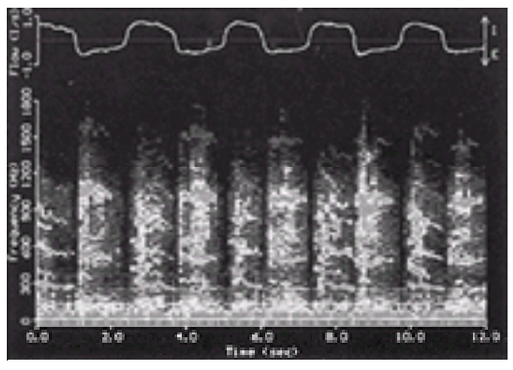

FIG. 20. Tracheal breath sounds in a patient with exercise-induced asthma. Sound spectrogram as described in Fig. 17. Polyphonic wheezing is present during both inspiration and expiration, seen as broad bands of intense sound with a narrow distribution of frequencies. Contributions of low-frequency muscle and cardiovascular sound are visible. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) *See color plate 7.*

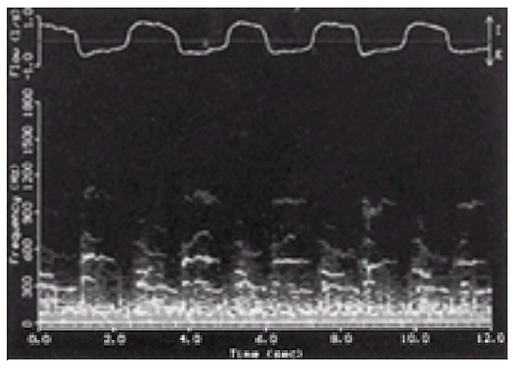

FIG. 21. Pulmonary breath sounds with wheezes. Sound spectrogram as described in Fig. 17. Sounds recorded over the right infraclavicular region in the same patient as in Fig. 20. Inspiratory and expiratory wheezes are seen as broad bands of intense sound with a narrow distribution of frequencies. The intensity of sound is less than in Fig. 20 and no sounds have frequencies higher than 900 Hz. (Reproduced from Pasterkamp H, et al. Digital respirosonography. *Chest* 1989;96:1405.) *See color plate 8.*

The best model for wheezes is thought to be sounds generated by uncoupled reeds, such as those of the oboe or clarinet. A disease process narrows the bronchus; as gas flows rapidly through the narrow region, the pressure falls because of the Venturi effect. Further narrowing occurs, almost to the point of closure, and opposite walls oscillate between the closed and nearly opened positions as air moves through, thus generating a sound. This mechanism of sound generation in collapsible tubes is known as *flutter.* The pitch of the note is determined by the tightness of the closure and by the mass and elastic properties of the solid structures set into vibration. The pitch of the sound is not affected by the length of the column of air in the airway. Thus, a high-pitched sound may be generated by marked narrowing of a main bronchus, as by tumor or fibrous stenosis, and a sound of similar pitch may also be generated from an orifice of comparable diameter in a small airway. Detailed reviews of the mechanism of wheeze generation have been published.

Wheezes vary widely in pitch, depending on the exact character of the narrowing in the bronchus. The bronchial obstruction that produces a wheeze may be caused by secretion, by an inflammatory or other structural change, or by dynamic compression of the airway. Because the airways narrow during expiration, wheezes are more frequent during expiration than inspiration.

Based on their time of appearance during forced respiration, wheezes may also be classified into one of two categories: random onset and simultaneous onset. Random-onset wheezes may be single or multiple, may be inspiratory or expiratory in timing, and may start and end at different times. The pitch of the sounds may vary considerably. The wheezes of asthma are an excellent example. Simultaneous-onset wheezes are expiratory sounds composed of several harmonically unrelated musical notes that tend to start and end simultaneously and are generated during forced expiration in all types of chronic air flow obstruction. A large number of distant, high-pitched, piping wheezes become audible suddenly during a forced expiration, presumably as the equal pressure point migrates peripherally and sounds are simultaneously generated from dynamically compressed airways.

Simultaneous-onset wheezes can often be produced by normal persons performing a forced expiratory effort. The sound produced in normal persons occurs only during very severe effort, tends to be relatively low in intensity, and occurs only toward the end of expiration; with experience, the physician can learn from the amount of effort used whether the simultaneous-onset wheeze indicates disease or is a normal phenomenon. Random-onset wheezes may, of course, be heard in obstructive airways disease before the sudden onset of simultaneous-onset wheezing; they are never heard in normal persons. Simultaneous-onset wheezes may be the only wheezes heard in patients having severe obstructive air flow disease with scanty secretions.

Crackles

Crackles are short sequences of sound with a duration shorter than 20 ms and usually shorter than 10 ms. They range from one to 20 cycles; usually no more than five cycles exceed the noise level in the recording (Fig. 22 and Fig. 23). Crackles may be few in number or may occur as showers, so close together that the individual sounds almost merge. Crackles occur during both inspiration and expiration, but they are more intense and more frequent during inspiration. The number of crackles heard tends to increase with increasing depth of respiration.

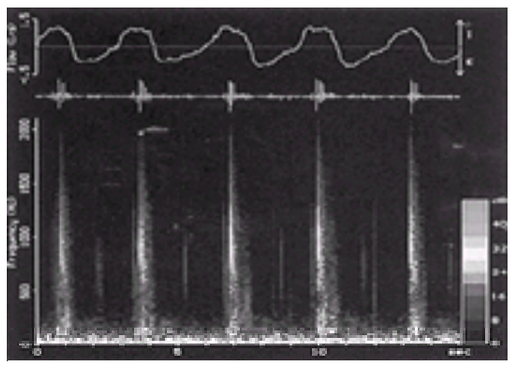

FIG. 22. Mid to late fine inspiratory crackles in a 60-year-old man with interstitial pulmonary fibrosis. These were recorded over the right posterior lung base. The broad frequency distribution is typical for fine crackles (coarse crackles would be contained largely below 1000 Hz). There are a few expiratory crackles as well. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) *See color plate 9.*

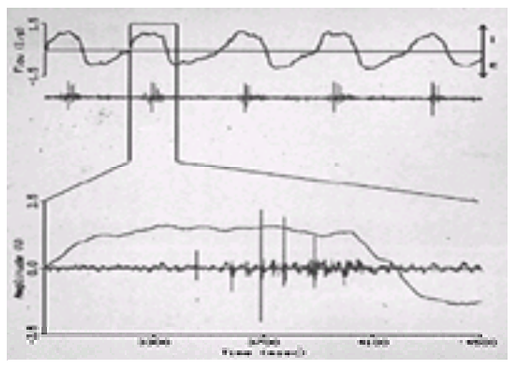

FIG. 23. The upper two records are the same as in Fig. 22. One expiration and a small part of the adjacent inspiration are shown on an expanded time-based display. The mid to late crackles are well shown. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) *See color plate 10.*

The words *fine, medium, coarse, wet,* and *dry* are often used by physicians to describe crackles but are not useful in distinguishing between disease categories. If the only information available is the character of the crackles, one cannot tell pulmonary edema from bronchopneumonia. There seems to be little purpose in dividing crackles into categories other than coarse and fine (Table 8). A recent study has confirmed the distinguishing characteristics of the fine crackles of interstitial lung disease in comparison with the coarse crackles of bronchiectasis, COPD, and congestive heart failure.

The mechanism of production of crackles is still unclear. They may be caused by air bubbling through secretions or by the sudden opening of a succession of small airways, with rapid equalization of pressures causing a series of implosive sound waves. In pneumonia and pulmonary edema, surfactant integrity is affected and respiratory air spaces readily collapse. In diffuse interstitial pulmonary fibrosis, thickening and distortion of the alveolar walls also result in instability of the air spaces, causing them to collapse during ordinary expiration, with the generation of crackles on the succeeding inspiration. Each collapsed respiratory air space opens suddenly at about the same lung volume in successive breaths as opening pressure is reached (Fig. 22 and Fig. 23).

In elderly patients without apparent lung disease, it is not uncommon to auscultate crackles at the lung bases that disappear as several deep breaths are taken. These are known as *atelectatic crackles.* Their likely mechanism is loss of surfactant with air space collapse. They disappear with successive deep breaths as surfactant is replenished and air space stability is restored. These crackles can be induced at the lung bases of normal young persons by having them breathe at low lung volume, especially if they breathe 100% oxygen, which washes out the nitrogen from the lungs and accentuates microatelectasis.

Crackles may be absent during ordinary respiration and become audible only during the deep inspiration that follows a cough or when the physician listens over the dependent lung with the patient in lateral recumbency. When the clinician must listen to a patient in lateral recumbency, it is important to remember that air motion is relatively smaller in the uppermost than in the lowermost lung. Thus, if the diseased lung is uppermost, the degree of expansion may not be sufficient to reach the critical opening pressure of the respiratory air spaces and thus generate crackles. On the other hand, when the same lung is listened to in the nether position, the increased proportion of ventilation going to that lung may generate crackles or wheezes. The same rationale applies in the evaluation of a patient who has symptoms of lung disease but negative findings on chest roentgenogram and no obvious findings when examined in the sitting position. The patient should be listened to in both lateral recumbent positions during ordinary and forced expiration, as well as in the upright position.

Showers of fine, mid to late inspiratory crackles are heard at the lung bases in interstitial lung diseases. These crackles (“velcro” crackles) sound like a velcro fastener being opened; they have a recurrent rhythm characterized by similar spacing and relative loudness. Fine crackles with these characteristics are heard in about 60% of patients with various forms of chronic interstitial pulmonary fibrosis but are heard in only about 20% of those with sarcoidosis and other granulomatous lung diseases. The fine crackles of interstitial lung disease appear to correlate with the pathologic severity of the disease, the evidence of radiographic honeycombing, and the severity of the physiologic abnormality (Fig. 24). Scanty expiratory crackles are also audible in interstitial lung disease.

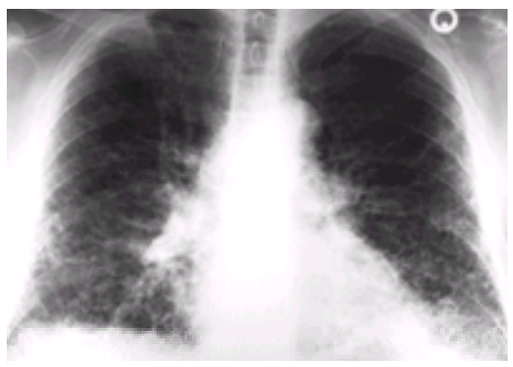

FIG. 24. Honeycombing is present, predominantly at the lung bases, in this case of severe interstitial pulmonary fibrosis. Note that fibrosis is so severe that the margins of the chest wall, diaphragm, and mediastinum are all rendered indistinct and shaggy. Early findings of interstitial pulmonary fibrosis may be seen on high-resolution chest CT before becoming visible on standard chest radiographs.

Crackles are heard in many lung disorders characterized by parenchymal disease: congestive heart failure, pneumonia, bronchiectasis, and cystic fibrosis. Crackles are also frequently heard early in inspiration in patients with chronic obstructive lung disease. These inspiratory crackles are coarse, loud, scanty, audible at the mouth as well as over the chest, and often associated with a few late-expiratory crackles. They are believed to be generated by air flowing through an airway intermittently occluded by mucus or a poorly supported bronchial wall.

Quiet breathing in normal persons is a virtually silent phenomenon, but in many patients with chronic bronchitis or an exacerbation of asthma, a noise is generated during inspiration that is audible with the naked ear at a distance from the mouth. A physician can often assess the presence of airways obstruction when noisy breathing is heard while speaking with the patient on the telephone.

Pleural Friction Rub

Pleural friction rubs are sounds heard over areas where roughened visceral and parietal pleurae rub over each other during respiration. The cause of the roughening is usually a fibrinous or organizing exudate. The characteristic grating or creaking sound is usually loudest at the end of inspiration, but a rub may be heard during both phases of respiration. Pleural friction rubs vary greatly from breath to breath and may be heard only during a deep respiration. They are usually most evident over the lower lateral and anterior thorax, because this is the location of greatest chest wall motion. Very loud rubs may produce palpable vibrations. Pleural friction rubs are usually readily identified, but it may sometimes be difficult to differentiate them from muscle sounds or from very coarse crackles.

Mediastinal Crunch

Mediastinal crunch is a series of crackles that are synchronous with the heartbeat and audible even when the breath is held. These crackles are produced by air in the areolar tissues of the mediastinum. The sound is often accentuated in left lateral recumbency. Mediastinal crunch is usually more sensitive than the chest roentgenogram in detecting mediastinal emphysema, but roentgenographic signs may precede mediastinal crunch when the air collects predominantly in the posterior mediastinum.

Adventitious Sounds Originating in the Chest Wall

Crackling sounds are produced when hair is trapped between the skin and stethoscope. Although these sounds may simulate crackles coming from the underlying lung, they tend to be closer to the ear and, with experience, are usually easily recognized. Firmer application of the stethoscope or wetting the skin stops them.

Low-pitched rumbling, muffled, distant, sometimes roaring sounds may be heard during contraction of chest wall muscles. Muscle sounds may be varied by changing the patient's position. They often occur in a chilly or nervous patient who is shivering and are usually easily distinguished from crackles, which are higher-pitched and more discrete.

COMMON PULMONARY SYNDROMES

Pneumonia

The findings of parenchymal consolidation with patent bronchi vary depending on the completeness and extent of disease (Fig. 25). Chest wall motion, as determined by inspection and palpation, ranges from normal to impaired. Similarly, the percussion note ranges from normal to impaired. When consolidation is complete, the breath sounds heard over the periphery have a tubular quality, the spoken voice is increased in intensity, E-to-A change is present, and the syllables of the whispered voice can be clearly identified. Alterations in breath sounds and in spoken and whispered voice are less striking when the consolidation is patchy. Whispered pectoriloquy often gives a clear indication of the presence of consolidation, even when it is difficult to be certain of the significance of a slightly increased harshness and prolonged expiratory phase of the breath sounds. In general, increased transmission of the whispered voice is more easily identified than increased palpable vibration from the spoken voice or the E-to-A change.

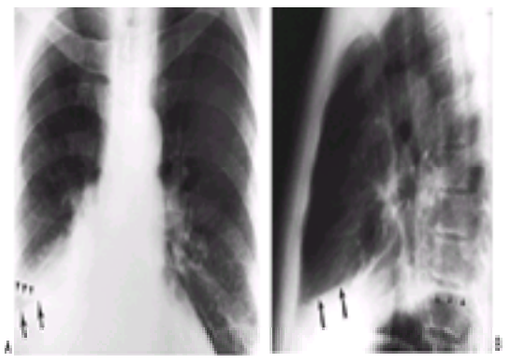

FIG. 25. A,B: Two regions of pneumonia are demonstrated in this patient, one lobar and one segmental. On the frontal view, the upper margin of a right middle lobe pneumonia is sharply demarcated by the minor fissure (*arrows*). More superiorly on the frontal view and posteriorly on the lateral view is a second segmental consolidation, also sharply demarcated inferiorly, in this case by a lower lobe superior accessory fissure (*arrowheads*). These consolidations are quite dense and do not demonstrate air bronchograms.

In pneumonia, there may be no positive findings on physical examination if the process is interstitial, or if 1 to 2 cm of aerated lung separates the disease process from the chest wall surface. If the consolidated lung lies beneath the structures of the shoulder girdle, lung abnormalities may not be evident, even if the pneumonia extends to the visceral pleura.

When the consolidation is patchy and interspersed with aerated lung tissue, breath sounds and whispered voice sound changes may be minor, and crackles may be the major evidence of parenchymal lung disease. However, it must be stressed that in most instances crackles indicate the presence of parenchymal lung disease without establishing the nature of the process. The presence of crackles in a patient who has had tuberculosis or some other pulmonary problem but who is not acutely or severely ill may merely denote a residuum of the old disease. Conversely, crackles of recent origin or occurring in an acutely and severely ill patient make pneumonia a likely diagnosis.

When pulmonary consolidation is accompanied by an obstructed bronchus, the findings are very similar to those noted in pleural effusion—that is to say, motion of the thorax is decreased, vocal fremitus is absent, percussion note is impaired, and breath and whispered voice sounds are absent. The findings are similar in patients with pleural fibrosis, except that there may be a decrease in the size of the ipsilateral hemithorax. With massive pleural effusion, the trachea and lower mediastinum may be shifted to the contralateral side; with pleural or pulmonary fibrosis, the mediastinal shift occurs to the ipsilateral side.

Obstruction of Air Flow

Moderate upper airway obstruction causes a sensation of difficult breathing but may produce few physical findings. As the obstruction becomes high-grade, wheezing and stridor become evident. The history and time course of onset are important. Slow progression in a smoker suggests the possibility of upper respiratory tumor. Sudden onset should raise the possibility of acute infection or aspiration of a foreign body. A history of endotracheal intubation suggests the possibility of tracheal stenosis.

There are few outward manifestations of abnormality in patients with mild air flow obstruction resulting from bronchial and bronchiolar disease or emphysema. In cases of moderate air flow obstruction, when the patient is asked to empty the lungs forcibly and completely, it is evident that expiration is prolonged and difficult, with incomplete pulmonary emptying. The degree of expiratory slowing may be estimated by measuring the forced expiratory time (normally 4 seconds or less) with a watch and a stethoscope. Auscultation over the larynx permits accurate determination of the end of expiration. Sounds are audible at this site at the low air flows occurring near residual volume (Fig. 18), when breath sounds are no longer audible over the lungs. As the process becomes severe, the patient's distress is evidenced by labored breathing, use of the accessory muscles of respiration, inspiratory retraction of the supraclavicular fossae and lower interspaces, and positioning of the chest near total lung capacity.

Differentiation of air flow obstruction caused by asthma from that caused by chronic bronchitis or emphysema (COPD) depends on the history. Recent acute onset and a history of atopy or recurrent bouts of reversible air flow obstruction support the diagnosis of asthma. Slowly progressive worsening of symptoms, even with recent worsening, suggests COPD. It may not be possible to exclude emphysema with certainty in a chest radiogram taken during a severe asthmatic episode; loss of lung overdistension and attenuation of the vascular pattern in a film taken with the patient in remission establishes the diagnosis. Mild or moderate emphysema is not readily diagnosed in a plain chest radiogram unless bullae are present; CT of the chest is a much more sensitive diagnostic tool, although CT is not indicated for routine diagnostic evaluation.

The key finding of wheezes in chronic air flow obstruction was referred to earlier in the chapter, but it must be remembered that when airways obstruction is very severe, wheezes may completely disappear, along with a marked decrease in the intensity of breath sounds. The velocity of air flow is insufficient to generate sound. The reappearance of wheezes indicates diminished severity of airways obstruction, perhaps in response to treatment.

Pneumothorax

The findings in pneumothorax depend on the size of the pleural air space. Motion may be normal or diminished, fremitus may be decreased to absent, the percussion note is usually normal, and breath and whispered voice sounds are decreased to absent.

Pleural Effusion

The impaired percussion note in pleural effusion extends further paravertebrally and laterally than it does in the midscapular line. This is because no lung is present medially and laterally beneath the percussing fingers, whereas in the scapular line there is just a thin layer of fluid overlying the lung. Breath sounds with a bronchial character and an E-to-A change may frequently be heard over the thin layer of fluid at the upper end of an effusion. This physical finding may be helpful in determining the site for a thoracocentesis. Elevation of the diaphragm, as in ascites, hepatomegaly, or subphrenic abscess, may simulate the findings of a pleural effusion. The chest radiogram is of great help in diagnosing small pleural effusions when physical findings are normal or equivocal. The radiogram is the only way of diagnosing loculated pleural effusions that do not present on the chest wall.

Interstitial Pulmonary Fibrosis

Interstitial pulmonary fibrosis is defined as an inflammatory process of varying etiology involving the respiratory air space walls that is accompanied by varying amounts of fibrosis. Patients may be symptom-free and come to medical attention because of the findings in a chest radiogram. Others are seen with cough, which is usually

nonproductive. Yet others seek attention because of effort dyspnea of recent onset. The history may give no hint of etiology. It may suggest the presence of a systemic disease; may reveal prior inhalation of a biologically active dust, such as asbestos or silica; or may reveal that the patient has lived in an area where an infection, such as one of the deep mycoses, is endemic. Alternatively, the patient's lifestyle may raise the possibility of HIV infection or may support a diagnosis of lung disease resulting from the intravenous injection of fibrogenic material, such as talc.

Physical examination usually discloses constant, fine, end-inspiratory crackles, which tend to be most evident at the lung bases. With advanced disease, the chest wall is diminished in volume at full inspiration, there may be right ventricular lift, and the pulmonic second sound may be accentuated, indicating the presence of pulmonary hypertension and right ventricular hypertrophy. The general examination may reveal the stigmata of a systemic disorder, such as rheumatoid disease.

The chest radiogram generally shows a diffuse parenchymal pulmonary infiltrate with a pattern that varies depending on the etiology of the process. When the plain chest radiographic findings are normal, the diagnosis may be supported by pulmonary function tests that show normal air flow, decreased vital and total lung capacity, deceased carbon monoxide diffusing capacity, and resting hypoxemia without hypercapnia that worsens with exercise. The presence of typical crackles also supports the diagnosis. The greater sensitivity of CT may reveal abnormalities not seen on the plain chest film. It is important when considering the differential diagnosis of the patient with dyspnea and normal parenchyma on CT to keep in mind the relatively rare occurrence of primary pulmonary hypertension. These patients often consult physicians for many months before the cause of their problems is established.

Deep Venous Thrombosis and Pulmonary Embolism

Each year in the United States, about 500,000 episodes of pulmonary embolism occur, which cause about 50,000 deaths. Hence, it is difficult for a practicing general physician or pulmonologist to long escape contact with this ubiquitous disease. Its underlying cause is predominantly deep venous thrombosis, risk factors for which include injury to the pelvis or lower extremities, surgery of the lower extremities, any surgical procedure requiring >30 minutes of general anesthesia, burns, pregnancy and the postpartum state, previous deep venous thrombosis, failure of the right side of the heart, prolonged bed rest, age >70 years, obesity, and use of estrogenic drugs. Deep venous thrombosis and pulmonary embolism should always be considered together. If a pulmonary embolus is suspected, a quest for the source of the embolus must follow immediately; the diagnosis of deep venous thrombosis must immediately raise the question of whether a pulmonary embolus is present.

Neither condition can be diagnosed on purely clinical grounds; deep venous thrombosis is confirmed only about half the time when clinical signs (pain, heat, redness, swelling) are present, and about half the proven incidents of recent-onset deep venous thrombosis are asymptomatic. Contrast venography, impedance plethysmography, and duplex ultrasonography are the three methods currently in use for diagnosing deep venous thrombosis (Chapter 66).

Prospective studies have shown that pulmonary embolism occurs in about 40% of patients with proven deep venous thrombosis. The most common symptoms of acute embolism are dyspnea and palpitations. Hemoptysis and pleuritic chest pain are consequences of infarction, which is an infrequent complication of embolism that occurs 12 to 36 hours after embolism. Angina, syncope, and recent onset of an arrhythmia may also accompany a pulmonary embolus. On examination, tachycardia and tachypnea may be observed. With severe embolism, signs of pulmonary hypertension may be present. The chest radiographic findings are usually normal. Large central emboli may produce enlargement of the hilar pulmonary artery shadow and give rise to peripheral oligemia. Atelectasis, which develops because of decreased surfactant production, may produce a shadow in the chest film. An infarct appears as a pleura-based shadow of any shape and is often accompanied by a pleural effusion.

A negative perfusion scintiscan excludes the diagnosis of pulmonary embolism. Perfusion defects when present are nonspecific. With larger defects, a ventilation scan in which defects match the perfusion is nondiagnostic. If the perfusion defects are well ventilated, the probability of embolus is high and the pulmonary angiogram can be bypassed. The pulmonary angiogram is the definitive test for pulmonary embolism (Chapter 66).

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CHAPTER

15 Aerosols

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INTRODUCTION

Aerosols are defined as any mixture of solid or liquid particles or droplets that are stable as a suspension in air. They play an important role in respiratory medicine in several different ways. First, some aerosols (e.g., toluene diisocyanate, thermophilic actinomycetes) produce lung disease in susceptible individuals, whereas other aerosols worsen pre-existing disease (e.g., sulfur dioxide or ozone in asthma and chronic bronchitis). Second, aerosols are invaluable in diagnosing and assessing the severity of lung disease (e.g., radiolabeled aerosols to detect pulmonary embolism; aerosols containing methacholine, histamine, or distilled water to determine airway hyperreactivity). Third, they are used to treat an expanding list of lung diseases (e.g., asthma, cystic fibrosis) and to anesthetize the respiratory tract before diagnostic and therapeutic procedures, such as bronchoscopy. Finally, aerosols are used in research to define pathogenic mechanisms in several lung diseases (e.g., produce disease models in animals).

This chapter is designed to provide an overview of aerosols in respiratory medicine, including their physical characteristics and deposition patterns, the devices used to generate aerosols, the role of aerosols in the diagnosis and treatment of lung diseases, the unique features of aerosol delivery during mechanical ventilation, and the determinants of systemic bioavailability from aerosols. Several comprehensive reviews of aerosol generation, deposition, and therapy are available (see reference list) for those interested in more detailed information about this important area.

CHARACTERISTICS OF AEROSOLS

Aerosols are characterized as being of uniform (monodisperse) or varied (heterodisperse) size. Monodisperse aerosols have a geometric standard deviation less than 1.2 (see below). Environmental aerosols and aerosols used in clinical practice are heterodisperse. The range of particle size is wide: aerosols formed as condensation nuclei are usually between 0.001 and 0.1 µm in diameter, those created by cigarette smoke and automobile exhaust are between 0.1 and 1 µm, and aerosols formed by pollens and grinding or mining activity are most typically between 3 and 20 µm in diameter. Therapeutic aerosols tend to be in the 1- to 5-µm range. In general, very small particles are breathed in and out of the lung without being deposited. However, condensation nuclei can grow and coalesce to form particles in the 0.1- to 10-µm size range, which favors deposition in the lung. Large particles (10 µm) characteristically settle out of aerosols, especially if a holding chamber is used, and penetrate poorly into the lung.

Most aerosols generated are heterodisperse. They fit a log-normal distribution in which a plot of particle density (number of particles per given size) versus the logarithm of size yields a bell-shaped normal distribution curve (Fig. 1). The mass median aerodynamic diameter (MMAD) of an aerosol is the aerodynamic diameter around which the mass is centered. It takes into account aspects of particles that are difficult to measure (e.g., shape and density), and it is the key determinant of particle deposition in the lung. The aerodynamic diameter (d_a) of a sphere is described as $d_a = d\ddot{O}p$, where d is the physical diameter of the particle and p is its density. The width of the size distribution is represented by the geometric standard deviation (s_g), which is the ratio of the size below which 84.13% of the mass resides to that below which 50% of the mass resides. Values of s_g of 1.2 indicate a narrow size distribution and define monodisperse aerosols. Although it is possible to generate aerosols with a narrow size distribution, most therapeutic aerosols have s_g values of 1.6 to 2.0, indicating a broad size distribution, in which a proportion of the particles will likely not be deposited in the lung.

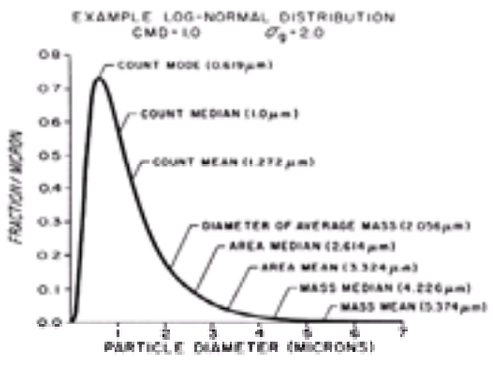

FIG. 1. An example of the log-normal distribution in normalized linear form of aerosol particle sizes for a count median diameter (CMD) equal to 1 µM and a geometric standard deviation equal to 2. Particle density is on the y-axis and particle size is on the x-axis. (Reprinted with permission from *Aerosol Sci* 1971;2:289.)

DEPOSITION OF AEROSOLS IN THE LUNG

The major mechanisms by which aerosols deposit in the lung are inertial impaction, sedimentation, and diffusion. Electrostatic precipitation and interception also play a role, but mostly under select circumstances. A particle deposits by impaction when its inertia is such that it is unable to continue to flow with the air stream as the air stream changes direction. This occurs in the upper airways when the air stream curves sharply in the nose, between the pharynx and the larynx, and in the lower airways at airway bifurcations. The degree of impaction is proportional to d^2Q, where d is the diameter of the particle and Q is the velocity of the air stream. As a result, the number of particles impacting increases with increasing flow rates, with larger particle size, with the acuteness of the angle through which the air stream turns, and with decreasing airway diameter.

Sedimentation is primarily responsible for the deposition of particles that do not impact a surface when entering the lung. Such particles, usually less than 5 µm in size, are subject to gravitational forces based on the square of their diameter. Sedimentation is enhanced by breath holding and slow, steady breathing.

Brownian diffusion is the major mechanism by which particles 0.5 µm in diameter deposit in the lung. These particles deposit in distal, nonairway lung units, and they comprise only a small fraction of the total pulmonary deposition of therapeutic aerosols. Deposition of condensation nuclei in the lung occurs mostly by diffusion.

Most aerosols are charged. As a result, electrostatic precipitation can contribute to the deposition of very small particles in the lung. Electrostatic precipitation may be most significant outside the lung, in that it increases the deposition of therapeutic aerosols in narrow plastic tubes and thereby decreases delivery to the lung, especially

when dry powders are inhaled.

Interception occurs when the distance to a surface is less than the diameter of a particle. Its major role is in the deposition of fibers (e.g., fiberglass, asbestos) on airway walls. It is of little importance in the delivery of therapeutic aerosols.

The therapeutic relevance of particle size and its effects on deposition are apparent from reports indicating that for both ipratropium bromide and albuterol, particle sizes £2.8 µm provide optimal bronchodilation. Larger particles, which would be expected to exhibit greater upper airway impaction, are less effective.

FACTORS INFLUENCING AEROSOL DEPOSITION IN THE LUNG

For the purpose of describing particle deposition in the lung and the effects of various factors on deposition, the lung can be divided into three compartments: nasopharyngeal, tracheobronchial, and pulmonary. The major determinants of particle deposition are different for each. Inertial impaction is most important in the nasopharyngeal compartment, inertial impaction and sedimentation are both important in the tracheobronchial compartment, and sedimentation and diffusion are important in the pulmonary compartment (Fig. 2).

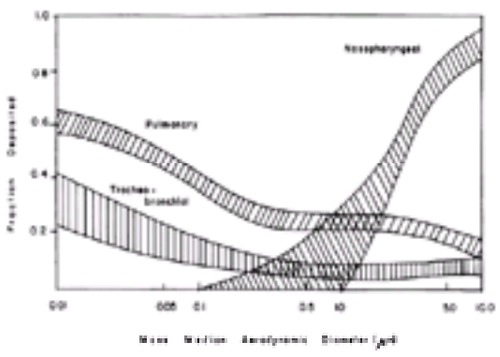

FIG. 2. Particle deposition in the respiratory tract, based on the three-compartment model of the International Committee on Radiation Protection. Each of the *shaded areas* indicates the variability of deposition for a given mass median (aerodynamic) diameter in each compartment when the geometric standard deviation varies from 1.2 to 4.5 and the tidal volume is 1450 mL. (Reprinted with permission from *Health Phys* 1966;12:173.)

In addition to particle size, factors that can influence aerosol deposition in the lung include airway geometry, the breathing pattern, and the presence of airway disease. Normal subjects differ widely in airway geometry. In those with smaller conducting airways, central (i.e., tracheobronchial) deposition of aerosols is greater than in those with larger airways. Breathing pattern also can influence deposition. Rapid inspiration and inhalation of an aerosol that is injected into the air stream at the middle or end of an inspiration increase central deposition. In contrast, slow inspiration, aerosol inhalation at the beginning of a breath, and a breath hold at the end of inspiration increase peripheral (e.g., pulmonary) deposition. Increased minute ventilation, as occurs during exercise, increases particle deposition in the lung. However, the deposition pattern may be altered by changes associated with the increased minute ventilation, such as greater inspiratory flow rates and decreased ability to humidify the inspired particles fully (reduced hygroscopic growth).

Another factor influencing aerosol deposition is its tonicity. There may be growth or shrinkage of nonisotonic particles as they pass through humidified airways. Obviously, a change in particle size will alter the deposition pattern.

Airway narrowing resulting from any cause affects particle distribution in the lung. As explained above, this has been noted for normal subjects with airways of different sizes, but it is more pronounced in the presence of lung disease. Most diseases are associated with increased airway and decreased pulmonary deposition. For example, the reduced airway caliber of patients with cystic fibrosis enhances delivery to the tracheobronchial compartment by 200%–300%. A similar phenomenon is seen in patients with asthma and chronic obstructive lung disease from other causes.

The changes in deposition pattern produced by disease and other factors have potential therapeutic and diagnostic implications that may differ depending on the specific drug or chemical administered. For example, the b-adrenergic agonist terbutaline produces an equivalent degree of bronchodilation and improvement in gas exchange regardless of whether it is deposited predominantly in the central airways or in the peripheral airways. In contrast, in patients with asthma, central deposition of methacholine produces a greater degree of bronchoconstriction than does peripheral distribution. Body position may also influence aerosol deposition. The importance of this phenomenon is obvious when aerosolized pentamidine is used to prevent *Pneumocystis carinii* pneumonia in immune-compromised patients. When a patient is in an upright position with a normal breathing pattern, less medication reaches the upper lung zones, and disease preferentially develops there.

Whether breathing is through the mouth or nose is another factor that can influence aerosol deposition. Because of the narrow nasal cross-sectional area (producing a high linear velocity), sharp bends, and hairs, most large particles (10 µm) and a high proportion of soluble gases are removed in the nose. Each of these features favors impaction. In addition, humidification causes growth of hygroscopic particles, further favoring impaction.

Finally, it is important to consider that deposition is different from retention. Retention reflects deposition plus clearance. Clearance mechanisms, including translocation of deposited particles, may have a major effect on the ability of aerosols to cause or treat disease. This concept is discussed in Chapter 2.

AEROSOL-GENERATING DEVICES

A number of inhalational devices are available to produce aerosols of respirable particles. They include pressurized metered-dose inhalers (MDI), nebulizers (jet and ultrasonic), and dry-powder inhalers. Each of these categories comprises several devices with differing characteristics. Production lots of the same device may vary such that particle distribution in the lung and the effects of the material being delivered are altered. When characterizing any aerosol-generating device, it is crucial to differentiate between the “metered” dose, the “delivered” dose, and the “respirable” dose. The metered dose is the dose filling and subsequently emptied from the metering device. The delivered dose is the dose exiting the device. The respirable dose is the dose exiting the device with an aerodynamic diameter of 6 µm or less.

Metered-Dose Inhalers

MDIs have achieved great popularity for the treatment of airways disease. Their advantages are that they are small and convenient to use, and they accurately deliver multiple doses of a drug. The drugs in MDIs are either dissolved or suspended as fine crystals in a liquid propellant mixture—usually chlorofluorocarbons (CFCs). Surfactants are added to increase the stability of the aerosolized suspensions. There are several disadvantages and problems associated with MDIs. One is the use of CFCs as a major component of the propellant. Their adverse impact on the atmosphere has resulted in a worldwide ban that will eventually make these chemicals unavailable for use in MDIs. It is anticipated that other chemicals will be adequate replacements. A second disadvantage is the sensitivity of the MDI to technique (e.g., inspiratory flow rate) and the difficulty some individuals have in coordinating triggering of the device and breathing pattern. If the MDI is triggered well after inspiration has begun, less drug reaches the lung and its distribution is not the same as when triggering occurs early during inspiration. A third problem is the initial rapid velocity imparted to the aerosol as it leaves the device. This can cause discomfort and coughing in some individuals, which may lead to discontinuation of the medication. In addition, a large number of particles deposit in the oropharynx, decreasing the dose available to the lung. It has been estimated that only about 10% of a drug dose is delivered to the lung from MDIs, while 80% or so is deposited in the oropharynx. A less commonly appreciated problem is the effect of environmental temperatures on particle size and therefore lung deposition. Lower temperatures result in larger particles and decreased lung deposition. Keeping the device in an inside pocket rather than a purse and warming it in the hand before using it out of doors in cold weather should minimize this problem.

Several innovations have been devised to deal with some of the problems associated with MDIs. One is a breath-actuated device (Autohaler and others), which triggers the MDI valve at the start of inspiration. Also, initial velocity is lower, so that oropharyngeal deposition is decreased. However, individuals with arthritis or weakness involving the hand muscles may be unable to set the trigger. In addition, the device requires sealing the lips around the mouthpiece. This is at variance with recommendations by manufacturers of other devices that the MDI be placed a few inches outside the open mouth. A second innovation has been spacer devices. They come in a variety of sizes and shapes; costs and convenience also differ. All reduce the need to synchronize triggering of the inhaler with the onset of inspiration, and they decrease oropharyngeal and increase lung deposition. They are of greatest benefit in young children, the elderly, and in anyone inhaling corticosteroids or other medication with the potential for producing adverse events when deposited in the oropharynx.

Nebulizers

Nebulizers (jet, ultrasonic) are effective when high doses of drugs need to be administered. They are also appropriate for infants and young children, who cannot use hand-held devices. Their major advantages are that coordination with the respiratory cycle is not required, and they are effective even when patients have very low inspiratory flow rates. The major disadvantages are their large size and the need for an external power source. Both of these factors limit a patient's mobility.

Jet nebulizers produce an aerosol by moving a blast of air across a narrow nozzle into which liquid has been drawn according to the Bernoulli principle. When the air hits the liquid, small droplets are formed. Because the air stream is curved in the nebulizer before the aerosol exits, larger particles (10 μm) are removed. The distribution of particles generated by a nebulizer and subsequent deposition in the lung depend on the nebulizer (model, lot, and individual unit), the number and size of baffles, the diameter of the exhalation port tubing, the use of vents, gas flow rates, fill volume in the nebulizer reservoir, viscosity and surface tension of the solution, and ambient temperature and humidity. Because of these factors, it is important to know the specific characteristics of the unit being used and to follow the manufacturer's recommendations regarding proper operation carefully.

Ultrasonic nebulizers use a piezoelectric crystal, operating in the range of 1 to 3 MHz, that transforms high-frequency electric oscillations into mechanical oscillations, thereby providing energy for producing an aerosol. Output tends to be greater than from a jet nebulizer, but particle size is usually larger. With both types of nebulizers, much of the drug initially placed in the nebulizer remains there (on the walls) after the treatment is completed. Further, the concentration of the drug being administered may increase during the time the solution is being nebulized.

Dry-Powder Inhalers

Dry-powder inhalers have been available for years. They include the Spinhaler and Rotahaler, used to deliver a single dose of cromolyn sodium, albuterol, or beclomethasone from a capsule; the Diskhaler, which provides several doses of drug from a packet containing individual compartments; and the Turbohaler, which delivers as many doses of drug from a single container as a typical MDI.

The major advantages of dry-powder inhalers are breath actuation, which reduces difficulties with triggering the device at the start of inspiration, and the absence of CFCs. Disadvantages are those associated with any breath-actuated device—variable delivery at very low rates of flow (30 to 60 L/min) and the need to insert the device in the mouth and seal the lips. Nonetheless, these devices are very effective for delivering bronchodilators and corticosteroids to the lungs of patients with airway disease.

AEROSOLS FOR THE DIAGNOSIS AND TREATMENT OF LUNG DISEASE

Aerosols are used to diagnose and help control several lung diseases. The two most frequent and established diagnostic uses are for ventilation scans in suspected pulmonary embolism and for the identification and measurement of the severity of airway reactivity in patients suspected of having asthma. The principles and technical aspects of ventilation lung scanning are found in chapters on pulmonary embolism and ventilation-perfusion lung scan. Airway reactivity to a number of nonspecific (e.g, methacholine, histamine, distilled water) and specific (e.g., antigen) bronchoprovocation agents is determined by administering aerosols containing increasing concentrations of these substances while measuring the effect of each concentration on pulmonary function. The major advantage of performing bronchoprovocation testing with aerosols rather than administering these chemicals systemically is the elimination or reduction in systemic responses. Additional information on bronchoprovocation testing is found in chapters on asthma, airway reactivity, and bronchoprovocation testing.

Aerosols can also be used to measure peripheral airway size, epithelial permeability, regional ventilation, and gas mixing in the lung. For example, peripheral airway size has been measured using a monodisperse di-2-ethylhexylsebacate aerosol with particles approximately 0.9 μm diameter. The results correlate well with mean lung density derived by chest computed tomography (CT) and with measurements of diffusing capacity and FEV_1. Alveolar epithelial permeability has been measured in numerous research studies using aerosols of technetium Tc99m DTPA (diethylenetriamine penta-acetic acid).

In addition to their value in diagnosing and managing lung disease, aerosols are invaluable for treatment. Saline aerosols are useful to add moisture to the airways to prevent and treat inspissated secretions. A more frequent use is for the delivery of drugs. The advantages of delivering drugs by this route are several. First, high therapeutic concentrations of some drugs can be achieved within the respiratory tract while systemic concentrations remain low and side effects are few. Some examples are aerosolized b_2-adrenergic agonists and corticosteroids for the treatment of asthma, antibiotics such as the aminoglycosides and amphotericin B, chemotherapeutic agents for the treatment of lung cancer, and cyclosporine for the prevention and treatment of lung allograft rejection. Second, aerosol delivery of some soluble and easily absorbed drugs provides a rapid and convenient route to the bloodstream. Atropine, lidocaine, and epinephrine fit into this category. Third, aerosols provide access for some enzymes, other proteins, and chemicals that ordinarily do not have access to the respiratory tract because of size or charge. Recombinant human deoxyribonuclease (DNase) for the treatment of cystic fibrosis, antioxidant enzymes such as catalase and superoxide dismutase, surfactant, and immune modifiers are just a few examples.

AEROSOL DELIVERY DURING MECHANICAL VENTILATION

Inhaled medications, especially bronchodilators such as b_2-adrenergic agonists and anticholinergic agents, are commonly administered to patients receiving mechanical ventilation. However, there is controversy as to the best method of delivery to such patients. For example, it has been reported that delivery of b_2-adrenergic agonists by MDI through a cylindrical chamber is superior to nebulizer delivery under *in vivo* and *in vitro* conditions. In contrast, others have suggested that even large doses of b_2-adrenergic aerosols administered by MDI to ventilated patients fail to have any appreciable physiologic effects, whereas nebulizers produce significant bronchodilation. Recently, studies using *in vitro* models of mechanical ventilation have examined the effect of different jet nebulizers and MDIs with actuator devices on the delivery of albuterol to the lung under various conditions. These studies suggest the following: (1) Adaptors play an important role in the ability of MDIs to deliver albuterol during mechanical ventilation; (2) important technical differences exist between these devices, which when not used properly can influence drug delivery; (3) spacer design is of prime importance for MDI effectiveness; (4) MDI delivery systems may be sensitive to humidification and synchronization with inspiration, such that delivery decreases with increased humidification and with lack of synchronization; and (5) jet nebulizers and MDI/actuator devices deliver comparable amounts of medication, but the latter require more direct therapist time.

It has also been shown that the delivery of an aerosol from an ultrasonic nebulizer during mechanical ventilation is inefficient and influenced by several factors, including the nebulizer used, the amount of solution placed in the nebulizer (more solution in some nebulizers results in a higher percentage of the total volume delivered to the lung), the addition of an aerosol storage chamber (increases delivery), the respiratory rate and minute ventilation (decreasing either one increases aerosol delivery), and inspiratory time (increasing this time increases delivery).

The important message is that under certain circumstances, aerosol drug delivery to patients receiving mechanical ventilation may be considerably less than anticipated. As a result, it may be necessary to give larger-than-usual doses of drug and titrate the dose according to effectiveness and toxicity.

DETERMINANTS OF SYSTEMIC BIOAVAILABILITY

It has been recognized for some time that the administration of certain medications via the airways can produce clinically significant systemic concentrations. Some examples are epinephrine, atropine, and lidocaine. The first two have been administered through endotracheal tubes during cardiopulmonary resuscitation. Systemic lidocaine toxicity with seizures is a serious complication during topical anesthesia for procedures such as bronchoscopy, especially when given to elderly individuals or those with liver disease.

The issue of systemic absorption and bioavailability is also important when drugs are delivered by aerosol to treat lung disease, especially as new inhaler delivery systems are designed to enhance lung deposition. An excellent review of this subject is provided by Lipworth. Systemic bioavailability is a consequence of absorption from the gastrointestinal tract and the lung. The amount of drug reaching the systemic circulation from the gastrointestinal tract depends on the amount deposited and the rate of first-pass metabolism in the liver. The systemic effects of inhaled corticosteroids absorbed from the gut appear to be limited by extensive first-pass metabolism. This has been reported to be 80% for beclomethasone, 89% for budesonide, and 99% for fluticasone. According to studies in which mouth rinsing, gargling, and the ingestion of charcoal were used to reduce gut absorption, it appears that systemic bioavailability of these three corticosteroids is mainly determined by absorption across the lung vascular bed. A similar conclusion has been reached for the b_2-adrenergic agonist albuterol.

As a result, it should be anticipated that aerosol delivery systems that improve lung deposition will increase lung bioavailability and at the same time enhance systemic absorption. If so, it may be necessary, as more efficient drug delivery systems are developed, to re-examine the amount of medication administered by aerosol to

patients with disease.

AEROSOLS IN RESEARCH

Studies have been performed in animals and humans using aerosols to define the role of environmental pollutants in human disease. Several investigators have explored the effects of oxidant and aerosol exposure on healthy subjects and patients with asthma. For example, by using sulfuric acid aerosols to sensitize the airways to ozone, it has been possible to quantify the effects of these pollutants on airway inflammation, physiology, and symptoms. Studies have also been performed with aerosols to test the validity of commonly used tests. One example is the commonly used technique of sputum induction to identify *Pneumocystis carinii* in the lung. Using an aerosol of technetium-labeled human serum albumin to measure lung clearance, it was found that sputum induction with 3% saline solution significantly increases tracheobronchial clearance rates.

In summary, aerosols play a major role in the diagnosis and treatment of lung disease. One can anticipate continued interest in this area, with increased use of aerosols to deliver new pharmacologic agents to treat lung diseases and also to deliver drugs that are rapidly inactivated in the gastrointestinal tract or liver to the systemic circulation, making it possible to bypass the intravenous and subcutaneous routes. However, caution must be exercised when this route of delivery is used, as the epithelium lining the lungs can be easily damaged. The potential local toxicity of agents delivered directly to the lung via aerosol must be considered and care taken to ensure this does not happen during the course of treatment.

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CHAPTER

16 Theophylline and Glucocorticoids

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THEOPHYLLINE

Theophylline, or 1,3-dimethylxanthine, has been used as a bronchodilator in patients with asthma and chronic obstructive pulmonary disease (COPD) for more than 60 years. The specific mechanism of action of theophylline is not well understood, but it likely involves a constellation of effects, including phosphodiesterase inhibition and adenosine antagonism.

Mechanism of Action

Phosphodiesterase inhibitors reduce intracellular degradation of cyclic AMP, thus prolonging the intracellular effects of cyclic AMP: relaxation of bronchial smooth muscle and suppression of mast cell mediator secretion. Theophylline is a weak, nonselective phosphodiesterase inhibitor. In fact, at the usual therapeutic serum concentrations, it inhibits only 10%–20% of phosphodiesterase activity. For this reason, it remains controversial whether the bronchodilator activity of theophylline is predominantly a consequence of phosphodiesterase inhibition.

Another possible mechanism is adenosine inhibition. Adenosine is a naturally occurring purine nucleoside that has been shown to be a bronchoconstrictor in patients with asthma. Local adenosine concentrations increase with methacholine and allergen stimulation, presumably because of mast cell release. Theophylline selectively inhibits adenosine-induced bronchoconstriction at the usual therapeutic concentrations. Evidence against this mechanism is the observation that some methylxanthines that are clearly active bronchodilators do not antagonize adenosine.

Other possible mechanisms of theophylline-induced bronchodilation include inhibition of the generation of contractile prostaglandins, modulation of intracellular calcium, and increased synergy between phosphodiesterase inhibitors and adenylate cyclase activators (e.g., b-adrenergic agonists).

Role of Theophylline as a Bronchodilator

Theophylline is less potent as a bronchodilator than are inhaled or subcutaneously injected b_2-adrenergic agents. It protects against exercise-induced bronchoconstriction, although it is not as effective as inhaled albuterol in terms of peak effect. On the other hand, sustained-release preparations of theophylline provide a longer duration of action than inhaled b_2-adrenergic agents, except salmeterol. This longer duration of action of 12- and 24-hr sustained-release preparations of theophylline can be helpful for patients with symptoms of nocturnal asthma or COPD.

When added to a regimen of inhaled corticosteroids and b_2-adrenergic agents, theophylline also reduces the frequency and severity of asthma symptoms in patients with moderately severe or severe chronic asthma. An additive, steroid-sparing benefit is seen when theophylline is added to a regimen of alternate-day prednisone or high-dose, daily inhaled beclomethasone.

In the setting of acute severe asthma, data are conflicting regarding the benefit of adding theophylline to the usual emergency regimen of nebulized adrenergic agents. On the other hand, theophylline may be beneficial in patients admitted to the hospital with status asthmaticus. In either situation, the drug should be continued and levels optimized in patients already on maintenance doses of theophylline.

In patients with COPD, even when spirometry findings are not improved, theophylline therapy is associated with a decrease in dyspnea. Theophylline also appears to benefit patients with COPD who are already taking ipratropium bromide and a b-adrenergic agent. Patients who have difficulty inhaling bronchodilator medication, despite education and the use of chamber or spacer devices, may derive greater benefit from orally administered theophylline.

Evidence for Anti-inflammatory Activity

Some patients with asthma experience significant deterioration when theophylline therapy is withdrawn. Because this deterioration appears greater than what would be expected based on the bronchodilating capacity of the drug, it has been hypothesized that theophylline has anti-inflammatory activity.

There is evidence that theophylline has weak anti-inflammatory activity. Although theophylline does not influence the immediate allergic response at moderate serum concentrations, it attenuates the bronchoconstriction associated with the late allergic response, possibly through an inhibitory effect on the cellular infiltration associated with the late-phase allergic response; theophylline reduces the levels of CD4 lymphocytes typically seen during this response. In patients with moderately severe asthma who are taking high-dose inhaled corticosteroids, withdrawal of theophylline results in an increase in CD4 and CD8 cells in the bronchial submucosa that correlates with a decrease in FEV_1 (forced expiratory volume in 1 second). Bronchial biopsy studies have shown a decrease in EG2-positive activated eosinophils immediately below the basement membrane in patients with mild asthma treated with theophylline. On the other hand, theophylline does not affect the increase in peripheral eosinophil counts associated with allergen challenge and does not inhibit allergen-induced increases in airway methacholine responsiveness, all evidence against significant anti-inflammatory activity.

Respiratory Muscle Effects: Force and Endurance

Theophylline has positive inotropic effects on normal diaphragm, but effects are hard to demonstrate if concentrations are in the normal therapeutic range. In patients with COPD, theophylline improves the strength of the fatigued diaphragm and makes the diaphragm more resistant to fatigue. These effects may help patients with asthma or COPD who are being weaned from mechanical ventilation, or are experiencing worsening of air flow obstruction.

Clinical Use

The specific indications for theophylline therapy may be found in Chapter 40 (Bronchial Asthma) and Chapter 43 (Clinical Aspects of COPD) of this book, and in recently published guidelines. Because of the narrow toxic-to-therapeutic window, use of this drug requires close attention to dosage, serum levels, and potential

interactions with other drugs.

Once the decision has been made to initiate oral theophylline therapy in an adult, the drug should be started at a low dose (12 to 16 mg/kg daily, up to a maximum of 300 to 400 mg/d) and titrated slowly upward. The dose should be decreased if the patient experiences nausea, headache, tachycardia, or other side effects. The final daily regimen should be guided by the degree of symptom control, side effects, and measurement of serum levels; in general, one should aim for a therapeutic serum level of 5 to 20 µg/mL. Therapeutic serum levels should be lower in elderly patients with COPD, may be higher in younger patients with asthma, and should be between 8 and 12 µg/mL in pregnant women. The serum level should be measured about halfway into a dosing interval.

Shorter-acting theophyllines have been largely supplanted by 12- and 24-hr sustained-release preparations. Patients should be instructed to take medication at the same time each day with respect to meals. Theophylline has been used extensively in pregnancy without evidence of adverse effects for the neonatal, but serum levels need to be monitored closely and should not exceed 12 µg/mL.

The main indication for intravenous administration of theophylline is an inability to take oral medication or evidence of impaired gastrointestinal absorption. Otherwise, sustained-release oral preparations provide stable blood levels and are just as effective as systemically administered preparations.

Aminophylline, a salt of theophylline with 80% bioavailability, is frequently used for intravenous therapy. Patients with an adequate serum level on admission who are switched to intravenous therapy do not need a loading dose. If the theophylline level is subtherapeutic, a supplemental loading dose can be given: each milligram of aminophylline per kilogram of body weight will increase the serum concentration by 2 µg/mL. If the outpatient oral dose of theophylline is known, then the dose of aminophylline to be given over 24 hrs as a continuous infusion can be determined by multiplying the total daily dose of theophylline by 1.25. The loading dose for patients not previously on oral therapy is 2.5 to 5.6 mg/kg of lean body weight, given intravenously over 20 to 30 minutes. The usual maintenance dose of aminophylline is 3 to 9 mg/kg/hr.

Another alternative for intravenous use is anhydrous theophylline in 5% dextrose. The usual adult loading dose for this preparation is 5 mg per kilogram of lean body weight, and the usual maintenance dose is 2 to 8 mg/kg/hr.

The maintenance dose of both aminophylline and theophylline should be decreased in older patients, and in those who have liver disease, congestive heart failure, fever, or are taking interacting drugs. Higher initial infusion rates should be used for smokers and children. Daily determinations of serum concentration should guide further dose adjustments.

The theophylline dose should be adjusted during addition or withdrawal of medications that affect theophylline metabolism (Table 1). Because theophylline is metabolized in the liver by the P_{450} system, many medications that are similarly metabolized alter theophylline clearance or are themselves affected by theophylline. When in doubt about a potential drug interaction, it is important to educate patients regarding potential toxicity, to assess theophylline serum levels more frequently, and to consider empiric reductions in the theophylline dose. For instance, the theophylline dose should be reduced by half when patients are taking erythromycin, clarithromycin, quinolone antibiotics, zileuton, or oral contraceptives. Another macrolide antibiotic, azithromycin, is metabolized in the liver, but not by the cytochrome P_{450} enzymes, so adjustments in theophylline dose are not necessary. The theophylline dose should also be reduced by half when maintenance therapy with phenytoin, carbamazepine, or other P_{450} enzyme inducers is discontinued. Amoxicillin, cefaclor, co-trimoxazole, and doxycycline do not appear to interact with theophylline.

Drugs that decrease theophylline clearance
Allopurinol — Propafenone
Birth control pills — Propranolol
Calcium channel blockers — Quinolones
Cimetidine — Ranitidine
Clarithromycin — Tacrine
Erythromycin — Thiabendazole
Methotrexate — Troleandomycin
Mexiletine — Zileuton
Drugs that increase theophylline clearance
Barbiturates — Rifampin
Phenytoin
Other interactions with theophylline
Increased lithium clearance
Increased furosemide diuresis
Enhanced β-adrenergic effects: "toxic synergism" (e.g., isoproterenol, ephedrine, albuterol)
In combination with reserpine may result in tachycardia
Decreased zafirlukast clearance
In combination with ketamine may lower seizure threshold
In combination with halothane may cause ventricular arrhythmias

TABLE 1. *Theophylline drug interactions*

Adverse Effects

The most common adverse effects are nausea, abdominal discomfort, vomiting, diarrhea, diuresis, headache, and jitteriness. Side effects tend to increase as the serum level increases but may be seen with low therapeutic levels (5 to 10 µg/mL). Although excessively high serum levels are generally accompanied by nausea and abdominal discomfort, dangerous toxicity can develop in patients without these symptoms. Therefore, monitoring of serum levels is extremely important when therapy is initiated or changed, and then at 6- to 12-month intervals. Signs and symptoms associated with toxic levels include palpitations, premature ventricular contractions, atrial tachyarrhythmias, tremors, seizures, and gastrointestinal bleeding.

Treatment of Theophylline Intoxication

Theophylline poisoning may result from inadvertent iatrogenic overdose, patient error, or suicide attempt. Serious toxicity is associated with levels greater than 30 µg/mL, and serious adverse effects are more likely to be seen at any given blood level in patients with chronic intoxication than with acute overdose. Serum levels correlate poorly with occurrence of life-threatening events. Metabolic disturbances are more common with acute intoxication.

Electrocardiographic and hemodynamic monitoring are vital components of supportive care, because of the risk of cardiac arrhythmias. Sinus tachycardia and atrial and ventricular dysrhythmias are all manifestations of theophylline toxicity. Treatment is recommended only for serious arrhythmias causing unstable hemodynamics. Adenosine, verapamil, and digoxin have been used to treat supraventricular tachyarrhythmias, and lidocaine and phenytoin for ventricular arrhythmias.

Some patients require volume repletion, because of the diuretic effect of theophylline. Metabolic acidosis is common; conservative treatment is advisable. Hypokalemia, caused by hypercatecholemia and intracellular redistribution of potassium, is seen in 30% of patients with chronic intoxication and in 85% of patients with acute overdose. Frequently, potassium levels normalize spontaneously, and vigorous repletion is not necessary.

Seizures are usually treated with diazepam or phenobarbital; phenytoin is not recommended. Refractory status epilepticus may require general anesthesia with pentobarbital or thiopental and paralyzing agents. Prophylactic phenobarbital may be used for patients with serum levels ³50 µg/mL, although this has not be studied in clinical trials.

Prevention of absorption is particularly important, because of the prevalent use of sustained-release theophylline preparations. Stomach emptying is recommended for patients who have ingested a large quantity of a slow-release preparation within 1 hour of seeking medical attention. Otherwise, it is better to inhibit absorption with 50 to 100 g of activated charcoal, given orally with 70% sorbitol (75 to 100 mL). This therapy enhances theophylline clearance in patients with moderate intoxication, but it should not be administered to patients who have depressed pharyngeal reflexes or are vomiting.

Charcoal hemoperfusion is indicated when the serum level is ³80 µg/mL in acute intoxication; ³60 µg/mL in chronic intoxication; or ³40 µg/mL if the patient is 6 months of age greater than 60 years old, has significant liver or cardiac disease, or cannot tolerate activated charcoal. Hemodialysis doubles theophylline clearance and may be helpful when hemoperfusion is not available. It should be combined with oral activated charcoal therapy. Other modalities, such as peritoneal dialysis, plasmapheresis, and hemofiltration, are unlikely to be beneficial.

GLUCOCORTICOIDS

Glucocorticoids are effective in the treatment of a wide spectrum of pulmonary diseases because of their broad anti-inflammatory activity. Asthma, COPD, sarcoidosis,

interstitial fibrosis, hypersensitivity pneumonitis, and bronchiolitis obliterans organizing pneumonia all respond significantly or partially to glucocorticoids. Unfortunately, glucocorticoids also have significant potential side effects that require careful monitoring and patient education. This section focuses on general concepts regarding the mechanisms of action, administration, and adverse effects of systemically administered glucocorticoids.

Mechanisms of Action

Recent research has increased our understanding of the cellular effects of glucocorticoids and provided insight into the reasons why glucocorticoids have such widespread anti-inflammatory effects. Glucocorticoids, when administered orally or intravenously, circulate in the blood either unbound or associated with cortisol-binding globulin. Free glucocorticoid (GC) diffuses into the cytoplasm of cells and binds to glucocorticoid receptors (GR) to form a GC-GR complex.

The GC-GR complex translocates into the cell nucleus and binds to DNA, resulting in either positive or negative modulation of gene transcription. Glucocorticoids also influence posttranscriptional events, such as RNA translation and protein synthesis and secretion (e.g., by altering the stability of certain cytokine messenger RNAs to change the intracellular steady state). Alternatively, the nuclear transcription factors NFkB and AP-1 may bind the GC-GR complex, preventing translocation into the nucleus.

Anti-inflammatory Effects

Glucocorticoids, through their effects on gene transcription and translation in many different cells, inhibit or suppress several steps in the inflammatory process. Glucocorticoids affect lymphocyte cytokine production, distribution, and activation in several ways. They inhibit transcription, directly or indirectly, of many cytokines, including interleukin-1 (IL-1), tumor necrosis factor-a (TNF-a), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, IL-4, IL-5, IL-6, and IL-8. Trafficking of leukocytes to sites of inflammation is diminished by glucocorticoids, because of a redistribution of lymphocytes out of the vascular compartment and a downregulation of adhesion molecules. Production of integrins and selectins is inhibited by glucocorticoids through their effect on IL-1 and TNF-a. Elaboration of vascular cell adhesion molecule-1 is indirectly reduced through the decrease in IL-4 and GM-CSF production. Suppression of IL-2 production is an important effect of glucocorticoids and results in decreased activation and proliferation of lymphocytes. Phospholipase A_2 release via the annexin family of proteins, which includes lipocortin-1, is inhibited, leading to decreased production of proinflammatory arachidonic acid metabolites. Fibroblast activity is downregulated, resulting in reduced synthesis and secretion of certain cytokines, collagen, and prostaglandins. Secretion of proinflammatory molecules by mast cells and basophils is suppressed, as is basophil activation and mediator release. Although mast cell mediator release is not directly inhibited, mucosal mast cell numbers are significantly reduced. Eosinophil accumulation at inflammatory sites is decreased, probably because of several glucocorticoid effects: decrease in circulating numbers of eosinophils, inhibition of synthesis of IL-4 and IL-5, inhibition of expression of adhesion molecules, and increased local apoptosis. Microvascular leakage of fluids is also decreased. IgE levels are decreased over time, possibly by immunoglobulin catabolism and inhibition of cytokines (e.g., IL-4) that promote IgE production.

Bronchial biopsy studies in patients with asthma who are taking inhaled budesonide or beclomethasone for 3 to 4 months have revealed a decrease in airway eosinophils, mast cells, and lymphocytes. This effect is not seen with inhaled terbutaline. A similar decrease in inflammatory cells is seen in bronchoalveolar lavage studies.

Clinical Pharmacology

Several different glucocorticoid analogues have been developed for clinical use. These compounds differ in their absorption and distribution characteristics, glucocorticoid receptor-binding affinities, elimination rates, topical versus systemic potencies, and mineralocorticoid activities. The choice of a specific analogue and dose depends on the disease being treated and its severity. These issues are reviewed in the chapters on individual diseases.

Certain general observations can be made about systemic glucocorticoid use. Smaller doses administered more frequently are more immunosuppressive than larger doses administered less frequently. A longer biologic half-life may be preferred to maintain the desired clinical effect through the day. However, when the duration of action extends through the night, the risk for hypothalamic-pituitary-adrenal (HPA) axis suppression and other glucocorticoid-related adverse effects increases. Topical or focal application of glucocorticoids results in less toxicity than systemic administration and is the preferred route of administration presuming the desired clinical affect can be achieved. Thus, airway diseases, such as asthma and COPD, can usually be managed with inhaled glucocorticoids, but pulmonary parenchymal diseases, such as interstitial pulmonary fibrosis, require systemic glucocorticoid therapy.

In balancing the need to suppress disease against the desire to protect the HPA axis, a compromise arrangement is to administer analogues with intermediate biologic half-lives (prednisone and methylprednisolone) in one to three doses during the day and early evening, but not at bedtime. As patients' symptoms improve, doses can be consolidated and reduced in frequency. When the prednisone equivalent dose is at or below 30 mg/d, attempts should be made to switch to an alternate-day dosing regimen to reduce further glucocorticoid-related morbidity and enhance recovery of the HPA axis. After patients have been on systemic glucocorticoid therapy for longer than 3 weeks, the glucocorticoid dose needs to be tapered gradually to allow recovery of the HPA axis; the longer the duration of therapy, the slower the taper.

Timing of the dose of oral glucocorticoids may affect the therapeutic result, especially if the disease exhibits diurnal variation. For instance, patients with asthma tend to have nocturnal symptoms when their disease flares. A late-afternoon dose of prednisone may provide better nocturnal symptom control than the usual morning dose.

Glucocorticoid Preparations

Several glucocorticoids are available in the United States for oral or parenteral use: hydrocortisone, prednisone, methylprednisolone, triamcinolone, dexamethasone, and Celestone. Hydrocortisone (half-life, 1.9 hours) is usually used for physiologic replacement or “stress” coverage, because of its rapid onset of action and long history of efficacy. It can be given orally or parenterally. Its mineralocorticoid effects are helpful in patients who need physiologic replacement, but they may be undesirable in patients requiring the medication for immunosuppression or anti-inflammatory activity.

Prednisone is a widely used oral glucocorticoid that is inactive until converted in the liver to prednisolone by reduction at the 11-keto position. Its relative potency is approximately four times that of hydrocortisone.

Methylprednisolone differs from prednisolone in having a methyl group in the 6a position; like prednisolone, it is active without hepatic conversion. The relative potency of methylprednisolone is five times that of hydrocortisone. Its mineralocorticoid effects are slightly less than those of prednisone, and it is available for both oral and intravenous use.

Triamcinolone is essentially devoid of mineralocorticoid activity. It is available as a suspension for intramuscular use. Its potency is about five times that of hydrocortisone. Response among patients is not uniform, but a single parenteral dose four to seven times the oral daily dose controls symptoms for about 4 days up to 4 weeks. Its major role is in treating patients who are noncompliant with oral medications.

Dexamethasone has very little salt-retaining effect, which is beneficial, but its biologic half-life is even longer than that of prednisone or methylprednisolone, increasing its potential to cause morbidity. Its relative potency is about 20 to 25 times that of hydrocortisone.

Celestone is a suspension of betamethasone sodium phosphate and betamethasone acetate available for intramuscular use. The onset of action of the betamethasone esters varies, so a single intramuscular injection may provide prompt as well as sustained glucocorticoid therapy, but this is variable. As with the use of intramuscular triamcinolone, the daily glucocorticoid effect in an individual patient is difficult to titrate. This drug is usually reserved for patients who are not able to take oral glucocorticoid preparations.

Glucocorticoid Resistance

Although glucocorticoids are the most effective anti-asthma medication currently available, some patients with chronic asthma do not experience the expected improvement in symptoms and pulmonary function following oral glucocorticoid administration. This phenomenon of glucocorticoid resistance has been explored most fully in patients with asthma, but it may also pertain in other diseases that can be treated with glucocorticoids.

One definition of glucocorticoid resistance is a lack of improvement of 15% in FEV_1 after 2 weeks of treatment with prednisone at a dose of 20 mg/d, or its equivalent. In addition to failing to show an improvement in respiratory function, some patients are resistant in that they do not exhibit the clinical features of hypercortisolism and their morning cortisol level is normal. These patients usually have familial glucocorticoid resistance, which is associated with normal glucocorticoid receptor binding but low numbers of receptors. Patients with acquired glucocorticoid resistance usually do experience glucocorticoid-induced side effects, including suppression of the morning cortisol level, with high-dose oral glucocorticoids. These patients have normal numbers of glucocorticoid receptors but exhibit decreased glucocorticoid

receptor binding.

The first step in evaluating suspected glucocorticoid resistance is to determine whether the patient is adhering to the recommended dosing schedule and whether persistence of asthma triggers in the environment are responsible for the lack of response. Once these have been excluded, the most common cause for apparent glucocorticoid resistance is severe airway inflammation that ultimately requires higher corticosteroid doses over a more prolonged period. Other possible explanations would be decreased absorption or impaired metabolism of the active moiety.

In patients who have refractory asthma, the absorption and clearance of orally administered glucocorticoids should be assessed by measuring peak and trough blood levels of the specific glucocorticoid administered (available only in specialized laboratories), in addition to morning cortisol and total eosinophil levels. Enhanced plasma clearance of prednisolone or methylprednisolone has not been demonstrated to occur except in the presence of medications that enhance cytochrome P_{450} metabolism.

Another possible explanation for a lack of response to prednisone is a problem with the conversion of prednisone into biologically active prednisolone in the liver. This may be tested by administering methylprednisolone at a dose that is 80% of the usual prednisone dose and repeating spirometry after 2 weeks. If the problem is hepatic conversion of prednisone, the patient's symptoms will improve on methylprednisolone. Additionally, the total eosinophil count can be measured and compared during the two regimens.

Patients with familial glucocorticoid resistance, a rare autosomal dominant disorder with variable penetrance, have high circulating levels of cortisol and adrenocorticotropic hormone. These patients may also demonstrate signs and symptoms of excessive levels of nonglucocorticoid adrenal hormones (e.g., hypertension, hirsutism, menstrual irregularities, hyperkalemia). Measurement of endogenous cortisol levels helps to identify these rare patients. Referral to a specialized center for assessment of the cellular response to glucocorticoids may be necessary to complete the evaluation.

The treatment of glucocorticoid resistance depends on the exact mechanism (acquired or familial) and the degree of resistance. Conventional therapies, such as theophylline, salmeterol, terbutaline, ipratropium, nedocromil, or cromolyn, should be optimized in patients with asthma, while remembering that only the latter two medications have significant anti-inflammatory activity.

Steroid-sparing and other immunomodulatory therapies, such as methotrexate, cyclosporine A, intravenous immunoglobulin, and gold salts, may be considered, but studies have not shown dramatic responses in asthma. The 5-lipoxygenase inhibitor, zileuton, and the leukotriene receptor antagonist, zafirlukast, have recently been released and may be helpful in these patients. Another strategy is to try an alternate glucocorticoid analogue, such as oral methylprednisolone or triamcinolone, instead of prednisone. Ongoing, uncontrolled inflammation will likely require a course of high-dose, possibly intravenous, glucocorticoid therapy. Subsequently, the patient's glucocorticoid sensitivity is usually improved and the glucocorticoid dose can then be tapered.

Complications of Glucocorticoid Therapy

Oral glucocorticoid therapy is frequently associated with side effects that tend to become more serious and more prevalent as the dose and duration of therapy increase. Certain adverse effects, such as insomnia, emotional lability, increased appetite, and weight gain, are characteristically observed early in therapy. Insomnia can be decreased by consolidating most or all of the glucocorticoid dose to the early morning. Patient education and reassurance help with emotional instability, but serous problems in the face of an ongoing need for glucocorticoid therapy may require psychiatric assistance. Nutritional counseling helps to offset weight gain.

HPA axis suppression is to be expected when systemic therapy lasts longer than 3 weeks. After this time, steroid therapy needs to be tapered; the longer the duration of therapy, the slower the taper. The rate of tapering depends on the disease activity and the rate of adrenal recovery. When the dose of prednisone has been 30 mg/d for several weeks, a decrease in the daily dose of 10 mg every 1 to 3 weeks is usually acceptable. If the daily dose has been 20 mg, the decreases may be 5 mg every 1 to 3 weeks. With a daily dose of 10 mg, the incremental decreases may need to be 1 to 2 mg. When systemic glucocorticoid therapy is discontinued, a stimulation test with cosyntropin (Cortrosyn) can be used to determine whether the HPA axis has recovered.

Stress glucocorticoid coverage should be administered for 1 year after completion of systemic glucocorticoid therapy. Patients on high-dose inhaled glucocorticoids should also receive stress coverage during acute illnesses. Despite laboratory evidence of significant adrenal suppression with chronic glucocorticoid therapy, serious, clinically significant adverse events resulting from iatrogenic adrenal suppression are very rare.

Elevations in serum glucose are common during glucocorticoid therapy, but only in patients with underlying glucose intolerance. Patients need to be educated about signs and symptoms of hyperglycemia, and those who already require oral hypoglycemic agents or insulin should have frequent blood glucose determinations. Hypertension and acne usually occur in patients who have other underlying risk factors. Likewise, the risk for peptic ulcer disease appears to be more related to coexistent risk factors, such as nonsteroidal anti-inflammatory therapy.

The relative risk for infectious complications related to steroid therapy is about twice that of controls and varies according to the type of disease being treated, as well as the duration and intensity of therapy. The most common infectious side effect is oropharyngeal thrush, typically associated with inhaled steroids but also seen with oral steroid use, particularly when accompanied by antibiotic therapy. Patients who have never had varicella are at increased risk for generalized varicella and should receive hyperimmune immunoglobulin should they be exposed to someone with active varicella. Patients with a varicella skin rash should be treated with oral or intravenous acyclovir.

A controversial question has been whether all patients with a positive tuberculin skin test (purified protein derivative or PPD) who require glucocorticoid therapy should receive prophylaxis with isoniazid, assuming they have never previously received treatment. The current practice guideline is not to give isoniazid to patients who require intermittent steroid bursts for asthma. On the other hand, patients who require long-term glucocorticoid therapy should receive prophylactic isoniazid, barring other contraindications.

Steroids cause bone loss by decreasing the intestinal absorption and increasing the renal secretion of calcium. These changes in calcium metabolism result in lowering of serum calcium levels, which induces secretion of parathyroid hormone to facilitate resorption of calcium from bones. In a study of patients with asthma, long-term steroid treatment resulted in trabecular, but not cortical, bone loss, a pattern consistent with osteoporosis.

A reasonable strategy for patients receiving short, intermittent courses of oral glucocorticoid or high-dose inhaled glucocorticoid is to recommend that they ingest the recommended daily amounts of calcium (1500 mg in adults) and vitamin D for their age and follow a regimen of daily weight-bearing exercise for 30 to 60 min.

When patients begin long-term glucocorticoid therapy, it is important to assess the presence of other modifiable risk factors for osteoporosis, such as a sedentary lifestyle, menopause, overreplacement of thyroid hormone, and cigarette smoking. Sex hormones should be replaced if deficient. Bone density measurement of the hip and lumbar spine should be performed at baseline. If baseline bone density is adequate, primary prevention is accomplished by maintaining a daily calcium intake of 1500 mg/d through diet or supplements, and supplementing the dietary intake of vitamin D with 800 IU of vitamin D/day or 0.5 µg of calcitriol (1,25-dihydroxycholecalciferol) per day. Vitamin D supplementation maybe associated with hypercalcemia and hypercalciuria. It is recommended that serum and urinary calcium levels be measured 1 month into therapy. A low dose of a thiazide diuretic and sodium restriction can be initiated if the 24-hour urinary calcium excretion is 300 mg/d. Calcium and calcitriol supplementation may also need to be decreased. Six to 12 months after initiation of glucocorticoid therapy, a repeated bone density measurement will reveal whether this initial strategy has been successful, or whether further intervention is needed. If baseline bone density is low, consideration should be given to starting hormone replacement therapy, a bisphosphonate, or calcitonin. At this point, consultation with a rheumatologist or endocrinologist would be appropriate.

Osteonecrosis (avascular necrosis) of bone is a known complication of systemic glucocorticoid therapy, although the exact mechanism is not understood. Typically, it occurs in patients on long-term glucocorticoid therapy, but it has been described with short-term, high-dose therapy. The joints most commonly affected are the hips, knees, and shoulders. When the area involved is small, treatment can be conservative, with avoidance of weight-bearing activity and relief of pain using nonsteroidal anti-inflammatory agents or other analgesics. More severe cases require bone grafting or joint replacement.

Cataract development related to glucocorticoid administration is usually associated with higher doses and longer duration of therapy. Intraocular pressures should be monitored in patients on long-term systemic glucocorticoid therapy, because of the increased risk for glaucoma.

Steroid-induced myopathy is also associated with higher doses and longer duration of therapy. It may be a cause of diminishing exercise tolerance in the face of stable spirometry and usually improves as steroids are tapered.

Long-term systemic use of glucocorticoids in children may result in growth retardation. Studies are ongoing as to whether inhaled glucocorticoids alone have a

significant effect on growth.

Relatively few adverse drug interactions have been described in association with glucocorticoid use. Phenobarbital, phenytoin, and carbamazepine increase cytochrome P_{450} activity, thereby reducing the effectiveness of prednisolone, methylprednisolone, and dexamethasone. Erythromycin and ketoconazole impair prednisolone and methylprednisolone elimination. Rifampin decreases the effectiveness of prednisolone and methylprednisolone. Cimetidine does not interact with prednisolone, methylprednisolone, or dexamethasone, but antacids decrease the bioavailability of prednisolone. Although there is no direct drug interaction, patients receiving insulin or oral hypoglycemic agents for glucose intolerance will likely need dose adjustments as glucocorticoid therapy is added or tapered.

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CHAPTER

17 Surfactant

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INTRODUCTION

In 1929, Von Neergard calculated that surface tensions in the alveoli and distal air spaces are large enough to cause collapse of the airways during normal lung functions. He postulated the existence of a substance capable of lowering airway surface tension. In 1955, two independent research laboratories isolated a material from the alveolar lining of lungs that was capable of dramatically lowering airway surface tension (surfactant). In 1959, Avery and Mead reported that alveolar washings from premature infants with infant respiratory distress syndrome (IRDS) lacked the normal amount of surface tension-lowering capacity. In 1961, it was shown that phospholipid isolated from the alveolar lining fluid of beef lungs possesses surface tension-lowering properties. These phospholipids contain hydrophilic and lipophilic moieties, which result in their forming a filmy monolayer over the aqueous alveolar luminal surface. Surfactant was found to be synthesized by type II pneumocytes and continually secreted into the air spaces, and to contain associated proteins with diverse biologic functions. Finally, in 1980, Fujiwara and associates reported the first successful use of exogenous surfactant therapy for infants with IRDS. Today, exogenous surfactant therapy for infants with IRDS is considered a clinical standard of care.

SYNTHESIS, METABOLISM, AND FUNCTIONS OF ENDOGENOUS SURFACTANT

Surfactant Lipids

Lipids constitute approximately 90% of surfactant isolated from human lungs. The lipid moiety comprises a mixture of phospholipids (90%) and other lipids (10%). The two principal phospholipids are phosphatidylcholine (PC), the most abundant phospholipid, and dipalmitoylphosphatidylcholine (DPPC), which may be the most important one. All phospholipids are structured so that they possess a polar head and a pair of hydrophobic tails, making them ideal molecules to form lipid-water interfaces, as they do in cell membranes. Most of the surface tension-lowering properties of surfactant reside in the DPPC molecule. It is the saturated palmitic acid residues that make the DPPC molecule unique, allowing them to be packed together tightly to form a monolayer with tensile strength at the air-fluid interface. The polar head of each DPPC molecule is charged, so that it has an affinity for molecules of water in the alveolar lining fluid. The long hydrophobic tails are directed away from water molecules and project into the air space. The repulsion of water molecules from the air-fluid interface results in a dramatic lowering of the surface tension in the air spaces (Fig. 1). The net effect is to retard the development of atelectasis and lung edema, to decrease lung compliance, and to diminish work of breathing. Some evidence suggests that the lipid component of surfactant may play a role in host defense, having been implicated in both bacterial killing and suppression of stimulated lymphocytes; most investigators believe that the surfactant-associated proteins play an important immunomodulatory role.

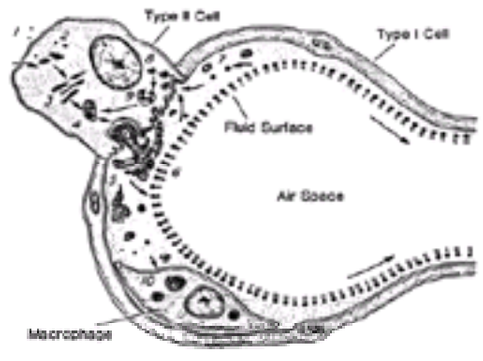

FIG. 1. Schematic diagram of a single alveolus emphasizing the movement of surfactant components through the type II cell and alveolar liquid. Components and compartments are not to scale. Key: *1,* surfactant precursors such as glucose, amino acids, and fatty acids; *2,* endoplasmic reticulum; *3,* Golgi apparatus; *4,* lamellar bodies; *5,* tubular myelin; *6,* surface film with adsorbed phospholipids; *7,* vesicular and myelin forms of surfactant possibly derived from material desorbed from the film; *8* and *9,* endocytotic compartments such as multivesicular bodies; *10,* alveolar macrophage. (From Hawgood S, Clements J. Pulmonary surfactant and its apoproteins. *J Clin Invest* 1990;86:1–6.)

Surfactant-Associated Proteins

Proteins constitute approximately 10% of isolated surfactant. Most protein found in surfactant appears to have diffused in passively from serum. Only 20% is synthesized locally. To date, three apolipoproteins (surfactant-associated proteins) have been well characterized: SP-A, SP-B, and SP-C. A fourth protein, SP-D, has been described, but there is debate in the literature regarding whether SP-D is a true apolipoprotein or simply a contaminating protein. Each surfactant-associated protein has a unique structure and function, summarized in Table 1.

	Protein structure	Functions
SP-A	Globular protein with a collagen-like domain and a short N-terminal structural similarity to C1q	Assists in the formation of tubular myelin Enhances macrophage function Inhibits surfactant secretion Promotes reuptake of surfactant
SP-B	Small cationic protein with α-helix folding	Assists SP-A in tubular myelin formation Enhances spreading of lipid film in air-liquid interface
SP-C	Small cationic protein with α-helix folding	Enhances spreading of lipid film in air-liquid interface
SP-D	Large collagenous glycoprotein	Possible role in pulmonary host defense

TABLE 1. *Surfactant-associated proteins*

SP-A is a large, collagen-like protein. It is the most ubiquitous surfactant-associated protein and appears to perform diverse functions critical to both surfactant homeostasis and immunoregulation. First, SP-A has been shown to assist in the conversion of newly secreted surfactant precursor into tubular myelin, believed to be the intracellular source of the phospholipids and the surfactant film. SP-A also participates in the regulation of surfactant homeostasis by inhibiting surfactant synthesis and promoting surfactant uptake by type II pneumocytes. Second, SP-A has clearly been shown to regulate inflammation. It enhances the activity of pulmonary macrophages. Of interest, SP-A has structural similarities to C1q of the complement cascade, possibly accounting for its ability to activate macrophages. It appears that binding of SP-A to pulmonary pathogens such as *Mycobacterium tuberculosis* permits uptake of the organisms by a specific SP-A receptor on macrophages, suggesting that SP-A may function as a hapten as well as a nonspecific activator and suppressor of intra-alveolar inflammatory effector cells.

SP-B is a small, hydrophobic protein that appears to co-operate with SP-A in the formation of tubular myelin and possibly to play a role in the packing of surfactant precursor in lamellar bodies. Additionally, SP-B has been shown to enhance the spreading of surfactant lipids in a monolayer film. SP-C is another small, hydrophobic protein that is structurally similar to SP-B. The only known role of SP-C is that it functions like SP-B to enhance the spreading of surfactant lipids in the air spaces. SP-D is a recently described large glycoprotein that many investigators believe may function to enhance the clearance of microorganisms from the airways. Not much is known about SP-D at present. There is disagreement about whether SP-D is a surfactant apoprotein or a contaminating plasma protein.

Surfactant Synthesis, Secretion, and Uptake

The lipid and protein components of surfactant are synthesized in the type II pneumocyte. Surfactant lipid is made and stored in lamellar bodies within the cell. Stimulation of the type II pneumocyte may result in the secretion of surfactant material from lamellar bodies into the air space, where it is rapidly transformed into tubular myelin with the assistance of SP-A and SP-B. The precise pathways of surfactant-associated protein synthesis and incorporation into the lipid components of surfactant have eluded scientists to date. It is not clear whether the protein components become associated with the lipid components in the lamellar bodies, after secretion of tubular myelin into the air spaces, or both.

Several stimuli can induce surfactant synthesis and/or secretion in vitro (Table 2). These include glucocorticoids, b-adrenergic agonists, estrogen, and thyroxine, which share the ability to enhance both the synthesis and secretion of surfactant. Stretching of the lung via mechanical ventilation also results in surfactant secretion. Downregulators of surfactant secretion include SP-A and b-adrenergic blockers. Corticosteroids are an extremely important inducer of surfactant synthesis and is used for clinical purposes. Glucocorticoid levels rise dramatically in the normal fetus late in gestation just before the production of surfactant. Glucocorticoid treatment of pregnant women prior to giving birth to children at risk for IRDS increases the rate at which alveolar type II cells mature and the production of surfactant.

Promoters of synthesis	Promoters of secretion
Ambroxol	Ambroxol
cAMP	β-Agonists
β-Agonists	Estrogen
Estrogen	Mechanical ventilation
Glucocorticoids	Prostaglandins
Thyroxine	Thyroxine
Inhibitor of synthesis	Inhibitors of secretion
Testosterone	SP-A
	β-Blockers

TABLE 2. *Factors involved in regulating surfactant synthesis and secretion*

Studies of surfactant synthesis indicate that new surfactant is being generated continuously and is not degraded in the airways. Therefore, mechanisms for surfactant clearance must exist. Some of the excess surfactant is undergoes phagocytosis by alveolar macrophages or is removed from the airway by the mucociliary elevator. There appears to be a sophisticated system by which type II cells “recycle” DPPC by taking it up, packaging it back into lamellar bodies in the cytoplasm, and resecreting it. SP-A appears to mediate partly the reuptake of DPPC by type II pneumocytes. Impaired mechanisms for clearance and recycling may cause alveolar proteinosis, a disease characterized by excess surfactant accumulation in alveoli. Surfactant homeostasis is an area of vigorous ongoing research.

THERAPEUTIC USE OF EXOGENOUS SURFACTANT PREPARATIONS

As described above, surfactant is necessary to prevent atelectasis and lung edema, and to maintain normal lung compliance. As atelectasis, lung edema, and reduced lung compliance occur in IRDS and many acute lung disorders in adults, it is not surprising that the effects of instilling exogenous surfactant into the lung have been the subject of considerable study. The therapeutic possibilities seem particularly attractive in critically ill patients undergoing mechanical ventilation, in whom there is ready access to a delivery conduit. Although the concept is superficially simple, practical issues have posed complex problems. Where will large quantities of human surfactant come from? Unlike many human bioactive substances, such as insulin, surfactant is predominantly lipid and thus cannot be cloned by recombinant DNA technology, so the molecular revolution has not solved the availability problem. Nor can human surfactant be isolated from human blood, like clotting factors or a_1-antiprotease; the human lung is presently the only source of human surfactant. Can animal surfactant be used? Can an artificial lipid surfactant be synthesized, and if so, what components of surfactant are most useful to instill? Must the human apoproteins be added? How can a large volume of liquid be delivered and spread evenly through the lung without causing respiratory compromise during delivery? These are some of the questions that must be answered prior to the use of surfactant as accepted practice.

Available Surfactant Preparations

The surfactant preparations may be divided into two groups: natural preparations and synthetic preparations. The natural surfactants are derived from animal sources, with bovine and porcine sources being the most common (Table 3). A natural surfactant can be prepared from human amniotic fluid, but this is not yet commercially available. Natural surfactants are either prepared by extraction from minced lung tissue or from lung lavage material. Lung lavage material has a theoretical advantage over minced lung material in that it contains less cellular and blood-derived contaminants, but obtaining it in large quantities is a laborious process. To date, there are no data from clinical studies to suggest that lung lavage preparations are more efficacious than lung mince preparations.

Name	Trade name	Source	Ingredients	Company
Surfactant TA	Surfacten	Bovine lung mince	Phospholipids, SP-B, SP-C, palmitic acid, tripalmitin	Terumo (Tokyo, Japan)
Curosurf	Curosurf	Porcine lung mince	Phospholipids, SP-B, SP-C	Chiesi Farmaceutici (Parma, Italy)
Survanta	Beractant	Bovine lung mince	Phospholipids, neutral lipids, fatty acids, SP-B, SP-C, palmitic acid, tripalmitin	Abbott Laboratories (Chicago, IL)
Alveofact	Alveofact	Bovine lung lavage	Phospholipids, cholesterol, SP-B, SP-C	Thomas GmbH (Bitersch, Germany)
Calf lung surfactant extract	CLSE	Calf lung lavage	Phospholipids, cholesterol, cholesterol esters, SP-B, SP-C	Privately produced in Canada
Infasurf	Infasurf	Calf lung lavage	Phospholipids, SP-B, SP-C	Forest Laboratories (St. Louis, MO)

TABLE 3. *Natural surfactant preparations*

Several animal-derived surfactants are in clinical use. They differ considerably in composition, as both the extraction methods and addition of specific lipids may alter the final composition of the extract sold commercially. Surfacten was developed by the Fujiwara group in Japan and was the first surfactant preparation to be successfully employed to treat infants with IRDS. It is made from bovine lung mince and is supplied as a powder that must be reconstituted in sterile saline solution. Beractant is also prepared from bovine lung mince and is similar to Surfacten. It is supplied as a liquid and thus requires no mixing. Curosurf is prepared from porcine lung mince and is supplied as a liquid. It has the highest concentration of phospholipids (80 mg/mL) of all the natural surfactants. Alveofact is derived from bovine lung lavage material. In addition to phospholipids, it contains cholesterol and other lipids. Infasurf (CLSE) also contains cholesterol and cholesteryl esters in addition to phospholipids.

There are currently two synthetic surfactant preparations available, ALEC and Exosurf (Table 4). ALEC contains DPPC and other phospholipids but does not contain any surfactant-associated proteins. The phospholipid concentration is approximately 100 mg/mL, highest of all surfactant preparations. Exosurf contains DPPC, hexadecanol, and tyloxapol. Like ALEC, it does not contain any surfactant-associated proteins. The phospholipid concentration of Exosurf when diluted as directed is much lower than that of ALEC. It is not clear whether the lack of surfactant-associated proteins in these preparations is a disadvantage. A recent meta-analysis comparing Exosurf with natural surfactants suggested that improvements in lung compliance and oxygenation were delayed in infants treated with Exosurf in comparison with those treated with natural surfactants, but both natural surfactants and Exosurf were efficacious and resulted in a clear reduction in morbidity and mortality in treated infants, with no statistically significant difference in mortality rates. Large, prospective, controlled clinical trials would be helpful to determine if the natural surfactants are superior to synthetic preparations, but even if performed carefully, these studies would be extremely difficult to interpret because of the marked differences in the available natural and synthetic preparations and the likelihood that continuous adjustments will be made in the composition of future preparations.

Name	Trade name	Ingredients	Company
Artificial lung-expanding compound (ALEC)	Pumactant	DPPC, unsaturated phosphatidylglycerol	Britannia Pharmaceuticals (Redhill, England)
Exosurf	Exosurf	DPPC, hexadecanol, tyloxapol	Burroughs Wellcome (Research Triangle Park, NC)

DPPC, dipalmitoylphosphatidylcholine.

TABLE 4. *Synthetic surfactant preparations*

Methods for Delivery of Surfactant Therapy

The goal of administration of surfactant is to deliver the drug in a simple fashion that minimizes physiologic disturbances and spreads surfactant evenly through the lung. There are two obvious ways to attempt this: tracheal instillation or aerosolization. After Avery and Mead published their findings in 1959, scientists in the 1960s experimented with surfactant therapy for infants with IRDS. Aerosolized delivery of surfactant was employed by most investigators. No beneficial effect of treatment could be demonstrated. It was because of these difficulties that Fujiwara and colleagues chose direct tracheal instillation as the method of drug delivery in their landmark study. At present, all the manufacturers of commercially available surfactants recommend tracheal instillation as the method of choice for drug delivery, but there are considerable differences in the specifics of recommended delivery. Some companies advocate multiple dosing; others suggest directed positioning of patients after instillation to facilitate drug distribution.

Tracheal instillation has been proved effective in a large number of clinical trials involving thousands of patients. Tracheal instillation allows for drug to be delivered to airways that are not being ventilated, whereas aerosolized surfactant is delivered only to ventilated lung segments. Tracheal instillation techniques are relatively simple and do not require any specialized equipment. However, there are also disadvantages. First, patients must be intubated and on mechanical ventilation for the drug to be given. Repositioning and interruption of the ventilator circuit in hypoxemic patients may result in worsening hypoxemia. Also, as most of the surfactant preparations require large volumes of drug to be instilled, transient obstruction of the airways may occur and result in respiratory and hemodynamic instability.

Despite early disappointment with aerosol delivery, there is renewed interest in the use of this technique to circumvent the problems with tracheal instillation outlined above. Aerosolization is a noninvasive technique with which physicians, nurses, and respiratory therapists are familiar, making it readily acceptable. Significant problems remain. Aerosolization results in a smaller dose of surfactant delivered to the patient compared with tracheal instillation because of the inefficiency of the delivery devices currently available, especially in ventilated patients. When a jet nebulizer is used in the ventilator circuit at high flow rates, large particles impact in the inspiratory circuit and never reach the lung, whereas particles of 1 μ in diameter may be taken into the lung only to be exhaled. There may be foaming of the surfactant aerosol and subsequent malfunctioning of valves in the expiratory circuit. These technical difficulties remain to be overcome, and trials must be performed in humans to compare the clinical efficacy of aerosolized versus tracheally instilled surfactant.

A number of factors may influence the distribution of surfactant in the lungs, regardless of the mode of drug delivery employed. The type of surfactant preparation may be of importance. The natural surfactants containing SP-B and SP-C may spread more rapidly and evenly in the air-liquid interface of the alveoli. Some in vitro data suggest that the synthetic preparations, which lack surfactant-associated proteins, spread more slowly and have higher minimal surface tensions than the surfactants that contain proteins. The clinical significance of these findings is still uncertain. The volume of fluid instilled also influences the distribution of surfactant in the lung. A more homogeneous distribution of surfactant is achieved when it is given in larger volumes of vehicle. However, larger volumes are potentially hazardous, as they are associated with a greater frequency of respiratory and hemodynamic instability during and immediately after the instillation process. Finally, it is possible that the mode of ventilation may influence the distribution of surfactant after it is administered through the endotracheal tube. Standard practice has employed conventional, volume-cycled ventilatory modes after delivery of the drug. However, some investigators have studied the effect of high-frequency ventilation in animal models of lung injury. The results have been conflicting, so more research will be required to determine whether ventilatory modes may significantly affect drug distribution.

CLINICAL APPLICATIONS OF SURFACTANT THERAPY

Infant Respiratory Distress Syndrome

IRDS is at present the only clinical condition for which surfactant instillation has been proved beneficial. The maturation of the fetal lung occurs late in the process of gestation. Type II pneumocytes begin to mature and develop lamellar bodies at approximately 24 weeks of gestation, but dramatic increases in the phospholipid concentration of amniotic fluid are not seen until approximately 28 weeks. Therefore, children born prematurely may not have a sufficient quantity of biologically active surfactant necessary to maintain normal lung function and are at risk for IRDS. More than 35 randomized, controlled trials of exogenous surfactant therapy for IRDS have been performed. The results, which have been dramatic, include a decreased incidence of pneumothorax, improved oxygenation, decreased dependence on mechanical ventilation, and a reduction of mortality. Clearly, the reduction in infant mortality rates observed in the 1980s in the United States was partially a consequence of the introduction of exogenous surfactant therapy.

Some now recommend surfactant therapy prophylactically in premature infants. Meta-analyses of data from clinical trials performed in the United States and abroad have answered important questions regarding surfactant therapy for IRDS. For example, it is clear that surfactant therapy given to infants in the delivery room who are at risk for IRDS is effective in lowering both the incidence and severity of the syndrome. However, trials comparing prophylactic therapy with rescue therapy have failed to demonstrate superiority of one style of treatment. Most investigators agree that prophylactic therapy should be given to infants at high risk for IRDS by someone with experience in neonatal resuscitation. Infants who are at low risk may be observed carefully for signs of respiratory insufficiency and treated if deterioration develops.

Some cases of IRDS do not respond to surfactant therapy. Approximately 10%–20% of infants treated with exogenous surfactant for IRDS fail to demonstrate any significant clinical response. These infants sometimes have been given an incorrect diagnosis and actually have other diseases, such as pneumonia or congenital heart disease. Meta-analyses suggest that other complications of prematurity, such as patent ductus atreriosis and interventricular hemorrhage, are unaffected by exogenous surfactant therapy.

Meconium Aspiration Syndrome

Meconium aspiration syndrome (MAS), which occurs secondary to fetal inhalation of meconium into the lungs, usually during labor, results in respiratory embarrassment shortly after birth. Infants with MAS may have hypoxemia, noncompliant lungs, and ventilator-associated barotrauma, just like infants with IRDS. Because MAS resembles IRDS clinically, many have postulated that meconium in the lungs of the neonate may interfere with the activity of surfactant. Experimental studies suggest reduced surface tension-lowering ability of surfactant after meconium contamination. In clinical and experimental studies, surfactant has resulted in improvements in lung compliance and oxygenation. The available data are promising, but randomized, controlled trials in a large number of patients need to be performed to establish a significant outcome benefit.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a disorder in which the fetus develops with a defect in the diaphragm that allows abdominal contents to migrate into the thoracic cavity and compress the lung. This compression results in pulmonary hypoplasia, characterized by a reduced number of alveoli, and smooth-muscle hyperplasia in pulmonary arterioles. The hypoplastic lungs of these neonates are also deficient in surfactant. Infants with CDH are usually born at term and experience respiratory compromise early after birth. Surgery corrects the diaphragmatic defect, but the immature lung persists; the mortality rate for infants with CDH is approximately 30%–50%. Current data on exogenous surfactant therapy for infants with CDH are limited, but reports suggest that surfactant may improve oxygenation in these infants and facilitate support with mechanical ventilation. Further investigation of exogenous surfactant therapy for children with CDH is ongoing.

Adult Respiratory Distress Syndrome

Adult respiratory distress syndrome (ARDS) was named after IRDS because of the clinical similarities. Both syndromes are manifested by respiratory failure, poorly compliant lungs, alveolar flooding, and profound hypoxemia. Surfactant abnormalities and alveolar damage are present in each disorder. However, there are important differences. First, although alveolar damage is present in both syndromes, the alveolar injury occurs for different reasons. The primary abnormality in IRDS is immaturity of the lung and a primary deficiency of biologically active surfactant. This results in atelectasis in surfactant-poor areas and overdistention and hyperoxic exposure in alveoli in overventilated lung units. Overdistention and oxidant injury probably result in secondary alveolar disruption and injury. In contrast, an inflammatory alveolar injury is the primary pathophysiology of ARDS. The end result is alveolar disruption and pulmonary capillary leakage of serum proteins and water into the alveolar spaces. Surfactant processing and surface tension-lowering activity are impaired in this abnormal alveolar environment. Thus, the surfactant abnormalities in IRDS are fundamentally distinct from those of ARDS. Infants with IRDS cannot synthesize surfactant, whereas the surfactant in the lungs of patients with ARDS is inactivated by contaminating serum proteins, oxidants, and poorly characterized aberrations in surfactant homeostasis. This poses two questions in ARDS that are not relevant in IRDS: (1) Is the surfactant deficiency of ARDS an important factor in poor outcome or just an epiphenomenon? (2) Will exogenous administered surfactant function well in the ARDS inflammatory milieu? Neither question has been answered to date.

Available results of clinical trials are disappointing. As has often been the case with ARDS, small studies with encouraging results have been superseded by large, multicenter trials with negative findings, most recently a large, multicenter study of 498 patients with sepsis-induced ARDS, in which patients received treatment with either aerosolized Exosurf or placebo for 5 days. Preliminary summary data reported nationally suggested no differences in mortality, although final publication of the study is pending. There are a number of reasons that may explain the lack of efficacy. Exosurf lacks surfactant-associated proteins. The dose of surfactant employed was low, normalized to weight, and given in proportion to the usual dosage regimens for IRDS. On the other hand, employing large doses of surfactant in adults may be problematic because of the large volumes (70 to 300 mL, depending on the preparation) that are required. Also, as discussed above, a number of questions remain unanswered regarding the most efficient means of delivering the drug. Finally, there is the matter of timing. Unlike the onset of IRDS, the onset of ARDS is difficult to determine with precision, and the most severe respiratory failure may occur late as a result of nosocomial pneumonia or other complications. Should surfactant be administered as an adjunct to maximal ventilatory support, or should patients identified as being at risk for ARDS receive surfactant? Thus, the issue of surfactant therapy in ARDS perfectly illustrates the problems associated with translating this “simple” therapy into a practical regimen.

Future Applications

Surfactant, because of its beneficial effects of increasing lung compliance and oxygenation and preventing atelectasis, can be viewed as a nonspecific supportive therapy likely to provide physiologic benefit regardless of the nature of respiratory failure; it has therefore been postulated that exogenous surfactant therapy may be useful in a wide range of adult diseases, including pneumonia, pulmonary fibrosis, asthma, chronic bronchitis, and after lung transplantation. Surfactant abnormalities have been described in each of these disorders. However, all the problems associated with ARDS therapy might be expected to occur and even be exacerbated in this heterogeneous group of disorders, and no large, controlled trials in humans to date have demonstrated a benefit of exogenous surfactant therapy in any of them. However, speculation and optimism continue, and research is ongoing in each of these areas.

Despite the advances of the last 40 years of research, many questions regarding the function and metabolism of surfactant remain unanswered. As progress is made in understanding the mechanisms of surfactant function in health and disease, new treatment strategies may be designed. On the horizon, investigators are working to prepare more efficacious synthetic and natural surfactants, so-called “designer surfactants” containing higher concentrations of surfactant-associated proteins and a wider range of phospholipids. Others are working to improve dosing regimens and drug delivery. Finally, clinical studies are under way to study the effects of various surfactant preparations in a wide range of disorders, including ARDS, and as postoperative respiratory support after lung transplantation. Clearly, a vast potential market for effective surfactant therapy exists that will undoubtedly continue to drive research and product development in this area. It is hoped that patients with a variety of lung disorders will ultimately benefit.

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CHAPTER

18 Interstitial Lung Diseases

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GENERAL CONSIDERATIONS AND NOMENCLATURE

The interstitial lung diseases (ILD) are a group of disorders of both known and unknown etiology that are characterized by inflammation and fibrosis. Table 1 is a list of some of the pulmonary disorders commonly associated with ILD. This chapter covers two types of ILD of unknown cause: idiopathic pulmonary fibrosis (IPF) and ILD associated with the systemic rheumatologic disorders. The clinical presentation, physiology, pathology, and management of IPF are discussed first, and subsequently aspects of ILD associated with the systemic rheumatologic diseases.

Idiopathic
Idiopathic pulmonary fibrosis
Familial pulmonary fibrosis
Hamman-Rich syndrome
Sarcoidosis
Bronchiolitis obliterans organizing pneumonia
Systemic rheumatic disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren's syndrome
Systemic sclerosis
Dermatomyositis/polymyositis
Mixed connective tissue disease
Ankylosing spondylitis
Occupational
Silicosis
Asbestosis
Berylliosis
Coal worker's pneumoconiosis
Hard metal pneumoconiosis
Infectious
Fungal disease
Postviral
Miscellaneous
Sequelae to adult respiratory distress syndrome
Hypersensitivity pneumonitis
Drugs
Oxygen toxicity
Radiation toxicity

TABLE 1. *Common cause of pulmonary fibrosis*

IDIOPATHIC PULMONARY FIBROSIS

In the mid-1930s, Hamman and Rich first described a series of patients in whom developed what today is considered a variant of IPF. For a period of time, however, the term *Hamman-Rich syndrome* was used to denote most cases of pulmonary fibrosis. This term is now reserved for cases of acute interstitial pneumonitis (AIP) with a rapidly progressive and often fatal course. Several other names have been proposed for IPF, including *cryptogenic fibrosing alveolitis, diffuse interstitial lung disease,* and *interstitial pulmonary fibrosis.* Each of these names has merit; however, we refer to the disorder in this chapter as *IPF.* IPF has also been subdivided into usual interstitial pneumonitis (UIP) and desquamative interstitial pneumonitis (DIP). We recognize this classification and, when necessary, refer to differences between these two subdivisions of IPF. It should be noted, however, that many investigators do not use these terms and consider UIP and DIP as different manifestations of IPF.

Epidemiology

The prevalence of IPF has been estimated to be about 3 to 5/100,000. It is second only to sarcoidosis as a cause for ILD of unknown etiology. Prevalence estimates vary, however. For example, one study using a New Mexico lung disease registry estimated the prevalence of pulmonary fibrosis at 29/100,000 for male patients and 27/100,000 for female patients. This estimate may reflect the prevalence for the entire United States, or it may represent employment in local mining industries resulting in occult pneumoconiosis, migration of persons with chronic lung disease to New Mexico, or over-ascertainment of cases based on the use of administrative coding. In the New Mexico population, IPF accounted for 45% of all ILD. Based on autopsy studies, IPF may be 10 times more common than is clinically recognized. Few studies have examined ethnic or racial predilections for IPF; in one study of indigenous African patients, the clinical spectrum and frequency of illness were similar to those of other groups.

Although by definition “idiopathic” pulmonary fibrosis has no known cause, it is conceivable that inhaled particulate dust or other material could cause this disorder. Of interest, 70% of patients with presumed IPF had organic dust exposure in one study. Curiously, up to 40% of IPF patients may recall an antecedent viral-type illness accompanied by cough, fever, and malaise. However, despite intense investigation, there is no clear evidence implicating an infectious etiology for IPF.

The association between IPF and cigarette smoking has generated considerable interest. Of patients with IPF, 60%–80% are either current or former smokers. Cigarette smoking is a plausible IPF risk factor, as it may alter pulmonary immune function, reduce clearance of inhaled agents, and increase permeability of the respiratory epithelia. Cigarette smoking influences bronchoalveolar lavage fluid (BALF) cellularity and is the strongest independent predictor of increased BALF neutrophils and eosinophils (Table 2). Smoking may also cause respiratory bronchiolitis, an entity histologically similar to DIP; this may, in turn, lead to fibrosis.

	Nonsmoker volunteers (n = 111)	Smoker volunteers (n = 19)	IPF study subjects (n = 83)
Cells/mL, $\times 10^4$	12.7±9.1***	48.9±40.2*	28.0±24.4
Macrophages/mL, $\times 10^4$	12.1±10.0***	47.4±39.6**	22.4±21.8
Lymphocytes/mL, $\times 10^4$	0.8±1.0	0.7±0.7	1.6±3.0
Neutrophils/mL, $\times 10^4$	0.1±0.2***	0.6±0.9*	2.8±7.3
Eosinophils/mL, $\times 10^4$	0.0±0.1***	0.1±0.2***	1.2±2.8
Percent lavage return	75.9±15.9	70.7±17.7	73.7±14.7

From Schwartz DA, Helmers RA, Dayton CS, Merchant RK, Hunninghake GW. Determinants of bronchoalveolar lavage cellularity in idiopathic pulmonary fibrosis. *J Appl Physiol* 1991;71:1658. Reproduced with permission.

*Values are means ± SD. Values for *p* were computed by comparing nonsmoker volunteers with patients having IPF and by comparing smoker volunteers with patients having IPF.

*$p < 0.01$; **$p < 0.001$; ***$p < 0.0001$.

TABLE 2. *Comparison of BAL cellularity between patients with IPFand both nonsmoker and smoker volunteers*[a]

Clinical Presentation

History

The typical patient with IPF is between 40 and 60 years of age. Symptoms of the disease frequently develop 1 to 2 years before the patient seeks attention. Men are affected slightly more commonly than women. Dyspnea at rest (and worsened by exertion) and a nonproductive cough are the most common symptoms. Constitutional symptoms of malaise and weight loss are seen in some cases. Even in the absence of a well-recognized rheumatologic disease, arthralgias without actual joint inflammation may be present.

The medical history, including a comprehensive symptoms review, occupational history, and family history, is invaluable in differentiating IPF from other types of ILD. A familial form of IPF, thought to be autosomal dominant with variable penetrance, has been described.

Sudden onset of respiratory symptoms with a clinical presentation suggestive of the adult respiratory distress syndrome (ARDS) (but for which no underlying cause is apparent) should raise suspicion of AIP or the Hamman-Rich syndrome. Individuals affected by AIP are often younger adults or even children. Although this disorder has a poor prognosis, patients who recover may have completely normal pulmonary function. Like AIP, bronchiolitis obliterans with organizing pneumonia (BOOP) may develop in an abrupt fashion, but it reflects a pattern of injury in the small airways and the adjacent pulmonary parenchyma. It is often responsive to therapy and usually has a good prognosis.

Physical Examination

Physical examination findings generally include tachypnea, basilar crackles, and exercise-induced cyanosis. Chest crackles occur in 60%–75% of cases; typically they are fine and late in inspiration, and they are often described as “velcro rales.” Crackles are more common in IPF than in other forms of ILD, such as sarcoidosis, and are thought to be associated with subpleural fibrosis. Mid- and late-expiratory crackles may be detected. These more subtle findings are believed to be caused by vibrations of the airway walls and may be a clinical indicator of disease severity. Clubbing is present in about 65% of cases of IPF. It occurs more commonly in men and may begin early in the disease course. Of note, full-blown hypertrophic osteoarthropathy is rare. In one study, clubbing correlated with the extent of smooth-muscle proliferation in fibrotic pulmonary lesions. With the onset of secondary pulmonary hypertension, signs of right-sided heart failure, such as jugular venous distension, an accentuated P_2 heart sound, and pedal edema, become apparent.

Evaluation for characteristic manifestations of systemic rheumatic disease, including physical examination findings and results of selected laboratory studies, complements the history in excluding ILD associated with specific illnesses.

Diagnostic Studies

Physiologic Evaluation

Results of pulmonary function studies are among the best indicators of the severity of IPF. Diminished single-breath diffusion capacity of carbon monoxide (D_LCO), in particular, is one of the earliest and most sensitive physiologic abnormalities of IPF. It has been recommended that D_LCO be corrected for alveolar volume (D_LCO/V_A, or KCO), because KCO is a more useful indicator of the severity of gas exchange impairment during exercise and the degree of pulmonary vascular involvement. It is not clear, however, whether D_LCO or KCO is the best index of impairment. Reduction in lung volumes typical of restrictive disease is also noted. The degree of reduction in lung volumes and increase in lung elastic recoil directly correlate with the extent of fibrosis. There is, however, a very poor correlation between lung volumes and inflammation. The reduction in lung volumes also causes a reduction in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) as measured by spirometry. Because the reductions in FEV_1 and FVC are usually of equal magnitude, there is often no evidence of airway obstruction. A widened alveolar-arterial gradient in partial pressure of oxygen [$P(A\text{-}a)O_2$], worsened by exertion, is also a useful parameter to monitor in patients with IPF.

Comorbid obstructive lung disease caused by cigarette smoking may complicate interpretation of pulmonary function data in patients with IPF, because of increased residual volume (RV) and functional residual capacity (FRC) resulting from trapping of air. The presence of both obstructive and restrictive lung diseases has opposite effects on measures of air flow and lung volumes, and smoking may appear to “normalize” these physiologic measures in IPF. The D_LCO is an accurate method of assessing lung function in patients with IPF who smoke and have obstructive lung disease. To confound matters further, small-airway obstruction is often present in early IPF, independently of smoking, and may influence physiologic parameters such as mid-expiratory flow rates. About two thirds of patients have morphometric and physiologic evidence of small-airway involvement, indicated by abnormalities of flow-volume curves and dynamic compliance.

Initially, it was thought that a fall in arterial PO_2 was most caused by diffusion abnormalities. More recent work suggests that arterial hypoxemia is explained best by ventilation-perfusion mismatch and to a lesser extent by a diffusion limitation. Patients with IPF have higher pulmonary arterial pressures both at rest and during exercise than patients who have other causes of ILD. Although pulmonary arterial hypertension may be mainly caused by destruction of blood vessel in fibrotic lung, pulmonary vasoconstriction caused by alveolar hypoxia is also important.

Physiologic changes in lung function during both exercise and sleep provide useful clues about the severity and functional consequences of IPF. Although exercise causes significant hypoxemia in most patients with long-standing IPF, there is generally little or no change in PCO_2. A small percentage of patients with early IPF may have normal or even improved levels of arterial blood gases during exercise. Pulmonary edema at maximal exercise, rather than inspiratory muscle fatigue, may account for exercise limitations observed in some patients with IPF. O_2 desaturation also develops in patients with IPF during REM sleep, similar to that seen in patients with chronic obstructive pulmonary disease (COPD). Insufficient ventilatory response to hypercapnia accounts for larger falls in O_2 saturation during sleep. Overall, O_2 desaturation during sleep is usually mild and less severe than that observed during exercise.

Like patients with COPD, patients with IPF expend about 120% of their predicted energy expenditure for body size. This is a principal component of the weight loss seen in IPF.

Quality-of-Life Evaluation

Quality-of-life considerations are of paramount importance in assessing disease severity and response to therapy. The sensation of dyspnea and limitations of physical activity are the most important considerations. Dyspnea may be quantitated (grades 1 through 4) in a simple and reliable manner, as outlined in the American Thoracic Society Shortness-of-Breath Scale. Various ordinal dyspnea scales, such as the Baseline Dyspnea Index (BDI), Medical Research Council (MRC) scale, and Oxygen-Cost Diagram (OCD), also provide semiquantitative information on disease-specific health-related quality of life (HRQL) and have good reliability. These measures of dyspnea are significantly associated with physiologic parameters of lung function. Severe breathlessness is correlated with lower resting D_LCO and an accelerated ventilatory response to exercise. Dyspnea is related to reduced lung compliance and increased elastic work of breathing. In addition to dyspnea, other disease-associated factors clearly affect patients' quality of life. The Chronic Respiratory Questionnaire and the St. George's Respiratory Questionnaire evaluate a range of pulmonary symptoms. The short-form 36 (SF-36), a generic functional assessment instrument well validated for many chronic illnesses, has been used to measure HRQL in chronic obstructive pulmonary disease, and it correlates well with the BDI. For health outcomes research, a generic instrument such as the SF-36 may be preferred to disease-specific scales for comparing health states of patients having pulmonary disease with those of patients having other chronic conditions.

Both dyspnea and quantitative declines in pulmonary function are relevant to the determination of disability. Impairment rating may be defined by pulmonary function tests; 35.6% of patients with IPF are impaired, with an FVC of 50% or D_LCO of 40%. This percentage is considerably higher than that for individuals with either sarcoidosis (12.1%), pneumoconiosis (13.6%), or asbestos exposure (1.1%).

Pulmonary Imaging

Plain Chest Radiography

Up to 10% of patients with IPF have normal chest x-ray findings despite significant functional impairment. When radiographic abnormalities are seen, the most characteristic finding is prominent bibasilar reticular or reticulonodular infiltrates (Fig. 1). These abnormalities progress to honeycombing late in the course of disease. Although the basilar findings are most easily appreciated on plain film radiograph, IPF is a diffuse process. Pleural findings on plain film are uncommon. To better quantitate and communicate plain radiographic findings, the International Labour Office (ILO) scoring system, developed for occupational lung disease, can be used. This scoring system is reliable and correlates to some degree with physiologic data. Table 3 describes demographic, clinical, and radiographic characteristics in a representative group of patients with IPF.

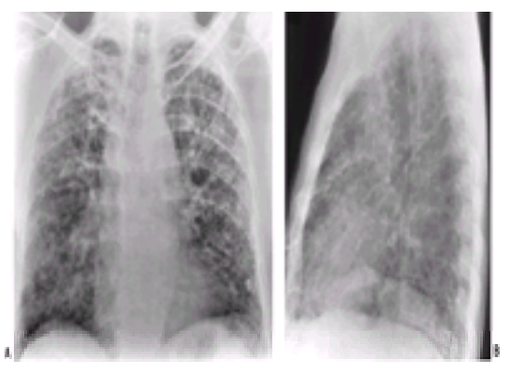

FIG. 1. Posteroanterior (**A**) and lateral (**B**) chest radiographs of a patient with IPF. A diffuse reticulonodular infiltrate is present throughout the lung with somewhat greater involvement peripherally. Cystic honeycombing is apparent in both lower lung fields.

Parameter	Value
Sex	
Male	15 (62.5%)
Female	9 (37.5%)
Age, y*	63.4 ± 12.5
Smoking history	
Never	8 (33.3%)
Formerly	14 (58.3%)
Currently	2 (8.3%)
Pack-years of cigarette smoking*	24.38 ± 21.79
Chest x-ray findings	
ILO category	
0	1 (4.2%)
1	10 (41.7%)
2	11 (45.8%)
3	2 (8.3%)
Pleural disease	
Present	5 (20.8%)
Absent	19 (79.2%)
Dyspnea class	
1	2 (8.3%)
2	8 (33.3%)
3	1 (4.2%)
4	6 (25%)
5	7 (29.2%)

From Hartley PG, Galvin JR, Hunninghake GW, et al. High-resolution CT-derived measures of lung density are valid indexes of interstitial lung disease. *J Appl Physiol* 1994;76:271. Reproduced with permission.

IPF, idiopathic pulmonary fibrosis; ILO, International Labour Office.

*Values are means ± SD.

TABLE 3. *Demographic, clinical, and radiographic characteristics of 24 patients with IPF*

Computed Tomography

Computed tomography (CT) is superior to plain radiography in evaluating IPF. CT may also be more useful than chest radiography in assessing the location of disease and in suggesting sites for biopsy. CT has the advantage over plain radiographs of eliminating superimposition of structures, thereby allowing better definition of the type, severity, and distribution of abnormalities seen in IPF. Subpleural shadowing is well visualized on CT and predominates in the posterior lower lobes.

Fast scan times of 1 to 2 seconds allow high-resolution, thin-section scans (high-resolution CT). High-resolution CT is often performed with the patient both supine and prone to detect minimal pathologic changes. Cystic air spaces (“honeycomb” cysts) measuring 2 to 20 mm in diameter are detected in 90% of high-resolution CT scans, compared with 30% of plain radiographs. On high-resolution CT, IPF tends to have a patchy, peripheral distribution throughout the lung (Fig. 2). The presence of subpleural fibrosis seen in IPF by high-resolution CT may help differentiate it from sarcoidosis. High-resolution CT may be especially useful in the evaluation of patients with concomitant IPF and emphysema, who may have normal spirometric findings and lung volumes. Computer-aided diagnosis using clinical, plain radiographic, and high-resolution CT values is experimental but may prove useful in the future.

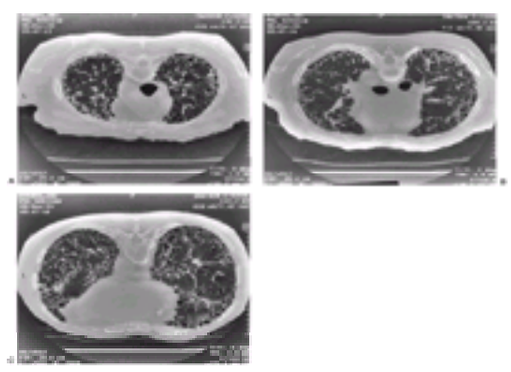

FIG. 2. High-resolution chest CT (1.5-mm slices) of a patient with IPF. Apical (**A**), midlung (**B**), and basilar (**C**) cuts are shown. These sections demonstrate marked peripheral fibrotic changes with cystic honeycombing most prominent at the bases of the lungs.

The utility of high-resolution CT for measuring disease severity and progression is controversial. A “ground-glass” appearance seen on high-resolution CT is thought to be indicative of active areas of inflammation, which may have potential therapeutic or prognostic importance. Reticular patterns seen on high-resolution CT often correspond histologically with areas of fibrosis. Traction bronchiectasis and bronchiolectasis are often found in areas of fibrosis. Despite its many attributes and the increased sensitivity of high-resolution CT over plain radiographs, there are some significant limitations to this methodology. The overall sensitivity of high-resolution CT for biopsy-proven IPF is only 88%. Therefore, although sensitive, it may miss mild cases of IPF detected by biopsy or suggested by an abnormal D_LCO. Parenchymal opacification (“ground-glass changes”) detected by high-resolution CT may not be useful to guide therapy. For instance, it may be difficult with high-resolution CT to separate inflammation from fibrosis in all cases. In one study, ground-glass appearance correlated with inflammation in 65% and fibrosis in 54% of cases of diffuse lung disease. Ground-glass infiltrates have also correlated poorly with regions of inflammation in bleomycin-induced pulmonary fibrosis of rats. It is important to note that high-resolution CT provides only a limited sample of the chest and may miss a patchy process. On the other hand, IPF is diffuse and should therefore be an ideal disease to be studied using this technique. To minimize interobserver and intraobserver variability in interpretation of high-resolution CT and provide a quantitative measurement correlated with dyspnea and physiologic parameters, investigators have examined the utility of a computer-derived density analysis of lung parenchyma, with some success.

Gallium Scanning and Other Nuclear Imaging

Scanning with gallium citrate Ga 67 is a highly sensitive test for acute lung inflammation, but its very poor specificity limits its clinical usefulness. Further, the technique is poorly standardized, although computerized imaging methods may lessen the variability. Indium-labeled neutrophil scans have been successfully used in animal models to differentiate between normal animals and those having experimental alveolitis with increased neutrophils in the lung. Overall, ventilation-perfusion scans are not helpful in the routine assessment of IPF disease activity or in assessing response to therapy.

Magnetic Resonance Imaging and Positron Emission Tomography

The usefulness of magnetic resonance imaging (MRI) in detection and surveillance of IPF has been limited historically by long imaging times that require careful respiratory gating techniques to minimize artifact from respiratory movements. MRI provides qualitative rather than quantitative information about IPF. Positron emission tomography (PET) has been used in pilot studies to evaluate variations in pulmonary vascular permeability seen in IPF. The high cost and restricted availability of PET technology are likely to limit its common use. Neither modality has a role in the routine evaluation or management of IPF at this time.

Laboratory Studies

Although laboratory studies may be useful in excluding other causes of ILD, serum and urine biochemical and serologic studies are of limited value in the management of IPF. The erythrocyte sedimentation rate is elevated in approximately 50% of cases. Polyclonal gammopathy resulting from nonspecific B-cell activation is noted in about 75% of patients. Even in the absence of a clearly defined rheumatologic disorder, elevations are seen in serum rheumatoid factor (30%) and antinuclear antibody (ANA) (15%). Measurement of serum levels of complement and immune complexes is nonspecific and not a reliable indicator of disease activity.

Bronchoalveolar Lavage

BAL is performed by instilling aliquots of saline solution through a flexible bronchoscope that has been “wedged” into a third- or fourth-order bronchus. With this technique, recovered fluid may be evaluated for cell number and differential analysis, cultures may be obtained, and secreted proteins can be identified and quantitated. BAL has been useful in the evaluation of lung cancer and infections. Its role in the management of IPF and other ILD has been controversial. Nevertheless, it can be extremely useful in the evaluation of alveolar inflammation, which can be used to establish a diagnosis, monitor response to therapy, and predict a patient's prognosis. Increased numbers of lymphocytes are seen in patients with more active inflammation and suggest an improved response to corticosteroid therapy. Neutrophils with or without eosinophils are increased in IPF BALF specimens, and neutrophilia portends a poor prognosis. BAL has been examined to assess its effectiveness as a surveillance and staging tool. BAL may be of limited value because technique is not standardized. Samples from different parts of the lung vary in cellularity, limiting reliability of BAL. It is important for both investigators and clinicians who plan to follow serial BAL in a particular patient to adopt standardized techniques to avoid high intrasubject variability. Correlation between BAL and high-resolution CT is essential to define better the role of BAL in assessment of inflammation. At the present time, BAL is still considered a research tool with no proven clinical utility in the management of IPF.

Lung Biopsy

The necessity to perform an open lung biopsy for the diagnosis of IPF is debated by many chest physicians. In the United Kingdom, the diagnosis is usually based on purely clinical grounds. Because IPF is a patchy disease, a negative or nonspecific transbronchial biopsy specimen may represent either an inadequate sample or a sample of an unaffected region of the lung. Several studies have also shown that the amount of tissue obtained by transbronchial lung biopsy is not sufficient to make a diagnosis of IPF. Transbronchial lung biopsy is often used, however, to exclude the presence of other disorders, such as hypersensitivity pneumonitis or BOOP. Many practitioners recommend an open lung biopsy for all patients with a negative transbronchial lung biopsy result if clinical suspicion of IPF is high. For many patients, open lung biopsy is required to establish a definitive diagnosis. Open lung biopsy is the “gold standard” for IPF diagnosis. With open lung biopsy, infectious and neoplastic processes can be excluded, and the specimen may provide some staging information useful for planning a treatment program. For diffuse pulmonary infiltrates of unknown etiology, open lung biopsy results in management changes in up to three quarters of all patients.

At the time of open lung biopsy, it is necessary to sample not only the most grossly affected areas, but also more central areas that are in earlier stages of the disease process. High-resolution CT before biopsy can be useful in localizing areas of particular interest. Although some disagree, it is recommended that the tip of the lingular segment and the right middle lobe be avoided, as these areas often have nonspecific changes. Open lung biopsy may result in serious complications 11%–23% of the time. This rate depends in part on the degree to which the patient is immunocompromised at the time of the procedure. The use of video-assisted thoracoscopic surgery, or thoracoscopy-guided lung biopsy, has significantly limited the need for open lung biopsy in selected centers. The diagnostic accuracy is essentially equal to that of open lung biopsy, and patients have less morbidity and shorter hospital stays.

Given the generally poor prognosis of IPF, coupled with the potential morbidity and mortality associated with open lung biopsy, many physicians decide to forego the surgical procedure when they strongly suspect the presence of IPF. Any decision to perform open lung biopsy must take into account the likelihood of the diagnosis without the test as well as the complications associated with its performance. Under certain circumstances, open lung biopsy may be omitted.

Pathology

On gross inspection, the lungs are small, with a nodular pleural surface. The subpleural areas of the lung parenchyma are most severely affected, with the development of honeycomb cystic changes in late-stage fibrosis. Fibrosis often occupies about 20% of the lung volume (Fig. 3).

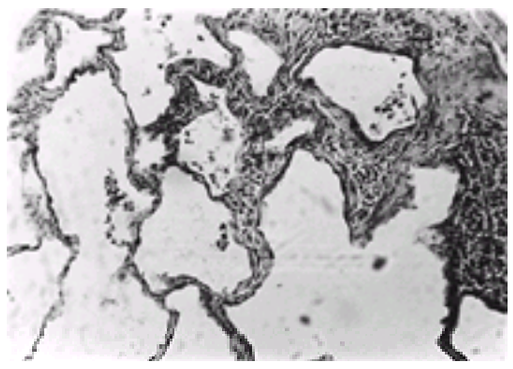

FIG. 3. Histology of open lung biopsy specimen from a patient with IPF. This reveals patchy dense fibrosis adjacent to normal alveoli. Original magnification × 200.

From a histopathologic perspective, IPF can be divided into usual interstitial pneumonitis (UIP) and desquamative interstitial pneumonitis (DIP). DIP is characterized by mild inflammation of the alveolar interstitium, relative preservation of the alveolar architecture, and the presence of large numbers of macrophages in the alveolar air spaces. In UIP, the alveolar wall is thickened with inflammatory cells and connective tissue. There is often also a reorganization of the parenchyma. DIP and UIP may simply represent different stages of the same pathologic process. Of interest, different histopathologic patterns frequently are noted even in the same specimen.

Alveolitis is thought to be the initial abnormality in all cases of ILD. Infiltrates of lymphocytes and plasma cells are noted early in the disease, with interstitial edema and eventual loss of type I epithelial and capillary endothelial cells. Desquamation, indicative of an active inflammatory process, occurs when type II pneumocytes and alveolar macrophages fill the alveolar lumen. Type II pneumocytes proliferate in areas of less severe fibrosis, whereas cuboidal and metaplastic squamous epithelial cells renew epithelium in areas of very severe lung damage. Dense alveolar septal fibrosis occurs in later stages because of the accumulation of fibroblasts and collagen within the interstitium. The pleura is also abnormal in IPF; it thickens and becomes more vascular. It is lined by hypertrophied and hyperplastic mesothelial cells. The larger airways show increased amounts of muscle and glandular tissue.

Histologic scoring systems have been developed by several groups to provide reproducible, standardized reporting techniques for clinical trials. Scoring systems use different pathologic parameters, such as the level of fibrosis and cellularity of specimens, which are uniformly interpreted by panels of pathologists. Semiquantitative systems are faster and may provide as much correlation with clinical parameters as more detailed morphometric analyses.

Ultrastructural features of IPF may be different from those observed in ILD associated with systemic rheumatologic disorders. Endothelial cell swelling and intracellular tubuloreticular structures are noted in patients with rheumatic disease-associated ILD, but not in IPF. These tubuloreticular structures are similar to those observed in viral pneumonia.

In AIP, in contrast to IPF, there are intra-alveolar hyaline membranes, interstitial septal widening, endothelial and epithelial damage, and fibroblast proliferation without extensive collagen deposition. These pathologic features are identical to findings in ARDS. However, ARDS often resolves without permanent damage, whereas fibrosis associated with hyperplastic type II pneumocytes often develops within a few weeks of onset of AIP. Pneumocytes proliferate, and the collapsed alveoli

coalesce into a single thickened septum. Type I pneumocytes proliferate along the denuded basal lamina of the alveolar septa. As the disorder progresses, intra-alveolar exudates are incorporated into the alveolar wall, contributing to its thickness. Ultrastructural changes of AIP include folding of the alveolar septa with collapse of entire alveoli and apposition of their walls. Ultimately, honeycombing appears, occasionally within weeks, and the final histology of AIP is identical to that seen in IPF. In fact, it has been hypothesized that the sequence of lung injury in individual areas of the lung are similar in IPF and AIP.

Pathogenic Theories

IPF is most likely an immune-mediated illness, and it probably results from a host response to an as-yet-unknown respiratory antigen. Although many cells play important roles in perpetuating the immune response, tissue damage is predominantly mediated by alveolar macrophages and neutrophils. Macrophages directly damage the lung parenchyma and also attract and activate neutrophils and other inflammatory cells. Direct pulmonary damage is mediated by macrophage production of free oxygen radicals; alveolar macrophages are an important source of oxygen radicals in the lungs. Of interest, excessive production of free oxygen radicals in patients with IPF correlates with abnormal physiologic parameters. Macrophages release products chemotactic for neutrophils (leukotriene B_4), growth factors for fibroblasts (platelet-derived growth factors, fibronectin, and insulin-like growth factor), and proinflammatory cytokines (interleukin-1b and tumor necrosis factor-a). Macrophages release both IL-lb and its specific inhibitor, IL-1 receptor antagonist (IL-1RA); the IL-1b/IL-1RA ratio is increased in patients with IPF, resulting in a proinflammatory environment. Macrophages also recruit mesenchymal cells to the lung and activate them as part of the fibrotic process.

Neutrophils also appear to have a number of potential pathogenic roles in IPF. Neutrophils release oxidants and proteinases, like collagenase, that are locally destructive. In normal persons who do not smoke, very few neutrophils are seen in the lower respiratory tract, but in patients with active IPF, the neutrophil represents up to 20% of BALF cells. Eosinophils release similar compounds as well as other toxic products, such as eosinophil major basic protein.

As is true of all immunologic illnesses, lymphocytes are central to the inflammatory cascade. B lymphocytes produce IgG, and IgG-containing immune complexes can be found in inflamed lung; although these complexes are associated with IPF, their pathogenic role is speculative. T lymphocytes may also play a prominent role, both in an autoimmune reaction against alveolar antigens and in enhancement of matrix production. Activated T cells produce cytokines that stimulate proliferation of fibroblasts and lead to increased collagen synthesis.

Mesenchymal cells of the interstitium synthesize type I collagen, type III collagen, fibronectin, and other matrix proteins prominent in fibrotic lungs. In IPF, these cells are numerous in the alveoli as well as in the interstitium. Both the amount of matrix proteins synthesized as well as their composition may be altered in IPF.

Treatment

As is true for many relatively rare, serious disorders of unknown cause, there is much dogma but few controlled studies evaluating IPF management. Because duration of disease is such a potent predictor of outcome, careful comparisons of therapeutic protocols are confounded by differing definitions and duration of disease. For most physicians, prednisone is the drug of first choice, and immunosuppressive agents are generally reserved for corticosteroid failures. Although early alveolitis is clearly more responsive to anti-inflammatory therapy than later, more fibrotic disease, improvements in survival with aggressive treatment are reported even in patients who have more advanced disease.

General Supportive Measures

As in the management of chronic obstructive lung disease, pulmonary rehabilitation and/or O_2 therapy are recommended for patients with limited exercise tolerance and severe arterial hypoxemia. O_2 therapy improved exercise tolerance in subjects with IPF in some but not in all studies. Continuous low-flow O_2 should be prescribed for all patients with demonstrated resting hypoxia, especially in the presence of cor pulmonale or polycythemia. Exercise- or sleep-induced desaturation should be treated with O_2 to maintain a saturation of 90%.

Vasodilators have been used in IPF as therapeutic agents for pulmonary hypertension. Isosorbide dinitrate, nitrendipine, nifedipine, and hydralazine have all been evaluated in small studies. Although nifedipine has been shown to blunt an exercise-induced increase in pulmonary vascular resistance in some studies, there is no clear evidence that any of the vasodilators have a role in the therapy of IPF. Use of these agents may be dangerous and lead to a worse outcome or even death.

Corticosteroids

Despite their significant short- and long-term toxic effects, corticosteroids remain the mainstay of therapy. Patients with highly cellular infiltrates have the best response to corticosteroids, but measurable improvements in pulmonary function are found in no more than 30% of cases. With corticosteroids, subjective improvement occurs in more than half of cases.

Early use of high-dose corticosteroid is recommended to provide the best chance for recovery. Improvement, if it is going to occur, is usually noted within several weeks. Corticosteroid therapy is begun with a daily dose of 0.5 to 1 mg of prednisone per kilogram of body weight, or the equivalent. Because of the toxicity of corticosteroids at this level, once improvement has been noted (or after 4 to 8 weeks), the dose is tapered to 20 mg/day or less.

Immunosuppressive Agents

Antimetabolites and cytotoxic drugs, broadly classified as immunosuppressive agents, have been used in numerous small clinical trials with variable results. The rationale for use of these drugs is based on both the need for steroid-sparing agents and the poor overall response of most patients to corticosteroids alone.

Azathioprine, typically administered at a dose of 2 to 3 mg/kg, has been used in conjunction with high-dose corticosteroids in several studies. As might be expected, the most favorable responses were noted in subjects with less fibrosis seen on biopsy. Favorable trends were noted in some of the studies, but there is still no clear evidence that this agent benefits patients with IPF. Azathioprine is generally well tolerated. In a few patients, evidence of significant hematologic abnormalities develops; therefore, careful monitoring of blood counts is imperative. A secondary malignancy is also a potential concern for patients.

Cyclophosphamide has also been used extensively in patients with IPF. Although several studies show benefits in isolated pulmonary parameters, others demonstrate no improvement or even a poorer outcome as a consequence of life-threatening infectious sequelae. A randomized, controlled trial of 43 patients with previously untreated IPF showed that the combination of prednisolone with cyclophosphamide was slightly superior to prednisolone alone in improving symptoms. Unfortunately, survival (although better in the cyclophosphamide group) was not significantly improved, and both groups demonstrated high overall mortality. Intermittent intravenous therapy, as biweekly pulses of between 500 and 1800 mg per dose) appears to be as effective as daily oral therapy. The benefits of cyclophosphamide may be attributable to the reduction of lung neutrophilia. With cyclophosphamide, improvement is slow, necessitating a prolonged course of up to 6 months with very careful hematologic monitoring for neutropenia. The risks for hemorrhagic cystitis and secondary malignancy, particularly uroepithelial and hematologic cancers, limit the long-term utility of this therapy. Intravenous administration may result in less bladder toxicity and allow easier monitoring of hematologic parameters. Of some concern is the development of interstitial pneumonitis secondary to cyclophosphamide therapy.

Chlorambucil, at doses between 2 and 6 mg daily, can be used as an alternate to cyclophosphamide in the treatment of IPF. It has the advantages of lower cost and an improved risk-benefit ratio, particularly because of less concern about urinary excretion of active metabolites. Close monitoring of blood counts is still very important. Preliminary studies suggest that the efficacy of chlorambucil is equivalent to that of cyclophosphamide.

Another agent with actions that may complement the effects of corticosteroids is cyclosporine A. This agent is a potent suppressor of T-lymphocyte function, and it could be useful in suppressing the cell-mediated immune responses in IPF. Because there is a high incidence of drug-induced hypertension and nephrologic toxicity associated with cyclosporine, and because there is no consensus regarding its usefulness in IPF, cyclosporine therapy is not standard at this time.

Miscellaneous Other Pharmacotherapeutic Agents

Low-dose oral colchicine is well tolerated, and it has been associated with an improvement in lung function in several small studies and case reports. Colchicine suppresses fibroblast function in vitro. The antimalarial agent chloroquine has also been successful in anecdotal use. D-penicillamine has been used to treat ILD associated with systemic sclerosis, and a small study reported better outcomes for patients with IPF who were taking this agent. Unfortunately, treatment-limiting hematologic toxicity, proteinuria, and dyspepsia are seen in a high percentage of penicillamine-treated patients.

Organ Transplantation

In selected patients with end-stage ILD, unilateral lung transplantation may provide a good functional result and can significantly improve quality of life. In terms of prolonging survival, 45% of IPF patients who receive a single lung are alive for 1 year or longer, and some have survived for up to 4 years after surgery. Unilateral transplant may be superior to total heart-lung transplant in terms of lowered surgical morbidity and mortality. In addition, single-lung transplantation potentially extends the opportunity for lung transplantation to twice the number of recipients. Physiologically, IPF and other restrictive lung diseases are most appropriate for single-lung transplantation. In these diseases, the native lung typically has very low compliance, so that ventilation and perfusion to the transplanted lung are better than in patients with emphysema who receive a single lung.

Monitoring Disease Activity

Because of the high mortality of IPF, survival is the most important marker of treatment success. Nevertheless, pulmonary function test results, bronchoscopic findings, and radiographic studies have a role in monitoring disease progression. In addition, Watters and colleagues have developed a clinical, radiographic, and physiologic (CRP) scoring system that correlates well with both pathologic changes and quality-of-life factors. In pulmonary function studies, a significant decline in D_LCO or FVC is indicative of a poor therapeutic response. The $P(A\text{-}a)O_2$ gradient also can be followed, but this is somewhat variable and may not correlate well with disease progression.

Natural History and Prognosis

Despite optimal therapy, the 5-year survival for IPF remains no better than 50%. Although mean survival is estimated at 4 years, rare patients may persist with end-stage but stable fibrosis for periods of 20 years or more. A favorable response to treatment with corticosteroids is an excellent long-term prognostic factor. Symptoms of 1 year in duration also are associated with a better outcome. Younger age, female sex, less dyspnea, fewer radiographic abnormalities, absence of right-axis deviation on electrocardiogram, and higher arterial PO_2 are other demographic and clinical factors that predict longer survival. The survival of patients with advanced disease or progressive reductions in physiologic tests (³10% in FVC or ³20% in D_LCO) is significantly worse. Cigarette smoking is the only potentially modifiable risk factor. It is associated with a poorer outcome in a dose-dependent manner. Despite the prompt response of some patients to therapy and apparent complete clinical remission, relapse can occur as many as 12 years later.

Respiratory failure from intractable hypoxemia accounts for many deaths in IPF (38.7%); this is frequently associated with the development of an acute pulmonary infection. The development of pulmonary hypertension and cor pulmonale is an indicator of imminent decline; this ultimately occurs in about 70% of patients with IPF. Other causes of death include heart failure, pulmonary embolism, and lung cancer.

Cancer

Bronchogenic cancer develops during the course of illness in approximately 5%–10% of patients with IPF. This represents an excess relative risk for lung cancer of almost 10 in comparison with a similar age- and sex-matched group. This risk ratio may be an underestimate, as many early lung carcinomas may be missed because of the shortened life expectancy of patients with IPF. It has been noted that the excess risk for cancer in male patients with IPF cannot be accounted for by cigarette smoking alone. Adenocarcinoma occurring in the periphery is the most common lesion, although all cell types have been described.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH SYSTEMIC RHEUMATIC DISORDERS

Many types of lung disease are associated with rheumatoid arthritis; the connective tissue disorders, including systemic lupus erythematosus (SLE), Sjögren's syndrome, systemic sclerosis (SSc), and dermatomyositis/polymyositis; mixed connective tissue disease (MCTD); and the seronegative spondyloarthropathies, principally ankylosing spondylitis. Of all the types of respiratory disorders associated with systemic rheumatic disorders, one of the most difficult to diagnose accurately and manage is ILD. Table 4 compares and contrasts IPF with two of the rheumatic diseases most commonly associated with ILD. The true prevalence of ILD in rheumatic disorders is unknown, and estimates vary depending on the diagnostic method used. Plain chest radiographs are least sensitive, whereas pulmonary function tests detect lung disease at an earlier stage. High-resolution CT and BAL detect more subtle abnormalities not identified by other modalities. As in IPF, the gold standard of diagnosis remains histologic examination of an open lung biopsy specimen.

	IPF	RA	SSc
Association with cigarette smoking	+ + +	+ +	–
Symptoms			
Pleurisy	+	+ +	+
Dyspnea	+ + +	+ +	+ + +
Signs			
Clubbing	+ + +	+	–
Nailfold capillary changes	–	–	+ + +
Arthritis	+	+ + +	+
Skin changes	–	+	+ + +
Serologic studies			
Rheumatoid factor	+	+ + +	–
Antinuclear antibodies	+	–	+ + +
Pulmonary function studies			
D_LCO decline	+ + +	+ +	+ +
Lung volume reduction	+ + +	+ +	+ +
Pulmonary radiography			
Fibrosis	+ + +	+ +	+ +
Lung nodules	–	+ +	–
Pleural disease	–	+ + +	–
Response to therapy	poor	fair	poor
Association with pulmonary malignancy	+ +	+	+ +
Survival	poor	fair	poor

IPF, idiopathic pulmonary fibrosis; RA, rheumatoid arthritis; SSc, systemic sclerosis; D_LCO, diffusing capacity of lung for carbon monoxide; +, infrequent or mild; + +, occasional or intermediate; + + +, very common or severe.

TABLE 4. *Comparison of common types of interstitial lung disease: clinical and pathologic manifestations*

Rheumatoid Arthritis

Rheumatoid arthritis is the most common form of inflammatory arthritis, with a worldwide prevalence of 1%. It affects women more frequently than men, in a ratio of 3:1. Rheumatoid arthritis is a symmetric, inflammatory polyarthritis with a myriad of extra-articular features. Pulmonary manifestations range from common pleural effusions to rare bronchiolitis obliterans. The diagnosis of rheumatoid arthritis is based on the characteristic historical feature of morning stiffness, evidence on physical examination of swollen and tender joints, and supportive laboratory data, including a high titer of serum rheumatoid factors and characteristic bone erosion detected by radiograph. The American College of Rheumatology has developed rheumatoid arthritis classification criteria useful in clinical studies. Rheumatoid arthritis causes substantial morbidity, predominantly from progressive joint destruction, that results in a 50% work disability rate after 10 years of active disease. Rheumatoid arthritis also leads to premature mortality, shortening life expectancy by 8 to 13 years on average. Mortality is most often related to infectious illnesses. Rheumatoid arthritis is strongly associated with an increased frequency of the class II major histocompatibility complex (MHC) serotype HLA-DR4, and specific DR4 haplotypes (HLA-DRB1*0401 and *0404) predict more severe rheumatoid arthritis.

Epidemiology

Rheumatoid lung involvement may be manifested by many disease patterns. Although pleuropulmonary disease is seen quite often, ILD may be most common overall, based on series of patients undergoing lung biopsy.

Ellman and Ball were the first to link diffuse pulmonary fibrosis with rheumatoid arthritis. Since that time, numerous case series and several controlled studies have confirmed their observation. Many authors now refer to this entity as *rheumatoid arthritis-associated interstitial lung disease* (*RA-ILD*). The reported prevalence of RA-ILD ranges from 2% to 40% of patients with rheumatoid arthritis. Variability in prevalence relates to different diagnostic modalities used to define this condition. Whereas only about 1%–5% of patients with suspected RA-ILD have abnormalities detected by plain chest radiography, the percentage of affected individuals increases dramatically if diagnosis is established by abnormal pulmonary function studies (about 40%) or abnormal tissue histology (up to 80% of patients).

Prior investigations into risk factors for RA-ILD have yielded disparate results. Although rheumatoid arthritis is three times more common in women than in men, RA-ILD has a stronger male predilection. Traditional measures of severity of rheumatoid arthritis, such as serum rheumatoid factor and subcutaneous nodules, Sjögren's syndrome, antirheumatic therapies, immunogenetic markers of disease severity (HLA-DR4 and HLA-B40), and cigarette smoking, all have been identified as potential predictors of RA-ILD, although other studies have failed to confirm these associations. The two risk factors that have generated the most interest have been cigarette smoking and serum rheumatoid factor. As in IPF, cigarette smoking has a consistently positive association with RA-ILD based on multiple epidemiologic analyses (Fig. 4). A positive correlation between rheumatoid factor titer and abnormal diffusion capacity has also been demonstrated. Cigarette smoking is also associated with elevated serum rheumatoid factor. It is uncertain whether rheumatoid factor plays an independent pathogenic role in RA-ILD or is only an

epiphenomenon. In conjunction with rheumatoid factor, smoking may synergistically contribute to diminished DLCO. Whether cigarette smoking alone is responsible for many of the pulmonary features of rheumatoid arthritis is also a point of contention.

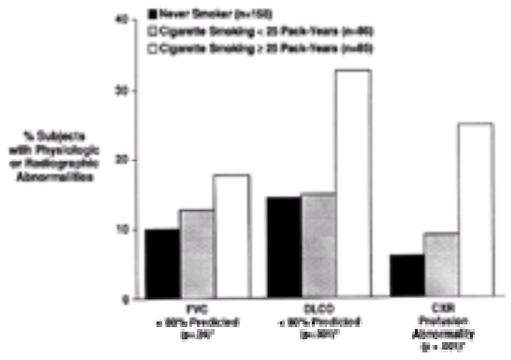

FIG. 4. Bar graph histogram demonstrating the association of cigarette smoking (expressed in pack-years) with abnormalities in pulmonary function studies (diffusion capacity of carbon monoxide [*DLCO*], forced vital capacity [*FVC*]) and chest radiograph (*CXR*) profusion abnormalities (interstitial infiltrates). Values for *p* are for the c^2 trend test. (Reproduced with permission from Saag KG, Kolluri S, Koehnke RK, Georgou TA, Rachow JR, Hunninghake GW, Schwartz DA. Rheumatoid arthritis lung disease; determinants of physiologic and radiologic abnormalities. *Arthritis Rheum* (1996;39:1714. Reproduced with permission.)

Many studies of RA-ILD have selected subjects with known pulmonary symptoms or have utilized control populations of patients without rheumatoid arthritis. Additionally, very few studies have been large enough to estimate with confidence the confounding risks of occupational exposures or infectious agents. Thus, knowledge about risk factors for the development of ILD in rheumatoid arthritis patients is limited.

Clinical Presentation

In all but a few studies, RA-ILD follows the development of joint disease, although the time interval from disease onset to lung involvement is often as short as 5 years. The medical history and physical examination are neither sensitive nor specific for the diagnosis of RA-ILD, but certain clinical features are common. In contrast to patients with IPF, many patients report symptoms of dyspnea or pleuritic chest pain. Clubbing has also been detected in some series, but less often than in IPF and usually later in the course of the disease. Chest crackles are strongly correlated with radiographic changes. Recurrent bronchitis with sputum production may occur in well-established RA-ILD. A surprisingly low percentage of patients with RA-ILD have pulmonary disease-related disability. This may be because physical disability resulting from rheumatoid arthritis limits patients' functional status and precludes exertional activities strenuous enough to produce pulmonary symptoms.

Diagnostic Studies

Physiologic Evaluation

Pulmonary function tests suggest a diagnosis of RA-ILD in a high percentage of clinically significant cases. Abnormality in diffusion capacity is the best predictor of fibrosis on biopsy. Indeed, reductions in diffusion capacity may precede other extra-articular manifestations of rheumatoid arthritis in many patients. Frequently, the coexistence of both restrictive and obstructive airway disease in cigarette smokers with rheumatoid arthritis confounds the interpretation of pulmonary function test abnormalities. In these patients, although both lung volumes and flows may be normalized, DLCO can be markedly reduced. Obstructive changes may also result from coexisting bronchiectasis or bronchiolitis obliterans. Because of the high concurrence of chronic disease-associated anemia, in rheumatoid arthritis it is necessary to adjust the DLCO reading for the hemoglobin level.

Pulmonary Imaging

Characteristic ILD findings are present on chest radiographs in about 12% of patients with rheumatoid arthritis. The plain radiographic appearance is identical to that of IPF except for an increased prevalence of nodules and pleural thickening. High-resolution CT can be used to identify very early evidence of RA-ILD, which may not be visible on plain radiographs. High-resolution CT often reveals fibrotic changes in the periphery, similar to those of IPF, as well as subpleural nodules and cavitations that are unique to RA-ILD. Some patients with rheumatoid arthritis who have abnormalities visible on high-resolution CT but not on plain x-ray films also have physiologic abnormalities. The clinician must be aware that the significance of high-resolution CT abnormalities in asymptomatic patients without other diagnostic abnormalities is unclear from both a therapeutic and prognostic perspective.

Laboratory Studies

No serologic study is sufficiently accurate to assist in the diagnosis of RA-ILD. As noted, serum rheumatoid factor is a strong predictor of RA-ILD, but it is not a good screening test. A study of 600 patients with rheumatoid arthritis and controls identified the ANA as a potential marker of disease.

Bronchoalveolar Lavage and Lung Biopsy

Although BAL is of greater value in excluding infectious and neoplastic causes of ILD, it may provide usefully prognostic information in RA-ILD. Both neutrophilic and lymphocytic alveolitis have been described in the BALF of patients with RA-ILD. As in IPF, elevated lymphocyte counts in BALF occur early in RA-ILD, whereas a neutrophilic predominance is found later in the disease process. Despite the value of BAL, the gold standard in the diagnosis of interstitial fibrosis is histopathologic examination of open lung biopsy specimens. In the absence of nodules that raise the index of suspicion, and because results are unlikely to alter clinical therapy, open lung biopsy is less often performed in RA-ILD than in IPF.

Pathology

The histologic features of RA-ILD are nearly indistinguishable from those of IPF. Biopsies show thickened alveolar septae and in some cases alveolar cell hyperplasia. Lymphocytic infiltration of the alveolar wall and cuboidalization of the type I pneumocytes are also present. Features that help differentiate RA-ILD from IPF include the prominent lymphocytic infiltrates, hyperplasia of lymphoid follicles, and characteristic rheumatoid pulmonary nodules. Rheumatoid nodules in the lung, the only pulmonary lesion specific to rheumatoid arthritis, impart a better prognosis. Disease based in the pleurae is more common in RA-ILD than in IPF and may help further separate the two entities.

Treatment and Prognosis

The treatment of RA-ILD is confounded by the fact that many of the traditional therapies used to manage both the articular and extra-articular manifestations of rheumatoid arthritis may also cause pulmonary toxicity. Intramuscular gold, cyclophosphamide, and methotrexate have all been linked to pneumonitis that may mimic early pulmonary fibrosis. Because methotrexate is currently the most commonly used second-line agent for the treatment of rheumatoid arthritis, pulmonary toxicity attributable to this therapy is of special concern. Unfortunately, there are no pathognomonic findings of methotrexate pneumonitis, and like RA-ILD, it may present with nonspecific bilateral reticulonodular or interstitial infiltrates. In one study, methotrexate did not cause restrictive disease or abnormalities with gas exchange, but instead it was associated with air trapping. Although some studies have suggested that methotrexate, gold, or D-penicillamine may be independent risk factors for RA-ILD, most investigations have failed to substantiate these associations.

Careful monitoring of RA-ILD progression is crucial in guiding therapy, as many potential therapeutic agents may cause significant iatrogenic morbidity. Therapy of early, symptomatic RA-ILD consists of high-dose corticosteroids, usually given as 1 mg of prednisone per kilogram of body weight, or the equivalent. It is important to start corticosteroids early in the inflammatory phase, as more advanced fibrotic disease is steroid-resistant. For RA-ILD that is refractory to corticosteroids or necessitates protracted high-dose therapy, cyclophosphamide, methotrexate, and more recently cyclosporine have been used with anecdotal success.

Survival statistics for RA-ILD are limited. For many individuals with mild disease, the prognosis is better than for IPF. However, among patients with extensive manifestations, the 5-year survival rate for RA-ILD is reported to be as low as 39%. Prognosis is significantly improved if a component of the fibrosis appears to be drug-related. As in IPF, histologic findings of UIP portend a particularly bad prognosis. Likewise, very rare upper lobe fibrosis, akin to ankylosing spondylitis, is also a

poor prognostic factor. Lastly, bronchogenic carcinoma can complicate rheumatoid arthritis. Controversy surrounds the potential independent roles of cigarette smoking, commonly used immunosuppressive agents, and the underlying rheumatoid arthritis disease process in carcinogenesis.

Systemic Lupus Erythematosus

SLE is a heterogeneous multisystem disorder of unknown cause with a predilection for young black and Asian women. SLE is diagnosed on the basis of a constellation of characteristic symptoms, signs, and laboratory abnormalities. Because SLE is a clinical diagnosis and there are no pathognomonic features, SLE is both underdiagnosed and overdiagnosed by many physicians. It is estimated that the average patient with lupus waits for 2 years from the time of symptom onset until a correct diagnosis is achieved. Although some individuals, particularly those with discoid skin lesions, have a milder disease course, organ involvement affecting the kidneys, central nervous system, or respiratory tract is associated with significant morbidity and premature mortality.

Epidemiology

The most common form of lupus lung disease is pleurisy with or without pleural effusions; pleuropulmonary disease has an overall prevalence in SLE of about 70%. In addition, both acute and chronic ILD frequently develops in SLE. In most cases, ILD occurs in patients who have had other serious SLE-associated organ disease, although it may rarely precede the development of frank SLE. Studies that assess the frequency of lupus lung disease are predominantly small, uncontrolled investigations that suffer from referral and selection biases. Clinically significant ILD occurs in 3% of adult patients with SLE. However, physiologic abnormalities are noted in up to 88% of cases.

Several independent reviews have shown that parenchymal lung disease coincides directly with other manifestations of SLE in 20% of cases. In autopsy series of SLE, infection, congestive heart failure, coagulopathy, and O_2 toxicity account for the majority of the pulmonary abnormalities. These studies, however, are potentially limited by the selection of specific subsets of SLE patients likely to undergo autopsy and of those seen in referral centers.

Clinical Presentation

Numerous pulmonary SLE syndromes have been defined that present with clinical parameters suggestive of ILD.

Acute Lupus Pneumonitis

This fulminant process almost always develops in patients with established SLE. Patients are acutely ill, with the rapid development of tachypnea, dyspnea, fever, cough, and occasionally blood-tinged sputum. Physical examination and laboratory studies demonstrate cyanosis and hypoxemia, and chest examination with radiography reveals prominent alveolar consolidation findings. The most important differential diagnostic considerations are elimination of both conventional and atypical infectious etiologies. Of concern, up to 75% of patients with acute lupus pneumonitis have persistent lung dysfunction after resolution of the acute process.

Chronic Interstitial Disease

Chronic ILD may develop independently of acute pneumonitis or as its sequela. Dyspnea both at rest and with mild exertion is the predominant symptom. Cough and pleuritic chest pain each are reported in about two thirds of cases. Unlike IPF, chronic ILD is associated with pleuritis in about 40% of cases. Clubbing of the digits is also considerably less common than in IPF and is perhaps secondary to decreased digital perfusion resulting from Raynaud's phenomenon. Chronic ILD is more common in the subset of SLE patients who display overlapping features of scleroderma, such as edema of the hands and abnormalities of the nailfold capillaries.

Acute Reversible Hypoxemia

A syndrome of reversible hypoxemia has been observed in hospitalized SLE patients that is independent of pulmonary parenchymal infiltrates. This presentation has been attributed to pulmonary leukoaggregation in SLE patients who are acutely ill. These white cell clumps lead to substantial ventilation-perfusion mismatching.

Acute Pulmonary Hemorrhage

The sudden development of severe pulmonary insufficiency coupled with hemoptysis and rapidly progressive infiltrates should raise strong concerns about pulmonary hemorrhage. Pulmonary hemorrhage may complicate acute lupus pneumonitis or can occur independently. Unexpected elevation in D_LCO, blood visualized by bronchoscopy, and hemosiderin-laden macrophages visible on biopsy all support this very serious complication.

Shrinking Lung Syndrome

Shrinking lung syndrome is another type of lupus-associated lung disease that may mimic ILD. Basilar atelectasis is a frequent radiographic finding that can be at least partially attributed to this pathologic process. Shrinking lung syndrome is not an intrinsic pulmonary disorder, but rather is caused by diaphragmatic dysfunction and respiratory muscle weakness that result in restrictive physiologic parameters and an elevated diaphragm. Some lupus patients may also demonstrate decreased respiratory muscle strength in the absence of chest radiographic abnormalities.

Diagnostic Studies

Physiologic Evaluation

Pulmonary function tests are the most sensitive indicators of chronic ILD in SLE. Diminished lung volumes, low diffusion capacity, and abnormal compliance occur in both acute and chronic lupus ILD. In one study, D_LCO was reduced in 72% and lung volumes in 49% of all patients with SLE. Of younger patients with SLE (mean age, 15.5 years), restrictive pulmonary function test defects were found in 35% and diminished D_LCO in 25%. Decreased ability to generate inspiratory and expiratory pressures is observed in patients with diaphragmatic dysfunction. Curiously, in SLE patients without known lung disease, a significant and progressive longitudinal decline occurs in small-airway physiologic parameters but not in lung volumes or D_LCO. These changes are independent of smoking history.

Pulmonary Imaging

Plain radiographic findings are often normal early in the course of chronic lupus ILD. In contrast, in both later stages of chronic lupus ILD and acute lupus pneumonitis, prominent lower lobe infiltrates are present. Chest radiographs show abnormalities in about 30% of chronic ILD cases. As in other forms of ILD, high-resolution CT may noninvasively suggest the diagnosis of lupus ILD. A ground-glass appearance suggestive of more active inflammation has been correlated with a better response to therapy.

Laboratory Studies

ANA is detectable in the sera of 95% of patients with SLE. The most common ANA pattern is diffuse (also called *homogeneous*), but the peripheral (or rim) pattern is more specific. Although higher levels of antibodies to native (double-stranded) DNA and lower serum complement fractions are associated with more aggressive SLE in some patients, similar associations with lung disease have not been substantiated. Based on small series, the presence of antibodies to U1-RNP as well as SSA (Sjögren's syndrome antigen A) appears to be predictive of chronic restrictive lung disease and a decreased D_LCO. Because of very poor specificity, assays for immune complexes are not recommended for either the diagnosis or surveillance of SLE pneumonitis.

Bronchoalveolar Lavage and Lung Biopsy

Particularly with acute infiltrates, BAL is often necessary to exclude infectious causes. Some authors advocate repeated BAL as a measure of response to therapy, but this approach cannot be strongly advocated in SLE, as there is no evidence of improved management or outcome based on BAL findings.

Pathology

Many of the pathologic lesions of SLE lung disease are at least partially attributable to immune complex deposition. In acute pneumonitis, interstitial edema, hyaline membranes, acute alveolitis, arteriolar thrombosis, intra-alveolar hemorrhage, and alveolar cell hyperplasia are all seen on histology. Immune complexes are identified

in alveolar walls, interstitium, and near small vessels.

The pathology of chronic ILD is nearly identical to that of IPF. Chronic inflammatory cell infiltrates and deposition of immunoglobulins and complement are seen in the interstitium. In a large autopsy series, interstitial inflammatory infiltrates and thickening were ubiquitous, but significant fibrotic changes were not found. In this same series, the pattern of alveolar septal loss and panacinar emphysema was similar to the fibrosis of mild SSc. Rarely, lymphocytic interstitial pneumonitis has been seen in SLE. Thorough searches for chronic infectious agents have been consistently unrevealing in both acute and chronic lupus lung disease.

Treatment and Prognosis

After all types of both typical and opportunistic infections have been excluded, treatment of acute lupus pneumonitis begins with O_2 therapy, to correct hypoxemia, and moderate doses of corticosteroids (typically started at 1 mg of methylprednisolone per kilogram per day in divided doses). If pulmonary disease is refractory to this regimen, pulse methylprednisolone at 1 g/d, often for 3 days, has been advocated along with the concomitant use of immunosuppressive agents, such as intravenous cyclophosphamide. Plasmapheresis also has been used in rapidly deteriorating patients with anecdotal success.

The management of chronic ILD is more controversial. Treatment decisions should be geared toward alleviating symptoms, as few data exist to suggest that therapy alters disease progression. Chronic fibrosis indicated by irreversible honeycombing and the absence of inflammatory alveolitis is poorly, if at all, responsive to therapy. Pharmacotherapy should be reserved for patients with some evidence of an active inflammatory disease process, which is more likely to respond to the traditional agents. When treatment is indicated, corticosteroids remain the mainstay of the therapeutic armamentarium. They are usually administered as 40 to 60 mg of prednisone per day, or the equivalent. Steroid-sparing therapy with azathioprine or oral cyclophosphamide should be considered in refractory cases, or when treatment is necessary for a protracted period. Careful monitoring of physiologic studies and chest radiographs provides guidance on response to treatment.

Acute lupus pneumonitis carries a 50% mortality rate. Because improved chemotherapeutic regimens have increased the survival of patients with nonpulmonary manifestations of SLE, the final outcome of patients who have SLE associated with chronic lung disease often depends on the development of pulmonary hypertension and cor pulmonale. Reports of successful heart-lung transplantation in patients who have lupus-associated pulmonary hypertension without pulmonary fibrosis raise the hope that this therapy may be successful in patients with end-stage lupus lung diseases.

Sjögren's Syndrome

Sjögren's syndrome is an autoimmune exocrinopathy defined by the constellation of keratoconjunctivitis sicca and xerostomia. Sjögren's syndrome occurs as both a primary disorder and as a secondary condition in other rheumatologic disorders—most commonly, rheumatoid arthritis, SSc, and SLE. Although most patients with Sjögren's syndrome have symptoms limited to the exocrine glands, a myriad of well-described extraglandular features range from renal tubular acidosis to central nervous system lesions. Although Sjögren's syndrome is typically a benign lymphoproliferative disorder, progression to pseudolymphoma and frank B-cell lymphoma are uncommon but well-described disease transformations.

Epidemiology

The most common pulmonary manifestation of Sjögren's syndrome is desiccation of the airway (xerotrachea), leading to chronic cough and recurrent tracheobronchitis. Other types of pulmonary abnormalities that have been described include obstructive airway disease, lymphocytic interstitial pneumonitis (LIP), chronic interstitial fibrosis, pseudolymphoma, and pulmonary lymphoma. Pulmonary disease of all types occurs in up to 75% of patients with primary Sjögren's syndrome. In one study, significant pulmonary involvement was noted in 9% of 343 patients with Sjögren's syndrome. ILD detected in Sjögren's syndrome may begin as an LIP but can progress to frank pulmonary fibrosis. LIP is seen in about 1% of cases of Sjögren's syndrome, whereas nonlymphocytic ILD is observed in approximately 4% of patients with Sjögren's syndrome. More than half of all patients with Sjögren's syndrome and LIP also have rheumatoid arthritis; therefore, it is hard to know which pathologic process is directly responsible for this pulmonary condition. Not surprisingly, pulmonary involvement is both more common and more severe in secondary rather than in primary Sjögren's syndrome. Smoking is not a proven risk factor for the development of pulmonary disease in Sjogren's syndrome, as it is in RA-ILD and IPF.

Clinical Presentation

Characteristic clinical features of Sjögren's syndrome include sicca symptoms and, less commonly, salivary gland enlargement. Extraglandular tissues that can be involved include those of the central nervous system, gastrointestinal tract (primary biliary cirrhosis), and kidney (type II renal tubular acidosis). In one cross-sectional study, >40% of patients with recently diagnosed Sjögren's syndrome had respiratory symptoms in the absence of physical signs or radiographic evidence of lung disease. Dyspnea on exertion is a common complaint in these patients. Cough and pleuritic chest pain are also reported frequently and correlate with lymphocytosis on BAL. Wheezing is infrequently reported and clubbing is uncommonly seen except in patients in whom end-stage pulmonary fibrosis develops. The initial presentation of pulmonary Sjögren's syndrome may be misdiagnosed as an infectious pneumonia, because of the fevers and pulmonary symptoms and signs noted above. Pneumothorax also has been reported as a complication of LIP.

Diagnostic Studies

Physiologic Evaluation

D_LCO is diminished in about 19%–25% of patients with primary Sjögren's syndrome, often in the absence of radiographic abnormalities. The abnormality of diffusion capacity is more severe if Raynaud's phenomenon is present. Positive findings in biopsy specimens of minor salivary glands are correlated with a reduction in lung function. Although restrictive pulmonary disease patterns are most commonly reported, tests indicative of abnormalities in small-airway function also can be seen in the same patient.

Pulmonary Imaging

Bibasilar interstitial infiltrates are the most common plain radiographic finding of LIP. Nodular chest lesions secondary to atypical lymphoid hyperplasia are seen in the setting of pseudolymphoma. Most nodules are small, peripheral areas of consolidations, frequently containing air bronchograms. Multiple isolated nodules with better-defined margins, a more central location, and mediastinal adenopathy should raise concern of a transformation to a malignant pulmonary lymphoma.

Laboratory Studies

Although a variety of autoantibodies are frequently present in the serum of patients with Sjögren's syndrome, including rheumatoid factor (found in the majority of cases of both primary and secondary), ANA (70% of primary), SSA/Ro (70% of primary), and SSB/La (50% of primary), these serologic markers are generally indicative of nonpulmonary extraglandular disease and have very little bearing on pulmonary manifestations. Elevated levels of b_2-microglobulin are found in patients with lymphoproliferative complications and in subjects with obstructive airway disease.

Bronchoalveolar Lavage and Lung Biopsy

Patients with primary Sjögren's syndrome have a higher percentage of lymphocytes in their BALF than do normal controls, a finding potentially consistent with their underlying disease process.

Pathology

LIP consists mostly of large and small mature B lymphocytes and plasma cells. LIP is analogous to other aspects of Sjögren's syndrome; however, instead of infiltration of exocrine glands, the lungs are invaded by lymphocytes. Prolonged LIP may be complicated by amyloidosis. Pulmonary fibrosis can occur late in LIP, although a lymphocytic predominance may persist.

Lymphoproliferation in Sjögren's syndrome can progress to a pseudolymphoma. Pseudolymphoma is often heralded by a rising IgM level and the presence of germinal centers on lung biopsy. If malignant transformation follows, there is a notable decline in the IgM level, generalized hypogammaglobulinemia, and disappearance of rheumatoid factor. Patients usually have Sjögren's syndrome for 15 years or longer before malignant lymphoproliferation develops. If lymphoma occurs, the lungs are involved in at least 20% of cases.

An additional lymphoproliferative disorder that is included in the differential diagnosis of pulmonary Sjögren's syndrome is lymphomatoid granulomatosis. In this disorder, there is a proliferation of T lymphocytes (rather than the B lymphocytes of Sjögren's syndrome) and lesions exhibit angiodestructive infiltration, with frequent involvement of the upper airways in addition to the lungs. There are rare reports of concurrent lymphomatoid granulomatosis in patients with pre-established Sjögren's syndrome.

Although the cause of Sjögren's syndrome and its pulmonary syndromes are unknown, interesting work has focused on the potential role of viruses, such as the Epstein-Barr virus and retroviruses, as possible etiologic agents. Deposition of circulating immune complexes followed by complement activation appears to account partially for the pulmonary manifestations.

Treatment and Prognosis

Standard treatment of ILD associated with Sjögren's syndrome is not well established. In addition to general supportive measures, corticosteroids are often recommended for treatment of LIP despite an absence of good data to provide clear support for their beneficial use. Chloroquine has also been used successfully in case reports.

Pseudolymphomatous transformation is believed to merit aggressive chemotherapy with combined corticosteroid and alkylating agent regimens (chlorambucil or cyclophosphamide). When feasible, resection of lymphomatous mass lesions affords another therapeutic option.

Systemic Sclerosis

SSc, also called *scleroderma,* is a rare autoimmune disorder characterized by progressive fibrosis of the skin, vasculature, and internal organs. Estimates of the prevalence of SSc range from as few as 2 to as many as 265/100,000 people, and the predominance of women in their 50s is significant. Hidebound skin of the digits and distal extremities is the most characteristic finding of this disorder. Systemic sclerosis is subdivided into diffuse (dSSc) and limited (lSSc) variants. Limited SSc, or CREST (an acronym for *c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasia), has a significantly better short-term prognosis, with a paucity of proximal skin, renal, and intestinal involvement. However, over the long term, the life span of patients with CREST is also reduced, often because of the development of pulmonary hypertension. In the recent past, survival from dSSc was decreased most significantly by hypertensive renal crisis and end-stage renal disease. The advent of angiotensin-converting enzyme inhibitors has revolutionized the modern approach to dSSc and has significantly improved the short-term prognosis. Although pulmonary disease in dSSc is third in frequency, behind skin and gastrointestinal manifestations, it is now the most lethal feature of SSc. Interstitial pulmonary fibrosis remains one of the most difficult-to-manage aspects of this disabling and life-shortening disorder.

Epidemiology

Pulmonary disease is estimated to occur in 70%–85% of patients with SSc. The exact prevalence of lung disease is difficult to determine because of the rarity of SSc, difficulties with characterization of SSc subtypes, and the inaccurate diagnosis of the variable pulmonary pathologies. Although the percentage of ILD in dSSc is much higher, and although most serious end-stage fibrosis occurs in dSSc, ILD is also described in patients with lSSc. Severe restrictive lung disease appears more likely to develop in African-American men with cardiac involvement than in other demographic groups.

Intense interest has focused on potential environmental factors that may predispose to SSc, and such interest has been further increased by the development of scleroderma-like disorders, such as the 1981 toxic oil syndrome and the eosinophilia-myalgia syndrome caused by adulterated L-tryptophan. Of particular interest with respect to lung disease, exposure to silica may increase a person's risk for development of SSc 25- to 100-fold. More recently, attention has focused on the putative role of augmentation mammoplasty and the implantation of silicone elastomers in the development of SSc. Despite numerous associations noted in case reports and series of patients, large epidemiologic studies as yet have failed to confirm a significant association between exposure and disease.

Clinical Presentation

Sclerodermatous skin changes and Raynaud's phenomenon are frequent and striking physical findings that greatly aid in the differential diagnosis. Symptoms of pulmonary disease in SSc include dyspnea on exertion and an occasional dry cough. The presence of abnormal nailfold capillary loops with vessel dropouts, dilations, and severe ectasia help establish the diagnosis of an underlying connective tissue disorder and predict more severe pulmonary disease as manifested by a diminished DLCO. Pulmonary symptoms rarely antedate the skin manifestations of SSc, although cases of scleroderma *sine* scleroderma have been described. Hemoptysis, in some cases secondary to bleeding telangiectases, occurs uncommonly. SSc is associated with the development of significant impairment; the overall work capacity of patients with SSc is only 50% of the predicted normal. Although pulmonary disease contributes to this functional impairment, myocardial ischemia, ventricular arrhythmias, and limitations in locomotor function are also significant cofactors.

Diagnostic Studies

Physiologic Evaluation

Abnormalities in pulmonary function testing are detected in up to 70% of patients with CREST, often in the absence of symptoms or chest radiographic evidence of parenchymal disease. Decline in DLCO is more strongly correlated with abnormalities in nailfold capillaries than are decrements in lung volumes. Although 20% of patients with SSc who are nonsmokers have an isolated reduction in DLCO, they have a good prognosis overall in regard to pulmonary morbidity and mortality. A decline in DLCO in lSSc may be caused by Raynaud's phenomenon of the pulmonary vasculature. An increase in dead space ventilation in various connective tissue diseases associated with Raynaud's phenomenon lends credence to the theory of redistribution of blood flow resulting from pulmonary Raynaud's phenomenon. Whether pulmonary Raynaud's phenomenon coincides with digital Raynaud's phenomenon and how commonly pulmonary Raynaud's phenomenon occurs in SSc are matters of current controversy.

Pulmonary Imaging

In dSSc, diffuse or bibasilar infiltrates are the typical findings. A bibasilar reticulonodular pattern is also seen in cases of lSSc with pathologic evidence of UIP. As in ILD of other causes, the chest radiograph, albeit more specific, is considerably less sensitive for early ILD than are pulmonary function tests.

High-resolution CT has been evaluated as a diagnostic and surveillance tool for ILD in SSc. It is better than plain radiography in detecting interstitial pulmonary abnormalities that may indicate early disease, such as ground-glass opacities, and reticular abnormalities consistent with fibrosis. High-resolution CT showed changes consistent with ILD in 19 of 21 patients with SSc; in comparison, unequivocal ILD abnormalities were revealed by plain chest x-ray films in only 8 subjects. Areas of inflammatory ground-glass appearance on high-resolution CT correlate well with BAL findings of elevated percentages of eosinophils.

Laboratory Studies

ANA is present in the majority of patients with SSc, most commonly in a speckled pattern on immunofluorescence. Two serologic markers are of particular clinical interest in SSc: antibodies to centromere (ACA), detected in about 50%–80% of patients with limited disease, and anti-Scl-70 (an antibody to DNA topisomerase I), seen in one third of patients with diffuse SSc. Although ACA is generally protective for lung involvement, anti-Scl-70 predicts restrictive lung involvement and other ominous visceral disease in many studies. In one study, antihistone antibodies, seen commonly in drug-induced lupus, were predictive of more severe pulmonary fibrosis in SSc.

Bronchoalveolar Lavage and Lung Biopsy

BAL is touted by many as a useful tool for accurately identifying patients with SSc and active alveolitis who may respond to aggressive anti-inflammatory therapy. Neutrophil influx associated with increased collagen production may be an early pathologic finding in SSc-associated pulmonary fibrosis. Collagenase activity is significantly elevated in patients with BAL neutrophilia, suggesting an increased level of matrix turnover. However, a lymphocyte predominance is more frequently seen in many patients, particularly if they have secondary Sjögren's syndrome. Increased ratios of lymphocytes to granulocytes are associated with milder impairment in physiologic parameters.

Pathology

Interstitial fibrosis, bronchiolectasis with cyst formation, and intimal proliferation with medial hypertrophy of small pulmonary vessels are the classic histologic findings of

ILD associated with dSSc. Based on open lung biopsy specimens in which IPF was compared with SSc, endothelial or epithelial injury and focal lymphoid hyperplasia may differentiate SSc from IPF. Raynaud's phenomenon of the lungs may account for some of the changes noted on pulmonary function studies and may play a role in the development of secondary pulmonary hypertension. Both lung fibrosis and vascular hyperplastic changes are common in SSc and may independently contribute to right-sided heart failure. Patients with lSSc can have pathologic features of UIP, particularly those who present with bilateral lower lobe infiltrates.

Treatment and Prognosis

No pharmacologic agent has been identified that is of unequivocal value in modifying the natural course of lung disease in SSc. Notwithstanding, therapeutic interventions may be indicated for severe pulmonary disease if diagnostic evidence of an active inflammatory process is found. For instance, in patients with rapidly declining lung function and an increased proportion of lymphocytes on BAL, high doses of corticosteroids and immunosuppressive therapy are reasonable. This regimen may lead to a decrease in pulmonary inflammation, as assessed by BAL. Based on retrospective data analysis and open-label trials, cyclophosphamide appears to improve FVC over time and should likely be added to corticosteroids in patients with refractory, inflammation-related pulmonary decline. Because of its ability to interrupt molecular cross-linking of collagen, D-penicillamine has been of considerable interest to many investigators as a potential disease-modifying agent in SSc. Despite negative findings in several studies, three small studies support a small but statistically significant benefit for D-penicillamine in treating lung disease. However, the true clinical benefits may be very limited. Further, poor patient tolerance and the hematologic and renal toxicity (of concern in a patient population at already at high risk for kidney disease) associated with D-penicillamine have substantially dampened enthusiasm for its use. A long-term study of high versus low-dose D-penicillamine is currently under way and, it is hoped, may resolve still unanswered questions about its clinical role in SSc-associated lung disease.

Several experimental therapies loom on the horizon. Small, open-label studies of interferon-g (IFN-g) have shown no serious adverse effects from this agent, and in one study patients treated with IFN-g showed mild improvement in some pulmonary parameters. IFN-g cannot be advocated as an effective conventional therapy at this time. In open-label trials and retrospective reviews, potassium *p*-aminobenzoate has been demonstrated to produce modest softening effects in sclerodermatous skin, and in one investigation it resulted in a slower decrease in vital capacity and DLCO.

Based on data from an inception cohort, the estimated 5-year survival rate for all patients with SSc is about 70%. However, the natural history of SSc is highly variable, and a large percentage of patients have a protracted disease course with survival in excess of 20 years. Worsening of ILD in SSc is less rapid than in IPF, and patients with fibrosis secondary to SSc may have a better long-term prognosis than those with other fibrotic lung diseases. Isolated impairment in DLCO (£55% predicted) does not indicate a poor prognosis. Although abnormalities in static lung compliance and diffusing capacity may worsen over time, the lung volumes did not appreciably deteriorate in one large series of untreated patients followed on average for 3 years. Abnormal cardiopulmonary signs and, in particular, severely impaired gas exchange (DLCO 40% of predicted) are associated with significantly worse survival in several series. Patients with long-term SSc tend to have a rate of decline in pulmonary function tests not substantially different from that of the general population, but this could be partially because of a survival bias. Anti SSA/Ro, the autoantibody seen most often in Sjögren's syndrome and potentially predictive of lung disease in SLE, is also a poor pulmonary prognostic marker in SSc based on results from small studies.

Death was caused by pulmonary hypertension in 60% of cases in one of the largest prospective series of patients with both dSSc and lSSc. Although pulmonary hypertension is a more common outcome in lSSc, secondary pulmonary hypertension may develop in patients with dSSc after years of pulmonary fibrosis. For patients with advanced interstitial disease in whom secondary pulmonary hypertension and cor pulmonale develop, long-term O_2 therapy at home may significantly lower pulmonary vascular resistance and improve quality of life and survival. Once cor pulmonale with peripheral edema has developed, the 5-year mortality rate for patients with SSc is 70%. In a subset of patients with severe pulmonary vascular changes, rapidly progressive respiratory failure and severe pulmonary hypertension often develop, and these patients die quickly.

Independently of cigarette smoking but in relation to pulmonary fibrosis, SSc confers an increased risk for lung cancer, with increased risks estimated at 4- to 17-fold. Alveolar cell carcinoma in particular, as well as lymphoma and leukemia, has been reported most commonly. Small-cell carcinoma of the lung in the absence of a history of smoking has also been noted.

Idiopathic Inflammatory Myopathy

The idiopathic inflammatory myopathies (IIM) comprise a group of illnesses including polymyositis (PM), dermatomyositis (DM), and inclusion body myositis. The IIM are rare, with 5 to 10 new cases per million per year in the United States. These related yet distinct disorders all produce nonsuppurative muscle inflammation that leads to weakness and disability. Inclusion body myositis, a disorder of older Caucasian men characterized by both distal and proximal weakness, is the least prevalent of the three condition and seldom has associated respiratory features; it is not discussed further here. Despite differing histopathologic findings and putative immunologic mechanisms, PM and DM have many characteristics in common, including a predilection for the proximal musculature and a spectrum of pulmonary disorders.

Epidemiology

Lung disease of all types occurs in up to 50% of cases of DM/PM. Pulmonary disease in IIM commonly occurs through four processes: (1) aspiration from bulbar weakness, (2) ventilatory insufficiency resulting from myositis of the chest wall and diaphragm, (3) secondary infection, and (4) ILD. The first three entities are discussed in Chapter xx; the remainder of this section focuses on IIM-associated ILD. Either radiographic or physiologic evidence of ILD is estimated to occur in from 5%–30% of large series of IIM. Ethnic and racial variation in prevalence of IIM-associated ILD is uncertain, but in one Japanese series radiographic evidence of ILD was reported in 81% of cases.

Clinical Presentation

Patients with IIM note prominent bilateral proximal weakness that inhibits simple activities of daily living. In patients with DM, a prominent, scaly erythroderma erupts in a v-shaped distribution on the chest and back. Over the knuckles of the proximal interphalangeal and metacarpophalangeal joints of the hands, a scaly rash known as *Gottron's papules* is nearly pathognomonic for DM. A heliotrope rash, a purplish edematous discoloration over the eyelids, is also often noted. Constitutional symptoms of fatigue, fevers, and weight loss are additional harbingers of IIM, and it is difficult to determine whether these are caused by myopathy or pulmonary pathology.

In as many as one third of cases, lung disease antedates muscle involvement or occurs in patients with only minimal myopathy. The antisynthetase syndrome, named for the response to autoantibodies to aminoacyl transfer RNA synthetase (discussed below), is an IIM variant in which seronegative, nonerosive arthritis, fevers, “mechanic's hands,” Raynaud's phenomenon, and ILD can strongly overshadow a mild or even clinically insignificant myopathy. Clubbing is uncommon in IIM-associated ILD but has been reported.

Diagnostic Studies

Physiologic Evaluation

Although ILD associated with IIM frequently causes physiologic abnormalities similar to those of IPF, additional physiologic parameters, such as maximal ventilatory volume (MVV) and inspiratory effort, should be measured. If results of these studies are abnormal, they point toward respiratory muscle weakness as an explanation for at least a component of the pulmonary findings.

Laboratory Studies

At a minimum, minor but usually striking elevations of muscle enzymes such as creatinine kinase and aldolase are almost always present at some point in the disease course of all patients with IIM. Diagnosis of PM/DM is ultimately confirmed based on characteristic abnormalities present on electromyographic recordings and muscle biopsy specimens. Elevations in erythrocyte sedimentation rate nonspecifically mirror changes in disease activity or herald the development of opportunistic infections. The ANA is elevated in a small percentage of cases, often indicative of antisynthetase antibodies. One of the most exciting serologic associations is the established relationship between antisynthetase antibodies and IIM-associated ILD.

Antibodies to histidyl tRNA synthetase, known as *anti-Jo-1,* occur in 25% of patients with DM/PM. Of special interest, this antibody is found in 50% of patients with IIM and concomitant ILD. The presence of this antibody in patients with IIM, therefore, should raise concern for concomitant ILD. Additionally, a small percentage of patients have antibodies to signal recognition protein (SRP), and they are less likely to have ILD. Autoantibodies to other amino tRNA synthetases have also been identified but are less strikingly associated with lung disease.

Bronchoalveolar Lavage and Lung Biopsy

The need for BAL and/or lung biopsy is uncertain. Histopathologic and BAL data may predict therapeutic response, but this has not been shown to significantly alter management or outcome.

Pathology

A mononuclear cell infiltration of the muscle and surrounding tissue with fiber degradation, regeneration, and fibrosis are the major systemic features of PM and DM. Of note, DM is not simply PM with a rash; it is a humorally mediated disease with immune complex deposition in the perimysium and a perivascular vasculitis that is presumed to be responsible for the pathology. PM results from lymphocytic infiltration of the true muscle fibers and is the manifestation of a cell-mediated immune process.

In the lungs, histologic features are typical for interstitial pneumonitis resembling IPF. Investigators have identified three major histopathologic groups for IIM-associated ILD that have prognostic significance: BOOP, UIP, and diffuse alveolar damage (DAD). Patients with BOOP had the best prognosis, while those with DAD fared the worst. A histologic finding seen more commonly in hypersensitivity pneumonitis than in ILD, Masson bodies and intra-alveolar buds are prominent in many cases of IIM-associated ILD. Immune complex deposition in the lungs has not been frequently detected in IIM-associated ILD. Several cases of pulmonary cryoglobulin deposition have been documented.

From a pathogenic perspective, antibodies to Jo-1 have been observed only in patients with myositis. An interesting line of investigation has detected amino acid homology between the Jo-1 antigen and the genomic RNA of certain picornaviruses. The authors speculate that as in pathogenic mechanisms proposed for other autoimmune disorders, such as reactive arthritis, molecular mimicry could lead to tissue damage. Curiously, patients with antisynthetase syndrome (antibodies to Jo-1) typically have an abrupt onset of symptoms in the spring of the year.

Treatment and Prognosis

High-dose corticosteroids, initiated with at least 1 mg of prednisone per kilogram of body weight, or the equivalent, in divided doses, forms the starting point for regimens directed at both the muscle disease and newly diagnosed pulmonary involvement. Methotrexate is a commonly used second-line agent for general manifestations of IIM, and despite its own association with pneumonitis, it is safe to use in IIM-associated ILD. Although some authors question the efficacy of cyclophosphamide in IIM, given its potential value in other types of ILD and anecdotal reports of its success in IIM, it is prudent to consider this agent if the patient is failing with other options. Cyclosporine has also led to improvement in patients with steroid resistant IIM-associated ILD. The effective use of intravenous immunoglobulin for refractory myositis has been reported in several case series and at least one controlled trial. Although study end points included only measures of motor function and no mention was made of lung involvement, given the reasonable safety of this therapy, it should be strongly considered as an early second-line agent.

For many patients, adequate control of muscle inflammation is achieved with anti-inflammatory agents. Notwithstanding, a significant percentage of individuals continue to require a maintenance dose of corticosteroid to avoid relapse. In these patients, sustained morbidity and even mortality may ultimately ensue from the treatment. With respect to IIM-associated ILD, response to corticosteroids and other immunosuppressive agents is variable. Some studies report very disappointing results, with up to 60% mortality despite aggressive therapy. In another series, the 5-year mortality rate for IIM with ILD was 40%. ILD with minimal myopathy is a poor prognostic sign.

An association between IIM and malignancy has been suspected for many years, and well-conducted population-based studies now fully support both a higher incidence of cancer and a higher rate of mortality from cancer. Adenocarcinoma (particularly ovarian cancer) is reported most commonly. Some authorities advocate aggressive cancer screening for all patients with newly diagnosed IIM. Based on the need to consider patient comfort and safety, avoid false-positive results that can occur with excessive testing, and constrain health care costs, we recommend a thorough physical examination (including breast, genital, and rectal examinations) and prudent use of age-appropriate and clinically directed cancer-screening modalities (i.e., Pap test, mammogram, flexible sigmoidoscopy) for all patients with newly diagnosed IIM.

Mixed Connective Tissue Disease

The term *mixed connective tissue disease* (*MCTD*) was coined in 1972 by Sharp to describe a subset of patients with connective tissue disease who have overlapping features of SLE, SSc, and idiopathic inflammatory myopathy. The initial cases described had a set of common clinical and laboratory features that, in addition to pulmonary disease, frequently included erosive inflammatory arthritis with diffuse hand swelling, esophageal dysmotility, myopathy, Raynaud's phenomenon, high-titer speckled ANA, antibodies to U1-RNP, and an absence of antibodies to Smith (Sm) and double-stranded DNA (dsDNA).

Not all experts agree that MCTD merits a separate diagnostic label. Physicians experienced in caring for patients with connective tissue diseases recognize that many patients with the idiopathic inflammatory disorders have variable presentations and often do not present with “classic” features of any one particular diagnostic entity. As such, it has been suggested that the MCTD paradigm is conceptually flawed, as it may not identify a unique patient population, provide direction on specific treatment options, or offer guidance on prognosis.

Epidemiology

Most of the pulmonary reports on MCTD have focused on pulmonary hypertension. However, ILD may be more frequent and severe in MCTD even than in SSc. In one series, 80% of all patients with MCTD had pulmonary disease, and 69% of the asymptomatic patients had pulmonary dysfunction on physiologic tests, chest radiographs, or both.

Clinical Presentation

The most common and worrisome pulmonary feature of MCTD, significant pulmonary hypertension, cannot be accurately predicted based on symptoms, signs, or laboratory data. Pleural effusions, not commonly seen in SSc, may aid in the differential diagnosis. When ILD occurs in MCTD, it mimics that seen in SSc.

As in the other connective tissue disorders, reduction in diffusion capacity is the single most sensitive test to show physiologic dysfunction in MCTD. Despite abnormal physiology, chest radiographs demonstrated identifiable abnormalities in only 21% of cases. A lower lobe predominance has been described most commonly. The features of patients who have SLE with U1-RNP and those of patients with scleroderma overlap; they include edematous hands and nailfold capillary loop abnormalities.

Treatment and Prognosis

Authors report pulmonary improvements in 38%–86% of patients with MCTD who are treated with corticosteroids and/or cyclophosphamide. Patients may have fatal outcomes related to respiratory disease, in part because the disease may not be diagnosed until it is far advanced. Pulmonary outcome is worse if features are more characteristic of SSc.

Seronegative Spondyloarthropathies

This group of heterogeneous disorders includes ankylosing spondylitis, psoriatic arthritis, reactive arthritis (Reiter's syndrome), and arthritis associated with bowel inflammation. Although these conditions are in many ways heterogeneous, they share common features, including inflammatory arthritis of the spine and sacroiliac joints, enthesopathy (inflammation at the insertion of ligaments and tendons into bones), an association with HLA-B27, and a spectrum of similar mucocutaneous lesions. The occurrence of ILD in ankylosing spondylitis is the best described, although similar changes have been reported in psoriatic arthritis with a lower frequency.

Clinical Presentation

Noninfectious fibrobullous disease of the lung upper lobes is nearly pathognomonic for ankylosing spondylitis. The abnormality usually appears late in the disease course and does not correlate with severity of extrapulmonary disease. In a series of 2080 patients with ankylosing spondylitis seen at the Mayo Clinic, the prevalence

was 1.3%.

The pulmonary process often begins unilaterally, with linear opacities on radiographs. As it advances, these changes can be seen in both apices, and bullae gradually develop. In advanced cases, pleural thickening and cavitary disease can occur and are not uncommonly confused with tuberculosis.

Pathology

Specimens show intra-alveolar fibrosis, hyalinized connective tissue, and degeneration of elastic fibrils. Despite extensive investigations, no infectious organism has been identified as an etiologic agent for these lesions.

Treatment and Prognosis

In one large study of 836 patients with ankylosing spondylitis, the number of cases of respiratory disease was 1.5 times higher than expected. Although many of the problems are caused directly by the fibrobullous disease, secondary infection of bullae with bacteria, mycobacteria, or fungi (particularly *Aspergillus*) may lead to considerable morbidity and mortality.

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CHAPTER

19 Immunologically Mediated Lung Diseases

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PULMONARY IMMUNE DEFENSE MECHANISMS

The lungs are defended by a successive series of mechanisms that for the most part prevent deposition of pathogens in the alveoli and eliminate those that do arrive there. The first line of pulmonary defense against infections consists of mechanical impediments to aspiration, such as cough and glottic closure. These mechanisms are largely defeated by tracheal intubation and anesthetics, which in part accounts for the increased risk for pneumonia in critically ill patients.

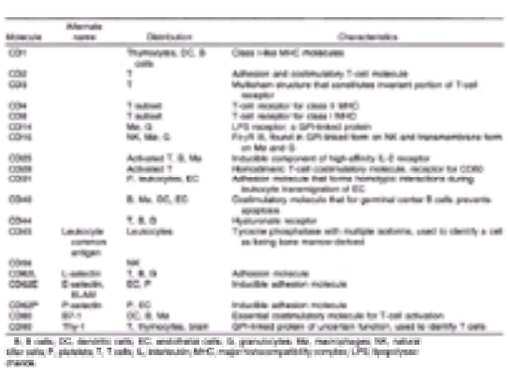
Deposition of airborne particles depends on aerodynamic size (See Chapter 1). Inhaled particles with an aerodynamic diameter than 2 to 5 mm seldom reach the distal air spaces, because they become trapped in the nose or conducting airways. Repeated branching of the airways is another physical facet of lung defense; it induces local turbulence, which causes particles to impinge at branch points. In these sites, particles are trapped in airway mucus and are carried away by normal ciliary motility and the mucociliary escalator. Particles in the 2- to 5-mm size range can remain in inspired air and be deposited in the alveoli. Of course, larger particles may also reach the alveoli when aspirated. Mucociliary clearance does not extend beyond the respiratory bronchioles. Thus, particles that reach the alveoli must be handled by cellular defenses.

Small numbers of pathogens reaching the alveoli can be contained by resident phagocytes without recruitment of bloodborne inflammatory cells. Alveolar lining fluid is also bacteriostatic, in part because of its high concentration of free fatty acids and in part because of the opsonic activity of specific proteins, notably surfactant protein A (SP-A) and immunoglobulins (Ig). Pathogens can at times survive these mechanisms, either because they arrive in large numbers, or because they are intrinsically resistant to elimination by them. In this case, recruitment of bloodborne phagocytes and specific immune responses must be mounted to aid in elimination. Because parenchymal inflammatory and immune responses have considerable potential to interfere with gas exchange, their development is under tight regulation.

Although this chapter focuses largely on the destructive aspects of immune mechanisms, it is important to recall that these potent processes have evolved precisely because they normally prevent pulmonary infection efficiently with minimal impact on the gas exchange function of the lungs. The introductory sections of this chapter detail the cellular and soluble components of pulmonary immune defense, describe the regulation of pulmonary immune response generation, and detail the mechanisms that control the recruitment of activated inflammatory cells to sites of pulmonary inflammation.

Cellular Effectors

The molecules on the surface of human leukocytes are named by a unique cluster of designation (CD) numbers. CD numbers are assigned by an international workshop; as of the Fifth International Workshop on Leukocyte Differentiation Antigens, held in November 1993, 130 CD numbers have been assigned. The characteristics of several important CD molecules are listed in Table 1.



Molecule	Name	Distribution	Characteristics
CD1		Thymocytes, DC, B cells	Class I-like MHC molecules
CD2		T	Adhesion and costimulatory T-cell molecule
CD3		T	Multimeric structure that constitutes invariant portion of T-cell receptor
CD4		T subset	T-cell receptor for class II MHC
CD8		T subset	T-cell receptor for class I MHC
CD14		Mø, G	LPS receptor; a GPI-linked protein
CD16		NK, Mø, G	FcγR III, found in GPI-linked form on NK and transmembrane form on Mø and G
CD25		Activated T, B, Mø	Inducible component of high-affinity IL-2 receptor
CD28		Activated T	Homodimeric T-cell costimulatory molecule; receptor for CD80
CD31		P, leukocytes, EC	Adhesion molecule that forms homotypic interactions during leukocyte transmigration of EC
CD40		B, Mø, DC, EC	Costimulatory molecule that for germinal center B cells prevents apoptosis
CD44		T, B, G	Hyaluronate receptor
CD45	Leukocyte common antigen	Leukocytes	Tyrosine phosphatase with multiple isoforms, used to identify a cell as being bone marrow-derived
CD56		NK	
CD62L	L-selectin	T, B, G	Adhesion molecule
CD62E	E-selectin, ELAM	EC, P	Inducible adhesion molecule
CD62P	P-selectin	P, EC	Inducible adhesion molecule
CD80	B7-1	DC, B, Mø	Essential costimulatory molecule for T-cell activation
CD90	Thy-1	T, thymocytes, brain	GPI-linked protein of uncertain function, used to identify T cells

B, B cells; DC, dendritic cells; EC, endothelial cells; G, granulocytes; Mø, macrophages; NK, natural killer cells; P, platelets; T, T cells; IL, interleukin; MHC, major histocompatibility complex; LPS, lipopolysaccharide.

TABLE 1. *CD number of important molecules*

The predominant phagocyte in the normal alveolar space is the alveolar macrophage (AM). These cells comprise 2%–5% of parenchymal cells in the normal human lung. Most AM are derived from bloodborne monocytes, although local macrophage proliferation may contribute to maintenance of AM numbers in the normal state. The primary function of AM is to ingest and eliminate foreign materials entering the alveoli. States in which AM are overwhelmed by substances that have undergone phagocytosis, as in silicosis or alveolar cell proteinosis, are characterized by increased susceptibility to opportunistic infections. AM avidly bind particles opsonized by IgG or complement because of their high-density surface expression of three classes of Fc receptors (FcR) and of two classes of complement receptors (CR1 and

CR3). However, to combat certain intracellular pathogens successfully, notably *Mycobacterium tuberculosis,* AM must be activated by lymphocyte-derived cytokines, such as interferon-g (IFN-g) or granulocyte-monocyte colony-stimulating factor (GM-CSF). Absence of these activating signals appears to be the principal cause of the increased susceptibility to opportunistic infections in AIDS. Activated AM secrete a wide variety of important enzymes, cytokines, and other mediators (e.g., complement components C1q, C2, C3, and C5) that are essential for clearance of opsonized organisms and immune complexes. Alternatively, AM can be induced (by signals that are currently uncertain) to differentiate along an alternative pathway with chiefly secretory activity. Secretory AM produce platelet-derived growth factor (PDGF), fibronectin, and insulin-like growth factor-1 (IGF-1). These factors probably are important in repair of lung injury as in wound repair elsewhere in the body, but they also may contribute to lung fibrosis by stimulating fibroblast recruitment and survival and collagen secretion. In addition to AM, the normal lungs contain interstitial macrophages. It is uncertain whether these cells, far less well characterized than AM, are an independent cell type or an intermediary stage between monocytes and AM.

Dendritic cells are the primary antigen-presenting cell in the airways and lung parenchyma. Dendritic cells are a type of bone marrow-derived cell unrelated to monocytes and macrophages. Antigen exposure induces large numbers of dendritic cells to be recruited to the airway epithelium. Dendritic cells carry antigens back to regional lymph nodes, where the dendritic cells bind to and potently activate naïve T cells. Hence, there is considerable experimental interest in manipulating dendritic cell numbers and function to control asthma and to facilitate protective immunization. Two types of dendritic cell are found in the lungs and in T-cell zones of lymph nodes: Langerhans cells (which express CD1 and contain Birbeck granules) and interdigitating or lymphoid dendritic cells (which do not express CD1 or contain Birbeck granules). Whether Langerhans cells and interdigitating dendritic cells are distinct cell types or different stages of the same lineage is unclear. Langerhans cells are increased in the bronchoalveolar lavage fluid (BALF) of smokers and are prominent in the lesions of eosinophilic granuloma. Demonstration of increased numbers of cells that are $CD1^+$ (by immunofluorescence) or that contain Birbeck granules (by electron microscopy) in BALF supports a diagnosis of eosinophilic granuloma. A third type of dendritic cells, follicular dendritic cells, is found within the lungs only in the B-cell zones of organized lymphoid tissue. The origin of follicular dendritic cells and their relationship to other dendritic cells are uncertain. Follicular dendritic cells retain immune complexes on their surfaces for prolonged periods, and therefore provide one explanation for the remarkable persistence of immune memory at sites of previous antigenic stimulation within the lungs.

Lymphocytes are crucial for the generation and regulation of all specific immune responses. Lymphocytes are divided into three major lineages: T cells, B cells, and natural killer (NK) cells. They are found in the normal lung in the following ratios: T cells, 70%–80%; B cells, 10%; NK cells, 10%.

T cells are central to the generation of protective and destructive immune response by their secretion of immunoregulatory cytokines; additionally, some are cytotoxic T lymphocytes (CTL). T cells are identified by surface expression of CD2, CD3, or Thy-1 (CD90). Almost all human T cells express either CD4 or CD8 surface receptors, which determine the class of major histocompatibility complex (MHC) molecules to which the T cell responds. $CD4^+$ T cells primarily induce ("help") both antibody production by B cells and maturation of $CD8^+$ CTL. A small group of $CD4^+$ function as class II-restricted CTL. $CD8^+$ T cells either mediate cytotoxicity or suppress other immune effector cells. Both $CD4^+$ T cells and $CD8^+$ T cells secrete cytokines, as discussed below.

Regardless of whether they express CD4 or CD8, mature T cells express a heterodimeric T-cell antigen receptor (TCR). In the vast majority, this TCR is composed of ab chains; these cells mediate virtually all the functions conventionally associated with T lymphocytes. The minority of T cells, which have gd variable chains, have been suggested to provide immune surveillance of mucosal surfaces. In some anatomic sites (e.g., skin and female urogenital tract), gd T cells exhibit very limited junctional diversity, suggesting that they should recognize a very restricted antigen repertoire. However, restricted diversity is not the case for lung gd T cells in the lungs. Despite the fact that gd TCR^+ cells have been isolated from the lungs or pleural spaces of humans and experimental animals, especially during the primary response to mycobacteria, most T cells in normal lung, in pulmonary granulomas, or adjacent to pulmonary tumors bear ab TCR.

B cells produce antibody when activated, secrete some cytokines, and serve as antigen-presenting cells for memory T cells. Initial B-cell activation leads to IgM secretion, whereas secretion of other Ig isotypes requires T cell-derived cytokines, which induce class switching of B cell Ig genes. B cells are identified by expression of surface Ig or B220 (a subspecies of CD45).

Most immunologists recognize NK cells as a separate lineage of lymphocytes, although the relationship of natural killer cells (NK) to lymphokine-activated killer (LAK) cells induced by high dose treatment with interleukin-2 (IL-2) remains controversial. NK cells require no prior activation or immunization to mediate their functions, which include cytotoxicity and cytokine production. Thus, NK cells are an important component of the innate immune system discussed below (see Innate Versus Specific Immunity). Human NK cells can be identified by surface expression of CD16 and CD56. How NK cells recognize their targets, tumors, and possibly other dividing cells, as well as some pathogens, is not understood. Within the lungs, NK cells are found primarily in the interstitium and are poorly represented in BALF. Some investigators have detected very little functional activity of human pulmonary NK cells, possibly because of the suppressive effects of AM and surfactant. NK cell deficiency is an extremely rare condition manifested by life-threatening relapsing herpesvirus and polymicrobial infections.

Neutrophils are rarely found in the alveoli or interstitium of normal subjects. However, the normal pulmonary vasculature contains a large population of neutrophils, which, because of their size, pass through alveolar capillaries much more slowly than do erythrocytes. In response to chemoattractants such as C5a, bacterial products such as lipopolysaccharide or formylmethionine-containing peptides, platelet-activating factor (PAF), leukotriene B_4 (LTB_4), or IL-8, these intravascular neutrophils are readily activated and recruited into the lung parenchyma. During transmigration, activated neutrophils can release three types of products destructive to lung parenchyma: reactive oxygen products, proteolytic enzymes, and products of lipid peroxidation. The reactive oxygen products of the respiratory burst (superoxide, hydrogen peroxide, hydroxyl radicals, and hypochlorous acid) react with essentially all cellular components, causing denaturation and cross-linkage of proteins, changes in the permeability of plasma membranes and cellular organelles, and base modifications or strand breakage in nucleic acids. Proteolytic enzymes such as elastase and metalloproteinases released from neutrophil granules can digest all components of the lung interstitium. Neutrophil oxidants act synergistically with these enzymes to cause local tissue damage; hypochlorous acid inactivates the proteolytic inhibitors (including a_1-antitryptase) that would otherwise check the action of neutrophil elastase. Oxidants are also essential for activation of neutrophil collagenase. Finally, lipid peroxidation products, especially LTB_4 and PAF, cause changes in vascular permeability and are chemotactic for neutrophils, eosinophils, and lymphocytes. For these reasons, it should not be surprising that the presence of increased numbers of neutrophils in BALF correlates with a poor prognosis in pulmonary fibrosis. Nevertheless, neutrophils are clearly important in clearance of certain pathogens from the alveoli (to a larger degree than previously recognized) and can also carry particles to regional lymph nodes for initiation of specific immune responses.

Eosinophils are a second type of granulocyte possessing considerable potential for tissue destruction via release of their granular proteins: major basic protein (MBP), eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin. MPB can damage epithelial cells directly; it also activates basophils, mast cells, neutrophils, and platelets. Major basic protein (MBP) may also increase airways hyperresponsiveness by blocking inhibitory M2 cholinergic receptors. Eosinophil degranulation is not inhibited by glucocorticoids.

Mast cells are increasingly recognized as integral components in the pulmonary immune response to various stimuli in addition to IgE. For instance, degranulation of mast cells can be triggered by complement fragments (C3a or C5a), eosinophil MBP, or substance P. On degranulation, mast cells liberate large quantities of LTB_4 and LTC_4, as well as prostaglandin D_2 (PGD_2) and PAF. These substances are potently chemotactic for inflammatory cells, and may increase the accessibility to the lung parenchyma of serum proteins such as immunoglobulins and complement components. Mast cells produce a spectrum of cytokines (IL-3, IL-4, IL-5, GM-CSF) similar to that of Th2 T cells (described below). Mast cell proteases, which constitute 20% of the cellular weight, can activate the Hageman factor-dependent pathways linking the complement, fibrinolytic, and kinin pathways. Additionally, cultured murine mast cells induce fibroblast proliferation in vitro through secretion of an uncharacterized soluble factor. Together with the observation of large numbers of mast cells in the lungs in idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis, these findings suggest that mast cells may be important in the generation of pulmonary fibrosis.

Type II alveolar epithelial cells are known chiefly for their capacity to secrete surfactant and to serve as a regenerative source for epithelium in the damaged lungs. However, based on recent studies showing their capacity to express class II MHC molecules and to elaborate IFN-g and GM-CSF, type II cells should also be considered as important components in pulmonary host defense.

Humoral Aspects of Pulmonary Host Defense

The humoral elements, including Ig and complement cascade components, are the early warning system of the respiratory tract against inhaled and aspirated pathogens. Ig and complement components opsonize pathogens, identifying them as foreign and facilitating their ingestion. Both of these humoral elements can directly lyse some pathogens (certain viruses by immunoglobulins, many bacteria by complement components). Products of complement activation are also chemotactic for phagocytic cells.

All the major Ig isotypes have been identified in bronchial secretions, although IgM and IgE are present in only minute quantities. IgA predominates in the upper and proximal airways. Most IgA appear to be secreted locally; at least 90% is dimeric (secretory) IgA linked by the J components. IgA is not an opsonin and does not activate complement. Instead, it blocks attachment of potentially pathogenic bacteria.

The concentration of IgG rises progressively in the lower respiratory tract until it predominates over IgA in BALF. IgG probably enters the lungs largely by transudation from the serum in normal hosts, whereas the increased relative amounts of IgG in the lower respiratory tracts of smokers may come from local secretion. The major

known role of IgG is complement-independent neutralization of viruses. IgG, especially of subclasses IgG_1 and IgG_3, efficiently opsonizes a variety of pathogens. AM have subclass-specific Fc receptors for IgG_1 and IgG_3. IgG_4, which does not fix complement and for which macrophages do not have Fc receptors, functions largely as a reaginic or cytophilic antibody that counteracts IgE by sterically hindering its binding to its cell-surface receptors.

Experimentally, antibody-secreting cells have been observed to persist within lung parenchyma for years after local antigenic stimulation. Deficiencies of IgG and especially of subgroups IgG_2 and IgG_4 are associated with chronic sinopulmonary infections. Although panhypogammaglobulinemia usually causes devastating immunodeficiency, the infections associated with IgG subclass deficiencies may be subtle and largely limited to the lungs. In cystic fibrosis, hydrolysis of alveolar IgG with removal of the Fc fragment by pseudomonal metalloproteinase may lead to impaired opsonization.

The complement system is analogous to the clotting or kinin pathways in its sequential activation of proteolytic factors that in turn activate the next downstream component. The central factor in the complement system is C3, which can be activated by either of two major pathways (Fig. 1). The classic pathway is usually activated by antigen-antibody complexes (immune complexes). Binding of the Fab portion of an antibody molecule activates the Fc portion, which is then capable of binding and activating the first three components of the classic pathway: C1q, C1s, and C1r. The proteolytic portion of this interaction, activated C1s, cleaves its targets C2 and C4 into an active complex (C4b,2a), called *classic C3 convertase.* By contrast, the more phylogenetically ancient alternative complement pathway is activated directly by complex polysaccharides such as fungal zymosan and bacterial lipopolysaccharide, leading to production of alternative C3 convertase (C3b,Bb). Both pathways converge to cleave C3 into C3b, which in turn activates the alternative pathway in a positive feedback loop to produce more C3 convertase. Consequently, the complement system can rapidly deposit large amounts of C3 on targets. Both of these convertases can also activate C5 to produce a cytotoxic terminal attack complex consisting of C5b,6,7,8,9. This sequential family of enzymes, each activating the next, provides for powerful amplification of inflammatory signals.

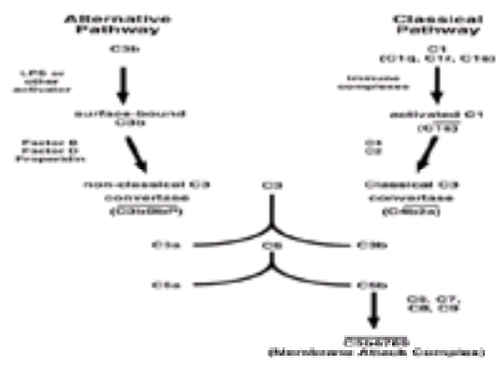


FIG. 1. Complement pathways. See text for explanation.

Proteolytic cleavage of C4, C3, and C5 produces high-molecular-weight fragments (C4b, C3b, and C5b), which attach to the target, and diffusible low-molecular-weight fragments or anaphylatoxins (C4a, C3a, and C5a), which mediate inflammation. Anaphylatoxins increase vascular permeability, induce contraction of smooth muscles, including those of the bronchi, and induce noncytotoxic release of histamine from mast cells and basophils.

Complement contributes to host defense against some pulmonary infections. Experimentally, mice depleted of complement by cobra venom factor have impaired clearance of *Streptococcus pneumoniae* or *Pseudomonas aeruginosa,* but not of *Klebsiella pneumoniae* or *Staphylococcus aureus.* Normal function of the classic complement pathway appears essential for clearance of immune complexes from the bloodstream, and patients with inherited deficiencies of C2 or C4 are at markedly increased risk for development of systemic lupus erythematosus. Massive activation of the complement system in gram-negative and gram-positive bacteremias may be one factor that mediates lung injury in the sepsis syndrome.

Because of its immense potential to destroy host tissues, the complement system is tightly regulated by a series of related plasma and membrane glycoproteins, called the *regulators of complement activation* (*RCA*) *cluster.* The RCA cluster comprises six proteins: decay accelerating factor (DAF, CD55), complement receptors type 1 (CR1, CD35) and type 2 (CR2, CD21), C4-binding protein (C4-bp), factor H, and membrane cofactor protein (CD46). The genes for all six are tightly clustered on the long arm of chromosome 1. RCA proteins regulate complement activation by interacting with C3b and C4b bound to targets or as part of C3 convertases via either of two mechanisms. The first mechanism is decay accelerating activity, by which the protease component of the C3 convertase (C2a or Bb) is cleaved from C4b or C3b, respectively. The second regulatory mechanism is cofactor activity, by which a cofactor protein binds to the C3b or C4b, rendering it susceptible to degradation by a plasma serine protease, factor I. There are additionally complement regulatory proteins outside the RCA. The serum protein C1 inhibitor antagonizes complement activation by releasing C1r and C1s from C1q, thereby blocking the classic pathway. Deficiency of C1 inhibitor causes angioedema. Mammalian membranes also possess an inhibitor of C8 binding, CD59, which prevents insertion of the membrane attack complex.

Cytokines in Immune Lung Defense and Disease

Cytokines are low-molecular-weight peptides (usually 20 kDa) that mediate intracellular communication and regulate cellular homeostasis, inflammation, and repair. Because they were originally identified through their production by and action on leukocytes, several cytokines have been termed *interleukins* (*IL*). However, it is now recognized that many cytokines can be produced by pulmonary interstitial and parenchymal cells, indicating that these cells can participate actively in both defense and immune injury of the lungs.

As of 1996, there are 17 commonly accepted interleukins (IL-1 through IL-17). For a peptide mediator to be recognized as an interleukin, it must have been molecularly cloned. This requirement prevents the previous confusion in which the same substance was referred to by multiple names based on bioassays (e.g., T-cell growth factor for IL-2). For purely historical reasons, such important, well-characterized cytokines as tumor necrosis factor-a (TNF-a), transforming growth factor-b (TGF-b), and IFN-g have not been assigned numbers as interleukins.

Most cytokines may have both stimulatory or inhibitory actions, depending on the cellular target and the concurrent actions of other cytokines. Attempting to explain the complexity of these interactions, Kunkel and associates have advanced the concept of cytokine networking, which highlights the dependence of cytokine secretion by certain cell types on more proximal cytokines (e.g., dependence of secretion of IL-8 by pulmonary fibroblasts on macrophage-derived IL-1 or TNF). Sporn and Roberts have likened the complex interplay of cytokines to a cellular signaling language, suggesting that the ultimate response of a target cell is determined by a number of different messages received concurrently at the cell surface. It is likely that individual immunologic lung diseases are not caused by deficiencies or excessive activities of single cytokines, but rather by the net effect of inflammatory and anti-inflammatory cytokines and other mediators.

Although most cytokines are produced by and affect a broad range of cell types, it is conceptually useful to divide these cytokines into three broad groups: inflammatory cytokines, lymphokines, and chemokines. The biochemical attributes of several important cytokines are summarized in Table 2.

Cytokine	M[a]	Structure	Source[b]	Target
Monokines				
IL-1	17.5	Monomer	Ma/M (E, F)	B, E, F, H, N, T
TNF-α	17	Homotrimer	Ma/M (F, T)	E, F, H, Ma/M, N
IL-6	23–30	Monomer (multiple isoforms)	Ma/M (E, F, T)	B, E, F, H, T
IL-12	35, 40	Heterodimer	Ma/M	T, NK
Lymphokines				
IL-2	15–17	Monomer	T	B, T, Ma/M
IL-3	20–26	Monomer	T	MC, N (other hematopoietic)
IL-4	20	Monomer	T, MC	B, T
IL-5	22	Homodimer	T, MC	B, Eo
IL-10	18	Homodimer	B, Ma/M, T	
IFN-γ	20–24	Heterodimer	T	B, Eo
GM-CSF	14–35	Monomer	T (E, F, M)	Eo, MC, Ma/M, N
Chemokines				
IL-8	6.5	Monomer	Ma/M, N (E, F, H)	N, T

IL, interleukin; TNF-α, tumor necrosis factor-α; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; B, B lymphocyte; E, endothelial cell; Eo, eosinophil; F, fibroblast; H, hepatocyte; M, monocyte; Ma, macrophage; MC, mast cell; N, neutrophil; NK, natural killer cell; P, platelet; SM, smooth muscle cell; T, T lymphocyte.

[a] Relative molecular weight of subunits (kilodaltons).

[b] Major source of cytokine (minor sources in parentheses).

TABLE 2. *Biochemical attributes of cytokines*

Inflammatory cytokines, which have both paracrine and endocrine effects, are secreted principally by monocytes/macrophages and by parenchymal cells. This group of cytokines consists of IL-1, TNF, IL-6, and IL-12, all of which have broad ranges of cellular targets. There are two varieties of IL-1, products of distinct genes: IL-1a, produced primarily as a cell-associated protein by endothelial cells, and IL-1-b, primarily a secreted protein. Although sharing only 26% homology at the amino acid level, these peptides interact with the same receptor with identical activities. IL-1 is secreted by macrophages in response to bacterial products and to phagocytosis of other particles. In response to macrophage-derived IL-1, endothelial cells and fibroblasts elaborate additional IL-1, thereby amplifying the inflammatory response. IL-1 induces endothelial cell expression of adhesion molecules and is chemotactic for lymphocytes. Prolonged local secretion of IL-1 is central to granuloma formation, especially in sarcoidosis. IL-1 is important as a competence factor for lymphocytes and as an inducer of angiogenesis and fibrosis. Distant effects of IL-1 include fever, anorexia, somnolence, leukocytosis, and decreased pain perception. A very important recent observation is the dynamic interplay between IL-1 and IL-1 receptor antagonist protein (IRAP), a pure receptor antagonist that blocks all effects of IL-1.

TNF-a (also called *cachectin*), also secreted in response to lipopolysaccharide and probably other pathogenic products, mediates most of the toxic effects of the sepsis syndrome. Of course, TNF also has a protective role, as it is chemotactic for inflammatory cells and activates neutrophils and endothelial cells. TNF-a appears to play a crucial role in the chronic interstitial pneumonitis associated with graft-versus-host disease and in experimental immune complex disease. TNF-b (also called *lymphotoxin*), a related protein, is secreted by cytotoxic lymphocytes. Although only 30% homologous to TNF-a, lymphotoxin binds to the same receptor and causes a similar range of effects.

IL-6 is a multifunctional mediator produced by a wide variety of cell types (including T cells, AM, mast cells, endothelial cells, and fibroblasts) in response to IL-1 and TNF-a. IL-6 has both local and systemic actions, with many of its effects overlapping or synergizing with those of IL-1 and tumor necrosis factor (TNF). For example, IL-6 is the major inducer of hepatic acute-phase reactants and is itself an endogenous pyrogen. It also induces terminal differentiation of B cells and T cells. IL-6 stimulates hematopoiesis by synergizing with IL-3 to induce stem cells to enter the cell cycle. IL-6 was originally described as IFN-b_2, but is now known to be unrelated to the other interferons.

IL-12 is a heterodimeric protein produced primarily by phagocytes in response to bacterial products and to a lesser degree by B cells and connective tissue mast cells. IL-12 acts as a growth factor for activated NK cells and T cells. It importantly pushes the balance of immune responses toward cell-mediated immunity by upregulation of IFN-g.

Lymphokines, secreted primarily by lymphocytes, have complex regulatory actions that account for many of the differences between nonspecific inflammation and specific immune responses. This group consists of IL-2, IL-3, the various colony-stimulating factors (of which only GM-CSF is considered here), IFN-g, IL-4, and IL-5. Lymphocytes are also potent secretors of IL-6 and have the capacity to elaborate TNF-a and TNF-b.

IL-2 is an essential growth factor for most T cells and some B cells. IL-2 also increases the cytotoxic activity of monocytes and macrophages, and, at least in pharmacologic dosages, results in endothelial cell damage. Local secretion of IL-2 within the lungs is especially prominent in active pulmonary sarcoidosis.

IL-3 is a growth factor for precursors of multiple hematopoietic lineages and for mast cells. It also may regulate the function of mature monocytes and eosinophils. Granulocyte-monocyte colony-stimulating factor (GM-CSF), in addition to stimulating the growth of granulocyte and monocyte precursors, potentiates microbial killing and production of IL-1 and TNF-a by mature macrophages, neutrophils, and eosinophils. GM-CSF potently inhibits neutrophil migration, immobilizing neutrophils at sites of inflammation. GM-CSF also increases phagocyte longevity at sites of inflammation by blocking apoptotic cell death.

IL-4 and IL-5, typically secreted together by both $CD4^+$ T cells and mast cells, regulate allergic responses by affecting multiple cell types. IL-4 is required for the generation of both primary and secondary IgE responses. Many actions of IL-4 antagonize those of IFN-g, although both IL-4 and IFN-g induce class II major histocompatibility complex (MHC) expression. Both IL-4 and IL-5 are growth and differentiation factors for B cells and T cells. IL-5 is chemotactic for eosinophils. IL-5 also supports the growth and differentiation of eosinophils and lengthens their survival in tissues by preventing their elimination by apoptosis. IL-5 further acts on basophils to increase their release of histamine and leukotrienes.

IFN-g is perhaps best known as the major macrophage-activating factor; it increases AM expression of Fc receptors and phagocytic capacity. IFN-g also increases the adhesiveness of endothelial cells for lymphocytes and induces expression of class II MHC molecules on macrophages and endothelial cells, permitting them to become antigen-presenting cells. IFN-g antagonizes the isotype-regulating actions of IL-4 and IL-5 on B cells. Additionally, IFN-g is a growth factor for fibroblasts, suggesting that it may be important in both normal wound repair and in fibrosis. Because steroids inhibit the release of IFN-g *in vitro,* one of their important therapeutic actions infibrotic lung diseases may be to inhibit fibroblast proliferation.

IL-10 is a 178-amino acid glycoprotein (expressed as noncovalently linked homodimers) that appears to be a natural brake on immune responses. IL-10 was initially identified as a T-cell product that suppressed production of other T-cell cytokines, especially IFN-g and IL-3. Subsequently, other cell types, including AM, have been shown to produce IL-10. IL-10 decreases production of TNF-a, IL-12, and the chemokines MIP-1a and MIP-2 (discussed below). IL-10 also decreases expression of class II MHC, of the adhesion molecules ICAM and VCAM, and of the co-stimulatory molecule B7-1 (CD80) on several types of antigen-presenting cells. IL-10 inhibits T-cell proliferation in vitro both by these effects and by directly inhibiting IL-2 mRNA elaboration.

A major conceptual breakthrough in understanding immunoregulation is the observation that $CD4^+$ T cells can be divided into at least two mutually exclusive subsets, Th1 and Th2, based on the range of lymphokines they secrete. Th1 cells produce IL-2 and IFN-g, whereas Th2 cells produce IL-4, IL-5, and IL-10; both subsets can produce IL-3, GM-CSF, and TNF. These two subsets differ in function: Th1 cells mediate delayed-type hypersensitivity reactions, activate macrophages for microbicidal functions, and induce IgG_1 and IgG_{22}, whereas Th2 cells provide superior help for antibody responses and induce IgG_4 and IgE. The two subsets are also mutually inhibitory. IFN-g (produced by Th1 cells) inhibits growth of Th2 cells, whereas IL-10 (produced by Th2 cells) inhibits cytokine secretion by Th1 cells. $CD8^+$ T cells principally secrete a Th1-like spectrum of cytokines, although examples of Th2-producing CD8 clones exist.

In some cases, the cytokine profile and hence the nature of the host response appears to be directed into one of two mutually exclusive patterns, namely, Th1-predominant delayed-type hypersensitivity responses or Th2-predominant antibody-forming responses. The classification of $CD4^+$ T cell clones into Th1 and Th2 subsets is well established in mice, in which strain differences in the balance between these two subsets lead to either fatal infection or protective immunity for several different pathogens. The classification also appears to pertain to humans. Whether dysregulation of the balance between these cross-regulatory T-cell subsets underlies any immunologic lung diseases, especially asthma, is a matter of active study. Th2 cells may play an important regulatory role in normal immune responses by limiting the tissue-damaging effects inherent in responses of Th1 cells and activated macrophages.

Chemokines form a large supergene family of small cytokines that possess important chemotactic, activating, and angiogenesis-influencing properties. Cross-linkage of internal cysteine residues is believed to render chemokines highly resistant to proteolytic degradation. Based on the position of the terminal four cysteine (C) residues, two major subfamilies of chemokines are distinguished: C-X-C (a) chemokines have an amino acid between the two cysteine residues, whereas C-C (b) chemokines do not. Distinction of these two subfamilies is important, as they differ in target specificity. C-X-C chemokines are predominantly chemotactic for granulocytes, whereas C-C chemokines are chemotactic for mononuclear cells. Both C-X-C and C-C chemokines can be elaborated by a wide variety of cell types, although there is a degree of stimulus specificity for their production. Recent evidence indicates that chemokines play a variety of roles other than leukocyte chemotaxis. For example, individual chemokines can promote or inhibit the proliferation of blood vessels during wound repair or tumor growth. One receptor for C-C chemokines, CC-CKR-5, was very recently identified as a cofactor in entry of wild-type HIV into cells.

IL-8 is the prototypic C-X-C chemokine. IL-8 is very potently chemotactic for neutrophils; some investigators have also suggested it is chemotactic for lymphocytes. IL-8 is a major cause of neutrophil recruitment in cystic fibrosis, bronchiectasis, chronic bronchitis, and empyema. Interestingly, elaboration of IL-8 is induced in pulmonary epithelial cells by neutrophil elastase and in mesothelial cells by asbestos. Signal transduction of IL-8, like that of other chemotactic stimuli such as f-MLP and C5a, occurs via GTP-binding proteins and activation of phosphatidylinositol-specific phospholipase C. Other C-X-C chemokines include ENA-78, *gro*-a, IP-10, MIP-2, and PF4.

Monocyte chemotactic peptide-1 (MCP-1) is the prototypic C-C chemokine. MCP-1 is a 13-kDa glycosylated, heparin-binding protein produced by AM, fibroblasts, and pulmonary epithelial and endothelial cells. It is chemotactic in vitro for T cells and monocytes. MCP-1 is induced by lipopolysaccharide (LPS), IL-1, TNF-a, IL-4, IFN-g, TGF-b, and PDGF. MCP-1 plays a crucial role in host defense against gram-negative organisms. Other C-C chemokines include MCP-2, MCP-3, RANTES, MIP-1a, and MIP-1b.

Innate Versus Specific Immunity

Recognition of infectious agents, especially bacteria, elicits a rapid and vigorous response of neutrophils and monocytes. This initial response does not depend on prior immunization, as does the specific immune response. Instead, this innate or natural immune response relies on a phylogenetically more primitive system that recognizes danger signals found on pathogens but not on mammalian cells. Examples of such danger signals are repeated polysaccharides, mannan, LPS, or

formylated peptides. Recognition of such signals mobilizes a vigorous but nonspecific response characterized by complement activation and recruitment of phagocytic cells. The alternative complement pathway is always activated in an antibody-independent fashion, via recognition of repeated polysaccharides (especially those lacking sialic acid) or LPS. However, even in the absence of specific antibody, complement activation can occur via the classic pathway following recognition of C-reactive protein, mitochondrial membranes, or naked DNA.

The best-understood danger signal to which the innate immune system responds is LPS of gram-negative bacteria. LPS is recognized by phagocytic cells owing to two proteins, CD14 and LPS-binding protein (LBP). CD14 is a 55-kDa glycoprotein expressed both as a membrane receptor linked to GPI (glycerol phosphatidylinositol) and as an abundant (3 g/mL) soluble serum protein (sCD14). Each CD14 molecule directly binds 1 to 2 LPS molecules. Recent evidence suggests that CD14 can bind other microbial products, including those of gram-positive organisms and possibly fungi. Binding of LPS to CD14 is markedly accelerated by the transfer protein LBP. LBP also catalyzes the transfer of LPS from CD14 to serum lipoproteins, which renders LPS biologically inactive. This process provides a means for temporally limiting responses to only newly formed LPS.

LPS is an extremely potent stimulant for phagocytic cells to produce IL-1, TNF-a, and IL-12. Sepsis is a failure to contain locally the response to LPS or other microbial products, resulting in dangerously high quantities of these inflammatory cytokines circulating throughout the body. Phagocytic cell production of IL-12 early in immune responses appears to be a crucial bridge between innate and specific immunity. IL-12 production biases responses towards cell-mediated Th1 responses and away from IgE secretion. LPS also nonspecifically activates components of specific immunity (e.g., by polyclonally activating B cells to secrete IgM). LPS inhaled in large amounts causes cotton worker's pneumoconiosis.

Recent evidence suggests that $CD4^+$,$NK1.1^+$ cells, another apparent component of innate immunity, constitute an antigen-independent pathway that provides IL-4 necessary to initiate Th2 immune responses. These natural T (NT) cells express a relatively invariant TCR and are activated by the nonclassic MHC class I-like CD1 molecules on macrophages. This capacity explains the otherwise puzzling dilemma of how Th2 responses can be initiated without pre-existing Th2 T cells.

RECRUITMENT OF INFLAMMATORY AND IMMUNE CELLS TO SITES OF INFLAMMATION

Enormous strides have been made in the last decade toward understanding the molecular basis of leukocyte recruitment. Considerable effort has been expended in this investigation, because it is widely anticipated that it will lead to the development of novel immunomodulatory therapies. This process involves an interaction in which both the leukocyte and the endothelial cell are active participants. Recruitment is a complex phenomenon facilitated by activation of either the leukocyte or the endothelial cell. For example, neutrophil activation leads to cytoplasmic stiffening, which increases retention within the pulmonary microvasculature. Endothelial cell activation rapidly leads to upregulation of a variety of adhesion receptors, detailed below. An additional means of arresting groups of activated leukocytes, even within the lumina of larger vessels, is adhesion of individual leukocytes to each other. These interactions (mediated by a host of receptor/ligand interactions, including LFA-1/ICAM, CD2/LFA-3, and CD44/hyaluronate) can contribute to tissue injury by leukostasis, as in cerebral lupus and possibly in sepsis.

The process of leukocyte recruitment can be divided into seven steps, each of which is controlled by multiple cell surface receptors and cytokines: (1) leukocyte rolling along endothelium; (2) leukocyte triggering; (3) firm adhesion to endothelial cells; (4) transmigration of the endothelial layer; (5) penetration of the vascular basement membrane; (6) migration through extracellular matrix into parenchyma; and (7) selective tissue retention.

Videomicroscopy studies indicate that neutrophils roll along vascular endothelia, making transient interactions that probably facilitate leukocyte arrest at sites of inflammation. Together with considerations of physical size, rolling probably accounts for the large pool of marginated neutrophils and lymphocytes within the pulmonary vasculature. In the case of neutrophils, rolling is mediated by the interaction of L-selectin with endothelial cell ligands bearing the sialylated carbohydrate sLEX. Initial adhesion of neutrophils to activated endothelia appears to be mediated in a similar fashion when carbohydrate determinants on the neutrophil are recognized by the inducible endothelial ligands E-selectin (CD62E) and P-selectin (CD62P). A subgroup of human memory T lymphocytes also binds to E-selectin, whereas other lymphocytes bind to the lymphocyte-specific endothelial ligand, VCAM, via the action of VLA-4 (CD29/CD49d). Expression of these endothelial ligands is regulated by inflammatory cytokines: IL-1 and TNF-a induce ICAM-1 and E-selectin, and together with IL-4 induce VCAM.

Triggering appears to be mediated by chemokine receptors that recognize chemokines presented by an endothelial cell surface protein such as CD44. Triggering increases the stability of the initial adhesion through rapid changes in the avidity of binding of leukocyte b_2-integrin receptors such as LFA-1 (CD11a/CD18) and MAC-1 (CD11b/CD18). Both of these b_2-integrins interact with ICAM-1 on the surface of endothelial cells. Changes in avidity are followed by changes in receptor density that result in firm adhesion and the transformation of the leukocyte from a spherical cell to an ameboid, motile cell.

Transmigration of endothelial cells depends on leukocyte b_2-integrins such as LFA-1 and on the homotypic interaction of CD31 on both leukocytes and endothelial cells. Interdigitation of CD31 is believed to act like a zipper, allowing reversible disruption of the endothelial cell tight junctions, permitting leukocyte transmigration without fluid leakage. LFA-1 is increased on human memory T cells, and has been suggested to be increased by IL-1.

Penetration of vascular basement membrane requires enzymatic digestion, which is mediated by leukocyte metalloproteinases, especially plasminogen activator bound to its receptor, and collagenases. It is likely that secretion of these potent enzymes, as well as of high concentrations of cytokines such as TNF, account in part for immune-mediated damage to vessel walls. The reparative phase of this immune angiitis can involve vessel wall fibrosis, resulting in some cases of pulmonary hypertension seen in association with a variety of interstitial lung diseases. Directed migration is necessary for inflammatory cells to arrive at sites of inflammation; migration is clearly increased by some cytokines *in vitro.* IL-1, IL-2, IL-4, IL-8, and IFN-g are all chemotactic for lymphocytes in vitro. RANTES, a C-C chemokine, is selectively chemoattractant for memory T cells.

Finally, selective retention is probably an important component of immune response generation. Lymphocytes are recruited to sites of inflammation nonspecifically (i.e., without regard to antigen specificity), but they are retained if activated by recognition of antigen, as described below. Selective retention could be mediated by the matrix-binding domains of the b_1-integrins VLA-4, VLA-5, and VLA-6, which are upregulated on human memory T cells. Chemokines and inflammatory cytokines could increase selective retention both by increasing surface expression and binding avidity of these adhesion receptors, and by acting at high doses as migration inhibition factors.

Generation of Pulmonary Immune Responses

To generate protective immune responses, nonself antigens must be recognized by lymphocytes. Each lymphocyte clone bears an antigen receptor that generally recognizes only a single antigen. B cells can be activated directly by binding of antigen to surface immunoglobulin molecules. However, in most biologically relevant cases, B-cell maturation to an immunoglobulin-secreting cell requires specific interactions with $CD4^+$ T cells through both receptor-mediated and cytokine-mediated interactions. Both of these interactions generally require recognition of the same antigen by the T cell and the B cell. This requirement is called a *cognate interaction.* Thus, T-cell help is mediated primarily by direct cell-to-cell contact, permitting considerable control over which individual B cells produce antibody.

T-cell activation is required to initiate and maintain immune responses to virtually all antigens of clinical relevance. T cells have heterodimeric antigen receptors composed of ab or td chains, which recognize antigen only as fragments in the context of appropriate MHC molecules on specialized antigen-presenting cells (Fig. 2). T cells are activated when they receive two types of signals. The first signal consists of recognition of polypeptide fragments displayed by MHC molecules of antigen-presenting cells. Antigen is recognized by a macromolecular complex consisting of (1) antigen-specific variable chains of the T-cell antigen receptor (TCR), (2) an MHC restriction element (CD4 or CD8), and (3) a signal-transduction complex collectively called *CD3.*

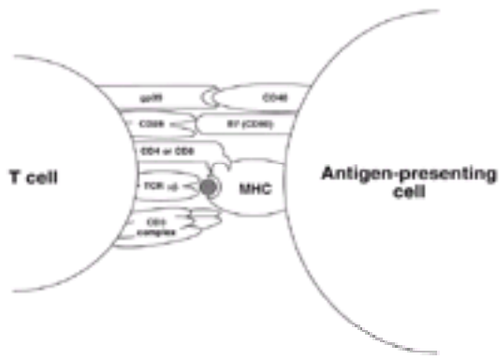


FIG. 2. Schematic representation of receptors involved in T-cell activation. Antigen is recognized in the context of the MHC molecule on the antigen-presenting cell by a complex including the TCR, the CD3 complex, and CD4 or CD8. T-cell co-stimulatory molecules, including CD28 and gp39, provide necessary second signals to permit

completion of the cell cycle.

$CD8^+$ T cells respond to antigen presented by class I MHC molecules, whereas $CD4^+$ T cells respond to antigen presented by class II MHC molecules. Class I MHC molecules present intracellular antigens, especially viral products. Class I MHC molecules are constitutively expressed by virtually all cell types. In contrast, class II molecules are constitutively expressed only by a few cell types, notably B cells and dendritic cells; however, class II MHC expression can be induced on many cell types by IFN-g. Because of this requirement for antigen presentation in conjunction with MHC molecules, regulation by lymphokines of the MHC expression of parenchymal cells such as fibroblasts and endothelial cells is central to the control of immune responses. Class II MHC molecules present extrinsic antigens, which enter the antigen-presenting cell by phagocytosis or pinocytosis.

A second type of signal, which is antigen-nonspecific and termed *co-stimulatory,* is required for complete activation leading to cell division. True co-stimulatory molecules fulfill two criteria. First, these molecules provide signals necessary (together with TCR or CD3 ligation) for activation of naïve T cells. Second, in their absence, stimulation via TCR or CD3 not only fails to activate the T cell but in certain settings induces it to become refractory to further stimulation or even die by apoptosis. Hence, the fate of an activated T cell can be determined by co-stimulatory signals during activation.

The best-understood of these necessary co-stimulatory receptors is CD28. Signaling through CD28 leads to IL-2 mRNA stabilization. CD28 recognizes two ligands displayed by antigen-presenting cells, B7-1 (CD80) and B7-2 (CD86). Human AM are deficient in expression of B7-1 and B7-2, even when stimulated with IFN-g. Proliferation of human $CD4^+$ T cells to recall antigen or anti-CD3 in the presence of AM improves if CD28 is cross-linked. These findings indicate that deficient co-stimulation through CD28 is a major reason for poor function of antigen-presenting cells, and suggest that AM may induce T-cell unresponsiveness or apoptosis. A second true co-stimulatory T-cell molecule is gp39, the ligand for CD40. CD40 is highly expressed by B cells and DC. Co-stimulatory activity that does not meet these two criteria has also been ascribed to adhesion molecules, including CD44, and b_1-integrins such as VLA-4 or b_2-integrins such as LFA-1. Proliferation of mitogen-activated lymphocytes is increased when these molecules are ligated. The conventional interpretation is that improved adhesion to the antigen-presenting cells increases proliferation because of enhanced signaling through TCR or CD3.

Lymphocyte Distribution and Recirculation

Thus, generation of immune responses is constrained both by the relative paucity of antigen-specific lymphocytes for any given determinant and by the necessity that antigenic determinants be presented by immunocompetent cells. The solution that has evolved to solve both of these constraints is drainage of antigens to lymph nodes, between which virgin lymphocytes continuously recirculate. In this way, the few lymphocytes specific for any given antigen have a greatly increased likelihood of being activated efficiently.

Lymphocytes enter organized lymphoid tissue principally by adhering to and crossing specialized postcapillary venules, known for their hypertrophied (“heightened”) endothelial cells as *high endothelial venules* (*HEV*). HEV endothelial cells express unique ligands, called *vascular addressins,* to which lymphocytes adhere. Lymphocyte recirculation is not random, but instead appears to be organized into several anatomic recirculatory circuits. One circuit involves the skin and extremities draining into the peripheral nodes. This circuit is controlled by the lymphocyte receptor L-selectin (CD62L), which binds an endothelial addressin called *glyCAM.* The other well-characterized circuit involves migration of IgA-secreting B cells from Peyer's patches to intestinal lamina propria. This circuit is controlled by the a_4b_7-integrin on lymphocytes, which binds an endothelial addressin called *MadCAM,* an immunoglobulin supergene family member.

Lymphocytes are found within the lung in four distinct anatomic compartments: (1) a marginated intravascular pool that differs in composition from peripheral blood, (2) the interstitium, (3) the alveolar spaces, and (4) organized lymphoid tissue. Organized lymphoid tissue includes lymphoid aggregates, both encapsulated and unencapsulated. Traditionally, bronchus-associated lymphoid tissue (BALT) is considered a part of the lymphoid compartment of the lung. BALT consists of nodules of unencapsulated lymphoid tissue lacking germinal centers, initially described in a variety of animal species. BALT nodules lie in immediate apposition to airways; their lymphocytic areas are separated from the airway lumina by a single layer of specialized epithelium (lymphoepithelium), through which lymphocytes and possibly antigens are believed to pass. However, the importance of organized intrapulmonary lymphoid tissue, especially BALT, in the generation of pulmonary immune responses has been questioned by some recent investigators. In fact, compared with that of experimental animals, the lung parenchyma of healthy humans contains relatively little organized lymphoid tissue and few parenchymal lymphocytes. Therefore, pulmonary immune responses are likely initiated in regional lymph nodes and mediated largely by recruitment of lymphocytes and other leukocytes from extrapulmonary sources, as discussed above.

Nevertheless, large numbers of lymphocytes can be released from enzyme-digested fragments of human lung tissue (probably reflecting recovery of cells from all four anatomic compartments, especially the marginated intravascular compartment), suggesting that overall the lung contains a large number of lymphocytes. Results of studies that have compared the phenotype and function of lymphocytes recovered from the lungs of patients with interstitial lung diseases indicate that alveolar lymphocytes closely resemble lymphocytes recovered from minced lung tissue (interstitial plus some organized lymphoid tissue). Thus, analysis of BALF is generally believed to reflect accurately processes occurring in the lung interstitium.

It has been suggested that the lungs and upper airways are part of the gastrointestinal circuit, comprising along with the gut, breast, and urogenital tract what has been called a *common mucosal immune system.* Supporting this hypothesis, BALT morphologically resembles gut-associated lymphoid tissue (GALT), such as Peyer's patches. Moreover, in adoptive transfer experiments, lymphocytes derived either from bronchus-associated lymphoid tissue (BALT) or from Peyer's patches repopulated both the lungs and the gut with IgA-bearing cells, whereas lymphocytes derived from peripheral lymph nodes did not. However, a number of findings are difficult to reconcile with the hypothesis that the lung parenchyma is part of a common mucosal immune system. Studies in several species have shown that lymphoblasts isolated either from bronchial nodes or from efferent pulmonary lymph localize to the lungs significantly better than to the gut or peripheral nodes. Moreover, two groups of investigators have found that antigen priming of the trachea does not result in significant dissemination of memory cells to the gut. These data argue that the lungs and their draining lymph nodes are not part of a common mucosal immune system, but instead constitute a separate recirculatory circuit. Also consistent with a separate pulmonary circuit of lymphocyte recirculation, experimental studies show that the initial immune response to intratracheal antigens occurs in the bronchial lymph nodes. This observation has led to the proposal that primary immune responses in lung parenchyma develop by recruitment of lymphocytes activated in these nodes back to the lungs. To date, however, no mechanism has been proposed to explain this postulated recruitment of lymphocytes back to lung parenchyma. In summary, despite compelling evidence from in vivo studies, it is uncertain whether there is a distinct recirculatory circuit involving the lung and bronchial lymph nodes, and if so, how important such a circuit is in the maintenance of immunologic lung diseases.

Analysis of surface markers shows that lung T cells are predominantly primed cells, that is, they are the progeny of cells that have been activated previously by encounter with an antigen. At present, it seems likely that accumulation of primed T cells in the normal lung results from their increased expression of adhesion receptors; however, in immunologic lung diseases like sarcoidosis, local lymphocyte proliferation may contribute as well.

In vitro studies have shown multiple factors that could limit lymphocyte activation and proliferation within the lungs. AM are poor antigen-presenting cells compared with other mononuclear phagocytes. Their poor antigen-presenting cellular function is explained by limited expression of class II MHC molecules in some species and by secretion of inhibitory factors, including prostaglandin E_2 (PGE_2), IL-1 receptor antagonist, TGF-b, and reactive nitrogen intermediates. In vitro, rodent and human AM block proliferation of mitogen-activated lymphocytes *in vitro* without interfering with CD3 downmodulation, CD25 expression, or IL-2 elaboration. AM also inhibit the antigen-presenting cellular function of pulmonary dendritic cells. Although AM can transport particles to mediastinal nodes to initiate immune responses, eliminating AM *in vivo* increases the pulmonary immune response, suggesting that their net effect is inhibitory. Alveolar lining fluid inhibits lymphocyte proliferation in vitro, in part because of its lipid components. BALF of sensitized guinea pigs before challenge with inhaled mycobacterial antigens increases pulmonary inflammation, supporting an immunosuppressive effect of normal alveolar lining fluid *in vivo*. Alveolar epithelial cells may also directly suppress lymphocyte proliferation via PGE_2 and by a mechanism not involving surfactant phospholipid or prostaglandins. Hence, factors secreted by both AM and alveolar epithelial cells appear able to block proliferation (but not necessarily cytokine secretion) of activated lymphocytes recruited to the lungs during pulmonary immune responses.

The factors that regulate physiologic immune responses to prevent prolonged interference with gas exchange are incompletely understood. Antigen elimination, through macrophage ingestion, is probably very important. Some lymphocytes migrate out of the lungs, probably to contribute to specific immune memory against pathogens. Recent evidence suggests that many activated lymphocytes die in the lungs by apoptosis, as do the majority of neutrophils and eosinophils. There are excellent teleologic reasons why lymphocyte apoptosis should contribute to immune response termination. By eliminating obsolete clones, apoptosis prevents competition with clones expanding in subsequent responses. Apoptosis also eliminates potentially autoreactive cells, especially activated B cells, which can produce novel autoantibodies during Ig gene hypermutation. The role of immunosuppressive cytokines, especially IL-10 and TGF-b, is just beginning to be explored, and it may lead to novel immunomodulatory therapies.

ALLERGIC PULMONARY TISSUE INJURY

There is evidence that four standard types of allergic tissue injury are operative in the lungs and play important roles in the pathogenesis of many of the interstitial and

immunologically mediated diseases discussed later in this chapter. One should remember that such classifications are by no means absolute, because in an actual disease process several types of hypersensitivity are likely to be operative, either simultaneously or at different stages of the disease.

Type I (Anaphylactic) Tissue Injury

Antigen characteristically reacts with specific antibody of the IgE class, which is attached to a basophil or mast cell by means of its Fc fragment. Both tissue mast cells and circulating basophils concentrate IgE on their surfaces; the surface of one cell contain 500,000 IgE molecules. IgE fixes to a glycoprotein receptor site on the cell membrane, resulting in an arrangement permitting exposure of the antibody-combining sites (Fab) to the surrounding milieu. Cross-linking of two IgE antibody molecules by specific antigen aggregates the corresponding IgE and receptor sites and results in the initiation of a series of cellular biochemical events culminating in the expulsion of secretory granule contents. The biochemical events involved in the secretory process have been well described, and they include an extracellular Ca^{++}dependent conversion of a membrane-associated serine esterase from its precursor to an activated form. Among the many preformed granule-associated and newly synthesized mediators released during type I (IgE-mediated) reactions are histamine; the leukotrienes C, D, and E; eosinophil chemotactic factor of anaphylaxis (ECFA); heparin; superoxide dismutase (SOD); peroxidase; prostaglandins; thromboxanes; PAF; neutrophil chemotactic factor of anaphylaxis (NCFA); bradykinin; major basic protein; and a wide variety of inflammatory factors of anaphylaxis that may be important in so-called late-phase reactions. Once these mediators are discharged or synthesized, they are active for finite periods. For example, histamine is destroyed by several enzymes found in all tissues. Other enzymes, proteases, or peptidases specifically destroy mediators such as leukotrienes and ECFA, and the prostaglandins are metabolized by dehydrogenases and reductases. Many of these mediators, before their deactivation, promote vasodilation and smooth muscle contraction, which are the pathophysiologic hallmarks of IgE-mediated allergic tissue injury. Activation of the complement cascade is not involved in this type of reaction, although effects identical to those noted in IgE-mediated reactions can be produced after nonimmunologic activation of the alternative pathway of complement. For example, the C5a component of complement can trigger release of all the above-mentioned mediators through a non-IgE-dependent mechanism. In the respiratory tract, it is well recognized that type I allergic tissue injury is operative in the production of uncomplicated seasonal allergic rhinitis and true allergic bronchial asthma.

Type II (Cytotoxic) Tissue Injury

Type II allergic tissue injury involves the reaction of specific complement-fixing antibody of the IgG or IgM class with an antigenic component of the cell or with an antigen or hapten firmly bound to a cell surface, which in turn causes activation of the complement cascade and resulting cell damage or death. An example of type II, cytotoxic allergic tissue injury at the pulmonary level might be that of Goodpasture's syndrome. The finding of complement receptors on the surface of AM and the detection of C3 bound to AM in lung biopsy specimens from patients with farmer's lung disease also suggests that type II reactions may be involved, to a minor extent, in the pathogenesis of certain forms of hypersensitivity pneumonitis.

Type III Allergic Tissue Injury

Type III allergic tissue injury (Arthus or serum sickness reactions) is produced by soluble circulating immune complexes, generally under conditions of slight antigen excess, that theoretically become trapped under endothelial cell linings along capillary membranes. There is mounting evidence that increased small-vessel permeability as a result of an antecedent type I allergic reaction plays an important role in allowing localization and entrapment of immune complexes in vessel walls and along basement membranes. Immune complexes then interact with serum complement and activate the complement sequence. The resulting complement-induced neutrophil chemotaxis ultimately leads to tissue destruction (basement membrane or endothelial cell damage plus necrosis and vasculitis) caused by lysosomal enzyme release. In tissue spaces such as the lung under conditions of relative antigen excess, complexes may tend to be insoluble and be removed by the reticuloendothelial system. In general, the organ or area of deposition of soluble immune complexes will determine the clinical picture. Serum sickness, the classic example of this type of reaction, was commonly seen in humans after administration of antitoxins or antibacterial sera prepared in nonhuman species (e.g., it may be seen after repeated administration of horse antitoxins). Currently, it is more commonly noted after administration of some drugs, including antibiotics, particularly penicillin and sulfonamides. The presence of serum precipitins, the time course of development of lung lesions, and the demonstration of dual type I and type III skin test reactions in some patients with hypersensitivity pneumonitis suggest that this mechanism may be partly involved in pathogenesis. However, other more recent evidence strongly indicates that AM activation and cell-mediated (delayed) hypersensitivity (type IV) play a more prominent role in production of these lesions. The histologic findings in lung biopsy specimens from patients with hypersensitivity pneumonitis also usually do not reveal the hemorrhagic necrosis, vasculitis, and polymorphonuclear cell infiltration characteristic of type III allergic reactions.

Type IV Allergic Tissue Injury

Type IV allergic tissue injury (delayed or cell-mediated hypersensitivity) is mediated through sensitized T cells plus other recruited effector lymphocytes and macrophages rather than through circulating or fixed antibodies, as in the previous three types. After antigen contact with sensitized cells, there is generally a latent period of 24 to 72 hrs before clinical expression of a type IV reaction. Complement is not involved in the reaction. The characteristic histologic lesions seen in type IV allergic tissue injury involves infiltration of tissues with the two effector cells of these reactions, lymphocytes and macrophages, often in a perivenular distribution. On contact with antigen, specifically sensitized T cells release lymphokines, which either directly lead to or augment the characteristic reactions of type IV allergic tissue injury.

Type IV allergic reactions can be passively transferred by specifically sensitized lymphocytes or by an enzyme-resistant dialyzable crude extract of lymphocytes called *transfer factor.* This factor may play an important role in converting nonsensitized lymphocytes to specific antigen-responsive cells, although more recent evidence suggests that it acts in a nonspecific manner. The production of certain lymphokines, such as interferon-g, on exposure of sensitized lymphocytes to antigen forms the basis for in vitro assays of the type IV reaction, as are employed in the diagnosis of certain forms of hypersensitivity pneumonitis.

Expression of cell-mediated immunity and of specific antibody reflect the activity of different types of $CD4^+$ T cells. T cells include $CD4^+$ (helper) and $CD8^+$ (suppressor/cytotoxic) subsets. $CD4^+$ cells can be divided into Th1, Th2, or Th0 subsets according to their patterns of cytokine secretion. Th1 cells preferentially secrete IL-2, IFN-g, and TNF-b; activate macrophages; and are responsible for cell-mediated immunity reactions and T-cell toxicity. Th2 $CD4^+$ cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13; provide help for immunoglobulin (particularly IgE and IgG_4) secretion; enhance eosinophil production, survival, and activity; and promote mast cell maturation and proliferation. Development of either a predominant Th1 or Th2 response in mice depends on many factors, including attributes of the antigen, site of delivery, adjuvant used, and type of antigen-presenting cell encountered. Cytokines secreted by one $CD4^+$ subset inhibit the development of the reciprocal subset, leading to a predominance of one of the subsets and polarization of the immune response. Th0 cells secrete a mix of cytokines characteristic of both Th1 and Th2 cells and may represent progenitors of both Th1 and Th2 cells. The above models developed in mice have not been entirely confirmed in humans in the sense that Th1 and Th2 cells may not exist as exact counterparts in humans. However, the concept that the cytokine milieu (derived from many possible sources, such as $CD4^+$, $CD8^+$, NK, mast cells, and gd T cells) at the time of $CD4^+$ cell differentiation determines the later pattern of cytokine secretion and function is valid. More recently, $CD8^+$ cells have been found to differentiate into Tc1 and Tc2 subtypes, with cytokine secretion profiles apparently similar to those of Th1 and Th2 $CD4^+$ cells.

EOSINOPHILIC PULMONARY SYNDROMES

In adult animals, most eosinophils are produced in the bone marrow and released into the blood; emergence time is generally 60 to 80 hrs and the half-life in the circulation is 8 to 12 hrs, but tissue half-life is approximately 24 hrs. T lymphocytes are necessary participants in the production of soluble eosinophilopoietic factors such as IL-3, IL-5, and GM-CSF by immunologic mechanisms in vitro and *in vivo*. Immunologically elicited eosinophilia is independent of B lymphocytes and antibody formation.

Eosinophils are positioned predominantly in tissues, but full expression of their unique functional capabilities requires directed influx, accumulation, and activation at sites of specific tissue reactions. Many distinct factors from several sources are known to be selectively chemotactic for eosinophils, including certain complement components, ECFA, certain leukotrienes, lymphokines, and chemokines. IL-4 selectively induces the appearance of specific adhesins (VCAM-1) on endothelial cells that interact specifically with eosinophils and basophils. This might explain the intermediate steps by which certain stimuli lead to the accumulation of eosinophils in tissue. As in the case of other leukocytes, eosinophils can respond to a variety of fluid phase and particulate stimuli with increased adherence, expression of membrane receptors, phagocytosis, cytotoxicity, enhancement of certain synthetic activities, lysosomal degranulation, and oxidative metabolism.

Eosinophilic granules contain a wide array of enzymes comparable with those in neutrophil lysosomes; however, the eosinophil lacks lysozyme, and there are many other major differences in enzyme content between eosinophils and neutrophils. Some eosinophilic granule enzymes and several cationic polypeptides that are present predominantly in eosinophils are of special importance in pulmonary eosinophilias and hypersensitivity reactions. At least three different cationic polypeptides are major constituents of eosinophilic granules. These are MBP and two eosinophilic cationic proteins (ECP). Eosinophils are capable of generating superoxide and hydroxyl radicals at rates higher than those observed in neutrophils, and the production of superoxide by eosinophils remains at maximal levels for several hours. The specificity and intensity of the microbicidal activity of eosinophils differs substantially from those of other leukocytes in that eosinophils have less bactericidal capacity. Other specialized functions of eosinophils, however, are operative in the destruction of metazoan nematodes, trematodes, and cestodes known to be characteristically associated with eosinophilia. The most striking degrees of eosinophilia are found during the tissue-invasive or tissue-migratory phases of helminthic infections. At least two different populations of eosinophils can be distinguished by density. Hypodense eosinophils are activated according to the criteria of partial degranulation,

increased oxygen consumption and deoxyglucose uptake, cytotoxicity against schistosomes, LTC_4 production, and expression of certain receptors for IgG, IgE, and complement. An increased number of hypodense eosinophils are found in some patients with asthma and may be the mediators of tissue damage in some of the syndromes described below.

Eosinophilic infiltrates around invading helminths and ticks have been documented for some time. Eosinophils adhere to helminths by C3b- and IgG-dependent mechanisms. They then degranulate and deposit granule-associated proteins on the surface of the helminth, leading to the appearance of microscopic defects in the organism's cuticle. ECPs are 10-fold more active in this regard than MBP. The efficiency of helminthicidal activity of eosinophils is enhanced markedly by ECFA and LTB_4. Several monokines and lymphokines also enhance eosinophilic helminthicidal activity.

Downregulatory eosinophilic activities are attributable to certain factors, including PGE_2, which suppresses the release of mediators by mast cells; MBP, which binds heparin; and a set of specific enzymes capable of degrading mediators. In addition, mast cell granules are ingested by intact eosinophils. Pertinent to the discussions in this text are the fact that at concentrations attained in the airways, MBP is capable of injuring bronchial epithelial cells and increasing airways permeability to luminal factors. It is clear that eosinophils are tissue cells with the capacity to augment and prolong or inhibit and terminate immediate and late-phase reactions evoked by mast cells and basophils. The net outcome of eosinophil-mast cell interactions at any time during the hypersensitivity response is likely a function of the relative number of each type of cell and their degree of activation. Eosinophils alone and in concert with mast cells and macrophages thus have the potential to participate in host defense or to promote processes that injure host tissues. The finding of elevated concentrations of specific eosinophilic constituents in sputum and lung tissues of patients with asthma and other inflammatory lung diseases of suspected allergic origin emphasizes the importance of further analysis of the eosinophil in normal lung function and lung diseases. Although eosinophilia can occur in association with many illnesses, it is generally most prominent in diseases affecting organ systems in contact with the external environment—namely, the skin, gastrointestinal tract, and respiratory tract. The eosinophilic involvement of the lung in many of these syndromes is well defined and of considerable clinical importance. The clinical features of eosinophilic syndromes are reviewed in the following sections.

The group of miscellaneous pulmonary eosinophilias generally characterized by eosinophilic radiodensities with or without peripheral blood eosinophilia is poorly understood and ill-defined. These eosinophilias are assumed to represent some type of altered immunologic response to exogenous allergens or infectious agents, but the etiologic agents and immunopathogenic mechanism involved usually are not known.

In 1952, Crofton and co-workers described these disorders as *pulmonary eosinophilias* and divided them into five general categories, with some degree of overlap, as follows:

Group 1:	Pulmonary eosinophilia (Loeffler's syndrome); pulmonary infiltrates with eosinophilia (PIE syndrome)
Group 2:	Prolonged pulmonary eosinophilia
Group 3:	Tropical eosinophilia
Group 4:	Pulmonary eosinophilia with asthma
Group 5:	Pulmonary lesions of polyarthritis nodosa

Crofton clearly recognized the inadequacy of this classification and, in an attempt to create order out of this heterogeneous group of diseases, decided that the generic term *pulmonary eosinophilia* could be used for the entire group. Despite many other useful classifications of this type, there are still few new data available concerning the immunopathogenesis and etiology of these diseases, with the exception of allergic bronchopulmonary aspergillosis (ABPA).

Loeffler's Syndrome

Loeffler's syndrome was described in 1932 as a benign and often symptomless association of transient migratory or successive pulmonary infiltrates and peripheral blood eosinophilia, generally lasting for 20 days. Because of the benign nature of this syndrome, few if any of the clinically documented cases were studied morphologically. Pulmonary eosinophilia that is more prolonged (group 2 of Crofton, lasting 6 months or longer) and frequently has a more severe clinical course has also been characterized. Overall, the primary features of Loeffler's syndrome are a high degree of peripheral eosinophilia together with rapidly fluctuating, varied, and fleeting chest roentgenographic shadows and a benign course. This syndrome has often been associated with infestation of parasites, including *Ascaris, Strongyloides, Necator americanus, Fasciola hepatica,* and *Entamoeba histolytica* among others.

Other, more severe types of pulmonary eosinophilia with features unlike those described by Loeffler and characterized by weight loss, high fever, and night sweats have also been described. These cases (chronic eosinophilic pneumonia) have usually been associated with massive pulmonary radiodensities in a pattern of a “negative image” of pulmonary edema, with peripheral but not central radiodensities. Despite the often life-threatening nature of these disorders, corticosteroid therapy usually induces complete clinical recovery and clearing of roentgenographic abnormalities within a few days, although symptoms may promptly recur on cessation of therapy. Patients tend to be middle-aged, Caucasian women with a history of asthma.

In all cases of suspected Loeffler's syndrome or chronic eosinophilic pneumonia, appropriate skin tests and serologic tests should be performed with various *Aspergillus* species in view of the emergence of ABPA and its increasing recognition in the United States.

Drug-Induced Eosinophilia

Pulmonary eosinophilia may occur after the administration of a variety of drugs, including para-aminosalicylic acid, penicillin, nitrofurantoin, chlorpropamide, sulfonamides, aspirin, acetaminophen, beclomethasone, carbamazepine, chlorpromazine, imipramine, mephenesin, metho- trexate, naproxen, diclofenac, certain phenylephrinecontaining nose drops, penicillamine, tetracycline, cromolyn sodium, inhaled pentamidine isethionate, inhaled heroin, and crack cocaine. An extensive list of drugs reported to be directly or indirectly associated with adverse pulmonary actions was compiled by Rosenow, and the subject of drug-induced pulmonary disease is discussed in more detail in Chapter 22 in this text. In many cases, the relationship between eosinophilia or other lung lesions and drug administration is primarily anecdotal, but in others peripheral or pulmonary eosinophilia is clearly associated with drug administration.

A specific cause of eosinophilia with pulmonary infiltrates caused by ingestion of a drug was identified in subjects who used L-tryptophan as a sleeping aid. It is likely that a contaminant (designated as *peak E*) found in some lots of L-tryptophan is responsible for the syndrome. Although pulmonary involvement is not uniform in the eosinophilia-myalgia syndrome, dyspnea and cough occur in 60%–70% of reported cases and pulmonary radiodensities occur in approximately 20%–50% of such cases. The radiodensities tend to be basilar and resemble those seen in interstitial fibrosis. Histologically, there is pulmonary vasculitis and perivasculitis associated with a mild chronic interstitial pneumonitis. Pleural effusions, arterial hypoxemia, and pulmonary hypertension are common. BAL during acute illness demonstrates an increased number of eosinophils. Lavage several months after onset of symptoms may indicate lymphocytosis with a predominance of $CD8^+$ cells. Respiratory failure may result from muscle weakness.

Tropical Eosinophilia

Peripheral blood eosinophilia and asthma with or without eosinophilic infiltrates have been commonly associated with various parasitic infestations. The term *tropical eosinophilia,* a symptom complex of dyspnea, fever, intense eosinophilia, pulmonary infiltrates with or without wheezing, and weight loss, as defined by Weingarten, has been used to refer to many of these conditions. Unfortunately, the term has gradually come to be applied to virtually any case of pulmonary or blood eosinophilia occurring in a person who resides in a tropical area.

Intriguingly, in some cases of tropical eosinophilia, the pulmonary radiodensities can be minimal, whereas generalized lymphadenopathy and eosinophilia are far more prominent. It is not known why primarily pulmonary eosinophilic manifestations develop in some patients and more pronounced lymphadenopathy develops in others. Characteristics of tropical eosinophilia include extreme peripheral blood eosinophilia (generally 3000 eosinophils per cubic millimeter), often high titers of anti-filarial antibody, and extreme elevation of serum IgE, typically to 1000 ng/mL. In classic cases of tropical filarial eosinophilia caused by *Wuchereria bancrofti,* there is an absence of circulating microfilariae in the presence of high anti-filarial antibody titers. Lung biopsies, when performed in these cases, show varying degrees of parenchymal changes and, in more acute phases of the illness, patchy pulmonary lesions consisting of histiocytic and eosinophilic infiltrates in the alveolar, interstitial, and peribronchial spaces. With longer duration of disease (up to several months), massive eosinophilic pneumonias with occasional abscesses develop. In even more chronic cases, of several years' duration, marked fibrosis is often apparent.

Diethylcarbamazine is the drug of choice in patients with tropical eosinophilia. Most patients show considerable improvement after 2 weeks on this drug in a dose of 6 to 8 mg/kg/day, although relapses may be noted.

Many roundworm larvae and other parasites have also been reported to be associated with pulmonary eosinophilic infiltrates and wheezing. Among these are *Necator*

(hookworm), *Toxocara, Ascaris, Strongyloides,* microfilariae (*Wuchereria bancrofti*), *Ancylostoma braziliense* (creeping eruption), *Trichuris trichiura, Fasciola hepatica,* and others. Some of these diseases may be associated with type I (IgE-mediated) hypersensitivity in view of positive wheal and flare skin reactions to antigens derived from certain roundworms. Precipitating and complement-fixing antibody to parasites has also been detected in the sera of patients with some of these conditions.

Pulmonary Eosinophilias Induced by Fungi, Bacteria, and Related Agents

Certain fungal, bacterial, insect, and related antigens can produce eosinophilia and pulmonary radiodensities with asthma and, at times, alveolitis. Among these are inhaled mites, grain dusts, coffee dusts, grain weevils (*Sitophilus granarus*), and proteolytic enzymes derived from *Bacillus subtilis,* the latter being used in the preparation of washing powders. These agents commonly produce asthma, and only occasional cases of eosinophilic or related pneumonia have been reported. Only one of such induced conditions—ABPA, which is associated with fungal antigens, namely *Aspergillus fumigatus* and a few other fungal species—has been well described.

Allergic Bronchopulmonary Aspergillosis

The previously described ill-defined diseases characterized as PIE syndrome, Loeffler's syndrome, or chronic pulmonary eosinophilia stand in sharp contrast to the well-described entity of ABPA, which also presents a pattern of wheezing, peripheral blood and sputum eosinophilia, and fluctuating pulmonary infiltrates. With the original general description of ABPA by Hinson and colleagues in 1952 and the development of diagnostic tests for the disease, many of the ill-defined eosinophilic pneumonias continue to fall into this better-defined category. ABPA has long been known to be common in the United Kingdom, where it is the cause of 50%–80% of the cases of pulmonary eosinophilia. Originally, it was not recognized with great frequency in the United States and was considered a rarity. However, an increasing number of cases are being recognized, and some patients with asthma without evident ABPA have evidence of central bronchiectasis, the hallmark of ABPA. This raises the possibility that unrecognized ABPA may be common in the asthmatic population. It is likely that the syndrome is being missed in this country because of lack of availability or inadequate use of diagnostic tests and lack of familiarity with the syndrome.

There are no absolute criteria for the diagnosis of ABPA, but the disease is to be clearly distinguished from the two other forms of aspergillosis originally described by Hinson and co-workers—namely, the saprophytic form (aspergilloma, mycetoma) and the septicemic or pyemic form characterized by generalized mycotic abscesses and granuloma. McCarthy and Pepys, in an extensive review of 143 cases of ABPA, noted the following features: (1) intense blood and sputum eosinophilia; (2) wheezing and transitory pulmonary radiodensities (Fig. 3); (3) evidence of type I and type III skin reactions to *A. fumigatus;* (4) positive sputum cultures for *A. fumigatus* in 50% of cases; (5) the expectoration of brownish, tough sputum plugs containing fungal mycelia (Fig. 4); (6) the presence of serum precipitating antibody to *A. fumigatus* or related *Aspergillus* antigens by conventional double gel diffusion analysis (Fig. 5); and (7) the presence of central bronchiectasis (Fig. 6). Other strongly supportive features of the disease are dual (immediate and late) bronchial responses on bronchoprovocation challenge testing with *A. fumigatus* antigen, and dramatically elevated levels of serum total IgE, particularly after episodes of eosinophilic pneumonitis, with gradual return of serum IgE to normal during quiescent periods.

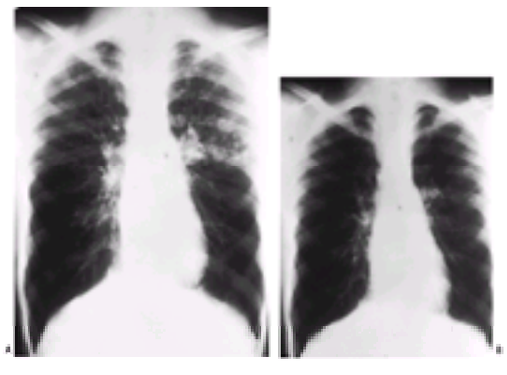


FIG. 3. A: Chest roentgenogram of a patient with ABPA at the time of hospital admission. Note the radiodensities in the left upper lobe. **B:** Chest roentgenogram of the same patient as in A after 1 week of corticosteroid therapy. Note almost complete resolution of the radiodensity in the left upper lobe.

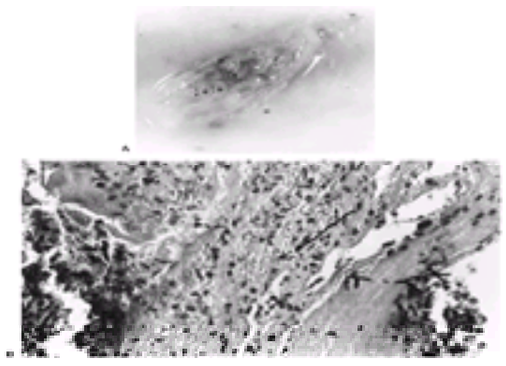


FIG. 4. A: Bronchial plug expectorated by a patient with ABPA. The plug is a cast of a medium-sized bronchus, is golden brown, and is composed of *Aspergillus* mycelial elements. **B:** An expectorated bronchial plug, composed of degenerating cells, mucus, amorphous debris, and *Aspergillus* organisms (branching, septate, methenamine silver-positive structures). Gomori's methenamine silver stain, ×400.

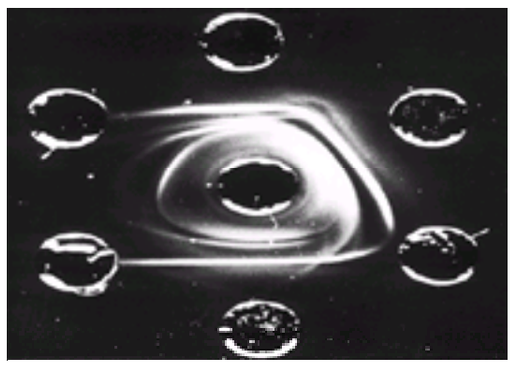


FIG. 5. Precipitin lines to *M. faeni* (“Ouchterlony” or double diffusion in agar technique). Central well contains serum from a patient with farmer's lung disease. Outer wells contain different preparations of *M. faeni* antigen. Note the multiple lines and lines of identity between the antigen preparations.

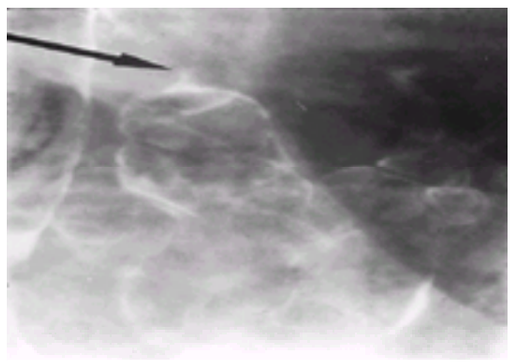


FIG. 6. Bronchogram from a patient with central bronchiectasis and ABPA. Note the greatly dilated proximal bronchi with normal distal bronchi (*arrow*). This is characteristic of central bronchiectasis. Note also the branching of the dilated bronchi, so that a gloved-finger radiodensity would result if the bronchiectatic cavity was filled with exudate.

There are no population-based studies of the incidence or prevalence of ABPA in unselected asthmatic patients. However, Schwartz and associates found that 28% of asthmatic patients seen in private allergy practice in Cleveland, Ohio, had positive immediate-type *Aspergillus* skin test reactivity. In a later study, these authors reported that 10%–28% of 100 asthmatic patients with positive *Aspergillus* skin test reactivity had ABPA according to sets of criteria that either included central bronchiectasis (10%) or did not include demonstrable central bronchiectasis (28%), as well as the presence of serum IgE and IgG anti-*Aspergillus* antibody or serum precipitins. Therefore, an estimate of the prevalence of ABPA in asthmatic patients is 2.5%–7%. Clearly, more community-based studies of the incidence and prevalence of ABPA are indicated.

Clinical Features and Sequelae

ABPA is almost always a complication of asthma, in that almost all patients with ABPA have had a previous ABdiagnosis of asthma. Acute symptoms are wheezing, localized transitory pulmonary infiltrates, chest pain, cough, and production of mucoid or mucopurulent sputum, often containing brownish flecks or plugs (Fig. 4). These symptoms usually occur in atopic individuals with a previous history of asthma and may occur in familial aggregates. This is not surprising, considering the familial nature of atopy and exposure to common sources of *Aspergillus* species. The disease often is incorrectly diagnosed as tuberculosis, bronchiectasis, or bacterial pneumonia. Although many patients in whom the disease initially is detected demonstrate isolated skin reactivity to *Aspergillus* antigens later in life, younger patients with the disease appear to have a high incidence of atopic respiratory disease and broad patterns of positive wheal and flare skin reactivity to common inhaled allergens. Wheezing, roentgenographic shadows, intensity of eosinophilia, and serum IgE response appear to be worse during the autumn and winter months, when *Aspergillus* spores are usually more prevalent in the atmosphere. At times, a source of *Aspergillus* can be identified, such as moldy marijuana, a municipal leaf-compost site, garden mulch, or a soy sauce and bean brewery.

Patients with an early onset of asthma often demonstrate a lengthy interval (mean, 24 years) between the onset of wheezing and initial detection of pulmonary radiodensities. This does not hold for the late-onset group, suggesting that intense and prolonged antigen stimulation is necessary for induction of ABPA in atopic subjects. During initial episodes, reversible airways obstruction is the rule, but obstruction tends to become more fixed later during the course of the disease, although cor pulmonale and pulmonary hypertension rarely are noted. Progressive central bronchiectasis commonly associated with upper lobe fibrosis is frequently present in chronic cases and often is a hallmark of the disease. A protracted course extended over many years with multiple episodic flares is the rule.

Patterson and colleagues reported their experience with 84 patients with ABPA followed for a mean of 5 years. They found that ABPA could be divided into five stages: acute (I), remission (II), exacerbation (III), corticosteroid-dependent asthma (IV), and fibrosis (V). Only 16 of the patients remained in remission, with most being in the corticosteroid-dependent asthma stage (38 patients) or the fibrotic stage. Most of the eligible patients (not in the fibrotic stage) experienced an exacerbation of ABPA despite alternate-day glucocorticoid therapy. This confirms the findings of earlier studies that ABPA tends to recur. It further implies that most patients with ABPA require long-term corticosteroid therapy and that doses sufficient to control asthma may not prevent flares of ABPA.

When patients with stage V disease (fibrosis) are considered separately, two subgroups are evident. The first includes those with low FEV_1 (forced expiratory volume in 1 second) 6 months after initiation of therapy (mean, 0.8 L). These patients have a very poor prognosis, all dying within 7 years (most of respiratory failure). Patients in the second group have less severe obstruction of air flow (mean FEV_1, 1.3 L) and survive 3 to 8 years taking moderate doses of glucocorticosteroids. These data are consistent with a beneficial effect of glucocorticosteroid therapy.

Roentgenographic Changes

Radiologic features of ABPA can be classified as acute or chronic changes. Chronic changes occur as a result of repeated episodes of acute disease and are often associated with physiologic impairment.

Acute Changes. Parenchymal abnormalities are the most common, manifested in 80%–90% of patients by the presence of ill-defined homogeneous radiologic shadows, without evidence of volume loss, that may be either limited (5 to 15 mm) or massive (lobar) in extent. These shadows can appear in any part of the lung but predominate in the upper lobes. They often resolve (e.g., are fleeting) after expectoration of a bronchial plug but tend to recur in the same location. Half of the episodes of homogeneous shadows (consolidation) leave permanent residue, mainly ring shadows. Corticosteroid therapy hastens resolution. Homogeneous shadows presumably are caused by bronchial obstruction with plugs, localized eosinophilic pneumonia, or both. Fig. 3 depicts the chest x-ray films of a patient with ABPA on admission to the hospital and 1 week later after glucocorticosteroid therapy.

Bronchial abnormalities occur in 50%–70% of episodes of acute ABPA and are manifested as tramline, parallel line, and ring shadows (which represent normal or abnormal bronchial walls) and“toothpaste”and“gloved-finger”shadows (which represent intrabronchial exudate). Tramline shadows are the thickened walls of undilated bronchi, so the distance between the walls is that of a normal bronchus. Parallel line shadows represent walls of bronchiectatic bronchi; the distance between the walls is greater than normal. Ring shadows are either bronchiectatic bronchi seen *en face* or small abscesses. When a normal or bronchiectatic bronchial segment becomes filled with exudate, tramline or parallel line shadows change to toothpaste shadows. Removal of the intrabronchial exudate may cause the tramline or parallel line shadows to reappear. Tramline, parallel line, and toothpaste shadows not only are present in patients with ABPA but also may occur in patients with asthma but no ABPA and those with cystic fibrosis and other pulmonary diseases.

Mucoid impaction of bronchi occurs in 15%–30% of patients with ABPA. A proximal impaction of large bronchi (toothpaste shadow) may extend into second-, third-, and fourth-order bronchi. Involvement of several second-order bronchi results in gloved-finger radiodensities, which are tubular radiodensities, 2 to 3 cm long and 5 to 8 mm wide, that branch distally from the hilus and represent dilated branching bronchi filled with inflammatory exudate (Fig. 7). These occur in 10%–20% of episodes of acute ABPA. Thirty percent of episodes of mucoid impaction of bronchi in ABPA cause permanent changes to bronchial walls.

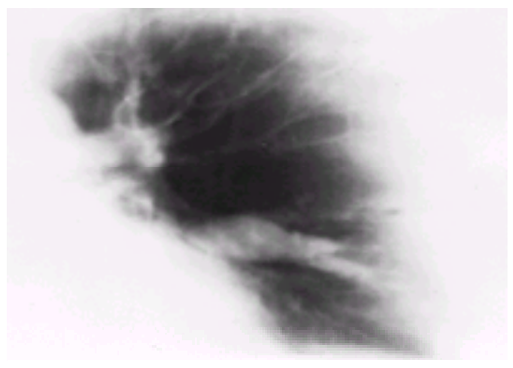


FIG. 7. Gloved-finger radiodensity in a patient with ABPA. This represents thick exudate in dilated third- and fourth-order bronchi, including branches.

Atelectasis of a lobe or a lung with evidence of shrinkage from occlusion of a bronchus by a plug is present in 10%–20% of patients with acute ABPA. Perihilar radiodensities simulating hilar adenopathy occur in 40% of episodes of ABPA. These represent central dilated bronchi filled with fluid and debris, associated with perihilar parenchymal infiltrates. Other acute changes include abscesses with air-fluid levels (10%–20%), diffuse nodulation (10%–20%), avascular areas (10%), and signs of hyperinflation (10%–30%). Pleural effusion occurs in 5% of episodes.

Chronic Changes. Chronic changes reflect permanent histologic abnormalities resulting from repeated acute episodes of ABPA. Bronchial wall changes (tramline, parallel line, and ring shadows) may persist. In addition, because pulmonary fibrosis generally occurs at these sites, the upper lobe usually is involved in chronic ABPA. Physiologic impairment in patients with fibrosis is often significant. The incidence of pulmonary fibrosis in patients with ABPA varies from none of 20 patients followed for 44 months to 18 of 50 patients (36%) followed for 11 years and is directly related to the frequency of acute episodes of ABPA. The association between ABPA and interstitial fibrosis with upper lobe predominance is so strong in Great Britain that a patient with this radiologic finding, a negative tuberculin skin test, and a positive immediate *Aspergillus* skin test reaction is considered to have ABPA.

Central bronchiectasis is apparently a unique feature of ABPA (Fig. 6). In contrast to saccular bronchiectasis, in which small bronchi and bronchioles are dilated, central bronchiectasis is associated with normal small bronchi and bronchioles. This probably is the result of growth of *Aspergillus* only in relatively large (second-, third-, and fourth-order) bronchi, with localized damage to bronchial walls and no injury to smaller bronchi. This peculiar pattern of bronchiectasis can occur even when chest radiographic findings are normal, presumably as a result of relatively few episodes of ABPA insufficient to cause tubular or ring shadows. In instances of severe bronchiectasis, the characteristic changes can be visible on plain films or tomograms without bronchographic dye. It should be noted that bronchography is associated with more complications in asthmatic patients than in normal subjects and that 4 of 16 patients with ABPA who underwent bronchography in the early experience of the Northwestern group had adverse reactions to dye.

High-resolution computed tomography (CT) of the chest detects central bronchiectasis in 35%–40% of the bronchi of patients with ABPA. Interestingly, 5%–15% of the bronchi of control subjects (asthmatic patients with skin test reactivity to *Aspergillus* but without a diagnosis of ABPA) also demonstrate central bronchiectasis. Thus, it is possible that central bronchiectasis is more common than previously appreciated in asthma and may not be unique to ABPA. Alternatively, some of the *Aspergillus*-sensitive asthmatic patients may have ABPA. The resolution of this question awaits further development of specific and sensitive diagnostic tests. In a direct comparison, using bronchography as the gold standard, high-resolution CT was 100% sensitive in detecting central bronchiectasis in patients with ABPA. When individual bronchial segments were compared, CT was 83% sensitive and 92% specific. In view of these findings, the safety and noninvasive nature of CT negates the need for bronchography in patients with suspected ABPA. Table 3 lists the radiologic features of ABPA.

Abnormality	Approximate frequency, %
Central bronchiectasis	100
Homogeneous shadows ("fleeting infiltrates")	80–90
Parallel line shadows	70
Ring shadows	45
Lobar shrinkage	35
Toothpaste shadows	35
Honeycomb shadows (pulmonary fibrosis)	25
Tramline shadows	20
Atelectasis	20
Cavitation	15
Gloved-finger shadows	10

TABLE 3. *Radiologic features of allergic bronchopulmonary aspergillosis*

Diagnostic Considerations

Positive sputum cultures for *A. fumigatus* are found in 50% of the patients, often associated with brownish flecks or sputum plugs containing *Aspergillus* mycelia. Such positive cultures may have little clinical meaning, however, because *A. fumigatus* is ubiquitous and many patients with chronic lung disease have positive *Aspergillus* sputum cultures.

Most patients with ABPA also demonstrate serum precipitating antibody against *A. fumigatus.* However, anti-*Aspergillus* and related antifungal antibody is detectable in the population at large when more sensitive procedures are employed, strongly suggesting that antifungal antibody *per se* only reflects environmental exposure to ubiquitous antigens. Also, precipitins diminish remarkably after treatment with corticosteroids and may be undetectable after 2 years, only to reappear following another episode of pneumonitis.

There are significant problems with antigen preparations used to test for the presence of sensitization to *Aspergillus.* Crude *Aspergillus* antigen from either culture supernatant or mycelia are used clinically. Because these materials include a variety of proteins (including proteolytic enzymes), lipids, lipoproteins, and other substances, and because the method of preparation is not standardized, there are substantial differences between different preparations. The precipitin test with crude *A. fumigatus* is adequately sensitive for practical diagnostic purposes but is inadequate for specificity. Serum IgE and IgG anti-*Aspergillus* antibodies are higher in patients with ABPA than in comparable *Aspergillus*-sensitive asthmatic patients without ABPA. There is some evidence that serum IgA (particularly IgA_1) antibody against *Aspergillus* increases before and during flares of ABPA. It is possible that selected serologic and immunologic findings (skin test reactivity, elevated serum IgE, elevated levels of serum IgE and IgG anti-*Aspergillus* antibody) in patients without demonstrable central bronchiectasis represent a stage of ABPA (ABPA-serologic or ABPA-S). It remains to be seen how frequently ABPA-S precedes ABPA-central bronchiectasis (ABPA-CB) and whether therapy can influence this progression.

There is substantial overlap of antibody levels of asthmatic patients with ABPA and those without ABPA but with positive skin test reactivity to *Aspergillus.* This has led to efforts to purify various *Aspergillus* components to increase specificity. The level of IgE antibodies that react with a concanavalin A nonbinding fraction has been reported to distinguish between *Aspergillus*-sensitized asthmatic patients with and without ABPA. A major 18-kD allergenic *Aspergillus* protein cloned and expressed in bacteria has been useful in distinguishing asthmatic patients or patients with cystic fibrosis with ABPA from those with sensitization to *Aspergillus* but without ABPA, in that sera from patients with ABPA exhibit more IgE and IgG_4 anti-*Aspergillus* antibody. However, some patients with ABPA who had positive skin test reactivity to commercial *Aspergillus* preparations had negative skin tests to the recombinant protein. This illustrates the issue of proper antigen selection. It is likely that different patients respond to slightly different antigenic *Aspergillus* epitopes, so that it is unlikely that any purified antigen will detect all patients with ABPA.

In addition to serologic assays, stronger diagnostic evidence for the role of hypersensitivity to *A. fumigatus* in ABPA comes from the demonstration of dual immediate type I and late or type III skin reactions to this agent. In most patients with ABPA, positive skin tests have been more reliable than precipitins as diagnostic aids. Dual skin reactions also correlate with the elicitation of similar dual early and late bronchial and nasal responses to *Aspergillus* antigen on provocative challenge. There is, however, considerable controversy over the type of reagent best suited to elicit the dual skin test response. There is also controversy over whether the late skin test response represents a local type III immune complex-mediated reaction or a late-phase IgE-dependent reaction. The controversy over the optimal reagent might be expected in view of the lack of precise information on characterization and purification of appropriate antigens. Pepys and McCarthy originally used a saturated ammonium sulfate precipitated protein extract of *A. fumigatus* prepared according to the method of Longbottom, but most preparations marketed today for skin testing consist of crude extracts of the mat and spores. All these agents seem satisfactory, provided that sufficiently high concentrations of the crude antigen are employed. Skin test reactive materials are also present in culture filtrates of the organisms, but there are no adequate studies comparing culture filtrates with mycelial extracts, nor are there any standards of potency for these extracts. In addition, there is a problem with specificity of the skin test in ABPA. In a group of asthmatic patients without aspergillosis and a group of normal subjects, skin tests were positive in 12% and 4%, respectively. There is also evidence to indicate the antigens that react in the skin are not among those detected with a precipitin test and that the *Aspergillus* antigens that elicit IgE antibodies in patients with ABPA do not elicit IgG antibodies.

In addition to skin tests, precipitins, and other immunoassays, lymphocyte stimulation studies with *Aspergillus* antigens have been employed as diagnostic aids in allergic aspergillosis. Lymphocyte proliferation in response to *Aspergillus* antigens may be a feature of ABPA. In one study comparing antigen-induced lymphocyte transformation, precipitins, and skin reactivity, it was noted that patients with aspergilloma had a low incidence of wheal and flare skin reactivity and low lymphocyte responses to *Aspergillus* antigens *in vitro* but extremely high levels of precipitins. On the other hand, patients with ABPA all have immediate positive wheal and flare reactivity but low levels of precipitins. The invasive cases of *Aspergillus* were too heterogeneous to characterize completely.

A limited number of BAL specimens from patients with ABPA have demonstrated increased numbers of neutrophils and eosinophils and increased concentrations of IgG, IgA, and IgM antibodies directed against *Aspergillus* antigens, suggesting local production of these antibodies.

ABPA can occur in patients with cystic fibrosis with an incidence of up to 1% annually and a prevalence of 10%–15%. Because patients with cystic fibrosis without ABPA are subject to episodes of fleeting radiodensities (infectious pneumonia and atelectasis) and have bronchiectasis, an increased prevalence of atopy, and a higher prevalence of *Aspergillus* colonization of the respiratory tract and sensitization to *Aspergillus* compared with age-matched controls, the diagnosis of ABPA can be difficult to establish. There is some evidence that cystic fibrosis patients with ABPA exhibit increased levels of serum IgE and IgG (especially IgG_1 and IgG_4) antibodies to *Aspergillus* and evidence of lymphocyte sensitization when compared with cystic fibrosis patients without ABPA. In addition, peripheral blood B cells from patients with cystic fibrosis and ABPA secrete increased amounts of IgE, and T cells secrete factors that increase B-cell IgE production (perhaps IL-4). Many of the indicators of sensitization to *Aspergillus* in such patients wane spontaneously, so that it can be difficult to determine the importance of these indicators in a patient with cystic fibrosis. In any case, new pulmonary densities in conjunction with deterioration of pulmonary function tests, evidence of sensitization to *Aspergillus,* and elevation of serum IgE in some patients with cystic fibrosis respond to the addition of corticosteroids to antibiotic therapy.

Immunopathogenesis

Currently, there is some evidence to support the contention that a combination of IgE-mediated type I hypersensitivity and immune complex-mediated type III hypersensitivity plays an important role in inducing ABPA. In ABPA in humans, inhibition of type I pulmonary reactions with cromolyn sodium has also prevented the occurrence of subsequent late bronchial pulmonary provocation challenge reactions, whereas the administration of corticosteroids inhibits the late, but rarely the early, responses. In addition, human serum that contains high levels of IgE antibody, when injected intradermally into primates, leads to increased translocation of specific IgG-containing human hyperimmune serum into the skin sites. These findings suggest that deposition of immune complexes is facilitated by IgE antibody acting as a“gatekeeper.”Other evidence for a possible role of type I and type III hypersensitivity in ABPA is obtained from the appearance of dual skin reactivity and pulmonary lesions in a primate challenged by aerosol with *Aspergillus* antigen following passive infusion of serum from a patient with the disease who had both precipitins and reaginic activity against *A. fumigatus.* In contrast, similar challenge after passive transfer of serum containing anti-*Aspergillus* reaginic activity with no precipitins failed to produce such lesions on challenge. There are many alternative explanations for the pathogenesis of ABPA. In view of the high levels of IgE (as high as 90,000 ng/mL of serum) and the fact that most of this IgE is not specific for *A. fumigatus,* Patterson has suggested that *A. fumigatus* growing in the respiratory tract may result either in stimulation of helper T cells for IgE production (i.e., Th2 cells) or of B lymphocytes capable of producing IgE. The Th2 characteristics of *Aspergillus*-specific $CD4^+$ cell lines derived from peripheral blood of patients with ABPA supports this hypothesis. There is also mounting evidence that pharmacologic intermediates such as ECFA and leukotrienes (i.e., LTB_4) released by basophils during type I reactions can attract eosinophils to the site of the initial allergic reaction, resulting in late-phase IgE-dependent eosinophilic reactions. Eosinophil-derived cationic proteins, MBP, and peroxidase are all capable of further stimulating mast cells and basophils to release mediators, and they can damage pulmonary tissues directly as well. Finally, mediators released from eosinophils, such as LTC_4, can act as further late-phase bronchoconstrictors and secretagogues for bronchial glands and epithelial cells. These late reactions are not precipitin-dependent and are not associated with deposition of complement or immunoglobulin. Furthermore, they can be inhibited by agents that inhibit the type I reaction. It is likely that such a mechanism involving attraction of eosinophils to the site of intense type I allergic reactions by chemotactic agents released during the reaction will be shown to be important in the production of many types of eosinophilic pneumonia.

Although attractive, the preceding formulation does not explain the distinction between those asthmatic patients with positive skin tests to *Aspergillus* and circulating IgG anti-*Aspergillus* antibody but without ABPA (25%–30% of unselected asthmatics) and those asthmatic patients in whom ABPA develops (probably 5% of unselected asthmatics). A possible explanation is the observation that circulating basophils from patients with ABPA release more histamine when exposed to both *Aspergillus* antigen and anti-human IgE. This suggests that asthmatic patients in whom ABPA is destined to develop have abnormal basophils that release more mediators on contact with *Aspergillus.* The basis for this abnormality (intrinsic to the cell or a result of exposure to serum factors) has not been elucidated.

Pathologic Features

Lung biopsy of confluent patchy infiltrates demonstrates an interstitial granulomatous infiltrate with a predominance of eosinophils. MBP (derived from eosinophils) is present in the interstitium and in macrophages as well as in activated lymphocytes (increased expression of IL-2R). Mucous plugs containing eosinophils and Charcot-Leyden crystals may be visible in large bronchi, and their presence correlates with shadows seen on chest roentgenograms. Bronchial biopsy generally demonstrates basement membrane thickening, mucosal edema, hypertrophy of mucous glands and smooth muscle, infiltrates of neutrophils and eosinophils, atrophic cilia, some mucous plugs firmly attached to the bronchial wall with profuse intraluminal mucopurulent secretions, and areas of bronchial wall squamous metaplasia.

It should be noted that the tissue reaction in ABPA overlaps with those of other clinical, radiologic, and pathologic entities. Mucoid impaction of the bronchus is often present in ABPA, although it can occur without evidence of sensitization to *Aspergillus.* Eosinophilic pneumonia can be present in ABPA and is believed to be the cause of many of the fleeting radiologic shadows. Finally, the pathologic entity of bronchocentric granulomatosis (BCG) as described by Katzenstein and associates is often found in ABPA. Katzenstein's series of 23 patients with BCG included 10 with asthma. Nine had eosinophilic pneumonia, nine had fungi present in resected specimens, and four had positive serum precipitins to *Aspergillus.* Skin testing was not reported in this series. It is probable that some of these patients had ABPA. Therefore, one of the common causes of BCG may be ABPA. In this regard, Bosken and associates reported that 18 of 18 excised lungs from patients with ABPA demonstrated mucoid impaction of the bronchus, BCG, or both.

Prognosis

There is a lack of prospective population-based studies of the outcome of patients with ABPA. It is clear that some patients progress to end-stage pulmonary fibrosis with cor pulmonale and that some maintain stable pulmonary function tests for many years. Because reports of ABPA originate from referral centers (and thus may not be representative of all patients with ABPA), it is difficult to determine the fate of unselected ABPA patients. In a retrospective study, Malo and coworkers found that after 5 years asthmatic patients with ABPA had more compromised pulmonary physiologic tests than did asthmatic patients without ABPA. Both groups (asthmatics with and without ABPA) had features of asthma (decreased flow rates, increased lung volumes), but asthmatic patients with ABPA tended to exhibit decreased diffusing capacity and total lung capacity. This is compatible with the superimposition of a restrictive defect (pulmonary fibrosis associated with bronchiectasis) on a pre-existing obstructive defect (asthma).

Therapy

Treatment of ABPA is directed toward three goals: treatment of the symptoms of asthma, resolution of acute symptoms of ABPA, and prevention of permanent lung damage. Therapy consists of 40 to 60 mg prednisone daily in divided doses for 2 weeks. The prednisone is rapidly tapered to a maintenance dosage, 0.5 mg/kg on alternate days, and is maintained at that level for 3 months. It should be noted that this schedule is empiric, as there have been no formal studies of different glucocorticoid schedules. Flares can occur while a patient is taking low-dose corticosteroids. Follow-up consists of monthly, and then bimonthly, serum analyses of IgE levels and chest radiographs for 2 to 3 years. If there are no flares, monitoring can be at semiannual intervals, as most patients destined to have recurrent episodes have their first flare within 3 years after the first episode. However, it should be noted that an occasional patient may have a flare after an extended remission.

Systemic glucocorticoid treatment (20 to 40 mg of pred- nisolone per day) significantly hastens clearing of pulmonary radiodensities, so that 4 weeks after the onset of infiltrates, 58% of the new radiodensities cleared in treated patients, in contrast to 23% in untreated patients. In addition, clinical symptoms of asthma, expectoration of bronchial plugs, and sputum production remitted more quickly in treated patients. Permanent lung damage, as manifested by new persistent pulmonary radiodensities, is less frequent if patients are treated. Safirstein and associates, in a retrospective review of patients followed for 5 years, found that therapy with as little as 7.5 mg of prednisone daily prevented the appearance of new radiologic shadows, whereas new persistent shadows appeared in 7 of 19 patients who were not treated with steroids. Capewell and associates, in another retrospective study, found that treatment with 20 mg or more of prednisolone per day was associated with more frequent resolution of radiodensities and peripheral blood eosinophilia, in comparison with treatment with no drug or 20 mg/d.

Twenty percent to 35% of ABPA flares are asymptomatic and can be detected only radiologically. In addition, some patients with ABPA experience only one episode during their lifetimes, and others exhibit flares only at long intervals. This has led to attempts to identify those patients with ABPA most likely to benefit from glucocorticoid therapy. Such patients would be those with frequent flares of acute ABPA resulting in chronic radiologic changes and physiologic impairment.

The striking increase in total IgE in patients with acute ABPA has been used to monitor patients. Most of the IgE is not directed against *Aspergillus* antigens but rather is nonspecific. Total serum IgE increases during flares of ABPA and in some instances before flares. This has led to the recommendation that serial IgE determinations be obtained and patients be treated on the basis of rising concentrations of IgE. Although *Aspergillus* is a potent stimulus for IgE production, it is not the only cause of rising IgE levels. Reed's group demonstrated that most (9 of 13), but not all, increases in serum IgE levels in ABPA were associated with flares. Therefore, it is somewhat precarious to initiate corticosteroid therapy solely on the basis of increasing serum IgE.

The following treatment regimens cannot be recommended and have not been demonstrated to be effective in controlled studies, although there have been anecdotal reports of effectiveness: (1) hyposensitization therapy with *Aspergillus* species (which may cause immediate bronchospasm, would also raise IgG levels to *Aspergillus,* and could theoretically worsen the disorder); (2) inhaled corticosteroids; (3) systemic or inhaled antifungal agents, such as ketoconazole, natamycin, or itraconazole.

Allergic Bronchopulmonary Mycosis

Recently, a series of cases that clinically resemble ABPA, without evidence of sensitivity to *Aspergillus* but with evidence of sensitization to dematiaceous hyphomycetes *Curvularia* and *Drechslera, Candida, Helminthosporium, Fusarium, Rhizopus, Penicillium, Torulopsis, Bipolaris*, or *Pseudallescheria boydii,* have been reported. The course of this illness (allergic bronchopulmonary mycosis) is currently unknown but presumably resembles that of ABPA. However, it appears that most instances of allergic bronchopulmonary fungal disease are caused by exposure to *Aspergillus,* although other fungi rarely can cause a similar clinical and radiologic syndrome.

Other Forms of Pulmonary Eosinophilia

In addition to ABPA and the forms of eosinophilia described in this chapter, one must consider several other types of pulmonary eosinophilia in the differential diagnosis. Among these are allergic granulomatous angiitis, a probable variant of polyarteritis, characterized by severe asthma and intense peripheral blood eosinophilia plus prominent granulomatous infiltrates and Churg-Strauss vasculitis.

Hypereosinophilic syndrome, a separate form of pulmonary eosinophilia, is defined by peripheral and bone marrow eosinophilia and infiltration of multiple organs by mature eosinophils. Any organ system may be involved, but characteristically the lung, heart, skin, muscle, and central nervous system are more prominently affected. The heart is almost uniformly affected, and the lungs are involved in 50% of cases. This disease take several forms. A more benign form consisting of hypereosinophilia with lung involvement and angioedema is often responsive to steroids. In other patients, severe cardiac or central nervous system impairment develops that is unresponsive to either steroids or cytotoxic agents, and in a few cases overt eosinophilic leukemia with documented cytogenic abnormalities develops. Because this disease is of unknown etiology, one must rule out parasitic, allergic, or other autoimmune or related etiologies. The most common pulmonary defect in hypereosinophilic syndrome appears to be a paroxysmal nocturnal cough without airways obstruction. A few patients have underlying asthma. Treatment depends on proving the existence of progressive organ system involvement. In this event, corticosteroid therapy is initiated, and if a response does not occur, treatment with hydroxyurea and occasionally vincristine may result in improvement. When patients are unresponsive to steroids, hydroxyurea often has altered survival rates significantly.

Finally, in the United Kingdom, where ABPA constitutes 50%–80% of all pulmonary eosinophilic pneumonias, those pulmonary eosinophilias that do not fulfill the diagnostic criteria for ABPA are considered merely as a single category of cryptogenic pulmonary eosinophilia. In describing 27 cases of this syndrome, McCarthy and Pepys noted that the cryptogenic form was associated with a lesser degree of blood and sputum eosinophilia when compared with ABPA and that it more frequently involved younger women. There was also no seasonal predilection in the cryptogenic variety. Cough and sputum production were not prominent, and the brownish mucous plugs noted in ABPA rarely were seen. These patients did not have a type I or type III skin test reaction to *Aspergillus,* high levels of circulating total IgE, or cytophilic antibody directed to *Aspergillus,* and did not progress to the bronchiectasis, fibrosis, and atelectasis that are often noted in ABPA. The fact that systemic polyarteritis was ultimately diagnosed in several patients of this series with cryptogenic eosinophilia suggests that many of these cases were perhaps variants of allergic granulomatous angiitis.

Acute Eosinophilic Pneumonia

Recently, a small number of patients with acute onset of fever, diffuse radiodensities, and hypoxemia, at times progressing to adult respiratory distress syndrome (ARDS), with a high proportion of eosinophils in bronchoalveolar lavage (BAL) specimens and sputum and many eosinophils in the pulmonary parenchyma, have been described. Peripheral blood eosinophilia is usually present during the course of the illness, but often not at presentation. The chest radiographic densities are diffusely distributed and not peripheral and therefore are different from those described in chronic eosinophilic pneumonia. CT demonstrates diffuse bilateral ground-glass densities, micronodules, or both. These patients do not have evidence of parasitic infection or atopic disease. Mild cases of acute eosinophilic pneumonia improve rapidly without specific therapy, whereas more severe cases respond promptly to corticosteroid therapy with no permanent sequelae. In some patients, acute eosinophilic pneumonia is related to exposure to environmental fungi or ascarids, with some evidence of sensitization to these antigens. The relationship of this syndrome to other forms of PIE and ARDS is unknown.

HYPERSENSITIVITY PNEUMONITIS

The term *hypersensitivity pneumonitis* (or *extrinsic allergic alveolitis,* the British term) denotes a group of lung diseases caused by inhalation of a wide variety of different materials that are usually organic and always antigenic. The stereotypic clinical events are transient fever, hypoxemia, myalgias, arthralgias, dyspnea, and cough that occur 2 to 9 hrs after exposure and resolve in 12 to 72 hrs without specific treatment.

Hypersensitivity pneumonitis was first clearly described in Dr. Jon Finsen's doctoral thesis in 1874, when he described *heykatarr* in Iceland.

> “This is a chronic chest disease. I do not know its incidence, as my observations thereupon are incomplete. The disease occurs only in winter, or rather during the time when the animals are kept inside, and is found only in the man whose job it is to loosen the hay in the barn and handle it before it is fed to cattle. The hay is always more or less dusty and has to be shaken to eliminate the dust before it is used as fodder. When this dust is inhaled, especially when the harvesting has been difficult and the hay has moulded in the barn, the man who works with the hay becomes ill with this disease, which lasts as long as he continues the same occupation, but usually disappears in summer. The disease expresses itself by cough, rather scant expectoration, and chest heaviness, especially in the evening (the hay is usually loosened in the afternoon, i.e., when it is intended to be given in the evening and the next morning). When examining the chest of those men, I have on a few occasions found signs of bronchitis, but in most cases I have never found anything abnormal. I have never had the occasion to examine a patient during an acute episode.”

This syndrome was described again in British farmers in the 1930s and called *farmer's lung disease.* Dr. Finsen's description is notable for the association of the illness with a particular environmental exposure, its relationship to the season of the year, its occurrence several hours after exposure, the nature of the symptoms, and even the association with bronchitis. Many other diseases have since been described that exhibit the same clinical features and are denoted as hypersensitivity pneumonitis. Despite the terms *hypersensitivity* and *allergic,* hypersensitivity pneumonitis is not an atopic disease and is not associated with increases in IgE or eosinophils. Drug reactions are sometimes described as representing hypersensitivity pneumonitis, usually because certain BALF findings resemble those in hypersensitivity pneumonitis. However these reactions are not hypersensitivity pneumonitis, as the inciting agent is administered systemically and the pathogenic mechanisms are likely different from those of hypersensitivity pneumonitis.

Table 4 is a listing of currently described examples of hypersensitivity pneumonitis.

TABLE 4. *Currently described examples of hypersensitivity pneumonitis*

Some of these diseases have apparently disappeared from the originally described clinical settings (e.g., bagassosis in Louisiana) but presumably exist in areas with similar agricultural or industrial settings, and other diseases are being newly recognized (e.g., potato riddler's lung and machine operator's lung). Both the disappearance of previously described examples of hypersensitivity pneumonitis and the appearance of new examples are the consequence of changing agricultural and/or industrial practices that result in changes of exposure of subjects to antigenic material that can cause hypersensitivity pneumonitis. At the present time, farmer's lung disease, bird fancier's disease, ventilator lung, and Japanese summer-type hypersensitivity pneumonitis (in Japan) are the most commonly recognized forms of

hypersensitivity pneumonitis.

Recognition of new examples of hypersensitivity pneumonitis usually requires a cluster of new cases with a unifying exposure history. Because complete occupational and vocational histories are at times not obtained from patients with pneumonia, it is likely that substantially more examples of hypersensitivity pneumonitis exist that have not yet been recognized and described. For example, introduction of a new metal-working fluid led to recognition of machine operator's lung in an auto parts manufacturing facility because of the clustering of cases and a common, unusual exposure (pseudomonads in cooling fluid).

Clinical Presentation

There are two different clinical presentations of hypersensitivity pneumonitis.

Acute hypersensitivity pneumonitis (dyspnea, nonproductive cough, myalgias, chills, diaphoresis, lassitude, headache, and malaise) occurs 2 to 9 hrs after a particular exposure, peaks typically between 6 and 24 hrs, and resolves without specific treatment in 1 to 3 days (sometimes longer after a particularly intense exposure). Patients exhibit fever, tachypnea, bibasilar rales, and occasionally cyanosis. Fig. 8 diagrams the course of acute hypersensitivity pneumonitis. There is peripheral blood leukocytosis with neutrophilia and lymphopenia, but not eosinophilia, and BAL neutrophilia.

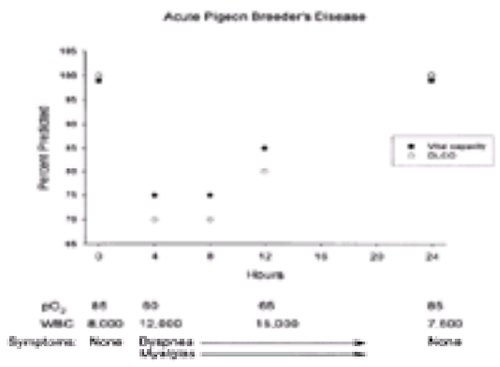


FIG. 8. Diagram of a typical episode of acute pigeon breeder's disease induced by exposure to pigeon serum at 0 h.

Chronic hypersensitivity pneumonitis is characterized by progressively more severe dyspnea, nonproductive cough, weight loss, and often anorexia in a patient exposed to a recognized cause of hypersensitivity pneumonitis. Symptoms are usually present for months to years. There is typically no fever, but tachypnea and bibasilar dry rales are usually present. Symptoms and signs of cor pulmonale are not uncommon at presentation. In general, clubbing occurs infrequently, although Selman, using retrospective chart review, reported clubbing in up to 50% of subjects with pigeon breeder's disease in Mexico City.

A proportion (20%–40%) of patients with chronic hypersensitivity pneumonitis first have symptoms of chronic bronchitis (e.g., chronic productive cough), some even without radiologic parenchymal densities on standard chest radiographs. There is substantial morphologic evidence of bronchitis in the large airways of patients with farmer's lung disease. As most patients with hypersensitivity pneumonitis are nonsmokers without any other cause for the development of chronic bronchitis, these symptoms are likely to be a result of hypersensitivity pneumonitis and may correlate with evidence of airway hyperreactivity in patients with chronic hypersensitivity pneumonitis.

The reasons for the different clinical presentations (acute and chronic) of hypersensitivity pneumonitis are not clear, but they could include differences of intensity and duration of exposure (i.e., low intensity and long duration tending to cause chronic hypersensitivity pneumonitis, and high intensity and short duration tending to cause acute hypersensitivity pneumonitis). This is most clearly demonstrated in hypersensitivity pneumonitis caused by exposure to birds. Bird fancier's disease (chronic exposure to low amounts of bird antigens) is associated with chronic hypersensitivity pneumonitis. Pigeon breeder's disease presents differently in different geographic areas. Intermittent exposure of pigeon breeders to large amounts of pigeon antigens in the United States and Europe is associated with acute disease and a good prognosis, whereas chronic exposure to a few household pigeons in Mexico is associated with chronic disease and a much poorer prognosis. In the United States and Europe, pigeon breeders keep their animals in an enclosure separate from their living areas and visit it periodically, so that exposure is intermittent. In Mexico, birds are kept in living quarters, so that exposure is continuous. It is of interest that bird antigens can persist in a room for a substantial length of time (18 months) after removal of the birds, so that Mexicans with pigeon breeder's disease would be expected to be exposed to pigeon antigens for prolonged periods of time even after removal of the pigeons. Therefore, pigeon breeder's disease in Mexico resembles bird fancier's disease in the United States and Europe in type of exposure, clinical presentation, and prognosis, and differs from pigeon breeder's disease in the United States and Europe. Because the relevant antigens are similar in these two examples of bird-associated hypersensitivity pneumonitis, it is likely that type of exposure, not antigen characteristics, determines clinical presentation and prognosis.

Although the recognition of a new example of hypersensitivity pneumonitis is usually associated with the acute presentation of hypersensitivity pneumonitis, most patients with well-recognized types of hypersensitivity pneumonitis have chronic disease. This might be related to the difficulties in establishing a link between chronic disease and chronic exposure, as opposed to the relative ease in making the association of acute disease and acute exposure.

The above discussion indicates that hypersensitivity pneumonitis, and particularly chronic hypersensitivity pneumonitis, may be more prevalent than is readily apparent and may be a cause of some cases of idiopathic pulmonary fibrosis. Detailed histories are not always obtained from patients with idiopathic pulmonary fibrosis, serum antibody to the agent responsible for hypersensitivity pneumonitis tends to wane after cessation of exposure, and high-resolution CT scans of the chest in chronic hypersensitivity pneumonitis can resemble those of idiopathic pulmonary fibrosis, so it is possible that some patients with idiopathic pulmonary fibrosis have chronic hypersensitivity pneumonitis.

Radiology

In acute hypersensitivity pneumonitis, chest radiographs demonstrate diffuse, poorly defined nodular radiodensities, at times with areas of ground-glass radiodensities or even consolidation. These radiodensities tend to occur in the lower lobes and spare the apices. Linear radiodensities (presumably representing areas of fibrosis from previous episodes of acute hypersensitivity pneumonitis) may also be present. The nodular and ground-glass densities tend to disappear after cessation of exposure, so that the chest radiograph findings may be normal after resolution of an acute episode of hypersensitivity pneumonitis. Figure 9 demonstrates radiologic resolution of acute hypersensitivity pneumonitis. High-resolution CT often demonstrates ground-glass densities better than chest radiographs and at times reveals a diffuse increase of pulmonary radiodensity, but findings may also be normal after resolution of an acute episode. Pleural effusions or thickening, calcification, cavitation, atelectasis, localized radiodensities (coin lesions or masses), and intrathoracic lymphadenopathy are rare.

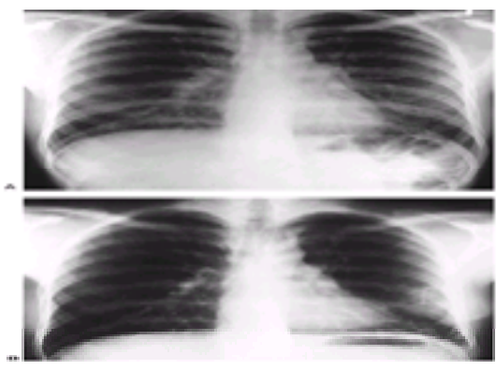


FIG. 9. A: Chest radiograph of a patient with pigeon breeder's disease having symptoms of fever, dyspnea, and bibasilar rales. The patient had kept pigeons for 5 years and was seen with fever, dyspnea, and myalgias approximately 8 hours after cleaning the pigeon coop. He had serum antibody to pigeon dropping extract. Note 2- to 3-mm nodules bilaterally in lower lobes. **B:** Chest radiograph of the same patient 2 weeks later. No specific treatment was given. Note clearing of the lower lobe nodules and the staples in the left chest from the open lung biopsy.

In chronic hypersensitivity pneumonitis, diffuse linear and nodular radiodensities with upper lobe predominance, sparing of the bases, and volume loss (Fig. 10) are apparent on chest radiographs. Pleural effusions and thickening are very unusual, although subcutaneous emphysema (presumably as a consequence of pleural rupture caused by bronchiolitis and lobular overinflation) has been reported.

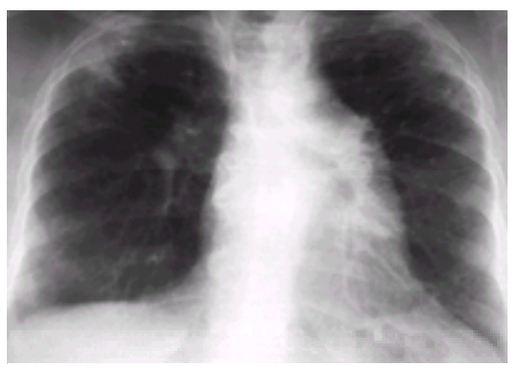


FIG. 10. Chest radiograph of a patient with bird fancier's disease who was first seen with progressive dyspnea and weight loss. She had kept two or three parakeets in her home for the past 15 years and did not notice episodic fever or acute dyspnea. Her serum was positive for precipitins to parakeet serum, and she had severe restrictive disease and resting hypoxemia. Note the diffuse radiodensities, loss of volume of the upper lobes, and pulmonary hypertension.

High-resolution CT of patients with chronic hypersensitivity pneumonitis demonstrates several patterns. Most commonly, there are multiple centrilobular nodules, 2 to 4 mm in diameter, throughout the lung fields, with some areas of ground-glass radiodensities, especially in the lower lobes (Fig. 11). The nodules are seldom attached to the pleura or bronchovascular bundles, as they are in sarcoidosis, and the border between the nodules and the surrounding lung is well demarcated. There are also well-delineated areas of increased radiolucency; these are presumably overinflated pulmonary lobules subserved by partially occluded bronchioles. The ground-glass densities and micronodules tend to resolve after cessation of exposure. Although these findings are suggestive of hypersensitivity pneumonitis, they are found in only a subset (50%–75%) of patients with hypersensitivity pneumonitis, and high-resolution CT findings in hypersensitivity pneumonitis can resemble those of idiopathic pulmonary fibrosis. Cormier reported a substantial prevalence of mild to moderate emphysema detectable by high-resolution CT in nonsmoker patients with farmer's lung disease. It is not clear if this represents lobular overinflation or emphysema. Magnetic resonance imaging (MRI) is inferior to high-resolution CT in demonstrating anatomic detail, but it is equal to CT in demonstrating ground-glass areas and may be useful in determining the course of ground-glass densities without necessitating radiation exposure.

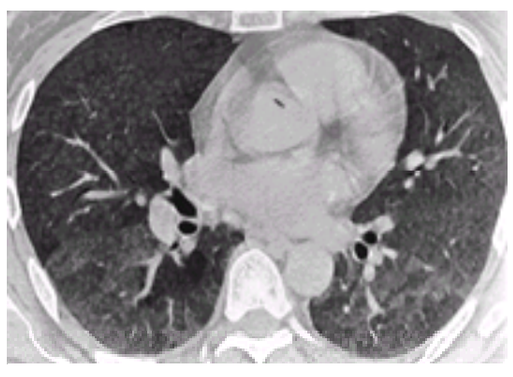


FIG. 11. High-resolution CT of a nonsmoker with exposure to both birds and shells who had progressive dyspnea, weight loss, hypoxemia, and a restrictive ventilatory defect. Note the diffuse nodular radiodensities in the lower lobes with areas of ground-glass densities posteriorly.

Epidemiology

The prevalence of hypersensitivity pneumonitis is quite variable in different populations, presumably related to differing intensity, frequency, and duration of inhalation exposure. Among pigeon breeders, 8%–30% of those who are members of pigeon-breeding clubs and participated in surveys exhibited pigeon breeder's disease. Among farmers, 0.5%–5% have symptoms compatible with farmer's lung disease. The prevalence of symptoms is decreased in farms that use hay-drying methods that reduce exposure to the responsible antigens and is increased following a wet summer season.

The population at risk and the season of the year of occupance vary with the type of hypersensitivity pneumonitis. For example, most cases of farmer's lung disease occur in cold, damp climates in late winter and early spring, when farmers (usually men) use stored hay to feed their livestock. Pigeon breeder's disease occurs chiefly in men in Europe and the United States; it occurs predominantly in women in Mexico because of differing patterns of exposure, but there is no seasonal preference in either population. Bird fancier's disease in Europe and the United States occurs in subjects who keep domestic birds and does not exhibit a predilection for either sex. Japanese summer-type hypersensitivity pneumonitis occurs mostly in women not employed outside the home from June to September in warm, moist areas of Japan.

Unlike what occurs in other pulmonary diseases, there is a remarkable predominance of nonsmokers (80%–95%) among patients with all types of hypersensitivity pneumonitis, substantially greater than the proportion of nonsmokers in similarly exposed subjects who are not ill. The mechanisms of this striking phenomenon are unknown, but they could include smoking-induced alterations of lung defense mechanisms or immunologic reactivity. This clinical finding indicates that active smoking weighs substantially against a diagnosis of hypersensitivity pneumonitis.

An important feature of hypersensitivity pneumonitis is the great variability in susceptibility among exposed populations and the apparent resistance to illness of most exposed individuals. Possible reasons include differences of exposure or differences among hosts, either inborn or acquired. There are no differences in the prevalence of atopy or of HLA-A, -B, -C, or -DR haplotypes in exposed subjects with and without hypersensitivity pneumonitis. There is an increased prevalence of HLA-DPb1 glutamate 69 in berylliosis, a disease with many similarities to hypersensitivity pneumonitis, but HLA-DP haplotypes have not been reported in hypersensitivity pneumonitis. The prevalence of hypersensitivity pneumonitis, unlike that of most other lung diseases, is not increased but rather is substantially decreased in cigarette smokers. This protection against development of hypersensitivity pneumonitis in smokers extends to serum antibody, so that smokers have a lower prevalence of serum antibody than apparently equally exposed nonsmokers. The reasons for these phenomena are unknown but could include depression of immune responses to antigen delivered to the lung, which is well documented in smokers.

Pathology

Lung biopsy specimens (almost always from patients with chronic hypersensitivity pneumonitis) show chronic interstitial inflammation with infiltration of plasma cells, mast cells, histiocytes, and lymphocytes, usually with poorly formed nonnecrotizing granulomas. There is often bronchiolitis and sometimes (25%–50%) bronchiolitis obliterans (Fig. 12). Organizing pneumonia is often also present, so that 15%–25% of patients with hypersensitivity pneumonitis have bronchiolitis obliterans with organizing pneumonia (BOOP). Conversely, in patients with recognized BOOP, hypersensitivity pneumonitis may be the cause. Interstitial fibrosis is often present to a varying extent. Unlike what is seen in sarcoidosis, the interstitial inflammatory cell infiltrate is distal as well as proximal to the granulomas. The granulomas do not occur in groups and do not tend to occur near bronchi or in subpleural locations; they are often adjacent to bronchioles and usually occur singly. These characteristics help to differentiate hypersensitivity pneumonitis from sarcoidosis. Giant cells, at times with Schaumann or asteroid bodies or cholesterol clefts, are present both within and outside the granulomas. Foamy AM are often observed in patients with hypersensitivity pneumonitis caused by bird exposure (Fig. 13). Vasculitis and eosinophilia are not evident.

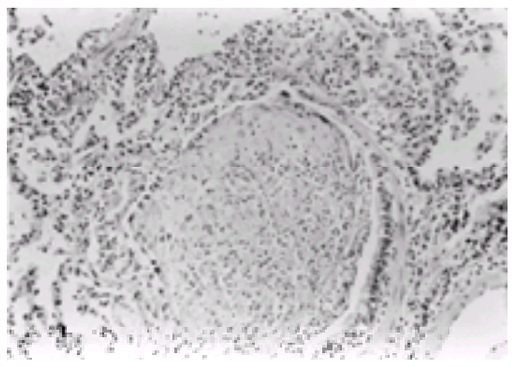


FIG. 12. Bronchiolitis obliterans in the same patient with pigeon breeder's disease as in Fig. 9.

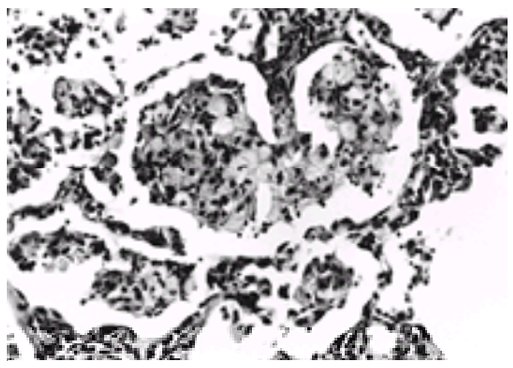


FIG. 13. Foamy alveolar macrophages in the same patient as in Fig. 10.

The specific histologic changes of hypersensitivity pneumonitis, when present, can be diagnostic. However, the granulomas and respiratory bronchiolitis may not be present years after cessation of exposure, so that only interstitial inflammation and fibrosis remain. Therefore, these changes are quite specific, but their sensitivity is unknown.

Differential Diagnosis

The symptoms, signs, and laboratory findings of acute hypersensitivity pneumonitis can resemble those of many other lung diseases, including pulmonary edema, bronchoalveolar cell carcinoma, organic dust toxic syndrome (ODTS), and some forms of pneumoconiosis. Acute hypersensitivity pneumonitis is most often confused with infectious pneumonia (usually thought to be of viral or mycoplasmal origin) and at times with psittacosis in subjects exposed to birds.

ODTS has been described in some of the same populations exposed to materials that cause hypersensitivity pneumonitis. ODTS, which occur in a larger proportion of the exposed population than hypersensitivity pneumonitis, is characterized by transient fever, dyspnea, nonproductive cough, peripheral blood leukocytosis, and BALF neutrophilia; unlike hypersensitivity pneumonitis, however, it is not associated with chest radiographic changes, permanent lung damage, or prior sensitization (as indicated by the absence of serum antibodies). Endotoxin, activated complement, and cytokine released from AM have been implicated as mediators of ODTS. Patients who present with ODTS tend to have had a more intense exposure of shorter duration than those who present with farmer's lung disease.

Exposure to the same agents that cause ventilator lung may result in humidifier fever. This is characterized by fever, chills, myalgias, arthralgias, headache, malaise, cough, dyspnea, peripheral blood leukocytosis, and arterial hypoxemia that begins 4 to 12 hrs after exposure. Some investigators report decreased lung volumes with normal flow rates (“restrictive pattern”) and decreased diffusing capacity, whereas others report normal lung volumes and diffusing capacity. The clinical syndrome remits after 12 to 24 hrs without specific therapy. Symptoms and signs are exaggerated after exposure that follows a period of no exposure (such as vacation or a weekend), but then they become blunted despite continued exposure (“Monday illness”). Monday illness with tolerance to apparently the same exposure later in the work week also occurs in byssinosis and metal fume fever. All signs and symptoms of humidifier fever remit after cessation of exposure, and no permanent physiologic or roentgenologic changes occur. Serum antibodies to thermophilic organisms are rarely present, but antibodies are often present to extracts of humidifier water or slime, gram-negative and gram-positive bacteria (*Bacillus, Flavobacterium, Pseudomonas, Streptomyces*), fungi (*Cephalosporium, Penicillium, Sporotrichum, Aspergillus, Fusarium, Mucor, Phoma, Rhizopus*), or amebae.

There is evidence that some cases of humidifier fever may be caused by endotoxin. Many of the symptoms of humidifier fever can be reproduced by exposure to endotoxin. Rylander described a printing factory in which symptoms of humidifier fever developed in 20 of 50 workers. The humidifier water was heavily contaminated with pseudomonads and endotoxin, and airborne endotoxin was detected in the factory atmosphere when the humidifier was operating. However, other investigators have not detected endotoxin in humidifier water using a pyrogen assay, so that the role of endotoxin in humidifier fever is uncertain.

Treatment consists of removing subjects from exposure to contaminated humidifier water by frequent cleaning of the humidifiers or by changing their job location. It is frequently difficult to clean humidifiers permanently, as any agent used to cleanse water must be removed before humidifiers can be put back in use, so that workers are not exposed to the cleansing agent. Prognosis in humidifier fever after removal from exposure seems to be excellent, as no permanent physiologic or roentgenologic changes occur.

Chronic hypersensitivity pneumonitis resembles idiopathic pulmonary fibrosis, and in some instances the two are indistinguishable. The differential diagnoses includes pulmonary fibrosis of other causes (chemotherapeutic agents, radiation, inhaled toxins, sarcoidosis, idiopathic pulmonary fibrosis, pneumoconiosis) and heart failure.

A thorough and complete occupational and vocational history is essential to diagnose both forms of hypersensitivity pneumonitis. The history should seek to establish a link between a particular exposure (at work, home, or elsewhere) and previous episodes of pneumonia. Information about other exposed individuals with similar symptoms should be sought.

If the history suggests a relationship between exposure and pulmonary symptoms, evidence of sensitization and the nature of the pulmonary inflammatory response should be determined. Sensitization is indicated by the presence of serum antibody to an agent known to cause hypersensitivity pneumonitis. A large proportion of lymphocytes in BALF (usually >40%) is suggestive of hypersensitivity pneumonitis, although many other pulmonary processes can cause BALF lymphocytosis.

Evidence of repetitive appropriate symptoms and laboratory and radiologic abnormalities associated with exposure to a particular environment is sufficient to diagnose hypersensitivity pneumonitis. In questionable instances, a natural exposure (i.e., documentation of appropriate symptoms and laboratory abnormalities after exposure to an environment suspected of causing hypersensitivity pneumonitis) can be used to diagnose hypersensitivity pneumonitis. A natural exposure challenge should not be considered positive unless there is objective evidence of a change in temperature, total peripheral white blood cell number, chest radiograph or high-resolution CT, or increased alveolar-arterial gradient as reflected by the development or worsening of decreased arterial oxygen tension. In some patients, lung biopsy may be required to differentiate hypersensitivity pneumonitis from other causes of diffuse pulmonary inflammation and/or fibrosis. Transbronchial lung biopsy specimens often do not provide sufficient material to establish fully the presence and interrelationships of granulomas, bronchiolitis, and interstitial inflammation, so that either open or thoracoscopic lung biopsy is often required.

Deliberate aerosol inhalation exposure to the suspected antigens should not be performed outside research settings because of the lack of standardized antigens, the possibility of severe adverse effects from the inhaled material in a sensitized person, and the need to demonstrate the lack of a reaction in normal subjects without prior exposure to the same material, thereby possibly inducing sensitization in previously unsensitized individuals.

Terho and colleagues have established major and minor criteria for the diagnosis of farmer's lung disease. An adaptation of their criteria follows.

Major criteria for hypersensitivity pneumonitis:

1. Evidence of exposure to appropriate antigen by history or detection of serum antibody
2. Symptoms compatible with hypersensitivity pneumonitis
3. Findings compatible with hypersensitivity pneumonitis on chest radiographs or high-resolution CT

Minor criteria:

1. Bibasilar rales
2. Decreased diffusing capacity
3. Arterial hypoxemia, either at rest or during exercise
4. Pulmonary histologic changes compatible with hypersensitivity pneumonitis Positive natural challenge
5. BALF lymphocytosis

The diagnosis is confirmed if the patient fulfills all the major criteria and at least four of the minor criteria, and if all other diseases with similar symptoms can be ruled out (e.g., sarcoidosis). Normal chest radiographic findings are acceptable if pulmonary histology is compatible with hypersensitivity pneumonitis. A normal result of high-resolution CT eliminates the possibility of active or chronic hypersensitivity pneumonitis but is possible between acute episodes, so that a normal CT result is acceptable if compatible pulmonary histologic changes are present.

Laboratory Findings

In addition to peripheral blood leukocytosis with neutrophilia, usually BALF lymphocytosis is present (typically 40%–80% of BALF cell number increased two- to fourfold) when BAL is performed 5 days or more after the last exposure. Earlier lavage (especially <48 hours after exposure) is characterized by BALF neutrophilia. BALF lymphocytosis, at least in dairy farmers, is related to continued antigenic exposure and not to the presence of disease, and it does not predict outcome. In most instances of hypersensitivity pneumonitis, the BALF lymphocytes are virtually all $CD3^+$ with a relative increase of $CD8^+$, cells so that the CD4/CD8 ratio is <1. Many of the $CD8^+$ cells express CD57, a marker of cytotoxic cells, and also express CD25 (the IL-2 receptor) and other activation markers. However, the BALF CD4/CD8 ratio is 1 in ventilator lung, some cases of bird fancier's disease, and some cases of farmer's lung disease in Japan, although the BALF CD4/CD8 ratio is <1 in Japanese summer-type hypersensitivity pneumonitis. These differences between Japanese and non-Japanese patients with some types of hypersensitivity pneumonitis might be related to different types of exposure, differing periods of time between last important exposure and BAL, or genetic differences. In support of the importance of timing between last exposure and lavage, Soler demonstrated that cessation of exposure is associated with an increase of BALF $CD8^+$ cells. There is some suggestion that an increase of BALF $CD8^+$ cells is associated with protection against pulmonary fibrosis. BALF NK cell activity is increased in patients with hypersensitivity pneumonitis who continue to be exposed to the responsible antigen. The killer cell activity is found in cell populations with characteristics of both NK cells and non-NK cells, including LAK cells. Most of the $CD3^+$ cells are TCR ab^+, but there is an increase of TCR gd^+ cells and some tendency towards T-cell oligoclonality as demonstrated by increased V_b8, V_b6 and V_b5 TCR usage in some patients with hypersensitivity pneumonitis. BALF macrophages display many aspects of activation, including spontaneous secretion of TNF-a and IL-1 and expression of CD25. Monokines that can activate macrophages and cause chemotaxis of $CD8^+$ cells (i.e., MIP-1a, MCP-1, and IL-8) are present in BALF and AM from patients with acute hypersensitivity pneumonitis. Mast cells, often with ultrastructural markers of degranulation, are increased in both the lung parenchyma and BALF of patients with hypersensitivity pneumonitis. The concentration of IgG, IgM, IgG, and albumin are increased in BALF, presumably as a result of pulmonary inflammation. BALF histamine and tryptase is increased in some patients with acute hypersensitivity pneumonitis.

Virtually all patients with hypersensitivity pneumonitis have easily demonstrable antibody (typically IgG, IgM, and IgA) to the offending material in serum and often also in BALF. A multitude of methods have been used to demonstrate antibody (ELISA and variants, indirect immunofluorescence, complement fixation, latex agglutination, counterimmunoelectrophoresis, radioimmunoassay, Western blot). As most clinical studies have used simple agar diffusion (“Ouchterlony”) methods to detect antibody, this is considered the standard method, but other methods are also acceptable (Fig. 5). The key issue is the ability of the antigen to detect antibody in the serum of patients with hypersensitivity pneumonitis. This varies with the methods of bacterial growth (for bacterial antigens) and of extraction of soluble antigens from either cultured material or material that causes hypersensitivity pneumonitis (e.g., hay in farmer's lung disease, bird droppings in bird fancier's disease). Because antigen preparations are not standardized, it is difficult to be confident of the meaning of a negative result unless the antigens have been tested against panels of sera from patients with and without hypersensitivity pneumonitis, so that reports of a negative hypersensitivity pneumonitis panel do not exclude the diagnosis of hypersensitivity pneumonitis. At times, it is useful to use antigens prepared from the environment suspected of causing hypersensitivity pneumonitis. This is especially important in patients with ventilator lung.

Serum antibody is also present in many subjects who are exposed but not ill, in virtually the same amounts as in patients with hypersensitivity pneumonitis. Therefore, the presence of antibody indicates exposure and sensitization and not necessarily disease. There is some suggestion that the presence of IgG and IgA antibody to *Trichosporon cutaneum* correlates with symptoms in subjects with Japanese-type hypersensitivity pneumonitis, whereas IgG antibody alone correlates with exposure but no symptoms. This correlation of exposure and symptoms with IgA antibody is not found in pigeon breeders or farmers. In asymptomatic pigeon breeders, the prevalence of antibody to pigeon antigens is 30%–60%. In farmers, the prevalence of anti-*Micropolyspora faeni* serum antibody is 2%–27%. The occurrence of serum antibody is not consistently related to apparent exposure (i.e., hours or intensity of exposure) in most instances of hypersensitivity pneumonitis. This may be related to a threshold effect, in that most exposures are above the minimum required to induce antibody and increases above that threshold are not associated with increases of the prevalence of antibody. In addition, serum antibody tends to wane after cessation of exposure, so that patients with chronic hypersensitivity pneumonitis who have not been exposed for some time may not have demonstrable antibody. In farmer's lung disease, approximately 50% of patients with initially positive serum antibody to *M. faeni* (*Saccharopolyspora rectivirgula*) lose demonstrable antibody 6 years after cessation of exposure. Farmers who continue to farm also lose detectable antibody (35%–50% in 5 years), and in some asymptomatic farmers initially without serum antibody, antibody later develops without farmer's lung disease. In pigeon breeder's disease and bird fancier's disease, approximately 50% of patients with initially positive serum antibody to avian antigens lose demonstrable antibody 2 to 3 years after cessation of exposure. Therefore, it is possible no serum antibody will be detectable in patients with hypersensitivity pneumonitis, either because an inappropriate antigen is used or because antibody has waned since the last exposure.

Nonspecific markers of inflammation, such as sedimentation rate and C-reactive protein, are often elevated during an acute episode of hypersensitivity pneumonitis. There are a few reports of increased prevalence of rheumatoid factor in patients with hypersensitivity pneumonitis. Antinuclear antibody or other autoantibodies are not present. There is increased uptake of gallium 67 in the lungs of patients with active hypersensitivity pneumonitis, which declines with improvement of the disease. Serum angiotensin-converting enzyme is not elevated, as it is in sarcoidosis.

Skin tests (of either immediate or delayed type) to detect sensitization to the suspected antigens are not useful, as extracts of agents that cause hypersensitivity pneumonitis produce nonspecific reactions that do not indicate sensitization and do not discriminate between sensitized and unsensitized subjects. In addition, preparations of antigens that cause hypersensitivity pneumonitis are not readily commercially available. Early reports indicated that some patients with hypersensitivity pneumonitis demonstrate 4- to 8-hour skin test reactivity (“Arthus type”), which correlates with the presence of serum antibody. However, the presence of this reaction does not add information important in the diagnosis of hypersensitivity pneumonitis, as antibody can be readily detected in serum.

Tests designed to detect cell sensitization (most commonly antigen-induced lymphocyte proliferation or lymphokine secretion) are not useful in the clinical diagnosis of hypersensitivity pneumonitis, although they have been performed in specialized research settings. Patients with hypersensitivity pneumonitis have depressed delayed-type skin reactivity to recall antigens, similar to that observed in patients with sarcoidosis.

Pulmonary function tests typically demonstrate a restrictive ventilatory defect with small lung volumes, normal or increased flow rates, increased lung elastic recoil, and usually decreased diffusing capacity. There is frequent occurrence of a mild obstructive defect and increased upstream airway, resistance probably related to either bronchiolitis or emphysema. Arterial hypoxemia with hypocapnia, reflecting an increased alveolar-arterial oxygen gradient, is common either at rest or after exercise.

Many (20%–40%) patients with hypersensitivity pneumonitis exhibit increased nonspecific airway reactivity, which may be related to increased numbers of mast cells in the lung and BALF or to bronchial epithelial damage, and in some (5%–10%) clinical asthma develops. The increased airway reactivity and asthma tend to diminish after cessation of exposure.

Pathogenesis

Multiple immunologic markers present in subjects with hypersensitivity pneumonitis suggest that immune mediation is important in the pathogenesis of this syndrome. In addition, the necessity for previous sensitization (indicated by the presence of serum antibody in virtually all patients with hypersensitivity pneumonitis) suggests immunologic mediation.

The presence of serum antibody in patients with hypersensitivity pneumonitis and the timing of symptoms after exposure (2 to 9 hrs) led to the hypothesis that

hypersensitivity pneumonitis represents an example of immune complex-mediated lung disease. However, the presence of antibody in subjects who are exposed but not ill, the lack of correlation between the presence of serum antibody and abnormalities on pulmonary function tests, the lack of evidence of complement consumption during acute exposure, the pathologic features that include granulomatous changes, and findings from animal models strongly suggest that cell-mediated immune processes are very important in hypersensitivity pneumonitis.

Many of the agents responsible for hypersensitivity pneumonitis can act as adjuvants and are particulate (promoting retention of antigen within the lung for prolonged periods of time), persistent, and nondegradable. They can interact with humoral mediators (complement and antibody) and cells in the lung to produce inflammation. The agents can induce injury by causing polymorphonuclear leukocytes and macrophages to release phlogistic substances such as reactive oxygen compounds, proteolytic enzymes, and products of arachidonic acid metabolism (prostaglandins and leukotrienes). The agents can also cause the production and release of IL-1, TNF-a and IL-6 from macrophages and lymphokines (IL-2, interferon-g, and B-cell growth and differentiation factors) from lymphocytes. Injury to the lung caused by the above factors could enhance pulmonary exposure to inhaled antigen, which might promote immunologic sensitization and subsequent further pulmonary damage. The result of all these processes is pulmonary inflammation.

In animal models of hypersensitivity pneumonitis, T cells and macrophages are central in the induction and expression of hypersensitivity pneumonitis. Macrophage-derived cytokines, such as IL-1a, IL-6, TGF, and TNF-a, seem to play a central role in models involving intrapulmonary administration of materials that cause hypersensitivity pneumonitis.

Administration of cyclosporine A ameliorated pulmonary lesions in animals subjected to airway challenges with *Thermoactinomyces vulgaris,* another agent causing hypersensitivity pneumonitis, and nude mice did not exhibit pulmonary lesions of hypersensitivity pneumonitis after exposure that produced lesions in thymus-intact littermates. Ability to express pulmonary lesions can be transferred with T cells from sensitized mice. Pulmonary fibrosis induced by repeated challenges with *M. faeni,* but not an increase of BALF inflammatory cells, can be reduced by administration of anti-CD11a, implicating integrins in the processes that lead to fibrosis in this model.

Adoptive transfer models of hypersensitivity pneumonitis allow differentiation between direct lung damage (toxicity), sensitization (the development of antibody and cellular reactivity), and the results of immunologic reactions (the interaction of antigen with antibody and/or cells). We have developed such a model in inbred guinea pigs and mice that allows transfer of susceptibility to *M. faeni* by cultured cells from sensitized animals.

Culture of peritoneal exudate, spleen, or peripheral or lung-associated lymph node cells with a soluble extract of *M. faeni,* the agent that causes farmer's lung disease, confers the ability to induce susceptibility to pulmonary injury in recipients of transferred cells 4 days after an intratracheal injection of *M. faeni.* The pulmonary injury is characterized by increased number of mononuclear cells in the lungs in both perivascular and peribronchiolar locations. This phenomenon depends on sensitization of the donor with *M. faeni,* culture with soluble *M. faeni,* and the number of transferred cells, and it persists for at least 8 weeks after cell transfer. Serum from sensitized animals cannot transfer experimental hypersensitivity pneumonitis. Three different mouse strains (C3H/HeJ, SJL/J, and C57Bl/6) do not differ in response. The postculture cells responsible for transfer are $CD3^+$, $CD4^+$, $CD8^+$, and $SIGM^-$ T cells. Development of cells able to transfer depends on the presence of $CD3^+$ and $CD4^+$ but not $CD8^+$ cells at the onset of culture. The transferring cells are a mixture of naïve and memory (as defined by CD44, CD45RB, and L-selectin, markers) $CD4^+$ cells. The presence of recipient $CD3^+$ and $CD4^+$ but not $CD8^+$ cells is required for expression of adoptive experimental hypersensitivity pneumonitis. IFN-g and IL-2 are present in substantial quantities in culture supernatants, suggesting a predominance of Th1 $CD4^+$ cells. The presence of serum IgG_4 antibody to pigeon antigens correlates with lack of symptoms in pigeon breeders. As IgG_4 is an immunoglobulin isotype that is induced by IL-4 and suppressed by IFN-g, this suggests that hypersensitivity pneumonitis may be characterized by predominance of Th1 type immunologic reactivity.

Prognosis and Treatment

Prognosis varies considerably with the type of hypersensitivity pneumonitis or even the geographic location. For example, farmer's lung disease has a good prognosis in Quebec, even in farmers who continue to farm. However, in Finland it often results in significant physiologic impairment and even death. Pigeon breeder's disease in the United States and Europe has an good prognosis, whereas the same disease in Mexico has a 30% 5-year mortality. The reasons for these differences are not clear, but they likely include differences in the antigen, differences in the nature of the exposure, or both.

Removal from exposure to the offending antigens is usually sufficient to effect a resolution of symptoms and physiologic abnormalities within a few days for acute hypersensitivity pneumonitis and within a month for chronic hypersensitivity pneumonitis. In some patients, symptoms and signs of pulmonary fibrosis persist more than 6 months, which suggests a poor outcome. Removal from exposure completely is most effective, but cleaning of the environment in situations in which removal is impractical (e.g., Japanese summer-type hypersensitivity pneumonitis) can prevent further episodes of hypersensitivity pneumonitis. There is one report of resolution of symptoms of hypersensitivity pneumonitis after installation of filters in an air-conditioning system, which greatly lowered mold colony counts. Pigeon lofts in which litter materials designed to absorb pigeon excreta are not used have significantly lower levels of airborne pigeon antigens than lofts in which litter material is used. It is not known whether avoidance of litter materials is associated with a decrease in pigeon breeder's disease.

Systemic glucocorticosteroids are sometimes required to treat severe disease, although there is no formal evidence that such treatment is associated with long-term improvement in symptoms or radiologic or pulmonary function test abnormalities. The usual treatment is 40 to 60 mg of prednisone or prednisolone per day for 2 weeks, followed by a gradual decrease to no medication within 1 to 2 months. Patients with farmer's lung disease treated with prednisolone demonstrated slightly more rapid resolution of some radiologic abnormalities (ground-glass opacities) and physiologic abnormalities (slight improvement of diffusing capacity, no difference in lung volumes or arterial oxygen tension) than did untreated patients. However, there were no differences between the groups 6 months after the diagnosis of hypersensitivity pneumonitis. The above evidence suggests that systemic steroids may slightly increase the rate of resolution of acute pulmonary inflammation but have little or no effects on chronic residue of hypersensitivity pneumonitis. Inhaled glucocorticosteroids, nonsteroidal anti-inflammatory agents (cromolyn or nedocromil), and systemic immune modulators are not indicated in the treatment of hypersensitivity pneumonitis.

If patients are removed from exposure before permanent radiologic or physiologic abnormalities develop, the prognosis is excellent, with little evidence of long-term ill effects. If removal from exposure is impossible, the use of efficient masks during exposure can result in the prevention of acute hypersensitivity pneumonitis and is associated with an excellent prognosis. If exposure persists, some patients (proportion unclear, but probably 10%–30%) will progress to diffuse pulmonary fibrosis with resultant cor pulmonale and premature death. Mortality from farmer's lung disease is reported to be between 0% and 20% and usually occurs after 5 years of recurrent symptoms, although there are a few case reports of death after acute massive exposure to antigen. The prognosis varies considerably with different types of hypersensitivity pneumonitis. In general, long-term, relatively low-level exposure seems to be associated with a poorer prognosis, whereas short-term, intermittent exposure is associated with a better prognosis. This is well illustrated by pigeon breeder's disease, which in the United States and Europe has an excellent prognosis; most patients were asymptomatic and no deaths had occurred 10 years after diagnosis in a group of 24 patients with pigeon breeder's disease. In contrast, for patients in Mexico City who have pigeon breeder's disease, the mortality is 30% after 5 years. Unfortunately, many patients who present with chronic hypersensitivity pneumonitis also have pulmonary fibrosis and physiologic abnormalities that are only partially reversible after cessation of exposure.

Markers of pulmonary inflammation at the time of presentation, such as a high proportion of BALF lymphocytes, neutrophils, or mast cells, or the presence of procollagen III, hyaluronic acid, fibronectin, and fibroblast growth factors in BALF, do not predict outcome.

In conclusion, hypersensitivity pneumonitis is an immunologically mediated lung disease in which T cells and macrophages play important roles. It is diagnosed by a careful history and appropriate laboratory tests. Avoidance of exposure is usually associated with a good prognosis. Because of constantly changing environmental exposures, new examples of hypersensitivity pneumonitis are constantly being described and represent a continuing challenge to astute clinicians.

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CHAPTER

20 Systemic Sarcoidosis

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INTRODUCTION

Between 1865 and 1875, Sir Jonathan Hutchinson is believed to have encountered the first case of what we now recognize as sarcoidosis. In 1889, Besnier described a patient with raised violaceous facial lesions that he called *lupus pernio.* His report was followed by one by Tenneson describing the presence of granulomas and the absence of tubercle bacilli in similar skin lesions. In 1899, Boeck described a patient with pronounced lymphadenopathy and multiple nodules of the skin, face, and back. When these lesions were examined histologically, Boeck was struck by their close resemblance to a sarcoma and gave them the name *benign sarcoid.* Schauman in 1914 and Kuznitsky and Bittorf in 1915 recognized that sarcoid skin lesions, lupus pernio, and visceral lesions were all part of the same multisystem disorder. This important observation set the stage for the recognition of sarcoidosis as a distinct entity. In the years since its recognition, sarcoidosis has been the topic of intense investigation. These studies have shed light on some of the clinical manifestations, epidemiologic characteristics, and pathogenic mechanisms of the disease. However, although commonly encountered and frequently diagnosed, sarcoidosis is still poorly understood. Its etiology is unknown, our knowledge of its pathogenesis is incomplete, and its diagnosis, staging, and treatment are steeped in controversy. In this chapter, we have attempted to outline the areas of certainty and uncertainty regarding this disorder. We also hope to provide a rational approach that can be used for evaluating and treating affected patients.

DEFINITION

A number of attempts have been made to formulate a definition of sarcoidosis. In 1948, the National Academy of Sciences proposed a definition that was essentially an extensive clinical definition of the manifestations of the disease. In 1976, the Subcommittee on Classification of the Seventh International Conference on Sarcoidosis proposed the following definition:

> Sarcoidosis is a multisystem granulomatous disorder of unknown etiology most commonly affecting young adults and presenting with bilateral hilar adenopathy, pulmonary infiltration, and skin or eye lesions. The diagnosis is established most securely when clinical or radiographic findings are supported by histologic evidence of widespread noncaseating epithelioid granulomas in more than one organ or by a positive Kveim-Siltzbach skin test. Immunologic features are depression of delayed-type hypersensitivity, suggesting impaired cell-mediated immunity and increased or abnormal immunoglobulins. There may also be hypercalciuria with or without hypercalcemia. The course and prognosis may correlate with mode of onset. An acute onset with erythema nodosum heralds a self-limited course and spontaneous resolution, whereas an insidious onset may be followed by relentless progressive fibrosis. Corticosteroids relieve symptoms and suppress inflammation and granuloma formation.

This definition is dated, overly descriptive, and its sheer bulk limits its utility. It is more useful to define sarcoidosis as a systemic granulomatous disorder of unknown etiology. In this definition there are three points that need emphasis: that sarcoidosis is a systemic disorder, that it is a granulomatous disorder, and that, despite many attempts, its etiologic agent or agents are unknown.

EPIDEMIOLOGY

The majority of patients with sarcoidosis are either asymptomatic or have such trivial symptoms that they do not bother to consult a physician. This makes an accurate assessment of the incidence of sarcoidosis in the United States difficult. Best estimates are that sarcoidosis in the United States occurs in 1 in 10,000 people per year, making for some 22,500 cases annually. Within the United States, sarcoidosis is 10 times more frequent in black than in white persons. It was thought to be particularly prevalent in the southeastern states. However, more recent epidemiologic studies have cast some doubt on this latter contention, as corrections of previous studies for differences in black and white population densities and new case-matched studies have shown that the incidence of sarcoidosis in the south and southeast is similar to that in other parts of the United States.

In parts of the world where mass radiographic screening is performed, more accurate estimates of the prevalence of sarcoidosis can be obtained. These studies have shown a prevalence rate of 64/100,000 in Sweden and 20/100,000 in the United Kingdom. Interestingly, rates as high as 200/100,000 are noted among Irish women of childbearing age, whereas the disease is quite rare in China and southeast Asia.

ETIOLOGY

The granulomatous lesions in sarcoidosis are similar to those caused by infectious agents, such as mycobacteria and fungi, or inorganic agents, such as zirconium and beryllium, and to those seen in hypersensitivity reactions to organic agents, such as thermophilic actinomycetes. These similarities have caused many to speculate that infectious agents or organic or inorganic dusts may be etiologic in sarcoidosis. Particular interest has been directed at the possibility that sarcoidosis is the result of an unusual host response to a common agent, or the result of an infection by, or inhalation of, a poorly characterized agent. Efforts to test these speculations have been ongoing for many years. These studies have failed to observe consistent associations between the occurrence of sarcoidosis and a person's place of birth, place of residence, or personal history of allergies, drug ingestion, exposure to pets, or occupational exposure. In addition, contentions that common and exotic agents such as viruses (including human immunodeficiency virus, or HIV-2), corynebacteria, fungi, and pine pollen play an etiologic role have not stood up under close scrutiny. The polymerase chain reaction (PCR) has recently been used to reinvestigate the role mycobacteria play in this disorder. Using this technique, some investigators have reported enhanced detection of mycobacterial DNA in patients with sarcoidosis. These studies overall had a high rate of false-positive PCR reactions. In contrast,

others have found mycobacterial DNA in only a small minority of patients with sarcoidosis. As a result, it cannot be concluded that *Mycobacterium tuberculosis* is etiologic in the majority of cases of sarcoidosis. Additional studies will be required to clarify this issue.

Epidemiologic studies have demonstrated that sarcoidosis is commonly encountered in people from northern Europe, is more common in American blacks than American whites, and can cluster in families. These observations suggest that genetic predisposition may be an important variable in disease acquisition. However, to date, no consistent mode of inheritance has been found. In addition, most studies have shown no consistent association between human leukocyte antigen (HLA) type and disease. The report that sarcoidosis is five and a half times as frequent in American blacks that are HLA-Bw15-positive than in those lacking this antigen is interesting, but it will require additional confirmation.

PATHOLOGY

The histologic features of sarcoidosis consist of varying degrees of granulomatous inflammation, interstitial pneumonitis, and tissue fibrosis. Which of these lesions predominates depends on the stage of the patient's disease.

Granulomatous Inflammation

The epithelioid granuloma is the characteristic lesion of sarcoidosis. These granulomas are usually not necrotic. When necrosis occurs, it is usually minimal and confined to the central portions of the lesion. The granulomas are usually distinct, even when densely clustered. Epithelioid cells and multinucleated giant cells are found in the center of the granulomas. They are intermingled with and surrounded by macrophages, monocytes, and lymphocytes (Fig. 1). In some cases, the granulomas are surrounded by fibroblasts and fibroblast-derived connective tissue products. The epithelioid cells are felt to be derived from tissue macrophages and are approximately 20 µm in diameter and 25 to 45 µm in length. They have ample, pale-staining cytoplasm, well-defined boundaries, and a central or eccentrically placed oval nucleus. Ultrastructural studies reveal abundant mitochondria, abundant rough and smooth endoplasmic reticulum, large numbers of vesicles, and a well-developed Golgi apparatus, suggesting that these cells have an enhanced secretory capacity. The multinucleated giant cells are believed to form from fused epithelioid cells. They are 150 to 300 µm in diameter and resemble the epithelioid cells ultrastructurally.

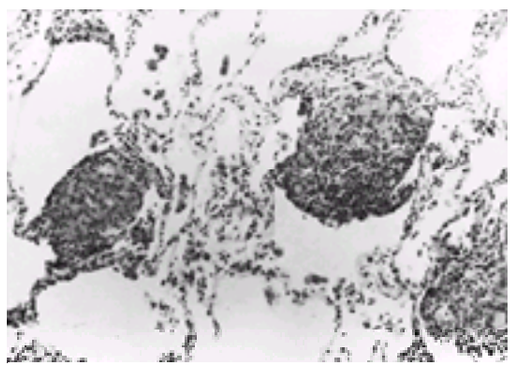

FIG. 1. Lung biopsy specimen demonstrating noncaseating granulomas in the lung interstitium.

The lymphocytes in and around these granulomas are often larger and contain more organelles than their circulating relatives. Characterization using monoclonal antibodies has shown that most of the T cells express the CD4 (OKT4) antigen, which is usually associated with a helper/inducer phenotype, and a minority express the CD8 (OKT8) antigen, which is usually associated with a cytotoxic/suppressor phenotype. As a result, the ratio of helper/inducer lymphocytes to cytotoxic/suppressor lymphocytes (CD4/CD8 ratio) in sarcoid granulomas is increased and parallels that noted in the cells obtained by bronchoalveolar lavage (BAL).

Noncaseating granulomas may be found in any organ in the body. In the lung they tend to be peribronchial, interstitial, and subpleural in location. Perivascular granulomas are also commonly noted. These lesions rarely extend past the vascular adventitia, and luminal distortion and endothelial cell disruption are rare. True vasculitis can be found in 42%–67% of lung biopsy specimens in sarcoidosis. However, in the vast majority of cases, the vasculitis is a minor aspect of the lesion. When vasculitis is prominent, alternative diagnostic possibilities should be considered, such as necrotizing sarcoidal vasculitis or Wegener's granulomatosis.

Interstitial Pneumonitis

Although the epithelioid granuloma is the characteristic lesion of sarcoidosis, it is probably not the first lesion to be present. The granulomas are preceded by, and then noted in conjunction with, an interstitial pneumonitis characterized by macrophages and lymphocytes, the majority of which are T cells. The macrophages and lymphocytes in these infiltrates appear to be activated, as they are larger and contain more organelles than corresponding cells in the circulating pool. The exact relationship between the intensity of the interstitial pneumonitis and the density of granuloma formation is not understood. The possibility that the granulomas are a consequence of the interstitial pneumonitis may explain why most studies find that the granulomas are most prominent when the interstitial pneumonitis is least intense, and vice versa.

Tissue Fibrosis

The interstitial pneumonitis and granulomatous inflammation seen in sarcoidosis are dynamic processes. Some lesions remain cellular for an extended period of time. In contrast, the majority resolve, either spontaneously or in response to steroid therapy. Approximately 75%–80% of these resolving lesions heal with preservation of the normal parenchymal architecture. In the rest, the fibroblasts at the periphery of the granulomas proliferate and increase their production of collagens and other matrix molecules. As a result, the granuloma is replaced in a centripetal fashion with scar tissue. In the process, normal alveolar and bronchial architecture are distorted and the pulmonary vascular surface area is compromised. Bronchiectasis and cystic parenchymal lesions can result, and in the most severe cases, honeycombing and pulmonary hypertension can occur.

IMMUNOPATHOGENESIS

Sarcoidosis is the prototypic example of a compartmentalized immune response. Heightened cell-mediated immunity is seen within the lung and at other sites of disease involvement. In contrast, depressed cell-mediated immunity, often with cutaneous anergy, is seen in the peripheral circulation. Studies during the last few decades have added significantly to our understanding of the cellular events involved in the inflammatory and fibrotic phases of this disease. As a result, we have an improved understanding of the state of activation and effector function of the cells in sarcoidal infiltrates, a picture of how these alterations mediate pulmonary inflammation, and a preliminary understanding of the role that cytokines may play in granuloma formation.

T Cells

In sarcoidosis, helper T lymphocytes accumulate at sites of disease activity. The ratio of helper ($CD4^+$) to suppressor ($CD8^+$) cells is increased in bronchoalveolar lavage fluid (BALF). The T cells that accumulate in the lungs of patients with sarcoidosis and are found in BALF are activated, as they express markers of cell-surface activation, such as the major histocompatibility complex (MHC) DR antigen, the VLA-1 late activation antigen, and the interleukin-2 (IL-2) receptor (Tac antigen). Unlike unstimulated T lymphocytes, they also spontaneously produce a variety of cytokines, including IL-2, interferon-g (IFN-g), monocyte chemotactic factor (MCF), and a factor (possibly IL-6) that induces the differentiation of B cells to immunoglobulin-secreting cells. The IL-2 that is produced by sarcoid T cells appears to bind to the IL-2 receptor and stimulates T-cell proliferation in an autocrine and/or paracrine fashion. Interestingly, although BALF T cells are spontaneously activated, like peripheral lymphocytes, their response to “recall” antigens such as purified protein derivative (PPD) and *Candida* is decreased. The reason for this is not clear. This decreased memory function may explain in part the cutaneous anergy observed clinically in some patients with sarcoidosis.

T cells recognize foreign antigens via their T-cell receptors (TCR). Each T cell expresses a receptor for a unique antigen. The diversity of receptors necessary to encode an appropriately diverse immune repertoire is generated by creating TCR that differ in the constant (C), joining (J), and variable (V) regions of the two proteins that make up the heterodimeric TCR complex. In an attempt to identify the agent(s) causing the lymphocytosis in sarcoidosis, the TCR on the surface of BALF and peripheral blood lymphocytes have been extensively studied. These studies have shown that BALF T lymphocytes are not a clonal population. Some studies have, however, detected a distinct bias for the use of TCR with the V_b8 and $V_a2.3$ variable region subtypes and the C_b1 constant region subtype. Others have reported

subgroups of individuals who have sarcoidosis with expression in blood or lung of one or more of five V_b gene families (V_b5, V_b8, V_b15, V_b16, V_b18). These findings suggest that T-cell activation in sarcoidosis is not a nonspecific process. Instead, the lymphocytosis appears to be a specific response to a limited number of antigens.

The majority of T cells in sarcoidosis lesions express a and b TCR proteins (e.g., they are ab T lymphocytes). However, a subgroup of individuals with sarcoidosis has been reported in which the BALF T lymphocytes contain gd TCR. This observation is quite interesting, as gd T cells may play an important role in the cellular immune response to mycobacterial antigens and mucosal immunity. Immunohistochemical studies, however, have failed to detect gd T cells within sarcoid lymph nodes. This discrepancy has not yet been resolved. However, it may reflect differences in the kinetics of T-cell accumulation, as gd T cells may be found only at sites of active early alveolitis.

T-Lymphocyte Subsets

Recent studies of murine, and to a lesser extent human, lymphocytes have demonstrated the existence of subpopulations of cells based on the patterns of cytokines that they produce. Two major subpopulations of CD4 (and other) lymphocytes have been noted, Th1 (T helper) and Th2 cells. Th1 cells produce IFN-g and IL-2, cytokines that are important in macrophage activation. These cells are felt to be mediators of delayed-type hypersensitivity responses. In contrast, Th2 cells express IL-4 and IL-5, cytokines that are important in antibody-mediated responses, IgE class switching, and eosinophilia. Th2 cells are therefore felt to be mediators of humoral and eosinophil-mediated disorders, such as atopy and allergy. These lymphocyte subsets also cross-regulate each other, with Th1 cell-derived IFN-g downregulating the cytokine production and proliferation of Th2 cells, and Th2-derived Il-4 and Il-10 having similar inhibitory effects on Th1 cells. In addition, the macrophage-derived cytokines IL-10 and IL-12 play an important role in the regulation of these processes, with IL-12 augmenting Th1 responses and IL-10 augmenting Th2 responses.

The Th1-Th2 paradigm provides a theoretical explanation for why cell-mediated immunity dominates in some circumstances, whereas antibody-based responses predominate in others. A variety of lines of evidence suggest that Th1-mediated processes play an important role in sarcoidosis. A variety of experimental granulomatous models have been shown to be Th1-mediated. In addition, BALF studies of patients with sarcoidosis have demonstrated increased levels of IFN-g, IL-2, and IL-12 and low or undetectable levels of IL-4, IL-5, and IL-10. Similarly, T cells from the lungs of patients with sarcoidosis produce exaggerated amounts of IL-1 and IFN-g. Additional experimentation will be required to confirm the impression that sarcoidosis is a Th1-predominant disorder.

Monocytes/Macrophages

Monocytes, macrophages, epithelioid cells, and giant cells are important participants in the alveolitis of patients with sarcoidosis. The macrophages appear to be activated in vivo, because, in contrast to the alveolar macrophages of normal persons, they spontaneously release proinflammatory cytokines, such as IL-1, IL-6, tumor necrosis factor (TNF), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), and secrete increased quantities of 1,25-dihydroxyvitamin D, angiotensin-converting enzyme, and reactive oxygen metabolites, such as hydrogen peroxide. Sarcoid alveolar macrophages also have an increased capacity to present antigen compared with normal macrophages. This may reflect the increased adhesiveness of sarcoid macrophages and lymphocytes. In accord with this concept, sarcoid alveolar macrophages express increased amounts of the cellular surface adhesion molecules leukocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1). In addition to secreting cytokines, these macrophages express cell surface IL-2 receptors and can thus be activated by the IL-2-secreting T cells at sites of inflammation.

Fibroblasts

Fibroblasts have been traditionally thought of as effector cells that, under the influence of T cells and macrophages, produce matrix components, such as collagen. The demonstration that IL-1 and TNF regulate fibroblast production of types I and III collagen has provided additional support for the concept that dysregulated cytokine production by activated mononuclear cells can lead to fibroblast activation and tissue fibrosis in sarcoidosis. It is now being increasingly appreciated, however, that fibroblasts are also important immune effector cells at sites of inflammation. IL-1 and TNF can induce fibroblast production of a wide variety of cytokines, including IL-6, monocyte chemotactic peptide-1 (MCP-1), IL-8, IL-11, leukemia inhibitory factor, G-CSF, and GM-CSF. IL-6, MCP-1, and the CSFs may be particularly important in sarcoidosis. IL-6 activates the acute-phase response, B-cell immunoglobulin production, and T-cell proliferation; MCP-1 recruits fresh peripheral blood monocytes to sites of inflammation; and the CSFs activate local macrophages. IL-1 and TNF can also increase the adherence of T lymphocytes to lung fibroblasts, a mechanism by which fibroblasts may contribute to the compartmentalized activation of T cells seen in this granulomatous disorder.

Mechanisms of Tissue Inflammation in Sarcoidosis

Inflammatory responses in the sarcoid lung are therefore regulated, at least in part, by a complex network of interacting cytokines. The majority of the alveolar macrophages in the lung are derived from circulating blood monocytes. They enter the lung along chemotactic gradients and have a limited but definite capacity to proliferate locally. Infectious agents and/or noxious stimuli that reach the lung via the airways can activate resident macrophages to produce TNF, IL-6, IL-8, transforming growth factor-b (TGF-b), platelet-derived growth factor (PDGF), modest amounts of soluble IL-1b, and insulin-like growth factor (IGF). IL-8, in conjunction with IL-1, TNF, activated complement fragments, and other chemotactic agents, activates and recruits leukocytes to the lung. This recruitment is at least partially a consequence of cytokine-enhanced endothelial cell adhesion molecule expression. The cytokines also interact with antigen-presenting cells (such as alveolar macrophages and/or dendritic cells) to activate T lymphocytes. Activated T lymphocytes express high-affinity IL-2 receptors and produce a variety of cytokines, most notably IL-2, IFN-g, and IL-6. IL-2, as noted above, acts in an autocrine and/or paracrine fashion to stimulate lymphocyte proliferation. IFN-g and IL-2 activate local macrophages, and IL-6 contributes to the proliferation and terminal differentiation of B lymphocytes into antibody-producing plasma cells. IL-1, TNF, and other moieties also stimulate local stromal cells, such as fibroblasts, to produce cytokines such as IL-6, MCP-1, IL-1a, and colony-stimulating factors. These proinflammatory molecules further augment local T-cell and B-cell responses and activate local macrophages. The IL-1, TNF and IL-6 that are produced also enter the systemic circulation, where they stimulate the production of acute-phase proteins and induce fever. In addition, TGF-b, IL-1, PDGF, and IGF may also stimulate the fibrotic response, as under appropriate circumstances each can stimulate fibroblast proliferation and/or collagen production.

As noted above, the alveolar macrophages and T cells in the lungs of patients with sarcoidosis appear to be activated in vivo. These cells express cytokine receptors and produce, in an exaggerated fashion, many of the cytokines responsible for the interactions noted above. Specifically, alveolar macrophages express IL-2 receptors and produce IL-1, TNF, GM-CSF, PDGF, and TGF-b. T-cell IL-2 receptor expression and IL-2, IFN-g, and MCF production are also augmented. The IFN-g that is produced may be a key mediator in the pathogenesis of this disorder, as IFN-g activates macrophage IL-1 production, 1,25-dihydroxyvitamin D production, hydrogen peroxide production, IL-2 receptor expression, and macrophage fusion into multinucleated giant cells. MCF encourages monocyte entry into sites of inflammation, and the IL-1 and TNF that are produced activate stromal cell IL-6 production. IL-1, TNF, and IL-6 induce fever and stimulate the heightened acute-phase response characteristically seen in patients with sarcoidosis. The elevated levels of IL-6 may also contribute to the polyclonal hypergammaglobulinemia seen in this disorder.

The Kveim Reaction

It has been known since 1941 that in patients with sarcoidosis a localized cutaneous nodule often develops 2 to 6 weeks after intradermal injection of an extract of spleen or lymph node from another patient with sarcoidosis. Biopsy specimens of these Kveim-Siltzbach test lesions exhibit histopathologic similarities to sarcoid granulomas. Moreover, Kveim-Siltzbach lesions and sarcoid granulomas have a similar distribution of $OKT4^+$ and $OKT8^+$ lymphocytes and a similar distribution of specific Vb and T-cell subsets. Despite these similarities, there are several reasons why the Kveim reaction cannot be classified as a true immunologic response. First, a delayed-type hypersensitivity reaction becomes positive within 48 to 72 hours and resolves within a week. In contrast, Kveim nodules develop after 4 to 6 weeks and persist for several months. Second, despite an intensive search, a specific antigen has not been identified in this material. Attempts to induce patient lymphocytes to proliferate or secrete cytokines after in vitro exposure to Kveim material have been largely unrewarding.

CLINICAL MANIFESTATIONS

The manifestations of sarcoidosis in persons who come to medical attention vary with their ethnic and racial background and the degree to which the local medical community utilizes chest radiographic screening that would detect milder or asymptomatic forms of the disease. Sarcoidosis can involve and cause symptoms in virtually any organ in the body. A detailed description of every manifestation is beyond the scope of this chapter. Instead, attention is focused on the major modes of presentation and patterns of organ involvement.

Presentation

As many as 50% of patients with sarcoidosis are asymptomatic at the time of diagnosis. Physicians become aware of these patients as a result of abnormalities noted incidentally on chest x-ray films that have been performed for other reasons. Patients who are symptomatic at the time of presentation generally have pulmonary, ocular, dermatologic, or systemic complaints (Table 1). Overall, pulmonary symptoms are noted in 15%–40% of patients presenting with sarcoidosis. Shortness of breath, dyspnea on exertion, cough, and substernal chest pain are common. Between 10% and 32% percent of patients with sarcoidosis present with skin lesions. Erythema nodosum is seen approximately twice as often as the other, more specific skin manifestations, and is frequently found in association with fever, malaise, and

polyarthralgias. Maculopapular lesions, nodules, and ulcers also can be presenting manifestations. Granulomatous infiltration of old scars resulting in swelling, purple discoloration, and occasionally tenderness also may cause the patient to seek medical attention. Approximately 10%–25% of patients present with ocular symptoms, most commonly caused by acute uveitis and consisting of redness of the eye, tearing, cloudy vision, and photophobia. This type of acute ocular involvement is often seen in association with erythema nodosum and bilateral hilar adenopathy. Systemic symptoms are reported by approximately 40% of patients and are more common in blacks and Asians from the Indian subcontinent. The fever is usually mild, and weight loss is usually limited to 5 to 15 lb within the preceding 3 months. However, temperatures as high as 104°F, more severe weight loss, and night sweats, anorexia, fatigue, and myalgias are well described.

Complaint	Percentage of patients
Asymptomatic	12–35
Systemic	15–40
Fatigue	20–30
Malaise	15
Weight loss	20–30
Fever	15–22
Night sweats	15
Weakness	10
Chills	10–15
Respiratory	15–40
Cough	30–40
Dyspnea	20–30
Sputum production	10–12
Hemoptysis	1–3
Chest pain	15–25
Skin lesions	10–28
Ocular symptoms	10–20
Joint complaints	5–17
Neurologic symptoms	2–5
Cardiac symptoms	1–5

TABLE 1. *Presenting complaints of patients with sarcoidosis*

Intrathoracic Involvement

Respiratory tract involvement is the most common manifestation of sarcoidosis. In 90% of patients, signs and symptoms of respiratory sarcoidosis are present at some time during the disease. The true incidence of respiratory involvement may actually be higher, as biopsy specimens of patients with sarcoidosis whose lungs are radiographically and physiologically normal often reveal granulomas. Parenchymal lung involvement and lymph node enlargement are the most common thoracic manifestations. Airway, pleural, and blood vessel involvement are also well documented.

Lymph Node and Parenchymal Involvement

By international convention, a staging system for sarcoidosis has been devised based on the appearance of a patient's chest x-ray film (Table 2). Up to 8% of patients present with stage 0 disease. They have evidence of extrathoracic disease and normal chest x-ray findings. As mentioned, a high percentage of these patients have granulomas on lung biopsy, indicating subclinical involvement of the pulmonary parenchyma. Approximately 40%–60% of patients present with stage I disease. The chest x-ray films of these patients demonstrate bilateral hilar lymphadenopathy, with or without paratracheal adenopathy, but without radiographically apparent lung infiltrates. Stage II radiographs are noted in 15%–30% of patients at the time of diagnosis. These radiographs demonstrate bilateral hilar adenopathy (with or without paratracheal adenopathy) with associated lung field involvement. The remaining 10%–15% of patients with sarcoidosis present with stage III radiographs, which show lung field involvement only. Patients without adenopathy whose lung field involvement is notable for severe pulmonary fibrosis, volume loss, cysts, bullae, and honeycombing are defined as having stage IV disease by some (but not all) investigators (Fig. 2).

Stage	Radiographic abnormality
0	None
I	Hilar, mediastinal, or paratracheal adenopathy
II	Hilar, mediastinal, or paratracheal adenopathy with pulmonary parenchymal abnormalities
III	Pulmonary parenchymal abnormalities without adenopathy
IV	Fibrobullous pulmonary paraenchymal disease without adenopathy

TABLE 2. *Staging of sarcoidosis by chest radiograph*

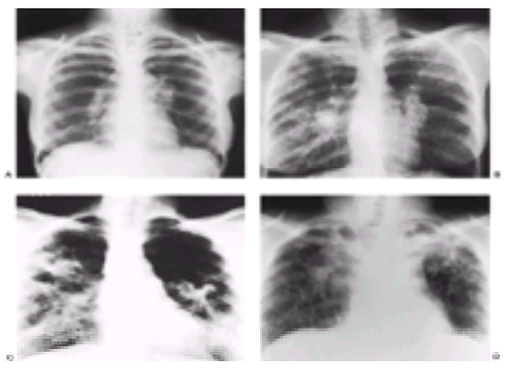

FIG. 2. Radiographs illustrating the different stages of sarcoidosis. **A:** Stage I. Bilateral hilar adenopathy and paratracheal adenopathy with normal lung fields. **B:** Stage II. Bilateral hilar adenopathy with interstitial lung field involvement. **C:** Stage III. Lung field involvement only. **D:** Stage IV. Severely fibrotic lungs with volume loss and cyst formation.

Radiographically, bilateral hilar adenopathy is the most common pattern of lymph node involvement in sarcoidosis. This enlargement can be striking, causing some to refer to the lymph nodes as “potato” nodes. Paratracheal adenopathy has been reported in up to 71% of cases. This adenopathy is less common on the left, because the left paratracheal lymph nodes are located more posteriorly, are smaller in size, and are fewer in number than their counterparts on the right. Aortopulmonary window and subcarinal adenopathy are noted in 33%–75% and approximately 21% of patients, respectively. By virtue of their location, these lymph nodes can, on rare occasion, cause symptoms by compressing the esophagus and nearby bronchi and vessels. When sarcoidosis causes anterior mediastinal lymph node enlargement, hilar adenopathy is almost always present. Lymphomas, metastatic malignancies, and other pathologic conditions must be strongly considered when isolated anterior mediastinal adenopathy is present. Similarly, posterior mediastinal adenopathy and unilateral hilar adenopathy are rare in sarcoidosis and should cause the physician to pursue other diagnostic possibilities. Parenchymal involvement in sarcoidosis can take on a variety of radiographic appearances. It is most commonly symmetric, diffuse and reticular, reticulonodular, or finely nodular in appearance. Symmetric bilateral lesions of the upper lobe or lesions predominant in the mid-lung field are also well documented, as are diffuse alveolar infiltrates. Unilateral disease, multiple large nodules, and even solitary nodules have been reported. However, alternative diagnostic possibilities must always be looked for when these patterns are noted. When sarcoidosis progresses, the parenchymal infiltrates become coarser and coalesce, and pulmonary architecture becomes distorted. This can cause the development of bronchiectasis, cysts, bullae, and, at worst, a honeycombed lung with volume loss, signs of pulmonary hypertension, and cor pulmonale.

Computerized tomography (CT) and magnetic resonance imaging (MRI) of the chest are more sensitive than plain chest radiographs, as they can reveal focal pulmonary parenchymal abnormalities in patients with stage O or stage I disease by chest radiograph. It has been suggested that the presence of ground-glass densities on CT in sarcoidosis and other infiltrative lung diseases may correlate with an inflammatory state likely to be responsive to treatment. The practical value of

this information in terms of prognosis or correlation with functional status remains to be determined.

The architectural distortion that takes place in patients with advanced sarcoidosis predisposes them to a number of complications. Areas of cavitation and bronchiectasis are susceptible to repeated infections. In addition, mycetoma caused by *Aspergillus* (and rarely other fungi) can form in these cavities and have been reported in as many as 40% of patients with cavitary disease. Progressive pleural thickening in the area around a cavity may be the earliest indication that an aspergilloma is forming. CT may be useful in demonstrating these structural abnormalities. Diagnosis requires the presence of IgG-precipitating antibodies to the fungus and demonstration of a mycetoma in the cavity by conventional chest radiography or CT. These aspergillomas can cause hemoptysis that, on occasion, may be life-threatening. Treatment of patients with mycetoma and massive hemoptysis is often problematic, as their underlying respiratory insufficiency precludes surgery for some and increases the risk of surgery for the others. In patients who cannot be treated surgically, anecdotal evidence suggests that bronchial arterial embolization and intracavitary instillation of amphotericin B may be useful. Less commonly, in patients with mycetoma a hypersensitivity reaction develops to the colonized fungus. This can be manifested as a bronchospastic lung disorder with many of the clinical and immunologic characteristics of allergic bronchopulmonary aspergillosis.

Airways Involvement

Endobronchial biopsy specimens reveal a granulomatous infiltration of the mucosa and submucosa in 30%–70% of patients with sarcoidosis. At its mildest, this involvement does not alter the appearance of the bronchial mucosa. When more severe, nodules are seen, and a cobblestone pattern has been described. As in the interstitium of the lung, this granulomatous infiltration can lead to a fibrotic reaction causing fixed lesions and, in its most severe form, diffuse bronchial stenosis with bronchial occlusion (Fig. 3). Endobronchial involvement can be seen in all radiographic stages of the disease. The lesions may cause airway narrowing, atelectasis, and ventilation-perfusion mismatching. The clinical manifestations of patients with severe endobronchial involvement are often different from those of the usual patient with sarcoidosis. Like patients with asthma, chronic obstructive pulmonary disease (COPD), or upper airway obstruction, they can have repeated pneumonias and bronchitis and experience dyspnea, stridor, chronic cough, and recurrent episodes of bronchospasm. Bronchiectasis may also result.

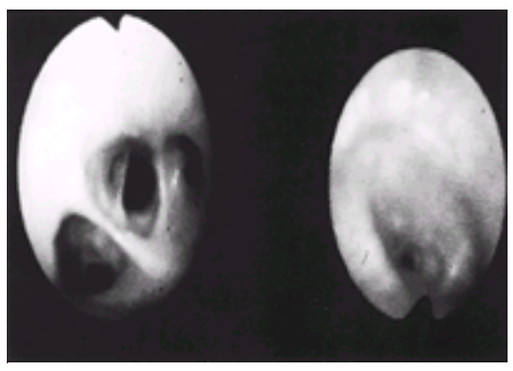

FIG. 3. Comparison of the appearance of a normal endobronchial tree (*left*) and the endobronchial tree of a patient with bronchial stenosis caused by sarcoidosis (*right*).

Pleural Involvement

Pleural involvement in sarcoidosis is relatively uncommon, occurring in 1%–12% of patients. This involvement can be manifested as pleural thickening, pleural effusion, or spontaneous pneumothorax. Effusions occur with equal frequency on the right and left and are bilateral 33% of the time. They are usually small or moderate in size. Massive effusions are rare. Pleural biopsy may show noncaseating granulomas, and presumably this granulomatous infiltration is the cause of the effusion. Vascular compression from mediastinal adenopathy is rarely a cause of pleural effusion in patients with sarcoidosis. The pleural fluid is usually exudative, occasionally hemorrhagic, and usually shows a predominance of lymphocytes. An increase in eosinophils may also be seen. Effusions have been described in patients with all radiographic stages of sarcoidosis. However, they are more common in patients with widespread parenchymal lung disease and have not been reported as the sole manifestation of the disease. The presence of a pleural effusion in a patient with sarcoidosis must always be interpreted with caution, and other causes of pleural disease, including tuberculosis, mycotic or bacterial infections, congestive heart failure, and malignancies, must always be considered. The natural history of pleural effusions in sarcoidosis is not totally known. Most appear to resolve without gross residua, either spontaneously or in association with steroid therapy. Progression to chronic pleural thickening has been reported.

Spontaneous pneumothorax in sarcoidosis is usually caused by the rupture of subpleural blebs or the necrosis of subpleural granulomas. This occurs most commonly in patients with advanced fibrotic lung disease with upper lobe bullae, but it can also occur in patients with stage O or stage I disease.

Pulmonary Vasculature

Granulomatous vasculitis involving both arteries and veins has been described in patients with sarcoidosis but is generally asymptomatic. On rare occasions, it can cause pulmonary hypertension.

Pulmonary Physiology

In 1940, Bruce and Wassen demonstrated a reduction in vital capacity and total lung capacity in the first study of the lung function of patients with sarcoidosis. Subsequent studies have confirmed these observations and have demonstrated that although the pulmonary physiologic parameters of some patients with sarcoidosis are normal, in most cases they are not. Like most other interstitial lung diseases, sarcoidosis commonly causes restrictive physiology and a gas transfer abnormality. The restrictive defect is manifested by reduced lung volumes and decreased lung compliance in the presence of normal large-airway function. The gas transfer abnormality is characterized by a reduced diffusing capacity for carbon monoxide.

Dysfunction of large and small airways resulting from the peribronchial distribution of granulomas is also an important component of the pathophysiology of sarcoidosis. Large-airways obstruction with a decreased FEV_1/FVC ratio is noted in a minority of patients. It has been described in all radiographic stages of sarcoidosis but is more common in patients with stage III or stage IV disease. It is usually caused by bronchial distortion and/or bronchiectasis from granulomas, edema, and scarring. It is rarely reversible and may cause symptoms of wheezing and dyspnea. If appropriately tested for, small-airways dysfunction can be seen in the majority of patients with sarcoidosis. These alterations are the result of peribronchial and endobronchial involvement or airways hyperreactivity and can be seen in all radiographic stages of the disease.

Patients with normal or mildly abnormal pulmonary function tests usually have normal alveolar-arterial oxygen gradients, normal arterial blood gases, and normal exercise tests. Occasionally, exercise testing unmasks modest abnormalities in the alveolar-arterial oxygen gradient, even in patients with stage O or stage I sarcoidosis. As the disease worsens, the alveolar-arterial oxygen gradient at rest increases. This is followed by exercise-induced desaturation and then hypoxia at rest. When carbon dioxide retention is noted, it is almost always the result of advanced disease, often with incipient respiratory failure.

The fact that a significant percentage of patients with stage O or stage I disease on chest x-ray films have restrictive pulmonary function demonstrates that pulmonary function tests are more sensitive in detecting parenchymal lung disease than are chest radiographs. Increases in alveolar-arterial oxygen gradient with exercise may be the most sensitive physiologic parameter, followed by the carbon monoxide diffusing capacity and then the vital capacity. Overall, the degree of physiologic impairment in sarcoidosis correlates with the radiographic stage of disease. Patients with stage O or stage I disease usually have mild physiologic derangements, and patients with stage III or stage IV disease tend to be the most severely restricted (and/or obstructed). The overlap between these categories is large enough, however, to make it difficult and not clinically useful to predict a given patient's pulmonary function from the radiographic stage.

Studies of structure-function relationships in sarcoidosis have shown that pulmonary function tests generally correlate with the overall severity of morphologic changes on lung biopsy. Patients with normal or minimally abnormal pulmonary function tend to have mild inflammatory changes with minimal fibrosis on biopsy. Patients with severely abnormal pulmonary function tend to have more extensive inflammatory changes and/or severe fibrotic changes on biopsy. However, these studies have also shown that the correlation between physiologic abnormalities and pulmonary histology has limitations. Pulmonary function tests may differentiate extremes of histology but do not accurately differentiate moderate from severe disease. In addition, pulmonary function tests do not distinguish the degree to which a defect is caused by interstitial pneumonitis, granulomas, or fibrosis. Thus, in a given individual at a single point in time, pulmonary function tests cannot predict with absolute certainty the

severity, character, or reversibility of the histologic lesion that is present.

Studies of the natural history of sarcoidosis have demonstrated that pulmonary physiologic alterations over time tend to correlate with changes in the severity and activity of disease. Patients whose parenchymal lesions are improving roentgenographically usually have an improvement in their vital capacity and diffusing capacity. Similarly, patients whose parenchymal sarcoidosis is radiographically stable or worsening usually exhibit declines in their vital capacity and/or diffusing capacity. The correlations between histologic severity, disease progression, and pulmonary function provide the rationale for the use of pulmonary function tests in the ongoing evaluation of patients with sarcoidosis. It is important to point out, however, that at the present time there are no pulmonary function criteria that allow the clinician to predict accurately the natural history or response to therapy of a given patient.

Extrathoracic Manifestations

Ophthalmic

In 1936, Heerfordt's syndrome of uveitis, salivary gland involvement, seventh cranial nerve palsy, and fever was recognized to be a form of sarcoidosis. Subsequent studies have shown that the eye and adnexa are involved in 11%–60% of patients with sarcoidosis and that ocular involvement is an important cause of morbidity in this disorder. The types of ocular disease noted in patients with sarcoidosis can be conveniently classified according to whether they involve the anterior eye, the posterior eye, or the orbit and other structures.

The anterior structures of the eye are involved in 80%–90% of patients with ophthalmic sarcoidosis. Granulomatous uveitis and granulomatous conjunctivitis are the two most common lesions. Iris nodules, band keratopathy, and interstitial keratitis occur far less frequently. The granulomatous uveitis can be acute or chronic. Patients with acute uveitis can experience the sudden onset of unilateral optic injection with tearing, blurred vision, and photophobia. Physical examination often reveals circumcorneal ciliary injection, aqueous cells and flares, and “mutton fat” keratitic precipitates. In contrast, chronic uveitis develops more slowly and insidiously. It may be unilateral or bilateral, and when symptomatic, it usually causes pain and blurring of vision. Although keratitic precipitates are often noted, ciliary injection can be absent. Chronic uveitis can lead to adhesions between the iris and lens, glaucoma, cataract formation, and blindness. Chronic uveitis is often seen in association with other manifestations of chronic sarcoidosis, such as lupus pernio, cutaneous plaques, bone lesions, and pulmonary fibrosis. Granulomatous involvement of the conjunctivae occurs in 10%–60% of patients. These conjunctival lesions can appear as tiny, translucent, pale yellow conjunctival follicles. Biopsy specimens of normal-appearing conjunctivae also can show granulomatous inflammation. This involvement can be asymptomatic or cause irritation, resulting in a gritty feeling in the eye.

The posterior structures of the eye are involved in approximately 25% of patients with ocular sarcoidosis. The retina, vitreous, and optic nerve can all be affected. Chorioretinitis, periphlebitis, and chorioretinal nodules are the most frequent lesions. Periphlebitis may be associated with visible evidence of lymphocytic infiltration of venous walls, termed “candle wax drippings.” Cellular aggregates (particularly $CD4^+$ T lymphocytes), hemorrhage and opacities in the vitreous, and local neovascularization are less common. Optic nerve involvement in sarcoidosis can take a number of forms. Papilledema resulting from increased intracranial pressure, optic atrophy, papillitis, optic neuritis, and optic disk granulomas are all well documented. Ninety-five percent of patients with posterior eye involvement also have anterior eye involvement. In addition, the presence of posterior eye involvement should alert the clinician to possible concomitant central nervous system disease, as the incidence of central nervous system involvement is increased in these patients.

Granulomatous infiltration of the lacrimal gland is the most common form of orbital involvement, occurring in 5%–15% of patients with ocular sarcoidosis. It is usually bilateral, often associated with parotid swelling, and can be the sole ocular manifestation. Chronic mass effect from extralacrimal soft-tissue involvement may also be seen. Hyposecretion of tears may occur with any of these and can cause a severe sicca syndrome mimicking that of Sjögren's syndrome. Retro-orbital granulomas are a less common orbital manifestation of sarcoidosis that have been reported to cause unilateral proptosis and hamper extraocular muscle function.

Lymphadenopathy

Granulomatous infiltration of lymph nodes is found in up to 95% of patients with sarcoidosis and may be solely microscopic. Granulomatous involvement may cause visible and palpable adenopathy that is usually symmetric and rarely massive. The nodes tend to be firm, rubbery, discrete, mobile, and painless and are rarely associated with changes in the overlying skin, ulceration, or sinus formation. All major lymph node groups can be involved. Cervical, axillary, epitrochlear, and inguinal lymphadenopathies are found in the order noted. The cervical lymph nodes are enlarged on the right more often than on the left and in the posterior triangle more often than in the anterior triangle. Preauricular, postauricular, submaxillary, submental, mesenteric, and retroperitoneal nodes also can be enlarged. Occipital lymphadenopathy is rare. Massive involvement of retroperitoneal or abdominal lymph nodes may rarely cause abdominal discomfort sufficient to warrant systemic therapy.

Cutaneous Involvement

Cutaneous involvement is seen in 20%–50% of patients with sarcoidosis and can be conveniently divided into two categories: nonspecific, nongranulomatous lesions and specific, granulomatous lesions. Erythema nodosum is the principal nongranulomatous skin lesion, occurring in 9%–17% of patients. Most commonly it is manifested as subcutaneous, erythematous, tender nodules that involve the anterior tibial and other extensor surfaces. Its onset is usually sudden, and its appearance may herald the beginning of the disease. It may be accompanied by a flulike syndrome with fever, fatigue, and polyarthralgia. In addition, it often exists in association with acute uveitis, an elevated sedimentation rate, and bilateral hilar adenopathy. As the lesions of erythema nodosum resolve, they become ecchymotic (erythema contusiformis) and can leave localized areas of hyperpigmentation. Biopsy specimens of erythema nodosum reveal a septal panniculitis. Erythema nodosum is not specific for sarcoidosis. The clinical picture and histology of erythema nodosum associated with sarcoidosis are indistinguishable from those of erythema nodosum associated with other diseases. However, the presence of erythema nodosum in sarcoidosis appears to have prognostic import. Patients presenting with erythema nodosum, polyarthralgias, and bilateral hilar adenopathy (Löfgren's syndrome) have a particularly favorable outcome, with at least 90% experiencing a spontaneous resolution of their disease within 6 to 12 months. In addition, in white patients, erythema nodosum alone may correlate with an improved prognosis.

Granulomatous skin lesions occur in 10%–35% of patients with sarcoidosis. In general, their presence confers an unfavorable prognosis, suggests a higher likelihood of extensive disease, and may warrant local or systemic treatment. Lupus pernio is a granulomatous lesion that is specific for sarcoidosis. It is a chronic, violaceous, nodular or plaquelike eruption on the nose, cheeks, and ears (Fig. 4) and can be associated with fusiform swelling and mutilation of the fingers. Its onset is usually insidious, its course is usually chronic, and it commonly results in significant scarring and deformity. It is most common in women between 40 and 60 years of age and is often associated with other manifestations of chronic sarcoidosis, such as pulmonary fibrosis, bone lesions, uveitis, and upper respiratory tract involvement. Granulomatous infiltration also may cause papules, plaques, nodules, ulcers, ichthyosiform lesions, psoriasis-like lesions, and scarring alopecia. Scarring is not a frequent outcome of these lesions, as it is in lupus pernio.

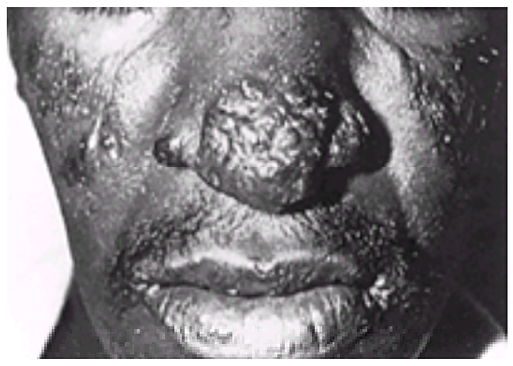

FIG. 4. Raised lesions of lupus pernio.

Neuroendocrine Involvement

Sarcoidosis causes clinically detectable nervous system disease in 10% of patients. Pathologic studies have shown that subclinical nervous system infiltration occurs in up to 15% of patients. Among patients with clinical neurosarcoidosis, 50%–75% have neurologic manifestations as their presenting feature. Multiple neurologic lesions are present in one third of such patients. Any structure in the central or peripheral nervous system may be involved, resulting in a wide spectrum of clinical disease.

Neurosarcoidosis may cause significant morbidity. It is also associated with a 10% mortality rate, which is approximately twice that of sarcoidosis in general.

A basal granulomatous meningitis is the most common pathologic lesion in the central nervous system of patients with sarcoidosis. It is clinically apparent in approximately two thirds and pathologically present in virtually all patients with central nervous system involvement. The basal predilection of these lesions explains the frequent involvement of the optic nerve, optic chiasm, pituitary, hypothalamus, and periventricular areas. This granulomatous meningitis also can extend along the perivascular space and disrupt the local parenchyma and vascular structures.

Cranial nerve involvement has been reported in 24%–73% of patients with neurosarcoidosis. Seventh (facial) nerve involvement is the most common neurologic manifestation of sarcoidosis. It usually presents as a unilateral peripheral lesion but may also occur bilaterally or in association with other cranial nerve abnormalities. The resulting palsy generally resolves spontaneously, but relapses can occur and result in sequelae such as spasms and contractions. The optic nerve is the next most frequently involved cranial nerve; symptoms and signs include decreased or blurred vision, papilledema, optic atrophy, visual field defects, and pupillary abnormalities. Visual evoked potentials may be abnormal in an asymptomatic patient with optic nerve involvement. Cranial nerves IX and X are the third most commonly involved cranial nerve complex in sarcoidosis; their involvement results in dysphagia, hoarseness, an absent gag reflex, an immobile soft palate, and vocal cord dysfunction. The eighth cranial nerve is the fourth most commonly affected; involvement results in deafness, vertigo, and a sensory-neural hearing loss.

Peripheral nerve involvement has been noted in 15%–18% of patients with sarcoidosis presenting as a mononeuropathy or polyneuropathy with sensory and/or motor abnormalities. As a result, pain, paresthesias, muscle weakness, and depression of tendon reflexes may be found. In one series, ulnar and peroneal nerves were the most frequently involved. A Guillain-Barré–like syndrome has also been described.

Meningeal involvement, with aseptic meningitis, has been reported to be present in 64% of patients with neurosarcoidosis, although most are asymptomatic. In these patients, examination of the cerebrospinal fluid generally shows hyperproteinorrachia, hypoglycorrhachia, and a lymphocytic pleocytosis. Cerebrospinal fluid levels of angiotensin-converting enzyme are elevated in 55% of patients. Cerebrospinal fluid levels of angiotensin-converting enzyme must be interpreted with caution, however, as similar elevations may be found in the setting of bacterial meningitis and tumors of the central nervous system. In patients with known systemic sarcoidosis and suspected neurosarcoidosis, an elevated level of angiotensin-converting enzyme in the cerebrospinal fluid may be helpful in following disease progression or response to therapy.

Hypothalamic-pituitary abnormalities have been noted in approximately 25% of patients with neurosarcoidosis. These patients manifest signs and symptoms caused by (1) anterior pituitary insufficiency, (2) abnormalities of water metabolism, and (3) compression or infiltration of the nearby optic chiasm. The pituitary and hypothalamus can be separately involved. Most studies show extensive infiltration and/or mass lesions in the hypothalamus, with a lesser degree of pituitary involvement. Central diabetes insipidus is the most common manifestation of hypothalamic sarcoidosis. Hypothalamic hyperphagia has also been described. Anterior pituitary insufficiency most commonly presents as gonadal dysfunction with decreased libido, impotence, or amenorrhea, and less commonly as hypothyroidism or adrenal insufficiency. A significant percentage of these patients have elevated prolactin levels and normal pituitary responses to hypothalamic releasing hormones, suggesting that the hypothalamus and hypothalamic stalk are the major sites of involvement.

The abnormal water metabolism that is found in most patients with hypothalamic-pituitary sarcoidosis appears to be of multifactorial origin. In some patients it is the result of partial or complete diabetes insipidus. Other patients appear to have primary abnormalities of thirst. Either or both these abnormalities may result in chronic hypernatremia.

Granulomatous masses may involve any part of the central nervous system. Whereas most of these are diffuse or infiltrating, some are manifested as space-occupying lesions. The clinical presentation of these lesions is not significantly different from that of mass lesions caused by other processes and can include headaches, seizures, localized neurologic dysfunction, papilledema, and uncal or cerebellar tonsillar herniation.

Intracranial hypertension can occur in sarcoidosis as a result of a number of mechanisms. Involvement of the ependyma and choroid plexus can alter cerebrospinal fluid dynamics. Chronic meningitis can cause obliteration of the subarachnoid space and aqueductal stenosis, and intraventricular granulomas can cause outlet obstruction of the fourth ventricle.

The symptoms that result from central nervous system lesions in sarcoidosis can vary depending on the anatomic site of the infiltrative process and the degree to which intracranial pressure is increased. Increased intracranial pressure can cause headache, nausea, vomiting, lethargy, and cranial nerve palsies. Cortical infiltration can mimic cerebrovascular accidents, and basal ganglion involvement can lead to a wide range of extrapyramidal manifestations, including choreiform movements, hemiballismus, and parkinsonism. Seizures occur in 5%–22% of patients with neurologic sarcoidosis. *Grand mal* seizures are most common, but partial, jacksonian, psychomotor, and myoclonic seizures can occur. The presence of seizures is generally associated with a poor prognosis. Patients may respond to corticosteroid therapy. Low-dose whole-brain radiation therapy has also been described as potentially beneficial.

Vascular compromise, manifested as strokes or transient ischemic attacks, rarely occurs in sarcoidosis. This is surprising, as perivascular and vascular infiltration of the meningeal and cerebral vessels, often with local infarction, is well described pathologically. Spinal cord involvement is also extremely rare in sarcoidosis; when present, it is caused by local meningeal involvement with extramedullary compression or intramedullary mass formation.

The diagnosis of neurosarcoidosis is generally facilitated by evidence of sarcoidosis in other organs. Compatible neurologic findings supported by CT, MRI, or cerebrospinal fluid data in the setting of histologic confirmation from other tissues may be adequate for diagnostic purposes. However, this may not obviate the need to examine neurologic tissue in situations in which other etiologies cannot adequately be ruled out.

The diagnosis of nervous system sarcoidosis in the absence of other manifestations of sarcoidosis may be extremely difficult. Biopsy of neurologic tissue or tissue from other, seemingly less involved organs (such as the lung or conjunctivae) may be necessary. Guidance for these biopsies may be provided by CT, MRI, pulmonary function tests, slit-lamp examination, or gallium scanning. The abnormalities noted with these studies are, however, often not specific for sarcoidosis.

Muscle

Skeletal muscle involvement in sarcoidosis can be documented in up to 80% of patients. In the vast majority, this involvement is asymptomatic. Symptomatic muscle disease may be manifested as nodules, myalgias, and frank myopathy. Acute myopathy, although rare, is more common in women. It presents as a polymyositis-like syndrome with muscle pain, weakness, and tenderness. Chronic myopathy is somewhat more common and generally poorly responsive to corticosteroids. It presents with the gradual onset of weakness and wasting and is associated with elevated levels of muscle enzymes and a myopathic electromyogram.

Liver

Although the liver is involved pathologically in 60%–90% of patients with sarcoidosis, clinically significant hepatic disease is infrequent. Small periportal granulomas are noted most commonly. A nonspecific mononuclear cell infiltrate with varying degrees of fibrosis can also be seen. The majority of patients are asymptomatic and have only low-grade increases in serum alkaline phosphatase, transaminases, or bilirubin levels. In some cases, modest hepatomegaly may be found. In a minority of patients, more serious involvement may take the form of chronic hepatocellular injury with secondary cirrhosis, hepatic encephalopathy, portal hypertension, or bleeding esophageal varices. Cases of Budd-Chiari syndrome have been reported. Sarcoidosis may also be associated with chronic intrahepatic cholestasis, which can be difficult to differentiate from primary biliary cirrhosis, and with extrahepatic biliary tract obstruction resulting from granulomatous involvement of the hepatic duct and surrounding lymph nodes.

Hepatic sarcoidosis may also be manifested as a fever of unknown origin (FUO). Patients with hepatic sarcoidosis presenting with FUO often also have abdominal organ, spleen, and lymph node involvement.

Spleen

Granulomatous infiltration of the spleen occurs in up to 60%–90% of patients with sarcoidosis; disease is usually clinically silent. Splenomegaly develops in 5%–15% of patients; in a minority of these, complications such as hypersplenism, splenic rupture, portal hypertension, and abdominal pain develop. Sarcoidosis is only one of many disorders that cause splenic granulomas. Thus, it is important to interpret splenic granulomas in the clinical context in which they are noted.

Heart

The most common cardiac abnormality in sarcoidosis is cor pulmonale, resulting from severe pulmonary disease. Primary cardiac involvement also occurs and is clinically recognizable in 3%–5% of patients. Granulomas, however, are found in up to 30% of patients with sarcoidosis at autopsy. No portion of the heart is immune to granulomatous infiltration. The myocardium is most frequently involved, with the left ventricular free wall being affected most commonly. Involvement of the ventricular

septum, the right ventricular free wall, and the atrial wall follow in order of decreasing frequency. When the left ventricle is involved, the granulomas are most commonly located in the papillary muscles and the free wall below the papillary muscles. The extent of infiltration and scarring and its proximity to vital structures such as the atrioventricular node and conduction pathways appear to be crucial determinants of the clinical import of cardiac involvement. The abnormalities that result from these lesions are quite varied, including arrhythmias, bundle branch blocks, congestive heart failure, mitral regurgitation, ventricular aneurysms, pericardial effusions, and sudden death.

Ventricular tachycardia is the most frequent major arrhythmia occurring in patients with cardiac sarcoidosis. Its appearance usually indicates extensive inflammatory scarring of the heart. Ventricular fibrillation and atrial arrhythmias are less commonly noted. When atrial arrhythmias exist, they are usually the result of atrial dilatation arising from left ventricular dysfunction and not the result of direct granulomatous infiltration. Complete heart block and bundle branch blocks also occur. They are usually caused by involvement of the cephalad portion of the intraventricular septum near the atrioventricular node and conduction bundles, respectively.

Valvular disease occurs in 3% of patients. Mitral regurgitation is well described and may be the result of papillary muscle dysfunction caused by infiltration of the papillary muscle or the left ventricular free wall below the papillary muscle. More often, the lesion is the result of altered papillary muscle dynamics resulting from left ventricular dilatation or dysfunction.

Extensive ventricular involvement can cause congestive heart failure. Ventricular aneurysms that exacerbate congestive failure and arrhythmias can also form. An association between long-term corticosteroid therapy and the development of aneurysms has been reported. However, definitive documentation that steroid therapy predisposes to aneurysm development is still lacking.

There are a number of reasons why establishing a clinical diagnosis of cardiac sarcoidosis may be problematic. First, the clinical manifestations of the disease—chest pain, palpitations, congestive heart failure, electrocardiographic changes, syncope, and light-headedness—are also manifestations of other, more common cardiac disorders. Second, when sarcoidosis causes cardiac dysfunction, it often does not cause dysfunction in other organ systems. Thus, the majority of patients with cardiac sarcoidosis do not have overt lung, eye, or skin involvement that might cause a physician to suspect this disorder.

As many as half of all patients with cardiac sarcoidosis may have electrocardiographic abnormalities. Ventricular arrhythmias are evident in up to 22% of patients. Because of this, Holter monitoring has been suggested as part of the routine evaluation of patients with sarcoid. Subclinical cardiac dysfunction can occasionally be detected by cardiopulmonary exercise testing. Endomyocardial biopsies are useful when they yield myocardial granulomas, but a nonspecific lymphocytic myocarditis is commonly encountered. In addition, the diagnostic sensitivity of endomyocardial biopsies is likely quite variable, given the patchy distribution of granulomatous changes in the heart and the inability of the procedure to obtain samples from the area of the heart that is likely involved. Lastly, a number of investigators have described a pattern of inhomogeneity of thallium uptake in the myocardium of patients with cardiac sarcoidosis. Involved areas are visualized as thallium defects at rest, which then disappear with exercise. This “reverse distribution” pattern is the opposite of that seen during thallium imaging in patients with ischemic coronary disease. The sensitivity and specificity of the “reverse distribution pattern” has not been defined. It is clear that the criteria for patient selection for exercise testing, endomyocardial biopsy, and thallium scanning are poorly defined, and the prognostic significance of cardiac abnormalities found are still unknown.

Electrolyte Abnormalities

Approximately 11% of patients with sarcoidosis are hypercalcemic. The hypercalcemia tends to be episodic in patients with acute sarcoidosis and persistent in patients with chronic disease. It can be mild or severe and life-threatening, and in some patients it is the sole reason for treatment with systemic steroids. Hypercalciuria occurs in 15%–60% of patients with sarcoidosis. When severe, it can cause nephrolithiasis, nephrocalcinosis, and renal insufficiency.

The hypercalcemia and hypercalciuria of sarcoidosis are at least partially a consequence of increased intestinal calcium absorption. This increased absorption is the result of elevated levels of 1,25-dihydroxyvitamin D caused by the accelerated conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. The increased 1-hydroxylation occurs in a parathyroid hormone-independent fashion in the macrophages of sarcoidal granulomas. Thus, sunlight exposure worsens the hypercalcemia seen in these patients.

Increased osteolysis also appears to play a role in the calcium disorder seen in some patients with sarcoidosis. This heightened resorption may may be a direct effect of osseous granulomas, or of bone-resorbing soluble factor(s) such as osteoclast-activating factor.

Kidney

Renal insufficiency in sarcoidosis is generally the result of hypercalcemia and/or hypercalciuria. Granulomatous changes are noted in the kidneys of 4%–40% of patients but rarely cause clinically significant renal dysfunction.

Granulomatous renal arteritis, glomerulonephritis, and altered renal tubular function have been rarely reported. Some investigators feel that sarcoid nephritis is a steroid-responsive disorder. Others believe that although steroid responses can be seen, relapses are common, and renal failure often occurs within 5 years of the clinical onset of the disease.

Joints

Joint signs and symptoms occur in approximately 10%–35% of patients with sarcoidosis. The major manifestations are an acute and chronic polyarthritis.

The acute polyarthritis is seen early in the course of the disease. It is usually a symmetric peripheral arthritis and periarthritis that most commonly involves the ankles and knees, and less commonly the elbows, wrists, and the small joints of hands and feet. Histologically, there is a nonspecific inflammatory synovitis. The clinical presentation includes pain, tenderness, restricted motion, soft-tissue swelling, and joint effusions that can be transient and occasionally precede other signs of the disease. This form of joint involvement is frequently seen in association with bilateral hilar adenopathy, fever, and erythema nodosum (Löfgren's syndrome), and is generally associated with a high rate of spontaneous remission. Erythrocyte sedimentation rates may be elevated. In the absence of bone involvement, radiographic studies are usually normal or reveal soft-tissue swelling. Rarely, periarticular osteoporosis is noted. Acute polyarthritis occurs more commonly in women than in men. It also is more likely to develop and be associated with uveitis, erythema nodosum, and spontaneous remission in individuals who are HLA-B8-positive.

A relapsing chronic polyarthritis develops in 3%–6% of patients with chronic sarcoidosis. Some of these patients have had a previous episode of acute sarcoid polyarthritis, but the majority have not. The shoulders, knees, wrists, ankles, and small articulations of the hands are most commonly involved. Erythema nodosum and fever are uncommon. This involvement can be asymmetric and is rarely monarticular. Radiographic studies reveal soft-tissue swelling, periarticular osteoporosis, mild narrowing of the joint space, and well-defined eccentric erosions. In addition, articular destruction and collapse may result from inflammatory extension into subchondral bone. Histologically, the process is characterized by a granulomatous inflammation of the synovium, articulations, and tendon sheaths. Synovial fluid analysis reveals increased protein, increased leukocytes, and occasionally a lymphocytosis of the joint fluid.

Bone

Osseous involvement occurs radiographically in 1%–13% of patients and is generally associated with chronic sarcoidosis. It is more common in blacks than in whites and is rarely seen without chronic cutaneous lesions (such as lupus pernio), ocular sarcoidosis, and overt lung involvement. Radiographically, sarcoidosis can affect the skeleton in a focal or generalized and usually asymmetric fashion and can cause osteolytic and, less commonly, osteosclerotic lesions. In all cases, these lesions are not specific for sarcoidosis, radiographically resembling the lesions of other diseases. Osteoporosis, cortical thinning, well-defined cysts, and rarefactions are the usual types of lytic lesions. They are encountered most frequently in the hands, with the wrists and feet being less commonly involved. When diffuse, they can cause a latticework or honeycomb pattern. In general, they are not associated with periosteal reactions or sinus tracts, and the joints are not involved except when bone adjacent to the joint is destroyed. Osseous sarcoidosis is generally asymptomatic except in cases in which soft-tissue swelling or bony deformity causes local symptoms. The prognosis for the small number of patients with progressive destructive bony changes is poor, as these lesions tend to be unresponsive to treatment.

Upper Respiratory Tract

Sarcoidosis involves the upper respiratory tract in approximately 2%–6% of patients. Although occasionally seen as an isolated lesion, it is most common in symptomatic patients with manifestations of chronic sarcoidosis, including lupus pernio. The nasal mucosa, pharynx, larynx, nasal bones, and palate can all be involved. Sarcoidosis causes the nasal mucosa to appear erythematous and granular. Epistaxis, stuffiness, crusting, and nasal discharge are common symptoms. In addition, adhesions, polypoid lesions, submucosal nodules, ulcerations, septal perforations, paranasal sinus extension, osteolytic destruction of the nasal bone, and saddle-nose deformities have all been described. Biopsies of the nasal turbinate may need to be performed to differentiate sarcoidosis from other nasal disorders.

Hematologic Manifestations

Hematologic manifestations of sarcoidosis include anemia, lymphopenia, eosinophilia, and thrombocytopenia. Of these, lymphopenia is the most common, occurring in more than half of patients with active disease. A low CD4 count is seen in the peripheral blood, although BAL often reveals an increased number of CD4 cells. Examination of the bone marrow may reveal granulomatous changes.

ESTABLISHING THE DIAGNOSIS

To establish the diagnosis of sarcoidosis, three criteria must be met: (1) The patient's clinical and radiographic presentation must be compatible with sarcoidosis, (2) a biopsy must demonstrate noncaseating epithelioid cell granulomas, and (3) other causes of granulomatous infiltration must be carefully excluded.

The first criterion for diagnosis is usually not difficult to meet, even though the clinical presentation of sarcoidosis varies widely depending on the type and extent of organ involvement. Tissue biopsy specimens can be obtained from a number of sites in the body. The sensitivity of some biopsy techniques for making the diagnosis of sarcoid are detailed in Table 3. The optimal site from which to take a specimen depends on the clinical manifestations, personal preferences, and the procedures that are performed proficiently at a given institution. The gold standard procedure is thoracotomy with open lung biopsy and lymph node sampling, which yields noncaseating granulomas in 90%–100% of patients with sarcoid. Muscle biopsy, scalene node biopsy, and mediastinoscopy also have high sensitivity. However, because of the invasive nature of these procedures and their small but definite incidence of serious complications, they are not the initial diagnostic procedure of choice. Thoracoscopic biopsy may also have a high yield. However, experience with this approach is still quite limited. At our institution, bronchoscopy with transbronchial biopsies is often the procedure of first choice. Because granulomas tend to congregate in the peribronchial area, the diagnostic yield of transbronchial biopsy is high. The procedure can be performed with topical anesthesia in an awake patient with minimal discomfort, and the risk for major complications (pneumothorax, bleeding, respiratory distress) is low. With bronchoscopy, granulomas are obtained in 70%–90% of patients with Stage I disease, 85%–95% of patients with Stage II disease, and 80%–90% of patients with Stage III disease. To achieve this level of sensitivity, it is recommended that at least 4–10 biopsies be obtained. 85%–95% of patients with stage II disease, and 80%–90% of patients with stage III disease. An added advantage of bronchoscopy is that it allows other specimens to be collected for cytologic and microbiologic examination to help rule out other conditions.

Site	Percentage of patients with sarcoidosis having a positive biopsy result	Comments
Skin	30–90	Biopsy of normal skin or erythema nodosum of little value
Liver	75	Large number of diseases cause hepatic granulomas; must be interpreted with caution
Muscle	50–85	Optimal sensitivity requires large biopsy specimen with extensive sectioning and pathologic examination
Conjunctiva	10–63	
Minor salivary gland	58	
Lacrimal gland	21	Higher sensitivity if only enlarged gland or glands that take up gallium 67 are sampled
Scalene lymph node	47–82	
Mediastinoscopy		
Stage I	90–95	
Stage II	90–95	
Stage III	50–63	
Bronchoscopy with transbronchial biopsy		Optimal sensitivity requires up to 4–10 biopsy specimens
Stage I	70–93	
Stage II	85–95	
Stage III	90–100	
Open lung biopsy	90–100	

TABLE 3. *Selected biopsy sites in sarcoidosis*

Biopsy of the skin, conjunctivae, salivary glands, and lacrimal glands may also reveal the diagnosis. Skin biopsies are useful only when the skin is clinically involved by lesions other than erythema nodosum. Biopsies of normal skin and erythema nodosum lesions provide little help in establishing the diagnosis. For conjunctival biopsy to be optimally sensitive, biopsy of clinically involved conjunctivae is necessary, and the fixed tissue must be carefully sectioned and intensively examined. The utility of blind biopsies of normal conjunctivae is still controversial. Similarly, lacrimal biopsies are positive most frequently when the gland is enlarged or positive on gallium scan.

The third criterion for diagnosing sarcoidosis is the exclusion of other causes of tissue granulomatosis (Table 4). Mycobacterial infection, fungal infection, berylliosis, hypersensitivity pneumonitis, granulomatous vasculitis, foreign-body granulomas, and granulomatous reactions in lymph nodes draining malignancies all need to be considered. Mycobacterial and fungal infections can usually be excluded by appropriate staining and culturing of tissue and secretions. However, the proper use and utility of PCR are still being evaluated. In addition, although up to 50% of patients with sarcoidosis are anergic, they usually demonstrate cutaneous sensitivity to tuberculin when actively infected with *M. tuberculosis.* A thorough history may be all that is required to rule out berylliosis and hypersensitivity pneumonitis. When hypersensitivity pneumonitis needs to be considered in greater depth, IgG-precipitating antibodies to the suspected causal antigen should be sought. The beryllium-induced blast transformation assay may be used to make a diagnosis of berylliosis. Histologic examination alone may be adequate to rule out the granulomatous vasculitides, foreign-body granulomas, and concomitant malignancies. If uncertainty remains, a biopsy specimen from a second site may be required.

Infectious diseases
Mycobacteria
Fungi
Leprosy
Syphilis
Cat scratch disease
Parasitic infection
Inflammatory diseases
Sarcoidosis
Berylliosis
Hypersensitivity pneumonitis
Granulomatous vasculitides
Eosinophilic granuloma
Foreign body reactions
Biliary cirrhosis
Crohn's disease
Neoplastic diseases
Lymphoma
Carcinoma
Other
Hypogammaglobulinemia

TABLE 4. *Differential diagnosis of noncaseating granulomas*

Clinical findings and liver biopsy may not allow the physician to differentiate with confidence chronic intrahepatic cholestasis caused by sarcoidosis from primary biliary cirrhosis. Assays for serum antimitochondrial antibodies can be helpful in these cases, because they are positive in 99% of patients with primary biliary cirrhosis and are usually negative in sarcoidosis. In addition, the demonstration of extrahepatic granulomas can be used to support a diagnosis of sarcoidosis.

Crohn's disease also can be difficult to differentiate from sarcoidosis. Both are characterized by the presence of noncaseating granulomas and may be associated with similar dermatologic, hepatic, and ocular lesions. In addition, patients with Crohn's disease may have abnormalities on pulmonary function tests and increased numbers of $OKT4^+$ lymphocytes on BAL. At present, these two diseases are probably best distinguished on the basis of clinical differences. Crohn's disease is usually localized to the digestive tract. In contrast, sarcoidosis is a systemic disease with prominent respiratory, ophthalmic, and cutaneous lesions.

Asymptomatic patients with normal physical examination findings and bilateral hilar adenopathy and patients with bilateral hilar adenopathy and erythema nodosum or uveitis have sarcoidosis with such a high frequency that biopsy confirmation of the diagnosis may not be necessary. This view, however, remains somewhat controversial. Many still feel that histologic confirmation of the diagnosis is essential, as infections, particularly tuberculosis and fungal infections, and neoplasms, particularly lymphomas and primary lung cancers, can cause asymptomatic hilar adenopathy.

Gallium 67 scanning, measurement of serum angiotensin-converting enzyme levels, and BAL with analysis of the recovered cell populations were felt to provide highly specific information allowing a diagnosis of sarcoidosis. However, all these tests are not sufficiently sensitive or specific to be used alone to establish the diagnosis. Gallium scans are positive in only two thirds of patients with sarcoidosis, and increased gallium uptake is seen in many other inflammatory lung disorders. Whereas gallium uptake in cranial, mediastinal, and hilar areas has been postulated to be helpful in diagnosing sarcoidosis, the specificity of these patterns is problematic. Serum levels of angiotensin-converting enzyme are elevated in only 50%–80% of patients with sarcoidosis. Although rare, angiotensin-converting enzyme levels can also be elevated in a wide spectrum of granulomatous and nongranulomatous disorders (Table 5). A predominantly lymphocytic BALF is also not specific for

sarcoidosis, being present in hypersensitivity pneumonitis, berylliosis, lymphomas, and tuberculosis.

Sarcoidosis
Gaucher's disease
Leprosy
Amyloidosis
Multiple myeloma
Lymphoma
Berylliosis
Farmer's lung
M. avium-intracellulare infection
Hyperthyroidism
Alcoholic hepatitis
Diabetes with retinopathy
Histoplasmosis
Silicosis

TABLE 5. *Selected diseases in which elevated serum levels of angiotensin-converting enzyme have been reported*

A positive Kveim-Siltzbach test result has also been proposed as specific for sarcoidosis. The test is performed by injecting a sterile suspension of sarcoidal tissue intradermally. In patients who have a positive Kveim test result, a nodule will form at the site of the injection in 2 to 6 weeks. The test is then completed by taking a biopsy sample of the nodule and demonstrating that it contains noncaseating granulomas. Many investigators have reported that with properly standardized extract, the test is sensitive and specific for sarcoidosis. However, it is positive most often in patients with typical sarcoidosis. It is far less sensitive in patients with atypical presentations, in whom additional diagnostic studies must be performed. In addition, the test delays a diagnosis by 2 to 6 weeks. Kveim biopsy findings can be difficult to interpret, and patients cannot receive corticosteroid therapy until the test is completed. At present, the lack of readily available standardized antigen extract and the availability of other reliable diagnostic procedures has markedly reduced the use of the Kveim-Siltzbach test in the United States.

EVALUATING THE EXTENT AND SEVERITY OF ORGAN INVOLVEMENT

The extent and severity of organ involvement in sarcoidosis must be assessed when the disease is first diagnosed and periodically thereafter. Assessment must be tailored to the individual patient. There are, however, a number of tests that should be considered for all patients. A complete blood cell count and platelet count provide information about the patient's hematologic profile. Periodic chest x-ray studies and pulmonary function testing help to assess a patient's lung involvement. Initial pulmonary function testing should include spirometry, lung volumes, and diffusing capacity. Patients without obstructive physiology can then be followed with serial measurements of vital capacity and diffusing capacity. An electrocardiogram is adequate initial screening for cardiac involvement in patients without cardiac symptoms. Periodic slit-lamp examinations should be obtained regardless of whether ocular signs or symptoms are present. Liver function tests, including alkaline phosphatase levels, provide an indication of hepatic involvement. Serum calcium, blood urea nitrogen, and creatinine levels should be checked, and a 24-hour urine calcium collection should be performed. These tests may be repeated as necessary to assess therapeutic response.

PROGNOSIS

The majority of patients with sarcoidosis have a good prognosis. In approximately two thirds of patients, the disease resolves spontaneously with minor or no residua. In the other third of patients, the disease smolders or worsens. Overall, 15%–20% of patients suffer a permanent loss of lung function, and approximately 5% die of the disorder. These deaths are most commonly caused by respiratory failure with cor pulmonale and right-sided heart failure. Hemoptysis secondary to bronchiectasis or aspergillomas, arrhythmias resulting from cardiac involvement, nervous system involvement, and uremia are less common causes of death. A number of variables appear to have prognostic import. Those that correlate with a good prognosis include an acute disease presentation plus the presence of erythema nodosum (in whites), acute iritis, a stage I radiograph, and few manifestations of extrathoracic disease. Poor prognostic variables include an insidious disease presentation plus a stage III or IV chest radiograph, bone involvement, lupus pernio, chronic uveitis, upper respiratory tract involvement, bronchial involvement, cor pulmonale, nephrocalcinosis, and hepatomegaly. Genetic background also may have prognostic import. American blacks have a worse prognosis than American whites. In addition, HLA-B8 has been associated with spontaneous disease resolution, and HLA-B13 has been associated with a chronic, persistent form of the disorder.

A rough correlation exists between radiographic stage and the course of intrathoracic disease. Patients with stage I disease have the best prognosis, with approximately 50%–80% experiencing spontaneous radiographic resolution within 1 to 5 years. Approximately 10% of these patients maintain stage I radiographs for long periods of time, and 15%–30% progress to stage II to stage IV disease. Patients presenting with stage II radiographs have a somewhat less favorable prognosis. Approximately 40%–60% of these patients experience a spontaneous radiographic resolution or remission. The remainder have a chronic stage II radiograph or progress to stage III or stage IV disease. Patients with stage III radiographs have the worst prognosis, with spontaneous radiographic resolution occurring only 12%–35% of the time. The remaining patients usually maintain their stage III radiographs, with only 5%–10% progressing to stage IV disease.

ASSESSMENT OF DISEASE ACTIVITY

The signs and symptoms of sarcoidosis can be the result of inflammation or fibrosis. Inflammatory lesions are felt to be potentially reversible, whereas fibrotic lesions are not. Chronic inflammation in sarcoidosis has also been postulated to lead to tissue fibrosis. As a result, it has been assumed that treatment decisions might be made on a more rational basis and a patient's response to anti-inflammatory agents predicted more accurately if patients with active inflammation could be differentiated from those with largely fibrotic disease. This would allow the physician to identify and aggressively treat the patients who are at the greatest risk for development of tissue fibrosis and most likely to benefit from the therapeutic intervention. It would also allow the physician to avoid steroid-induced side effects in patients who are likely to improve spontaneously or not respond to steroid therapy. Clinical signs and symptoms and physiologic abnormalities provide some prognostic data. However, their utility in an individual patient is limited. As a result, a number of other assessment techniques have been employed. Gallium 67 radioisotope scanning, determination of serum angiotensin-converting enzyme activity, and evaluation of BALF have received the most attention.

Angiotensin-Converting Enzyme

Angiotensin-converting enzyme, a normal constituent of the endothelium, converts angiotensin I to angiotensin II. Leiberman et al. reported that in contrast to normal controls, 15 of 17 patients with clinically active sarcoidosis had increased levels of serum angiotensin-converting enzyme. Subsequent studies showed that angiotensin-converting enzyme was aberrantly produced in these patients by granulomatous tissue. Initial reports suggested that angiotensin-converting enzyme levels could be used for diagnosis and assessment of disease activity. Unfortunately, elevated serum levels of angiotensin-converting enzyme are found in only 50%–75% of patients with clinically active sarcoidosis, and the enzyme may be elevated in a number of other conditions, such as hepatic cirrhosis, hyperthyroidism, and diabetes mellitus (Table 5). When elevated, enzyme levels do seem to correlate with the clinical activity in some patients. However, subsequent studies have found angiotensin-converting enzyme determinations to be no more sensitive than chest radiographs in determining the need for treatment. In addition, it has been reported that steroid therapy may lower serum angiotensin-converting enzyme levels independently of changes in disease activity. Thus, the clinical utility of serum angiotensin-converting enzyme levels in staging sarcoidosis remains unsettled.

Gallium 67 Scanning

Another staging procedure, often used in conjunction with BAL, is radioisotope scanning with gallium 67. After intravenous injection, this isotope is actively taken up by inflammatory tissue and accumulates in the lungs and other involved organs of patients with clinically active sarcoidosis. Gallium 67 scanning may provide an index of macrophage activation in patients with sarcoidosis, because it appears that alveolar macrophages are the primary pulmonary inflammatory cells that incorporate gallium 67. As with BAL, the value of this technique in staging has been called into question. However, it may be useful in separating fibrotic from inflammatory disease, and in localizing extrapulmonary sites of disease activity. Gallium 67 scanning is relatively noninvasive and is easily performed serially. The disadvantages of this technique are that it is nonspecific, expensive, and difficult to quantitate, and it exposes the patient to radiation.

Bronchoalveolar Lavage

In the early 1980s, investigators defined two groups of patients with sarcoidosis based on the proportion of T lymphocytes in their BALF. Patients with 28% T lymphocytes in their BALF were said to have “high-intensity alveolitis,” and those with 28% BALF T lymphocytes had “low-intensity alveolitis.” It was proposed that patients with high BALF lymphocyte counts, particularly in association with positive gallium scans, are likely to deteriorate clinically. However, several studies have raised questions about the usefulness of BALF lymphocyte counts alone as a measure of disease activity, response to therapy, or prognosis. Two prospective studies

in patients with newly diagnosed, untreated sarcoidosis followed for long periods of time showed no correlation between BALF lymphocyte counts and initial radiographic findings, pulmonary function abnormalities, need for steroid treatment, and, importantly, long-term outcome. Foley and co-workers found that an increase in the BALF lymphocyte count and CD4/CD2 ratios were actually associated with an improved prognosis. The lack of correlation between BALF lymphocyte counts and disease activity and prognosis has also been noted by Ceuppens and co-workers. They did find, however, that a decrease in or return to normal of the T-cell helper-suppressor ratio accompanied or preceded clinical and radiologic improvement and response to corticosteroid therapy. Thus, quantification of lung T cells does not provide usable prognostic information. In addition, the utility of BALF histamine, angiotensin-converting enzyme, procollagen III aminopeptide, fibrinogen, and vitronectin levels in predicting disease chronicity or the development of fibrosis remains to be proved. Other soluble BALF components, including immunoglobulins, surfactant proteins, reactive oxygen species, and antiproteases, have also been evaluated. Correlation of their presence in lavage fluid with prognosis or disease progression remains an area of ongoing investigation.

BALF cytokine levels might provide prognostic information. Alveolar macrophages from patients with sarcoidosis have been demonstrated to express increased levels of mRNA for TNF-g, IL-6, IFN-g, GM-CSF, and IL-1. It has been suggested that increased levels of each of these cytokines as well as of interleukin-8 in BALF may parallel disease activity. Whether measurements of these and other cytokines in BALF will prove clinically useful in predicting the prognosis of sarcoidosis is unknown.

Measurement of potential serum markers of disease activity may also be useful in this regard. A soluble form of the IL-2 receptor (sIL-2R) is released by activated T cells in many granulomatous disorders. As sIL-2R is easily detectable in serum, several investigators have attempted to use sIL-2R levels to stage disease activity. These studies have found that the levels of sIL-2R are markedly increased in the serum of patients with active sarcoidosis, are significantly lower in patients with inactive disease, and fall with clinical improvement. Although the levels of serum sIL-2R correlate well with clinical parameters, their correlation with BALF T-cell counts, CD4/CD8 ratios, and BALF T-cell HLA-DR expression is poor. If these promising early reports are substantiated, the measurement of serum sIL-2R or BALF levels of sIL-2R may prove to be useful in predicting activity of sarcoidosis.

In summary, measurement of BAL cell profiles, soluble protein levels and cytokine levels, gallium scanning, and serum ACE levels have not been consistently shown to be good predictors of disease progression or response to therapy in patients with sarcoidosis. It is clear, however, that at some centers and in some patients, these assays, particularly if used in serial fashion, have been useful in prognosis and prediction of therapeutic response. At present, it is not clear if the conflicting reports in the literature reflect the true lack of utility of these assays or differences in the patient populations being studied. At present, these tests cannot be relied upon to the exclusion of clinical judgement in making decisions regarding patient management. Thus, until more information is available and newer assays are tested further, it seems most prudent to use traditional criteria, including clinical symptoms, pulmonary function tests, and chest radiographs, as well as indices of inflammation in assessing patients with sarcoidosis.

TREATMENT

It is not necessary to treat all patients with sarcoidosis. Decisions regarding treatment must be individualized, and are best based on individual manifestations of the disease and the clinical course of a given patient.

Extrapulmonary Disease

There is general agreement that systemic therapy with corticosteroids is indicated for any patient with life- or organ-threatening disease and for patients with refractory or progressive organ involvement (or symptoms) that have not responded to topical or symptomatic therapy. Some of the indications for systemic steroids in patients with extrapulmonary sarcoidosis are shown in Table 6. When systemic therapy is required for life-threatening disease, it is recommended that treatment be initiated with 40 to 60 mg of prednisone, given orally, once each day. After a clinical response has been achieved, the daily dose may be tapered by 5 to 10 mg/month. When the daily dose has been reduced to the equivalent of 20 mg of prednisone per day, a schedule of 40 mg on alternate days may be instituted. In patients without life-threatening complications, treatment may be initiated with 40 to 60 mg of prednisone on an alternate-day regimen. This dose is slowly tapered during the next 12 to 18 months, with the rate of taper and ultimate duration of therapy tailored to the clinical status of the patient. If disease reactivation occurs during dose reduction, the daily or alternate-day dose of prednisone should be increased by 10 mg and this dose administered for 2 to 3 months before tapering is attempted again. Some patients may require prolonged or even lifelong therapy.

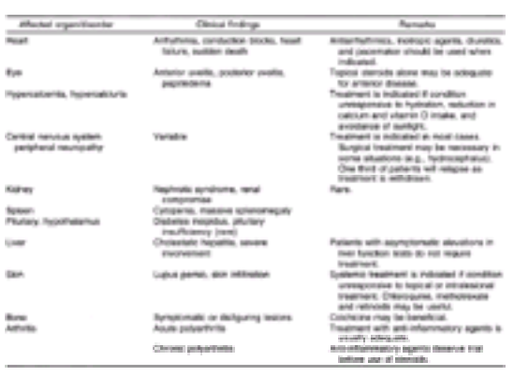

TABLE 6. *Extrapulmonary sarcoidosis: indications for systemic treatment*

It is important to realize that parenteral corticosteroid is not required for all extrapulmonary manifestations of sarcoidosis. Topical steroids are often effective in the treatment of anterior uveitis. Intradermal steroids, chloroquine, methotrexate, and retinoids may cause regression of sarcoid skin lesions, and nonsteroidal anti-inflammatory agents are useful in controlling joint pain and systemic manifestations of sarcoidosis. Colchicine is considered to be particularly effective in the treatment of the arthralgias and periarthritis of sarcoidosis, and mild hypercalcemia can occasionally be managed with hydration, a low-calcium diet, and avoidance of sunlight and vitamin D. Ketoconazole may also be useful in the treatment of hypercalcemia and hypercalcuria, as it decreases the synthesis of 1,25-dihydroxyvitamin D.

Pulmonary Disease

The present treatment of patients with pulmonary sarcoidosis remains a subject of considerable controversy. Given the variability in clinical course, the high rate of spontaneous remission, and the lack of reliable indicators of prognosis, the criteria for initiating and altering systemic treatment with corticosteroids remain ill-defined. This controversy is augmented by the realization that although steroids cause radiographic and functional improvement, their ability to alter the natural history of sarcoidosis is difficult to document.

Some authors advocate treatment of all patients with pulmonary sarcoidosis regardless of symptoms or physiologic abnormalities. Most, however, feel that only patients who are symptomatic or whose condition is deteriorating should be treated. An approach in accordance with this view is summarized below.

1. Patients with stage I disease are often asymptomatic and usually have normal or near normal pulmonary function. They should be carefully observed with serial chest radiographs and pulmonary function tests initially every 3 months. If disease progresses radiographically or if pulmonary function significantly declines (15% decrease in lung volumes or diffusing capacity), treatment with steroids should be initiated.

2. Patients with stage II or stage III disease with normal or near normal pulmonary function and minimal symptoms should be followed serially and treated if they progress as described for stage I patients. Patients presenting with significantly abnormal pulmonary function (lung volumes and/or diffusing capacity 65% of predicted) warrant an empiric trial of steroids. The indices of inflammation noted above are often helpful in defining parameters of disease activity that can be followed in these patients. Clinical status and pulmonary function should also be monitored and chest radiographs taken periodically.

3. Patients presenting with fibrobullous disease (advanced stage III or stage IV) also warrant an empiric trial of steroids. Although the likelihood of reversing fibrotic changes is small, patients with concomitant pulmonary inflammation may improve significantly with therapy.

4. Patients with severe, end-stage lung disease despite treatment may be candidates for single lung or heart-lung transplantation. Referral to an appropriate transplantation center should be made, preferably before the onset of cor pulmonale.

These recommendations parallel those recently made by Sharma in a commentary for the American Thoracic Society.

There is little agreement as to the amount of steroid necessary to adequately treat pulmonary sarcoidosis. Initial dosages, daily versus alternate day regimens, and schedules for tapering vary institutionally and among practitioners. The response (or lack thereof) of the individual patient will largely dictate his or her regimen. In severe cases of pulmonary sarcoidosis, up to 60 mg of prednisone daily may be used as an initial dose. In most other cases, a lower prednisone dose of 40–60 mg every other day can be used from the outset. The patient is then observed on therapy for up to several months.

In patients who appear to respond, the initial prednisone dose (40–60 mg/day) is maintained for 3 to 6 months and then reduced by 5 to 10 mg every 1 to 3 months. This usually results in a total duration of therapy of between 12 and 15 months. In patients who do not respond, steroids are tapered and discontinued more rapidly.

Relapses can occur during the treatment period. When a relapse occurs, the most recent effective dose should be reinstituted for 2 to 3 months and then tapering should be attempted. A few patients require lifelong steroid therapy, although usually at relatively low doses. Others have remissions, only to have reactivation of disease years later. For these reasons, most patients with sarcoidosis should remain under observation indefinitely and have their disease activity periodically reassessed.

Agents Other Than Steroids

The use of cytotoxic agents in the treatment of refractory sarcoidosis is based on uncontrolled studies that claim or refute therapeutic success with a variety of agents. Methotrexate has been used in uncontrolled trials in low doses (e.g., 10 mg/week) with some success, particularly in patients with severe skin involvement. Long-term therapy with methotrexate carries the risk for hepatotoxicity. Serial liver biopsies may be required to monitor this potential problem. Cyclophosphamide, azathioprine, and chlorambucil have also been used and appear to be of limited value. Cyclosporine has been reported in case studies to be of benefit in pulmonary sarcoidosis refractory to corticosteroids. Thalidomide has also been reported to be of benefit in one case of cutaneous and pulmonary sarcoidosis. There are no known advantages of any of these agents. The choice between these drugs is best dictated by the clinician's familiarity with each and the patient's clinical presentation. In cases in which active sarcoidosis is not adequately treated with high-dose steroids or in which the patient cannot tolerate steroids because of side effects, a trial of one of these agents may be warranted.

Transplantation

End-stage organ failure may develop in patients with severe sarcoidosis. In such situations, transplantation of solid organs, including lung, heart, liver, and kidney, has been successfully performed. It has been well documented that noncaseating granulomas can be seen in lung and heart allografts after transplantation. This finding appears to be specific for patients with sarcoidosis and is not observed in allografts of patients who have undergone transplantation for other diseases. Fortunately, clinical disease caused by recurrent sarcoidosis in the transplanted organ is uncommon. This may be in part a consequence of the uniform use of immunosuppressive agents to prevent transplant rejection. As sarcoid recurrence in allografts appears to be associated with little in the way of clinical symptoms or organ dysfunction, transplantation remains a viable option for patients with sarcoidosis-induced end-stage organ failure.

Interestingly, there have been case reports in which sarcoidosis appears to have been transmitted via organ donation. Experience is not yet broad enough to determine if subsequent clinical manifestations related to sarcoidosis will be severe enough to exclude persons with sarcoidosis from organ donation.

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CHAPTER

21 Major Pulmonary Disease Syndromes of Unknown Etiology

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INTRODUCTION

Pulmonary inflammation and fibrosis may concur in the context of myriad acute and chronic disorders affecting the lung parenchyma or small airways (e.g., bronchioles). The etiologies of these various disorders have not been clarified, but clinical, radiographic, and physiologic features are often distinctive and overlap between the various disorders. These heterogeneous chronic interstitial lung diseases (CILD) share many of the following clinical features: exertional dyspnea; bilateral infiltrates on chest radiographs; physiologic abnormalities of restrictive lung defect, decreased diffusing capacity (D_LCO), and increased alveolar-arterial oxygen gradient [$P(A - a)O_2$] at rest or with exertion; absence of pulmonary infection and neoplasm; and histopathologic features of inflammation and fibrosis, with or without granulomatous or vascular lesions in the pulmonary parenchyma. Some of the CILD primarily involve alveolar walls and interstitium, but proximal airways may be involved incidentally. In addition, a group of disorders preferentially involve the small airways (terminal and respiratory bronchioles); the distal alveolar spaces may be involved incidentally or may be spared. Disorders affecting the small airways alone are usually characterized by exertional dyspnea; clear chest radiographs with preserved or increased lung volumes; physiologic defects of airways obstruction, air trapping, impaired D_LCO, and widened $P(A - a)O_2$; absence of infection and neoplasm; histopathologic features of constricted small-airway lumina (i.e., constrictive or obstructive bronchiolitis). The spectrum of clinical, radiographic, physiologic, and histopathologic manifestations is wide, and significant overlap between these diverse disorders exists.

Many of these CILD are discussed in detail elsewhere in this text, and their features are not reiterated here; they include idiopathic, collagen vascular-associated, and radiation- or drug-induced pneumonitis/fibrosis; pneumoconiosis and pneumonitis of occupational or environmental origin; sarcoidosis; eosinophilic pneumonias; hypersensitivity pneumonitis; and rare inherited diseases (e.g., neurofibromatosis, tuberous sclerosis, Hermansky-Pudlak syndrome, metabolic storage disorders, and hypocalciuric hypercalcemia). This chapter discusses in detail selected major disease syndromes of unknown etiology exhibiting distinctive clinical, radiographic, or histopathologic features. The clinical course and treatment of these diverse disorders are variable and are discussed in detail in the following sections.

DISEASES OF THE BRONCHIOLES AND SMALL AIRWAYS

Bronchiolitis Obliterans with Organizing Pneumonia

A wide spectrum of inflammatory disorders may involve terminal and respiratory bronchioles, resulting in diverse clinical syndromes. The literature is confusing, as the terms *bronchiolitis obliterans* (with or without organizing pneumonia), *cryptogenic organizing pneumonia, obliterative* (*mural*) *bronchiolitis,* and *organizing pneumonia* have often been used interchangeably to refer to a heterogeneous group of bronchiolar inflammatory disorders with diverse clinical expression. We first review bronchiolitis obliterans organizing pneumonia (BOOP), also called *cryptogenic organizing pneumonia.* BOOP may complicate collagen vascular disease, exposures to toxic fumes or pharmacologic agents, organ transplantation (e.g., bone marrow or lung), or specific pulmonary infections (e.g., *Legionella,* viruses, *Mycoplasma* species). When no cause can be elicited, the term *idiopathic BOOP* or *idiopathic cryptogenic organizing pneumonia* has been applied. BOOP is characterized by a subacute process, focal alveolar infiltrates (mimicking pneumonia), and granulation tissue obstructing small bronchioles and extending into the lung parenchyma. The prognosis and clinical expression of BOOP differ markedly from those of other disorders involving small bronchioles, to be discussed later (e.g., obliterative bronchiolitis, diffuse panbronchiolitis, respiratory bronchiolitis).

Epidemiology

The precise incidence of BOOP is not clear, as many cases have likely erroneously been ascribed to other disorders (e.g., desquamative interstitial pneumonitis, eosinophilic pneumonia, pulmonary fibrosis). BOOP probably has been underrepresented in the literature, as cases lacking histologic confirmation have not been reported. In 1985, Epler and colleagues identified 67 patients with BOOP (17 of whom had collagen vascular disease) gleaned from a review of 2500 open lung biopsies performed from 1950 to 1980. Investigators at Ohio State University detected 16 cases of BOOP within a 4-year period, accounting for 4% of referrals for obstructive lung disorders. Cordier et al. detected 16 cases of BOOP in 6 years at a leading referral center in France. Katzenstein and colleagues identified 24 cases by retrospective review of pathologic files at the University of Alabama from 1972 to 1984. These and other studies suggest that even large referral centers diagnose only two to four cases of BOOP annually. BOOP usually presents in the fifth through sixth decades of life, but persons of any age may be affected. There is no sex predominance.

Clinical Features

Nonproductive cough, dyspnea, fever, weight loss, and malaise are typical presenting features. Despite pronounced constitutional symptoms in some patients, extrapulmonary involvement does not occur. The course is usually subacute, with symptoms developing within 2 weeks to 6 months. An antecedent upper or lower respiratory tract infection or flulike illness is noted in 40%–60% of patients within 1 to 3 months of onset of symptoms. Crackles are present on physical examination in 60% of patients; 40% manifest a mid-inspiratory squeak. Despite the presence of airways obstruction, overt wheezing is rare. Clubbing is not a feature of BOOP, as in is in several other CILD. No characteristic laboratory aberrations are noted. The eythrocyte sedimentation rate is elevated in 80% of cases; one third exhibit leukocytosis.

Chest Radiographic Findings

Chest radiographs reveal single or multiple segmental or lobar alveolar infiltrates in more than two thirds of patients (Fig. 1). A basilar predominance is more common, but any lobe can be affected. Patchy, unilateral or bilateral air space consolidation, often with air bronchograms, has been noted in 62%–79% of patients. In some patients, the infiltrates migrate or wax and wane, either spontaneously or in apparent response to antibiotics. The fleeting nature of these infiltrates may cause them to be mistaken for pneumonia, particularly when patients have been treated with antibiotics. Dense lobar infiltrates with consolidation contrast sharply with the interstitial nature of infiltrates seen in idiopathic pulmonary fibrosis (IPF) and many other CILD. However, diffuse reticulonodular infiltrates, indistinguishable from those of IPF or other CILD, are noted in 20%–40% of cases of BOOP (Fig. 2). In 4%–10% of cases, chest radiographic findings are normal or exhibit only hyperinflation. Pleural effusions, cavitary lesions, and intrathoracic lymphadenopathy are not features of BOOP. The pattern on chest radiographs influences prognosis. Dense alveolar infiltrates are associated with a pronounced component of organizing pneumonia, a more acute course, and greater responsiveness to corticosteroids (Fig. 3). By contrast, a diffuse reticulonodular or interstitial pattern has been associated with a more chronic course and lower rate of response to therapy.

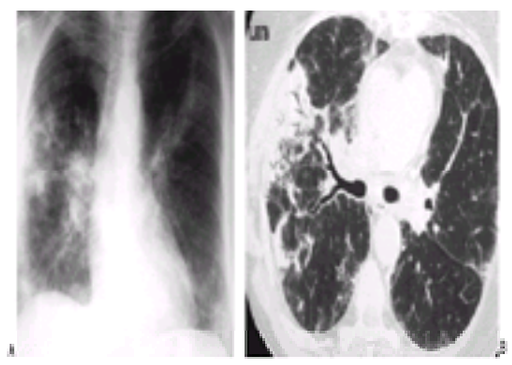

FIG. 1. A: Bronchiolitis obliterans organizing pneumonia. PA chest radiograph from a 67-year-old woman demonstrates patchy bilateral infiltrates. She had been given three prior courses of antibiotics by her personal physician during the preceding 7 weeks because of persistent cough, fever, and dyspnea, with no improvement. Changes revealed by transbronchial lung biopsy were consistent with BOOP, and corticosteroids (1 mg of prednisone per kilogram of body weight per day) were initiated. **B:** CT demonstrates dense alveolar infiltrates with striking air bronchograms in the periphery of the right lung.

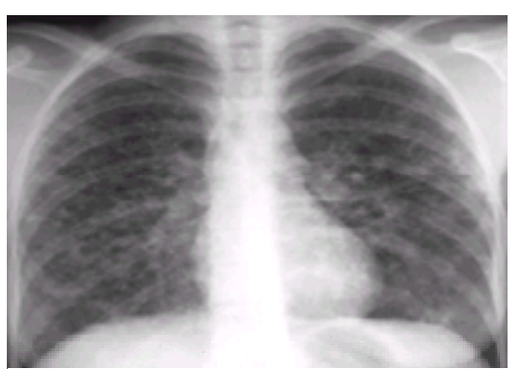

FIG. 2. Bronchiolitis obliterans organizing pneumonia. Chest radiograph demonstrates diffuse reticulonodular infiltrates in a 27-year-old woman who presented with a 6-week history of cough and progressive dyspnea. Transbronchial lung biopsies demonstrated features consistent with BOOP. Corticosteroid therapy (60 mg of prednisone daily for 1 month, with a subsequent taper) was initiated, with complete resolution of symptoms and normalization of chest radiograph. (Reproduced with permission from Neagos GR, Lynch JP III. Making sense out of bronchiolitis obliterans. *J Respir Dis* 1991:12;807.)

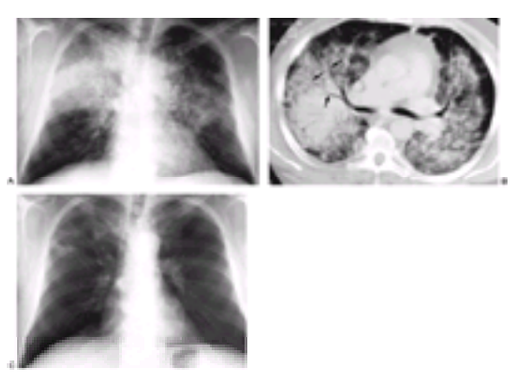

FIG. 3. A: Bronchiolitis obliterans organizing pneumonia. PA chest radiograph from a 62-year-old man demonstrates confluent alveolar infiltrates in both upper lobes with extensive air bronchograms. He had been treated with broad-spectrum parenteral antibiotics for 2 weeks without improvement and with worsening findings on

chest radiographs. **B:** High-resolution CT from the same patient demonstrates confluent alveolar infiltrates and striking air bronchograms (*arrows*). Transbronchial lung biopsies demonstrated typical features of BOOP. Corticosteroids were initiated, and the process resolved during the next few weeks. **C:** PA chest radiograph from the same patient 3 weeks after institution of corticosteroid therapy demonstrates nearly complete resolution of alveolar infiltrates.

High-Resolution Thin-Section Computed Tomography

High-resolution thin section computed tomography (CT) typically reveal single or multiple focal alveolar nodular infiltrates or areas of consolidation (with air bronchograms) (Fig. 1B and Fig. 3B). In some cases, a feeding vessel or bronchus leading into the area of consolidation or nodular opacity may be seen. Reticulonodular interstitial infiltrates are noted in one quarter of patients. Other findings include ground-glass opacities and peribronchiolar nodules extending into the lung parenchyma in a centrifugal fashion from involved airways. Honeycombing is not seen in BOOP. Pleural effusions are observed in <10% of patients and are rarely prominent. Mediastinal lymphadenopathy has been noted, but is usually minor (lymph nodes <1.5 cm in size).

Pulmonary Function Tests

A restrictive defect, with reductions in lung volumes (e.g., vital capacity, total lung volume) is characteristic of BOOP. Other physiologic aberrations include reduced D_LCO, hypoxemia, and a widened $P(A - a)O_2$. Despite the involvement of small airways, a purely obstructive defect is rare (except in smokers). The lack of obstruction has been attributed to the patchy nature of airway involvement. Some regions are completely obstructed (resulting in loss of entire units and reduced lung volumes), whereas other areas are spared. Bronchodilators are generally ineffective. Functional deficits may markedly improve or normalize following corticosteroid therapy.

Histopathologic Features

The histologic hallmark of BOOP is polypoid masses of granulation tissue filling (and obstructing) terminal and respiratory bronchioles and alveolar ducts (Fig. 4). The plugs of loose granulation tissue are composed of aggregates of inflammatory cells, edematous fluid, debris, fibrin, and fibrous connective tissue. The inflammatory infiltrate is composed of lymphocytes, plasma cells, foamy macrophages, and scattered polymorphonuclear leukocytes, eosinophils, and multinucleated giant cells. Extension of the inflammatory process to contiguous alveolar ducts and alveolar spaces results in the “organizing pneumonia” component. Fibrous connective tissue (e.g., fibroblasts, myofibroblasts, collagen) may extend from the small-airway lumina into the alveolar spaces, but extensive fibrosis or honeycombing is lacking. Even when extensive consolidation is present, the alveolar architecture is preserved. These histologic features have variably been ascribed to organizing pneumonia, lipoid pneumonia, cholesterol pneumonia, and resolving pneumonia. Other distinctive features of BOOP include bronchocentricity and patchy involvement; these features can readily be appreciated on low-power magnification of lung biopsy specimens. This “organizing pneumonia” component has been associated with an excellent prognosis and high rate of response to corticosteroid therapy. Histologic features of BOOP overlap with those of other inflammatory lung disorders (especially hypersensitivity pneumonitis, desquamative interstitial pneumonitis, chronic eosinophilic pneumonia, and pulmonary infections). Foamy macrophages in alveolar spaces may erroneously suggest the diagnosis of desquamative interstitial pneumonitis (DIP). BOOP differs from constrictive or mural bronchiolitis obliterans (to be discussed later), which is characterized by fibrous connective tissue obliterating bronchioles and alveolar ducts but lacks an intense inflammatory component. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsies (TBB) can substantiate the diagnosis of BOOP in some cases, provided the salient histologic features are present and alternative causes have been reliably excluded. BAL in BOOP reveals increases in polymorphonuclear leukocytes (often exceeding 40%), with less striking increases in eosinophils or lymphocytes. These findings are nonspecific. Patients who have marked increases in BAL fluid lymphocytes generally have a more acute course, more prominent component of organizing pneumonia, and higher rate of corticosteroid responsiveness compared with patients who have low or normal BAL lymphocyte counts. Increases in BAL neutrophils or eosinophils have limited prognostic value. Given the patchy nature of BOOP and the small sample size of TBB, video-assisted thoracoscopic lung biopsy should be performed in equivocal or nondiagnostic cases.

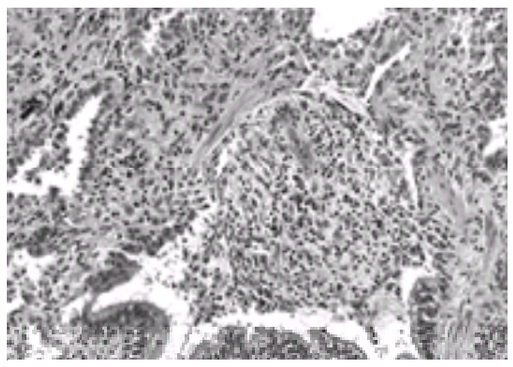

FIG. 4. Bronchiolitis obliterans organizing pneumonia. Photomicrograph of open lung biopsy specimen demonstrates a plug of organizing granulation tissue within a respiratory bronchiole. A peribronchiolar mononuclear inflammatory cell infiltrate is also evident. H&E stain, oil immersion. (Reproduced with permission from Neagos GR, Lynch JP III. Making sense out of bronchiolitis obliterans. *J Respir Dis* 1991:12;801.)

Pathogenesis

Although the pathogenesis has not been elucidated, BOOP likely represents a distinctive and stereotypic host response to diverse injurious or inflammatory stimuli. The frequent association of antecedent viral or respiratory tract infection in idiopathic BOOP suggests that inhaled antigens may induce bronchiolar or alveolar injury. The histologic features of BOOP are usually of uniform age, suggesting that BOOP is an inflammatory reaction to one injurious stimulus, not to recurrent injury. Immune complex deposition in response to inhaled antigens may elicit a brisk inflammatory response. The prominence of neutrophils and neutrophil products in BAL fluid suggests a role for neutrophils in the pathogenesis. However, lymphocytes and macrophages undoubtedly are also important. The evolution of the lesions depends on the balance between the inflammatory process and reparative mechanisms (e.g., fibrosis, remodeling).

Therapy

Corticosteroids are the cornerstone of therapy for BOOP. Studies assessing optimal dose or duration of corticosteroid therapy for BOOP have not been performed. Most investigators advocate initial treatment with prednisone (1 mg/kg/day), but lower doses may be adequate in mild cases. Favorable responses are achieved with corticosteroids in 60%–80% of cases. Symptomatic improvement may be evident within 2 to 3 days; radiographic resolution usually ensues within 1 to 4 weeks. Corticosteroid therapy has been associated with marked reduction in BAL fluid neutrophils, collagenase activity, and myeloperoxidase activity in responding patients. The dose and rate of taper of corticosteroid need to be individualized according to clinical symptoms and results of chest radiographs and pulmonary function tests. In patients showing prompt and dramatic responses to corticosteroids, the dose may be tapered to 40 mg/day within 2 to 6 weeks. A more gradual taper may be appropriate for patients with persistent disease. The dose of prednisone may be tapered to 20 to 30 mg on alternate days within 4 to 6 months, provided patients remain in continuous remission. Because of the potential for relapse with premature discontinuation of therapy, low-dose corticosteroids should be continued for a minimum of 12 to 18 months unless serious adverse effects develop. Prolonged therapy may be required for selected patients exhibiting a propensity to relapse. Serious sequelae associated with BOOP are rare. Pulmonary fibrosis occurs in <20% of patients and fatalities in 3%–10%. Immunosuppressive or cytotoxic agents should be considered in patients failing to respond or experiencing adverse effects of corticosteroids. Data evaluating these agents are limited to anecdotal cases and small series.

Rapidly Progressive BOOP

A subset of patients with BOOP exhibit a more fulminant course, leading to death or severe fibrosis and honeycombing. Cohen et al. articulated the clinical features of 10 such patients seen at three medical centers from 1979 to 1992. The onset of symptoms was rapid (ranging from 3 days to 2 months). Bilateral basilar crackles were noted in 9 of 10; all had dyspnea and hypoxemia. Nine required mechanical ventilatory support. All but one patient were current or former smokers. Possible etiologic factors included connective tissue disease, nitrofurantoin, gold, and exposure to birds. BAL (performed in five patients) demonstrated increases in eosinophils and/or neutrophils. Histopathologic features were consistent with BOOP, but features of diffuse alveolar damage, alveolar septal inflammation, end-stage fibrosis, and honeycombing were also present. Despite aggressive therapy with corticosteroids in all patients (five of whom also received immunosuppressive agents), seven died. Although data regarding therapy are limited, we advise treating with “pulse” methylprednisolone (1000 mg daily for 3 days), followed by high-dose prednisone (1 mg/kg

per day for 2 weeks, with a gradual taper). Cyclophosphamide or azathioprine should be added for steroid-recalcitrant cases.

Obliterative Bronchiolitis (Constrictive Bronchiolitis)

Obliterative bronchiolitis (OB) is a rare disorder characterized by progressive fibrosis and obliteration of bronchiolar lumina, resulting in progressive dyspnea and air flow obstruction. The terms *constrictive bronchiolitis, mural bronchiolitis,* and *pure bronchiolitis obliterans* are synonymous. Most cases of OB have occurred in the context of specific underlying disorders or risk factors, including collagen vascular disease (particularly rheumatoid arthritis), inhaled toxins, drugs (e.g., penicillamine), lung or bone marrow transplantation, infection, and diverse autoimmune, inflammatory, and vasculitic disorders. When no associated disorder can be identified, the term *idiopathic* is used. The prevalence is not known, but idiopathic OB is much less common than BOOP. Turton and colleagues detected 10 patients with OB among 2094 patients with airways obstruction. Five had rheumatoid arthritis; two had an antecedent chest infection; three cases were idiopathic. Many cases of OB diagnosed before 1985 likely represented BOOP.

Clinically, OB differs markedly from BOOP in clinical features, prognosis, and responsiveness to therapy. Patients with OB present with dyspnea and severe air flow obstruction, which progresses relentlessly during weeks to months. Severe reductions in FEV_1 and FEV_1/FVC ratio are characteristic. Air trapping (increased residual volume, or RV) or hyperinflation (increased total lung capacity, or TLC) are common associated features. Chest radiographic findings are usually normal or demonstrate only hyperinflation. However, diffuse reticular or finely nodular shadows, reflecting peribronchiolar inflammation and fibrosis, may be observed. High-resolution CT may reveal peribronchiolar nodular infiltrates and patchy increases in attenuation, accentuated by expiration, which reflect localized air trapping.

Histopathology

Obliterative (constrictive) bronchiolitis is centered on membranous and respiratory bronchioles and is characterized by fibrosis in submucosal and peribronchiolar regions, encircling and encroaching bronchiolar lumina. Necrotic bronchiolar epithelial cells and a mixed polymorphous inflammatory infiltrate may be seen. As the lesion progresses, peribronchiolar fibrosis dominates, resulting in concentric narrowing (and cicatrization) of bronchiolar lumina. Intrabronchial tufts of granulation tissue and extension to the alveolar interstitium are not seen, as they are in BOOP. The lesions are patchy and may be missed, even on open lung biopsy, unless several sections are reviewed. Remnants of destroyed bronchioles may occupy only a few millimeters; the surrounding lung parenchyma may be normal. Serial sections and trichrome stains may be required to identify the progressive narrowing of the caliber of bronchiolar lumina and the peribronchiolar scars. Late findings including bronchiolectasia with mucostasis, distortion of airway walls, bronchial metaplasia, and smooth-muscle hyperplasia.

Therapy

OB typically progresses relentlessly to severe air flow obstruction and ultimately death. In contrast to BOOP, OB rarely responds to therapy. Because of the devastating course, high-dose corticosteroids or immunosuppressive or cytotoxic agents are generally tried, but results have been disappointing.

Bronchiolitis Obliterans Complicating Bone Marrow Transplantation

Bronchiolitis obliterans is a well-recognized complication of bone marrow transplantation, principally in allogeneic recipients manifesting chronic graft-versus-host disease in skin, mucous membranes, liver, or extrapulmonary sites. Bronchiolitis obliterans complicates allogeneic bone marrow transplantation in 10%–12% of long-term survivors with graft-versus-host disease. The prevalence in allogeneic recipients without graft-versus-host disease or autologous recipients is rare (<1%). Bronchiolitis, occasionally with fibrinous obliteration of lumina, is the cardinal feature on lung biopsy or necropsy. The clinical course is indolent, developing 1.5 to 10 months after transplantation. Pulmonary symptoms include cough (60%), dyspnea (50%), wheezing (25%), or coldlike or flulike symptoms (25%). Declines in FEV_1 and VC and increases in RV are characteristic. Chest radiographic findings are normal or reveal mild hyperinflation in 80% of affected patients. In the remaining patients, reticular or finely nodular infiltrates may be noted. The diagnosis of OB can be presumed in bone marrow transplant recipients with a chronic course, progressive air flow obstruction, and lack of evidence for infection. BAL may be adequate in this context to exclude infection. TBB is more specific, but the risk may not be justified, particularly when thrombocytopenia or severe air flow obstruction is present. Prognosis is poor. Augmented immunosuppression is usually administered, but improvement occurs in <20% of patients.

Bronchiolitis Obliterans Complicating Lung Transplantation

Bronchiolitis obliterans, believed to represent a form of chronic lung allograft rejection, complicates lung or heart-lung transplantation in 30%–60% of recipients. Clinically, OB is characterized by progressive airways obstruction, cough, dyspnea, and recurrent lower respiratory tract infections. OB develops 9 to 18 months following lung or heart-lung transplantation. The lesion is never seen in the first 60 days after transplantation. Prevalence approximates 30% by 2 years after transplantation. By 5 years, OB syndrome develops in >50%. Histologically, bronchiolitis obliterans in affected lung allografts is similar to constrictive bronchiolitis or pure bronchiolitis obliterans, described earlier. Dense fibrous plaques narrow or obliterate the small airways. Submucosal and epithelial mononuclear cell infiltrates may be present, but the dense perivascular lymphocytic infiltrates characteristic of acute allograft rejection are lacking. Concomitant features include mucostasis, foam cells in distal airways, and epithelial metaplasia. Lymphocytic bronchitis or bronchiolitis, characterized by peribronchiolar and peribronchial lymphocytic infiltrates, but without fibrosis, may be a precursor of OB in some recipients. Risk factors for development of OB include recurrent episodes of acute allograft rejection, cytomegalovirus (CMV) pneumonitis, large-airway ischemic injury in the initial period after transplantation, heightened immunologic activity against the donor (as assessed by the primed lymphocyte test), and enhanced cell-mediated cytotoxicity. CMV infection may upregulate class I and II histocompatibility (HLA) antigens on epithelial and endothelial cells, thereby amplifying the process. Lung or heart-lung transplant recipients with OB demonstrate submucosal and intraepithelial mononuclear cell infiltrates, enhanced expression of class II HLA antigens on bronchiolar epithelial and lung endothelial cells, and increased number of dendritic cells (e.g., antigen-presenting cells) in the airways. These features support the premise that OB is a form of chronic lung allograft rejection. In other organ allografts, chronic rejection is associated with disappearance or dissolution of structures within the allograft [e.g., vanishing bile duct syndrome (liver), disappearance of renal tubules (kidney), accelerated coronary artery disease (heart)].

The course of OB is indolent. Asymptomatic reductions in expiratory flow rates (e.g., $FEF_{25\%-75\%}$, FEV_1) usually precede the onset of clinical symptoms. Initial symptoms are nonproductive cough, “bronchitis,” or “chest cold.” Physical examination findings are usually unimpressive, but rales or rhonchi develop later. Chest radiographic findings are usually normal, but hyperinflation or bronchiectatic changes develop in the late phases. Once airways obstruction occurs on pulmonary function tests, a downhill course is nearly inevitable. A rapid course (with fall in FEV_1 below 40% of predicted) can occur as early as 3 to 4 months in some patients. In others, pulmonary function stabilizes after an initial decline. Gas exchange is preserved until late in the course. Airways become colonized with *Pseudomonas aeruginosa, Staphylococcus aureus,* or *Aspergillus* species. Progressive dyspnea ensues, which may culminate in respiratory failure. The diagnosis of OB can be established by TBB in more than 75% of affected patients. Because the lesion is patchy, a negative biopsy result does not exclude OB. In this context, a clinical diagnosis of OB syndrome can be made if a sustained and progressive loss in FEV_1 (>15% decline) or $FEF_{25\%-75\%}$ (>25% decline) has been documented and alternative causes of airways obstruction have been excluded.

Once developed, OB typically worsens, but the rate of progression is highly variable. Augmented immunosuppression with pulse methylprednisolone, antilymphocytic agents (e.g., antilymphocyte sera or globulin, OKT3 antibody), FK506, and aerosolized cyclosporine have been tried for OB or OB syndrome, with anecdotal successes. However, sustained remissions are unusual, and most patients experience continued or persistent decline in pulmonary function. Because the prognosis in untreated patients is dismal, most investigators treat OB aggressively with two to four cycles of augmented immunosuppression. The risk-to-benefit ratio of this approach is uncertain, as the rate of complications and short-term and long-term efficacy have not been well defined. In our experience, response to therapy is rarely dramatic. The lesions stabilize (often for 6 to 24 months) in some patients, but one third or more of affected recipients die of respiratory failure within 2 to 3 years of onset of symptoms. Secondary bacterial or fungal pneumonias may accelerate the course. Aggressive treatment and prophylaxis of airway infections may reduce the risk for secondary infections and prolong survival. It is hoped that prophylactic regimens against CMV and improved operative techniques to reduce large-airway ischemia may lower the incidence of OB. Repeated transplantation has been performed in patients with progressive OB refractory to augmented immunosuppressive therapy. Success with repeated transplantation has been less than with initial transplant procedures. Given the scarcity of donor organs, repeated transplantation for OB is controversial.

Follicular Bronchiolitis

Follicular bronchiolitis, a rare disorder most commonly seen in association with rheumatoid arthritis or other connective tissue disorders, exhibits features that overlap with those of OB and BOOP. The relationship of follicular bronchiolitis to these other bronchiolar disorders is not clear. Pulmonary function tests may reveal restriction or airways obstruction. In contrast to OB, which results in intramural or intraluminal compression and distortion of bronchioles, follicular bronchiolitis typically compresses bronchioles externally from lymphoid follicles. A pronounced lymphocytic infiltration within bronchiolar walls may also be evident. Chest radiographs demonstrate reticular or reticulonodular opacities, corresponding to these peribronchiolar cellular infiltrates. The prognosis is more favorable than in OB, as approximately 50% respond to corticosteroid therapy.

Respiratory Bronchiolitis

Respiratory bronchiolitis is a rare disorder of cigarette smokers with features overlapping with those of BOOP. Lung biopsy reveals clusters of pigmented, golden-brown macrophages in respiratory and membranous (terminal) bronchioles and adjacent alveolar spaces. Chronic inflammation and fibrosis may be present but are invariably mild. Most patients are asymptomatic or note mild cough or dyspnea. Chest radiographic findings may be normal or demonstrate accentuated bronchopulmonary markings (“dirty lungs”) resembling those of chronic interstitial pneumonitis. Constitutional symptoms, fever, or dense alveolar infiltrates do not occur in respiratory bronchiolitis, as they do in BOOP. Prognosis has been favorable, but data have been derived from a few small series.

The histologic lesion termed *respiratory bronchiolitis* was initially described by Niewoehner and associates in 1974 as an incidental necropsy finding in young asymptomatic smokers who died of nonpulmonary causes. The cardinal feature was clusters of pigmented macrophages in respiratory and terminal bronchioles. The macrophages had abundant cytoplasm with finely, granular, golden-brown pigment. The coarse granules typical of hemosiderin were absent. Peribronchiolar inflammation or fibrosis was noted but was never severe. This lesion was referred to as *small-airways disease* and was believed to represent a reaction to cigarette smoke with minimal clinical significance. In 1987, Myers and colleagues described a similar lesion in six smokers in whom open lung biopsies had been performed for suspected CILD. Four of the cases were identified during a review of all open lung biopsies at the University of Alabama from 1972 to 1984; two additional cases had been referred for pathologic consultation. All were heavy smokers, usually in the third or fourth decade of life. Five had mild symptoms of cough or dyspnea. Chest radiographs demonstrated bilateral interstitial or reticulonodular infiltrates in five. The dominant histologic feature was aggregates of pigmented macrophages within respiratory and terminal bronchioles and adjacent alveolar ducts and spaces. Electron microscopy demonstrated numerous phagolysosomes and “smoker's inclusions” within alveolar macophages. Severe fibrosis or honeycombing was uniformly absent. The prognosis was excellent. In 1989, Yousem et al. extracted 18 cases of respiratory bronchiolitis from the open lung biopsy files of Boston University and an extensive pulmonary pathology consultation collection. All 18 patients were smokers; mean age was 36 years. Symptoms were mild and were limited to cough, dyspnea, or sputum production. Chest radiographs revealed bilateral reticulonodular infiltrates, with a basilar predominance, in 13 patients (72%). Chest radiographic findings were normal in five patients (28%). Pulmonary function tests revealed consistent reductions in diffusing capacity; mild degrees of airway obstruction, with preserved lung volumes, were also noted. Open lung biopsies demonstrated pigmented macrophages in bronchioles and alveolar spaces, with bronchiolar and peribronchiolar inflammation or fibrosis. Severe fibrosis or honeycombing was never evident. The clinical course was benign. Symptoms resolved in 13 patients (81%); five (19%) remained stable; none worsened. Symptoms improved in 12 of 15 following cessation of smoking. Of three patients who continued to smoke, symptoms persisted in two. Only two patients were treated with corticosteroids; symptoms improved in both. Since these sentinel reports, the clinicopathologic syndrome of respiratory bronchiolitis-associated ILD has been further characterized. Cough, dyspnea, and sputum production are the predominant symptoms. Bilateral basilar rales are noted in 40% of patients; clubbing does not occur. Chest radiographs may show fine reticulonodular interstitial infiltrates, bronchial wall thickening, and ring shadows with normal lung volumes. High-resolution CT has been performed in only a few patients. Fine irregular nodules (2 to 3 mm) are most characteristic. Additional features include foci of patchy ground-glass opacities, atelectasis, emphysema, and peripheral blebs. BAL profiles in respiratory bronchiolitis are similar to those of smokers and do not manifest the striking neutrophilia observed in BOOP. Histologically, the strictly peribronchiolar distribution of respiratory bronchiolitis contrasts with the patchy, subpleural involvement noted in usual interstitial pneumonitis (UIP). Honeycombing, a cardinal feature of UIP, is absent in respiratory bronchiolitis. Intra-alveolar accumulation of macrophages may be observed in DIP. The process is uniform and diffuse with DIP and lacks the peribronchiolar distribution seen in respiratory bronchiolitis. The prognosis in respiratory bronchiolitis is excellent, even in the absence of therapy. No deaths have been attributed to respiratory bronchiolitis, and serious pulmonary fibrosis is rare. However, data are limited, and long-term observational studies involving large numbers of patients with respiratory bronchiolitis are lacking. Smoking cessation is the cornerstone of therapy. Corticosteroids should be reserved for patients with persistent or progressive symptoms despite smoking cessation.

Diffuse Panbronchiolitis

Diffuse panbronchiolitis (DPB) is a chronic, progressive bronchiolar inflammatory disorder characterized by pansinusitis, cough, sputum production, diffuse micronodular shadows on chest radiographs, progressive bronchiectasis, and increases in cold-agglutinating antibodies. Panbronchiolitis shares many features with cystic fibrosis, but these disorders are unrelated. The etiology of DPB is not known, but a strong genetic basis is evident. Virtually all cases have been described in Japan and Korea. Fewer than 10 patients with DPB have been described in the United States. More than 60% of patients with DPB express HLA-B54, an antigen restricted to Oriental populations. The incidence of HLA-B54 is 10%–11% in Japanese and Chinese populations and 3% in Koreans. By contrast, HLA-B54 is invariably lacking in Caucasians, blacks, Hispanics, and American Indians.

Clinical Features

Characteristically, chronic sinusitis begins in the second or third decade of life. Chronic cough, sputum production, and bronchiectasis follow 10 or more years after the onset of sinusitis. In time, colonization of the lower respiratory tract with *Hemophilus influenzae* and eventually *P. aeruginosa* develops. Once colonization with *P. aeruginosa* occurs, the course accelerates. Repetitive suppurative infections lead to progressive respiratory failure. Pulmonary function tests in DPB demonstrate airways obstruction, hypoxemia, and air trapping (increased RV). Chest radiographs demonstrate widely disseminated, small (1 to 4 mm), ill-defined nodules, with a predilection for the lung bases. Lung volumes may be normal or increased during the early phases, but destruction of bronchioles and lung parenchyma eventually results in volume loss. Ring shadows, tramlines, and dilated, ectatic bronchioles reflect cystic bronchiectasis. High-resolution CT reveals diffuse nodular and rounded opacities (representing fluid-filled or inflamed bronchioles), dilated bronchi and bronchioles, bronchiolectasis, and cystic bronchiectasis. In contrast to BOOP, DPB is not characterized by dense focal alveolar infiltrates. BAL reveals intense neutrophilia (typically exceeding 40%); lymphocytes are usually normal or slightly increased. Erythrocyte sedimentation rate and levels of C-reactive protein are usually elevated. Serum immunoglobulins are normal or increased. Persistent elevation of polyclonal cold-agglutinating antibodies is a distinctive feature. Although circulating antibodies against *Mycoplasma pneumoniae* are absent, many patients respond clinically to long-term therapy with erythromycin, suggesting an infectious etiology.

Histologic Features

The distinctive early lesion of DPB are small, poorly circumscribed nodules centered on respiratory bronchioles (bronchiolocentric). These nodules correspond to dense peribronchiolar and intraluminal infiltrates of acute and chronic inflammatory cells. An alveolar component is lacking or minimal. The walls of respiratory bronchioles are thickened; airway lumina may be filled with mucus or intraluminal neutrophils. Foamy macrophages and proliferating lymphoid follicles are common associated features. As the disease advances, destruction of bronchiolar walls results in bronchiolectasis and proximal bronchiectasis. Narrowing and obliteration of bronchiolar lumina, ectatic bronchioles, hypersecretion of mucus, and cystic destruction of proximal bronchioles and bronchi may ensue. Histologic features of DPB overlap with those of obliterative (constrictive) bronchiolitis, but the high frequency of sinus and lower respiratory tract infections and bronchiectasis characteristic of DPB are lacking in OB.

Therapy

The prognosis of DPB is poor, with a 5-year survival from the time of diagnosis of 40%; 10-year survival is 25%. Corticosteroids or immunosuppressive agents are not efficacious and may exacerbate infections. Long-term low-dose erythromycin (600 mg/d) ameliorates symptoms and chest radiographic and physiologic findings in some cases, and is recommended. Its impact on long-term prognosis has not been defined. The mechanism of action of erythromycin is not clear, as the dose is below the minimal inhibitory concentration (MIC) for most pathogenic organisms cultured from sputum.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis (BCG), a granulomatous inflammatory disorder involving and destroying bronchi and bronchioles, was initially described in 1973 by Averill Liebow, a renowned pulmonary pathologist. Bronchial walls were infiltrated and replaced by inflammatory cells (predominantly eosinophils, lymphocytes, and mononuclear cells), with extensive necrosis. Bronchial lumina were filled with necrotic exudate, inflammatory cells (particularly eosinophils), epithelioid cells, and multinucleated giant cells. Foci of organizing pneumonia were observed in the distal alveolar spaces and interstitium. Pulmonary vessels contiguous to involved bronchi were often surrounded by inflammatory cells, but true vasculitis was lacking. Predominant clinical manifestations included fever, cough, malaise, dyspnea, and wheezing. Chest radiographs demonstrated patchy infiltrates, consolidation, mucoid impaction, or atelectasis. We are reluctant to make the diagnosis of BCG, as virtually all cases are associated with a specific underlying disease. Asthma or allergic bronchopulmonary aspergillosis (ABPA) has been noted in 30%–50% of cases of BCG. In this context, blood or tissue eosinophilia, increased serum IgE levels, or intrabronchial *Aspergillus* hyphae may be found. Findings of BCG have been described in Wegener's granulomatosis, rheumatoid arthritis, BOOP, and diverse infectious etiologies. It is likely that BCG represents a hypersensitivity response to a variety of intrabronchial antigens rather than a specific disease entity. Therapy should be directed to the underlying disease. Corticosteroids are highly efficacious for ABPA or asthma. When BCG is caused by an infectious granulomatous process (e.g., tuberculosis, fungal infection, nocardiosis, echinoccosis), antimicrobial therapy directed against the responsible organism may be curative.

PULMONARY VASCULITIS

Systemic necrotizing vasculitis involving the lung occurs primarily in the context of the granulomatous vasculitis syndromes (e.g., Wegener's granulomatosis, Churg-Strauss angiitis, lymphomatoid granulomatosis) or pulmonary-renal syndromes (e.g., microscopic polyangiitis, pauci-immune glomerulonephritis). Classic

polyarteritis nodosa rarely involves the lung. Pulmonary arterial aneurysms are well-recognized complications of Takayasu's disease. Pulmonary hemorrhage (usually caused by capillaritis) rarely complicates Behçet's disease or Henoch-Schönlein purpura.

Antineutrophil Cytoplasmic Antibodies

Circulating autoantibodies directed against cytoplasmic components of neutrophils and monocytes (e.g., ANCA) are frequently found in patients with necrotizing small-vessel vasculitis, associated with pulmonary capillaritis or glomerulonephritis. ANCA with differing antigenic specificities have been noted and have differing prognostic and clinical significance. Antibodies with antigenic specificity for proteinase 3 exhibit a cytoplasmic pattern on immunofluorescence (c-ANCA); antibodies with antigenic specificity for myeloperoxidase (MPO) exhibit a perinuclear pattern (p-ANCA). Antibodies with distinct antigenic determinants are observed in different types of vasculitis. c-ANCA (PR3-ANCA) are detected in 70%–93% of patients with untreated Wegener's granulomatosis and may be found in patients with microscopic polyangiitis (MPA) or Churg-Strauss syndrome (CSS). More than 50% of patients with MPA, CSS, or pauci-immune glomerulonephritis demonstrate circulating p-ANCA (MPO-ANCA), whereas p-ANCA is rarely found in Wegener's granulomatosis. Detectable ANCA (typically p-ANCA) are present in <20% of patients with macroscopic polyarteritis nodosa (PAN). c-ANCA is relatively specific for small-vessel vasculitis (>90% specificity), but p-ANCA may be observed in a myriad of inflammatory disorders in which vasculitis is lacking (e.g., collagen vascular disease, inflammatory bowel disease).

Wegener's Granulomatosis

Wegener's granulomatosis, the most common of the pulmonary granulomatous vasculitides, typically involves the upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea), lower respiratory tract (bronchi and lungs), and kidneys, with varying degrees of disseminated vasculitis. Major histologic features include a necrotizing vasculitis involving small vessels (i.e., arterioles, venules, and capillaries), extensive necrosis, and granulomatous inflammation. The estimated prevalence of Wegener's granulomatosis is between 1.3 to 3 cases per 100,000 persons per 5-year period. The peak incidence is in the fourth through sixth decades of life; children or adolescents are rarely affected. There is no sex predominance.

Clinical Features

Clinical manifestations are protean, and virtually any organ can be involved. Upper airway symptoms often dominate. Pulmonary involvement occurs in more than two thirds of patients; glomerulonephritis, in 55%–85%. Although Wegener's granulomatosis usually involves multiple organs, limited variants exist involving only one or two organs. This subset of patients has a more favorable prognosis. DeRemee proposed a staging classification based on involvement of ear, nose, throat (E), lung (L), and kidney (K), to stratify patients with single or multiorgan involvement. Other diagnostic criteria proposed by the American College of Rheumatology in 1990 include nasal or oral inflammation, abnormalities on chest radiographs, abnormal urine sediment, and granulomatous inflammation on biopsy. Many classic features lacking in the early phases of the disease may evolve months or even years after the initial presentation. High titers of circulating c-ANCA may support the diagnosis in the appropriate clinical context, even when histologic features are not definitive. However, the specificity of c-ANCA has been challenged.

Upper Airway Involvement

The upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea) is involved in >90% of patients. Chronic persistent sinusitis, epistaxis, and otitis media are often the presenting and dominant clinical features of Wegener's granulomatosis, but they are often mistakenly thought to represent allergic or infectious etiologies. Sinus radiographic or thin-section CT findings are abnormal in >85% of patients with Wegener's granulomatosis. Thickening or clouding of the sinuses is characteristic; erosion or destruction of sinus bones may occur. Secondary pyogenic sinus infections are common and may be difficult to distinguish from exacerbations of Wegener's granulomatosis. Otologic involvement occurs in 30%–50% of patients. Otalgia and refractory otitis media are common early symptoms of Wegener's granulomatosis. Chronic otitis media, chronic mastoiditis, or hearing loss develops in 15%–25% of patients. The nasopharynx is involved in 60%–80% of patients. Clinical manifestations include epistaxis, nasal septal perforation, persistent nasal congestion or pain, and mucosal ulcers. Saddle nose deformity, resulting from destruction of the nasal cartilage, occurs in 10%–25% of patients. Sore throat or hoarseness may reflect ulcerations or granulomatous involvement of the pharynx or vocal cords. Despite the propensity for Wegener's granulomatosis to affect the upper respiratory tract, histologic confirmation may be difficult. Biopsy specimens of upper airway lesions often demonstrate nonspecific findings of necrosis and chronic inflammation. The cardinal histologic features of vasculitis and granulomatous inflammation may be lacking. A review of 126 biopsy specimens from upper airway or nasopharyngeal lesions in patients with Wegener's granulomatosis seen at the National Institutes of Health revealed the triad of granulomas, vasculitis, and necrosis in only 16% of specimens. Dual features of vasculitis plus granulomas or vasculitis plus necrosis were each noted in 21% of patients. Generous samples of involved sites or samples from additional sites are critical to substantiate the diagnosis. Ocular involvement occurs in 20%–50% of patients with Wegener's granulomatosis. Manifestations may be superficial (e.g., conjunctivitis, scleritis), but uveitis, vasculitis, or compression of the optic nerve may lead to blindness in 2%–9% of patients. Proptosis from a retro-orbital granulomatous inflammatory process has been described in 10%–22% of patients and may compromise the blood supply to the optic nerve. In this context, surgical decompression may be required in patients failing to respond to aggressive medical therapy.

Involvement of Trachea and Bronchi

Stenosis or narrowing of the trachea or major bronchi from granulomatous involvement develops in 10%–30% of patients with Wegener's granulomatosis. The rate of asymptomatic involvement of major airways is even higher. Tracheal or bronchial involvement is nine times more common in female patients and is usually associated with severe sinusitis. Tracheal stenosis is usually circumferential and localized, extending only 3 to 5 cm below the glottis. However, more extensive involvement of the distal trachea or main bronchi may occur. A recent study from the Mayo Clinic cited endobronchial abnormalities in 30 of 51 patients (59%) with Wegener's granulomatosis undergoing bronchoscopy. Four (13%) had tracheal or bronchial stenosis. Extensive endobronchial abnormalities were noted in 11 patients with normal chest radiographic findings. Ulcerating tracheobronchitis was the most common lesion and eventually resulted in progressive stenosis in seven patients followed on a long-term basis. Persistent dyspnea or wheezing may reflect scarring at the site of previous endobronchial inflammation. Stridor or wheezing is a clinical clue to the development of large-airway (trachea or main bronchi) stenosis. Truncation (flow rate limitation) of the inspiratory portion of the flow-volume loop is a sensitive indicator of physiologically significant upper airway obstruction. When the site of obstruction is fixed, both inspiratory and expiratory portions are affected (Fig. 5). Bronchoscopy or spiral CT more objectively quantitates the degree of airway stenosis. Histologic confirmation of the diagnosis is difficult, as endobronchial biopsies usually demonstrate nonspecific changes (e.g., necrosis or inflammation). In the Mayo Clinic study, endobronchial biopsy specimens fulfilled specific histologic criteria for Wegener's granulomatosis in only 3 of 17 patients. Serum titers of c-ANCA did not correlate with endobronchial inflammation. Severe stenosis of large airways may necessitate treatment with YAG (yttrium-argon-garnet) laser, dilation, or placement of Silastic airway stents. Severe upper airway obstruction may mandate tracheostomy. Tracheal reconstruction has been successfully performed in patients with severe tracheal stenosis refractory to medical therapy but is a formidable undertaking.

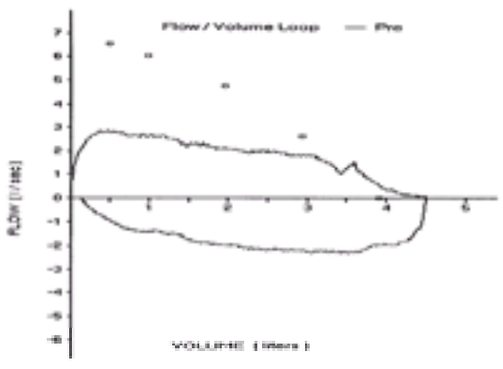

FIG. 5. Wegener's granulomatosis. Flow-volume loop from a 34-year-old woman with tracheal (subglottic) stenosis caused by Wegener's granulomatosis. Note the truncation of both inspiratory and expiratory limbs, consistent with fixed upper airway obstruction.

Lung Involvement

Pulmonary symptoms (e.g., cough, dyspnea, hemoptysis) are noted in approximately one third of patients with Wegener's granulomatosis, caused by parenchymal necrosis, endobronchial inflammation and cicatrix formation, or alveolar hemorrhage. Pulmonary function tests may demonstrate airways obstruction (particularly when endobronchial involvement is prominent), restriction, or mixed patterns. Despite a relatively low prevalence of clinical symptoms, abnormalities on chest radiographs are noted in more than 80% of patients at some point during the course of the disease. Single or multiple nodules or nodular infiltrates are characteristic; cavitation is noted in one quarter (Fig. 6). Other features include focal pneumonic infiltrates (Fig. 7), large mass lesions (Fig. 8), pleural effusions, stenosis of trachea or bronchi, or

atelectasis. Hilar or mediastinal lymphadenopathy has only rarely been described. Extensive alveolar or mixed interstitial alveolar infiltrates may be seen in patients with pulmonary capillaritis and alveolar hemorrhage (Fig. 9). Open (or thoracoscopic) lung biopsy is usually required to substantiate the diagnosis of pulmonary Wegener's granulomatosis. When focal pulmonary infiltrates or nodules are present, the triad of vasculitis, granulomas, and necrosis can be found in >90% of patients by surgical biopsy. By contrast, the yield of endobronchial or transbronchial lung biopsies is only 3%–18%. Massive alveolar hemorrhage is a rare but potentially fatal complication of Wegener's granulomatosis, reflecting diffuse injury to the pulmonary microvasculature. In this setting, rapidly progressive glomerulonephritis is present in >90% of patients. By contrast, 40% manifest upper airway symptoms. The role of surgical lung biopsy in the setting of diffuse alveolar hemorrhage is controversial. Histopathologic features are usually nonspecific. Alveolar hemorrhage dominates. Inflammation and necrosis of the alveolar capillaries (termed *capillaritis*) may be noted, but the granulomatous vasculitis or extensive parenchymal necrosis characteristic of Wegener's granulomatosis at other sites is lacking. For severe pulmonary hemorrhage, we believe the risk of surgical lung biopsy outweighs the benefit. A presumptive diagnosis of diffuse alveolar hemorrhage (DAH) can often be established on the basis of clinical and radiographic features, circulating c-ANCA, and bronchoscopy with BAL. Large numbers of hemosiderin-laden macrophages, bloody or serosanguinous BAL fluid, and absence of infectious etiologies support the diagnosis of DAH (Fig. 10). Biopsy of extrapulmonary sites of involvement may substantiate the diagnosis. However, DAH is a medical emergency requiring aggressive therapy with intravenous pulse methylprednisolone (1 g daily for 3 days) pending the results of a diagnostic workup with biopsies and ancillary laboratory studies. Conventional therapy with oral cyclophosphamide and a tapering regimen of corticosteroids are appropriate once the diagnosis of Wegener's granulomatosis has been confirmed.

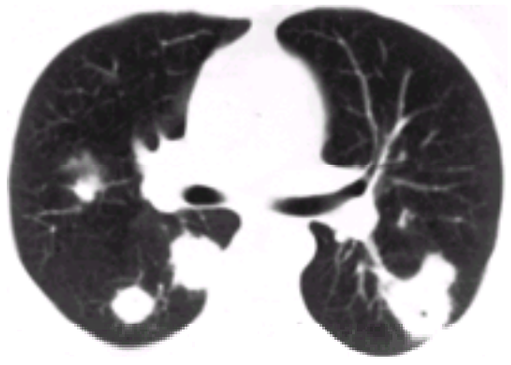

FIG. 6. Wegener's granulomatosis. CT demonstrates multiple focal nodules in a 40-year-old man. Open lung biopsy demonstrated a necrotizing granulomatous vasculitis consistent with Wegener's granulomatosis. (Reproduced with permission from Orens JB, Sitrin RC, Lynch JP III. The approach to nonresolving pneumonia. *Med Clin North Am* 1994: 78;1160, Fig. 8B.)

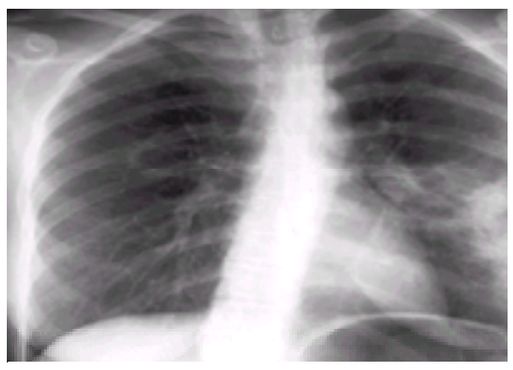

FIG. 7. Wegener's granulomatosis. PA chest radiograph demonstrates dense focal alveolar infiltrates in an 18-year-old female patient with sinusitis, cough, fever, and cutaneous nodules. Serum antineutrophil cytoplasmic antibody was positive (c-ANCA titer of 1:1200). Skin biopsies demonstrated a leukocytoclastic vasculitis. Sinus biopsies revealed a granulomatous necrotizing vasculitis consistent with Wegener's granulomatosis. Chest radiographs normalized within 2 weeks of initiation of cyclophosphamide and prednisone therapy.

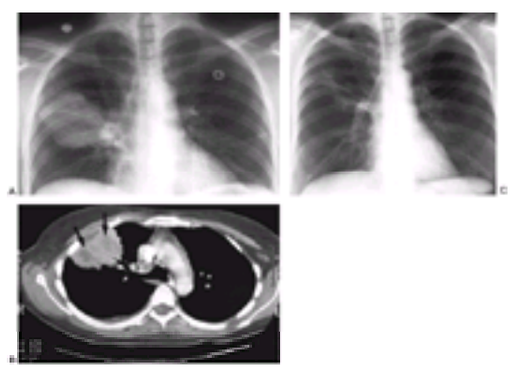

FIG. 8. A: Wegener's granulomatosis. PA chest radiograph demonstrates right upper lobe mass in a 36-year-old woman with leukocytoclastic vasculitis, fever, sinusitis, and cough. **B:** CT in the same patient reveals a mass lesion in the anterior segment of the right upper lobe with areas of focal necrosis (*arrows*). Transbronchial lung biopsies demonstrated granulomatosis vasculitis with extensive necrosis and a polymorphous inflammatory cell infiltrate consistent with Wegener's granulomatosis. **C:** PA chest radiograph from same patient 5 weeks after initiation of therapy with cyclophosphamide and prednisone, showing nearly complete resolution of right upper lobe mass.

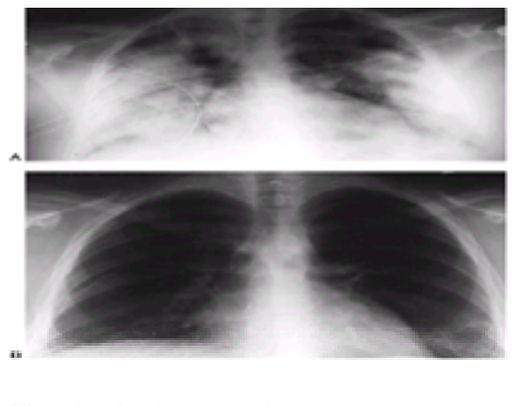

FIG. 9. A: Alveolar hemorrhage caused by Wegener's granulomatosis. PA chest radiograph from a 13-year-old girl demonstrates extensive, confluent alveolar infiltrates. She presented with severe dyspnea, fever, and hemoptysis. Urinalysis demonstrated microscopic hematuria and proteinuria. Open lung biopsy demonstrated massive pulmonary hemorrhage and capillaritis but no granulomas. Review of a prior sinus biopsy demonstrated extensive necrosis and inflammatory exudate with occasional multinucleated giant cells but no definite vasculitis. Pulse methylprednisolone, followed by oral prednisone and cyclophosphamide, was instituted. **B:** PA chest radiographs from the same patient 3 weeks later demonstrate complete clearing of the alveolar infiltrates. After institution of therapy, she remained asymptomatic. Cyclophosphamide was discontinued after 15 months, and prednisone was discontinued after 18 months.

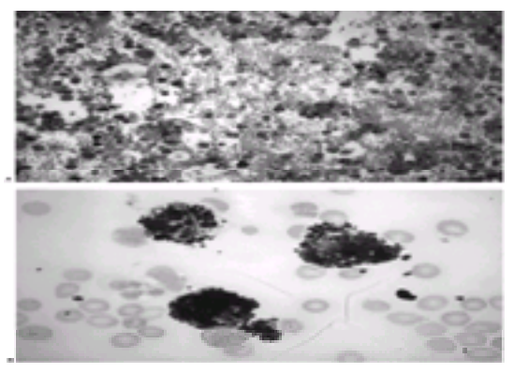

FIG. 10. A: Hemosiderin-laden macrophages. Photomicrograph of BAL fluid demonstrating numerous hemosiderin-laden macrophages with adjacent red blood cells indicating alveolar hemorrhage. Wright stain, low power. **B:** Photomicrograph of BAL fluid showing hemosiderin-laden alveolar macrophages stained blue by iron stain. Prussian blue stain, high power. *See color plate 11.*.

Renal Involvement

Glomerulonephritis (pauci-immune) occurs in 70%–85% of patients at some point in the course of the disease, but only 11%–17% of patients exhibit severe renal insufficiency at presentation. Granulomatous vasculitis is observed in <8% of renal biopsy specimens from patients with Wegener's granulomatosis. The characteristic renal lesion of Wegener's granulomatosis is a segmental focal glomerulonephritis. With more fulminant forms, a necrotizing, crescentic glomerulonephritis is observed. Immune complexes have been noted in a minority of cases. These histologic findings are nonspecific and can be found in diverse immune-mediated or infectious disorders. Clinically evident renal insufficiency may be subtle and progress indolently. Microscopic hematuria or proteinuria precedes detectable abnormalities of renal function. Once renal failure is present, rapid progression may ensue within days or weeks. Aggressive and prompt institution of therapy is mandatory to avert irreversible renal damage. Even in oliguric renal failure, substantial recovery of renal function can be achieved in most patients. Chronic renal failure remains a major cause of death, and 10%–30% of patients with Wegener's granulomatosis eventually require long-term dialysis. Renal transplantation has been successfully accomplished in patients with end-stage renal disease in whom Wegener's granulomatosis is in complete remission. Recurrence of Wegener's granulomatosis has been rare following transplantation. Other rare urologic complications of Wegener's granulomatosis include necrotizing vasculitis involving the ureters, penis, or prostate (anecdotal reports).

Central or Peripheral Nervous System Involvement

Central or peripheral nervous system involvement occurs in <4% of patients at initial presentation, but eventually it develops in 10%–34%. Mononeuritis multiplex or polyneuritis accounts for >50% of neurologic complications. Other manifestations include cerebral infarction or hemorrhage, cranial nerve palsies, focal deficits or seizures from cerebral mass lesions, diabetes insipidus (secondary to granulomatous involvement of the hypothalamus), quadriparesis or paraparesis (reflecting involvement of the spinal cord microvasculature), generalized seizures (reflecting meningeal involvement), and visual loss (from compression of the optic nerve or vasculitis of the vasculature). Vasculitis of the central nervous system has only rarely been confirmed histologically, because of inaccessibility or risks associated with biopsies. The diagnosis is usually supported by histologic confirmation at extraneural sites or by noninvasive studies (e.g., electromyelogram, magnetic resonance imaging, or CT of the brain) in patients with neurologic symptoms and previous documentation of Wegener's granulomatosis. Cerebral angiography is ill advised, because the small vessels affected in Wegener's granulomatosis are below the sensitivity of angiography. In some patients, biopsy of the sural nerve or other affected nerves may substantiate the diagnosis.

Other Organ Involvement

Constitutional features (e.g., malaise, fatigue, fever, weight loss) occur in one third or more of patients with Wegener's granulomatosis. Nondeforming polyarthritis involving medium and large joints occurs in two thirds of patients and parallels activity of the systemic disease. Articular symptoms usually remit with cytotoxic or corticosteroid therapy. Cutaneous lesions are present in 40%–50% of patients during the course of the disease. Manifestations are protean and include palpable purpura, subcutaneous nodules, papules, petechiae, ulcers, and nonspecific erythematous or maculopapular rashes. Skin biopsy may demonstrate granulomatous vasculitis with necrosis but most often reveals nonspecific changes of leukocytoclastic vasculitis. Cardiac involvement is rarely documented ante mortem, but prevalence rates of 10%–15% have been estimated. Coronary arteritis and pericarditis are the most common clinical features. Cardiomyopathies, conduction defects, and fatal arrhythmias may reflect necrotizing vasculitis or granulomatous inflammation involving the myocardium or coronary arteries. Gastrointestinal manifestations (e.g., abdominal pain, diarrhea, hemorrhage, and perforation) have been cited in <5% of patients with Wegener's granulomatosis. This may in part reflect inaccessibility of lesions or lack of an aggressive diagnostic approach. In a review of the literature, granulomatous or vascular lesions within the gastrointestinal tract were found in 23 of 59 necropsies performed in patients with Wegener's granulomatosis.

Histopathology

The cardinal histopathologic features of Wegener's granulomatosis include a necrotizing vasculitis affecting arterioles, venules, and capillaries; granulomatous inflammation; geographic parenchymal necrosis; hemorrhagic infarcts; and areas of fibrosis. Well-formed sarcoidlike granulomas are uncommon, but multinucleated giant cells, epithelioid cells, and collections of histiocytes are usually evident in involved organs. Vascular walls are infiltrated by mononuclear cells and neutrophils, with occasional multinucleated giant cells and eosinophils (Fig. 11). Fibrinoid necrosis and thrombosis within vascular lumina are early findings. Later, fibrosis of vascular walls may result in stenosis or obliteration of the lumina. A pronounced fibroblastic component, with concentric rings of collagen and connective tissue matrix, may be present. These histologic features may not be found if small or nonrepresentative biopsy specimens are obtained. Granulomas and vasculitis of small vessels may be observed with infections (particularly with mycobacterial and fungal etiologies). Thus, special stains should be performed in any granulomatous or necrotic lesion to exclude infectious causes.

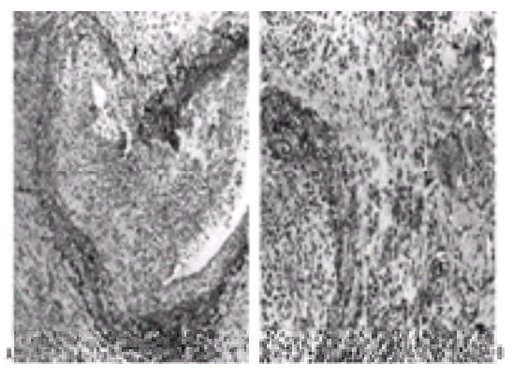

FIG. 11. A: Wegener's granulomatosis. Photomicrograph of lung biopsy specimen demonstrates transmural inflammation of a small vessel with partial destruction of elastin framework (*arrow*). Note the inflammation of the intima and marked narrowing of the vascular lumen. Pentachrome stain. (Courtesy of Andrew Flint, M.D., Department of Pathology, University of Michigan Medical Center.) **B:** Photomicrograph of lung biopsy specimen demonstrating multinucleated giant cells surrounding necrotic debris (*arrows*). A markedly inflamed blood vessel is present in the left portion of the field. Pentachrome stain. (Courtesy of Andrew Flint, M.D.)

Laboratory Features

Anemia, thrombocytosis, or leukocytosis has been noted in 30%–40% of patients with Wegener's granulomatosis. Leukopenia or thrombocytopenia is rare in the absence of cytotoxic therapy. Peripheral blood eosinophilia is not a feature of Wegener's granulomatosis. Polyclonal hypergammaglobulinemia occurs in up to 50% of patients. Serum complement levels are normal or elevated. Circulating immune complexes have been found but are of no clinical value in either the diagnosis or follow-up. Renal function tests (serum creatinine, blood urea nitrogen) and urinalysis should be obtained in all patients initially. Striking increases in erythrocyte sedimentation rate and levels of C-reactive protein are characteristic of active, generalized disease. However, erythrocyte sedimentation rate or levels of C-reactive

protein can be normal with active disease, particularly when only a single site is involved. Serial determinations of the erythrocyte sedimentation rate or levels of C-reactive protein are useful in monitoring the disease but are nonspecific, as elevations may occur in the presence of coexisting infections. c-ANCA are helpful in the initial diagnosis of Wegener's granulomatosis and in monitoring response to therapy. Increases in c-ANCA have been noted in >90% of patients with active generalized Wegener's granulomatosis, and in 40%–70% of patients with active regional Wegener's granulomatosis. Changes in c-ANCA usually correlate with disease activity and are unaffected by intercurrent infections. However, c-ANCA titers may persist in 30%–40% of patients even after complete clinical remission has been achieved. Serial determinations of c-ANCA provide a useful adjunct to the clinical data, but treatment decisions should not rely exclusively on c-ANCA titers.

Pathogenesis

The cause of Wegener's granulomatosis is unknown. The preponderance of disease in the upper and lower respiratory tracts, the intensity of mononuclear infiltrates, and the granulomatous character are consistent with an exaggerated cellular immune response to inhaled antigen(s). Increases in serum immunoglobulins, B-cell activity, circulating autoantibodies (c-ANCA), and immune complexes suggest that humoral mechanisms are also operative. The presence of polymorphonuclear leukocytes in the inflammatory vasculitic process, and of circulating autoantibodies directed against neutrophil cytoplasmic components, suggest a role for neutrophils and c-ANCA in the pathogenesis and evolution of the disorder. Exacerbations of Wegener's granulomatosis during intercurrent infections, and the frequent relapses observed in patients with Wegener's granulomatosis who are chronic nasal carriers of *S. aureus,* suggest that infections may amplify the inflammatory process, possibly by eliciting an antibody and acute-phase response.

Therapy

Before therapy became available, >80% of patients with Wegener's granulomatosis died within 3 years of onset of symptoms, usually of progressive renal insufficiency. Corticosteroids improved survival modestly. In the 1970s, the introduction of cyclophosphamide led to dramatic improvement in prognosis and survival. Oral cyclophosphamide (1 to 2 mg/day) combined with corticosteroids (1 mg/kg/day, with taper) is the treatment of choice for Wegener's granulomatosis. Remissions are achieved in 70%–93% of patients with this regimen; early mortality has been <15%. Late sequelae of vasculitis (e.g., cerebrovascular accidents, myocardial infarction, renal failure, hypertension) or complications of cyclophosphamide therapy (e.g., opportunistic infections, neoplasms) contribute to long-term mortality and morbidity. The dose of cyclophosphamide may need to be adjusted to maintain acceptable blood counts (particularly a leukocyte count of >3000/mm3). Corticosteroids ameliorate many of the inflammatory manifestations of Wegener's granulomatosis and are important as adjunctive therapy. The dose of corticosteroid needs to be individualized according to the clinical response and presence or absence of adverse effects. We attempt to taper to alternate-day prednisone (e.g., 60 mg every other day) within the first 2 to 3 months. Thereafter, we taper the prednisone gradually by 10-mg decrements every 1 to 3 months, until a maintenance dose of 15 to 20 mg every other day is achieved. Thereafter, the rate of taper may be slowed. Cyclophosphamide should be continued for a minimum of 12 months after complete clinical and laboratory remission has been achieved. Shorter duration of therapy has been associated with unacceptably high rates of relapses and late sequelae. Relapses occur in 20%–50% of patients as the regimen is tapered or discontinued, but reinstitution of therapy is usually efficacious. Prolonged therapy may be required in patients exhibiting a propensity to relapse. Unfortunately, cyclophosphamide is associated with a myriad of complications. Opportunistic infections (particularly herpes zoster) occur in 20%–30% of patients receiving cyclophosphamide. Other complications include bone marrow toxicity, pulmonary toxicity, alopecia, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, hepatotoxicity), stomatitis, infertility, and oligospermia. Cyclophosphamide may induce both solid and hematologic neoplasms. Malignant lymphomas or hematologic malignancies have been noted in 1%–3% of patients with Wegener's granulomatosis who are receiving cyclophosphamide. Hemorrhagic cystitis occurs in 30%–50% of patients but is severe in <6% of patients. A recent, long-term study of 146 patients with Wegener's granulomatosis treated with cyclophosphamide cited seven cases of transitional cell carcinoma of the bladder. Antecedent hematuria had been noted in all patients. The risk for bladder carcinoma correlated with duration and total dose of cyclophosphamide therapy; cigarette smoking may amplify the risk. The incidence of bladder cancer following first exposure to cyclophosphamide is 5% at 10 years and 16% at 15 years. The risk persists for many years after discontinuation of cyclophosphamide. Serial urinalyses at 3- to 6-month intervals are advised in patients receiving cyclophosphamide and are sensitive in detecting bladder carcinomas. The presence of hematuria (macroscopic or microscopic) warrants cystoscopy. Intermittent intravenous high-dose (pulse) cyclophosphamide has been used to treat Wegener's granulomatosis, but results have been unimpressive. Early responses were noted in 13 of 14 patients treated with pulse cyclophosphamide in a nonrandomized trial at the National Institutes of Health. However, sustained remissions were achieved in only three patients (21%). Pulse cyclophosphamide is less toxic than daily oral cyclophosphamide but is less effective and is not recommended.

Other Therapeutic Options

In view of the rarity of Wegener's granulomatosis, prospective, randomized trials assessing therapy have not been performed. Anecdotal successes have been noted with other immunosuppressive or cytotoxic agents (e.g., azathioprine, methotrexate, and chlorambucil), but we consider these agents as second-line. Chlorambucil (Leukeran) may be oncogenic, and data are limited evaluating its efficacy as therapy for Wegener's granulomatosis. We do not employ chlorambucil in the treatment of Wegener's granulomatosis. Azathioprine (Imuran) is clearly less effective than cyclophosphamide, but it may be effective in maintaining remissions in patients experiencing adverse effects from cyclophosphamide. In an early report from the National Institutes of Health, cyclophosphamide successfully induced remissions in all 10 patients whose disease had been refractory to therapy with azathioprine. Azathioprine cannot be considered a first-line agent. Oral methotrexate, administered once weekly, may be used for patients with Wegener's granulomatosis in whom serious adverse effects develop from cyclophosphamide. A recent prospective (but nonrandomized) study at the National Institutes of Health treated 42 patients who had non–life-threatening Wegener's granulomatosis with oral methotrexate (mean dose, 20 mg/week) combined with corticosteroids. Treatment regimens before entry into the study included no prior therapy (16); corticosteroids alone (14); corticosteroids plus trimethoprim/sulfamethoxazole (6); cyclophosphamide plus corticosteroids (4); azathioprine (2). The four patients receiving cyclophosphamide were switched to methotrexate because of toxicity (hemorrhagic cystitis or leukopenia). All other patients had failed to achieve remissions with prior treatment regimens. Exclusion criteria included acute renal failure, pulmonary hemorrhage, serum creatinine levels of >2.5 mg%, and chronic liver disease. However, all patients had active disease at entry into the study, including glomerulonephritis in 21 (50%) and lung involvement in 22 (52%). Methotrexate was initiated at a dose of 0.3 mg/kg once weekly and was increased to tolerance up to a maximal dose of 20 to 25 mg once weekly. Prednisone was initiated at a dose of 1 mg/kg daily and gradually tapered as improvement occurred. Remissions were achieved in 30 of 42 patients (71%). Median time to remission was 4.2 months. Of the 30 patients achieving remission, 11 (36%) relapsed at a mean of 29 months. A second remission was induced in six of eight patients following a second course of methotrexate and prednisone. Toxicity was generally mild, but *Pneumocystis carinii* pneumonia developed in four patients (two of whom died). Methotrexate pneumonitis developed in three, which resolved with cessation of therapy. Asymptomatic elevation in transaminases was noted in 24% and always resolved with reduction of dose. Titers of c-ANCA did not correlate with disease activity. These data are encouraging and support the use of methotrexate plus prednisone in patients experiencing adverse effects from cyclophosphamide and as initial therapy in patients with mild Wegener's granulomatosis. Additional data are required to evaluate the role of methotrexate as therapy for Wegener's granulomatosis more fully.

Trimethoprim/Sulfamethoxazole

Anecdotal responses have been observed with trimethoprim/sulfamethoxazole (T/S), but firm data affirming the efficacy of T/S are lacking. In a nonrandomized clinical trial, DeRemee and colleagues at the Mayo Clinic cited favorable responses with T/S in a subset of patients with Wegener's granulomatosis. DeRemee added T/S to a previously failing regimen of cyclophosphamide/prednisone in 31 patients with indolent but progressive Wegener's granulomatosis. Favorable responses were noted in 26 patients; late relapses were observed in four patients in this group. In addition, T/S was given as initial therapy in 15 patients with limited Wegener's granulomatosis. In this context, 14 responded; only three experienced late relapses. On the basis of these favorable results, DeRemee advocated T/S (one double-strength tablet twice daily) as initial therapy for patients with limited disease (lacking renal disease or generalized vasculitis) or for patients with progressive disease despite cyclophosphamide and corticosteroids. If no improvement was evident after 8 weeks, prednisone and/or cyclophosphamide were introduced. Although other investigators have cited favorable responses with T/S, data are limited. A prospective study at the National Institutes of Health found that T/S (alone or combined with corticosteroids) as initial therapy for Wegener's granulomatosis was ineffective in all nine patients. Nonetheless, a role for T/S in attenuating the course of the disease is plausible. Stegeman and colleagues evaluated the efficacy of T/S in preventing relapses in patients with Wegener's granulomatosis who were in remission during or after treatment with cyclophosphamide and prednisone. Patients were randomized to either T/S (160 mg trimethoprim/800 mg sulfamethoxazole) twice daily or placebo in addition to conventional treatment with cyclophosphamide and prednisone. At 24 months of follow-up, 82% of patients assigned to T/S were in remission, compared with only 60% in the placebo group. The annual rate of respiratory and nonrespiratory infections was also lower in the T/S group. Titers of ACNA did not differ between groups. Although this study did not address T/S as primary (initial) therapy for Wegener's granulomatosis, T/S did reduce the rate of relapses in patients with Wegener's granulomatosis following conventional treatment with cyclophosphamide/prednisone. Its mechanism of action is not known, but T/S may suppress autoantibody formation by direct antimicrobial effects or by indirect immunosuppressive or anti-inflammatory effects. Relapses of Wegener's granulomatosis are more frequent coincident with respiratory infections or in patients with chronic nasal carriage of *S. aureus.* Low-grade bacterial infection may prime neutrophils to express target antigens (e.g., c-ANCA) on the cell surface and may trigger local immune responses. The antimicrobial effect of T/S may abrogate these effects, thus limiting neutrophil activation and further tissue damage. Although these data are intriguing, the role of T/S has not been defined. In view of its low toxicity, T/S may be considered as adjunctive therapy in patients with persistent, indolent disease despite cyclophosphamide and corticosteroids. We do not believe T/S should supplant conventional therapy with cyclophosphamide/corticosteroids.

Polyarteritis Nodosa

Classic (macroscopic) polyarteritis nodosa (PAN) is a necrotizing vasculitis involving small and medium-sized muscular arteries. PAN differs from Wegener's granulomatosis in that microscopic vessels (e.g., small arterioles, venules, capillaries) are spared, and a granulomatous component is lacking in PAN. Macroscopic aneurysms involving the renal, mesenteric, or hepatic arteries can be demonstrated by angiography in more than two thirds of patients. Clinical manifestations

predominantly affect the kidneys, gastrointestinal tract, central nervous system, skin, heart, and viscera. Clinical lung involvement complicates PAN in <2% of cases. Most previous reports of PAN with lung involvement probably represented either Churg-Strauss Syndrome (CSS) or microscopic polyangiitis (MPA). These entities are discussed in detail later in this chapter. Circulating ANCA (typically p-ANCA) have been detected in <20% of patients with PAN. By contrast, circulating ANCA (typically c-ANCA) are found in most patients with Wegener's granulomatosis, MPA, or CSS. Most cases of PAN are primary or idiopathic, but secondary forms (e.g., caused by hepatitis B virus or tumor antigens) are well recognized. Patients with PAN and hepatitis B antigenemia are usually treated with antiviral therapies in combination with plasmapheresis or immunosuppressive agents. For PAN without hepatitis B antigenemia, corticosteroids (alone or in combination with cyclophosphamide) are the mainstay of therapy. Five-year survival exceeds 75% but may be worse in the presence of adverse prognostic factors (e.g., gastrointestinal tract or central nervous system involvement, renal failure, loss of >10% of body weight, age of >50 years). The optimal doses of corticosteroid have not been delineated in randomized trials. For mild to moderate cases, initial therapy with prednisone (1 mg/kg per day for 1 month), followed by a gradual taper, is reasonable. For more severe or fulminant cases, we initiate therapy with high-dose intravenous methylprednisolone (500 to 1000 mg daily for 3 days), followed by oral prednisone (1 mg/kg/day or the equivalent) for 4 to 6 weeks. The dose of corticosteroid and rate of taper need to be individualized according to the response and clinical course. Cyclophosphamide is a highly effective drug for PAN, even in steroid-refractory cases. We routinely add oral cyclophosphamide (2 mg/kg/day) to corticosteroids, but some investigators reserve this agent for more severe or steroid-recalcitrant cases. Randomized European multicenter trials cited higher response rates (and fewer relapses) in regimens employing oral cyclophosphamide plus corticosteroids compared with corticosteroids alone. Survival did not differ between groups. Intravenous pulse cyclophosphamide (administered once monthly) may be less toxic than oral cyclophosphamide and appears to be equally efficacious. Patients responding to therapy with cyclophosphamide should be continued on this agent for at least 1 year after induction of remission. Relapses warrant reinstitution of therapy with corticosteroids plus cyclophosphamide. Plasmapheresis can be considered as adjunctive therapy in patients with fulminant PAN refractory to conventional therapy but should not be used routinely. In two randomized trials (that included patients with PAN or CSS), the addition of plasma exchange to prednisone or prednisone and cyclophosphamide did not improve prognosis or mortality.

Microscopic Polyangiitis

Microscopic polyangiitis (previously termed *overlap polyangiitis syndrome*) has clinical and histopathologic features overlapping with those of classic PAN and CSS. Predominant clinical manifestations are glomerulonephritis and pulmonary capillaritis (manifested as alveolar hemorrhage), but other organs may be involved. Microscopic polyangiitis is rare, with an estimated prevalence of 2.4 cases per million (range, 0.9 to 5.3). Mean age at onset is approximately 50, but all ages may be affected. There is a slight male predominance. As its name implies, microscopic polyangiitis (MPA) involves small vessels (arterioles, venules, and capillaries). MPA appears to be identical to what Zeek termed “hypersensitivity angiitis” in 1952. In the mid-1980s, the term *microscopic polyarteritis* was adopted to distinguish this disorder from macroscopic (classic) PAN. Capillaries are invariably involved in MPA, but arterioles may be spared. Thus, the term *microscopic polyangiitis* has replaced *microscopic polyarteritis.* Circulating ANCA (usually c-ANCA) have been demonstrated in a majority of patients with MPA, suggesting a possible relationship with other ANCA-associated pulmonary vasculitides (e.g., Wegener's granulomatosis and CSS). The defining criteria for MPA are less crisp than those for either Wegener's granulomatosis or CSS. In 1994, a panel of experts convened at the Chapel Hill Consensus Conference to provide defining criteria for vasculitis. MPA and PAN were distinguished primarily by histologic features. Small vessels (capillaries, venules, arterioles) were invariably involved in MPA but were always spared in classic PAN. Medium-sized or small arteries could be affected in either MPA or PAN. Granulomas were absent in both disorders.

Clinical Features

The predominant manifestations of MPA are alveolar hemorrhage and rapidly progressive glomerulonephritis, features rarely seen in classic PAN. The clinical features of MPA were articulated by Savage and colleagues in 1985. A necrotizing, crescentic glomerulonephritis with few or no immune deposits (termed *pauci-immune*) is characteristic of MPA. Alveolar hemorrhage occurs in 30%–50% of patients and is often the dominant (and most life-threatening) manifestation (Fig. 12). A prodromal respiratory illness precedes the onset of vasculitis in one third of patients. Arthralgias and myalgias may be prominent. Sinus or upper airway involvement may occur but is rarely a prominent or presenting feature. Oral ulcers have been noted in up to 21% of patients with MPA and may mimic Wegener's granulomatosis. Cutaneous involvement (leukocytoclastic vasculitis) is common. Renal infarcts, renal vasculitis, and visceral aneurysms, cardinal features of PAN, are rarely observed in MPA. Peripheral neuropathy occurs in 50%–80% of patients with PAN, but in only 10%–20% of patients with MPA. Circulating immune complexes and rheumatoid factor have been noted in 40% of patients with MPA and antinuclear antibodies in 21%. These nonspecific tests have been supplanted by ANCA, which have been detected in 50%–90% of patients with MPA. By contrast, ANCA are present in <20% of patients with PAN. Several features of MPA (e.g., circulating ANCA, small-vessel vasculitis, glomerulonephritis, and pulmonary capillaritis) may be observed in patients with Wegener's granulomatosis or CSS. Both of these latter vasculitic disorders exhibit a granulomatous component, which is lacking in MPA. Asthma or eosinophilia (in blood or tissue), characteristic features of CSS, are not found in MPA. A firm diagnosis of MPA requires that these alternative diagnoses be definitely excluded.

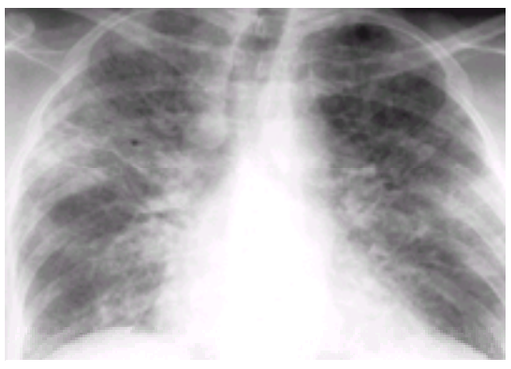

FIG. 12. Alveolar hemorrhage caused by microscopic polyangiitis. PA chest radiograph demonstrates diffuse alveolar infiltrates involving all lobes. Within 24 hours, the infiltrates worsened and severe respiratory failure developed; mechanical ventilatory support with positive end-expiratory pressure (PEEP) at 16 cm H_2O was required to achieve acceptable oxygenation. Because of the severity of respiratory failure, no lung biopsy was performed. Urinalysis demonstrated numerous red cells and occasional red cell casts. Serum creatinine level was 1.4 mg%. One gram of pulse methylprednisolone (Solu-Medrol) was administered daily for 3 days. Renal biopsy demonstrated glomerulonephritis and a necrotizing vasculitis involving renal arterioles; no granulomas were present. Cyclophosphamide was instituted (2 mg/kg daily) and corticosteroids were continued. Within 5 days, the infiltrates had cleared completely and serum creatinine level was 0.6 mg%.

Histopathology

Like other ANCA-associated vasculitides, MPA principally affects small arterioles, venules, and capillaries. A granulomatous component is lacking and eosinophils are rare or absent, in contrast to what is observed in CSS and Wegener's granulomatosis. Immune complexes are nondetectable or present in only small amounts in involved tissue (*pauci-immune*).

Treatment

Diverse regimens employing prednisone, azathioprine, cyclophosphamide, and plasmapheresis, alone or in combination, have been used to treat MPA. Because of the rarity of MPA, data regarding therapy are limited. Treatment regimens have been extrapolated from studies that have incorporated patients with MPA, CSS, and PAN. In this context, overall survival appeared to be similar with various regimens, including corticosteroids alone, corticosteroids plus oral cyclophosphamide, corticosteroids plus intravenous cyclophosphamide, corticosteroids plus plasma exchange, and corticosteroids plus cyclophosphamide plus plasma exchange. Plasmapheresis adds another level of complexity and should be reserved for fulminant or refractory cases. Most investigators use oral cyclophosphamide (2 mg/kg/day) and corticosteroids (1 mg/kg/day, with gradual taper), similar to the regimen used in Wegener's granulomatosis. Favorable responses are achieved in >80% of cases; 10-year survival exceeds 70%. As with Wegener's granulomatosis, treatment should be continued for a minimum of 1 year after complete clinical and laboratory remission has been achieved.

Churg-Strauss Angiitis (Allergic Angiitis and Granulomatosis)

CSS, also termed *allergic angiitis and granulomatosis,* was originally reported in 1951 by Churg and Strauss, who described 13 patients with asthma, peripheral eosinophilia, constitutional symptoms, and systemic necrotizing vasculitis. These investigators noted that CSS shares histologic features with PAN, but is distinct from classic PAN. In 1957, Rose and Spencer identified 32 patients with asthma and features consistent with CSS from a necropsy series of 111 patients with PAN. Only sporadic reports of CSS were described during the next two decades. In 1977, Chumbley and co-workers reviewed 30 patients with CSS seen at the Mayo Clinic during a 24-year period. A review of the files of the Armed Forces Institute of Pathology in 1981 revealed only four cases of CSS. As of 1982, only 138 cases of CSS had been published. The annual incidence of CSS has been estimated at 2.4 cases per million. In 1984, Lanham and colleagues reported 16 additional patients with

CSS (only eight of whom had histologic confirmation of vasculitis) seen at a large referral hospital in England during a 6-year period, and suggested that the rarity of CSS in part reflected the stringent criteria required for the diagnosis. They suggested that the diagnosis of CSS could be made even when not all classic criteria (e.g., necrotizing vasculitis, extravascular granulomas, tissue eosinophilia) were present. A concept of “limited forms” of CSS, analogous to limited Wegener's granulomatosis, has been suggested. Cardinal features required for the diagnosis include an allergic diathesis and eosinophilic component (either in blood or tissue).

Clinical Features

Pulmonary involvement (characteristically manifested as asthma) is present in virtually all patients. Focal alveolar infiltrates are present on chest radiograph in 30%–70% of cases. Diffuse alveolar hemorrhage is a rare complication. Pulmonary nodules or cavitary lesions are rarely observed in CSS, as they are in Wegener's granulomatosis. Typically, a history of atopy and asthma precedes the development of vasculitis by months or even years. Hay fever, nasal polyposis, allergic rhinitis, and sinusitis are noted in more than two thirds of patients. Otolaryngeal manifestations include nasal crusting or nasal polyposis in up to 75% of patients with CSS and nasal perforation in 5%. Peripheral blood eosinophilia is usually prominent during the asthmatic and vasculitic phases. Increasingly severe and more frequent exacerbations of asthma precede the development of necrotizing vasculitis. Constitutional symptoms are usually prominent. Fever, weight loss, or malaise are noted in >90% of patients. Arthralgias or myalgias occur in one third of patients. Central or peripheral neurologic involvement occurs in 40%–63% of patients with CSS. Peripheral neuropathy or mononeuritis multiplex predominates; cerebral infarction has rarely been described. Cutaneous manifestations (e.g., subcutaneous nodules, purpura, or petechiae) occur in two thirds of patients. Skin biopsy may demonstrate nonspecific findings of leukocytoclastic vasculitis; when dense eosinophilic infiltrates are noted, the diagnosis of CSS is strongly suggested. Cardiac involvement occurs in 30%–50%. Cardiac failure and pericarditis are the most common clinical manifestations. Cardiac involvement may reflect primary coronary vasculitis or eosinophilic endocarditis with associated fibrosis. Abdominal viscera are involved in 20%–40%. Abdominal pain or perforation of a viscus resulting from ischemia are well-recognized complications. Renal failure is rare with CSS, but hypertension develops in nearly 50% of patients. The mean age of onset is in the middle to late 40s, but the range is wide (14 to 75 years). Laboratory studies demonstrate elevations in the erythrocyte sedimentation rate and blood eosinophil counts in >80% of patients during acute exacerbations. Both erythrocyte sedimentation rate and blood eosinophil counts usually correlate with activity of disease. Circulating ANCA (both p-ANCA and c-ANCA) have been noted in a majority of patients with CSS.

Histopathology

The salient histologic features of CSS include a necrotizing vasculitis involving small arteries and veins, with eosinophilic and granulomatous components. The pronounced eosinophilic and granulomatous character distinguishes CSS from other pulmonary vasculitides. Eosinophilic infiltration of vascular walls is usually striking; mononuclear cells, neutrophils, and occasional multinucleated giant cells are also present. Granulomas and eosinophils in extravascular tissues are hallmarks of the disorder. Palisades of histiocytes and giant cells surround a central eosinophilic core. The diagnosis can be supported even when histologic features are not definitive, provided the clinical and laboratory features are characteristic. The lesions in diffuse alveolar hemorrhage demonstrate nonspecific findings of capillaritis.

Therapy

Corticosteroids have been the mainstay of therapy, with remissions in >80% of patients. Immunosuppressive and cytotoxic agents have also been tried. Prospective, randomized trials (that enrolled patients with PAN or CSS) have evaluated various medical regimens, including corticosteroids alone; corticosteroids plus oral cyclophosphamide; corticosteroids plus pulse cyclophosphamide; corticosteroids plus plasma exchange; and the combination of corticosteroids, cyclophosphamide, and plasma exchange. Long-term (10-year) survival is similar with the various regimens (3-year survival, 80%–90%; 10-year survival, 72%–78%). Pulse (once-monthly intravenous high-dose) cyclophosphamide was comparable with oral cyclophosphamide and steroids for PAN or CSS. Given the high remission rate with corticosteroids and the potential late sequelae associated with cytotoxic agents, we consider prednisone as first-line therapy for mild to moderate cases of CSS (1 mg/kg/day for 4 weeks, followed by a gradual taper). Oral cyclophosphamide (2 mg/kg/day) is added for more fulminant cases or when unfavorable prognostic features are present [e.g., proteinuria >1 g/day, severe gastrointestinal involvement, cardiomyopathy, renal insufficiency (serum creatinine levels of >1.6 mg%), or central nervous system involvement]. Asthma, polyarthritis, myalgias, ophthalmologic signs, weight loss, or cutaneous involvement do not influence prognosis. For fulminant or refractory cases, more rapid control of the disease can be accomplished with aggressive combination therapies. In this context, pulse methylprednisolone (1 g daily for 3 days) followed by oral prednisone (1 mg/kg/day) combined with cyclophosphamide (2 mg/kg/day) is advised. Plasma exchange may be added in patients failing or experiencing adverse effects from therapy, but it has been associated with an increased risk for infectious complications. Plasmapheresis may be given three times per week for the first 2 to 3 weeks, and at decreasing frequency during the next 2 to 4 months.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) was initially described in 1972 as a necrotizing vasculitic disorder having several features in common with Wegener's granulomatosis and atypical lymphoma. Histologic features include atypical lymphohistiocytic infiltrates surrounding small and medium-sized arteries and veins, associated with pronounced necrosis of involved organs. The angiocentric pattern, presence of multinucleated giant cells, granulomatous component, and mixed inflammatory cellular infiltrates mimic Wegener's granulomatosis. However, the pronounced cellular atypia resembles a lymphoid malignant disorder (Fig. 13). Clinical manifestations of LYG are protean. Virtually any organ can be involved, but pulmonary, constitutional, neurologic, and cutaneous manifestations predominate. Glomerulonephritis has only rarely been noted. Aberrations on chest radiographs are almost invariably present (Fig. 14). Multiple nodular lesions are typical, but single mass lesions, alveolar infiltrates, cavitary lesions, or pleural effusions may be found. In early studies, anecdotal responses were noted with regimens employing oral cyclophosphamide and corticosteroids (similar to treatment of Wegener's granulomatosis). Subsequent studies have failed to substantiate benefit from corticosteroids alone or in combination with immunosuppressive or cytotoxic agents. Recent investigations utilizing molecular biologic and immunohistochemical techniques (e.g., T-cell gene rearrangements, monoclonal stains) suggest that most (if not all) cases of LYG represent diverse lymphoreticular disorders, including malignant lymphoma, angioimmunoblastic lymphadenopathy, and T-cell lymphomas. LYG should not be classified as a true vasculitis, but rather as a stereotypic response to diverse lymphoreticular disorders. Although optimal therapy has not been clarified, combination chemotherapeutic regimens for malignant lymphoma are appropriate for many patients.

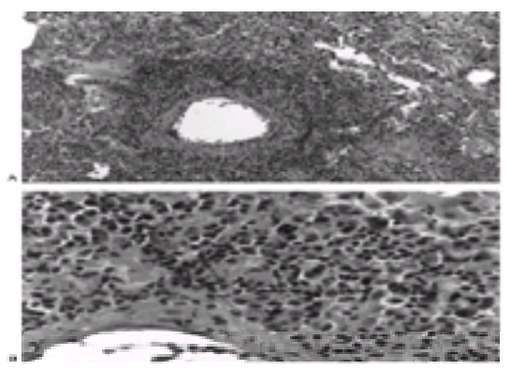

FIG. 13. A: Lymphomatoid granulomatosis. Photomicrograph of open lung biopsy specimen demonstrates intense mononuclear infiltrates surrounding a blood vessel. H&E, high power. (Courtesy of S. Hammar, M.D, University of Washington, Seattle.) **B:** Photomicrograph of specimen from same patient showing polymorphous infiltrate composed of atypical lymphoid and histiocytic cells. Granuloma is not a characteristic histologic abnormality despite the suggestion in the term. H&E, oil immersion. (Courtesy of S. Hammar, M.D, University of Washington, Seattle.)

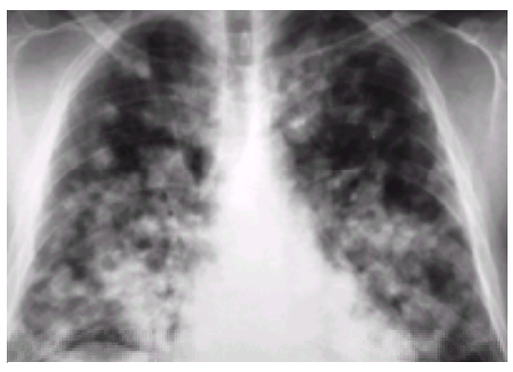

FIG. 14. Lymphomatoid granulomatosis. PA chest radiograph demonstrates multiple nodular mass densities throughout both lung fields. Open lung biopsy specimen

demonstrates changes consistent with lymphomatoid granulomatosis.

Behçet's Syndrome

Behçet's syndrome is a systemic vasculitis whose major manifestations include oral and genital ulcers, iritis, phlebitis, and nervous system involvement. Recurrent venous thromboses occur in one quarter of patients with Behçet's syndrome. Other possible sites of involvement include skin, gastrointestinal tract, kidneys, heart, joints, and epididymis. Lung involvement occurs in only 1%–5% of cases. Diverse pulmonary manifestations include transient infiltrates, mass lesions, pleural effusions, hemoptysis, aneurysms of the pulmonary arteries, arterial and venous thromboses, pulmonary infarcts, and pulmonary hemorrhage. Massive, fatal hemorrhage from rupture or erosion of pulmonary arterial aneurysms has been described. Behçet's syndrome is more common in the eastern Mediterranean basin but is worldwide in distribution. The onset of disease is most common in the third through fifth decades of life. Histologic features are nonspecific. A necrotizing vasculitis (composed of lymphocytes, plasma cells, and polymorphonuclear leukocytes) involves arteries, veins, and capillaries. Varying degrees of fibrosis, thrombosis, and necrosis are evident. The etiology is not known, but deposits of immune complexes and complement may be prominent in involved tissues. Because of the rarity of this disease, controlled therapeutic trials have not been performed. Corticosteroids, combined with cyclophosphamide or azathioprine, are most commonly employed. Colchicine has been advocated as adjunctive therapy for arthralgias or erythema nodosum. When pulmonary arterial aneurysms are documented, prompt resection should be accomplished.

Hughes-Stoven Syndrome

In 1959, Hughes and Stoven described a symptom complex of pulmonary artery aneurysms and recurrent venous thromboses (especially of the vena cava). A review of the literature up to 1981 identified only 12 patients with Hughes-Stoven syndrome; 11 were young males. Symptoms included fever, central nervous system symptoms resulting from increased intracranial pressure, hemoptysis, arthralgias, and skin rash. Nine died of massive hemoptysis caused by rupture of pulmonary arterial aneurysms. Surgical resection of pulmonary aneurysms was accomplished in all three survivors. Cerebral thrombophlebitis was present in 6 of these 12 cases. Histologic features of involved tissue demonstrated a necrotizing vasculitis. Most if not all cases of “Hughes-Stoven syndrome” likely reflect unrecognized pulmonary vasculitis from other causes (e.g., CSS, Behçet's syndrome).

Takayasu's Arteritis

Takayasu's arteritis is a rare vasculitis primarily affecting large vessels (e.g., aorta and its branches). It may cause arterial stenoses, aneurysms, and distal arterial insufficiency. The most common site of involvement is the subclavian arteries, near their junction with the aorta. The absence of radial pulses has given rise to the term *pulseless disease.* Most series have been reported from Japan, the Orient, and Mexico. Takayasu's arteritis is rare in the United States and Europe. Only 32 cases were given the diagnosis at the Mayo Clinic between 1971 to 1983. The incidence among Caucasians has been estimated at 2.6 cases per million per year. Most patients present between ages 20 and 30; the disease is rare in the elderly. There is a striking female predominance.

Clinical Features

Dominant clinical manifestations, which are related to cessation of blood flow in the aorta or its branches, include claudication of arms or legs, dizziness (reflecting occlusion of the carotid or vertebrobasilar arteries), ischemic cardiac disease, visual loss, and back pain (reflecting aortic aneurysms). Multiple vascular bruits or absent or reduced pulses are characteristic findings on physical examination. Fever, malaise, weight loss, and anemia are noted in more than one third of patients and myalgias or arthralgias in nearly 60%. Elevations in the erythrocyte sedimentation rate may be striking and may be a surrogate marker of disease activity. Results of tests for antinuclear antibodies and rheumatoid factor are negative. Renovascular hypertension occurs in approximately 40% of patients. Aortic insufficiency or aneurysms of the root of the aorta, when present, are major causes of death and warrant surgical correction. Pulmonary vasculitis is rarely recognized ante mortem, but pulmonary arterial aneurysms or stenoses have been documented in up to 50% of patients by pulmonary angiography or necropsy. The diagnosis of Takayasu's disease is usually made on the basis of aortic angiographic findings of occlusions, stenosis, luminal irregularities, tortuosity, or aneurysms in a young woman with arterial occlusive symptoms. Dilatation of the aortic root or aortic insufficiency may occur. Similar findings may be observed on pulmonary arteriography. Bypass grafts for aortic occlusive lesions have been successfully performed in some patients. Histopathology is rarely confirmed, except at the time of resection or bypass of arterial lesions. Salient features are a granulomatous, sclerosing arteritis indistinguishable from giant cell (temporal) arteritis.

Therapy

Corticosteroids are the cornerstone of therapy. Most experts initiate therapy with prednisone (1 mg/kg/day) for 4 to 6 weeks, followed by a gradual taper according to symptoms and sedimentation rate. Cyclophosphamide should be considered for severe cases or patients failing corticosteroids. With aggressive medical therapy, survival exceeds 90%, and severe sequelae can be averted. Factors associated with increased mortality include severe systemic hypertension, aortic incompetence, and marked aneurysm formation. Far-advanced stenoses or occlusions caused by inactive, sclerotic lesions are not influenced by immunosuppressive therapy. In these circumstances, when symptoms of vascular compromise are evident, angioplasty, surgical reconstruction, or bypass grafts should be performed.

Henoch-Schönlein Syndrome

Henoch-Schönlein syndrome is a necrotizing vasculitis principally affecting children; major manifestations are palpable purpura, hematuria, and abdominal pain. Lung involvement is exceedingly rare, but extensive alveolar hemorrhage and capillaritis have been described. Henoch-Schönlein syndrome is caused by circulating immune complexes, with IgA reacting to target antigens in the renal glomerulus, skin, or gastrointestinal tract. A small-vessel vasculitis, associated with pronounced deposition of IgA in glomerular capillaries and affected vessels, is pathognomonic. Henoch-Schönlein syndrome is often self-limited and may not require therapy. Corticosteroids should be considered for severe or protracted cases.

ALVEOLAR HEMORRHAGE SYNDROMES

Autoimmune diffuse alveolar hemorrhage (DAH) may occur as a result of diffuse injury to the pulmonary microvasculature (termed *capillaritis* or *endotheliitis*). The course is typically abrupt, associated with bilateral alveolar infiltrates, hemoptysis, hypoxemia, and iron deficiency anemia. Glomerulonephritis is present in the vast majority of cases of DAH with immune-mediated causes (hence the term *pulmonary-renal syndromes*). Etiologies of DAH include antiglomerular basement membrane disease, systemic necrotizing vasculitis, idiopathic glomerulonephritis (immune complex or pauci-immune), collagen vascular disease, bone marrow transplantation, HIV infection, and exposure to exogenous agents or drugs. Idiopathic pulmonary hemosiderosis, a rare cause of recurrent DAH, occurs primarily in children and remains a diagnosis of exclusion.

Diagnostic Evaluation of Diffuse Alveolar Hemorrhage

The clinical features of DAH may be similar, regardless of etiology. Hemoptysis and a fall in the hematocrit support the diagnosis of DAH but are etiologically nonspecific. Nonimmune causes of DAH include endobronchial tumors, ulcerative tracheobronchitis, arteriovenous malformations or aneurysms, hemorrhagic pneumonia, bronchiectasis, congestive heart, failure, uremia, thrombocytopenia, coagulopathy, pulmonary veno-occlusive disease, and massive pulmonary embolism. The nonimmune causes must be excluded in patients with severe DAH. Depending on the clinical scenario, coagulation profiles and ancillary tests (e.g., echocardiogram, pulmonary angiography) may be required to establish a specific diagnosis. Fiberoptic bronchoscopy is useful to look for a site of active bleeding and rule out an infectious etiology. The role of lung biopsies is controversial and will be discussed later. Urinalysis and renal function tests should be performed in cases of suspected DAH, as rapidly progressive glomerulonephritis is a nearly invariable feature of immune-mediated pulmonary-renal syndromes. A battery of serologic studies may disclose an immunologic cause of DAH. These include antinuclear antibody (ANA), antineutrophilic cytoplasmic antibody (ACNA), antiglomerular basement membrane antibody (anti-GBM antibodies), and serum complement. However, the results of tests for anti-GMB antibodies or ANCA may not be available for several days. In this context, biopsy of kidney, lung, or other involved sites (e.g., skin, sinuses) may be required.

The role of open (or thoracoscopic) lung biopsy in the evaluation of DAH is controversial. Lung biopsies are seldom definitive, as gross and histologic findings may be similar irrespective of underlying etiology. Lung biopsies typically demonstrate flooding of alveolar spaces with blood, associated with diffuse injury to the pulmonary microvasculature (capillaritis). Capillaritis is a distinctive histologic lesion characterized by neutrophilic infiltration of capillaries, fragmented neutrophils (leukocytoclasis), and necrosis of the capillary walls. However, this lesion is nonspecific and may be seen in DAH complicating a variety of immune disorders (e.g., systemic necrotizing vasculitis (SNV), systemic lupus erythematosus, anti-GBM disease, idiopathic or immune complex-mediated rapidly progressive glomerulonephritis). Hemosiderin-laden macrophages within the alveolar spaces and interstitium may reflect prior episodes of DAH. Immunofluorescent studies are difficult to interpret in lung tissue and may be misleading. Surgical (open or thoracoscopic) lung biopsy carries significant morbidity, with the potential for prolonged air leak and secondary infections in patients with DAH and marginal pulmonary reserve. Thus, we see no role for surgical lung biopsy in patients with severe or acute DAH. Fiberoptic

bronchoscopy with BAL, which can be performed with little morbidity even in intubated patients, is usually adequate to exclude infectious etiologies and may support the diagnosis. Gross blood in the airways, bloody or serosanguinous BAL fluid, and hemosiderin-laden macrophages in BAL fluid strongly suggest DAH in the appropriate clinical setting. Thoracoscopic lung biopsy may have a role in selected patients with a more indolent course, negative serologies, and nondiagnostic renal biopsy and bronchoscopy.

Serologies, renal biopsies (with immunofluorescent stains), or biopsies of extrapulmonary and extrarenal sites (when vasculitis is present) may differentiate the various causes of pulmonary renal syndromes. When urinary sediment or renal function tests suggest glomerulopathy, percutaneous renal biopsy (to include immunofluorescent stains) should be performed. Renal biopsies in immune-mediated DAH demonstrate focal or diffuse glomerulonephritis, with extracellular proliferation (crescents) and necrosis. These findings, although distinctive, are nonspecific. However, the pattern of immunofluorescent staining is pivotal in establishing a specific etiologic diagnosis. A linear pattern of immunofluorescence is pathognomonic for anti-GBM disease. Either a lumpy-bumpy pattern (indicating immune complexes) or negative immunofluorescence (termed *pauci-immune*) can be seen with SNV, systemic lupus erythematosus, or idiopathic rapidly progressive glomerulonephritis. In critically ill patients with severe DAH, percutaneous renal biopsy may be logistically difficult or impractical. In this context, empiric therapy with pulse methylprednisolone (1 g daily for 3 days), possibly combined with cytotoxic agents or plasmapheresis, is reasonable pending results of serologic studies.

Specific Disorders Associated with Diffuse Alveolar Hemorrhage

Antiglomerular Basement Membrane Disease

Antiglomerular basement membrane (anti-GBM) disease, also termed *Goodpasture's syndrome,* is the prototype of pulmonary-renal syndromes, manifested as DAH and rapidly progressive glomerulonephritis (RPGN). Isolated RPGN without DAH may occur, but isolated DAH without RPGN is exceptionally rare. Anti-GBM disease accounted for 18%–32% of immune-mediated DAH syndromes in two recent series. Anti-GBM disease typically presents in patients between 20 and 40 years of age. There is a distinct male predominance. A specific cause has not been elucidated, but exposure to inhaled hydrocarbons and antecedent viral illnesses (particularly influenza) have been cited as risk factors. Cigarette smoking enhances the risk for DAH in patients with circulating anti-GBM antibody.

Clinical Features

Pulmonary manifestations usually dominate in the early phases of the disease. Hypoxemic respiratory failure, with widespread alveolar infiltrates on chest radiographs, is characteristic. Hemoptysis occurs in 70%–80% of patients and anemia in 85%. In 20%–30% of cases, the disease is limited to the kidneys. Organs other than lung or kidney are not involved, but constitutional symptoms (e.g., fatigue, weakness) may be prominent. Gross hematuria has been noted in 10%–41% of patients with anti-GBM disease. Microscopic hematuria or proteinuria are virtually always present. Renal function may be normal in 40%–60% of patients at presentation, but progressive renal failure develops within days to weeks. Oliguria, severe renal failure, or >50% crescents on renal biopsy are associated with a poor prognosis and low rate of recovery of renal function. Early institution of therapy is critical to optimize outcome. Circulating anti-GMB antibodies are detectable by radioimmunoassay or enzyme-linked immunosorbent assay (ELISA) in >95% of patients. These assays are highly specific (95%) but are performed in only a few research laboratories, and results are usually not available for a few days. Prognosis for recovery is related to the severity of the renal lesion. Prompt therapy is mandatory to avert irreversible loss of glomerular function. Thus, percutaneous renal biopsy should be done in any patient with significant abnormalities in urinary sediment or renal function pending the results of serum anti-GMB antibody assays. Identification of the pathognomonic linear immunofluorescent pattern on renal biopsy allows institution of therapy with plasmapheresis and immunosuppressive/cytotoxic therapy (to be discussed later). Serial measurement of serum anti-GBM antibodies is invaluable to monitor the course of the disease. Results of other serologic studies are negative or nondiagnostic.

Histopathology

Renal biopsy with immunofluorescent stains is the preferred method of establishing the diagnosis. Conventional light microscopy demonstrates a proliferative glomerulonephritis with cellular crescents. Foci of interstitial fibrosis or tubular atrophy may be observed but are rarely prominent. These histologic features are nonspecific. However, intense immunofluorescent linear deposits of IgG along glomerular basement membranes are pathognomonic for anti-GBM disease. Linear deposits of IgM or IgA have rarely been described. As was discussed earlier, open (or thoracoscopic) lung biopsies are rarely helpful. Histologic features are dominated by extensive intra-alveolar hemorrhage and hemosiderin-laden macrophages. Foci of neutrophilic “capillaritis,” hyaline membranes, and diffuse alveolar damage are concomitant features. Extensive necrosis and large-vessel vasculitis are not found. These histopathologic features are nonspecific. Immunofluorescent stains of lung tissue are not reliable. Because of its potential morbidity, we rarely employ open or thoracoscopic lung biopsies in the evaluation of DAH. A diagnosis can usually be substantiated by renal biopsies, BAL, and appropriate serologic studies.

Pathogenesis

Anti-GBM antibodies are directed against the a_3 chain of type IV collagen, an antigen highly expressed in both alveolar and glomerular basement membranes. The stimulus for anti-GBM antibody formation remains speculative, but both environmental and genetic factors may play roles. A genetic susceptibility is plausible, as anecdotal cases of anti-GBM disease have been described in siblings, first cousins, and identical twins, and links between anti-GBM disease and the HLA-DR2 histocompatibility antigen have been noted. Exposure to cigarette smoke, hydrocarbon-containing solvents, hard-metal dust, influenza A2 virus, chlorine gas, and D-penicillamine have been associated with anti-GBM disease. These exogenous factors may injure the basement membrane, resulting in increased capillary permeability and exposure of the Goodpasture antigen (a_3 chain of type IV collagen), which elicits a helper T-cell response. Stimulation of IgG synthesis results in deposits of IgG along the alveolar and capillary basement membranes. Anti-idiotypic (blocking) antibodies and activated suppressor ($CD8^+$) T cells may facilitate resolution of the process, but this is speculative. Pulmonary edema, infection, and cigarette smoking have been associated with an increased risk for DAH in patients with circulating anti-GBM antibody, possibly because of increased lung capillary permeability that allows access of the antibody to the alveolar spaces.

Treatment

Before the availability of therapy, mortality associated with anti-GBM disease exceeded 90%, with mean survival of 6 months. Plasmapheresis, introduced as a therapeutic option for anti-GBM disease in the mid-1970s, was quickly adopted worldwide and is considered as part of standard therapy. Current therapy involves a combination of plasmapheresis (to eliminate circulating anti-GBM antibodies) plus immunosuppressive agents (to suppress antibody synthesis). Prognosis of anti-GBM disease is influenced by the severity of the renal lesion at the outset. In one study, 22 of 23 patients with oliguria or a serum creatinine level of 6 mg% failed to recover, even with aggressive therapy. By contrast, 15 of 17 with nonoliguric renal failure and a serum creatinine level of >6 mg% recovered or improved with plasmapheresis and immunosuppressive/cytotoxic therapy. Thus, prompt diagnosis and initiation of therapy are mandatory to avoid irreversible renal failure. Because of the rarity of anti-GBM syndrome, only one randomized trial has compared immunosuppressive therapy alone versus the combination of immunosuppressive therapy and plasmapheresis. In that study, combined therapy was associated with more rapid disappearance of anti-GBM antibody and improved renal function. End-stage renal disease requiring chronic dialysis developed in 6 of 9 patients treated with immunosuppressive agents alone (compared with 2 of 8 in the plasmapheresis group). The incidence of recurrent pulmonary hemorrhage was similar (4 in each group). Optimal dose and duration of plasma exchange have not been defined. Plasma exchanges have usually been done daily or every 2 to 3 days for the first 10 to 21 weeks, until clinical improvement has occurred and serum anti-GBM antibodies are nondetectable. Less frequent plasmapheresis (every 3 to 5 days) has been used, with purported success. The optimal immunosuppressive regimen has not been delineated. For acute, life-threatening DAH, pulse methylprednisolone (1 g daily for 3 days), following by a corticosteroid taper, is advised. Once the DAH is controlled, oral prednisone (1 mg/kg/day) may be substituted, and oral cyclophosphamide (2 mg/kg/day) or azathioprine (2 to 3 mg/kg/day) are added to suppress continued antibody synthesis. No studies have specifically compared cyclophosphamide with azathioprine, but we favor cyclophosphamide. Immunosuppressive agents should be continued until the clinical syndrome has resolved and anti-GBM antibodies have disappeared. In most cases, symptoms resolve and circulating antibodies clear within 8 weeks, irrespective of the initial titer. Renal function usually recovers in patients with minor functional impairment. Dialysis-dependent patients rarely recover renal function. A 4- to 6-month trial may be adequate in some cases. Long-term survival rates exceed 85%. Late recurrences have been rare.

Systemic Necrotizing Vasculitis

Pulmonary hemorrhage is a well-recognized complication of Wegener's granulomatosis and MPA, and may rarely complicate CSS, Behçet's syndrome, mixed cryoglobulinemia, and other systemic necrotizing vasculitides. Necrotizing vasculitis accounts for 40%–55% of DAH syndromes. Regardless of the specific underlying vasculitic disorder, rapidly progressive glomerulonephritis (RPGN) is a nearly invariable feature. A cardinal feature of DAH complicating vasculitis is diffuse damage to the pulmonary endothelium (capillaritis). The histologic features are nonspecific. Granulomatous or eosinophilic components, geographic necrosis, or vasculitis involving larger vessels (e.g., arterioles) are usually not evident. High-dose intravenous (pulse) methylprednisolone (1 g daily for 3 days) should be given for acute, fulminant DAH. Long-term therapy with oral cyclophosphamide and corticosteroids is appropriate for necrotizing vasculitis. The specific regimens have been discussed in greater detail in the sections on pulmonary vasculitis.

Collagen Vascular Disorders

Collagen vascular disorders, principally systemic lupus erythematosus (SLE), account for 10%–30% of pulmonary-renal syndromes. Pulmonary hemorrhage is a

well-recognized, albeit rare, complication of SLE, but only sporadic cases of DAH have been described complicating rheumatoid arthritis, progressive systemic sclerosis, polymyositis, or dermatomyositis. Recently, Schwarz and colleagues described two patients with polymyositis, progressive respiratory failure, and DAH secondary to pulmonary capillaritis. Management is similar to that for DAH complicating SLE. DAH complicating SLE usually occurs in patients with a prior history of SLE and active disease elsewhere (e.g., fever, arthritis, serositis). However, DAH has been the sole and presenting feature of SLE in some cases. As in other DAH syndromes, results of lung biopsies are nonspecific, showing hemorrhage and foci of capillaritis. Granular deposits of complement (C3) and IgG have been noted in some cases (suggesting immune complex deposits) but this has not been uniform. Intravenous pulse methylprednisolone is the treatment of choice for severe DAH. For less severe cases, high-dose prednisone may be adequate. Plasmapheresis or immunosuppressive/cytotoxic drugs may be required for patients failing to respond to corticosteroids.

Idiopathic Rapidly Progressive Glomerulonephritis

DAH may complicate idiopathic RPGN, a primary renal disorder of unknown etiology. Immune complexes are present in serum or renal tissue in 20% of patients with idiopathic RPGN. When no immune complexes are found, the term *pauci-immune glomerulonephritis* has been used. Clinical features of idiopathic RPGN are similar, irrespective of whether immune complexes are present. Progressive renal failure is the predominant manifestation and major cause of morbidity in this disease. Lung involvement (typically capillaritis) occurs in 20%–50% of cases but is rarely severe. Some patients manifest mild hemoptysis and transient alveolar infiltrates but are otherwise asymptomatic. However, occasional patients manifest life-threatening DAH and require mechanical ventilatory support. Fever, myalgias, malaise, and a flulike illness precede the renal lesion in nearly two thirds of patients. Other organs are not involved and systemic vasculitis is lacking. All ages may be affected, but idiopathic RPGN has a predilection for adults in the sixth and seventh decades; there is a male predominance (2:1 ratio). In untreated patients, progressive renal failure develops within a few weeks to months; nearly 75% require dialysis. The prognosis is poor among patients presenting with serum creatinine levels of >6 mg% or with oliguria. Renal biopsy demonstrates crescentic, rapidly progressive glomerulonephritis (with or without immune complexes). These features are nonspecific. Circulating ANCA (typically p-ANCA) are present in up to 70% of cases with idiopathic RPGN.

Optimal therapy is controversial. A variety of treatment regimens incorporating corticosteroids, immunosuppressive/cytotoxic drugs, and plasmapheresis, alone or in combination, have been tried. In one multicenter, randomized trial, survival and renal function were similar with three treatment regimens utilizing corticosteroids alone, corticosteroids plus oral cyclophosphamide, or corticosteroids plus intravenous cyclophosphamide. Most investigators treat initially with pulse methylprednisolone (30 mg/kg/day for 3 days), followed by high-dose prednisone (2 mg/kg on alternate days) until remission or stability has been achieved. Cytotoxic agents or plasmapheresis can be reserved for fulminant or corticosteroid-refractory cases. A prolonged course of therapy is usually not necessary, as it is in other pulmonary-renal syndromes. Therapy for 4 to 6 months may be adequate in responding patients.

Bone Marrow Transplantation

DAH has been noted in 6%–21% of bone marrow transplant recipients receiving high-dose chemotherapy. Acute respiratory failure and secondary infections are serious, and potentially lethal, complications of DAH. The etiology is likely diffuse injury to the pulmonary microvasculature resulting from the effects of chemotherapy or radiation, compounded by an intense cellular inflammatory response. The onset of DAH frequently coincides with marrow recovery and neutrophils within BAL fluid. High-dose corticosteroids have been associated with improved survival, supporting an immune-mediated mechanism. Methylprednisolone in intravenous doses of 125 to 250 mg every 6 hours for 3 to 5 days, followed by prednisone tapered gradually during 2 to 4 weeks, is suggested. Low-dose prednisone appears to be no better than supportive therapy (approximately 90% mortality).

Human Immunodeficiency Virus (HIV) Infection

DAH may rarely complicate HIV infection. Pulmonary vasculitis has been noted at necropsy in patients with acquired immune deficiency syndrome (AIDS). CMV exhibits tissue tropism for endothelial cells, and CMV pneumonitis has recently been implicated as a cause of DAH. Disseminated viremia, visceral involvement, microangiopathic anemia resulting from intravascular hemolysis, viral giant cells within pulmonary endothelial cells, and pulmonary capillaritis have been noted. Antiviral therapy (e.g., ganciclovir) is usually efficacious.

Exogenous Agents

DAH rarely complicates the administration of exogenous agents (e.g., trimellitic anhydride, isocyanates, lymphangiogram dye) or drugs (D-penicillamine, “crack” cocaine). Glomerulonephritis has been observed in DAH associated with D-penicillamine, but not with the other agents. Results of serologic studies (e.g., anti-DNA, ANA, anti-GBM antibody) have been negative. Lung biopsies have revealed nonspecific alveolar hemorrhage with no evidence for vasculitis or immune deposits. Treatment involves discontinuation or avoidance of the implicated agent or drug. For severe cases, a brief course of high-dose corticosteroids is warranted. Plasmapheresis may be considered for fulminant cases refractory to corticosteroids, but data supporting its use are lacking.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) is a rare cause of recurrent DAH of unknown etiology. It occurs almost exclusively in children. The natural history is variable, but repetitive episodes of DAH for many years is characteristic. Three-year mortality rates of 30%–50% have been cited. Extrapulmonary involvement does not occur, and vasculitis is lacking. Results of serologic studies (including anti-DNA, ANA, ANCA, serum complement) are negative. Because the clinical features of IPH overlap with those of other immune-mediated DAH syndromes, negative renal and lung biopsy findings are required to substantiate the diagnosis of IPH. Many of the reported cases of IPH in adults occurred before the availability of serologic markers (e.g., ANCA, anti-GBM antibody) or immunofluorescent studies. In many cases initially considered “idiopathic,” other features of systemic vasculitis or connective tissue disease developed months or even years after the initial presentation. In two studies comprising 85 patients with DAH, only one patient had IPH. The diagnosis of IPH can be made only in individuals with recurrent episodes of DAH, no extrapulmonary involvement, negative lung and kidney biopsy findings, negative serology findings, and no alternative etiology after an exhaustive investigation and long-term follow-up. Because of its rarity, optimal treatment of IPH is not known. Corticosteroids are the mainstay of therapy. Long-term (and possibly indefinite) therapy may be required to prevent recrudescent disease. Alternate-day corticosteroids should be considered after the first 6 to 12 months to minimize long-term side effects. Immunosuppressive or cytotoxic agents may be used in patients refractory to or experiencing adverse effects from corticosteroids. As circulating antibodies have not been identified, we see no role for plasmapheresis.

PULMONARY ALVEOLAR PROTEINOSIS

Pulmonary alveolar proteinosis (PAP), also termed *alveolar phospholipidosis,* is a rare syndrome of unknown cause originally described by Rosen and colleagues in 1958. They reviewed histologic material from 27 patients, referred from across the world, who had undergone lung biopsy or autopsy. The distinctive histologic features included extensive flooding of alveolar spaces with a granular, eosinophilic material; however, an inflammatory component was lacking. It has since been established that the intra-alveolar material is composed primarily of lipoprotein (surfactant apoproteins). This thick, viscid, surfactant-like material fills the alveolar spaces, resulting in cough, dyspnea, and impaired gas exchange. The exact incidence of PAP is unknown. By 1980, only 260 cases had been published. The prevalence has been estimated at one case per million adults per 5-year period. The disease is two to three times more common in male patients, most of whom are between 20 and 50 years of age, but all ages may be affected. The clinical features and course are variable, and spontaneous remissions occur in 20%–30% of cases. Some patients manifest a waxing and waning course for many years.

Clinical Features

Symptoms of cough and exertional dyspnea develop insidiously and typically progress for weeks or months. The cough is usually nonproductive, but some patients expectorate plugs of grayish-yellow viscid sputum. Hemoptysis has been noted in 3%–24% of patients. A sensation of chest tightness or heaviness is present in one third of patients. Constitutional symptoms of weight loss, malaise, and fatigue may be present, but extrapulmonary involvement does not occur. Up to 20% of patients are asymptomatic. Physical examination reveals rales over involved areas; wheezing is unusual. Cyanosis has been noted in up to 20% of cases, and clubbing in 29%–40%. Chest radiographs (discussed in greater detail below) typically reveal bilateral alveolar infiltrates. Serum lactate dehydrogenase (LDH) is increased in approximately 80% of patients; no other distinctive laboratory features exist. Patients with PAP have an increased susceptibility to infections with *Nocardia* species, *S. aureus, Mycobacteria,* and fungi. This heightened susceptibility to infections reflects defects in alveolar macrophage chemotaxis, phagocytosis, and microbicidal activity and obstruction of the alveolar spaces with the thick debris. Defects in alveolar macrophage function reverse following therapeutic whole-lung lavage. Because of the rarity of the disorder and the nonspecificity of symptoms, the mean interval between onset of symptoms and diagnosis often exceeds 1 year. Untreated PAP usually progresses indolently for months to years. Before the availability of therapy, one third of patients died of respiratory failure or infectious complications. Treatment with whole-lung lavage (to be discussed later) is usually efficacious, but relapses occur in 15%–30% of treated patients.

Chest Radiographs

Chest radiographs typically demonstrate symmetric, fluffy, perihilar alveolar infiltrates (a “bat wing” appearance) (Fig. 15A). Asymmetric or even unilateral involvement

occurs in 20% of patients. The infiltrates exhibit an alveolar or ground-glass pattern, but reticulonodular patterns or mixed interstitial-alveolar patterns have been noted. Differential diagnosis includes pulmonary edema (cardiac and noncardiac), BOOP, alveolar hemorrhage syndromes, DIP, and a wide spectrum of ILD. Persistent linear interstitial infiltrates have been noted in some patients, which may represent areas of fibrosis. Intrathoracic lymphadenopathy, cavitary lesions, or pleural effusions are not features of PAP. CT more clearly reveals the distinctive alveolar involvement, often with striking air bronchograms (Fig. 15B). However, chest CT is expensive and not required for either staging or follow-up of PAP.

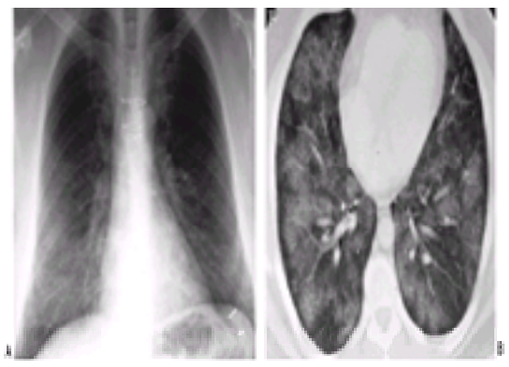

FIG. 15. A: Pulmonary alveolar proteinosis. PA chest radiograph demonstrates bilateral, predominantly basilar infiltrates in a 50-year-old man with progressive exertional dyspnea. **B:** CT in the same patient demonstrates multiple foci of ground-glass opacification throughout through parenchyma. Open lung biopsy demonstrates classic features of PAP.

Pulmonary Function Tests

The major physiologic aberration is intrapulmonary shunt, resulting in hypoxemia and a widened $P(A - a)O_2$. DLCO is usually reduced, but pulmonary function tests in PAP may be normal. Vital capacity or lung volumes are only mildly affected. Expiratory flow rates and FEV_1 are usually normal, but airways obstruction may be noted in smokers. These physiologic aberrations typically improve or normalize following treatment with whole-lung lavage.

Histologic Features

Grossly, the lung is consolidated, and alveolar spaces and respiratory bronchioles are filled with a granular, amorphous, acidophilic material (Fig. 16). The alveolar septa are usually normal. Interstitial inflammation and fibrosis are not features of PAP. However, hyperplastic type II pneumocytes may be observed. These histologic features bear some resemblance to those of *P. carinii* pneumonia but lack the interstitial inflammatory component, diffuse alveolar damage, and foamy intra-alveolar exudate seen in that condition. The intra-alveolar material in PAP contains phospholipids (surfactant-like material) that stain bright pink with periodic-acid Schiff (PAS) reagent and negative with alcian blue. The diagnosis of PAP has usually been established by open lung biopsy. However, the diagnosis can sometimes be made by fiberoptic bronchoscopy. The gross characteristics of BAL fluid are distinctive. The lavage effluent reveals thick, viscid, opaque, yellowish-white milky fluid that sediments into multiple layers on standing. Positive PAS and negative alcian blue stains of the foamy BAL fluid may confirm the diagnosis. Large numbers of PAS-positive, eosinophilic acellular bodies, and alveolar macrophages containing granular eosinophilic material within phagocytosomes or cytoplasm, may be found in BAL fluid. High levels of surfactant proteins A (SP-A) and D (SP-D) have been found in BAL fluid from patients with PAP; these stain intensely using immunohistochemical methods. These immunohistiochemic techniques are limited to a few research laboratories. SP-A is highly glycosylated, which may account for the positive PAS staining.

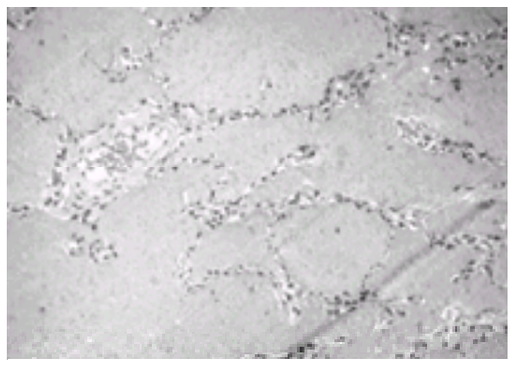

FIG. 16. Pulmonary alveolar proteinosis. Photomicrograph of open lung biopsy specimen demonstrates complete filling of alveolar spaces with a dense proteinaceous exudate. The alveolar architecture is preserved. H&E, high power. (Reproduced with permission from Lynch JP III, Chavis AD. Chronic interstitial pulmonary disorders. In: Victor L, ed. *Clinical Pulmonary Medicine.* Boston: Little, Brown; 1992:250, Fig. 11-15.)

BAL or transbronchial lung biopsies may substantiate the diagnosis, provided the typical PAS-positive intra-alveolar exudate is evident. Thoracoscopic or open lung biopsies are warranted when bronchoscopic findings are equivocal or nondiagnostic. Electron microscopy and transmission electron microscopy are primarily research techniques. These techniques demonstrate alveolar macrophages engorged with phagolysosomes, complex inclusions, lamellar bodies, cholesterol inclusions, and lipid droplets. Concentric, laminated lamellar bodies containing phospholipids, tubular myelin, and myelin structures within alveolar spaces or in BAL fluid are pathognomonic for PAP.

Pathogenesis

The pathogenesis of PAP is not known. The massive accumulation of surfactant-like phospholipids within the alveolar spaces suggests that abnormal turnover of phospholipids (e.g., by impaired clearance) or excessive production of surfactant (by type II pneumocytes) is responsible. Defects in the clearance or degradation of surfactant lipoproteins may reflect dysfunction of type II pneumocytes. The inciting signals or stimuli for PAP have not been identified, but a history of exposure to hydrocarbons, chemicals, chlorinated resins, fiberglass, aluminum, cadmium, titanium, silica, asbestos, volcanic ash, or a variety of solvents has been elicited in up to 50% of patients. Exogenous dusts or metals may overwhelm the normal clearance mechanisms of the lung. A variety of animal models resembling PAP have been produced by inhalation of fine dust particles (e.g., silica, crushed fiberglass, volcanic ash, bismuth, nickel, aluminum, antimony, titanium). In these models, inhaled dust particles elicit an influx of macrophages into the alveolar spaces, followed by proliferation of type II pneumocytes and accumulation of phospholipid. The alveolar macrophages ingest and become engorged with the phospholipid material. The alveolar spaces become filled with lipoproteinaceous material from the hyperplastic type II pneumocytes and disintegrating phospholipid-laden macrophages. These pathologic features strikingly resemble the lesion of PAP in humans. Chronic ingestion of certain drugs (e.g., amiodarone, chlorphentermine, and iprindole) induces a PAP-like reaction in animals. Inhibition of phospholipase may be responsible for the excessive accumulation of the lamellar, phospholipid inclusions in alveolar macrophages and within alveolar spaces in these affected animals. Cases of drug-induced PAP in humans have not been described, but these animal models may provide clues to possible mechanisms for PAP. No genetic basis for PAP has been found in humans, but PAP has rarely been reported in siblings. Lesions resembling PAP have been described in mice with severe combined immunodeficiency (SCID mice). These mice exhibit excessive amounts of eosinophilic surfactant-like material in alveolar spaces and BAL fluid and marked increases of SP-A and SP-B in BAL fluid. In animals, distinct forms of spontaneous PAP have been described. In one form, macrophages were unable to digest the phospholipoprotein complex. Other models are consistent with a defect in surfactant homeostasis. In humans, secondary forms of PAP (termed *pseudoproteinosis*) rarely complicate hematologic malignancies, AIDS, solid tumors, tuberculosis, specific infections, and interstitial pneumonitis. In these cases, involvement is usually focal and patchy. The intra-alveolar material in pseudoproteinosis may represent necrotic debris and exudate rather than the surfactant-like material characteristic of PAP. In secondary forms of PAP, remission of the underlying disease is the critical determinant of a successful outcome. Whole-lung lavage, the treatment of choice for primary PAP, is of doubtful value in secondary PAP.

Treatment

Corticosteroids, trypsin, heparin, acetylcysteine, and pancreatic enzymes have been used to treat PAP, but none are efficacious. Whole-lung lavage, introduced by Ramirez and colleagues in 1965, is the treatment of choice for PAP. Whole-lung lavage physically removes the copious, thick viscid material, allowing the alveolar spaces to re-expand and participate in gas exchange. When occupational exposure to solvents, chemicals, or dust is suspected as the cause, withdrawal from that occupation is warranted. Treatment is not required in every patient with PAP, as the disease may be mild and associated with minimal symptoms in some cases. Unilateral lung lavage has potential morbidity and should be performed by individuals who have experience with the technique. This is best accomplished under general anesthesia to ensure adequate control of the airway and optimal ventilatory management. A double-lumen endotracheal tube is placed. The most severely involved lung is allowed to deflate, and the opposite lung is ventilated with oxygen and anesthetic. Unilateral lung lavage is then carried out with successive aliquots (500 to 1000 mL) of sterile isotonic saline solution (warmed to body temperature), and the effluent is immediately suctioned and removed. With repeated instillation, the lavage effluent progressively thins. Chest percussion and rotating the patient during the procedure may enhance clearance of the thick, viscid material. The procedure is terminated after the lavage effluent no longer returns significant viscid material or markedly improves. The volume of fluid instilled is considerable, ranging from 20 to 50 L. The duration of the procedure takes on average 3 to 5 hours. Once it has been completed, the lavaged lung is ventilated. Extubation can usually be accomplished within 1 hour of completion of the procedure. Patients are observed to ensure adequate ventilation. Potential complications of the procedure include pneumothorax, pulmonary edema, spillage of lavage fluid into the contralateral lung, worsening respiratory failure, bronchospasm, and aspiration pneumonia. With proper technique and control of the airway, these adverse events occur in <5% of patients. Most patients can be discharged within 24 hours after lavage has been completed. Gradual improvement in symptoms, arterial blood gases, and chest radiographs occurs during the next few weeks. We prefer to wait 4 to 6 weeks before performing unilateral lavage of the contralateral lung. For more fulminant or severe cases, the contralateral lung can be lavaged immediately or a few days after the initial lavage.
Whole-lung lavage is highly efficacious. Symptomatic, physiologic, and radiographic improvement is noted in 75%–95% of patients. Fatalities are rare. Recurrent disease requires repeated lavage in 15%–30% of patients within 1 to 5 years. Serial chest radiographs, oximetry (or arterial blood gases), and LDH should be monitored at 3-month intervals for the first year to rule out relapse. Thereafter, follow-up at 6- to 12-month intervals may be adequate in asymptomatic patients. Recrudescent disease warrants repeated lavage.

EOSINOPHILIC GRANULOMATOSIS

Pulmonary eosinophilic granulomatosis (also termed *histiocytosis X* or *Langerhans' cell granulomatosis*) is a rare granulomatous disease usually seen in smokers. It may present with cough, dyspnea, and interstitial, reticulonodular, or cystic changes on chest radiographs. Eosinophilic granulomatosis (EG) accounts for <4% of chronic ILD. The precise incidence is unknown, but prevalence rates of one to five cases per million population have been suggested. Pulmonary EG is almost exclusively seen in Caucasians, suggesting a genetic predisposition, but a specific genetic defect has not been elucidated. There is a slight male predominance. Pulmonary EG is rare in children and typically affects adults between ages 20 and 50. More than 90% of patients with pulmonary EG are smokers, suggesting an etiologic relationship.

Clinical Features

Clinical features of pulmonary EG are variable. Ten percent to 25% of patients with pulmonary EG are asymptomatic, with incidental findings on chest radiographs. Cough and dyspnea are the most common symptoms, noted in 60%–75% of patients. Symptoms usually develop insidiously during several weeks or months. Physical examination is usually unremarkable, but rales, rhonchi, wheezes, or diminished breath sounds may be present. Clubbing occurs in <5% of patients. Pneumothorax, caused by rupture of subpleural cysts, occurs in 6%–20% of patients and may be the presenting feature (Fig. 17). Pneumothoraces frequently recur and may require surgical pleurodesis. At thoracotomy, numerous subpleural cysts and blebs are usually evident. Low-grade fever, malaise, weight loss, and anorexia are present in 15%–30% of patients. There are no distinctive hematologic or serologic aberrations in pulmonary EG. Blood eosinophil counts are normal. Extrapulmonary involvement (particular osteolytic bone lesions or diabetes insipidus) occurs in 15%–20% of adults with pulmonary EG. By contrast, EG in children (typically in children under age 10) is characterized by prominent osseous and extrapulmonary manifestations. The incidence of bronchogenic carcinoma is increased in smokers with pulmonary EG. In one study of 93 patients with pulmonary EG, five cases of bronchogenic carcinoma were noted, for an annual risk of 1040/100,000. Cigarette smoking amplifies the cancer risk.

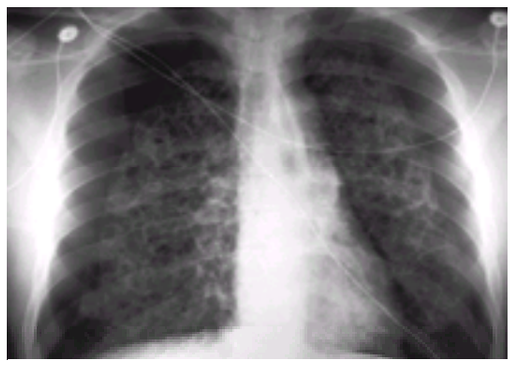

FIG. 17. Eosinophilic granulomatosis. PA chest radiograph demonstrates far-advanced cystic changes throughout lung parenchyma and bilateral pneumothoraces in a patient with pulmonary EG.

Chest Radiographic Features

Conventional chest radiographs typically reveal diffuse reticular, reticulonodular, or cystic lesions that preferentially involve the middle and upper lung zones, sparing the costophrenic angles (Fig. 18). Cystic radiolucencies, 5 to 15 mm in diameter, reflect dilated bronchi and bronchioles, with peribronchial thickening or areas of destroyed lung parenchyma. Nodules (typically 2 to 5 mm in size) are centered around bronchioles and reflect cellular granulomatous lesions (Fig. 19). The combination of pneumothorax, upper lobe cysts, and finely nodular lesions strongly suggests the diagnosis of pulmonary EG. Other CILD with a predilection for upper lobe involvement include sarcoidosis, granulomatous infections, silicosis, ankylosing spondylitis, and chronic eosinophilic pneumonia. Pleural effusions and intrathoracic adenopathy are not features of EG.

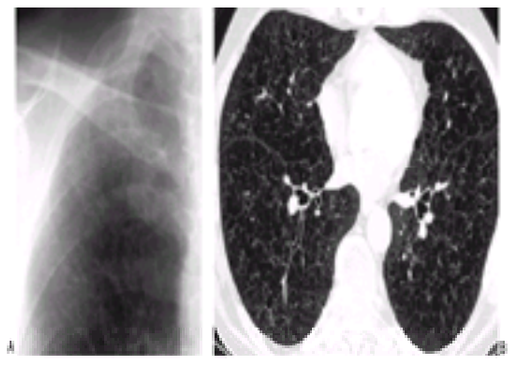

FIG. 18. A: Eosinophilic granulomatosis. Coned-down view of PA chest radiograph demonstrates finely nodular and cystic densities throughout lung parenchyma in a 56-year-old man with progressive cough and dyspnea. Transbronchial lung biopsies demonstrated typical histologic features of EG. S-100 stains were also positive. **B:** CT in the same patient demonstrates multiple, well-defined cystic spaces with walls measuring 1 to 2 cm in size. A few ill-defined, scattered interstitial nodules are also present but are subtle.

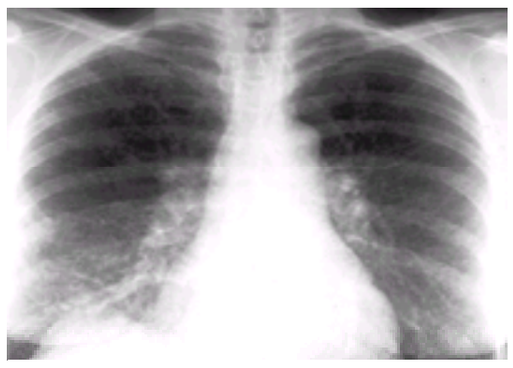

FIG. 19. Eosinophilic granulomatosis. PA chest radiograph demonstrates finely nodular densities throughout lung parenchyma in a 52-year-old woman with progressive cough and dyspnea. Transbronchial lung biopsies demonstrated typical histologic features of EG. S-100 stains were also positive.

High-Resolution Thin-Section Computed Tomography

High-resolution thin-section CT is far more accurate than conventional chest radiographs in defining the nature and extent of the parenchymal lesions. Numerous thin-walled cysts are observed in >90% of patients with pulmonary EG (Fig. 18B). Peribronchiolar nodules (typically 1 to 4 mm in diameter) are present concomitantly in 60%–78% of patients. The nodules, which correspond to cellular granulomatous lesions around small bronchioles, may be missed on conventional chest radiographs. Coalescence of nodules may result in lesions exceeding 10 mm. This nodular component rarely occurs in the absence of the cystic lesions. Foci of cavitation (resulting from necrosis within the peribronchiolar inflammatory nodules) have been noted on high-resolution CT in up to 20% of patients with pulmonary EG but are rarely evident on plain chest radiographs. As the disease progresses, the nodules are replaced by cysts, some of which become confluent. The cysts or nodules are usually associated with areas of intervening normal lung tissue. Shadows that appear reticular on chest radiographs actually represent the walls of cysts. The cystic lesions correspond to dilated small bronchi and bronchioles or destroyed lung parenchyma. In the early phases, cysts are round and small (<4 mm), but they may enlarge and assume distorted shapes. Confluence of cysts may result in bullous lesions exceeding 2 to 3 cm in diameter. Both the cystic and nodular lesions have a predilection for the upper and middle lung zones, with relative sparing of the costophrenic angles. There is no central or peripheral predominance. Cystic radiolucencies may be seen in other pulmonary disorders, but the nature and anatomic distribution of the cystic lesions in pulmonary EG are distinctive. The cysts in pulmonary EG are thin-walled, often regular in size, and are associated with nodules.

Numerous parenchymal cysts are the hallmark of lymphangioleiomyomatosis (LAM). In LAM, the cysts are distributed evenly throughout all lobes and lack the nodular component characteristic of EG. Honeycomb cysts are characteristic features of IPF or UIP. In contrast to cysts in pulmonary EG, honeycomb cysts in UIP have a distinctive affinity for subpleural, peripheral, and basilar regions of the lungs. Ground-glass opacities or septal bands are evident in IPF or UIP but are rarely a prominent feature of pulmonary EG. In chronic obstructive pulmonary disease, emphysematous “cysts” may be seen, but these are more irregular in size and have a thicker wall than the cysts of pulmonary EG. The combination of cysts and nodules strongly suggests the diagnosis of pulmonary EG, particularly when the lesions preferentially affect the middle and upper lung zones.

Pulmonary Function Tests

Aberrations in pulmonary function tests are noted in >80% of patients with pulmonary EG. Reduction in D_LCO occurs in 70%–80% of patients. Severe impairment in D_LCO is associated with more extensive honeycombing and a worse prognosis. Reductions in VC and/or TLC occur in 50%–80% of cases. Pure restrictive and mixed obstructive-restrictive patterns may be observed. The mean FEV_1 is often reduced, but the FEV_1/FVC ratio is usually normal or increased. Air trapping (increased RV) is noted in nearly 50% of patients with pulmonary EG, but hyperinflation (TLC >110% of predicted) is rare. Pulmonary function tests are normal in 15%–20% of patients with pulmonary EG. Pulmonary function tests may not correlate with symptoms or chest radiographs. Serial pulmonary function tests are advised to monitor the course of the disease. Cardiopulmonary exercise tests in patients with pulmonary EG usually show reductions in exercise tolerance, maximal workload, oxygen consumption (O_{2max}), and anaerobic threshold, and worsening gas exchange and increased ratio of dead space to tidal volume (V_D/V_t) with exercise. Several factors may limit exercise tolerance, including obliteration or loss of the pulmonary microvasculature, impaired pulmonary mechanics, air flow obstruction, and hypoxemia.

Histopathology

Histologically, pulmonary EG is characterized by inflammatory, cystic, nodular, and fibrotic lesions distributed in a bronchocentric fashion. The diagnosis of pulmonary EG usually requires thoracoscopic lung biopsy, but TBB may be adequate provided the salient features are present. The disease appears to evolve in distinct phases. Early in the course, proliferation of atypical histiocytes (i.e., Langerhans' cells) dominates. Later, granulomatous inflammation ensues, followed by destruction and fibrosis of lung parenchyma. In individual patients, all phases of the disorder may be seen concomitantly. Pulmonary EG may be strongly suspected by the distinctive distribution and pattern of lesions on low-power light microscopy. The combination of numerous peribronchiolar nodules and cysts, accompanied by intervening zones of normal lung parenchyma and a stellate pattern of fibrosis, is highly characteristic. Numerous discrete, focal nodules, representing cellular inflammatory lesions, may be seen under low-power magnification. The nodules are centered around bronchioles or may be distributed in subpleural regions. These lesions extend by fingerlike extensions into the adjacent alveolar interstitium, resulting in a distinctive star-shaped or stellate pattern (Fig. 20). High-power light microscopy may show intensely cellular granulomatous lesions involving bronchioles and alveolar walls. In some cases, plugs of immature connective tissue within bronchioles, alveolar ducts, and alveolar spaces may resemble BOOP. The granulomatous lesions are comprised of aggregates of Langerhans' cells (the cornerstone of the diagnosis) admixed with lymphocytes, plasma cells, eosinophils, macrophages, and neutrophils.

FIG. 20. Eosinophilic granulomatosis. Low-power photomicrograph of open lung biopsy specimen demonstrates stellate pattern of fibrosis. H&E stain. (Reproduced with permission from Lynch JP III and Chavis AD. Chronic interstitial pulmonary disorders. In: Victor L, ed. *Clinical Pulmonary Medicine.* Boston: Little, Brown; 1992:243, Fig. 11-14C.)

The cardinal histologic feature of pulmonary EG is the finding of aggregates of Langerhans' cells (also termed *histiocytosis X cells*) within the peribronchiolar nodules, air spaces, or alveolar interstitium (Fig. 21). Langerhans' cells are moderately large, ovoid histiocytes with pale eosinophilic cytoplasm, indented (grooved) nuclei, inconspicuous nucleoli, and finely dispersed chromatin. Langerhans' cells can usually be recognized under high-power light microscopy and may comprise >50 % of cells in the active cellular lesions in some patients. Langerhans' cells may be found in normal lung but rarely constitute >3% of cells. Eosinophils may be conspicuous, but the number of eosinophils is variable and is not a reliable diagnostic criterion. When light microscopic features are nondiagnostic, immunohistochemical stains [e.g., S-100 protein and common thymocyte antigen (OKT6)] or electron microscopy may substantitate the identity of Langerhans' cells. These ancillary techniques are discussed later. It should be emphasized that neither S-100 nor OKT6 stains are required to diagnose pulmonary EG, provided the light microscopic features on hematoxylin-eosin stains are distinctive.

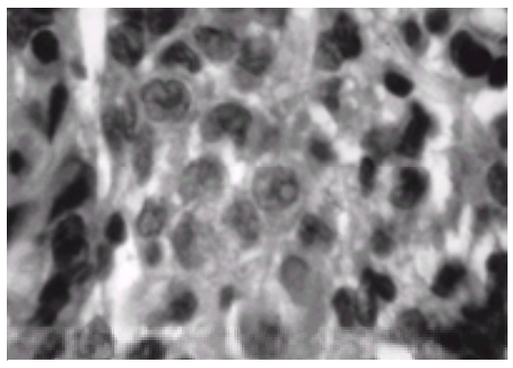

FIG. 21. Eosinophilic granulomatosis. Photomicrograph of open lung biopsy specimen demonstrates an intense cellular infiltrate with multiple Langerhans' cells exhibiting the characteristically clefted nuclei. H&E, high power.

As the inflammatory process evolves, bronchioles and alveolar interstitium may be destroyed or replaced by fibrotic connective tissue, resulting in dilated, distorted bronchioles and alveolar parenchymal cysts. Blebs, subpleural cysts, and interstitial and intraluminal fibrosis may be prominent. The pulmonary microvasculature may be infiltrated or destroyed, even in areas remote from the bronchocentric nodular lesions. In late phases of pulmonary EG, the distinctive Langerhans' cells and inflammatory cells may no longer be present, and the lung may take on the appearance of an end-stage honeycomb lung, indistinguishable from that of other CILD. The retention of a nodular or stellate configuration may be a clue to the diagnosis.

Ancillary Diagnostic Techniques

Historically, electron microscopy was used to identify Langerhans' cells when light microscopy was not definitive. Langerhans' cells contain distinctive intracytoplasmic rod- or racquet-shaped inclusions (termed *Birbeck granules* or *X-bodies*), 42 to 45 nm in thickness, that have trilaminar membranes and a central line (Fig. 22). Because of the complexity and expense of electron microscopy, immunohistochemical staining for S-100 protein or OKT6 has supplanted this technique. Immunostains for S-100 protein may distinguish Langerhans' cells from other histiocytes. This technique can be performed in paraffin-embedded biopsy specimens and is less time-consuming and avoids the sampling problems associated with electron microscopy. Large aggregrates of S-100-positive histiocytes within stellate nodules or granulomatous lesions are virtually pathognomonic of EG. Staining for S-100 is most intense in the active cellular lesions and diminishes in fibrotic or acellular areas. Langerhans' cells may be found in open lung biopsy specimens or BAL fluid in other ILD but are distributed randomly and in small numbers (rarely exceeding 2% of cells). Lung endocrine cells may also stain for S-100 protein but can be distinguished from Langerhans' cells by histologic criteria or counterstains (e.g., with chromogranin).

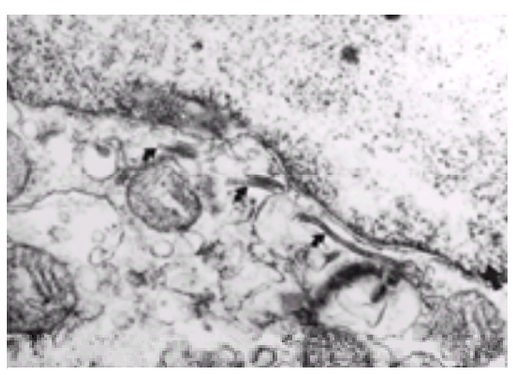

FIG. 22. Eosinophilic granulomatosis. Electron microscopy. Langerhans' histiocyte. *Curved arrows* depict Birbeck granules in the cytoplasm. *Straight arrow* points to the nucleus. (Courtesy of Theodore F. Beals, M.D., Department of Pathology, Veterans Affairs Medical Center, Ann Arbor, Michigan 48109.)

Langerhans' cells also express OKT6, whereas lymphocytes and monocytes do not. Intense staining for OKT6 may establish the diagnosis in equivocal cases, but this technique requires fresh or frozen tissue and so is less practical than S-100 staining. In addition, rare OKT6-positive cells may be observed in BAL fluid or lung tissue in patients with diverse pulmonary disorders. Chollet et al. analyzed BAL fluid from 131 patients with various pulmonary diseases. All 18 patients with pulmonary EG had OKT6-positive cells on BAL (mean, 5.6% cells). By contrast, the mean number of OKT6-positive cells in other conditions was only 0.20% (none exceeded 2.8%). Thus, >3% of cells staining for OKT6 is relatively specific for EG.

Langerhans' cells also express other markers, including HLA-DR, Fc receptor, CD4 antigen, CD1a and CD1c (markers of a family of antigen-presenting molecules), and leucyl-B-naphthylamidase. These latter techniques are limited to research laboratories.

It should be emphasized that the diagnosis of pulmonary EG can usually be established by conventional histologic stains (e.g., hematoxylin-eosin) and light microscopy. Because of the heterogeneous distribution of the lesions, surgical (e.g., open or thoracoscopic) lung biopsy is usually required to confirm the diagnosis. However, transbronchial lung biopsies may be adequate provided the salient histologic or immunohistochemical features are present. Because of the potential for sampling error associated with transbronchial lung biopsies, we obtain multiple (four to six) specimens from both the upper and lower lobes and employ S-100 stains when the diagnosis is suspected. When features are not definitive, thoracoscopic biopsy should be done.

Pathogenesis

The pathogenesis of pulmonary EG is unknown, but it probably represents an uncontrolled immune response initiated or regulated by Langerhans' cells. Langerhans' cells are prominent in the early inflammatory lesions and may act as accessory cells that drive the immune/inflammatory response. Proliferation of these atypical histiocytes (Langerhans' cells) may be a reactive or neoplastic process. Recent studies using X-linked polymorphic DNA probes in female patients with disseminated, osseous, or extrapulmonary forms of Langerhans' histiocytosis (histiocytosis X) were consistent with a clonal neoplastic disorder. The pathogenesis of these nonpulmonary forms of Langerhans' histiocytosis probably differs from that of pulmonary EG, a disease that differs markedly in clinical expression and prognosis. Pulmonary EG likely represents an exuberant immune (reactive) response to inhaled irritants or allergens. Tobacco smoke has been strongly implicated as a causative factor, as 90%–97% of patients with pulmonary EG are smokers. The peribronchiolar (bronchocentric) distribution of lesions is consistent with a response to inhaled stimuli. Cigarette smoke may stimulate and recruit Langerhans' cells to the lung. Replication of Langerhans' cells in the alveolar structures may perpetuate an alveolitis. Tobacco glycoprotein, a potent immunostimulant isolated from cigarette smoke, acts as a T-cell mitogen and may stimulate macrophage cytokine production (i.e., interleukin-1 and interleukin-6). The relevance of tobacco glycoprotein to pulmonary EG has not been elucidated, but altered peripheral blood lymphocyte responses to tobacco glycoprotein in vitro have been noted in patients with pulmonary EG. Cigarette smoking has been associated with hyperplasia of pulmonary neuroendocrine cells and increased levels of bombesin-like peptides in the lower respiratory tract. Bombesin is chemotactic for monocytes and mitogenic for fibroblasts, and it may play a role in inflammatory or fibrotic responses. Immunohistochemical stains have noted large numbers of bombesin-positive neuroendocrine cells in the lungs of patients with pulmonary EG (particularly within the airways). Open lung biopsies revealed a >10-fold increase in bombesin-like peptides in specimens from patients with pulmonary EG compared with specimens from normal smokers or patients with IPF. Although neither neuroendocrine cells nor bombesin-like peptides are specific for EG, these findings may provide clues to pathogenic mechanisms. Hyperplasia of neuroendocrine cells may recruit and activate mononuclear phagocytes and Langerhans' cells to the lung. Other immune effector cells (e.g., lymphocytes, monocytes, plasma cells, eosinophils) or humoral factors (e.g., immune complexes) may play contributory roles in the pathogenesis of pulmonary EG.

Course and Prognosis

The prognosis of pulmonary EG is variable. The disease stabilizes or becomes less severe in more than two thirds of patients, usually within 6 to 24 months of onset of symptoms. In 15%–31% of patients, the disease progresses, resulting in destruction of lung parenchyma and irrevocable loss of pulmonary function. Severe late sequelae include pulmonary fibrosis, cor pulmonale, and respiratory failure. Fatalities have been noted in 6%–25% of patients. Rarely, the course is rapid, progressing to respiratory failure within a few weeks. Multisystemic disease, honeycombing on chest radiograph, severe reduction in diffusing capacity (D_LCO), and multiple

pneumothoraces have been associated with a poorer prognosis.

Therapy

Because of the rarity of pulmonary EG and its highly variable natural history, the role of therapy is controversial. Cessation of cigarette smoking is mandatory. Corticosteroids, vinca alkaloids (vinblastine or vincristine), D-penicillamine, and a variety of immunosuppressive and cytotoxic drugs have been associated anecdotally with claims for success, but data affirming their efficacy are lacking. Prognosis for adults with localized pulmonary EG is generally excellent, so therapy should be reserved for patients with severe, progressive, and debilitating disease. Although controlled trials have not been performed, Schonfeld and co-workers cited improvement in 12 of 14 patients with progressive pulmonary EG following institution of prednisone (initial dose of 40 mg/day). Others have failed to confirm the efficacy of corticosteroids. Given the lack of firm data, we are skeptical about the benefit of corticosteroids. However, an empiric trial for 3 to 6 months is reasonable in selected patients with fulminant or severe disease. Prolonged therapy should be continued only for patients manifesting objective and unequivocal responses. Alternative agents (e.g., vinblastine, cyclophosphamide, or D-penicillamine) can be considered for corticosteroid-recalcitrant cases, but their efficacy has not been proved. We are reluctant to use these agents for pulmonary EG, because the potential for adverse effects (including oncogenesis) may outweigh the benefit. Single-lung transplantation has been successfully accomplished in patients with EG and end-stage pulmonary fibrosis.

LYMPHANGIOLEIOMYOMATOSIS

Pulmonary lymphangioleiomyomatosis (LAM) is a rare, idiopathic fibrocystic lung disorder almost exclusively affecting premenopausal women. LAM has very rarely been described in postmenopausal women. Anecdotal case reports of LAM in male patients likely represented tuberous sclerosis or diffuse pulmonary lymphangiomatosis, disorders that share clinical and histologic features with LAM. There is an understandable confusion in acknowledging the terms as representing separate clinical entities because of phonetic similarities. Several authors have previously used the term *lymphangiomyomatosis* rather than *lymphangioleiomyomatosis.* Diffuse pulmonary/intrathoracic lymphangiomyomatosis is characterized by dilated lymphatic vascular lesions; the condition occurs in male or female patients and is not associated with smooth-muscle proliferation. This variceal condition is clinically and histologically distinct from LAM.

LAM is exceptionally rare. Published data is derived from a few series (often extracted from consulting pathologists' files) and anecdotal case reports. In 1990, Taylor and colleagues reported 32 patients with LAM followed at Stanford and the Mayo Clinic. The largest clinical series, reported by Kitaichi et al. in 1995, described 46 patients with LAM from Japan, Korea, and Taiwan. Based on an informal consensus among experts, an estimated 200 to 300 patients have been accumulated through personal files and publications. Interested patients and/or family members recently compiled a list of an additional 100 to 150 affected patients and formed an LAM organization with the support of the National Institutes of Health in the United States. Owing to the nonspecificity of clinical findings and lack of awareness of LAM, the prevalence may be underestimated by historical analyses. Data from the Mayo Clinic suggest an apparent increase in the incidence of LAM in the last decade. This apparent increase could simply reflect an increased awareness of the disorder. Very rough estimates suggest a prevalence ranging from no to three cases per 100,000 population in the United States.

Clinical Features

The classic clinical presentation of LAM is quite distinctive. Women of childbearing age present with spontaneous pneumothorax, hemoptysis, slowly progressive exertional dyspnea, or chylothorax. The mean age at onset of symptoms is approximately 30 years. Dyspnea is nearly invariably present, beginning in the third or fourth decade of life, and progresses inexorably for years. Pneumothoraces occur in 50%–80% of patients with LAM. Chylous effusions occur in 7%–39%, and hemoptysis or focal alveolar hemorrhage in 28%–40%. The clinical course of LAM is heterogeneous. In early reports, most patients died of progressive respiratory failure within 5 to 10 years of onset of symptoms. The life expectancy appears to be highly variable, and prolonged survivorship has been noted in some patients. In the cohort of LAM patients from Stanford and the Mayo Clinic, 25 of 32 patients (78%) were alive 8.5 years after the diagnosis; mean survival was 10.0 years. Kitachi and colleagues cited a lower survival (38% at 8.5 years after the diagnosis) in a cohort of 46 patients with LAM in Asia. Studies assessing the impact of specific therapeutic modalities are lacking but are discussed later.

Pulmonary Function Tests

Pulmonary function tests in LAM typically demonstrate air flow limitation (often with air trapping), impaired D_LCO, and hypoxemia. Lung volumes are usually preserved and may be increased. In the series reported from Stanford and the Mayo Clinic, obstructive or mixed obstructive-restrictive defects were noted in 78% of patients. Reductions in D_LCO were noted in 96% and hypoxemia was present in 77%. In the series reported by Kitaichi et al., 29% exhibited a pure obstructive air flow limitation; restrictive defects or mixed obstructive-restrictive defects were noted in 26% and 36%, respectively. TLC was increased (>120% of predicted) in 30%. Reductions in D_LCO (<80% of predicted) and PaO_2 (<80 torr) were observed in 97% and 81% of patients, respectively. Resting arterial blood gases may be normal in the setting of mild disease, but decreases in PaO_2 and widened $P(A - a)O_2$ are typical as the disease progresses. Exercise performance is impaired; an excessive ventilatory response and increased dead space ventilation are characteristic features on formal exercise testing. Air flow obstruction and impairments in diffusing capacity, exercise capacity, and gas exchange correlate primarily with the extent of airway cystic lesions. However, muscular proliferation in small airways, destruction of pulmonary microvasculature, loss of alveolar support, and loss of parenchymal interdependence may be important contributory mechanisms of physiologic aberrations.

Chest Radiographs

Conventional chest radiographs demonstrate a wide spectrum of abnormalities. These include pneumothoraces; bilateral interstitial, reticulonodular, or cystic radiolucencies; pleural effusions; or hyperinflation (Fig. 23). Early in the course of the disease, chest radiographic findings may be normal. With disease progression, cystic lesions, reticulonodular infiltrates, or pneumothoraces invariably develop. Pneumothoraces have been noted at the time of presentation in 39%–53% of patients with LAM, and reticulonodular infiltrates in 47%–85%. As the disease progresses, both these features are present in >80% of patients. The reticulation actually represents the walls of the numerous alveolar cysts. In some cases, well-defined cystic or bullous lesions may be evident. Hyperinflation develops as the disease worsens and is seen in up to two thirds of patients in the late phases of the disease. Pleural effusions (typically chylous) occur in 11%–29% of patients. Mediastinal or hilar lymphadenopathy is not a feature of LAM.

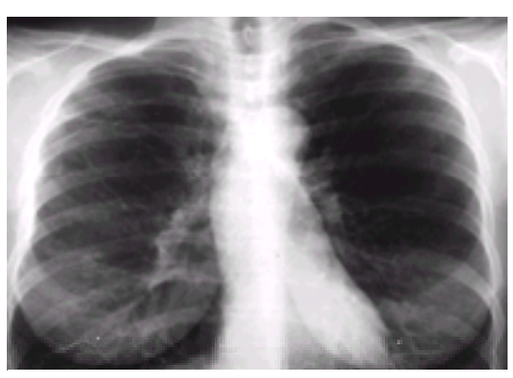

FIG. 23. Lymphangioleiomyomatosis. PA chest radiograph from a 39-year-old woman with LAM demonstrates severe hyperinflation and large cysts and bullous changes. Surgical clips are present on the right from a previous thoracotomy and pleurodesis for recurrent pneumothoraces.

High-Resolution Computed Tomography

High-resolution CT findings are highly distinctive in LAM. The cardinal feature is numerous thin-walled cysts (usually <20 mm in diameter) distributed diffusely throughout both lungs; the intervening lung parenchyma is normal (Fig. 24, Fig. 25, and Fig. 26). Nodules, interstitial fibrosis, cavitary lesions, and intrathoracic lymphadenopathy, features that may be observed in other CILD, are not features of pulmonary LAM. Focal ground-glass opacities have been noted in up to 59% of patients with LAM in some series, and may reflect focal alveolar hemorrhage, pulmonary hemosiderosis, or diffuse proliferation of smooth-muscle cells. However, the cystic lesions predominate. Cystic lesions may be seen on high-resolution CT in other pulmonary disorders (e.g., pulmonary EG, IPF, emphysema), but the distribution of cysts differs among these disorders. In LAM, the cysts are distributed throughout the lung fields, without a predilection for specific regions or lobes. By contrast, in pulmonary EG, the cysts are preferentially distributed in the upper or middle lung zones and are usually associated with a nodular component (which is lacking in LAM). In IPF, areas affected by the disease are patchy and heterogeneous, and cysts are preferentially distributed in the peripheral, subpleural, and basilar regions of the lungs. In addition, reticular or ground-glass opacities are usually prominent associated features in IPF. Cystic or bullous lesions seen in smokers with emphysema do

not have well-formed walls and tend to be more extensive in the upper lobes. Tuberous sclerosis, an autosomal dominant disorder associated with mental retardation and cutaneous manifestations, is associated with pulmonary cystic lesions indistinguishable from those of LAM in approximately 1% of patients. Tuberous sclerosis can be distinguished from LAM on clinical grounds, as neurologic or cutaneous manifestations are not observed in LAM.

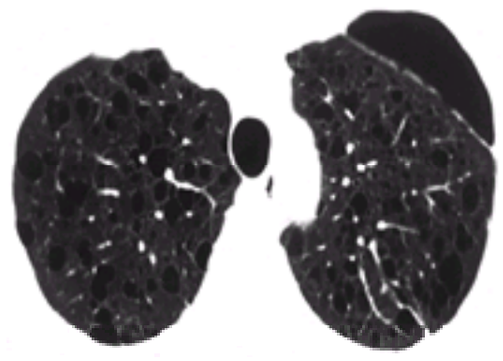

FIG. 24. Lymphangioleiomyomatosis. CT in a 41-year-old woman with LAM demonstrates multiple, thin-walled cystic radiolucencies in upper lobes bilaterally with large zones of intervening normal lung parenchyma, consistent with LAM.

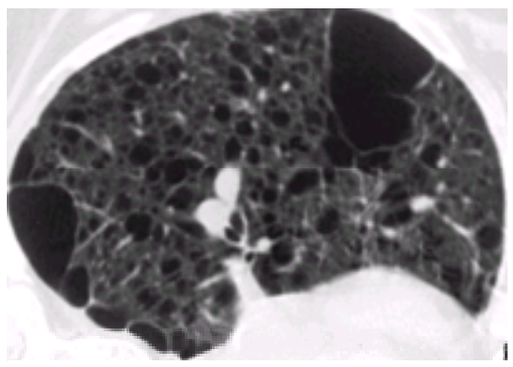

FIG. 25. Lymphangioleiomyomatosis. CT in a 44-year-old woman with LAM demonstrates multiple, thin-walled cystic radiolucencies bilaterally. Note the two large lesions, representing confluent cysts.

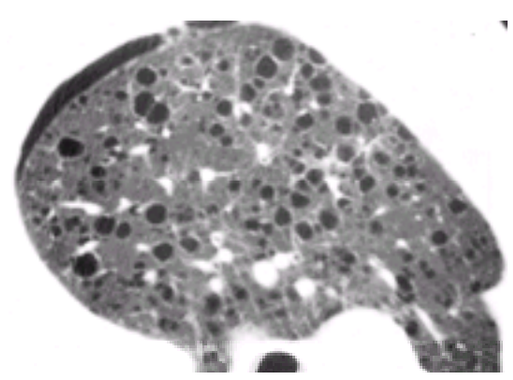

FIG. 26. Lymphangioleiomyomatosis. CT demonstrates multiple, thin-walled cystic radiolucencies throughout lung parenchyma. Note small associated pneumothorax, a typical finding in LAM. (Courtesy of R. Schmidt, M.D, Ph.D., University of Washington, Seattle.)

Histopathologic Features

At thoracotomy, innumerable small cysts are seen on the lung surface, ranging from a few mm to 3 cm (Fig. 27A). Light microscopy demonstrates diffuse proliferation of immature/atypical smooth muscle in the walls of the cysts and throughout the peribronchial, perivascular, and perilymphatic regions of the lungs (Fig. 27B, Fig. 27C). These proliferating smooth-muscle cells may form highly organized nodules or fascicles but are not considered malignant. The smooth-muscle cells are heterogeneous, and phenotypically they may exhibit features of either spindle cells or epithelioid cells. Electron microscopy shows myofilaments in the smooth-muscle cells of the lung lesions and dense deposits of collagen fibers. Extension of these smooth-muscle proliferations may destroy surrounding lung parenchyma, forming the characteristic cysts. The diffuse distribution of the muscular and cystic lesions explains the clinical manifestations of LAM. Compression of the conducting small airways results in air flow obstruction and alveolar disruption. Pneumothoraces result from rupture of subpleural cysts. Obstruction of pulmonary vessels may cause venular congestion and disruption, resulting in hemoptysis and hemosiderosis. Lymphatic obstruction may cause chylothorax. The extent of cystic LAM lesions on open lung biopsy is an important determinant of prognosis; predominantly cystic lesions suggest a worse prognosis and survival. The extent of smooth-muscle proliferation or hemosiderosis does not correlate with survival.

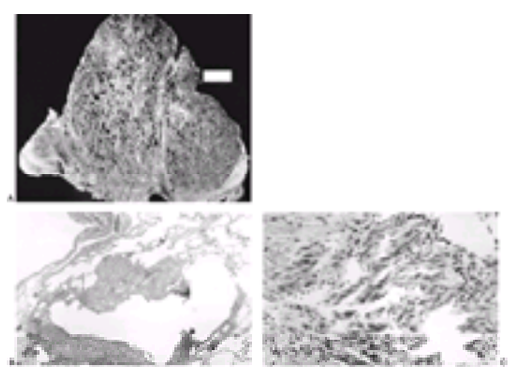

FIG. 27. A: Lymphangioleiomyomatosis. Gross appearance of lung removed from a patient with LAM. Note the numerous cysts throughout the lung parenchyma. **B:** Photomicrograph of lung biopsy specimen demonstrates aggregates of characteristic smooth-muscle bundles in the walls of cysts and in the peribronchial areas. H&E, low power. **C:** Photomicrograph of lung biopsy specimen demonstrates aggregates of characteristic smooth-muscle bundles with a spindle appearance. H&E, high power.

Immunohistochemical stains of the proliferating smooth-muscle cells in LAM are positive for muscle-specific actin, desmin, and melanoma-related marker (HMB-45). HMB-45 is never found in normal smooth muscle. In the absence of melanoma or clear-cell tumor of the lung (which also stains for HMB-45), positive staining for HMB-45 in the lung is highly specific (>95%) for LAM. Progesterone and estrogen receptors have been demonstrated in the nuclei of proliferating smooth muscle in some patients with LAM, but these findings are not consistently present.

Extrapulmonary lymphangioleiomyomas or cysts may involve the spleen, kidney, liver, abdominal or retroperitoneal lymph nodes, uterus, and ovaries in patients with LAM. Renal angiomyolipomas have been noted in 15%–47% of patients with pulmonary LAM and may give rise to local pain, bleeding, or compression of renal parenchyma.

Differential Diagnosis

The diagnosis of LAM is strongly suggested by the constellation of spontaneous pneumothorax, preserved or increased lung volumes, chylous pleural effusions, and air flow obstruction in women in the third or fourth decade of life. Hemoptysis may be an associated feature (noted in up to 40% of patients). When the clinical presentation is typical, the diagnosis can be strongly suspected based on the radiologic findings (particularly high-resolution CT). Other clinical entities that may be confused with LAM include pulmonary EG, metastatic low-grade sarcomas, tuberous sclerosis, emphysema, and small-airways disease with smooth-muscle proliferation. The diagnosis of LAM needs to be substantiated by lung biopsy. Transbronchial lung biopsy may be diagnostic in some cases, but surgical lung biopsy is warranted when TBB findings are nondiagnostic or equivocal.

Treatment

Given the rarity of LAM, controlled therapeutic trials have not been performed and optimal therapy is controversial. Although a specific hormonal abnormality has not been identified, LAM is exclusively a disease of women and may be exacerbated by estrogens (endogenous or exogenous) or pregnancy. Proliferation of uterine smooth-muscle cells is also regulated by estrogen. Treatment of LAM is directed toward reducing estrogens, either by surgical oophorectomy or anti-estrogen regimens (e.g., progesterone, tamoxifen, androgens, luteinizing hormone-releasing agonists). Exogenous estrogens are strongly contraindicated. Oophorectomy has been considered “gold standard” therapy by some, but results have generally been disappointing. In the retrospective review from Stanford and the Mayo Clinic, oophorectomy was ineffective in all 16 patients. Despite anecdotal responses of improvement or stabilization following oophorectomy, oophorectomy alone was never associated with improvement in the group of patients reported by Kitaichi and colleagues. Medroxyprogesterone acetate has been tried, either alone or combined with oophorectomy, as therapy for LAM. Intramuscular medroxyprogesterone acetate (400 to 800 mg monthly) alone was associated with stabilization or improvement in 2 of 19 and 4 of 8 patients in two series. This form of therapy appears to be more effective in managing chylous effusions; its efficacy in alleviating the airway or cystic lesions is less clear. Tamoxifen has been advocated by some, but data justifying its use are lacking. In four series, tamoxifen, given alone or in combination with other agents, was associated with improvement in only 2 of 31 treated patients. Tamoxifen has partial estrogen-agonist activity, so we believe this agent should not be used in LAM. Anecdotal responses have been cited with synthetic analogues of luteinizing-releasing hormone, but data are sparse. Interferon-a has been tried, but results have been unimpressive. Unfortunately, current therapeutic regimens for LAM are of limited efficacy. In the review by Kitaichi and colleagues, diverse therapeutic options were evaluated in 40 patients. Only two improved; nine stabilized, and the remaining patients deteriorated. In this cohort of patients, factors associated with a poor prognosis included worsening air flow obstruction at 2 years after the initial examination; increase in percentage of predicted TLC at 2, 3, and 5 years after the initial exam; predominantly cystic LAM lesions (compared with predominantly smooth-muscle proliferation) on open lung biopsy; and higher grades of histologically abnormal areas and cystic lesions on open lung biopsy.

Despite the lack of firm evidence that treatment reverses the course of the disease, the course of LAM in the absence of therapy is poor, with inexorable progression. The rate of progression of LAM varies widely among patients regardless of therapy. LAM has been known to continue even after menopause. Given the poor prognosis of untreated LAM, an empiric trial with intramuscular medroxyprogesterone acetate, oophorectomy, or both is reasonable. The influence of pregnancy on the outcome is unknown, but anecdotal cases have documented progression or acceleration of LAM during pregnancy. We believe pregnancy should be avoided, but this is best left to the informed patient's wishes. Unilateral lung transplantation is an established mode of therapy for far-advanced disease. Three-year survival following lung transplantation for LAM approximates 60%–70%. Recurrence of LAM has been reported in transplanted lung allografts in two patients with LAM, raising questions regarding the long-term outcome of transplantation in this patient population. It is hoped that ongoing research efforts and future studies will shed further light on the pathogenesis of LAM and provide new strategies for curative therapy.

PULMONARY AMYLOIDOSIS

Intrathoracic amyloidosis may rarely complicate primary or secondary amyloidosis in which systemic involvement is evident. In addition, primary pulmonary amyloidosis, lacking extrapulmonary or systemic components, may occur. Amyloidosis comprises a heterogeneous group of diseases characterized by deposition of an insoluble b-pleated fibrillar protein in the extracellular matrix of involved tissues. Amyloid protein takes up Congo red stain and exhibits apple-green birefringence under polarized microscopy (Fig. 28). Primary amyloidosis, the most common variant, can be idiopathic or associated with plasma cell dyscrasias (such as multiple myeloma). This is associated with deposition of the immunoglobulin light-chain fragment (amyloid AL). Secondary amyloidosis (amyloid AA) may complicate diverse chronic inflammatory conditions (e.g., bronchiectasis, tuberculosis, malaria, chronic infections, and diverse collagen vascular disorders or inflammatory disorders). Amyloid AA protein is an apolipoprotein associated with HDL-3 that is produced by proteolysis of serum amyloid A proteins. Familial amyloidosis has also been described. Amyloid protein may also be found with advanced age (senile amyloidosis). Prealbumin has been associated with familial and senile forms of amyloidosis. Clinically significant pulmonary involvement occurs in more than one third of patients with primary systemic amyloidosis but only rarely complicates secondary forms of amyloidosis. Primary or secondary forms of systemic amyloidosis differ from primary pulmonary amyloidosis, a disorder localized to the lungs, tracheobronchial tree, pleurae, and/or mediastinal lymph nodes.

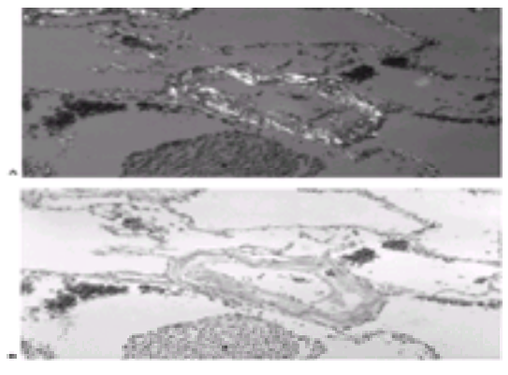

FIG. 28. A: Amyloidosis. Photomicrograph of open lung biopsy specimen demonstrates amyloid deposition within the wall of a pulmonary vessel. H&E. **B:** Photomicrograph of open lung biopsy specimen demonstrates amyloid deposit displaying apple-green birefringence under polarized microscopy following staining with Congo red.

Pulmonary Amyloidosis Associated with Primary Systemic Amyloidosis

Although it has long been recognized that primary systemic amyloidosis tends to involve the lung, reports of lung involvement have been infrequent. Although the prevalence of pulmonary involvement in primary systemic amyloidosis has not been elucidated, diffuse amyloid deposits in an alveolar septal pattern may occur. A recent review of the Mayo Clinic experience from 1980 to 1993 identified 35 patients with primary systemic amyloidosis, of whom 20 had pulmonary involvement manifesting as diffuse interstitial infiltrates; four had coexisting pleural effusions. The median survival in this series was 16 months. Because cardiac amyloidosis is a frequent concomitant feature, it is difficult to determine the influence of pulmonary amyloidosis on prognosis. However, the presence of pulmonary amyloidosis in patients with primary systemic amyloidosis is generally considered a harbinger of a poor outcome.

Localized or Primary Pulmonary Amyloidosis

Primary or localized pulmonary amyloidosis is characterized by amyloid deposits limited to the lungs and associated structures (i.e., tracheobronchial tree, lung parenchyma, pleurae, and hilar or mediastinal lymph nodes). Most patients with localized tracheobronchial amyloidosis are in the fifth to sixth decade of life. Amyloid deposition in the lung resulting from secondary or familial amyloidosis is not included in this category. In 1983, Thompson and Citron identified 126 published cases of primary pulmonary amyloidosis in the world literature (67 tracheobronchial, 59 lung parenchymal). Of the 67 patients with tracheobronchial disease, 57 had multifocal submucosal plaques and 10 had amyloid tumorlike masses. A review of three recent series cited involvement of the tracheobronchial tree in 23 of 89 patients with pulmonary amyloidosis.

Tracheobronchial amyloidosis is generally localized to the airways and spares the lung parenchyma. Relatively flat submucosal plaques of amyloid protein or tracheobronchial nodules may be seen. These may be single, diffuse, or multifocal and are not associated with systemic amyloidosis. Patients may be asymptomatic or

may have hoarseness, wheezing, dyspnea, hemoptysis, cough, atelectasis, recurrent pneumonia, or chronic infections. Respiratory symptoms may be related to airway narrowing or stenosis or involvement of the nasopharynx, sinuses, or larynx. Tracheobronchial amyloidosis has been associated with tracheobronchopathia osteoplastica, a rare disorder of unknown cause characterized by the presence of calcified or cartilaginous submucosal nodules within the tracheobronchial tree. Localized tracheobronchial amyloidosis is not associated with primary systemic amyloidosis, but its course may not be benign. In a study by Hui and colleagues at the Armed Forces Institute of Pathology, three of the seven patients for whom follow-up data were available died of respiratory failure or recurrent pneumonia. Management has included observation, intermittent bronchoscopic resection, surgical resection, and laser therapy. Resection or biopsy may be complicated by severe bleeding (see below).

Nodular Amyloid Lesions (Amyloidomas)

Localized pulmonary amyloid nodules (amyloidomas) are uncommon lesions that may be seen in older patients (on average in the sixth decade) and are generally not associated with primary systemic amyloidosis. Lesions may be single or multiple, ranging in size from 0.4 to 15 cm (average, 3 cm) (Fig. 29). Amyloidomas occur most frequently in the lower lobes and may be asymmetric when multiple nodules are present. Amyloidomas may calcify and rarely cavitate. Metaplastic bone or cartilage formation may occur. Amyloidomas are usually asymptomatic and present as incidental findings on chest radiographs (Fig. 29) or autopsy. However, cough or hemoptysis may occur. For solitary nodules causing symptoms, resection is usually curative. However, biopsy or resection of nodular mass lesions may cause significant bleeding (see below).

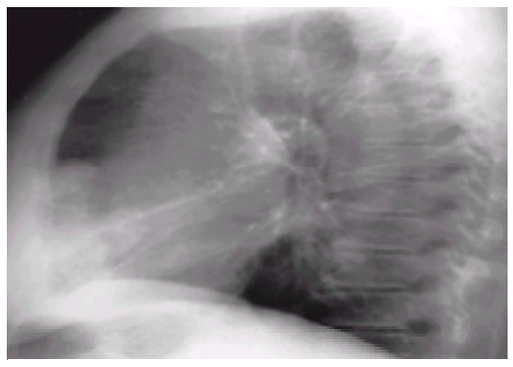

FIG. 29. Amyloidosis. PA chest radiograph demonstrates a solitary pulmonary nodule in the retrosternal space. Open lung biopsy specimen demonstrates typical features of amyloidosis. (Courtesy of D. Godwin, M.D., University of Washington, Seattle.)

Diffuse Interstitial Infiltrates

Amyloid deposits in the alveolar septa and interstitium may appear as reticulonodular or micronodular lesions on chest radiographs or CT scans and cause physiologic aberrations, including restrictive defects, decreased D_LCO, widened $P(A - a)O_2$, and pulmonary hypertension (Fig. 30). Alveolar septal amyloidosis is most commonly seen in primary systemic amyloidosis and is relatively uncommon in primary pulmonary amyloidosis. Although diffuse interstitial infiltrates were noted in 6 of 48 patients with primary pulmonary amyloidosis reported by Hui and colleagues from the Armed Forces Institute of Pathology, none of 17 patients with primary pulmonary amyloidosis recently reviewed by the Mayo Clinic group exhibited this radiographic pattern. Some authors have suggested that patients with interstitial pulmonary infiltrates likely represent a subset of patients with primary systemic amyloidosis and have unrecognized amyloid deposits in other organs. As the amyloid deposits and infiltrative process in the alveolar septa often involve the pulmonary vasculature, biopsy or resection of pulmonary lesions may be associated with an increased risk for bleeding.

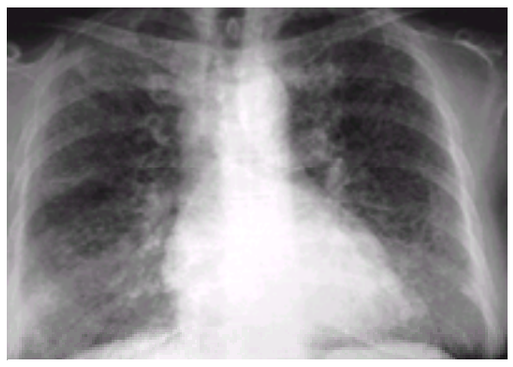

FIG. 30. Amyloidosis. PA chest radiograph demonstrates diffuse bilateral reticulonodular infiltrates in a patient with pulmonary amyloidosis. Small bilateral pleural effusions are also present. (Courtesy of D. Godwin, M.D., University of Washington, Seattle.)

Other Manifestations of Amyloid Deposits

Hilar and mediastinal adenopathy resulting from amyloid deposition may occur in conjunction with tracheobronchial amyloidosis and either primary or secondary forms of amyloidosis. The adenopathy may be unilateral or bilateral (with or without calcification). Pulmonary amyloidosis occurring in elderly patients has been termed *senile pulmonary amyloidosis.* Autopsy studies have detected senile pulmonary amyloidosis in approximately 10% of patients older than 80 years and in 50% of patients older than 90 years. These deposits are usually incidental findings and are not associated with primary systemic amyloidosis or specific symptoms. Pleural effusions (caused by amyloid deposits along the pleural surface) may occur in primary systemic amyloidosis or as a complication of primary pulmonary amyloidosis. Amyloid effusions are exudative and may be hemorrhagic. Transudative pleural effusions may reflect cardiac amyloidosis. Other rare pulmonary manifestations include obstructive sleep apnea (secondary to involvement of the tongue) and respiratory muscle weakness (caused by amyloid infiltrating the diaphragm).

Bleeding Manifestation with Amyloidosis

Hemoptysis may complicate any form of pulmonary amyloidosis (including alveolar septal or tracheobronchial involvement). Focal or diffuse hemorrhage may occur when amyloid deposits involve vessels. In one retrospective review by Yood and colleagues, 41 of 100 patients with amyloidosis experienced one or more episodes of bleeding (three of which were fatal). Manifestations included petechiae, ecchymoses, gastrointestinal bleeding, hematuria, hemoptysis, and bleeding after biopsy. Hemoptysis occurred in only two patients. Although the excessive bleeding associated with amyloidosis is most often caused by amyloid infiltration of blood vessels, isolated deficiency of factor X has been cited as a cause of the bleeding diathesis in some patients with amyloidosis. The risk for pulmonary hemorrhage following lung biopsy is of concern, but firm data assessing risks are not available.

Treatment of Amyloidosis

Unfortunately, no proven therapy for amyloidosis is available. In secondary forms of amyloidosis, aggressive treatment of the underlying disease may delay or reverse the deposition of amyloid protein. Alkylating agents may be effective in amyloidosis associated with plasma cell dyscrasias (e.g., multiple myeloma) but are of unproven efficacy in other forms of amyloidosis and may increase morbidity. Colchicine has been used in both primary and secondary forms of amyloidosis, but its value is doubtful. Interferon-a has been tried but appears to be ineffective. Anecdotal responses have been reported with dimethylsulfoxide and 4'-iodo-4'-deoxydoxorubicin (a new anthracycline), but data are sparse. No proven effective treatment is available for diffuse amyloid infiltrating the tracheobronchial tree or lung parenchyma. Resection of localized amyloid deposits surgically or by laser may be beneficial in symptomatic foci involving the trachea, larynx, or bronchi. In rare cases, laryngeal dilation or tracheostomy have been required. It is hoped that ongoing and future studies will provide strategies for new therapeutic approaches.

ACKNOWLEDGMENT

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CHAPTER

22 Drug-Induced Pulmonary Disease

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INTRODUCTION

Drug-induced disease is one of the most common iatrogenic illnesses. In the last decade, the lung has been recognized increasingly often as a target organ. Fewer than 25% of drug reactions are truly allergic in origin; the mechanisms of overdose, side effects, and drug interaction are predictable with most drugs. On the other hand, idiosyncratic and allergic or hypersensitivity reactions are unpredictable and are estimated to occur in about 5% of patients receiving any drug. In drug-induced pulmonary disease, an abnormality on the chest x-ray film or a symptom complex is the most common form of presentation. Drug-induced pulmonary disease is diagnosed by maintaining a high index of suspicion in the appropriate clinical setting.

In this chapter, we provide a brief overview of drug-induced pulmonary disease. There are many isolated case reports of drugs that are believed to have caused an adverse pulmonary reaction, but these are vague and doubtful and are excluded from the review. In the first part of the chapter, we discuss various pleuropulmonary patterns of response to drugs. The second part addresses the pulmonary effects of different categories of drugs, including anti-inflammatory, antimicrobial, and antineoplastic agents.

Table 1 summarizes the more common clinical presentations of pulmonary toxicity induced by noncytotoxic medications, including illicit drugs, and Table 2 does the same for pulmonary toxicity induced by cytotoxic agents, including radiation. Some unusual manifestations of drug-induced pulmonary toxicity are listed in Table 3. Not all the medications listed in the tables are discussed in the text.

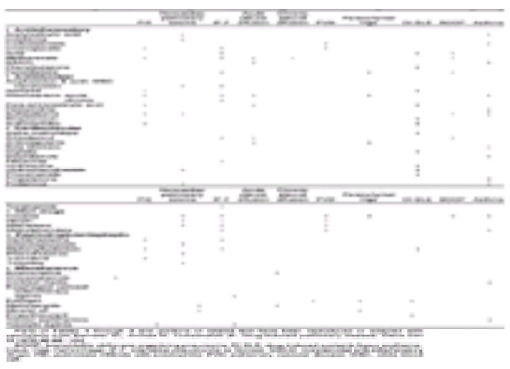

TABLE 1. *Clinical presentation of pulmonary toxicity induced by noncytotoxic drugs*

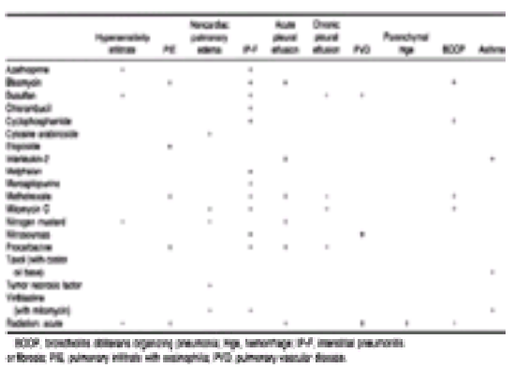

TABLE 2. *Clinical presentation of pulmonary toxicity induced by cytotoxic drugs and radiation*

Presentation	Causative agent(s)
Alveolar proteinosis	Busulfan
Bronchial necrosis	Radiation therapy, brachytherapy
Bronchospasm (paradoxical)	Nebulized β_2-adrenergic agonists Intravenous hydrocortisone
Calcification (parenchymal)	Antacids, calcium, phosphorous Vitamin D
Cough	ACE inhibitors
Goodpasture's syndrome	Penicillamine
Lung mass(es) ± cavitation	Amiodarone, bleomycin
Mediastinal widening	
Lymphadenopathy	Diphenylhydantoin, methotrexate Potassium iodide
Lipomatosis	Corticosteroids
Mediastinitis	Esophageal variceal sclerotherapy
Panlobular emphysema	Methylphenidate
Pneumothorax	Nitrosoureas, bleomycin
Pseudosepsis syndrome	Chronic salicylate intoxication

ACE, angiotensin-converting enzyme.

TABLE 3. *Unusual manifestations of drug-induced pulmonary toxicity*

PATTERNS OF RESPONSE

Hypersensitivity Reactions

Pulmonary responses to some drugs may be best thought of in terms of a hypersensitivity reaction (Table 1). Typically, the symptoms consist of cough, dyspnea, and fever, with the appearance of an infiltrate on the chest x-ray film. Occasionally, a pleural effusion is seen. In some instances, there may be laboratory manifestations characteristic of hypersensitivity responses, such as peripheral eosinophilia or, more specifically, a positive lymphocyte transformation test response to the offending drug. The adverse response usually remits after cessation of the drug. Corticosteroids may hasten the recovery, although they are generally not needed.

Noncardiogenic Pulmonary Edema

Several factors are responsible for the transvascular flow of fluid. One factor, the filtration coefficient of permeability of the vascular endothelium, is believed to be altered in cases of noncardiogenic pulmonary edema. Overdoses of sedatives and narcotics are most commonly associated with altered permeability of the pulmonary vasculature. Most patients with noncardiogenic pulmonary edema also display some degree of central nervous system depression; it is unclear whether the response represents a drug effect, “neurogenic pulmonary edema,” or a combination of the two. Other drugs that cause noncardiogenic pulmonary edema characteristically produce an idiosyncratic response within minutes to hours after absorption.

Interstitial Pneumonitis or Fibrosis

A number of drugs have the potential for causing either an interstitial pneumonitis or an interstitial fibrosis. In some cases, the interstitial pneumonitis has many of the features of a hypersensitivity state, and the difference may be semantic rather than real. In other cases, few features of a hypersensitivity state are seen, and the interstitial pneumonitis represents only the precedent inflammatory state of a fibrosing process.

Pleural Effusions

An acute pleural effusion in association with drugs has been reported to be part of a hypersensitivity reaction. Anticoagulants cause effusion by leading to a pleural hemorrhage. A chronic pleural effusion develops after long-term use of a drug. In some instances, this is a manifestation of a retarded hypersensitivity-like response (methotrexate and procarbazine) or is associated with an interstitial fibrosis (busulfan and methotrexate).

Pulmonary Vascular Responses

Busulfan and cromoglycate are included as possible causes of pulmonary vascular responses because biopsy specimens from patients who display hypersensitivity reactions to these drugs may show an inflammatory vascular response as well. It is unclear what role the angiitis *per se* plays in the development of these disease processes. Illicit drugs are capable of causing angiitis and hypertension; the drugs and their diluents are given intravenously and are filtered by the pulmonary capillaries, where they incite their untoward effects. Heroin-induced pulmonary edema is frequently encountered in urban medical centers. An overdose of methadone and propoxyphene (Darvon) can cause a similar reaction. Corticosteroids are mentioned as causing pulmonary vasculitis, but evidence is at best suggestive. In an autopsy review of patients with rheumatoid arthritis, pulmonary vasculitis was found to occur in 29% of patients receiving corticosteroids but in none of the patients who were not taking them.

Alpha-adrenergic nasal sprays have been associated with interstitial fibrosis and obliterated pulmonary vessels on histologic examination. This response, seen in patients who abuse the sprays on a long-term basis, may be caused by the effects of repeated vascular constriction. The chest roentgenogram shows normal parenchyma with prominent pulmonary vasculature. Pulmonary function testing reveals a drop in the DLCO (diffusing capacity) that is proportional to the degree of pulmonary hypertension.

Estrogen-containing drugs are also capable of causing pulmonary hypertension. Affected patients fall into two distinct categories: those with congenital heart disease and those without. In the first group, the relationship between estrogen and pulmonary hypertension appears to be well established, although uncommon; in the second group, the relationship remains only suggestive. Case reports have implicated oral contraceptives as a cause of “primary” pulmonary hypertension in patients who have taken the drug for 6 months to 5 years. In one study, predisposing factors for pulmonary hypertension were found in three of six patients (family history, corrected ductus, and connective tissue disease); the other three were apparently normal.

Pulmonary Parenchymal Calcification

Drug-related calcium deposition in the lungs is very rare. It is usually associated with the soft-tissue calcification seen in the milk-alkali syndrome or with hypercalcemic states of other causes. Drugs known to have precipitated calcium deposition include antacids, calcium, phosphorus, and high doses of vitamin D (Table 3).

Parenchymal Hemorrhage

Hemoptysis as the manifestation of an adverse drug effect is most frequently caused by a drug-related pulmonary embolus leading to pulmonary infarction. Pulmonary hemorrhage and hemoptysis can be a manifestation of penicillamine-induced Goodpasture's syndrome, lipoid pneumonia, or chronic radiation pneumonitis.

Spontaneous pulmonary hemorrhage has been reported in patients who were taking oral anticoagulants for 13 days to 3 years. Initial symptoms were dyspnea, hemoptysis, and cough. The presenting feature was either hemoptysis or an infiltrate on the chest roentgenogram. Anticoagulants also may cause a hemothorax, manifested as a pleural effusion associated with a decreasing hematocrit.

Mediastinal Manifestations

Although not necessarily representing a pulmonary disease, adverse mediastinal responses appear initially as an abnormality on the chest x-ray film. Diphenylhydantoin occasionally produces a pseudolymphoma syndrome, manifested as peripheral lymphadenopathy (Table 3). It produces mediastinal lymphadenopathy only rarely, however. The enlarged nodes regress 1 to 2 weeks after cessation of the drug. Potassium iodide has been reported to produce fever, cough, and pruritus, with hilar and mediastinal lymphadenopathy that cleared on discontinuance of the drug. Transient hilar adenopathy may accompany a hypersensitivity-like response to methotrexate. Mediastinal lipomatosis resulting from corticosteroid use is a well-recognized entity.

Drug-Induced Lupus Erythematosus

A number of drugs have been implicated as causative factors in the systemic lupus erythematosus (SLE) syndrome, and it is estimated that they play an activating role in 5%–12% of cases (Table 1). It is still controversial whether the drug exposes a latent case of lupus or actually causes the disease. Animal experiments have not helped to clarify this issue. Acetylator status may be important, for cases of hydralazine- and isoniazid-related SLE are noted more frequently in slow acetylators of these drugs.

The lungs and pleurae are involved in 50%–75% of cases of spontaneous SLE, whereas they are involved in 80% of cases of drug-induced SLE. Patterns of response include the following: (1) pleural effusion with or without pleuritic pain, (2) pleuritic chest pain with or without effusion, (3) atelectatic pneumonitis, (4) diffuse interstitial pneumonitis, and (5) alveolar infiltrates. Positive biochemical markers of SLE are found more frequently than are systemic signs, and the pleuropulmonary manifestations usually regress with removal of the agent.

It is estimated that >90% of cases of drug-induced SLE are caused by diphenylhydantoin, hydralazine, isoniazid, or procainamide. Sulfonamides that have been implicated include acetazolamide, sulfadiazine, sulfamethoxypyridazine, sulfasalazine, and sulfisoxazole.

Hydralazine differs from most drugs in this category in that only 25% of patients have pleuropulmonary symptoms. In one review, the percentages of symptomatic

patients found to have chest roentgenographic abnormalities were as follows: (1) pleural thickening (57%), (2) pleural effusion (36%), (3) pulmonary fibrosis (21%), (4) elevated hemidiaphragm (7%), (5) segmental atelectasis (7%), and (6) migratory pneumonitis (7%). Hydralazine-induced SLE is seen in 10%–20% of patients receiving prolonged therapy with doses of 400 mg/d or greater (although it has been reported in patients who received therapy for <1 month and those who received <100 mg/d). It is more common in women (50%–90%), Caucasians, and slow acetylators.

Procainamide-induced SLE is a time- rather than dose-dependent phenomenon. For example, in one study clinical SLE developed in 50% of patients by 3 months, and by 1 year all had a positive test for antinuclear antibodies (ANA). Resolution of the syndrome within a few days to weeks after discontinuance of the drug is the rule; occasionally, corticosteroids are necessary to control symptoms.

Drug-induced bronchospasm/asthma

Drug-induced bronchospasm is caused by a variety of agents (Table 1 and Table 2). Mechanisms are diverse and poorly understood. Acetylsalicylic acid produces worsening bronchospasm in about 4% of asthmatic patients. Other nonsteroidal anti-inflammatory agents (NSAIDs) can produce a similar reaction and should be avoided in aspirin-sensitive patients. Dipyridamole increases the concentration of the bronchoconstrictor adenosine, which can cause significant bronchospasm in some patients with underlying obstructive lung disease. Theophylline is the drug of choice for treatment and/or prophylaxis in these patients. Vinblastine appears to act synergistically with mitomycin to produce bronchospasm. Administration of nebulized medications, such as pentamidine, or propellants can further irritate already hyperreactive airways. Paradoxical bronchospasm (Table 3) has been reported with the use of nebulized beta agonists as well as intravenous hydrocortisone (not reported with other steroid preparations).

Bronchiolitis Obliterans Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) has been described as a response to a variety of medications (Table 1 and Table 2). Patients frequently have isolated or patchy air space opacities indistinguishable from those of idiopathic BOOP. This reaction is usually reversible with discontinuation of the drug and sometimes requires treatment with corticosteroids.

EFFECTS OF DRUGS AND RADIATION

Anti-inflammatory Agents

Sodium cromoglycate has been associated with a hypersensitivity-like response, accompanied by fever, eosinophilia, and pulmonary infiltrates.

Overdoses of acetylsalicylic acid (ASA) can produce central respiratory stimulation and noncardiogenic pulmonary edema. Therapeutic serum levels are in the range of 10 to 20 mg/dL. At levels of 35 mg/dL, respiratory alkalosis is seen. Severe hyperpnea is manifested at levels of 50 mg/dL. At a serum level of 45 mg/dL, noncardiogenic pulmonary edema is seen. The pulmonary capillary wedge pressure is normal. Abnormalities on chest x-ray films take 3 to 8 days to clear.

The ASA triad is a syndrome characterized by asthma, nasal polyposis, and drug sensitivity. It was initially described following the use of ASA, but other anti-inflammatory drugs can also produce this reaction (Table 1). The first manifestation of the syndrome is vasomotor rhinitis with a watery discharge. Typically, this develops in the second or third decade in a person who is not atopic and who has previously taken ASA. The reaction is at first intermittent, later perennial. It is followed by the appearance of nasal polyps, and by midlife most patients demonstrate an asthmatic response.

The syndrome is not a hypersensitivity response, despite the asthma and angioedema that may be seen following absorption of the drugs. Results of skin and immunologic tests are negative. Furthermore, other forms of salicylic acid (such as sodium salicylate) do not produce a response in the ASA-sensitive patient. The mechanism of action is postulated to be an inhibition of prostaglandin (PG) synthetase and a disruption in the balance between naturally occurring bronchoconstrictor (PGF_{2a}) and bronchodilator (PGE series) prostaglandins. The usual response to this disruption is bronchoconstriction, but bronchodilation also has been reported. Most of the drugs that produce this response fall into the broader category of anti-inflammatory nonsteroidal analgesics, and it is for this reason that the ASA triad has been called *analgesic asthma* by some authors.

The frequency of the syndrome in asthmatic patients is approximately 4%. Patients may or may not be atopic (3% vs. an expected 10% in one series). Family studies reveal rare clusterings.

Treatment starts with avoidance of the offending drug. Beta-adrenergic agonists reverse the airways response. Corticosteroids diminish the recovery time, but even pretreatment does not prevent the response. Nasal polypectomy is reserved for symptoms of nasal obstruction only; it does not alter the response to ASA, and the polyps usually recur.

Tartrazine (FD&C yellow dye No. 5) is not an analgesic, and it is not known to affect PG biosynthesis. However, it can provoke symptoms of the ASA triad in a small number of ASA-sensitive patients. As a dye, it is contained in a number of medications and food products.

Methotrexate is increasingly being used in low doses (lower than the usual chemotherapeutic dose) as an anti-inflammatory drug for a few conditions, especially rheumatoid arthritis and Wegener's granulomatosis. Typically, the patient is given 10 to 15 mg once a week. Pulmonary reactions develop in about 5% of these patients, most commonly in the form of granulomatous pneumonitis. The onset is insidious and associated with cough, dyspnea, and low-grade fever. Histologically, weakly formed granulomas are seen in most patients. In a recent prospective evaluation of 124 patients receiving low-dose methotrexate, pneumonitis occurred in 3.2% of patients. Pulmonary function tests did not allow detection before clinical symptoms. Methotrexate pneumonitis also seems to predispose patients to *Pneumocystis carinii* pneumonia.

Penicillamine can cause unique pulmonary complications, including BOOP, SLE, and Goodpasture's syndrome (Table 3).

Gold is widely used orally and intramuscularly for the treatment of rheumatoid arthritis. The intramuscular preparations can cause interstitial pneumonitis and fibrosis that is almost always reversible by discontinuation of the gold injections, but sometimes additional treatment with corticosteroids may be required.

Antimicrobial Agents

Griseofulvin, isoniazid, para-aminosalicylic acid, penicillin, streptomycin, the sulfonamides, and tetracycline are all capable of producing a drug-induced SLE syndrome. In addition, isoniazid has been reported to cause a hypersensitivity-like pneumonitis with peripheral eosinophilia. Penicillin has been reported as generating a hypersensitivity pneumonitis distinct from systemic anaphylaxis, with peripheral eosinophilia (as high as 80%), alveolar infiltrates, pleural effusions, and positive skin test results. Sulfonamides can cause a true Loeffler's syndrome, with fever, cough, dyspnea, migratory infiltrates, and peripheral eosinophilia. A hypersensitivity pulmonary response also has been reported following the use of a sulfonamide-containing vaginal cream.

Para-aminosalicylic acid is estimated to produce a hypersensitivity-like response in approximately 0.3%–5.0% of patients receiving the drug. Common adverse responses include fever (up to 10°F), rash, malaise, headache, dry cough, eosinophilia, alveolar infiltrates, and lymphadenopathy. Pleural effusion and hepatomegaly have been seen. The symptoms usually start during the third week of treatment and gradually disappear within 2 to 3 weeks after discontinuance of the drug. Cases of angioneurotic edema with laryngeal edema, cough, and wheezing also have been reported.

Of all the antimicrobial drugs, nitrofurantoin is perhaps the most commonly reported as causing an adverse pulmonary reaction. To gain an appreciation of the relative risk, the manufacturer collected data during a 16-year period. During that time, 237 cases of adverse pleuropulmonary reactions were reported in an estimated 44 million courses of the drug. Reactions to nitrofurantoin are classified as acute or chronic, with no definite relationship between the two types, although both can be fatal.

Lymphopenia is seen during the acute reaction, with a decrease in both the B- and the T-cell population. Results of the lymphocyte transformation test against nitrofurantoin need not be positive for a patient to display an adverse reaction. The following acute reactions are seen: (1) acute asthma (rare), (2) acute tracheobronchitis with a normal chest roentgenogram (very rare), (3) pleural effusions (usually seen in association with hypersensitivity pneumonitis), and (4) hypersensitivity pneumonitis (the most common response).

The onset of symptoms of the hypersensitivity pneumonitis usually occurs within 2 hours to 10 days after start of the medication (although onset has been known to be delayed as long as 1 year). Typically, the patient has fever, chills, dyspnea, and cough. This response is seen much more quickly after subsequent uses of the drug.

Physical examination often suggests more diffuse involvement than is seen on the chest roentgenogram. Pleuritic pain and pleural rubs may be present.

The roentgenogram reveals diffuse alveolar or alveolar-interstitial infiltrates. Pleural effusions may be present. Various degrees of peripheral eosinophilia can be seen, as well as eosinophils in the sputum.

Treatment is based on discontinuance and avoidance of the drug. Corticosteroids and antihistamines provide symptomatic relief. The infiltrates clear spontaneously within a 24- to 48-hour period.

The chronic reactions occur less commonly and are estimated to represent 3% of all pleuropulmonary reactions to nitrofurantoin. There is no relationship to the acute response, and deaths are more frequently encountered in this type. Two patterns of response occur—interstitial fibrosis and a desquamative interstitial pneumonitis.

The interstitial fibrosis starts insidiously after 6 months to 6 years of therapy. Symptoms are cough and dyspnea without fever, eosinophilia, or pleural effusion. Desquamative interstitial pneumonitis was described in three patients who received the drug for 2 to 5 years. In contrast to the symptoms of interstitial fibrosis, which show only a variable response to corticosteroid therapy, the symptoms of desquamative interstitial pneumonitis reversed well with treatment.

Sulfasalazine is an effective antibiotic for the treatment of inflammatory bowel disease. It has been reported to cause several pulmonary reactions, including BOOP, pulmonary infiltrates with eosinophilia, pulmonary fibrosis, and asthma. Some overlap may exist in these pathologic presentations. Treatment consists of discontinuing sulfasalazine and the administration of corticosteroids. Although most of the side effects of sulfasalazine are considered to be caused by sulfapyridine (the carrier component), mesalamine (the clinically beneficial component without the carrier sulfapyridine) has also been reported to cause pulmonary toxicity.

Pentamidine given intravenously or by nebulizer can cause bronchospasm. Pretreatment with nebulized albuterol or ipratropium may prevent this adverse effect.

Amphotericin B can be associated with impaired pulmonary function, particularly if administered with granulocyte transfusion. This has also been reported with the liposomal form of amphotericin B. The treatment is to stop the medication and administer corticosteroids. Concomitant granulocyte transfusion and administration of amphotericin B should be avoided.

Cardiovascular Agents

Amiodarone hydrochloride, an antiarrhythmic drug, can cause pulmonary toxicity in about 6% of patients receiving the drug. The clinical features include dyspnea, chest pain, cough, elevated sedimentation rate, and diffuse interstitial and patchy alveolar infiltrates in the roentgenogram. Histologically, an accumulation of foamy macrophages in the alveolar spaces, hyperplasia of type II pneumocytes, and widening of alveolar septa are noted. Increased levels of cytosolic free calcium may cause injury. Cessation of the drug and administration of corticosteroids lead to radiographic resolution in about 2 months.

Amiodarone pneumonitis rarely occurs in patients who have been taking the drug in doses of <400 mg/d for <2 months. The diagnosis of amiodarone pneumonitis is really one of exclusion. Pulmonary embolism, congestive heart failure, and pneumonia are the main differential diagnoses in patients suspected of having amiodarone pulmonary toxicity, and they should be excluded first. Computed tomography (CT) of the lung (without the administration of contrast) may be helpful, because amiodarone is an iodinated compound and appears more dense than usual infiltrates of other etiologies. Bronchoalveolar lavage may be helpful in excluding infection. Results of a gallium scan are positive in almost all patients with amiodarone pneumonitis. A positive gallium scan can help differentiate amiodarone pneumonitis from pulmonary embolism or congestive heart failure (in which the gallium scan is negative) as long as infection has been excluded as a cause for the positive scan. In patients receiving amiodarone, a picture suggestive of adult respiratory distress syndrome (ARDS) may develop when they are exposed to a high F_IO_2 (fraction of inspired oxygen), as during anesthesia for surgical procedures. In an unusual presentation, amiodarone pulmonary toxicity may take the form of parenchymal mass lesion(s), which may show cavitation (Table 3).

Angiotensin-converting enzyme (ACE) inhibitors can produce an irritating cough in about 10%–25% of patients receiving them. The cough occurs with all ACE inhibitors, and changing from one to another does not help. Cough usually resolves within 1 to 2 weeks of stopping the medication, which is both diagnostic and therapeutic.

Beta blockers can exacerbate chronic obstructive lung disease and precipitate bronchospasm. Some examples, in decreasing order of likelihood to cause bronchoconstriction, are propranolol, timolol, nadolol, atenolol, and labetolol. They should be used with extreme caution in patients with a potential for bronchospasm.

Hydrochlorothiazide can cause noncardiac pulmonary edema. Patients present with dyspnea, cough, and a low-grade fever within a few hours of taking the medication. The chest roentgenogram shows changes of pulmonary edema; in cases in which the wedge pressure has been measured, it has always been normal. Treatment is supportive, and the patient should avoid the medication thereafter.

Psychotropic Medications

Overdose of tricyclic antidepressants may be associated with pulmonary complications in about a third of cases, usually in the form of noncardiac pulmonary edema or aspiration. Treatment is supportive and may include mechanical ventilation.

A series of three cases of phenothiazine-induced pulmonary edema has been reported. The authors hypothesized that it is neurogenic in origin, caused by hypothalamic dysfunction.

Trazodone overdose has been reported to cause eosinophilic pneumonia and respiratory failure.

Illicit Drugs

The use of illicit drugs has reached epidemic proportions, resulting in an increased incidence of pulmonary toxicity. The pulmonary manifestations relate not only to the substance used, but also to the route of administration. Narcotic addiction remains a major health problem, with noncardiogenic pulmonary edema occurring as a complication of heroin, methadone, and cocaine abuse.

Pulmonary edema develops within a few hours of use, and the patient appears with constricted pupils and depressed respiration. The chest radiograph shows alveolar infiltrates, usually in “bat wing” distribution. Pathologic studies reveal congested, enlarged lungs with an influx of neutrophils and pigmented macrophages. The therapy is supportive, with administration of oxygen, narcotic antagonism, and mechanical ventilation if needed.

Cocaine is a highly addictive substance. Pulmonary complications are related to all forms of administration. Noncardiogenic pulmonary edema can occur with cocaine regardless of the route of administration. Increased membrane permeability probably occurs as a result of alveolar capillary injury. Pulmonary edema has been reported with freebase inhalation, intravenous freebase, and even “body packing” (smugglers swallowing packets of cocaine, which leak into the gastrointestinal tract). Other reported complications of smoking freebase cocaine include barotrauma, massive hemoptysis with diffuse alveolar hemorrhage, interstitial pneumonitis, recurrent pulmonary infiltrates with bronchospasm, and BOOP. Reduced diffusing capacity, decreased expiratory flow rates, and bronchial asthma have also been associated with smoking of freebase cocaine.

An acute pulmonary syndrome temporally related to inhalation of crack cocaine has also been described and is characterized by fever, hemoptysis, alveolar infiltrates, and respiratory failure. The lung tissue in this entity (“crack lung”) reveals alveolar hemorrhage, interstitial and intra-alveolar inflammatory cells, and deposition of IgE in lymphocytes and macrophages. The patients tend to respond to systemic corticosteroids.

Snorting cocaine causes cartilaginous ischemia and can lead to nasal septal perforation. Burns of the oropharynx and larynx can also occur from inhaling hot gases during smoking of freebase cocaine.

Miscellaneous Agents

Estrogens may produce an adverse pulmonary response through a number of mechanisms: pulmonary embolus, drug-induced SLE syndrome, and pulmonary hypertension. It has been estimated that the risk for development of thromboembolic disease in age-matched patients taking oral contraceptives is increased from 5 to 47/100,000. Some associated variables shown to increase the risk include advancing age, obesity, and prolonged bed rest. Thrombogenic risk is directly proportional to

the estrogen content of the oral contraceptives.

Pleural thickening is the most common pleuropulmonary side effect of long-term use of methysergide or bromocriptine. A ground-glass appearance on the chest x-ray film can clear spontaneously with cessation of the drug. A pleural effusion may be seen. Onset may be acute, with pleuritic pain and a rub, or may be more insidious. The effusion may be unilateral or bilateral. Pulmonary fibrosis also has been seen with long-term methysergide use. Onset is slow (6 months to 6 years), with cough and dyspnea. The fibrosis may be diffuse; alternatively, localized areas of pleuropulmonary fibrosis may resemble a mass lesion. The fibrosis may reverse on discontinuance of the drug.

Administration of contrast media is an underestimated cause of drug-induced bronchospasm. Most patients receiving intravenous contrast media show a subclinical reduction in FEV_1 (forced expiratory volume in 1 second) within 5 minutes; this returns to normal within 30 minutes. Severe reactions can occur but are relatively rare.

Esophageal variceal sclerotherapy with either sodium tetradecylsulfate, ethanolamine, or sodium morrhuate can cause changes on chest roentgenograms in up to 85% of patients, but these are rarely of clinical significance. Mediastinal widening resulting from noninfectious mediastinitis occurs in 33% of patients. Pleural effusion occurs in 25% of patients, atelectasis in 10%–15%, and pulmonary infiltrates in 10% of patients. Self-limited fever and chest pain are common in the first 24 hours after the procedure. Serious complications, including ARDS, occur in <2% of patients undergoing esophageal sclerotherapy, and these should be suspected if the fever and chest pain last for >24 hours.

Tocolytic medications (albuterol, terbutaline, ritodrine), used to inhibit uterine contractions during premature labor, can cause noncardiac pulmonary edema in 0.5%–5% of cases. These beta-mimetic drugs produce peripheral vasodilation and an increase in the intravascular fluid volume. When the drug is stopped, the vasomotor tone returns to normal, pushing excess fluid out into the tissues, including the lungs.

Antineoplastic Drugs

The adverse pulmonary responses most often produced by antineoplastic drugs are interstitial pneumonitis and interstitial fibrosis (Table 2). The distinction between these two patterns of response is not sharp, and there may be progression from one state to another. In general, the presentation of interstitial pneumonitis tends to be a systemic hypersensitivity response, with fever, malaise, and a rapid decline in respiratory function. Although both entities can emerge from days to years after a medication is started and resolve during days to months, interstitial pneumonitis is more likely to present earlier and resolve quickly. The pathologic differences are also not profound. Interstitial pneumonitis presents with evidence of larger numbers of inflammatory cells and less fibrosis than does interstitial fibrosis. Of the two, interstitial pneumonitis is the more likely to resolve on discontinuation of the drug.

Common symptoms include dyspnea and cough of insidious onset. The cough is usually dry, although a thick white sputum may be present at times. Malaise, fatigue, and fever are occasionally found. Physical examination generally reveals tachypnea and fine crackles that are heard best in the bases. An interstitial infiltrate is the most common roentgenographic abnormality. Pulmonary function testing is consistent with a restrictive ventilatory defect (low vital capacity or total lung capacity) and a reduced D_LCO; the flow rates are usually preserved. The D_LCO is the most sensitive parameter and can be used to follow the patient as a predictive test. Hypoxemia is common.

Diagnosis is made by lung biopsy. The list of causes of pulmonary infiltrates in the immunocompromised host always includes infection, and infiltrates should be sought with appropriate stains and cultures. Treatment is discontinuance of the agent. Steroids may or may not help but probably should be tried. The response may be followed by serial determinations of PaO_2 (partial pressure of arterial oxygen) and D_LCO and by chest roentgenograms.

Occasionally, factors such as total cumulative dosage, patient age, or prior use of agents that may act synergistically (e.g., radiation) can be used to anticipate an untoward response.

The manifestations of drug-induced pulmonary toxicity caused by antineoplastic agents are listed in Table 2.

Azathioprine

At least six cases of azathioprine hypersensitivity pneumonitis have been reported, but the incidence remains well below 1%.

Bischloroethylnitrosourea

Bischloroethylnitrosourea (BCNU) has been reported to cause interstitial pulmonary infiltrates. One report suggested a dose-related phenomenon; a hacking cough developed in 4 of 28 (14%) patients. The mean cumulative dose in patients with symptoms was 2030 mg/m^2; for those without symptoms, it was 710 mg/m^2. Interstitial infiltrates were seen on the chest roentgenogram in three of the four patients, but all four had interstitial fibrosis on lung biopsy. Symptoms progressed despite cessation of therapy, and one patient died of respiratory failure. Another study could find no dose-dependent relationship but suggested that interstitial infiltrates were more common when BCNU was used concomitantly with cyclophosphamide. Of the 10 patients, nine had received other agents capable of causing interstitial fibrosis. In both studies, the pulmonary function tests commonly showed a decreased D_LCO, PaO_2, and vital capacity. The projected incidence varied from 1.1% to 14%.

Another peculiar complication of nitrosoureas is pneumothorax (Table 3).

Bleomycin

Interstitial fibrosis is the most commonly mentioned adverse pulmonary response to bleomycin. An acute response consisting of cough and dyspnea has been reported, however. These symptoms may occur separately or together, and were found in 6% of 274 patients in one study. The cough may be so severe as to limit use of the drug. The response usually occurs shortly after injection, but a response did not develop in one patient until the eighth month of treatment. Tracheitis also has been described, although infrequently.

Bleomycin is deposited in the skin and lungs, and not unexpectedly, the two organs displaying the most serious side effects are the skin (ulcerations) and the lung (interstitial fibrosis). The pulmonary manifestation appears to be a result of toxic accumulation, although cases have been reported of a hypersensitivity reaction.

Four patients have been described in whom a reversible interstitial pneumonitis developed after they received total doses ranging from 133 to 1000 mg. Two of the four displayed peripheral eosinophilia (12%–16%), and biopsy of one showed eosinophilic infiltration of the distal air spaces. Pleural effusions, interstitial infiltrates, and alveolar infiltrates all appeared on the roentgenograms. Results of immunofluorescence studies for immunoglobulins, complement, and fibrinogen were negative. Corticosteroids were given to three of the four patients, and all four showed resolution of the infiltrates and symptoms.

Interstitial fibrosis occurs in approximately 11% of patients receiving the drug. The incidence is reported to be only 3%–5% when the total dose is below 450 mg, but 35.3% when the level of 500 mg is exceeded. In a histologic study of 37 patients (34 of 37 specimens were obtained at autopsy), 12 of 37 were found to have interstitial pneumonitis at different stages of development. Total doses ranged from 115 to 800 mg/m^2. Histologic changes consisted of fibrinous exudate, atypical proliferation of alveolar cells, hyaline membranes, squamous metaplasia, epithelial dysplasia of distal air spaces, and interstitial and intra-alveolar fibrosis. Alveolar septa were broadened, with edematous fluid and mononuclear inflammatory cell infiltration, and showed signs of extensive fibrosis. Work on animal models indicates that bleomycin-induced lung injury is characterized by an increase in collagen synthesis in the interstitium.

Bleomycin-induced pulmonary toxicity may therefore be seen as a spectrum of changes. The drug is accumulated in the lungs. There may be an initial toxic inflammatory response that later becomes fibrotic. The earlier the response is identified, the more amenable the lung is to full recovery. Fibrotic states are quite resistant to reversibility, even after cessation of the drug and with the use of corticosteroids. The D_LCO may be the most sensitive parameter for following the patient. Factors that appear to increase the toxic potential include (1) advancing age, (2) total cumulative dose (high F_IO_2), and (3) prior radiation to the thorax. The histologic changes of bleomycin-induced interstitial fibrosis resemble those of busulfan lung as well as desquamative interstitial pneumonitis. The chest roentgenogram shows a nonspecific interstitial pattern. The most severe changes in both the histologic picture and the radiographic appearance are in the lung bases and subpleural areas (as opposed to busulfan toxicity, in which the roentgenographic abnormalities are more pronounced near the hilum). Symptoms include dry cough and dyspnea. Physical examination reveals tachypnea, basilar crackles, and concomitant hyperpigmentation of the skin. Diagnosis is by lung biopsy (Fig. 1), although sputum cytology may be of assistance (Fig. 2). Treatment is discontinuance of the drug. Steroids have been effective in some cases. If the patient's condition demonstrates reversibility, the roentgenographic findings (Fig. 3) and pulmonary function test results usually improve.

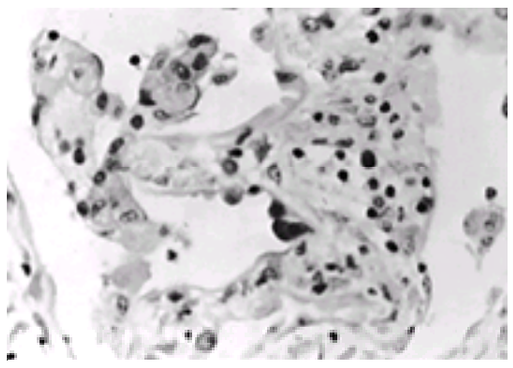

FIG. 1. Bleomycin lung. Hyperplastic alveolar epithelium, septal edema, septal fibrosis, and lymphocytic infiltrates are demonstrated in this open lung biopsy specimen. H&E, ×400. (Photomicrograph courtesy of Dr. G. Gephart, Department of Pathology, Cleveland Clinic Foundation.)

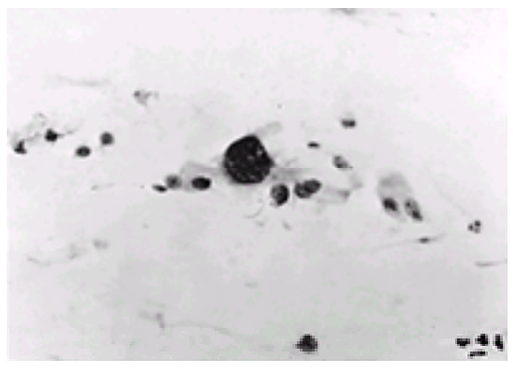

FIG. 2. An atypical cell from bronchial washings of a patient with bleomycin lung. The cell exhibits nuclear enlargement and hyperchromasia. Normal respiratory epithelium is also present. Papanicolaou's stain, x400. (Photomicrograph courtesy of Dr. G. Gephart, Department of Pathology, Cleveland Clinic Foundation.)

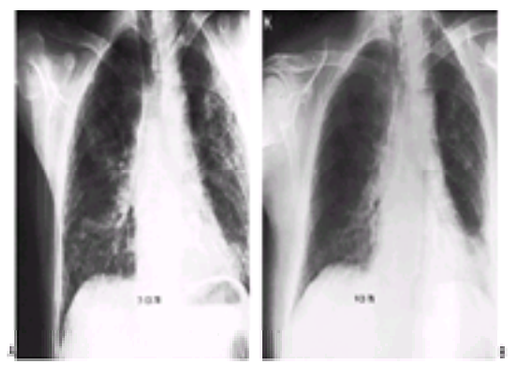

FIG. 3. Bleomycin pneumonitis. **A:** Posteroanterior chest x-ray film showing bilateral interstitial infiltrates. Total dose of bleomycin was 360 mg during 8 weeks. **B:** Marked clearing after steroid therapy. (Reproduced with permission from Brown L, et al. Successful treatment of bleomycin lung. *Cleve Clin Q* 1980;47:99.)

A more recently recognized pulmonary complication of bleomycin is BOOP presenting as nodular lesions mimicking metastasis.

Busulfan

Busulfan is considered the prototypic drug for cytotoxic drug-induced pulmonary damage. The usual case is one of long-term toxic damage to the lungs, with an insidious onset of symptoms after the patient has taken the drug for 3 to 4 years.

Abnormalities are found in pulmonary function tests or on the roentgenogram, or else symptoms are present in 2.5%–11.5% of patients treated with busulfan. Histologic evidence of toxicity can be seen in 12.5%–42.8% of all patients treated.

Histologic changes include organizing fibrinous edema with bizarre atypical cells (probably a type II pneumocyte). Alveolar lining cells and bronchiolar epithelial cells can both appear abnormal and may be dysplastic or neoplastic on sputum cytology. There may be evidence of edema or inflammatory cells in the interstitium or, more commonly, fibrotic changes.

The pulmonary function tests show hypoxemia, restriction, and a decrease in diffusing capacity. The D_LCO can be used to follow patients. Diffuse interstitial and alveolar infiltrates are typically seen on the chest x-ray film, but nodular densities, pleural effusions, or a normal picture may be seen as well.

Symptoms include cough, dyspnea, and fever. Diagnosis is made by sputum cytology or lung biopsy in the appropriate setting. Treatment is discontinuance of the drug and administration of corticosteroids. The damage is not commonly reversible.

Alveolar proteinosis has been reported in a number of patients receiving busulfan (Table 3). Unlike the usual type of alveolar proteinosis, busulfan-induced disease does not respond to therapeutic lavage.

Chlorambucil

Chlorambucil has been implicated as causing interstitial fibrosis in <5.1% of patients. Symptoms include the insidious onset of cough and dyspnea. Physical examination reveals fine basilar crackles and fever. Histopathology reveals alveolar lining cell dysplasia, interstitial round-cell infiltration, and interstitial fibrosis. Signs and symptoms show good reversibility following discontinuance of the drug and use of corticosteroids.

Cyclophosphamide

The pulmonary response to cyclophosphamide is similar to that seen with busulfan, although it is less common. The pulmonary function tests show hypoxemia, a decreased D_LCO, and restriction. Interstitial infiltrates are seen on the chest roentgenogram. Symptoms start insidiously; they include fever, cough, and dyspnea, and may develop after the patient has received the drug for many months. Diagnosis is by lung biopsy. Histologic study shows proliferation of atypical alveolar lining cells. Signs and symptoms may remit with discontinuance of the drug and the administration of corticosteroids.

Melphalan

Pulmonary toxicity is seen in <5% of patients receiving melphalan. Manifestations include interstitial fibrosis, plasma cell interstitial infiltration, and proliferation of bronchiolar and alveolar lining cells.

Methotrexate

An interstitial response to methotrexate may be acute or chronic, and is one of the more reversible of the cytotoxic drug-induced pulmonary reactions. This response has been described following the oral, intravenous, intramuscular, and intrathecal routes of administration.

In some patients, the reaction more closely resembles a hypersensitivity response, with the acute onset of transient hilar lymphadenopathy, eosinophilia, and defervescence with corticosteroids. In other cases, it is more characteristic of a direct toxic action, with fibrosis occurring while the patient is taking corticosteroids and the disability progressing to respiratory failure and death.

In one series, the incidence was 7 of 92, and in another it was approximately 2.5%. The incidence appears to be related to the frequency of dosing rather than to total dose (range, 40 to 6500 mg); the condition is rare, however, in patients receiving 20 mg/week.

There may be synergism with cyclophosphamide, especially in adrenalectomized patients, with an increased frequency and severity of response.

The histologic changes resemble those of desquamative interstitial pneumonitis or busulfan lung (but with fewer abnormal cells). There is alveolar damage, with hyaline membranes and prominent, sometimes atypical, alveolar lining cells; interstitial infiltrates with lymphocytes, plasma cells, and eosinophils; and occasionally, granulomas and giant cells or interstitial fibrosis.

The pulmonary function tests show restriction, hypoxemia, and a decreased D_LCO. There may be significant residual abnormalities following clinical recovery. The diffusing capacity is the most sensitive factor but does not allow detection of toxicity before clinical symptoms appear. The chest roentgenogram may be normal or show nodular or reticular nodular infiltrates in the bases and midlung zones, diffuse alveolar infiltrates, pleural effusions, or hilar lymphadenopathy. There may be permanent changes of pulmonary fibrosis.

The onset of symptoms usually occurs 10 days to 4 months after treatment starts. Typically, symptoms include cough, fever, and dyspnea. Headache and malaise are common prodromal symptoms. The differential diagnosis includes leukemic infiltrates (however, the patient is usually in remission when a methotrexate-induced reaction develops) and opportunistic infection. Diagnosis is by biopsy.

Treatment is cessation of the drug. Corticosteroids may hasten recovery. Approximately 7% of patients progress to interstitial fibrosis, and 8% die of respiratory failure.

Methotrexate also has been implicated as causing a pulmonary reaction that histologically resembles bronchiolitis obliterans.

Mediastinal and hilar adenopathy have also been described in patients receiving methotrexate.

Mitomycin

The incidence of pulmonary toxicity with mitomycin C is about 5%. The D_LCO declines by >20% in approximately one fourth of patients after they have received three cycles of chemotherapy. Unfortunately, the use of serial D_LCO measurements in patients receiving mitomycin cannot predict pulmonary toxicity. Typically, symptoms of cough, fatigue, and dyspnea develop insidiously during several months. The chest x-ray picture shows diffuse reticulonodular infiltrates, and physical examination reveals basilar crackles. Biopsy shows alveolar septal edema and fibrosis, alveolar lining cell hyperplasia, interstitial infiltration with mononuclear and plasma cells, and some atypia of the type II pneumocytes. Prednisone therapy can result in prompt clearing of both symptoms and roentgenographic abnormalities.

Nitrogen Mustard

Unilateral pulmonary edema was seen following instillation of nitrogen mustard into the pleural cavity for control of a recurrent pleural effusion in a patient with breast cancer. Other signs and symptoms included fever, cough, and rales. The reaction was self-limited and was believed to represent a local toxic reaction.

Procarbazine

A hypersensitivity response has been described following the use of procarbazine. It may start within hours of the first dose or may develop after the patient has received the medication for months. Diffuse interstitial infiltrates are seen on the chest roentgenogram. The reaction may terminate in respiratory failure. Pleural effusions and eosinophilia arise. Biopsy shows mononuclear and eosinophilic cell infiltrates and interstitial fibrosis. Diagnosis is by biopsy. Treatment is cessation of the drug and use of corticosteroids. The chest roentgenographic abnormalities may resolve within a month.

Common manifestations of pulmonary toxicity of the various antineoplastic medications are listed in Table 2. Table 3 lists some of the unusual manifestations.

Radiation

The effects of radiation on the lungs are shown in Table 2. Acute radiation pneumonitis can histologically mimic the effects of cytotoxic medications. Changes caused by radiation can resolve completely or progress to become subacute or chronic. Recent studies describe a pulmonary hypersensitivity reaction to radiation, with evidence of lymphocytosis in bronchoalveolar lavage fluid from areas outside the field of radiation. More recently, necrosis of the bronchus (Table 3) has been described following external beam radiation and brachytherapy.

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CHAPTER

23 Upper Respiratory Tract Infections

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INTRODUCTION

The goals of this chapter are threefold:

1. To present the anatomic, microbiologic, pathophysiologic, clinical, diagnostic, and therapeutic aspects of infections of the upper respiratory tract, which comprises the oral cavity, nose, pharynx, retropharyngeal tissues, paranasal sinuses, epiglottis, larynx, trachea, and bronchial tree down to the level of the bronchioles.
2. To clarify the relationship of infections in these areas to other diseases affecting the lungs, and the effects of such infections on ventilatory function in general.
3. To describe the complications of infections of the upper respiratory tract, including the syndromes with which they are associated, and methods of diagnosis and treatment.

INFECTIONS OF THE ORAL CAVITY

Infections of the oral cavity most commonly are odontogenic in origin, and, although rare, local spread to the deep fascial spaces may occur, with subsequent life-threatening parapharyngeal, retropharyngeal, or pleuropulmonary extension. It is beyond the scope of this chapter to describe all potential intraoral infections; only those infections with complications commonly involving the upper respiratory tract are reviewed.

Although the microbiologic aspects of abscesses of odontogenic origin are not fully elucidated, the evidence available suggests that anaerobes are involved at least as frequently as aerobes. The anaerobes involved most often are fusobacteria, *Bacteroides* species, and anaerobic streptococci, whereas the aerobic organisms most frequently isolated are streptococci. Except in hosts compromised by leukemia or diseases in which therapy has resulted in profound neutropenia, facultative gram-negative bacilli and *Staphylococcus aureus* are rarely isolated.

The parapharyngeal space is shaped like an inverted cone, with its base at the skull and its apex at the hyoid bone. Infections of this space may result from peritonsillar abscess, parotitis, mastoiditis, and molar tooth infection. Parapharyngeal abscess may invade the carotid artery or jugular vein, resulting in thrombosis and/or intravascular sepsis, sometimes with metastatic hematogenous spread and development of septic pulmonary emboli. The latter condition is referred to as *Lemierre's postanginal sepsis; Fusobacterium necrophorum* is the leading etiologic agent. Infection may spread to the mediastinum along the carotid sheath or extend into the retropharyngeal space. Appropriate treatment consists of antibiotics, surgical drainage, and emergency ligation of the carotid artery or jugular vein when involved.

The retropharyngeal space is located between the pharynx and prevertebral fascia extending from the base of the skull into the mediastinum. Infection of this space usually results from lymphatic spread to the retropharyngeal lymph nodes with subsequent suppuration and abscess. Afferent drainage to these nodes arises from the nasopharynx, adenoids, and sinuses. Retropharyngeal abscess is mainly a disease of young children, as these lymph nodes atrophy by 3 or 4 years of age. Common causative organisms include *Streptococcus pyogenes* and anaerobic bacteria. Spontaneous rupture into the pharynx may result in aspiration with pneumonia and empyema.

Ludwig's angina is a term that has been loosely applied to a heterogeneous array of infections involving the submandibular and sublingual spaces. First described in 1836, this is a diffuse, bilateral cellulitis of the floor of the mouth and upper cervical areas characterized by toxicity, fever, brawny indurated swelling of the submandibular space, tongue elevation, and dysphagia. A dental source of infection is found in 50%–90% of reported cases, with the second and third mandibular molars most commonly involved. Rapid progression of infection may result in edema of the neck and glottis, thereby precipitating asphyxiation. Treatment requires high-dose parenteral penicillin, airway monitoring, early intubation or tracheostomy when necessary, soft-tissue decompression, and surgical drainage.

RHINITIS

Acute rhinitis is a nonspecific term for infections of the internal nose and may represent the sole or main manifestation of the “common cold.” The common cold is a mild, self-limited, catarrhal syndrome that is the leading cause of acute morbidity and of visits to physicians in the United States. Annual epidemics of upper respiratory tract disease occur in the colder months in temperate areas, with a peak incidence from late August until spring in the United States. The major respiratory viruses causing colds include rhinoviruses, coronaviruses, parainfluenza viruses, and respiratory syncytial viruses. Influenza virus and adenovirus may produce the common cold syndrome but tend to be associated with more severe illness often involving the lower respiratory tract.

The incubation period is variable, averaging 48 to 72 hours. Cardinal symptoms are nasal discharge, nasal obstruction, sore throat, and cough. Median duration of illness is 1 week, although almost one quarter of colds last up to 2 weeks. Diagnosis of the specific virus involved is usually not possible on clinical grounds. Influenza and pharyngoconjunctival fever (adenovirus), however, when seen in a typical epidemiologic setting, can be recognized without benefit of viral culture or serologic tests. The main challenge to the physician is to distinguish the uncomplicated cold from the approximately 0.5% of cases with secondary bacterial sinusitis and the 2% with otitis media. Antibiotics have no place in the management of uncomplicated colds, but decongestants and cough suppressants may be beneficial. Although intranasal recombinant human interferon-a has been effective both as therapy and prophylaxis against rhinovirus infection, local nasal irritation has complicated long-term use, and activity against viruses other than rhinovirus has not been demonstrated.

SINUSITIS

The frontal, ethmoid, maxillary, and sphenoid sinuses are paired cavities, lined with mucosa, in the anterior portion of the skull. Predisposing factors to sinus disease can be categorized as local, regional, or systemic. The most common local predisposing cause of suppurative sinusitis is a viral upper respiratory tract infection. Inflammation and edema in the ostial-meatal complex can obstruct the sinus ostium, leading to hypoxygenation of the sinus, disturbed ciliary and mucous blanket function, and diminished local resistance. Other local nasal factors that cause obstruction in the ostial-meatal complex are nasal polyps, allergic rhinitis, foreign bodies, and nasal septal pathology. In hospitalized patients, nasogastric tubes may functionally obstruct sinus ostia, thereby predisposing to nosocomial sinusitis. The immotile cilia syndrome is another local factor predisposing to sinus disease, but it does not involve structural obstruction of sinus ostia. Regional factors include maxillary dental infections, and predisposing systemic factors include malnutrition, diabetes mellitus, long-term corticosteroid therapy, hypogammaglobulinemia, blood dyscrasias, and chemotherapy.

Although normal paranasal sinuses have long been thought to be sterile, transient colonization with organisms normally populating the upper airway may occur. Overgrowth of this transient resident flora may produce infection when local clearance mechanisms are impaired. In all studies of acute community-acquired maxillary sinusitis, >50% of isolates are either *Streptococcus pneumoniae* or unencapsulated *Haemophilus influenzae,* with *S. pyogenes, Branhamella catarrhalis,* and gram-negative bacilli accounting for the rest. Specimens for culture should be obtained by direct sinus aspiration, because nasal swabs and/or irrigation correlate with aspiration <65% of the time. When appropriate anaerobic cultures are performed, anaerobes can be isolated in at least 10% of acute cases, with a higher isolation rate of approximately 50% in chronic sinusitis. A mixed anaerobic infection with *Bacteroides* and anaerobic streptococci would suggest infection of odontogenic origin. Viruses have been isolated in approximately 15% of cases, usually in conjunction with or preceding bacterial infection. Invasive aspergillosis and rhinocerebral

phycomycosis occur in immunocompromised patients with granulocytopenia or uncontrolled diabetes mellitus with ketoacidosis, respectively.

Symptoms and signs suggesting acute sinusitis include purulent nasal discharge, facial pain or tenderness, nasal congestion, cough, fever, and a history of recent upper respiratory tract infection. In sphenoid sinusitis, headache is the most common initial symptom. Patients with chronic sinusitis often present with protracted nasal congestion, purulent nasal discharge, and facial pain. Because the typical complaints of acute sinusitis overlap with those of a prolonged but uncomplicated common cold, it may be difficult to make a diagnosis of sinusitis on clinical grounds. Valuable information may be obtained from transillumination of the maxillary and frontal sinuses. The finding of complete opacity of the sinus is strong evidence for the presence of active infection; conversely, the finding of normal light transmission is equally good evidence that no infection is present. Dullness, but not complete opacity, is less helpful. The most sensitive routine test for the diagnosis of acute sinusitis is radiologic examination of the sinuses; opacification, an air-fluid level, or mucosal thickening is strong evidence of active infection. The value of sinus radiology in patients with chronic sinusitis is limited, because radiographic abnormalities are persistent in such patients. Computed tomography (CT) and magnetic resonance imaging (MRI) are particularly useful in the examination of the ethmoid and sphenoid sinuses and for evaluation of suspected intracranial or orbital extension of infection.

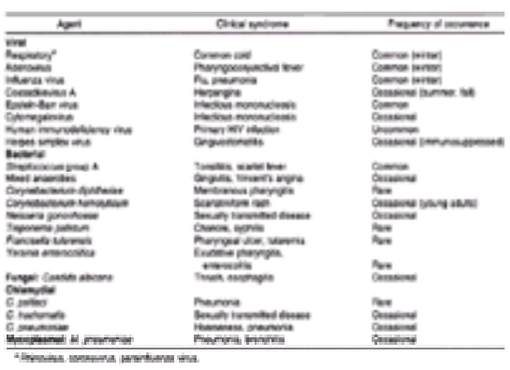
Nasal decongestants should be used in the supportive treatment of acute sinusitis, but antihistamines are to be avoided, as they may thicken purulent sinus fluid and impair drainage. Because sinus aspiration to determine a specific microbial etiology is not routinely indicated, empiric antimicrobial therapy should be primarily effective against *S. pneumoniae* and *H. influenzae.* Ampicillin or amoxicillin is recommended for the initial treatment of uncomplicated acute sinusitis. Sinusitis caused by b-lactamase-producing bacteria, including some strains of *H. influenzae* and *B. catarrhalis,* requires treatment with b-lactamase-resistant antimicrobial agents, such as amoxicillin/clavulanate, second-generation cephalosporins, trimethoprim/sulfamethoxazole, and the newer macrolides, azithromycin and clarithromycin.

Patients with cystic fibrosis or immotile cilia syndrome are predisposed to *Pseudomonas aeruginosa* and *Staphylococcus aureus* infection, whereas immunocompromised patients and patients with nosocomial sinusitis have a higher incidence of aerobic gram-negative bacterial infections, which are often polymicrobial. As mentioned earlier, cultures from patients with chronic sinusitis are often polymicrobial, and at least half harbor anaerobes. Empiric antimicrobial therapy in these unique clinical settings must be adjusted accordingly.

The principal goals of sinus surgery are to oxygenate, establish drainage, and remove diseased mucosa. Candidates for surgical intervention include those patients who have failed empiric therapy, who have rhinocerebral complications, or who have nosocomial infections or immunodeficiency. In addition, most patients with ethmoid or sphenoid disease or chronic sinusitis require corrective surgery. Therapy for fungal sinusitis requires immediate surgical debridement coupled with administration of systemic amphotericin B.

PHARYNGITIS

Acute pharyngitis is an inflammatory condition of the pharynx, and its principal symptom, sore throat, is a frequent accompaniment of many other respiratory illnesses. Many of the known microbial causes of pharyngitis are listed in Table 1, with the most common being group A streptococci, various respiratory viruses, and the Epstein-Barr virus associated with infectious mononucleosis. For the clinician, it is most important to differentiate viral from streptococcal pharyngitis, because of the latter's response to penicillin therapy and its potential sequelae of acute rheumatic fever and acute glomerulonephritis.



Agent	Clinical syndrome	Frequency of occurrence
Viral		
Respiratory[a]	Common cold	Common (winter)
Adenovirus	Pharyngoconjunctival fever	Common (winter)
Influenza virus	Flu, pneumonia	Common (winter)
Coxsackievirus A	Herpangina	Occasional (summer, fall)
Epstein-Barr virus	Infectious mononucleosis	Common
Cytomegalovirus	Infectious mononucleosis	Occasional
Human immunodeficiency virus	Primary HIV infection	Uncommon
Herpes simplex virus	Gingivostomatitis	Occasional (immunosuppressed)
Bacterial		
Streptococcus group A	Tonsillitis, scarlet fever	Common
Mixed anaerobes	Gingivitis, Vincent's angina	Occasional
Corynebacterium diphtheriae	Membranous pharyngitis	Rare
Corynebacterium hemolyticum	Scarlatiniform rash	Occasional (young adults)
Neisseria gonorrhoeae	Sexually transmitted disease	Occasional
Treponema pallidum	Chancre, syphilis	Rare
Francisella tularensis	Pharyngeal ulcer, tularemia	Rare
Yersinia enterocolitica	Exudative pharyngitis, enterocolitis	Rare
Fungal: Candida albicans	Thrush, esophagitis	Occasional
Chlamydial		
C. psittaci	Pneumonia	Rare
C. trachomatis	Sexually transmitted disease	Occasional
C. pneumoniae	Haemophilus pneumonia	Occasional
Mycoplasmal: M. pneumoniae	Pneumonia, bronchitis	Occasional

[a] Rhinovirus, coronavirus, parainfluenza virus.

TABLE 1. *Microbial agents associated with pharyngitis*

Viruses account for the majority of cases of pharyngitis in adults; mild-to-moderate pharyngeal discomfort frequently accompanies common colds. Sore throat is a major complaint in some patients with influenza, and the accompanying myalgia, headache, fever, and cough readily suggest the diagnosis. Adenoviral pharyngitis is usually more severe than the illness typical of the common cold, and conjunctivitis is a distinguishing feature present in one third to one half of cases. The presence of vesicles or shallow ulcers of the palate is characteristic of primary infection with herpes simplex virus, although gingivostomatitis is a more common presentation than acute pharyngitis. During the summer and fall months, pharyngitis caused by coxsackievirus, so-called herpangina, can be distinguished by the presence of small vesicles on the soft palate, uvula, and anterior tonsillar pillars. Exudative tonsillitis, fever, cervical adenopathy, and fatigue are characteristic features of infectious mononucleosis caused by Epstein-Barr virus, and approximately half of cases have associated generalized adenopathy or splenomegaly. Febrile pharyngitis has now been described as a characteristic feature of primary infection with human immunodeficiency virus, and it may mimic the mononucleosis syndrome.

Approximately 15% of all cases of pharyngitis are caused by group A streptococci, the bacterial pathogen most commonly isolated from patients of school age. It is not clear whether non-group A b-hemolytic streptococci, such as groups C and G, cause pharyngitis in nonepidemic settings. The severity of infection varies considerably, but generally there is marked pharyngeal pain, dysphagia, tender cervical adenopathy, and fever. In the majority of cases, an etiologic diagnosis is not possible on clinical grounds alone. For patients with mild illness, a throat culture should be obtained, with treatment dependent on a positive result. For patients with more severe clinical presentations, in whom prompt antimicrobial therapy would be beneficial, a rapid streptococcal antigen test should be performed. A positive result establishes the diagnosis of streptococcal pharyngitis, whereas a negative test result should be substantiated by a simultaneous throat culture.

The incidence of diphtheria has fallen dramatically in the past 50 years, but outbreaks still occur in unvaccinated populations in the United States. Most cases occur in the Southwest among blacks, Mexican-Americans, and American Indians. Pharyngeal diphtheria is characterized by small areas of exudate that coalesce to form a light- to dark-gray membrane that becomes progressively thicker and more difficult to remove. The condition usually involves little toxicity and only modest temperature elevation. Membranous spread to the larynx and trachea can cause life-threatening respiratory obstruction, characterized by inspiratory stridor and cyanosis. Secondary infection with streptococci or other bacteria may occur, and in such cases, toxicity, fever, and local pain may increase markedly. Lymphadenitis and subcutaneous swelling may result in a “bull neck” appearance. *Corynebacterium haemolyticum* has been increasingly identified as a cause of exudative pharyngitis in adolescents and young adults, and such infection may be associated with an erythematous, maculopapular, sometimes pruritic skin rash. Effective antimicrobial agents for either *C. diptheriae* or *C. haemolyticum* include penicillin, erythromycin, and tetracycline.

Pharyngitis accompanying sexually transmitted disease caused by *Neisseria gonorrhoeae, Chlamydia trachomatis,* and *Treponema pallidum* is not uncommon, but these agents would be rare causes of pharyngitis in an unselected general population. Gonococcal pharyngitis is being detected with increasing frequency, probably because of improved microbiologic isolation techniques and changes in patterns of sexual behavior. Asymptomatic gonococcal throat colonization is much more common than pharyngitis, as various series have shown that no more than 30% of those with positive pharyngeal cultures have any clinical manifestations. Ceftriaxone, administered intramuscularly in a single dose of 250 mg, is the drug of choice. Although *C. trachomatis* has been isolated from patients with pharyngitis, asymptomatic throat colonization occurs more often. Rarely, syphilis may present as a primary pharyngeal chancre.

Although exudative pharyngitis with cervical lymphadenopathy may complicate infection with *Yersinia enterocolitica* and *Francisella tularensis,* other manifestations of these systemic diseases usually dominate the clinical picture, and isolated pharyngeal disease would be quite rare. Similarly, when *Chlamydia psittaci, C. pneumoniae,* and *Mycoplasma pneumoniae* are associated with pharyngitis, the pharyngeal disease generally tends to accompany tracheobronchitis or pneumonia rather than occur as an isolated event.

EPIGLOTTITIS

First described in an adult, epiglottitis is a life-threatening disease observed most frequently in 1- to 6-year-old children, most often during the fall and winter. It is important to emphasize, however, that epiglottitis has been increasingly reported in adults during the past three decades. *Supraglottitis* may be the preferred term, as the infection involves the arytenoids, the aryepiglottic folds, and the epiglottis while sparing the pharynx, true vocal cords, and trachea. The infection can be primary or secondary to adjacent infections or trauma, and can result in acute diffuse inflammation, acute ulcerative inflammation, or epiglottitis with abscess formation on the free

edge, laryngeal surface, or lingual surface.

Acute epiglottitis develops in two distinct forms: gradually, within days, usually following an upper respiratory tract illness; or accelerated, within hours. The characteristic early symptoms are sore throat and dysphagia. Odynophagia thereafter becomes the predominant symptom and may be so severe that the patient would rather not eat or drink. The voice tends to be muffled rather than hoarse, and the temperature is usually strikingly elevated. Respiratory distress with tachypnea, dyspnea, and cyanosis occurs late and heralds acute airway obstruction. In this setting, the patient will be observed drooling, sitting up, leaning forward, and breathing quite deliberately. Examination should not be performed with the patient in the recumbent position. Despite the prominence of pain, the pharynx is usually normal in appearance. Attempts to visualize the epiglottis must be carried out with great caution, as even the slightest trauma can provoke acute respiratory obstruction. Auscultation of the chest may reveal inspiratory stridor. Cervical lymphadenopathy is present in about 25% of cases.

Roentgenograms of the chest often show hyperinflation, and there may be areas of atelectasis or pneumonitis. The epiglottic swelling can be seen on a lateral x-ray film of the neck. Laboratory examination shows an elevated white blood cell count with an increase in mature polymorphonuclear leukocytes and band forms.

Complications include septic arthritis, meningitis, empyema, and mediastinitis. Asphyxia and cardiopulmonary arrest are dreaded complications, and several factors contribute to the pathogenesis of respiratory tract obstruction. Edema of the lingual mucosa of the epiglottis causes curling of the epiglottis posteriorly and inferiorly, narrowing the air space, and edema of the aryepiglottic folds worsens the obstruction. During inspiration, these swollen structures are drawn downward into the airway, further reducing the size of the lumen. Inflammation of the supraglottic structures inhibits swallowing, leading to an accumulation of secretions and saliva that further compromises the airway.

Acute epiglottitis is a bacterial infection, as viruses have not been conclusively linked to the disease. In 80% of cases in children, *H. influenzae* type b can be isolated from the epiglottis and/or bloodstream. In adults, however, the etiologic agent is not always obvious, and blood cultures are negative in 70%–85% of cases. *H. influenzae* type b accounts for 20%–25% of cases in adults, with *Streptococcus pneumoniae,* b-hemolytic streptococci, viridans streptococci, nonencapsulated *H. influenzae, Moraxella catarrhalis,* and *Staphylococcus aureus* occasionally implicated. No etiologic agent can be recovered in up to 40% of adult cases.

The diagnostic and therapeutic approach depends on the clinical presentation. Unstable patients with “classic” epiglottitis (stridor, drooling, dyspnea, and fever) should be taken immediately to the operating room for direct laryngoscopy and nasotracheal or endotracheal intubation. Preparation should be made for emergency cricothyrotomy if intubation is not possible. The majority of adults and a large number of children, however, do not have classic presentations, and their management is less straightforward. In adults, indirect laryngoscopy or flexible nasal endoscopy is safe in the initial assessment, as no complications have been reported with this approach. Radiography, however, remains useful in differentiating other upper airway pathology (e.g., foreign body or abscess) from epiglottitis. In children, manipulating the upper airway is more hazardous, and radiography should be the initial procedure performed when suspicion of epiglottitis is low to moderate. The epiglottis of a stable child with normal radiographic findings should be visualized to rule out normal radiograph epiglottitis. Whereas intubation or tracheostomy is virtually mandatory in children with epiglottitis, whether this is appropriate in the management of adults remains a point of ongoing controversy. It is reasonable in adults to defer airway intervention as long as close follow-up by individuals specifically skilled in emergency airway control can be ensured. Stridor and infection with *H. influenzae* type b appear to increase the likelihood of acute airway obstruction.

Antimicrobial therapy should be directed against the common etiologic agents, and ampicillin/sulbactam, chloramphenicol, and second- or third-generation cephalosporins are reasonable choices until bacteriologic data are available. Although often administered in the hope of diminishing supraglottic edema, corticosteroids have not been conclusively shown to alter the course of the disease. Immunization against *H. influenzae* should reduce the incidence of childhood epiglottitis. The risk for development of invasive *H. influenzae* infection is considerably increased in both siblings and parents of patients with epiglottitis, and rifampin prophylaxis should be administered to these household contacts.

LARYNGOTRACHEOBRONCHITIS

Unlike epiglottitis, which is a bacterial disease, laryngotracheitis (croup) is usually the result of a viral infection. Peak incidence is in late fall, with a smaller peak in late spring; a pattern related to the prevalence of parainfluenza viruses in the community has been observed. The subglottic area and trachea are involved, whereas the area above the true vocal cords is spared. In children, croup usually occurs in the first half-decade of life and begins with rhinorrhea. The first sign of spread to the larynx is the gradual development of a harsh, barking cough and hoarse voice. Fever is variable. The major clinical features of croup are related to inflammatory edema and fibrinous exudate in the subglottic area, which narrows the airway and causes inspiratory stridor. Inflammation and edema commonly extend down the trachea and bronchi, producing thick, viscid secretions and ventilation-perfusion mismatch. Involvement of these lower airways, superimposed on the already-narrowed subglottic area, results in increased work of breathing and hypoxemia. As many as 3% of patients admitted with acute laryngotracheobronchitis may require an artificial airway for relief of obstruction, and this chance may reach 6% if sternal and chest wall retractions are present.

The findings on chest roentgenograms vary from normal to evidence of hyperaeration and sometimes areas of atelectasis. The white blood cell count is usually normal, and there may be a predominance of lymphocytes. Parainfluenza virus types 1 through 3 has been implicated most frequently, but influenza virus, respiratory syncytial virus, coronavirus, rhinovirus, adenovirus, enterovirus, and coxsackievirus are all capable of producing the disease. Measles is an infrequent cause.

For the clinician, the initial step in management is to distinguish croup from epiglottitis (Table 2). Treatment of croup in children consists of creating an atmosphere of cool, moist air and administering oxygen in a humidified milieu to avoid drying of the respiratory tract. Antibiotics ordinarily are not necessary. The use of adrenal glucocorticoids and/or racemic epinephrine is controversial, particularly the latter.

Feature	Croup	Epiglottitis
Patient age	Younger (6 mo–3 y)	Older (3–6 y)
Season	Late spring, late fall	All year
Antecedent illness	Rhinorrhea	Uncommon
Clinical appearance	Child is lying down	Child is sitting
	Nontoxic condition	Toxic condition
	Not drooling	Drooling
Cough	Barking in quality	Absent
Voice	Hoarse	Muffled
Fever	Variable	High-grade
Leukocytosis	Absent	Present
Progression	Usually slow	Rapid
Causative agent	Parainfluenza virus type 1	*Haemophilus influenzae* type b

TABLE 2. *Distinguishing features of croup and epiglottitis*

Laryngotracheitis is more complex etiologically in adults and in both children and adults compromised by hematologic malignancy or neutropenia. In noncompromised adults, laryngotracheitis is often manifested by hoarseness and substernal pain, frequently of a burning quality. Influenza virus, parainfluenza virus, and adenovirus are the likely offending agents, but in addition, bacteria (particularly *H. influenzae*) and *M. pneumoniae* can produce the syndrome. If the patient is compromised and neutropenic, opportunistic organisms such as *P. aeruginosa* and species of *Klebsiella, Serratia,* and *Enterobacter* can be responsible. If the individual has defective delayed immune mechanisms and oral thrush is present, the *Candida* infection may move from the oropharynx to the larynx and trachea. In patients who are receiving immunosuppressive agents for severe underlying disease, herpesvirus 1 or 2 may cause laryngotracheitis, and the use of multiple antibiotics in a compromised host may encourage candidal superinfection.

In healthy adults with laryngotracheitis, failure to improve with supportive therapy mandates obtaining a tracheal culture for both viruses and bacteria. In the compromised host, if cough specimens or blood cultures do not show a presumed etiologic agent, it is necessary to obtain proper cultures by laryngoscopy, tracheal intubation, or bronchoscopy. These procedures may be difficult in such persons if thrombocytopenia is present; sometimes broad antimicrobial therapy must be given in the absence of a precise microbial diagnosis, but this is obviously undesirable, and whenever possible, therapy should be guided by proper Gram's stains and cultures.

Bacterial tracheitis in infants and older children has features of both epiglottitis and croup. Clinically, it is characterized by fever, toxicity, brassy cough, and often inspiratory stridor. In most cases, chest roentgenograms show patchy or focal infiltrates. The epiglottic and aryepiglottic folds appear normal on direct examination, but subglottic edema is present. Purulent secretions that are often profuse and thick can be seen, and these can produce tracheal obstruction. The isolated organism is often *S. aureus,* and there is a satisfactory response to appropriate antimicrobial agents. Endotracheal intubation is usually required to maintain a patent airway and handle copious secretions.

ACUTE BRONCHITIS (OR TRACHEOBRONCHITIS)

Acute inflammatory disease of the trachea and bronchi can be caused by a variety of stimuli, including constituents of tobacco and cannabis; ammonia; trace metals, such as vanadium and cadmium; air pollutants, such as sulfur dioxide; nitrogen dioxide; vegetable substances, such as bagasse, cotton, flax, hemp, and paprika; and a farrago of infectious agents, including viruses, mycoplasmas, bacteria, and parasites.

The role of viruses in bronchial disease has been defined best by the Tecumseh studies of respiratory illness. Infectious agents include respiratory syncytial virus, rhinovirus, echovirus, parainfluenza types 1, 2, and 3, herpesvirus, coxsackievirus, influenza, coronavirus, and adenovirus. It is virtually impossible to separate one virus from another clinically. All those capable of producing pharyngeal and nasal disease also can cause bronchitis. Some assumptions can be made on the basis of age and season of the year. In the very young, respiratory syncytial virus, parainfluenza types 1 through 3, and coronavirus are most frequently isolated. Among patients from 1 to 10 years of age, parainfluenza types 1 and 2, enterovirus, respiratory syncytial virus, and rhinovirus predominate. Above that age, influenza A and B, respiratory syncytial virus, and adenovirus are found most frequently. Parainfluenza types 1 and 3 and rhinovirus are found most frequently in the fall; influenza, respiratory syncytial virus, and coronavirus cause infections for the most part in winter and early spring, whereas enterovirus induces infections in summer and early fall. There are differences in the capability of the different viruses to produce lower respiratory tract disease; for example, the disease caused by parainfluenza virus is likely to be more severe than that caused by rhinovirus.

The bacteria most often recovered in acute purulent bronchitis are *H. influenzae, Streptococcus pneumoniae,* and *Moraxella* (*Branhamella*) *catarrhalis.* Acute bronchitis and transient mild pneumonitis are sometimes early manifestations of *Salmonella typhosa* infection. *Bordetella pertussis* is responsible for whooping cough in children; it is less well appreciated that it also may cause acute and subacute bronchitis in adults, as may *Legionella* infections.

There is increasing evidence that yeasts and fungi may produce bronchitis in the absence of parenchymal disease. This is true of *Candida albicans* and *C. tropicalis, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis.* In the older literature, candidal bronchitis has been described in otherwise healthy hosts, but more recently it appears to be restricted to compromised hosts. *Geotrichum candidum* is also occasionally a cause of acute and subacute bronchitis.

As serologic analyses are performed more regularly, it has become clear that both *M. pneumoniae* and *C. pneumoniae* not infrequently cause acute bronchitis. Bronchitis also can occur during the migration of *Strongyloides* and *Ascaris* larvae, and a few cases of paroxysmal cough caused by the parasite *Syngamus laryngeus* have been reported either in residents of or visitors to Brazil, the Philippines, the West Indies, Puerto Rico, and British Guiana.

Cough is uniformly found in acute bronchitis, and it may be productive of mucoid or purulent sputum. The nature of the sputum may be helpful diagnostically. Except for adenovirus infections, the sputum in viral infections is almost always characterized by marked predominance of mononuclear cells on Gram's or Wright's stain. In contrast, in bacterial infections the sputum shows a predominance of polymorphonuclear leukocytes. *Mycoplasma* infections, like adenovirus infections, are usually associated with mononuclear cells, but there may be a striking predominance of polymorphonuclear leukocytes.

The cough may be accompanied by variable amounts of hemoptysis and/or substernal pain that is often described as being of a burning quality; it is usually accentuated on inspiration. Usually, the temperature is only minimally to moderately elevated; physical examination often shows harsh breath sounds, rhonchi, and variable amounts of expiratory wheezing.

Wheezy bronchitis is a specific clinical entity occurring for the most part in children who have a tendency to wheeze and a family history of atopy. Viruses appear etiologically related in only a minority of cases; rhinovirus and respiratory syncytial virus are the agents that have been most often isolated. The syndrome of intermittent, recurrent wheezy bronchitis in children also may result from reduced esophageal sphincter tone with reflux.

The organisms responsible for bronchitis in the compromised host may be quite different from the agents affecting the uncompromised individual. In older persons and immunocompromised hosts, herpes simplex virus type 1 may cause tracheobronchitis that may be manifested primarily by bronchospasm. Intravenously administered acyclovir is the treatment of choice. Such patients are also susceptible to gram-negative infections caused by species of *Klebsiella, Serratia, Enterobacter,* and *Pseudomonas.* If these gram-negative superinfections occur during antibiotic treatment of infections elsewhere, the organisms may be markedly resistant to antibiotics. The pharynx of alcoholics is colonized more frequently than the pharynx of nonalcoholics by enteric gram-negative organisms, particularly *Enterobacter* species and *Escherichia coli.* Pharyngeal colonization may be followed by aspiration and acute bronchitis.

The treatment of acute tracheobronchitis depends on the clinical setting in which it arises, the Gram's stain of expectorated sputum, the appearance of the sputum, and the findings on physical examination of the chest. If there are myriad polymorphonuclear leukocytes in the sputum, this suggests a bacterial etiology, and antibiotic administration can be predicated on the predominant organisms seen on smear. The bronchitis is not usually so severe as to mandate immediate therapy, and antimicrobial agents can be withheld until culture results are available. If no likely etiologic agent is recovered in culture and there are many polymorphonuclear cells in the sputum, the possibility of *M. pneumoniae* infection should be strongly considered. This usually responds to treatment with erythromycin or tetracycline.

If on routine culture no pathogenic micro-organisms are found and the sputum shows a polymorphonuclear predominance, acid-fast stains also should be obtained, and in appropriate geographic areas, potassium or sodium hydroxide preparations of sputum should be used to search for fungi and parasites.

The presence on physical examination of focal areas of diminished breath sounds suggests that inspissated mucus has caused atelectasis. This may be relieved by the use of humidifiers, bronchodilators, vigorous coughing, and, if needed, tracheal suction. Occasionally, there is diffuse diminution of air intake and/or inspiratory stridor; these findings indicate obstruction of major bronchi or the trachea, which requires sequentially vigorous coughing, suctioning, and intubation or even tracheostomy if needed.

The choice of antibiotic depends on the pathogen involved. There are striking differences in the penetration of antimicrobial agents into the bronchial secretions. However, it is still unclear whether the degree of antibiotic penetration can be related to clinical outcome. For empiric treatment of community-acquired acute purulent bronchitis, amoxicillin, second-generation cephalosporins, erythromycin, or tetracycline would be a reasonable choice. The newer macrolide antimicrobial drugs, clarithromycin and azithromycin, are very attractive agents for this indication, as their spectrum of activity includes the usual bacterial etiologic agents as well as *Mycoplasma* and *Chlamydia.* The choice of antimicrobial agent in nosocomial or ventilator-associated tracheobronchitis should be tailored to the specific organism isolated.

Acute bronchitis is ordinarily not a life-threatening disease. This permits an orderly search for a microbial etiology, careful assessment of environmental exposures, and evaluation for foreign body or esophageal reflux (or a tracheoesophageal fistula in infants). In most cases, supportive therapy, including adrenergic bronchodilators by aerosol if needed, suffices. If the bronchitis persists, fiberoptic bronchoscopy may be advisable. The disease may last for 6 to 8 weeks. A specific diagnosis can often be made only by the study of paired sera for rises in antibody titers against specific viruses. Exacerbations of chronic bronchitis in patients with chronic obstructive pulmonary disease are discussed in Chapter 43.

BRONCHIOLITIS

In the strictest sense, bronchiolitis, a disease of small airways, should be considered an illness of the lower respiratory tract; it is so frequently preceded by an infection of the upper respiratory tract, however, that it is included in the present chapter. Bronchiolitis is a disease of children. The annual incidence is six to seven cases per 100 children, with most cases occurring during the first 2 years of life.

Bronchiolitis was first described as a complication of measles and mumps, but in more recent years, it has been associated with most of the respiratory viruses, especially the respiratory syncytial virus. Although most cases of bronchiolitis are caused by viruses, *H. influenzae* type b and *M. pneumoniae* have been implicated in some cases. Outbreaks usually occur in winter and spring in temperate climates, epidemics usually being associated with respiratory syncytial virus, adenovirus, influenza, or parainfluenza virus.

Airways from 75 to 300 mm in diameter are involved. Following invasion by microorganisms, cellular infiltration and edema occur together with bronchiolar epithelial proliferation and necrosis. Mucous secretion is increased, after which mucus, inflammatory exudate, and cell debris obstruct the bronchioles. Adenoviruses cause a more severe disruption of the mucosa than do respiratory syncytial viruses and produce a necrotizing bronchiolitis, with a resultant higher mortality.

The initial symptoms of nasal discharge and cough are indistinguishable from those of the common cold. Within 1 to 2 days, fever and cough become prominent and are soon followed by tachypnea and suprasternal, substernal, and subcostal retraction. To prevent coughing and reduce the work of breathing, infants and children take rapid, shallow breaths. Deep breaths are accompanied by fine rales and diffuse expiratory wheezing and usually trigger a paroxysm of coughing. Hypercapnia and

cyanosis commonly occur as the work of breathing increases, and infants under 6 months of age may present with apnea.

The peripheral white blood cell count may be normal or moderately elevated. Blood gas analysis typically shows profound hypoxemia. Chest roentgenograms reveal hyperinflation, increased bronchial markings, and frequently areas of atelectasis or infiltrate. Densities on chest films may be more striking than the degree of clinical or radiographic evidence of small-airway obstruction, and thereby they may be misinterpreted as pneumonia. It should be emphasized, however, that these pulmonary densities represent predominantly areas of atelectasis.

A specific diagnosis often can be made retrospectively by study of paired sera for antiviral or antimycoplasmal antibodies. Nasopharyngeal secretions can be obtained for viral culture, but growth may require up to 14 days. Respiratory syncytial viral infection can be diagnosed rapidly by antigen detection using immunofluorescence techniques or ELISA (enzyme-linked immunosorbent assay).

In children under 2 years of age, the disease may be life-threatening, and therapy consists of oxygen and supportive treatment, with particular attention to proper ventilation. Corticosteroids are not effective. The value of aminophylline or b_2-adrenergic agents has not been established, although bronchodilators are frequently employed in the management of severely ill children. Ribavirin delivered by small-particle aerosol has been shown to hasten the clinical recovery and decrease virus shedding, although these effects are not dramatic. However, because it may cause irritation of the mucous membranes in caretakers, it is often delivered via an endotracheal tube in a closed system. Although antibiotics are not indicated in most children with bronchiolitis, nosocomial bacterial infections can occur in children receiving intensive supportive care. If the bronchiolitis occurs in fall and early winter, erythromycin should be considered for the possibility of *M. pneumoniae* infection. The incidence of nosocomial spread of respiratory syncytial viral infections is high, and preventive precautions should be implemented.

There is a high frequency of residual lung disease after an acute episode of bronchiolitis. In one series, most children studied 10 years after the disease showed some abnormality, including hyperinflation, small-airway disease, or abnormal gas exchange.

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CHAPTER

24 Community-Acquired Pneumonia

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INTRODUCTION

Community-acquired pneumonia affects almost 4 million adults annually in the United States, and as much as one fifth of these require hospitalization. Pneumonia is the sixth leading cause of death, and the No. 1 cause of death from infectious diseases. In addition, community-acquired pneumonia accounts for 1% of all patient visits to primary care providers who treat adults. In the outpatient setting, the mortality rate of pneumonia is <5%, but among patients with pneumonia who require hospitalization, mortality rates approach 25%, especially if the individual requires admission to the intensive care unit.

ETIOLOGY

No specific causative organism can be established in 30%–65% of patients with community-acquired pneumonia, despite vigorous bacteriologic and serologic testing for specific pathogens. The incidence of pneumonia attributable to individual pathogens varies considerably and depends on factors such as age, presence or absence of underlying disease, integrity of the immune response, and residence in long-term care facilities (Table 1). It is important to remember that 70%–80% of patients in whom community-acquired pneumonia develops are older than 60 years or have a coexisting medical condition. Those patients are more likely to be colonized with enteric gram-negative bacilli, staphylococci, and *Moraxella catarrhalis* than are young, otherwise healthy persons (Table 2). These epidemiologic differences mandate using individualized diagnostic and treatment strategies based on age and the presence or absence of coexisting medical conditions. At the same time, the therapeutic approach may of necessity be largely empiric, as determination of the specific etiologic pathogen is frequently impossible.

Pathogen	Percentage of cases (range)
Streptococcus pneumoniae	39 (9–76)
Haemophilus influenzae	10 (0–46)
Legionella species	5 (0–15)
Chlamydia species	5 (0–16)
Aerobic gram-negative bacilli	4 (0–20)
Viruses, including influenza virus	4 (0–18)
Staphylococcus aureus	3 (0–10)
Unknown	30 (0–49)

[a] Literature review of selected community-acquired pneumonia studies.

TABLE 1. *Prevalence of micro-organisms that cause community-acquired pneumonia*[a]

Condition	Commonly encountered pathogens
Alcoholism	Oral anaerobes, gram-negative bacilli, *Streptococcus pneumoniae*
COPD	*S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, gram-negative bacilli
Influenza season	*S. pneumoniae*, *Staphylococcus aureus*, influenza virus
Nursing home residency	*S. pneumoniae*, gram-negative bacilli, oral anaerobes, *H. influenzae*, *S. aureus*
HIV infection	*Pneumocystis carinii*, *S. pneumoniae*, *H. influenzae*, *Mycobacterium tuberculosis*

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

TABLE 2. *Epidemiologic conditions related to specific pathogens in patients with community-acquired pneumonia*

DIAGNOSTIC STUDIES

The diagnosis of pneumonia is based on clinical findings that include respiratory symptoms (cough, sputum production, dyspnea, pleurisy), fever, abnormal sounds on chest auscultation, leukocytosis, and an infiltrate on chest film. These findings, however, may not be present in all persons with depressed immunity, in the elderly, or in individuals with so-called atypical pneumonia. Findings suggestive of pneumonia may also be seen in patients with noninfectious illnesses (e.g., pulmonary embolism, certain autoimmune diseases, and malignancy). The diagnostic confusion created by varying clinical signs is further complicated by the inherent limitations of diagnostic testing. No single test reliably establishes the presence of pneumonia. Nevertheless, the benefit of establishing the infectious cause of pneumonia early in the course of the illness is undisputed, and certain standard tests should be considered (Table 3).

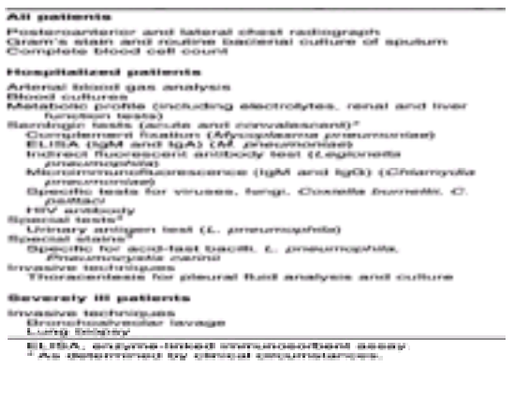

TABLE 3. *Diagnostic procedures for the evaluation of suspected community-acquired pneumonia*

A standard posteroanterior and lateral chest radiograph should be performed in all patients whose symptoms and physical examination suggest pneumonia. This test can be useful in assessing for the presence of pleural fluid, for differentiating pneumonia from conditions that may mimic it, and for demonstrating coexisting pulmonary diseases, such as sarcoidosis or bronchiectasis. Certain radiographic findings may lead to specific diagnoses—for example, cavitation suggestive of lung abscess, apical cavitation in tuberculosis, pneumatoceles in *Staphylococcus aureus* infection, and interstitial infiltrates in mycoplasmal, viral, or *Pneumocystis carinii* infections. The finding of multilobar involvement on chest films would also be helpful in identifying individuals at risk for more severe illness.

The acquisition of expectorated sputum for Gram's stain and culture is widely recommended for the initial evaluation of community-acquired pneumonia. To be of benefit, the specimen must be obtained carefully (admixed with as few oral secretions as possible), transported and processed quickly, confirmed as cytologically adequate (>25 white blood cells and <5 epithelial cells at x100 magnification), and obtained before institution of antimicrobial therapy. The sensitivity and specificity of routine bacterial cultures of sputum are poor, and these should generally be reserved for hospitalized patients. Inability to demonstrate a probable pathogen in an adequate respiratory tract sample may prompt consideration of legionellosis or infection with acid-fast bacilli, *Mycoplasma, Chlamydia, Pneumocystis,* or fungi in appropriate circumstances. Moreover, the identification on sputum Gram's stain of such virulent organisms as *S. aureus* or *Pseudomonas aeruginosa* should prompt consideration of inpatient care.

A number of invasive diagnostic techniques to obtain lower airways specimens, uncontaminated by oropharyngeal flora, have been described but are not indicated in most patients with community-acquired pneumonia. It may be useful, however, to have an early accurate diagnosis in patients who are severely ill and require admission to the intensive care unit, who are immunocompromised, or who are suspected of having HIV infection. In such patients, bronchoscopy with a protected specimen brush or bronchoalveolar lavage have reasonable sensitivity and specificity with low attendant risk and should be considered.

Routine laboratory tests are of little value in determining the etiology of pneumonia. These tests, however, may have prognostic significance, may influence the decision to hospitalize, and may affect the choice and dosing of antimicrobial therapy. Serologic testing is not useful in the initial management of pneumonia, but acute and convalescent serologic testing may help in the retrospective confirmation of a suspected diagnosis or in epidemiologic studies. Special serologic tests and stains are addressed later in the chapter as they pertain to specific etiologic agents.

HOSPITALIZATION AND SEVERE ILLNESS

The decision to hospitalize individuals with communityacquired pneumonia has historically been left to the experience and discretion of the admitting physician, as there are no firm guidelines. A series of well-recognized risk factors are indicative of an increased risk for death or a complicated course, and hospitalization should be strongly considered when multiple risk factors coexist (Table 4).

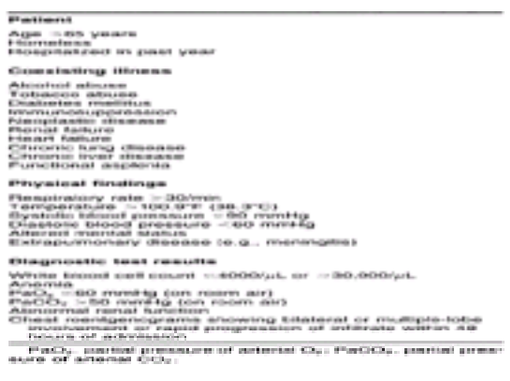

TABLE 4. *Factors that may increase morbidity and mortality in community-acquired pneumonia*

Multicenter prospective studies have validated these risk factors and identified five factors predictive of short-term mortality. These include age >65 years, altered mental status, abnormal vital signs, identification of a high-risk pathogen, and presence of neoplastic disease.

Although there is no universally accepted definition of severe community-acquired pneumonia, the presence of at least one of several recognized clinical findings justifies defining the illness as severe (Table 5). Severity of illness correlates well with likely etiologic pathogens. If severe pneumonia is identified, initial management in the intensive care unit is advised despite the lack of evidence that such support affects outcome.

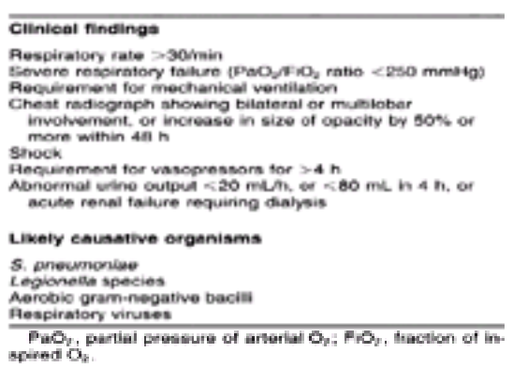

TABLE 5. *Severe community-acquired pneumonia: clinical findings and common pathogens*

In the remainder of this chapter, the specific pathogens most commonly encountered in patients with community-acquired pneumonia are reviewed, with an emphasis on the epidemiology, clinical presentation, diagnosis, and therapy for each. Certain pathogens may cause both community- and hospital-acquired infection, and those features unique to the hospital setting are reviewed in the following chapter.

PNEUMONIA CAUSED BY GRAM-POSITIVE BACTERIA

Pneumococcal Pneumonia

The incidence of pneumonia caused by *Streptococcus pneumoniae* has decreased sharply in many areas of the world. Surveillance studies now suggest an incidence of 20 cases of pneumonia per 100,000 young adults, as contrasted with an incidence of 700 cases per 100,000 young adults in the preantibiotic era. This reduction can be attributed in part to better hygiene and in part to the administration of antimicrobial agents to patients with upper respiratory tract infections before the onset of lower respiratory tract involvement. There is no evidence to suggest that the micro-organism is less prevalent in the community, that it has lost its virulence, or that natural host defenses have improved. Nevertheless, *S. pneumoniae* is still the most common cause of community-acquired pneumonia in patients of all ages, accounting for 15%–76% of cases in representative series.

Micro-organism

The pneumococcus, cultivated and isolated by Pasteur in 1881, is a gram-positive round, ovoid, or lanceolate coccus found in pairs or short chains. The distal ends of the paired cocci are usually pointed, and the organism has a capsule that is readily demonstrable on routine staining. More than 80 pneumococcal serotypes have been identified based on antigenic differences in their capsular polysaccharides. Serotypes are numbered in the order in which they have been identified, and virulent strains causing human disease were the earliest to be studied, identified, and assigned numbers. As a result, the lower-number serotypes are more likely to be implicated in human infection, and type 3 is considered the most virulent of the pneumococci. Unfortunately, the characteristic susceptibility of pneumococci to many antibiotic agents and the success of treatment regardless of the type involved have resulted in diminished interest in the antigenic structure of pneumococci, so that in most hospitals pneumococcal typing is no longer performed routinely. Serotyping may be useful, however, in areas experiencing an increasing incidence of penicillin-resistant pneumococcal disease. Certain serotypes (especially 6, 9, 19, and 23) have tended to be highly penicillin-resistant, and early recognition of their presence would facilitate empiric antimicrobial selection.

Susceptibility to Infection

The pneumococcus is the prototypic extracellular pathogen, capable of causing disease only as long as it remains outside phagocytes. Its rapid demise once ingested is largely the consequence of its inability to degrade its own hydrogen peroxide. The propensity for pathogenicity relates to the polysaccharide capsule that impairs phagocytosis. Effective clearance of the organism in the normal host, therefore, depends primarily on opsonization with immunoglobulin and complement. Pneumococcal infection is most prevalent in the extremes of life, with peak incidence rates occurring in newborns and infants up to 2 years old and adults in their 70s. Rates of disease in these groups appear related to lower reservoirs of antibody or to relatively weak immunoglobulin synthesis. A healthy adult is susceptible to pneumococcal pneumonia only if antibody to the capsular polysaccharide of the infecting serotype is lacking. In contrast, pneumococcal disease is greatly increased in people who have alterations in mucociliary clearance, defects of phagocytic function, defects in humoral immunity, alcohol or narcotic intoxication, malignancy, acquired immunodeficiency syndrome, and many other specific diseases (Table 6). A peculiar relationship between exposure to extreme cold and pneumococcal pneumonia has been observed for centuries, and the putative mechanism includes alterations in mucosal metabolism with impaired ciliary activity and depressed antibody secretion.

Defects of humoral systems
Immunoglobulin deficiency
Hypogammaglobulinemia
IgA deficiency
IgG subclass deficiency
Inadequate immunoglobulin production
Multiple myeloma
Chronic lymphocytic leukemia
Lymphoma
Human immunodeficiency virus infection
Sickle cell hemoglobinopathy
Bone marrow/renal transplantation
Chronic hemodialysis
Trauma; ??
C2, C3, or factor I deficiency
Defects of phagocyte function
Neutropenia
Hyposplenism, splenectomy
Alcoholism
Defects of mucociliary clearance
Viral respiratory infection
Chronic pulmonary disease
Asthma
Cigarette smoking
Chronic disease
Congestive heart failure
Renal failure, nephrotic syndrome
Cirrhosis
Autoimmune disease
Immunosuppression

TABLE 6. *Defects in host defense mechanisms that predispose to pneumococcal infection*

Pathogenesis

S. pneumoniae can be recovered from the nasopharynx of almost 40% of healthy adults, and an individual may carry up to four different serotypes. In both adults and children, most infections occur after the recent acquisition of a new serotype rather than after prolonged carriage. Binding to the nasopharynx is affected by interconversion between two phenotypes distinguished by colonial morphology—opaque and transparent. Transparent, but not opaque, variants adhere to nasopharyngeal epithelial cells.

Pneumococci gain access to the lung via aspiration of infected mucus and can be seen lining the alveolar walls early in disease, presumably via adherence to type II pneumocytes. Progression to pneumonia, however, requires additional events, as suggested by the association of pneumonia with pre-existing viral respiratory infection and the observation that the adherence of pneumococci in vitro is enhanced by viruses and cytokines. Pneumococci, especially transparent variants, bind avidly to interleukin-1-activated pneumocytes. This may involve an interaction between phosphorylcholine of the cell wall and platelet-activating factor (PAF) receptors, the latter upregulated by cytokine stimulation. Although pneumococci are generally not considered invasive for naive endothelial cells, cytokine activation leads to prompt entry. Again, PAF receptors appear to be the target and mechanism of entry.

The lung lesion of pneumococcal lobar pneumonia evolves in four overlapping stages: engorgement, red hepatization, gray hepatization, and resolution. Initially, alveolar capillaries become intensely congested, bacteria and edematous fluid are present in alveolar spaces, and the organism multiples without inhibition (engorgement). The edema-provoking factor consists of a pneumococcal cell wall complex of peptidoglycan and teichoic acid that binds to epithelia and endothelia. It elicits the production of interleukin-1 and the accumulation of a serous exudate.

Activation of procoagulant activity on the surface of endothelial cells leads to further capillary engorgement and diapedesis of erythrocytes into the alveoli (red hepatization). Endothelial activation also leads to accentuated PAF receptor expression, which is the major effector in the lung signaling leukocyte migration. Leukocytes move into the alveolar space by two mechanisms. Half are recruited by the CD18 family of leukocyte-adhesion molecules, and the remainder by a less well-understood CD18-independent pathway that is unique to pneumococcus-induced pulmonary inflammation. As exudate accumulates in the alveoli, capillaries are compressed and leukocyte content increases, giving “gray hepatization.” This leukocyte-rich exudate constitutes the first obstacle to further microbial multiplication. Before the appearance of antibody, extensive phagocytosis is achieved by a phenomenon (surface phagocytosis) in which polymorphonuclear leukocytes compress bacteria against the surface of alveoli or other leukocytes to facilitate ingestion. This defense is markedly enhanced by the appearance of specific antibody, present in detectable amounts between the fifth and tenth days, although more recent findings suggest that smaller amounts of opsonizing antibody may be present as early as 1 or 2 days after initiation of infection. If the patient's defense mechanisms have succeeded in destroying the pneumococci, the stage of resolution is reached, and macrophages can be seen within the alveolar spaces along with cellular debris. There is typically no necrosis of alveolar walls or interstitium, and the architecture of the lung returns to normal.

Traditionally, the capsule of the pneumococcus has been considered its most important virulence factor, in that it protects the organism from phagocytosis. The capsule

itself, however, is not toxic to the host, and at present pneumolysin, an intracellular protein, is the best candidate for a pneumococcus-derived toxin. Pneumolysin is not secreted but is released during bacterial lysis. It has not been identified free in the serum, but serum antibody to pneumolysin has been found after bacteremic pneumococcal pneumonia. The exact mechanism by which this toxin contributes to the virulence of the organism is unclear, but pneumolysin-negative pneumococcal mutants are significantly less virulent in mice. In addition, pneumolysin disturbs the structure and function of ciliated respiratory epithelium *in vitro* and is capable of inducing the salient histologic features of pneumococcal pneumonia.

Clinical Manifestations

Approximately half the patients give a history of upper respiratory tract infection followed in 2 to 14 days by evidence of lower respiratory tract involvement. The three most common early manifestations of pneumococcal pneumonia are fever, cough, and chest pain. Temperature is variable, ranging from 100°F to 106°F. Maximal fever is observed in the afternoon or evening, or it may be sustained with little diurnal change. The cough, which occurs in almost every case, is associated with the production of sputum in approximately 75% of patients. The sputum may have the classic rusty appearance, but just as often it is green (purulent). Frequently, streaks of blood are found in the sputum, and occasionally the cough is productive of frank blood. The chest pain is usually pleuritic, increasing in intensity during inspiration or cough. The pain is least severe when the patient is at rest, but the most comfortable position varies, with some patients preferring to lie with the painful side downward and others noting relief when the involved area is not in contact with any firm surface. Patients commonly feel chilly, and about half experience teeth chattering and shaking chills. Although a single shaking chill is characteristic, it is not uncommon for the patient to experience two to four such chills during a 48-hr period. Myalgia is commonly observed and may extend to tenderness of the thighs and calves. Severe myalgia, particularly that accompanied by vomiting, should strongly suggest the possibility of bacteremia. In approximately 10% of patients, herpes simplex lesions develop during the course of pneumococcal pneumonia.

Classically, physical examination reveals an acutely ill, perspiring patient who describes chest pain and splints on one side of the thorax. Tachycardia is usual in young patients, but in older patients heart rates are frequently between 70 and 100 beats/min. Examination of the chest reveals one of three findings in most patients. In some individuals, especially early in the course of the disease, bubbling rales and dullness to percussion may be the only abnormalities detected, perhaps correlating with the period of outpouring of fluid into the alveoli. A second group of patients shows the classic signs of consolidation: flatness to percussion, egophony, bronchophony, whispered pectoriloquy, and bronchial breathing. In patients with frank consolidation, frequently no rales or only a few crackling inspiratory rales are detected, and they increase as the pneumonia abates and the consolidation diminishes. In this group, a leathery pleural friction rub, heard throughout inspiration or only at the end of inspiration and expiration, may be associated with striking tenderness in the involved area of the chest. Finally, some patients may have one or more areas in which there is moderate dullness to percussion, inspiratory rales, and suppression of the breath sounds, which, although decreased in intensity, still appear harsh. As these patients presumably have mucous plugs in the smaller bronchial radicles and usually produce only scant amounts of sputum, pneumococci may not be detected in sputum cultures but found only in blood cultures. If pneumonia affects the lower lobes, abdominal pain may be a major manifestation and may be of such severity that the patient is admitted to the surgical service with a diagnosis of acute abdominal disease. In such cases, there may be considerable rigidity of the upper abdominal wall.

Laboratory Findings

The majority of patients with pneumococcal pneumonia have leukocytosis, although in 25% of cases the white blood cell count is normal. Leukopenia may be seen in overwhelming infections, and this poor prognostic factor generally occurs in alcoholic, malnourished, or elderly patients. The serum bilirubin may be increased to levels not exceeding 3 to 4 mg/dL. Levels of lactate dehydrogenase may be elevated. Hyponatremia resulting from inappropriate secretion of antidiuretic hormone has been reported. Measurement of arterial blood gases often reveals hypoxemia and occasionally hypocapnia.

Roentgenograms of the chest usually reveal dense homogeneous shadows involving all or part of one or more lobes (Fig. 1) and corroborate the findings of physical examination. If pneumococcal pneumonia is not apparent clinically, it is infrequently detected roentgenographically in an individual without chronic lung disease; however, in those with chronic lung disease, roentgenograms may show infiltrates that are undetectable on physical examination. In some cases, infiltrates are more patchy and less homogeneous. Those over the age of 65 may show more subtle manifestations early in the course of the disease, including less pleuritic pain and a lower incidence of shaking chills. Nevertheless, they are more likely to have multilobar involvement, and the chest x-ray film may show extensive coalescing infiltrates.

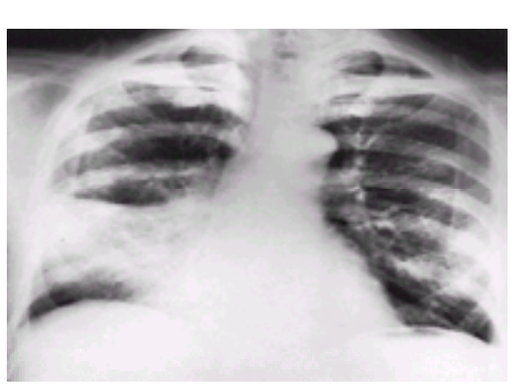

FIG. 1. Right middle lobe pneumococcal pneumonia.

Diagnostic Microbiology

A careful study of the sputum is the most important laboratory examination. In pneumococcal pneumonia, unlike most types of viral pneumonia, many polymorphonuclear leukocytes can be readily seen in sputum smears stained with Wright's or Gram's stain. Attempts to make a diagnosis based on an inadequate sputum specimen are largely responsible for studies claiming that sputum Gram's stain and culture are not reliable. To be reliable, sputum specimens must contain areas with at least 15 to 20 white blood cells and no epithelial cells in a standard microscopic field under ×1000 magnification. The characteristic gram-positive diplococci are generally seen in abundance (Plate 1). Results of a Gram's stain of the sputum can be used to guide therapy with considerable confidence, but Gram's stains alone without confirmatory cultures are not adequate. Results of blood cultures are positive in one fourth to one third of patients hospitalized with pneumococcal pneumonia.

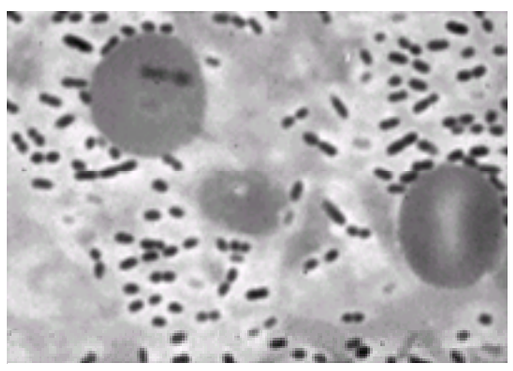

PLATE 1. *Streptococcus pneumoniae* in Gram's stain of sputum. x900. *See color plate 12.*

Therapy

In the pre-antimicrobial era, the “lysis-by-crisis” phenomenon of lobar pneumonia was one of the most dramatic events of clinical medicine. The crisis usually occurred 6 to 10 days after infection. The patient experienced profuse sweating, the temperature could drop 5°F to 6°F, dyspnea and tachypnea disappeared, and dramatic improvement ensued. Currently, this sequence is virtually never seen, because patients are treated with antibiotics as soon as the diagnosis is seriously entertained.

Penicillin remains the drug of choice, with the overwhelming majority of strains of pneumococci being sensitive to small concentrations of the antibiotic. Uncomplicated pneumococcal pneumonia responds to intramuscular penicillin procaine (600,000 units twice daily) or to intravenous aqueous penicillin G (500,000 units every 4 hours), each administered for 7 to 10 days. There is no evidence to suggest that the administration of larger amounts of penicillin effects clinical improvement more rapidly or that larger doses are needed if associated bacteremia or multilobar involvement is present. The administration of higher doses of penicillin or broad-spectrum antimicrobial agents has been shown to increase the likelihood of colonization and superinfection with other pathogens, usually gram-negative bacilli. In patients with meningitis, endocarditis, or arthritis, 20 million units of intravenous aqueous penicillin should be given daily, whereas 5 to 10 million units daily should be adequate for patients with empyema. Oral regimens, including penicillin phenoxyethyl or phenoxymethyl (250 mg every 6 hrs) and amoxicillin (500 mg every 8 hours), are also adequate. Erythromycin, chloramphenicol, vancomycin, imipenem, and many cephalosporins have been shown to be effective in pneumococcal pneumonia, although the response to treatment may be somewhat slower than with penicillin. Tetracycline should be avoided, as 5%–15% of strains are resistant. Pneumococcal meningitis is a well-recognized complication, especially in bacteremic pneumococcal pneumonia, and antimicrobial agents that have good penetration into cerebrospinal fluid should generally be chosen. The optimal duration of therapy is unknown, but therapy for 7 to 10 days, not to exceed 5 days after defervescence, seems appropriate.

Drug-Resistant Streptococcus Pneumoniae

During the past two decades, pneumococci moderately and highly resistant to penicillin alone and pneumococci multiply resistant to various antibiotics have been found throughout the world. By definition, strains with minimal inhibitory concentrations (MICs) of <0.06 mg/mL are regarded as susceptible, those with MICs of 0.1 to 1.0 mg/mL as intermediately resistant, and those with MICs of >1.0 mg/mL as highly resistant. About 2%–25% of strains isolated in the United States show intermediate resistance. The mechanism of resistance involves alterations in penicillin-binding proteins, as the organism does not produce b-lactamase. Mutation to high-grade resistance is thought to involve the acquisition of a packet of genetic material, because resistance to other antibiotics, such as chloramphenicol, erythromycin, and clindamycin, may be present. Of importance, these multiply resistant strains have remained susceptible to vancomycin. Notably, the serotypes accounting for the majority of resistant isolates are included in the currently available pneumococcal vaccine. Serotype 23F has been significantly associated with penicillin-cefotaxime resistance. Most clinical laboratories routinely test pneumococcal isolates for resistance to penicillin using a 1-mg oxacillin disk. As this does not discriminate between intermediately and highly resistant strains, penicillin MICs are required for these oxacillin-resistant pneumococci to determine the appropriate therapeutic agents. Intermediately resistant strains are readily treatable with increased doses of penicillin (150,000 to 250,000 units per kilogram per day), cefotaxime or ceftriaxone, or vancomycin. Ceftazidime is considerably less active and should be avoided. For highly resistant pneumococci, vancomycin should be considered the drug of choice. It is uncertain whether the prognosis of pneumococcal pneumonia is affected by the finding of penicillin resistance.

Prognosis

The mortality associated with pneumococcal pneumonia in a single lobe remains at approximately 1% despite appropriate antibiotic therapy. The majority of deaths are in patients who have severe underlying, concomitant illnesses or who are in the older age groups. The presence of bacteremia, leukopenia, or involvement of two or three lobes is said to increase the mortality to approximately 10%. In older patients with bacteremia, mortality ranges from 30%–60%. Pneumococcal pneumonia in four or five lobes remains a fearful disease, with a mortality rate that approaches 50%. It should be noted that 40% of all deaths caused by pneumococcal pneumonia occur within 24 hours of admission, and antimicrobial therapy does not alter this outcome.

Complications

Empyema

Empyema is now a relatively infrequent clinical complication of pneumococcal pneumonia, but effusions can be found by diligent search in about a third of cases. In patients with empyema, pleural pain continues; fever, which may have diminished initially after penicillin treatment, persists or recurs; and the patient remains toxic. Roentgenograms, especially lateral decubitus films, aid in confirming the diagnosis (Fig. 2).

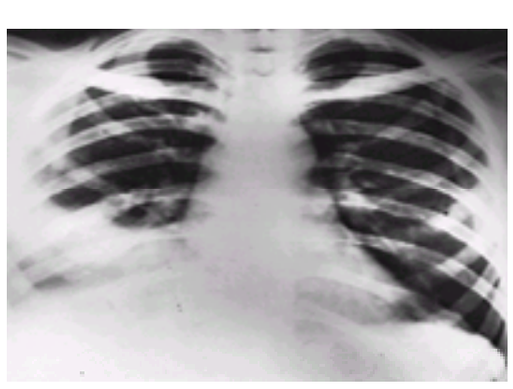

FIG. 2. Right lower lobe pneumococcal pneumonia and empyema in a 34-year-old man.

In all patients in whom empyema is strongly indicated, a diagnostic thoracocentesis should be performed. Fluid obtained shortly after the onset of empyema is cloudy and may contain 1000 to 600,000 leukocytes per milliliter, virtually all of which are polymorphonuclear cells. If the fluid is infected, its pH is usually <7.30. If empyema is untreated, the fluid subsequently assumes the appearance of frank pus. Initially, treatment may be conservative, consisting of repeated thoracocentesis. If the fluid does not become progressively thinner or if adequate drainage is not achieved, closed or preferably open thoracotomy should be performed.

Collection of sterile fluid. Although the cell count of this fluid may be high, ranging up to 300,000/mm^3, the percentage of mononuclear cells is usually considerably greater than that observed in empyema and the pH is >7.30. Even small effusions of this nature are causes for prolonged fever, and such fluids should be drained by needle aspiration.

Pericarditis

Precordial chest pain, persistent fever, or hypotension suggests the possibility of spread to the pericardium, an infrequent but dangerous complication of pneumococcal pneumonia. The three most reliable early signs in acute purulent pericarditis are the presence of a pericardial friction rub, the development of retrosternal dullness to percussion, and the appearance of Ewart's sign posteriorly at the angle of the scapula on the left or in the left basilar paravertebral area. Cardiac tamponade may develop in patients with pericarditis. Treatment of pericardial effusion is in general similar to that for empyema: aspiration and, if necessary, open pericardial drainage. If only a small effusion is present, no drainage may be needed.

Lung Abscess

Lung abscess following lobar pneumonia is extremely rare and occurs most frequently after infection with type 3 pneumococcus, which has a large capsule that inhibits phagocytosis. Prolonged antibiotic therapy (2 to 4 weeks) is usually required, and lung destruction may be so extensive that subsequent surgical intervention is necessary. There is no evidence that an abscess heals more quickly if the penicillin dose is increased or if multiple antibiotics are administered, but the risk for superinfection is great (Fig. 3). Occasionally, the abscess occurs because of a concomitant aerobic or anaerobic infection; in such cases, a change in the therapeutic regimen is mandatory.

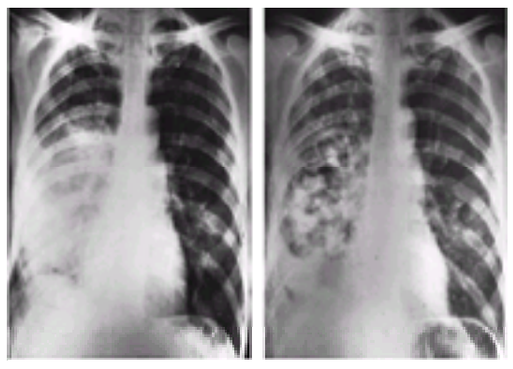

FIG. 3. Right lower lobe pneumococcal pneumonia (*left*) in a 46-year-old alcoholic, with abscess formation (*right*).

Atelectasis

Persistent fever and increasing dyspnea suggest atelectasis, which can usually be confirmed roentgenographically (Fig. 4). Vigorous tracheal suction and forced coughing may clear the mucous plugs, but if these procedures are not successful, bronchoscopy should be undertaken.

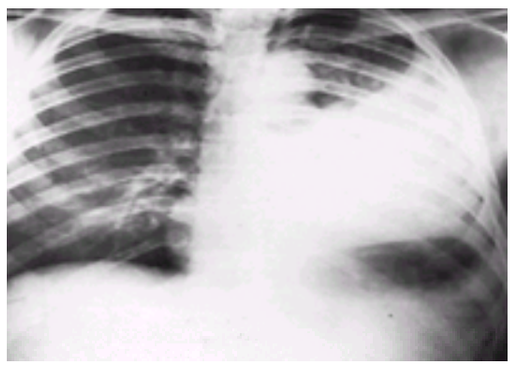

FIG. 4. Left upper and lower lobe pneumococcal pneumonia and atelectasis.

Delayed Resolution

Continued low-grade fever, rales, moderate dullness to percussion, and roentgenographic infiltrate may persist as long as 4 to 6 weeks in the absence of evidence of underlying bronchiectasis, obstructing neoplasm, or pulmonary superinfection (Fig. 5). This delayed resolution occurs primarily among older patients, in those suffering from malnutrition or alcoholism, and in some patients with chronic bronchitis, emphysema, and fibrosis. As the healing process cannot be hastened, it is fortunate that this common complication is benign. Repeated bacteriologic studies of sputum should be undertaken, and a single antibiotic agent may be continued at conventional dosage. In addition, bronchoscopy and cytologic examination of the sputum should be performed, as a small but significant number of these patients have obstructing neoplasms.

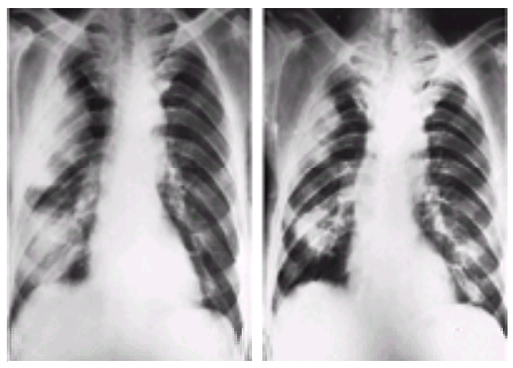

FIG. 5. Pneumococcal pneumonia (*left*) in a 40-year-old alcoholic with slow resolution within a 1-month period (*right*).

Endocarditis

In the course of bacteremia, pneumococci may light on normal or damaged heart valves, chordae tendineae, or papillary muscles. Endocarditis may occur concomitantly with the pneumonia, or there may be an excellent response to treatment of the pulmonary infection, followed by a period without fever and then a recurrence of fever after antibiotics have been discontinued. If endocardial involvement is associated with fever and other evidence of active infection, vigorous treatment should be undertaken: a minimum of 6 million units of penicillin per day for at least 4 weeks. However, when these cardiac complications occur in the absence of fever or evidence of active infection, they probably represent late rupture of a valve, chorda, or papillary muscle that was damaged by infection acquired during the bacteremia accompanying the pneumonia but was bacteriologically sterilized by treatment of the pneumonia. In these patients, a trial of antibiotics is warranted, but there is no evidence that the disease will be modified by such therapy. Surgical intervention may be necessary. Patients in whom pneumococcal endocarditis develops following pneumonia not infrequently have simultaneous evidence of pneumococcal meningitis.

Meningitis

One third to one half of adult patients with pneumococcal meningitis have concomitant or pre-existing pneumococcal pneumonia. Any patient with pneumococcal pneumonia who evidences disorientation, confusion, or somnolence should have a lumbar puncture to evaluate the possibility of pneumococcal meningitis. Although involvement of the meninges is usually apparent clinically, the manifestations can be extremely subtle.

There is some controversy as to the most effective treatment of pneumococcal meningitis, but it is unanimously agreed that an adequate regimen is large amounts of aqueous penicillin administered intravenously (minimal daily adult dose being 10 million units). Alternatives to penicillin include ampicillin, chloramphenicol, and a cephalosporin (cefuroxime, cefotaxime, or ceftriaxone). If moderately resistant strains of *S. pneumoniae* infect the meninges, penicillin is usually not effective.

Gangrene

On rare occasions, pneumococcal sepsis is followed by gangrene involving fingers, toes, nose, lips, and earlobes. In such cases, there is usually evidence of disseminated intravascular coagulation. This complication is particularly prevalent in those who have had a splenectomy.

Jaundice

Modest increases in serum bilirubin concentrations may occur in patients with pneumococcal pneumonia. Transaminase concentrations may be markedly elevated.

The mechanisms underlying the jaundice are not adequately defined, and the bilirubinemia ordinarily disappears in a few days. Physicians often forget that pneumococcal pneumonia may be associated with jaundice; the incorrect diagnosis most often made is Legionnaires' disease, because of the combination of pneumonia and liver dysfunction.

Prevention

The role of polyvalent pneumococcal vaccine is still unsettled. In some studies, it seems to be reasonably effective; in others, it does not. It is not entirely clear who should be vaccinated, although those with gamma globulin deficiencies, alcoholics, those over the age of 60 in institutions for long-term care, patients with sickle cell disease, HIV-infected patients, and those who have undergone splenectomy are certainly prime candidates. Some advocate the vaccine for all persons over the age of 60.

Streptococcal Pneumonia

In the pre-antimicrobial era, pneumonia resulting from group A b-hemolytic streptococci (*Streptococcus pyogenes*) was not uncommon in children after measles or pertussis or in adults after influenza. During the influenza pandemic of 1918–1919, severe streptococcal pneumonia, often culminating in death, assumed epidemic proportions in many areas of the world. The incidence of streptococcal pneumonia and bacteremia decreased markedly after the discovery and use of penicillin, but in recent years there has been an unexplained recrudescence of serious streptococcal disease. Currently, the total number of cases reported still is small, occurring for the most part in the very young, the very old, and the debilitated. Numerous epidemics have been reported in military recruit populations.

Clinical Manifestations

The onset is typically abrupt, with shaking chills, fever, and cough productive of purulent sputum. Hemoptysis and pleuritic chest pain are commonly observed. Cyanosis is noted in more severe cases. Rales and dullness are found on examination, but signs of frank consolidation are detected less frequently. The radiographic picture is that of bronchopneumonia, although one or more focal areas of pneumonitis may be seen. Empyema develops in 30%–40% of cases, and rapid pleural involvement is considered characteristic of this type of pneumonia.

Laboratory Findings

The leukocyte count is characteristically elevated, with a preponderance of mature and immature polymorphonuclear cells. Gram's stain of the sputum shows many polymorphonuclear leukocytes and gram-positive cocci in chains. An increasing percentage of streptococcal pneumonias are caused not by group A organisms, but rather by organisms belonging to groups B through G. Although specific clinical patterns have not been adequately defined for each group, it appears that *Streptococcus agalactiae* (group B) and *Streptococcus milleri* have the greatest propensity for abscess formation. Additionally, microaerophilic or anaerobic streptococci can cause pneumonia; in these cases, necrotizing pneumonia with empyema is frequently found.

In neonates, group B streptococci cause sepsis and diffuse pneumonitis. These infants, who become sick shortly after birth, are frequently very ill, with marked tachypnea and cyanosis. Roentgenograms usually show bilateral alveolar and interstitial infiltrates; in some cases, focal pneumonitis may be seen. Maternal vaginal colonization is the major risk factor for such infections.

Therapy

Penicillin is clearly the antibiotic of choice. Approximately 25% of group A b-hemolytic streptococci are no longer susceptible to tetracyclines. A penicillin dosage of 600,000 units two to four times a day is usually adequate, but some anaerobic streptococci are more resistant, requiring 3 to 6 million units per day. Cephalosporins, semisynthetic penicillins, erythromycin, and vancomycin can be used as alternatives to penicillin. If the infection is caused by group B, C, or G, therapy must depend on in vitro studies. Once severe streptococcal pneumonia is established, it may become a fulminating disease even if adequate amounts of antibiotics are administered. This is particularly true in group B infections in neonates, with mortality in these infants being about 30%. In adults, this characteristic is undoubtedly related in part to its frequent occurrence in persons whose antimicrobial defenses are impaired. In patients with empyema, conservative therapy with repeated thoracocentesis should be tried, especially while the fluid is still thin. Closed or open chest tube drainage may be needed for loculated fluid.

Staphylococcal Pneumonia

In previously healthy, young adults, *S. aureus* rarely causes pneumonia. Local pulmonary or systemic defenses of the host must be compromised before the organism can produce progressive disease. *S. aureus* accounts for 2%–9% of community-acquired pneumonias in the elderly or in patients with concomitant conditions, such as diabetes mellitus, chronic renal failure, bronchiectasis, lung carcinoma, defective polymorphonuclear leukocyte phagocytosis or killing, and intravenous substance abuse, or who are residents in a facility for long-term care. Infections may also occur in previously healthy adults following viral influenza with resultant impairment in bronchopulmonary clearance mechanisms.

Clinical Manifestations

The clinical manifestations of staphylococcal pneumonia vary considerably, depending on the setting in which it occurs. In the majority of patients who acquire the disease outside the hospital, especially those in whom staphylococcal pneumonia develops after viral influenza, the onset is sudden. Fever occurs uniformly and may be remittent or sustained in type. Most patients have pleuritic chest pain, shaking chills, and cough productive of sputum that is usually purulent and on occasion may also be blood-streaked. Gross hemoptysis occurs in a small number of patients. In infants and young children, cough and chest pain may be minimal, and the major manifestations are fever, dyspnea, and cyanosis.

On physical examination, the majority of patients appear extremely ill, with tachypnea, tachycardia, and commonly pleuritic pain. Cyanosis is often found, but hypotension is recorded infrequently. The findings on examination of the chest are generally indistinguishable from those already described for pneumococcal pneumonia. A pleural friction rub may be heard, accompanied by evidence of pleural fluid.

Laboratory Findings

Gram's stain of the sputum shows many polymorphonuclear leukocytes with intracellular and extracellular large, round cocci arranged in clusters. Specimens obtained from patients with staphylococcal pneumonia almost invariably show a heavy and virtually pure growth of *S. aureus.* If only small numbers are present, or if staphylococci are not clearly predominant, then staphylococcal pneumonia is an unlikely diagnosis.

For most adults with staphylococcal pneumonia, blood culture results are negative, the incidence of bacteremia being higher in infants. Leukocyte counts of 1000/mm^3 or less in individuals whose counts were previously normal are associated with a poor prognosis.

Chest roentgenograms typically show consolidation in a lobe or in smaller segments of one or more lobes. In some patients, patchy infiltrates in several areas of the lung suggest diffuse bronchopneumonia, and occasionally what appears to be an interstitial infiltrate is observed. Pleural or interlobar fluid may be detected. Single or multiple radiolucencies are often found in the areas of infiltration. In infants, pneumatoceles occur as frequently as abscesses, whereas in adults the radiolucencies almost invariably represent abscess formation. As cyst and abscess formation are not complications of staphylococcal pneumonia but rather an intrinsic part of the natural history of the disease, their presence does not imply a poor prognosis. Furthermore, the appearance of these lesions on the roentgenogram does not indicate failure of antibiotic therapy and does not necessitate a change in the antistaphylococcal regimen. In successfully treated patients, the vast majority of the abscesses and cysts disappear spontaneously and do not require adjunctive surgical treatment (Fig. 6). The x-ray film should ordinarily distinguish between upper respiratory tract-acquired and embolic staphylococcal pneumonia.

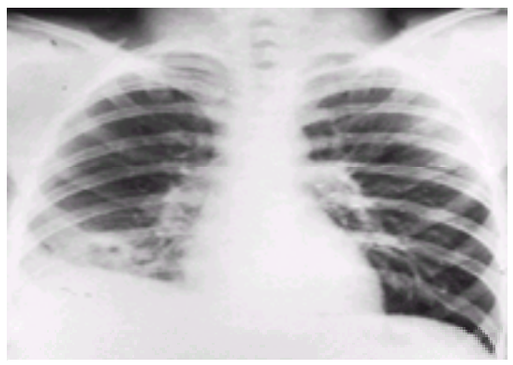

FIG. 6. Right lower lobe staphylococcal pneumonia in a 21-year-old man with prior viral influenza. Note two abscesses in the pneumonic area. These resolved completely in 2 weeks without a change in antistaphylococcal therapy. (Reproduced with copyright permission of The American Society for Clinical Investigation from Louria DB, et al. Studies on influenza in the pandemic of 1957–1958: II. Pulmonary complications of influenza. *J Clin Invest* 1959;38:213.)

Treatment

The mortality among patients who have been treated for staphylococcal pneumonia varies from 15%–50% in different series. Because mortality depends on the virulence of the micro-organism, the ability of the host to mobilize defenses, and the severity of the underlying disease, it is difficult to predict the outcome in any one individual, but it is clear that the presence of leukopenia and the demonstration of bacteremia are ominous prognostic signs.

Therapy should be initiated with large, parenterally administered doses of a penicillinase-resistant semisynthetic penicillin (methicillin, nafcillin, cloxacillin, or oxacillin) or a first-generation cephalosporin. Primarily bacteriostatic agents, including tetracycline, erythromycin, and chloramphenicol, are not advised as initial treatment in seriously ill patients. Clindamycin has significant antistaphylococcal activity but should not be considered a first-line agent. Imipenem also may be effective.

An increasing percentage of both community-acquired and nosocomial cases of staphylococcal pneumonia are caused by methicillin-resistant strains; for these, vancomycin given alone or together with either rifampin or an aminoglycoside is the agent of choice.

In vitro and in vivo animal studies suggest that in severely ill patients, the addition of an aminoglycoside to an agent such as oxacillin or nafcillin results in more rapid killing of the staphylococci. Although convincing clinical data are not now available, the current recommendation is that gentamicin or tobramycin be added to the semisynthetic penicillin for 5 to 7 days if the staphylococcal infection is overwhelming or life-threatening. Rifampicin is an effective intracellular antistaphylococcal agent and may be a useful addition to the antimicrobial regimen in recalcitrant cases.

Treatment should be continued for a minimum of 14 days. Even if adequate and appropriate therapy is given immediately, defervescence may be slow. Persistence of a moderately elevated temperature for 1 to 2 weeks does not in itself necessitate a change in the therapeutic regimen.

Complications

Meningitis

Staphylococcal meningitis with or without clinical evidence of brain abscess may complicate staphylococcal pneumonia. Cerebrospinal fluid examination reveals a variable cell count with a preponderance of polymorphonuclear leukocytes. The protein is elevated, but the glucose level may or may not be reduced. Treatment depends on in vitro susceptibility studies.

Empyema

Empyema develops in 15%–40% of patients with staphylococcal pneumonia, and *S. aureus* still accounts for about one third of all cases of pleural empyema. Acute empyema usually arises by direct extension from pneumonia or lung abscess, and therapy is similar to that described for empyema in pneumococcal pneumonia. Insertion of a chest tube, however, is usually necessary, and the presence of very thick pus makes open surgical drainage advisable early in the course of this disease.

Large Abscesses

Lung abscesses (Fig. 7) or pneumatoceles may become large enough to impair pulmonary function, or they may become secondarily infected. Under such conditions, drainage or excision by lobectomy is necessary.

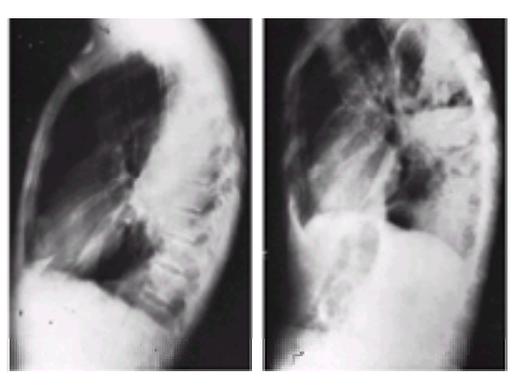

FIG. 7. Staphylococcal pneumonia (*left*) in a 47-year-old man. A large abscess (*right*) developed 1 week later.

Pneumothorax

A not uncommon complication, especially in infants and children, pneumothorax is not usually of grave prognostic import. Treatment depends on the size; a small pneumothorax will resolve spontaneously, but if a large pneumothorax or a tension pneumothorax is present, tube drainage should be used.

Bronchopleural Fistula

This complication usually occurs in patients who have underlying pulmonary diseases. It may be treated by surgical drainage of the empyema and prolonged antimicrobial therapy, but persistent fistulas should be excised surgically.

Miscellaneous Causes of Gram-Positive Pneumonia

Bacillus species can cause severe pneumonia in the compromised host. Only a small number of cases have been reported; most of the patients have had acute or subacute leukemia. However, in one case lethal gram-positive *Bacillus* pneumonia occurred in a previously healthy individual. The organism usually isolated is *Bacillus cereus,* but lethal pneumonia also has been caused by *Bacillus subtilis. B. cereus* multiplies within blood vessels, and as a result wedge-shaped, infarctlike lesions may be seen roentgenologically. Abscesses, cavities, and pneumonic infiltrates also may be found. The sputum is usually bloody, and pleural effusions are found frequently. The antibiotic regimen of choice depends on in vitro sensitivity patterns. The *Bacillus* species isolated from patients with pneumonia have been inhibited by tetracycline,

erythromycin, aminoglycosides, and chloramphenicol.

Corynebacterium (*Rhodococcus*) *equi* is a gram-positive coccobacillus responsible for suppurative bronchopneumonia in horses. In patients who are immunosuppressed, either because of an underlying disease or medications, the organism can cause severe pneumonia, with lobar or lobular infiltrates, infarctlike lesions, abscesses, or cavities. Manifestations include cough, chest pain, and hemoptysis. Pleural effusion may be present, and the organism may be recovered from the sputum or only from bronchial washings and/or pleural fluid. Erythromycin is thought to be the antimicrobial agent of choice (the isolates are also likely to be sensitive to vancomycin, gentamicin, tetracycline, and kanamycin), but too few cases have been reported to make a judgment about an optimal antimicrobial regimen.

Necrotizing pneumonia and empyema may be caused by *Clostridium perfringens.* Some cases follow trauma, surgery, or thoracocentesis, but in others no precipitating event has been noted. Pleural gas may be noted. Hemolysis, renal failure, and profound mental confusion are not present, as they are systemic clostridial infections, and the disease ranges from surprisingly mild to life-threatening. Penicillin, clindamycin, metronidazole, and chloramphenicol appear to be the agents of choice.

PNEUMONIA CAUSED BY GRAM-NEGATIVE BACTERIA

Community-acquired pneumonia is virtually never caused by enteric gram-negative bacilli in previously healthy, young adults. However, these organisms, predominantly Enterobacteriaceae, have been implicated in 3%–15% of cases. This relatively high prevalence of gram-negative bacillary pneumonia in large part reflects the inclusion of debilitated or elderly patients with serious pre-existing diseases. On the other hand, *Haemophilus influenzae* and *Moraxella* (*Branhamella*) *catarrhalis* have been increasingly recognized as pulmonary pathogens and account for 8%–20% and 1%–3%, respectively, of cases of community-acquired pneumonia.

Hemophilus influenzae **Pneumonia**

Because *H. influenzae* is part of the commensal oral flora, this organism was largely unappreciated as a significant pulmonary pathogen until recently. In recent years, there has been a clear increase in the occurrence of *H. influenzae* pneumonia, and it is second only to pneumococcal pneumonia as the most common community-acquired pneumonia in adults. *H. influenzae* pneumonia occurs in perfectly healthy people; in persons with chronic lung disease or other severe, underlying disease; in patients who have undergone splenectomy; and among chronic heavy abusers of alcohol. There is also an increased incidence in patients with disorders of gamma globulin synthesis, including those with chronic lymphocytic leukemia, multiple myeloma, human immunodeficiency virus infection, and the various IgG deficiencies. During epidemics of viral influenza, the incidence of *H. influenzae* pneumonia increases.

Kaplan and Braude, noting that severe infections with bacteremia occurred among adults primarily in alcoholics, performed studies suggesting that serum factors active against *H. influenzae* were less effective in patients with cirrhosis. Reduced effectiveness also was observed immediately after the ingestion of alcohol. These authors postulated that this relationship might be responsible for the enhanced susceptibility of these individuals.

Micro-organism

H. influenzae is a pleomorphic, gram-negative, coccobacillary organism. When grown under unfavorable conditions, it may appear filamentous and elongated and be mistaken for enteric gram-negative rods. It is a fastidious organism requiring special media that supply both X and V factors, such as chocolate or Levinthal agar. It may be recognized in sputum by Gram's stain (Plate 2) or by detection of specific capsular antigen. The encapsulated serotypes of *H. influenzae* (types a through f) can be differentiated by a variety of methods, including slide agglutination, counterimmunoelectrophoresis, and fluorescent antibody techniques. Each method is based on the use of antibodies directed against the capsular polysaccharide, a polymer of ribose and ribitol-5-phosphate.

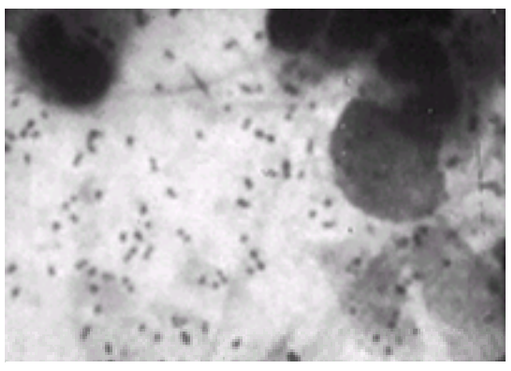

PLATE 2. *Haemophilus influenzae* in Gram's stain of sputum. X900. *See color plate 13.*

Pathogenesis

The development of invasive disease caused by *H. influenzae* follows colonization of the upper respiratory tract. The nasopharyngeal carriage rate for nontypeable strains varies from 50%–80%, in contrast to the carriage rate for type b *H. influenzae,* which is estimated at 3%–5%. Type b *H. influenzae* is responsible for 95% of systemic disease in children and a significant percentage of invasive bacteremic infections in adults. In contrast, nontypeable *H. influenzae* strains generally cause less severe local infection that spreads in a contiguous fashion within the respiratory tract, and these are the most common isolates causing pneumonia in adults.

Clinical Presentation

Two distinct presentations of *H. influenzae* pneumonia are recognized. The first occurs in infants or in patients with alcoholism or underlying immunodeficiency. In these individuals, the onset is typically rapid, with chills, fever, cough productive of purulent sputum, and pleural pain; the clinical features are indistinguishable from those of pneumococcal or other bacillary pneumonias. Bacteremia is common (up to 75% of cases in children), and the causative organism is almost always type b. Type b strains are responsible for about 10%–15% of pneumonias in adults. In contrast, adults with chronic lung disease usually experience a gradual onset, with low-grade fever, cough, increasing sputum production, worsening dyspnea, and occasionally myalgias and arthralgias. Bacteremia is rare in this setting, and the causative strain is invariably nontypeable.

Roentgenograms frequently show segmental lobar consolidation, but patchy bronchopneumonia and multilobular infiltrates may be seen. In patients with chronic lung disease, the initial chest radiographic findings may not be considered abnormal until after therapy, when improvement occurs in an area previously interpreted as chronic interstitial disease. Cavitary disease and empyema occur rarely, but parapneumonic effusions may occur in up to half of patients.

Diagnosis cannot be based solely on isolation of *H. influenzae* from the sputum, because nasopharyngeal carriage rates are so high. In addition, *H. influenzae* can be recovered from the sputum of most patients with chronic bronchitis if serial cultures are performed. Unless the organism is isolated from the bloodstream or pleural space, the diagnosis of *H. influenzae* pneumonia remains probable at best. Serologic methods, measuring antibodies against nonencapsulated *H. influenzae* strains by ELISA (enzyme-linked immunosorbent assay) from paired sera, may increase the ability to diagnose true *Haemophilus* infections. The sensitivity of this specific approach, however, is low.

Therapy

Until the early 1970s, *H. influenzae* was nearly uniformly susceptible to ampicillin, but during the past two decades, plasmid-mediated, b-lactamase-producing, ampicillin-resistant strains have been noted with increasing frequency. These organisms now constitute the majority of isolates in many centers. Chloramphenicol susceptibility has been preserved, however, as very few chloramphenicol-resistant strains have been reported. Ampicillin is not recommended as initial therapy, unless drug-susceptibility profiles confirm sensitivity. Type b *H. influenzae* has a propensity for invading the meninges, and empiric therapy ideally should have good cerebrospinal fluid penetration. Reasonable choices for initial therapy of invasive *Haemophilus* infections would therefore include ampicillin/sulbactam, chloramphenicol, second- or third-generation cephalosporins, and trimethoprim/sulfamethoxazole. Alternative agents include imipenem/ cilastatin, azithromycin or clarithromycin, and the fluoroquinolones, but the cerebrospinal fluid penetration may not be as reliable.

Active immunization against type b *H. influenzae* is now possible, as a vaccine composed of purified type b polysaccharide (PRP) is available. One of these commercially available PRP-conjugated vaccines should be routinely administered to children over the age of 15 months and to adults with conditions predisposing to invasive *Haemophilus* infection.

Outcome

Complications of *Haemophilus* pneumonia include empyema, meningitis, and septic arthritis. All are more likely to occur in the setting of bacteremia, alcoholism, splenectomy, or immunoglobulin deficiency. Mortality rates associated with *Haemophilus* pneumonia are <5% in young, healthy adults, but may be as high as 20%–30% among debilitated, elderly patients.

Moraxella (Branhamella) catarrhalis Pneumonia

Since Osler's time, when the organism was referred to as *Micrococcus catarrhalis,* this gram-negative coccobacillary organism has undergone several name changes. The designation *Neisseria catarrhalis* reflected its resemblance to *Neisseria* in appearance, but DNA homology suggested the genus be transferred to *Moraxella.* In 1970, in honor of Dr. Sarah Branham (for her contributions to the taxonomy of *Neisseria* species), the organism was assigned the genus *Branhamella.* At present, many prefer the designation *Branhamella,* as *Moraxella* implies limited pathogenicity.

This organism has long been recognized as an oropharyngeal commensal, and several studies have established that *B. catarrhalis* colonizes the nasopharynx of up to 7.4% of adults and 30% of children. *B. catarrhalis* is one of the three most common bacteria responsible for exacerbations of chronic bronchitis, and recent studies suggest it is responsible for 1%–3% of community-acquired pneumonias.

Micro-organism

B. catarrhalis is a gram-negative diplococcus shaped like a kidney bean, with its long axes paired side to side. The resemblance of a sputum Gram's stain from a patient with *B. catarrhalis* respiratory tract disease to the urethral smear from a patient with gonorrhea is striking. The organism readily grows on blood agar and can be easily distinguished from *Neisseria* species on the basis of sugar fermentation reactions. At present, 80%–90% of stains produce b-lactamase.

Clinical Manifestations

Chronic obstructive pulmonary disease is the most consistently reported underlying illness associated with *B. catarrhalis* respiratory tract infection, and the mean age of patients exceeds 60 years. Almost three fourths of infected patients are immunocompromised as a consequence of corticosteroid use, diabetes mellitus, or malignancy. Immunoglobulin deficiency is a quantitatively less important risk factor, but the clinical course appears more severe in this setting. More than 85% of cases occur from October through May.

Most cases of *B. catarrhalis* pneumonia are mild and present in a fashion suggesting an exacerbation of chronic bronchitis. There generally is minimal change in the patient's chronic cough, weakness, or dyspnea. In one fourth of patients, chills occur; in one third, pleuritic chest pain is present. Bacteremia, high fever, myalgias, pleural effusion, and empyema are rare. Patchy bronchopneumonia and interstitial or mixed interstitial-alveolar infiltrates are characteristic radiographic features. Lobar consolidation occurs in fewer than one third.

Diagnosis based on the traditional criterion of isolating the organism from blood or pleural fluid is difficult, as bacteremia and empyema are uncommon. A presumptive diagnosis of *B. catarrhalis* pneumonia is suggested by the clinical and radiographic signs of pneumonia, a good-quality sputum Gram's stain showing a predominance of gram-negative diplococci, and heavy growth of the organism on culture. It should be recognized that *B. catarrhalis* is frequently cocultured with other pathogens, especially *S. pneumoniae* and *H. influenzae.*

Therapy

Although 80%–90% of strains of *B. catarrhalis* produce b-lactamase, most of these strains have MICs to ampicillin of 2 mg/mL or less and are not labeled ampicillin-resistant. Clinical evidence suggests that all b-lactamase-producing strains of *B. catarrhalis* be considered ampicillin-resistant. Fortunately, these *B. catarrhalis* b-lactamases are inactivated by clavulanic acid and sulbactam, and have only moderate activity against second- or third-generation cephalosporins. Alternative, non-b-lactam antimicrobial agents include tetracycline, erythromycin, trimethoprim/sulfamethoxazole, and fluorinated quinolones.

Mortality directly attributable to pneumonia caused by *B. catarrhalis* is rare. Recent studies, however, have shown that up to 45% of patients die within 3 months, usually as a result of the underlying disease.

Neisseria meningitidis Pneumonia

Neisseria meningitidis was first reported as a respiratory pathogen after the influenza pandemic of 1918 and 1919. Thereafter, almost half a century elapsed before a renewed interest in the meningococcus as a cause of lower respiratory tract infection emerged in the 1970s. A majority of cases of meningococcal pneumonia have occurred in military populations, but this may only be a consequence of the ongoing surveillance of meningococcal disease by the armed forces. The association of meningococcal disease with antecedent influenza or adenoviral infection is well-known. Although spread of meningococcal infection beyond the nasopharynx almost exclusively requires bloodstream invasion, an inhalational rather than hematogenous pathogenesis is likely for meningococcal pneumonia.

There is nothing distinctive about its clinical presentation, and the onset may be sudden or more indolent. Patchy, lobular, or lobar infiltrates may be found, and in some cases, the pleura is involved. Bacteremia occurs in 15%–26% of cases. The presence of *N. meningitidis* in expectorated sputum may be easily overlooked unless it is specifically sought, and the use of selective culture media, such as Thayer-Martin medium, is helpful.

Confirmation of the meningococcus as the causative organism in bacterial pneumonia can be difficult. *N. meningitidis* can be recovered from the nasopharynx of 7%–13% of asymptomatic outpatients, and up to 30% of patients with acute respiratory infections but no clinical or radiographic signs of pneumonia have meningococcus-positive sputum. Therefore, to assign a causative role for the organism in pneumonia with confidence, it is necessary to isolate it from blood, pleural fluid, or lung aspirate.

The meningococci have remained broadly antibiotic-sensitive, and rapid clinical improvement on therapy is the rule. It should be noted that the administration of antibiotics (as opposed to sulfonamides) does not usually eliminate the carrier state. Rifampin and sulfonamides are effective agents for eradication of the carrier state and for prophylaxis of close contacts, but because of increasing reports of sulfonamide resistance, susceptibility studies should be performed.

Klebsiella pneumoniae (Friedländer's) Pneumonia

Micro-organism

In 1882, Friedländer discovered the organism that came to bear his name. It is a pleomorphic, encapsulated, fat, gram-negative rod that grows rapidly and aerobically on ordinary bacteriologic media. Four years later, in 1886, Escherich described *Aerobacter aerogenes.* Classified as separate species until recently, the two organisms are antigenically so similar that they have been combined into a single *Klebsiella* genus. *Klebsiella* types 1 through 6 are identical to Friedländer's bacillus types a through f, and *Klebsiella* types 7 through 80 are probably members of the old *A. aerogenes* group.

There are certain striking differences between Friedländer's bacillus (*Klebsiella* types 1 through 6) and higher *Klebsiella* serotypes: (1) Colonies of Friedländer's bacillus are far more mucoid and sticky because of their much larger capsules. (2) Differences in virulence for mice are marked. Friedländer's bacillus produces death within 24 to 48 hours after the intraperitoneal inoculation of small numbers of organisms, frequently <100 per mouse. Deaths after intraperitoneal infection with higher *Klebsiella* serotypes, on the other hand, rarely occur even at an inoculum size of a million organisms per mouse; indeed, many strains produce death only irregularly after an injection of 100 million to a billion bacteria per mouse. (3) The settings in which these two organisms cause pulmonary disease are not similar. Friedländer's bacillus characteristically produces pneumonia in men who are >40 years old and who are alcoholics or have chronic underlying disease, usually pulmonary in nature. Most patients with Friedländer's pneumonia enter the hospital with the disease. In contrast, pneumonia resulting from higher *Klebsiella* serotypes is usually acquired within the hospital environment, occurring in patients who are extensively treated with antibiotics and in whom pneumonia subsequently develops.

In the following discussion, the term *Friedländer's pneumonia* refers only to that caused by *Klebsiella* serotypes 1 through 6, most commonly types 1 and 2. Pulmonary infections caused by higher *Klebsiella* serotypes are discussed with pulmonary disease caused by *Escherichia coli*.

Clinical Manifestations

Friedländer's pneumonia, which accounts for <2% of patients hospitalized with bacterial pneumonia, is usually sudden in onset, with fever, cough, and pleuritic chest pain. In a minority of individuals, the cough is productive of the typical thick, gelatinous, red sputum. Most patients expectorate thick, greenish, purulent material that is frequently streaked with blood, whereas in some patients the cough is productive of frankly bloody sputum. On admission, patients may be seriously ill, with severe dyspnea, tachypnea, striking cyanosis, and hypotension, although many persons have considerably milder forms of the disease. Physical examination generally reveals the classic signs of consolidation, but sometimes only dullness to percussion, inspiratory rales, and diminished breath sounds are observed, the latter apparently because of obstruction of the smaller bronchi by plugs of gelatinous material. In some series, as many as one fifth of the patients have visible icterus.

Laboratory Findings

Gram's stain of the sputum shows many polymorphonuclear leukocytes and a myriad of short, fat, gram-negative, heavily encapsulated rods. The pleomorphism of the organism is frequently marked, and it may be so gram-variable that on examination of the sputum smear, a diagnosis of pneumococcal pneumonia may be made, especially by inexperienced observers. The leukocyte count is extremely variable. Although leukocytosis, sometimes with a count of up to 40,000/mm^3, is the rule, normal leukocyte counts or leukopenia may be observed. Frequently, normocytic, normochromic anemia either is present on admission or develops with startling rapidity after hospitalization. Blood culture results are positive in 20%–50% of cases.

The pneumonia more often affects the right side, with a predilection for the lower lobes and the posterior segment of the upper lobes, which suggests that the organisms have been aspirated from the mouth. Roentgenograms characteristically show massive consolidation with a fissure that bulges outward; this is apparently related to the extensive edema observed histologically (Fig. 8). Although the outward-bulging fissure is found frequently in Friedländer's pneumonia, this sign is by no means pathognomonic of infection with the organism that causes Friedländer's pneumonia, as it also may be observed in pneumonia caused by many other organisms. In 25%–50% of patients with acute Friedländer's pneumonia, one or more abscesses, usually not evident by physical examination, appear on the roentgenogram. The presence of abscesses and periodontal disease may tempt the physician to make a diagnosis of primary putrid lung abscess. The separation of the two diseases can often be made by smelling the sputum, which is not foul in Friedländer's disease.

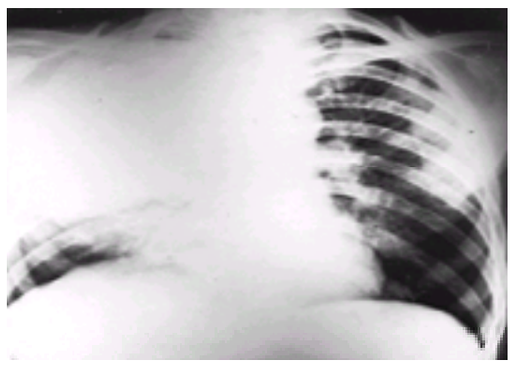

FIG. 8. Friedländer's pneumonia and empyema in a 52-year-old alcoholic. Note the bulging fissure.

Treatment

The micro-organism usually is susceptible in vitro to tetracyclines, chloramphenicol, cephalosporins, aminoglycosides, trimethoprim/sulfamethoxazole, the newer penicillins, such as piperacillin and mezlocillin, and the fluoroquinolones. The treatment of choice consists of a cephalosporin or b-lactam plus an aminoglycoside. Although this combination seems reasonable, there are no satisfactory data showing the advantages of giving both drugs rather than either one alone. Treatment should be continued for a minimum of 2 weeks.

Complications

Complications include empyema, pneumothorax, chronic pneumonia, spread to contiguous tissues, such as the pericardium, and hematogenous dissemination, especially to the meninges. In patients with empyema, open drainage usually is necessary because of the toxemia and thickness of the pus. Chronic Friedländer's pneumonia, which may follow the acute process, is characterized by progressive inanition, abscess formation, and anemia. It usually responds to prolonged antimicrobial therapy combined with careful supportive measures, but in some patients, lobectomy has to be performed for residual abscesses.

Escherichia coli Pneumonia

E. coli ranks after *K. pneumoniae* as the second most common cause of community-acquired gram-negative bacillary pneumonia. The “colon bacillus,” isolated in 1885 by Escherich, is a gram-negative, nonencapsulated bacillus. *E. coli* pneumonia may develop after a bacteremia originating from the genitourinary or gastrointestinal tract or by endogenous aspiration of the organism from a colonized oropharynx.

Patients with community-acquired *E. coli* pneumonia are usually middle-aged to elderly persons with underlying diseases, such as diabetes mellitus, cirrhosis, cardiac disease, and chronic lung disease. Several days of fever, chills, cough productive of purulent sputum, and pleurisy are generally reported. Alcoholics may present after a binge with pneumonia and meningitis. Tachycardia may be out of proportion to fever. Patchy lower lobe bronchopneumonia is typical, but occasionally lobar consolidation with abscess is seen. Parapneumonic effusion is common. The organism is generally readily recovered from blood, sputum, urine, and pleural fluid. Mortality rates vary from 29%–60%, and in survivors, fever ends by lysis.

Pneumonia Caused by *Proteus* Species

Proteus organisms are highly motile, gram-negative bacilli, notable for their characteristic swarming on agar. Patients acquire *Proteus* pneumonias after endogenous aspiration of pharyngeal secretions, and the typical patient is an elderly, alcoholic man with chronic lung disease. Worsening of bronchitic symptoms for several weeks culminates in an acute episode of fever, rigors, cough productive of purulent sputum, chest pain, and dyspnea. Signs of upper lobe consolidation are generally present. Radiographs show dense infiltrates in the posterior segments of the right upper lobe or superior segments of the right lower lobe, frequently with abscess formation. Pleural effusion is unusual, and healing results in a contracted fibrotic lobe. Species of *Proteus* may be cultured from the sputum as the predominant organism for long periods despite the use of antimicrobial agents.

Acinetobacter calcoaceticus Pneumonia

Acinetobacter is a gram-negative coccobacillus that can be easily misinterpreted as *Neisseria, Haemophilus,* or *Branhamella.* Patients with community-acquired *Acinetobacter* pneumonia are usually middle-aged to elderly persons with antecedent alcoholism and tobacco abuse. Occupational exposure to silica particles appears to be an additional risk factor. Patients have been ill for several days before admission with cough, fever, pleurisy, and bloody sputum. They typically present in severe respiratory distress, often sitting “bolt upright,” and half are in shock. Lower lobe consolidation and pleural effusion are common. Leukopenia with an absolute granulocytopenia is present in a majority of cases. Measurement of arterial blood gases shows profound hypoxemia. Blood, sputum, and empyema cultures yield *Acinetobacter.* Pneumonia progresses rapidly despite antimicrobial therapy, and death occurs in <72 hours.

Pseudomonas aeruginosa Pneumonia

Community-acquired *Pseudomonas aeruginosa* pneumonias are rare, accounting for <10% of gram-negative bacillary pneumonias in this setting. Although most patients are elderly with severe, chronic cardiopulmonary disease or malignancy, cases occasionally occur in normal hosts. At presentation, patients are toxic,

apprehensive, and confused, and exhibit chills, fever, and coughs productive of greenish sputum. Relative bradycardia and a reversal of the usual diurnal temperature curve (with elevation primarily in the morning) are typical.

Pulmonary infiltrates may be focal or diffuse, the latter mimicking cardiogenic pulmonary edema. The focal form may involve any part of the lungs, often with roentgenologic evidence of cavitation. Nodular infiltrates may be observed.

The diffuse form is a fearsome disease characterized by necrotizing pneumonia, vasculitis, frequent pulmonary hemorrhage, and abscess formation. Bacteremia is common and often accompanied by marked neutropenia. The nonbacteremic, focal form of *Pseudomonas* pneumonia carries a case fatality rate of 30%–60%. The bacteremic variety, which resembles pulmonary edema, is associated with a case fatality rate in excess of 80% unless treated promptly.

In *Pseudomonas* pneumonia, piperacillin, mezlocillin, ceftazidime, aztreonam, or imipenem combined with aminoglycoside should be adequate therapy.

Miscellaneous Causes of Gram-Negative Pneumonia

Evidence of pulmonary involvement may occur in typhoid fever. Indeed, cough is one of the early manifestations of the disease in as many as 25% of patients. Pulmonary infiltrates in typhoid fever are typically small and fleeting, and the pulmonary involvement is not a significant part of the disease process in the vast majority of patients. However, *Salmonella typhi* infection may be manifested by lobar pneumonia and/or empyema. Pneumonia also may be found in infections caused by *Salmonella* species other than *S. typhi,* especially *Salmonella choleraesuis,* which is the most invasive of the *Salmonella* species. Pneumonia, lung abscesses, and empyema may be the predominant manifestations of this disease.

Melioidosis, an acute, often lethal, disseminated infection acquired from rodents, cats, and dogs, is found primarily in Southeast Asia and the West Indies. The causative organism, *Pseudomonas pseudomallei,* is closely related antigenically to the agent responsible for glanders. Although the acute form of the infection is frequently fatal, there have been a small number of cases of chronic disease. These patients may have systemic disease without pulmonary parenchymal involvement, disseminated disease with secondary involvement of the lung, or primary pulmonary infection. In the lung, focal areas of pneumonic involvement rapidly form abscesses and cavities, followed sometimes by chronic empyema. The onset of the disease may be abrupt or the course may be indolent. Abscesses may appear in virtually any tissue of the body, and osteomyelitis with draining sinuses is observed frequently. Ceftazidime is the drug of choice. Extensive surgical drainage and debridement of diseased areas are also helpful.

Nodular infiltrates and pneumonia, occasionally with cavitation, also have been found in patients with *Yersinia enterocolitica* sepsis.

Legionellosis

In the summer of 1976, an epidemic of pneumonia occurred among persons attending a Legionnaires' convention in Philadelphia, Pennsylvania. In this predominantly older population, the case fatality rate was 16%. Approximately 6 months later, investigators from the Centers for Disease Control identified the causative agent as an aerobic gram-negative rod, *Legionella pneumophila.* It is now known that this organism caused epidemic pneumonia some 30 years before the Philadelphia epidemic. Species of *Legionella* account for 1%–4% of community-acquired pneumonias and rank among the top three microbial causes in several large-scale studies.

Micro-organism

Legionella is a pleomorphic bacillus that stains faintly gram-negative. There are at present >30 species, 20 of which have been implicated in human disease. The two most important are *L. pneumophila* and *Legionella micdadei* (the Pittsburgh agent). Within the species *L. pneumophila,* there are 10 serotypes, and most cases of legionellosis are caused by serotypes 1, 4, and 6. The organism can be seen by special tissue stains (modified Giemsa, Brown-Hopps, or Dieterle's stain), and *L. micdadei* can stain weakly acid-fast. *Legionella* organisms are nutritionally fastidious, and charcoal yeast extract agar is the medium of choice. The organism grows slowly; it takes up to 5 days for macroscopically visible colonies to appear. Aquatic environments are the natural habitat of *Legionella,* and this includes man-made habitats such as cooling towers, evaporative condensers, and potable-water distribution systems.

Epidemiology

Legionnaires' disease occurs in sporadic, endemic, and epidemic forms. Most epidemic Legionnaires' disease is caused by exposure to *L. pneumophila* aerosols in the workplace or in industrial or nosocomial settings. Hospital tap water has been frequently reported as contaminated with *Legionella* organisms—hence the current proscription against the use of tap water for irrigation of nasogastric tubes or any activity related to respiratory therapy. Several epidemics have been associated with retail stores or shopping malls.

Sporadic disease and miniclusters of Legionnaires' disease have been associated with proximity of patients residences to cooling towers. Recent interest has been focused on the home as a source of sporadic legionellosis, as 1%–30% of home heaters harbor *Legionella* organisms. The extent of bacterial colonization varies inversely with tank temperatures in this setting. As the water required to reduce *Legionella* colonization is quite high (55°C to 60°C), the potential risk for scald injuries likely outweighs the benefit in reducing disease.

Susceptibility to Infection

The incidence of legionellosis depends on the degree of contamination of the organism in the aquatic reservoir. Risk factors for the acquisition of disease include cigarette smoking, alcoholism, chronic obstructive pulmonary disease, and age. Immunosuppression is a major risk factor, and corticosteroid use is frequently reported. Transplant recipients appear to be at highest risk. The role of polymorphonuclear leukocytes in host defense is unclear, but patients with granulocytopenia are not at increased risk. Humoral immunity plays only a secondary role. Intracellular multiplication of *L. pneumophila* occurs within human monocytes, and cell-mediated immunity appears to be the primary host defense against *Legionella,* as is true for other intracellular pathogens.

Pathogenesis

Pathogenic organisms can enter the lung by aspiration, direct inhalation, and hematogenous dissemination from another focus. Oropharyngeal colonization with *Legionella* has not been demonstrated, so that subclinical aspiration of contaminated water or direct inhalation of aerosols is the likely mode of entry. The organisms probably are cleared by the mucociliary process, and this would be supported by the consistent epidemiologic association of increased risk for disease with conditions characterized by impaired mucociliary clearance (i.e., cigarette smoking, chronic lung disease, alcoholism). *Legionella* readily undergoes phagocytosis by resident alveolar macrophages, but phagosome-lysosome fusion is inhibited, allowing the organism to multiply and escape the microbicidal mechanisms of this cell. Cell-mediated immunity is the primary host defense against *Legionella,* and lymphocyte proliferation and cutaneous delayed hypersensitivity to *Legionella* antigens develop within the first 2 weeks of infection. Mononuclear cells respond to *Legionella* with the generation of monocyte-activating cytokines, but although the activated monocytes and alveolar macrophage inhibit intracellular multiplication of *Legionella,* killing is not enhanced.

Clinical Manifestations

Legionella infections may vary considerably in presentation, from an acute, self-limited, influenza-like illness (Pontiac fever) to a fulminant pneumonia syndrome with high mortality (Legionnaires' disease). The initial symptoms of Pontiac fever are predominantly malaise, myalgias, headache, and dry cough. The appearance of the chest radiograph is normal, and recovery within a week is the rule.

The incubation period for Legionnaires' disease is apparently 2 to 10 days, and the clinical manifestations vary from mild cough and fever to coma with diffuse pulmonary infiltrates and multiorgan system failure. An antecedent upper respiratory tract infection is reported only infrequently. The respiratory manifestations range from acute, subacute, or even chronic bronchitis to consolidating lobular or lobar pneumonia. Symptoms include malaise, muscle aches, headache, confusion, high fever, chills, and cough that is usually accompanied by some sputum production, with the sputum ranging in quality from serous and thin to thick and purulent. Hemoptysis occasionally may be a prominent manifestation. Pleuritic pain is not infrequent. Early in the course of the disease, there is often a pulse-temperature dissociation with relative bradycardia. This finding may be enormously helpful diagnostically and should not be ignored. Physical examination of the lungs may reveal only a few rales, or there may be more prominent findings, even evidence of frank consolidation.

Pleural effusion occurs in 24%–63% of patients; the fluid may show either a predominance of polymorphonuclear leukocytes or lymphocytes and on rare occasions may be hemorrhagic. Chest x-ray patterns are nondiagnostic. The initial involvement is unilateral in most patients, and the infiltrate is typically alveolar and segmental-lobar or diffuse and patchy. Interstitial infiltrates were described in 25% of patients in the Philadelphia outbreak in 1976. The initial area of infiltration often progresses to more widespread consolidation during the ensuing few days, even in the face of appropriate therapy. The extent of radiographic involvement does not

correlate with the severity of illness or ultimate outcome, but it does correlate with the presence of *L. pneumophila* in sputum. Cavitation of infiltrates occurs almost exclusively in immunocompromised patients. Hilar adenopathy and pneumatocele formation are rare.

The many extrapulmonary manifestations include mild to moderate liver dysfunction, hyponatremia, hypophosphatemia, diarrhea, abdominal pain, splenomegaly, renal dysfunction, pericarditis (with or without effusion), and myocarditis. There is a particular propensity for involvement of the central nervous system, including both the brain and spinal cord. Abnormalities of mentation without focal neurologic findings and aseptic meningitis are the most frequent findings.

It is important to stress that extrapulmonary manifestations suggest but do not document a diagnosis of *Legionella* pneumonia. Although they are common (gastrointestinal, neurologic, and laboratory abnormalities, including liver dysfunction, hyponatremia, hypophosphatemia, and hematuria), such clinical manifestations do not occur more frequently in Legionnaires' disease than in pneumonias of other etiology.

Laboratory Diagnosis

Five techniques are currently available for the specific diagnosis of Legionnaires' disease (Table 7). Sputum findings are variable; there may be few or many polymorphonuclear leukocytes. The organism does not stain well by Gram's method. Culture of the organism on selective media remains the definitive method of diagnosis, and maximal yield depends on specimen collection before antimicrobial therapy. The sensitivity of specimens obtained by bronchoscopy is essentially the same as that for sputum, and bronchoalveolar lavage gives higher yields than bronchial wash specimens. Blood culture results may be positive in up to 20% of cases.

Test	Sensitivity, %	Specificity, %
Culture		
Sputum	75	100
Transtracheal aspirate	90	100
Bronchial washings	75	100
Blood	20	100
Serology (IgG and IgM, acute and convalescent)	30–40	96
Direct fluorescent antibody	40–80	99
Urinary antigen	75–90	100
DNA probe	50–65	99

TABLE 7. *Specialized laboratory tests for the diagnosis of legionellosis*

No test is generally available to detect *Legionella* antigens in sputum, but a test to detect antigen in the urine is commercially available. Advantages include its sensitivity (75%–90%), specificity (99%), and relatively low cost, and the fact that test positivity persists for days, even during antibiotic therapy. The drawback is that only serogroup 1 of *L. pneumophila* is detected. This shortcoming is relatively minor, as this serogroup causes at least 70% of *L. pneumophila* infections.

Antibody estimation is probably the most widely used diagnostic tool. Maximal sensitivity requires both IgM and IgG determinations. Fourfold seroconversion is the definitive criterion, but this may take up to 9 weeks to be detected. In the first week of disease, 25%–40% of patients may have elevated titers.

Immunofluorescence microscopy, more commonly referred to as direct fluorescent antibody (DFA) testing, is an excellent method for detecting *Legionella* species in laboratory tract specimens. The DFA test is more likely to show positive results when multilobar infiltrates are present on chest films. Cross-reactivity with other gram-negative bacilli can give false-positive results.

The DNA probe methods are about as accurate as DFA testing. The DNA probe test may be preferable in high-volume laboratories, as interpretation requires less technical expertise. The polymerase chain reaction has been used experimentally to detect *L. pneumophila* DNA in clinical specimens, but its role is yet to be defined.

Therapy

There are three methods to determine the susceptibility of *Legionella* species to antimicrobial agents: extracellular testing, intracellular testing, and treatment studies of *Legionella*-infected guinea pigs. All three methods have been used to evaluate promising antimicrobial agents, as no controlled trials of treatment for Legionnaires' disease have been performed.

Erythromycin has historically been considered the treatment of choice based on retrospective analysis of outcomes of Legionnaires' disease. The Philadelphia epidemic fatality rates were twofold lower in erythromycin-treated patients than in those who were not treated with erythromycin. Doses of 2 to 4 g/d are advocated, preferably administered intravenously initially. Both clarithromycin and azithromycin are more active in vitro than erythromycin and have been successfully used in the treatment of Legionnaires' disease. They represent attractive agents for the oral treatment of legionellosis. Therapy should be continued for 3 weeks.

Rifampin is active against both intracellular and extracellular *Legionella* organisms. The use of rifampin as sole therapy for Legionnaires' disease has not been reported, and legionellosis has developed in individuals receiving rifampin for tuberculosis. Rifampin may have a synergistic effect when administered with erythromycin, but this benefit may be limited to the initial 3 to 5 days of treatment. Rifampin in doses of 600 mg twice daily should be considered for individuals with more serious disease.

Tetracycline was equivalent to erythromycin in lowering the case fatality rate in the Philadelphia outbreak. Doxycycline and minocycline appear to be more active in vitro than tetracycline, and they would be reasonable alternative agents for patients who cannot tolerate macrolides.

Increasing evidence now exists that fluoroquinolone antimicrobial agentss (ciprofloxacin, pefloxacin, ofloxacin) are superior in activity to erythromycin, and they have been successfully used for the treatment of Legionnaires' disease. There are no clinical data to demonstrate that combining a fluoroquinolone with either rifampin or erythromycin is more effective than the fluoroquinolone alone. Fluoroquinolones have no adverse effect on cyclosporine metabolism and should be considered the drug of choice for immunocompromised patients taking that agent.

Mycoplasma (Primary Atypical) Pneumonia

Micro-organismterm

The term *atypical pneumonia* was first used in 1938 to describe an unusual form of “tracheobronchopneumonia and severe symptoms.” The organism was first isolated in 1944 by Eaton, Meiklejohn, and von Herick from the sputum of patients who had cold agglutinin-positive, atypical pneumonia. Thereafter, the organism was called *Eaton's agent* until 1961, when Chanock identified it as belonging to the genus *Mycoplasma.*

The organisms contain both RNA and DNA, lack a cell wall, and can be identified by direct isolation on highly enriched artificial media. *Mycoplasma pneumoniae* has distinctive properties among human mycoplasmas in that it ferments glucose and causes b-hemolysis of guinea pig red cells, but the final identification is still by serology or specific growth-inhibition tests.

Clinical Manifestations

M. pneumoniae accounts for 2%–15% of all communityacquired pneumonias, but up to 30% of the pneumonias in adolescents and adults younger than 30. Mycoplasmas are of relatively low virulence; pneumonia develops in only 5%–15% of exposed persons.

The onset of the illness may be either insidious or acute. More than 80% of patients have cough and a temperature above 101°F. A persistent, racking, usually nonproductive cough is the hallmark of the disease; before fluorescent antibody techniques were developed, many observers stated that this cough was a uniform finding. More recent evidence, however, suggests that at least 10% of patients with pneumonia and elevated titers of specific antibody do not experience cough. The majority of patients notice pounding headache, usually frontal or generalized, that may be so severe as to be the dominant symptom. Myalgia is common, and coryza,

sore throat, and shaking chills all occur in approximately 25% of patients. Although chest discomfort is reported frequently, frank pleuritic pain occurs in 5% of patients. The pain usually is retrosternal and may be quite severe.

On physical examination, the patient usually appears moderately ill and frequently complains of either cough or headache, the latter markedly accentuated during periods of coughing. The heart rate often appears slow in relation to the degree of pyrexia. The frequent paroxysms of nonproductive cough may at times make the patient virtually incapable of carrying on a prolonged conversation. In patients with extensive pulmonary involvement, moderate or even marked cyanosis may be observed. A clue to the pulmonary diagnosis may be obtained by finding an inflamed tympanic membrane on otologic examination. Bullous myringitis, a frequently emphasized feature of this disease, actually occurs in 5% of patients. Examination of the lungs characteristically reveals fine to medium rales heard early or at the very end of the inspiratory cycle. Early in the course of the disease, physical examination of the lungs may reveal normal findings despite considerable infiltration shown roentgenographically. This discrepancy is notable, especially in the upper lobes, whereas in the lower lobes, which are more commonly involved, physical examination usually shows some abnormality and may give more evidence of pulmonary disease than the roentgenogram. As the disease progresses, dullness to percussion is observed, and the number and intensity of the rales increase so that rales, rhonchi, and wheezes of either a coarse or musical nature are readily detected. Evidence of frank consolidation, pleural friction rubs, and pleural effusion are less frequently found.

Roentgenographic and Laboratory Studies

Roentgenographic study of the chest shows nodular, patchy, or perihilar infiltrates that cannot be distinguished from those of various types of viral pneumonia and on occasion may simulate bacterial lobar pneumonia (Fig. 9). Rarely, *M. pneumoniae* infection has been associated with parenchymal lung abscesses. One or two lobes are involved in the majority of patients, but occasionally pneumonia may occur in four or five lobes. Hilar adenopathy can be found in up to 22% of cases. Roentgenographic findings suggest pleural fluid in <5% of patients. Because stained smears of the sputum show a marked predominance of mononuclear cells, the presence of large numbers of polymorphonuclear leukocytes should suggest another etiology for the pneumonia. However, in a small percentage of cases, the cellular response in the sputum is predominantly polymorphonuclear. During the first week of the disease, the blood leukocyte count is usually <12,000, but in approximately 10% of patients, the count is as high as 20,000/mm^3. During the second to third week of the disease, mild to moderate leukocytosis is common, and on occasion profound leukocytosis has been reported.

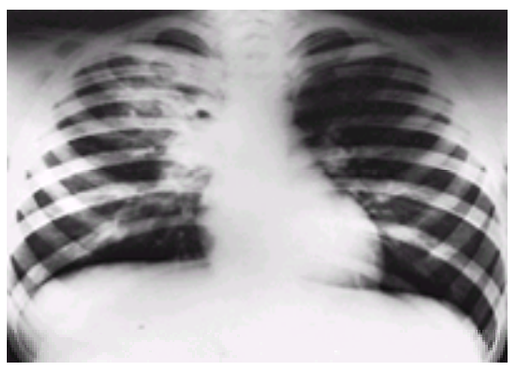

FIG. 9. *Mycoplasma* pneumonia in a 23-year-old man who seemed normal on physical examination.

Cold agglutinins appear in the blood 1 to 4 weeks after the onset of illness. Maximum titers are found in the second to sixth week of disease and may persist for several months. Cold hemagglutinins are helpful in the diagnosis of *Mycoplasma* pneumonia but are not diagnostic. Cold agglutinins do not develop at any time during the course of illness in 15%–30% of the patients who have pneumonia and a rising titer of antibody specific for *M. pneumoniae.* Furthermore, a considerable number of patients who have positive results on cold hemagglutinin tests do not show a rise in *M. pneumoniae*-specific antibody, the percentage ranging from 15%–65% in different series. Many other pulmonary and extrapulmonary diseases may produce elevation in the cold agglutinin titers; these diseases include influenza, rubella, cirrhosis, lymphatic leukemia, trypanosomiasis, leishmaniasis, relapsing fever, acute hemolytic anemia, pernicious anemia, paroxysmal cold hemoglobinuria, infectious mononucleosis, and psittacosis. In addition, a small number of patients have persistently high titers for unknown reasons. It has also been shown that certain individuals chronically have low cold agglutinin titers, which may rise to diagnostic levels with virtually any acute infection. Significant titers are at least 1:80, and it is not unusual to see levels of 1:1000 or more. Antibody to streptococcus MG also appears in the blood of 40%–60% of patients with *Mycoplasma* pneumonia. However, both cold agglutinins and streptococcus MG titers are negative in at least 20% of patients with pneumonia caused by *M. pneumoniae.*

Specific serologic tests include growth inhibition, ELISA, radioprecipitation, and complement fixation; a fourfold rise in complement-fixing titers is used most often for establishing a firm diagnosis.

Complications

The major complications of *Mycoplasma* pneumonia are related to the central nervous system and to the effects of cold agglutinins. On the third to thirtieth day of illness, manifestations of nervous system involvement develop in a small number of patients, including papilledema, disorientation, coma, neck stiffness, abnormal reflexes, and transverse myelitis. Lumbar puncture specimens may be entirely normal or may show elevation of the protein to as much as 300 mg/dL and pleocytosis to a maximum of several hundred cells. These may be predominantly polymorphonuclear leukocytes or, more commonly, predominantly mononuclear cells. Central nervous system involvement may be serious. Either meningitis or encephalitis may predominate clinically and result in death or be associated with permanent neurologic residua. Postmortem examination has shown focal hemorrhages, perivascular mononuclear infiltration, and less frequently glial proliferation. Nervous system involvement by *Mycoplasma* also may be expressed as cerebellar ataxia, peripheral neuropathy, or Guillain-Barré syndrome. Cold hemagglutinins in low titer represent no danger to the patient. On the other hand, when titers exceed 1:512, cold hemagglutinemia is potentially dangerous. Peripheral thrombophlebitis, which develops in some patients, may be associated with secondary pulmonary embolism. High-titer cold hemagglutinemia also may be associated with acute hemolysis related either to increased mechanical fragility of antibody-coated cells or to the simultaneous presence of a cold hemolysin. If intravascular hemolysis is rapid, hemoglobinuria may be observed. Occasionally, the use of ice packs, cold oxygen tents, or the administration of cold blood has been associated with arterial occlusion and gangrene, presumably related to intravascular thrombosis induced by cold agglutinins. Dermatologic manifestations usually consist of an erythematous maculopapular or vesicular rash, but the Stevens-Johnson syndrome may occur. Cardiac involvement is infrequent, but myocarditis, pericarditis, and complete heart block have been reported.

Course and Treatment

The course of *M. pneumoniae* pneumonia is variable, although recovery is the rule. Fever may last from 2 days to 2 weeks; it usually subsides by lysis. The cough does not usually subside until at least several days after the fever has disappeared. Malaise, cough, and radiographic abnormalities frequently persist for 2 to 6 weeks. Secondary bacterial infection occurs infrequently in patients with *Mycoplasma* pneumonia. Uncomplicated disease is not fatal in patients who have an inflammatory process in one or two lobes, but it is not generally appreciated that more extensive pulmonary involvement can be associated with some mortality.

In addition to careful supportive therapy, current evidence strongly favors the administration of tetracyclines or macrolides. These antibiotics inhibit the etiologic agent in tissue culture, and well-controlled studies have now demonstrated prompt clinical improvement, defervescence, and more rapid resolution of roentgenographic infiltrates after treatment with one of these drugs. Even after clinical improvement, *M. pneumoniae* may be found in throat cultures for a considerable period.

Chlamydia Infections

Chlamydia pneumoniae *Pneumonia*

C. pneumoniae has only recently been recognized as a pulmonary pathogen. This organism was initially referred to as the TWAR agent, after the laboratory designation of the first two isolates: TW-183 and AR-39.

Serologic studies have demonstrated that *C. pneumoniae* is the most common chlamydial species infecting humans. The prevalence of antibody to *C. pneumoniae* starts to rise in residents of industrialized countries at school age and steadily increases throughout life. Longitudinal studies suggest that only about 10% of infections lead to overt pneumonia. It is estimated that the organism accounts for 2%–10% of community-acquired pneumonias, depending on age and geographic locale.

Micro-organism

C. pneumoniae is an obligate intracellular bacterium having 10% genetic homology with the other *Chlamydia* species. Details of the pathogenesis of *C. pneumoniae* pneumonia are unknown. The agent multiplies in human alveolar macrophages, smooth-muscle cells, and endothelial cells and rapidly induces ciliostasis. Infection with *C. pneumoniae* leads to partial immunity, as reinfections generally do not take the form of pneumonia. When the reinfecting strain, however, is sufficiently different to escape immunologic defense mechanisms, the outcome can be more severe than the illness observed in primary infection. Little is known about the cellular immune response. An IgM response to protein antigens is seen in primary infections but is usually lacking in reinfections. There is also a marked IgA response in reinfections.

Clinical Manifestations

Clinical features of pneumonia attributable to *C. pneumoniae* are similar to those caused by *M. pneumoniae*. The illness is generally mild, but the course may be protracted, with symptoms persisting for 3 to 6 weeks. Severe pharyngitis, hoarseness, and upper respiratory tract symptoms are present in 40%–70% of patients. Fever and cough are common. A biphasic illness is frequently seen; patients seek medical attention with pharyngitis, recover, and then pneumonia develops 1 to 3 weeks later. Rales are almost always present on auscultation. Sputum production is scant and not purulent. In some series, up to 20% of individuals with chlamydial pneumonia are coinfected with other pathogens, such as influenza virus or *S. pneumoniae*. The peripheral blood leukocyte count and differential counts are usually normal, although an elevated erythrocyte sedimentation rate is found in 80% of cases. There are no characteristic radiologic findings. Single, subsegmental alveolar opacities appear frequently, although interstitial infiltrates may be more common in reinfections. Lobar consolidation, hilar adenopathy, and pleural effusion are uncommon.

Diagnosis

Definitive diagnosis requires isolation of *C. pneumoniae* or demonstration of an appropriate antibody response. Cultivation of the organism is difficult, and sensitivity of culture is only 50% in serologically verified cases. Direct antigen detection or fluorescent antibody staining of respiratory tract samples is insensitive. The two primary serologic tests for *C. pneumoniae* are complement fixation and micro-immunofluorescence. Complement fixation is genus-specific and measures antibody against all three *Chlamydia* species (*psittaci, pneumoniae, trachomatis*). The complement fixation test, however, may be useful only in primary infection, as results remains negative in 90% of reinfections. On the other hand, micro-immunofluorescence is specific for *C. pneumoniae* and can distinguish between IgM and IgG antibody. Circulating antibody may not be detectable, however, for 3 to 6 weeks. Criteria for diagnosis using micro-immunofluorescence have been established: a fourfold rise in antibody response, IgM titer ^{3}1:16, or IgG titer ^{3}1:512.

Complications

C. pneumoniae rarely causes life-threatening pneumonia, and most patients do not require hospitalization. Chronic *C. pneumoniae* infection of the lungs has been associated with chronic bronchitis, asthma, and sarcoidosis. Extrapulmonary manifestations include reactive arthritis and erythema nodosum. Dissemination via the bloodstream may explain the recent association of the organism with coronary artery disease and atherosclerotic lesions.

Treatment

Although no clinical studies of efficacy have been performed, tetracyclines, erythromycin, and fluoroquinolones have shown excellent in vitro activity. Tetracycline appears to be the drug of choice, at a dose of 2 g/d. Treatment should be administered for 2 to 3 weeks.

Ornithosis (Psittacosis)

Pathogenesis

Ornithosis is an acute pulmonary infection caused by *Chlamydia psittaci*. These obligate intracellular parasites are larger and more complex organisms than viruses, contain both DNA and RNA, have a cell wall similar in composition to that of some gram-negative organisms, and are stained by Giemsa but not by Gram's stain. Ornithosis is acquired by contact with both psittacine and nonpsittacine birds, including parrots, parakeets, lorikeets, cockatoos, chickens, pigeons, ducks, pheasants, and turkeys. Although the birds are sometimes sick, the disease is frequently acquired from animals that appear to be well. Infection follows inhalation of dried excreta and occurs most often in persons who care for the birds; it is uncommon in persons who visit people with psittacine birds but have no intimate contact with the birds. At least 25% of cases occur without a history of bird contact, and in a small number of cases, human-to-human spread of the disease has occurred.

Clinical Manifestations

After an incubation period, which is usually 7 to 15 days but may occasionally be considerably longer, the patient becomes acutely ill with a mild to moderate cough productive of small amounts of sputum, occasionally blood-streaked. Fever and myalgia are common, and approximately a third of patients experience shaking chills. Pleuritic chest pain occurs relatively infrequently. Hemoptysis also has been described.

The findings on physical examination are extremely variable. In severe cases, consolidation involving several lobes may be accompanied by a pleural friction rub, or examination may show only diffuse, moderate to coarse inspiratory and expiratory rales. In less severe cases, one or two lobes are involved and there are inspiratory rales but no frank consolidation. In some patients with pulmonary involvement, no abnormalities can be detected on physical examination. A few patients have moderate pleural effusion. Not infrequently, the heart rate is slower than expected in a patient with marked elevation in temperature. Splenomegaly is present in 10%–30% of patients. Severe lymphadenopathy, intense pharyngitis, pericardial friction rub, jaundice, evidence of meningoencephalitis, or any combination of these is found occasionally.

Roentgenographic and Laboratory Findings

The variable findings detected on physical examination are reflected in roentgenographic abnormalities. Focal areas of consolidation are seen in 10%–20% of cases. In others, there are small peribronchial or peripheral infiltrates or diffuse, bilateral, confluent pneumonia that is indistinguishable from overwhelming influenza virus pneumonia. Rarely, cavitation may be seen in areas of pneumonia. Mediastinal lymphadenopathy also has been described.

Examination of stained sputum smears usually shows few polymorphonuclear leukocytes, and there is rarely evidence on smear or in culture of secondary bacterial infection. The blood leukocyte count is commonly normal but may be elevated or low. Occasionally, serum titers of cold hemagglutinins rise during the course of ornithosis. The organism can readily be isolated from the sputum or the lungs, and frequently from other tissues at postmortem examination using tissue culture cells or embryonated chicken eggs. Complement-fixing antibodies appear in the serum in the second to fourth week of the disease, but their appearance may be delayed until the fourth to sixth week when patients are treated with antibiotics.

Complications

Complications arising from contiguous or hematogenous spread are reported with increasing frequency; these include pericarditis, myocarditis, hepatitis, meningitis, and encephalitis. If the central nervous system is affected, delirium, stupor, severe headache, and lymphocytic meningitis may be noted, but seizures are extremely uncommon. Hepatic involvement varies from mild to lethal and is characterized by striking hepatocellular abnormalities on liver function studies. Peripheral thrombophlebitis is a not infrequent complication and may cause death by pulmonary embolism.

The mortality associated with ornithosis is currently 2%–10%, with most of the patients dying of respiratory involvement, including the respiratory distress syndrome. In patients who die of ornithosis, the bronchial mucosa is ulcerated.

Treatment

The tetracyclines are the antibiotics of choice and are usually effective in modifying the course of the disease when given in a dosage of 1 to 2 g/d for 10 to 14 days. Chloramphenicol is an equally effective agent, and erythromycin also may be useful. The patient should be placed in strict isolation in view of the well-documented cases of human-to-human spread.

Other* Chlamydia *Infections

Chlamydia trachomatis usually causes conjunctivitis, trachoma, and urethritis. It also can cause interstitial pneumonia in infants. The infection, which usually appears in infants 2 weeks to 3 months old, is characterized by staccato cough, tachypnea, and variable degrees of cyanosis. There is little or no fever. Roentgenograms show alveolar and interstitial infiltrates. The course of the cases is generally protracted, lasting from several weeks to many months. Arterial oxygen saturations are often markedly reduced. The diagnosis is usually made by isolation of the organism from tracheal aspirations and by serologic tests. Genus-specific complement fixation and immunofluorescent antibody tests using lymphogranuloma venereum antigens are available, and there are now specific immunofluorescent antibody tests for *C. trachomatis*. Eosinophilia occurs frequently. In some instances, prolonged erythromycin therapy has appeared to be beneficial, but similar improvement has occurred with supportive therapy alone. If *C. trachomatis* infection is acquired in utero, lethal pneumonia can result. *C. trachomatis* also can cause pneumonia in adults, in both compromised and noncompromised persons, usually characterized by patchy infiltrates without frank consolidations. Mediastinal and supraclavicular lymphadenitis also has been described.

VIRAL RESPIRATORY TRACT INFECTIONS

Viruses may account for 5%–15% of community-acquired pneumonias. Viral respiratory illnesses are caused by >200 serologically distinct viruses, and the clinical manifestations of these illnesses, including rhinitis, tracheobronchitis, bronchiolitis, and pneumonia, are dictated by the principal sites of anatomic involvement. In contrast to bacterial respiratory tract infections, viral infections are transmitted primarily via aerosols or hand-to-hand contact. Although most patients have self-limited symptoms and do not require any specific treatment, some patients, particularly after an influenza illness, have serious secondary bacterial infections.

Influenza

Influenza was undoubtedly known to antiquity. In 1580 and 1782, ravaging epidemics occurred, but the damage therefrom was insignificant in comparison with that observed in the terrifying pandemic of 1918–1919, which struck in three waves, attacked an estimated 20 million persons, and killed 850,000 in the United States alone. Throughout the world, the number of deaths was estimated at 20 million. There is no better or more concise description of the illness produced by influenza viruses than that recorded by Short in 1580:

> “It began with a roughness of the jaws, small cough, then a strong fever with a pain of the head, back, and legs. Some felt as though they were corded over the breast and had a weight at the stomach, all of which continued to the third day at farthest; then the fever went off with a sweat or bleeding at the nose. In some few, it turned to a pleurisy or fatal peripneumony.”

Before 1950, it was never clear whether the pulmonary infection was related to the virus itself or to secondary bacterial invasion. This uncertainty was in large part caused by the absence of a defined etiologic agent, as influenza virus was not recovered from humans until 1933. The first opportunity for accurate assessment of the relative roles of the virus and bacteria in pulmonary complications came during the pandemics of 1957–1958 and 1968–1969. It is now clear that the following pulmonary syndromes may arise in patients infected with an influenza virus.

Lower Respiratory Tract Involvement Without Roentgenographic Evidence of Pneumonia

Within 48 hours after the onset of typical influenza, characterized by fever, dry cough, headache, myalgia, and prostration, the patient notes increased cough, which is at times productive of greenish or blood-tinged sputum. In some patients, this is associated with dyspnea and/or pleuritic chest pain of mild to moderate severity. Physical examination of the lungs reveals unilateral or bilateral inspiratory rales, which may be accompanied by diminished or harsh breath sounds. Occasionally, end-inspiratory wheezes and rales suggest bronchiolitis, and rarely a pleural friction rub can be detected. There is no evidence of consolidation, and roentgenographic findings either appear normal or show accentuation of bronchial markings in the lower lung fields. No evidence of concomitant bacterial infection is obtained. This benign complication of influenza is of importance only in that the patient should be observed closely for development of the more serious pulmonary syndromes detailed below, as well as, rarely, marked stridor resulting from virus-induced laryngitis.

The administration of antibiotics to patients having influenza with no evidence of lower respiratory tract involvement or to those with rales but no evidence of pneumonia is not of benefit and encourages colonization with antibiotic-resistant micro-organisms. These resistant organisms may subsequently be responsible for secondary bacterial pneumonia.

Secondary Bacterial Pneumonia

Secondary bacterial pneumonia is the most common pulmonary complication of influenza. This is not surprising, as the influenza virus damages cilia, delays leukocyte mobilization, promotes adherence of certain bacteria, and interferes with bacterial killing by polymorphonuclear phagocytes. In the majority of patients, the diagnosis can be established by history alone. The patient experiences typical influenza followed by a definite period of improvement. Indeed, such persons may feel well enough to return to their usual occupation. Then, 3 to 14 days after the initial influenza symptoms, the patient's condition worsens precipitously: Recurrence of fever is usually accompanied by shaking chills, pleuritic chest pain, and cough productive of bloody or purulent sputum. In approximately a third of the cases of secondary bacterial pneumonia there is no diphasic course, and pulmonary symptoms blend with the initial influenza.

Physical examination reveals focal involvement of the lung, often with the classic signs of consolidation, and physical findings are confirmed by roentgenogram. Gram's stains of sputum smears show many bacteria and polymorphonuclear leukocytes. Large numbers of bacterial pathogens, most frequently pneumococci, are recovered from cultures. Staphylococci, a rare cause of bacterial pneumonia in healthy adults, are also frequently isolated and are responsible for 15%–30% of bacterial pneumonias in patients who have pre-existing influenza. *Haemophilus influenzae* and *Streptococcus pyogenes* are the responsible micro-organisms in a small number of patients, as are *Escherichia coli*; strains of *Enterobacter, Serratia*, and *Klebsiella*; anaerobic cocci; and species of *Bacteroides*. In these individuals, there is no evidence of serious viral invasion of the lung, and the course and prognosis of this type of pneumonia are related completely to the nature and severity of the bacterial infection.

Primary Viral Pneumonia

A significant number of the deaths related to influenza can be ascribed not to concomitant bacterial infection, but rather to viral invasion of and multiplication within the lungs. These patients have a readily recognized clinical illness. Most have underlying cardiopulmonary disease or are pregnant. The initial symptoms are those of typical influenza, but within 12 to 36 hours the patient notes increasing dyspnea, usually accompanied by a cough productive of scant amounts of bloody sputum. On rare occasions, massive hemoptysis has been noted. Pleural pain is uncommon. At the time of hospitalization, respiratory distress is profound and is accompanied by striking tachypnea, tachycardia, and cyanosis. Abnormalities found on physical examination of the lungs vary with the stage of the disease process. Early in the course of the illness, inspiratory rales and occasional wheezes are heard primarily in the lower lung fields, but as the disease progresses, these findings spread to the entire chest. Evidence of consolidation is uncommonly found, and breath sounds are heard relatively well in the early phases of the infection. Thereafter, as dyspnea and cyanosis increase, breath sounds are suppressed throughout. When the pneumonia reaches its terminal phases, unbearable air hunger is the predominant symptom. Diffuse inspiratory rales, marked expiratory wheezes, and progressive prolongation of the expiratory phase of respiration are observed. The dyspnea and air hunger are frequently so intense and agitation so marked that patients cannot tolerate masks.

Laboratory studies reveal leukocytosis in the majority of patients. The cell count may be as high as 20,000/mm 3, with an increase in the number of polymorphonuclear leukocytes and band forms. Despite the increase in the number of polymorphonuclear cells in the peripheral blood, the sputum shows only a relatively small number, the majority of cells being mononuclear. This relationship in itself serves to distinguish this syndrome from the bacterial complications of influenza. Chest roentgenograms show extensive bilateral infiltrates that radiate from the hilum and simulate the findings in pulmonary edema of cardiac origin (Fig. 10). Occasionally, small pleural or interlobar effusions may be observed.

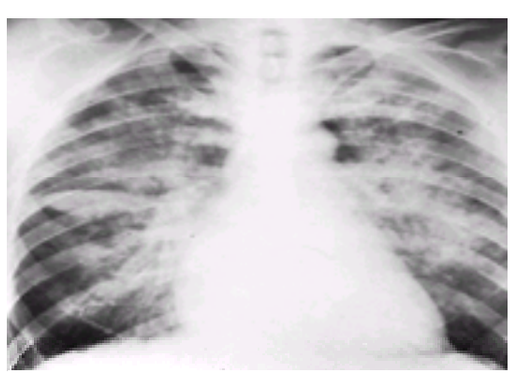

FIG. 10. Primary influenza virus pneumonia in a 49-year-old man with mitral stenosis. Infiltrates radiating from the hilum simulate the findings in cardiogenic pulmonary edema. (Reproduced with copyright permission of The American Society for Clinical Investigation from Louria DB, et al. Studies on influenza in the pandemic of 1957–1958: II. Pulmonary complications of influenza. *J Clin Invest* 1959;38:213.)

During the pandemic of 1957–1958, the mortality from primary influenza virus pneumonia approached 80%; it was also high in the pandemic of 1968–1969. At postmortem examination, there was evidence of tracheitis, bronchitis, and bronchiolitis, with loss of normal ciliated epithelial cells. The alveolar spaces were frequently filled with edematous fluid, and both mononuclear and neutrophilic infiltrates were found, often accompanied by intra-alveolar hemorrhage. A characteristic finding was the presence of an acellular hyaline membrane lining the alveoli. The virus was readily isolated from these lungs, usually in high titer. There usually was no evidence of congestive heart failure or concomitant bacterial infection.

There is no effective treatment for influenza virus pneumonia. There have been no controlled studies of amantadine treatment, so its use in this setting is based on anecdotal reports of a beneficial effect on peripheral airway resistance in uncomplicated influenza. There is currently no evidence that adrenal glucocorticoids are beneficial. Influenza virus pneumonia can be complicated by renal failure and disseminated intravascular coagulation.

In some cases, the pulmonary disease process produced by influenza viruses has been far milder than that observed during pandemics. Focal pneumonitis and lobular or even lobar consolidation have evidently been caused by the viral infection alone. Consequently, influenza virus infection should be considered in the differential diagnosis of any nonbacterial pneumonia.

Concomitant Influenza Virus and Bacterial Pneumonia

In the disease of combined etiology, there may be an interval as long as 4 days between the initial symptoms of influenza and evidence of pulmonary involvement; during this period, considerable improvement may be noted. In many patients, however, the pulmonary disease blends with the original influenza. Cough productive of bloody or purulent sputum, shaking chills, and pleuritic chest pain are reported in most cases. At the time of admission to the hospital, respiratory distress is usually severe, and most patients are cyanotic. Physical examination of the lungs reveals variable findings. The majority of patients have signs of local consolidation involving one or more lobes, and most of these in addition have manifestations of more extensive disease, evidenced by diffuse inspiratory rales and inspiratory or expiratory wheezes. In a minority of individuals, diffuse inspiratory rales or wheezes are present without evidence of focal consolidation. Roentgenograms show diffuse infiltrates similar to those observed in patients with primary influenza virus pneumonia, or a combination of diffuse infiltrates and areas of focal consolidation may be found.

Blood leukocyte counts vary from <1000 to 30,000/mm 3. If the leukocyte count is normal or elevated, adult and immature polymorphonuclear leukocytes predominate, whereas leukopenia is characteristically accompanied by granulocytopenia. Stained smears of the sputum show a large number of polymorphonuclear leukocytes even in patients who have profound peripheral leukopenia; in addition, myriad bacteria are observed.

In contrast to patients with secondary bacterial pneumonia, in whom the pathogen is usually the pneumococcus, approximately half the patients with combined viral and bacterial pneumonia are infected with S. aureus (Fig. 11). This frequency makes it mandatory that initial treatment be directed against the staphylococcus in patients in whom clinical evidence of influenza is followed by pneumonia that, on the basis of physical examination, roentgenograms, and Gram's stains of the sputum, is suggestive of combined viral and bacterial infection. Even with immediate and appropriate antibiotic therapy, the mortality approximates 50%. The combination of mixed influenza virus and bacterial pneumonia and leukopenia usually indicates staphylococcal infection, and a majority of these patients die. At postmortem examination, both pathogenic bacteria and influenza virus can be cultivated from the lungs. The diagnosis of staphylococcal infection in these patients is so likely, the mortality so high, and the time between initial pulmonary symptoms and death so short that antistaphylococcal therapy should be instituted immediately with antibiotics effective against penicillin-resistant staphylococci, such as nafcillin, oxacillin, or a cephalosporin; in communities where methicillin-resistant strains are common, it would be safer to start treatment with vancomycin.

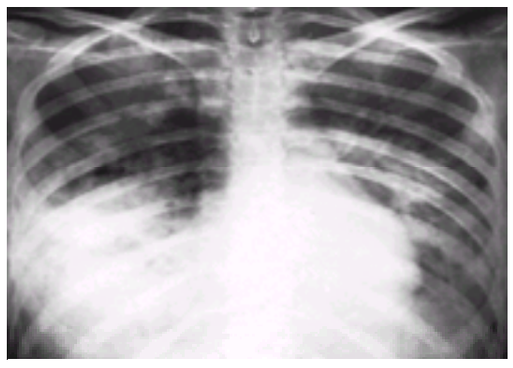

FIG. 11. Chest roentgenogram of a 21-year-old woman with combined staphylococcal and influenza virus pneumonia. (Reproduced with copyright permission of The American Society for Clinical Investigation from Louria DB, et al. Studies on influenza in the pandemic of 1957–1958: II. Pulmonary complications of influenza. *J Clin Invest* 1959;38:213.)

Several studies have produced additional information on three aspects of influenza infection. First, it has been demonstrated that viremia does occur in influenza, although the data currently available suggest it is infrequent. The virus has been isolated from visceral organs, including the spleen and liver, and has been recovered from the brain. Second, interesting epidemiologic evidence from Great Britain suggests that patients in whom staphylococcal complications of viral influenza develop either have active staphylococcal disease themselves (usually furunculosis) or have close contact with others having active staphylococcal lesions. Third, influenza viruses may cause hospital epidemics in which typical manifestations of influenza occur or in which the disease is manifested primarily by lung involvement in patients compromised by a variety of underlying diseases.

Interferon, arising from virus-exposed cells, appears in the lungs of experimental animals before specific antibody can be detected, but its role in recovery from human influenza is unclear. Amantadine hydrochloride prevents the entry of adsorbed influenza A virus into cells. It is useful prophylactically; it can prevent the clinical manifestations of influenza in about 70% of a population exposed to influenza type A viruses. In patients with influenza A and mild pulmonary involvement, amantadine may result in more rapid return of pulmonary function to normal, but this in itself probably does not justify the use of the drug in such cases. To be effective, amantadine must be given within 48 hours after the onset of clinical illness. Amantadine may be helpful in aborting influenza epidemics within hospitals.

Influenza can be prevented in most cases by immunization with appropriate vaccines. These must be changed constantly to include antigens from newly discovered strains of epidemiologic importance. During periods in which influenza is prevalent, older persons and those with underlying cardiopulmonary disease should be immunized. One problem of growing concern is that the major target group for immunization comprises persons <60 to 65 years old, but this group may show suboptimal antibody response to standard influenza immunization schedules.

Varicella

Epidemiology

Varicella is complicated by pulmonary involvement in the newborn, in approximately 10% of normal adults, in both children and adults who acquire the disease during therapy with adrenal glucocorticoids for another illness, in patients suffering from hematologic malignancy, and in pregnant women. The pulmonary manifestations may be overwhelming. The mortality in adults who are hospitalized ranges from 10%–24%, and in children receiving steroids and in neonates it is even higher. Death in children is often associated with secondary bacterial infection of the lung, especially staphylococcal infection, whereas in adults secondary bacterial infection is unusual and death occurs because of severe hypoxia secondary to the extensive viral pneumonitis. Figure 12 shows the roentgenogram of a 36-year-old woman who died 48 hours after hospitalization despite intensive respiratory care.

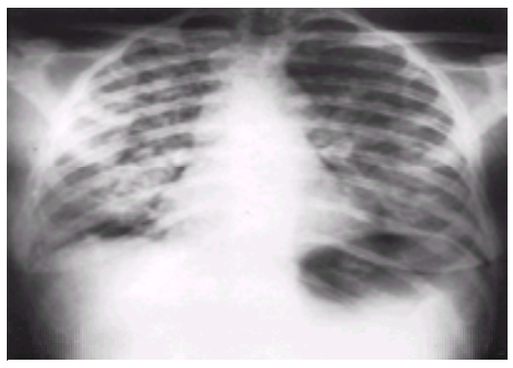

FIG. 12. Fatal varicella pneumonia in a 36-year-old woman. Note the coalescing nodular infiltrates.

Pulmonary involvement is characteristically found 2 to 5 days after onset of the rash. Three types may be distinguished clinically: (1) mild or subclinical disease characterized only by cough; (2) moderate to very severe pneumonia with marked cough and dyspnea, which is usually accompanied by both cyanosis and hemoptysis; and (3) overwhelming and fatal disease with profound cyanosis and shortness of breath. The only findings on physical examination in the patients with milder disease are fine rales and some roughening of the breath sounds. In more severely ill patients, rhonchi, inspiratory and expiratory wheezes, and striking suppression of breath sounds may be detected. In each of the three types, roentgenograms of the chest show diffuse bilateral nodular infiltrates, which in the patients with more severe disease may be coalescent. A small number of patients have pleuritic chest pain, which may be associated with pleural effusions that are occasionally massive. Roentgenographic infiltrates may clear rapidly, but not infrequently they resolve slowly, sometimes persisting for 2 to 4 weeks or longer. Late calcification may occur, and diffusion defects may be demonstrated for a prolonged period following clinical improvement. Examination of sputum smears shows predominantly mononuclear cells and giant cells; characteristic type A intranuclear inclusion bodies can sometimes be seen with Giemsa stain. The blood leukocyte count varies from normal to moderately elevated, usually with a predominance of polymorphonuclear leukocytes. Postmortem examination reveals hemorrhagic, edematous lungs with an interstitial mononuclear infiltrate, alveolar hemorrhage, and sometimes hyaline membranes lining the alveoli. There also may be hemorrhagic pleural blebs and, in the liver, spleen, and occasionally the kidneys, focal necrosis and hemorrhage.

Treatment

Acyclovir given intravenously appears to be effective therapy for varicella pneumonia. Reports documenting the safety and efficacy of acyclovir for varicella pneumonia complicating pregnancy have also appeared. Famciclovir would be a reasonable oral alternative to acyclovir, but its safety in pregnancy has not been established (category B). For individuals intolerant of acyclovir or suspected of having acyclovir resistance, intravenous foscarnet may be used. The safety of foscarnet in pregnancy has not been established (category C). Although varicella pneumonia may be excessively severe in patients receiving adrenal glucocorticoids, these drugs are advocated by many in the treatment of overwhelming pulmonary varicella infection. There are no adequate data to indicate whether such treatment is beneficial. Secondary bacterial infection should be suggested by the sudden appearance in the sputum of large numbers of polymorphonuclear leukocytes. Not only have prophylactic antimicrobial agents failed to prevent the secondary bacterial complications, but there is reason to believe that the bacterial invaders in patients receiving antimicrobial agents prophylactically are more likely to be antibiotic-resistant staphylococci and gram-negative organisms, which are currently considerably more difficult to treat. Antibiotics should therefore be withheld until there is evidence of bacterial superinfection. Patients with varicella pneumonia should be maintained in strict isolation, and special care should be taken to keep them separated from patients who are receiving adrenal steroids or who have hematologic malignancies.

Rubeola (Measles)

Rubeola is associated with three types of pulmonary complications. First, especially if the patient is very young or very old, the virus itself may produce interstitial pneumonia in the absence of bacterial infection. This type of pneumonia is acute and occurs concomitantly while, before, or more often shortly after the rash has reached its peak. Cough and dyspnea are found frequently, but only small amounts of sputum are produced and pleuritic pain is unusual. Roentgenograms show infiltrates radiating from the hilar areas. The blood leukocyte count is characteristically normal or reduced. Although the prognosis is usually good, measles virus pneumonia continues to carry a significant mortality, approximating 5%. In children it may be followed by bronchiectasis.

Second, bacterial pneumonia may complicate rubeola, usually occurring 1 to 7 days after the onset of rash. If the patient has typical measles, improves, and then begins to exhibit pulmonary symptoms, this is virtually pathognomonic of a bacterial superinfection. The bacteria most commonly involved are *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus,* and *Haemophilus influenzae*.

Third, when it is grown in human and monkey renal cell cultures, the measles virus produces multinucleated giant cells with characteristic inclusions. Giant-cell pneumonia apparently caused by the measles virus may follow overt measles in previously healthy children. Furthermore, in children with underlying disease, the measles virus may produce subacute or chronic, usually fatal, giant-cell pneumonia, which may occur with or without clinical evidence of typical measles preceding the pneumonia. Pathologically, giant-cell pneumonia is characterized by an interstitial mononuclear infiltrate, alveolar cell proliferation, and giant cells with intranuclear and intracytoplasmic inclusions.

No treatment other than supportive therapy is available for measles virus invasion of the pulmonary parenchyma. Treatment of secondary bacterial complications depends on the antibiotic susceptibility of the bacterial pathogen.

An additional form of pulmonary disease may occur in patients who have previously received killed measles vaccine and subsequently are given a live measles vaccine or are exposed to wild virus. Rash, lymphadenopathy, and pneumonitis may follow. The pulmonary infiltrate, which may not be accompanied by rash, may be interstitial, locular, lobar, or nodular. Nodular or interstitial infiltrates may persist for weeks or even months.

Adenovirus Infection

These viruses infect 8% of children and 1%–3% of adults annually. Adenovirus infections occur throughout the year, with a peak incidence of respiratory infections occurring in late winter to early spring. Adenoviruses are spread by intimate contact or aerosolization of infected secretions, and serotypes 3, 4, and 7 are more frequently associated with lung disease. The first isolation of adenoviruses from diseased patients occurred in a study of military recruits in 1954; these individuals had a variety of influenza-like syndromes, referred to as *acute respiratory disease*. In that report, one fifth of infected individuals required hospitalization.

Fever, headache, nasal congestion, hoarseness, and paroxysms of cough are the most common symptoms and usually last 3 to 5 days. On examination, cervical lymphadenopathy, laryngitis, and rales are common. Sputum examination may reveal either mononuclear cells or a predominance of polymorphonuclear leukocytes. The appearance of the latter does not in itself connote secondary bacterial infection, but bacterial superinfection does occur in a significant percentage of patients with adenovirus pneumonia. Although patchy or lobular infiltrates are found most frequently, there may be extensive consolidation. There are no specific drugs or therapeutic measures available for the treatment of adenovirus infections.

Hantavirus Infection

Hantaviruses are RNA viruses belonging to the family *Bunyaviridae*. Rodents are the primary reservoir for all hantaviruses and shed the virus in their saliva, urine, and feces. Humans acquire infection most often by inhalation of aerosols from rodent excreta. Person-to-person transmission does not occur. Hantaviral disease first became a public health concern in the United States in the 1950s, when soldiers serving in Korea were afflicted with an illness referred to as *Korean hemorrhagic fever* or *hemorrhagic fever with renal syndrome*. Only rarely have there been prominent pulmonary signs or symptoms. However, a new hantavirus was isolated in the southwestern United States in 1993 that caused hantavirus pulmonary syndrome. The deer mouse (*Peromyscus maniculatus*) has been determined to be the vector for this syndrome.

The mortality of hantavirus pulmonary syndrome is 10 times higher than that associated with Korean hemorrhagic fever. The syndrome is manifested by (1) a febrile illness (temperature ³101°F) occurring in a previously healthy person, characterized by unexplained adult respiratory distress syndrome or bilateral interstitial pulmonary infiltrates developing within 1 week of hospitalization with respiratory compromise requiring supplemental oxygen, or (2) an unexplained respiratory illness resulting in death in conjunction with an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable, specific cause of death. The agent of the syndrome is the first hantavirus to cause disease in North America. Now named *sin nombre virus*, it closely resembles a Prospect Hill strain of hantavirus

that is found in voles but is not pathogenic in humans.

The diagnosis is largely based on epidemiologic circumstances and a clinical triad of interstitial infiltrates with adult respiratory distress syndrome, hemoconcentration, and marked elevation of lactate dehydrogenase. Anecdotal evidence suggests ribavirin may be beneficial.

Respiratory Syncytial Virus Infection

Perhaps the most frequently involved virus in young children is the respiratory syncytial virus. Respiratory syncytial virus infection is seasonal, occurring from November through March. The frequency with which infant pneumonia or bronchiolitis is related to this agent obviously depends on the prevalence of the virus in the environment, but current data suggest that respiratory syncytial virus is responsible for 10%–40% of lower respiratory tract disease in infants and children. During epidemics, it may account for 50% of all pediatric hospital admissions.

The virus is most likely spread by aerosol or direct contact with infected specimens, and inoculation routes include the eyes, nasopharynx, and oropharynx. Incubation lasts 2 to 8 days. Respiratory syncytial virus may cause croup, bronchiolitis, or pneumonia, and the latter is more frequent with primary infection. Respiratory syncytial virus infection among adults is usually mild, but severe disease may be seen among institutionalized persons, the elderly, and patients with underlying cardiopulmonary disease. Abnormal roentgenographic findings may include interstitial infiltrates, bronchopneumonia, and diffuse pneumonia. A specific diagnosis can be made by obtaining nasopharyngeal secretions for viral culture. In addition, respiratory syncytial virus infection can be diagnosed rapidly by antigen detection using immunofluorescence techniques or ELISA. Although aerosolized ribavirin showed promise for respiratory syncytial virus pneumonitis in children, there is no convincing evidence for its benefit. Most authorities now recommend ribavirin only for severe respiratory syncytial virus disease in immunocompromised patients, but experience is anecdotal and efficacy has been dismal.

RICKETTSIAL DISEASE

Q Fever

Q (query) fever was first described in 1937 by Derrick, who detailed an acute febrile illness involving abattoir workers in Brisbane, Australia. Subsequently, Burnet in Australia and Cox in the United States isolated the causative organism and demonstrated that it was one of the rickettsiae. In honor of these investigators, the micro-organism is called *Coxiella burnetii*. *C. burnetii* is worldwide in distribution, the most common reservoirs being sheep, goats, cattle, and ticks. The organism is frequently shed in cows' milk, and the disease may spread by consumption of raw milk, by inhalation of contaminated dust, and occasionally by tick or animal bites. Recent outbreaks have been associated with infected parturient cats. Human-to-human transmission has been reported.

Clinical Manifestations

After an incubation period that ranges from 2 to 4 weeks, clinical evidence of disease appears, usually abruptly. Fever occurs in almost all patients, is frequently of considerable degree, and in untreated cases usually persists for a period of 10 days to 3 weeks, but it may remain for as long as 3 months. It then resolves by lysis. Severe headache, marked sweats, shaking chills, and diffuse myalgia are found in the majority of patients. One third to two thirds of patients report cough that, in contradistinction to that observed in primary atypical pneumonia, is usually not severe. It is typically nonproductive, although occasionally a small amount of sputum is expectorated, infrequently blood-tinged. From 10%–40% of patients experience mild to moderate chest pain that may be pleuritic in nature. Dyspnea is noted in a minority of cases, and vomiting, confusion, and abdominal pain occur uncommonly.

Although the patient usually appears acutely ill on physical examination and is markedly febrile, the pulse is relatively slow. The abnormalities in the lungs, ordinarily consisting of unilateral or bilateral fine inspiratory rales, are often confined to the lower lobes. On occasion, dullness to percussion, evidence of frank consolidation, a pleural friction rub, and signs of pleural effusion are noted. Splenomegaly occurs in 5%–10% of cases, and hepatomegaly, cyanosis, a maculopapular rash, and stiffness of the neck with resistance to flexion may be observed in a small number of individuals.

Roentgenographic and Laboratory Findings

The leukocyte count is usually normal or slightly elevated, with a moderate increase in the number of polymorphonuclear leukocytes. Stained smears of the sputum show predominantly mononuclear cells. The radiographic picture is variable. Segmental and subsegmental pleura-based opacities are common. Multiple rounded opacities have been reported following inhalational exposures. Pleural effusions are usually small but may be present in up to one third of cases. Hilar adenopathy may occur. Time of resolution ranges from 10 to 90 days. By injection of infected material into the peritoneal cavity of guinea pigs, *C. burnetii* can be isolated from the blood, sputum, or pleural fluid during the acute phase of the illness. Specific complement-fixing and agglutinating antibodies appear in the blood during the second to third week of illness and in most cases establish the diagnosis. The Weil-Felix reaction is invariably negative.

Complications

The pulmonary lesions heal without residua, and the complications of Q fever are found in extrapulmonary sites. The hepatitis may be severe and prolonged, even fatal, with marked icterus and derangement of liver function. Arthritis, iritis, pericarditis with pericardial friction rub, myocarditis, otitis, epididymitis, esophagitis, neuropathy, and radiculitis have all been reported. Although the lumbar puncture usually yields normal results despite the severe headache, the micro-organism has been isolated from the spinal fluid, and on rare occasions spinal tap has revealed lymphocytic meningitis. A small number of cases of endocarditis caused by *C. burnetii* have been described, most of them in the United Kingdom; in 80%, the aortic valve is involved with aortic regurgitation. Perhaps the most frequent complication is thrombophlebitis, which may be accompanied by pulmonary emboli. A significant number of patients in whom well-documented Q fever develops have persistent, vague aches and pains and fail to return to their original state of health for a substantial period of time. The mechanisms underlying these prolonged and at times incapacitating features have not been established, but they are not associated with demonstrable persistence of the micro-organism.

Treatment

Q fever is rarely a fatal disease. The micro-organism is susceptible in vitro to tetracyclines and chloramphenicol, and administration of one of these antibiotics in a dosage of 2 g/d in adults is usually associated with rapid defervescence and clinical improvement. However, in some patients treated with a tetracycline or chloramphenicol, improvement may be surprisingly slow, and relapse may occur after the antibiotics have been discontinued. These relapses usually respond promptly to reinstitution of the same antimicrobial regimen.

Scrub Typhus

Scrub typhus, a rickettsial disease caused by *Rickettsia tsutsugamushi*, is endemic in Japan, Southeast Asia, the southwestern Pacific, and Australia. It is transmitted to humans by mites, and after a 4- to 10-day incubation period a primary eschar appears at the site of the mite bite. The eschar and regional adenitis are found in at least 60% of patients with scrub typhus.

There are three potentially severe complications of the disease: myocarditis, encephalitis, and pneumonitis. Lung involvement, which varies considerably in its manifestations, is said to occur in 40%–50% of patients. Cough, the most frequent pulmonary symptom, may be productive of small amounts of blood-streaked sputum. Extensive pulmonary disease may cause dyspnea and cyanosis. The pneumonia is primarily interstitial in nature, and may be either localized or diffuse. Chest radiographs usually show patchy infiltrates, but lobar consolidation may be seen.

The average mortality is approximately 5% in untreated patients. Tetracyclines are the treatment of choice.

Rocky Mountain Spotted Fever

In Rocky Mountain spotted fever, chest complaints may be the presenting manifestations. Lung involvement is at first characterized by patchy pneumonitis or pleural effusion accompanied by nonspecific symptoms, including chest pain and cough. As the disease progresses, the local vasculitis and systemic thrombocytopenia may result in lung edema and/or hemorrhage. In some cases, the respiratory distress syndrome supervenes. Additionally, Rocky Mountain spotted fever myocarditis can result in congestive heart failure. Roentgenograms vary depending on the pathophysiology: There may be focal infiltrates, dense consolidation from hemorrhage or secondary bacterial infection, or diffuse bilateral infiltrates. In some cases, the lack of a rash and the prominence of pulmonary manifestations result in a substantial delay in establishing a correct diagnosis. Occasionally, myalgias involving thoracic muscles are so severe that a diagnosis of bacterial pneumonia or pulmonary embolus is mistakenly made.

ZOONOTIC PNEUMONIAS

Bacteria associated with domestic and wild animals are often capable of producing disease in humans, and spread may occur by direct contact, inhalation or ingestion, or animal bites or insect intermediates. These zoonotic bacterial infections have few unique clinical characteristics, and the diagnosis is often first considered after a provocative interrogation including travel history, occupation, hobbies, and contact with animals and insects. Although the diseases reviewed here are rare causes of respiratory infections in the United States, they can be severe, life-threatening, and contagious illnesses for which effective antimicrobial therapy is available.

Anthrax

Micro-organism

Bacillus anthracis, a large, aerobic, gram-positive, sporule-forming micro-organism, has played a major role in the history of microbiology. Isolated by Robert Koch in 1877, it consistently produced fatal infections in laboratory animals, and Koch's now famous postulates for determining whether an organism is a pathogen were based on his studies with anthrax.

Epidemiology

Pulmonary anthrax has never been a common disease. Some 200 cases were reported before 1900, and only a small number of cases have been reported since that time, with most of the patients having some contact with wool and wool processing. However, direct contact with wool or hides during processing procedures is not necessary; anthrax has occurred in persons who lived or frequently walked near tanneries but never had direct contact with such procedures. It should be emphasized that finished rugs and carpets are not a source of the infection.

The thoracic form of the disease is not ordinarily pneumonia. After spores have been inhaled, they are carried to the pulmonary parenchyma, where they undergo phagocytosis by macrophages and then are transported to regional lymph nodes, where they germinate. The germination of the spores produces a violent reaction in the host: Necrosis, hemorrhage, and edema lead to acute hemorrhagic mediastinitis. Subsequent pulmonary involvement is secondary to hematogenous spread of the bacteria. Like mediastinitis, this type of pneumonia is characteristically hemorrhagic. Although parenchymal lung involvement usually follows bloodstream dissemination, there have been reports of pneumonia with necrosis of alveolar walls that apparently occurred as a primary phenomenon following spore inhalation.

Clinical Manifestations

The course of the disease is usually diphasic. The patient initially experiences chills, fever, and myalgia. These symptoms are followed by a 1- or 2-day period during which there is either no change or some improvement; then, progressive disease ensues abruptly and is characterized by tachypnea, dyspnea, cyanosis, and cardiovascular collapse. Rales, and at times rhonchi and wheezes, may be heard in focal areas or diffusely throughout the lung fields. In some patients, dullness to percussion and altered breath sounds suggest consolidation. Chest roentgenograms show congestion, patchy infiltrates, areas of consolidation, and mediastinal widening. While the disease is fulminating, pleural effusion, subcutaneous edema of the chest and neck, splenomegaly, and meningitis may be observed. Most of the patients reported have died.

Therapy

As the anthrax bacillus is susceptible to penicillin and streptomycin, the treatment of choice for adults is 3 to 10 million units of penicillin per day. Some give streptomycin together with penicillin. Erythromycin, chloramphenicol, and tetracycline are alternate agents.

Brucellosis

Brucellae are small, gram-negative, coccobacillary aerobes that can be separated into four major species: *Brucella abortus, Brucella melitensis, Brucella suis,* and *Brucella canis.* Brucellosis occurs in susceptible individuals who deal with animals and animal products, veterinarians, farmers, and persons ingesting unpasteurized dairy products. The organism is acquired through ingestion or, rarely, contact. No human-to-human transmission has been reported.

The clinical presentation of brucellosis involves a variety of nonspecific constitutional symptoms, including relapsing fever and headache. Cough occurs in one fourth of cases, but other respiratory symptoms are notably absent. The most characteristic radiographic findings include perihilar thickening and peribronchial infiltrates, although nodular lesions and miliary infiltrates may be seen.

No data are available on sputum bacteriology, and blood culture findings are rarely positive. Cultures of biopsy specimens of granulomas are frequently positive, and the *Brucella* agglutination test is confirmatory. The most effective therapy is with tetracycline (1.5 to 2.0 g orally) and streptomycin (1.0 g intramuscularly) daily for 1 month.

Pasteurella multocida Pneumonia

Pasteurella multocida is the causative agent of hemorrhagic septicemia in animals and can be isolated from the respiratory tracts of a variety of domestic and wild animals. The organism is a small, gram-negative, bipolar-staining, nonmotile rod that grows well on blood agar, but its growth is inhibited on MacConkey media. In humans, three clinical patterns of disease are observed: (1) local suppuration or cellulitis following a bite or scratch; (2) meningitis or bacteremia; and (3) acute or subacute lung infection, sometimes accompanied by empyema. Although respiratory disease is rarely reported, sputum is the most common source of isolates in cases of animal-bite cellulitis.

Most cases of *Pasteurella* pneumonia occur in individuals with underlying chronic lung disease, including bronchiectasis, emphysema, and carcinoma. Spread to humans is probably from animals, but in only half the cases is there an exposure history. Lung involvement is probably initiated by aspiration of the oropharyngeal flora. Radiographic findings include lobar, multilobar, or diffuse patchy infiltrates with a tendency to spare the upper lobes. Pleural effusions are found in 20% of cases. Empyema and abscess formation occasionally occur. Diagnosis depends on isolation of the organism from sputum, pleural fluid, or blood. Penicillin is the drug of choice, as the majority of strains are exquisitely sensitive. Alternative choices include chloramphenicol, cephalosporins, and tetracycline.

Tularemia

Francisella tularensis is a tiny, gram-negative, pleomorphic, coccobacillary organism that grows poorly on artificial medium unless supplemented with serum, glucose, and cystine. There are approximately 150 cases of tularemia per year in the United States, and pulmonary disease occurs in 10%–15% of these cases. Tularemia can be transmitted to humans by wood ticks, dog ticks, the deer fly, and a variety of wild animals, notably the rabbit. Punched-out skin lesions with secondary lymph node involvement, the so-called ulceroglandular type, is the most common form of the disease; although pneumonic tularemia often arises from hematogenous dissemination from cutaneous foci, as many as 50% of patients with pleuropulmonary tularemia have no demonstrable disease of the skin or lymph nodes.

Respiratory disease often begins with a poorly productive cough, chest pain, and dyspnea. In airborne tularemia, sore throat has been observed in about one third of patients, and a similar proportion exhibit a skin rash, either erythema nodosum or erythema multiforme. The roentgenographic appearance varies from small areas of bronchopneumonia to extensive lobar or lobular consolidation, often with hilar adenopathy. Extension to the pleura is common. Only rarely are organisms seen on sputum Gram's stain, and because of the potential for laboratory-acquired infection, isolation should be reserved for special reference laboratories. The diagnosis can be established by demonstrating a rise in serologic agglutinations. The micro-organism is susceptible to streptomycin (or gentamicin), tetracycline, and chloramphenicol. Streptomycin remains the mainstay of therapy, with a dramatic response usually being observed within 24 to 48 hours of initiation of the antibiotic, in a dosage of 1.5 to 2.0 g/d.

Plague

Yersinia pestis remains a problem in China, India, Vietnam, and certain areas of the Middle East and Africa. In the past 15 years, a very small number of cases have been reported in the United States, most of these in California and New Mexico; in one case, a domestic cat was the source. Although the bacillus, first isolated by Yersin in 1894, has now been relegated to secondary importance among organisms parasitic to humans, its importance in medical history and perhaps in the course of our civilization is undeniable. During the plague epidemic of the fourteenth century, when many cases were pneumonic, the disease acquired its macabre figurative name, the Black Death. During that epidemic, it is estimated that one half to two thirds of the people in Great Britain died of this infection. In the sixteenth century,

ravaged the world for 30 to 60 years, “depopulated towns, turned the country into a desert, and made the habitations of men to become the haunts of wild beasts,” and during this period it is said to have killed some 100 million persons. During the seventeenth to nineteenth centuries, there was a striking decline in the incidence of the disease, and subsequently, because of higher standards of living, greater attention to personal hygiene, and vigorous efforts to control rat populations, plague virtually disappeared from many areas of the world.

Pneumonic plague is not the natural form of the infection in humans. Ordinarily, plague acquired from wild rodents through infective fleas occurs initially in the bubonic form. Progressive bubonic disease is associated with bacteremia in as many as 70%–85% of patients, and secondary lung involvement ensues in some. As in the epidemic of the fourteenth century, these individuals may spread the disease by the airborne route to other persons, in whom the lungs may become the initial site of invasion. Such patients usually have shaking chills and high fever. Their sputum varies from gelatinous to rusty, and on occasion there is profuse hemoptysis. Most striking in these patients is profound dyspnea and air hunger. Physical examination and chest roentgenograms show lobar pneumonia or diffuse involvement simulating pulmonary edema. The lung may be heavy, mimicking the roentgenogram of Friedländer's pneumonia. The disease is characteristically fulminating. The average survival time among untreated patients is 1.8 days. Postmortem examination of the lungs shows severe hemorrhage, coagulation necrosis, and infiltration by large numbers of polymorphonuclear leukocytes.

Treatment, which must be immediate if the patient's life is to be saved, consists of oxygen and antibiotics. The micro-organism is usually susceptible to streptomycin, other aminoglycosides, tetracyclines, and chloramphenicol, and the therapeutic regimen of choice appears to be one of the last two in combination with streptomycin or gentamicin. Patients with bubonic plague should probably be isolated, as some may have throat cultures positive for *Y. pestis.* Strict isolation precautions should be observed in cases of pneumonic plague, as the dangers to those attending such patients are great.

PARASITIC DISEASE

Three types of pulmonary disease are associated with protozoal or helminthic infection:

1. Loeffler's syndrome with no evidence of invasion of the pulmonary parenchyma
2. Parasitic disease with direct lung invasion
3. Pulmonary involvement resulting from direct spread from subdiaphragmatic lesions

Loeffler's Syndrome

In 1936, Loeffler described a series of cases characterized by pulmonary infiltrates and mild illness lasting for 3 to 8 days and accompanied by striking peripheral eosinophilia, with the peak of the increase in eosinophils usually following the maximal pulmonary infiltration. Roentgenographic abnormalities were patchy and fleeting. Moderate cough was noted, but most of the patients remained afebrile and sputum was ordinarily not produced. A great number of infections and drugs have been associated with the syndrome. Pulmonary eosinophilia has been observed in patients with certain bacterial and mycotic infections, including tuberculosis, brucellosis, coccidioidomycosis, aspergillosis, and histoplasmosis; in patients with allergic asthma; in individuals exposed to certain drugs, especially antibiotics; and in patients with intestinal parasitism by the following protozoa, nematodes, and trematodes: *Entamoeba histolytica, Trichinella spiralis, Trichuris trichiura, Enterobius vermicularis, Fasciola hepatica, Necator americanus, Taenia saginata, Ancylostoma braziliense, Ancylostoma duodenale, Toxocara canis, Toxocara mystax, Ascaris lumbricoides*, and *Strongyloides stercoralis.* The last four perhaps do not belong in this category, as there is considerable evidence to suggest that the pulmonary disease with eosinophilia is related to direct invasion of lung tissue. Because Loeffler's syndrome is benign, no specific therapy is required.

Parasitic Disease with Direct Lung Invasion

Schistosomiasis

Micro-organism

Pulmonary schistosomiasis, which may be caused by *Schistosoma mansoni, S. japonicum,* or *S. haematobium,* is a problem of considerable magnitude in areas of the Middle East, Asia, Africa, and Latin America. Free-swimming cercariae infect humans by penetrating the skin. The larvae (schistosomulae) gain access to the circulation, pass through the lungs, and eventually reach the portal and mesenteric vessels. During the period in which the larvae pass through the pulmonary vasculature, asthmatic symptoms may occur, but the major pulmonary involvement occurs later and is related to metastatic spread of ova produced by the adult worms through the systemic circulation to pulmonary vessels. The ova obstruct the arterioles, penetrate the arteriolar walls, and become the focus of obliterative granulomatous arteritis.

Clinical Manifestations

During the larval migration phase, symptoms include wheezing, dyspnea, and nonproductive cough. In a small number of cases, acute pneumonic schistosomiasis occurs 3 weeks to 3 months after the initial cercarial penetration. This is apparently related to an intense inflammatory response to invasion by ova. In such cases, schistosomiasis may be manifested as overwhelming, diffuse disease characterized by severe respiratory distress, productive cough, hemoptysis, cyanosis, and bilateral rales on physical examination of the chest, or there may be signs of focal consolidation. Pulmonary involvement in those in whom symptoms develop is usually chronic and accompanied almost uniformly by extensive extrapulmonary schistosomal involvement, including hepatosplenomegaly. Dyspnea is the most common symptom, and the majority of patients also have a cough that is ordinarily nonproductive. Both cyanosis and hemoptysis are rare.

Roentgenographic and Laboratory Findings

In those with symptoms related to larval migration, the chest roentgenogram appears normal or shows some nonspecific increase in markings. Some degree of eosinophilia is usually found, and this may be marked. In patients with acute pulmonary schistosomiasis, areas of consolidation or coalescing nodular infiltrates are found. The lung fields may appear normal roentgenographically, or there may be a diffuse fibrotic or nodular infiltrate. The vascular dilatation may be marked, as shown in Fig. 13, the roentgenogram of a 16-year-old girl with schistosomal cor pulmonale. Many, but not all, patients with acute pulmonary schistosomiasis have significant peripheral eosinophilia, but eosinophilia is ordinarily absent in patients with chronic obliterative arteritis. The stools of most are positive for *Schistosoma* ova. In addition, in as many as a third of patients who have a productive cough, *Schistosoma* ova may be demonstrated in the sputum.

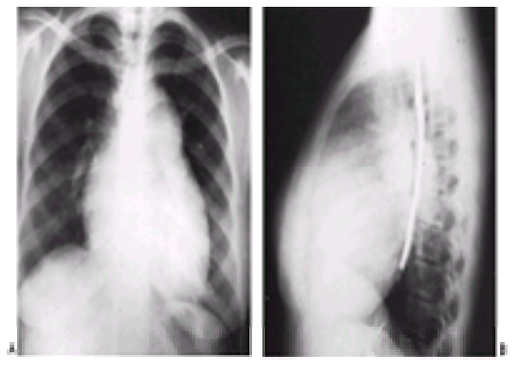

FIG. 13(A,B). Schistosomal cor pulmonale in a 16-year-old girl. Note the marked dilatation of the pulmonary artery segment.

Once cor pulmonale has appeared, antischistosomal therapy is ineffective. If ova are found in the sputum or if the patient has acute pulmonary schistosomiasis, praziquantel in a single oral dose of 40 mg/kg is now considered to be the drug of choice. It is uncertain whether therapy actually alters the natural course of acute schistosomal pneumonia.

Echinococcosis

Epidemiology

Hydatid disease of the lung is caused by infection with the larval form of *Echinococcus granulosus,* a small tapeworm of the dog. Human infection is especially prevalent in the Middle East, Australia, New Zealand, central Europe, and parts of Latin America, areas in which sheep are an important part of the economy. Hydatid disease is uncommon in North America, except in certain areas of Canada and Alaska.

The incidence of lung involvement in human echinococcosis ranges from 5%–25% in different series. Although pulmonary infection usually arises from primary hematogenous dissemination, it may be secondary to metastatic spread from a ruptured abdominal cyst. Almost all the pulmonary cases are caused by *E. granulosus* (*unilocularis*); only rarely is a case caused by the more malignant *E. multilocularis.* There is a clear predilection for the lower lobes, especially the right lower lobe. Approximately one third of patients with pulmonary echinococcosis also have clinical evidence of extrapulmonary hydatid disease.

Clinical Manifestations

Initial symptoms consist most commonly of cough, hemoptysis, and pleuritic pain. Sputum production is usually sparse, and characteristically there is little fever. Physical examination is frequently unrewarding. Clubbing of the fingers and toes is detected infrequently. Chest roentgenography shows one or more discrete, round lesions that typically are sharply defined with little surrounding inflammatory response and are sometimes calcified. These lesions are frequently mistaken for metastatic carcinoma.

Hydatid involvement of the thoracic cavity also may take the form of primary mediastinal disease (Fig. 14), which occurs most commonly in the posterior mediastinum. Anterior mediastinal involvement may be associated with Horner's syndrome (miosis, ptosis, and diminished sweating ipsilaterally).

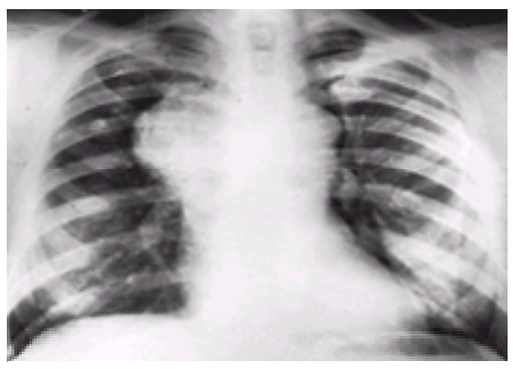

FIG. 14. Mediastinal echinococcosis. Note the thin rim of calcium in the cysts.

Laboratory Findings

Laboratory analysis in patients with echinococcosis reveals a normal total leukocyte count. Eosinophilia, generally moderate, is found in 50% of patients. Careful examination of sputum or of the sediment from material aspirated from the thoracic cavity may reveal hooklets or scoleces. Precipitin, complement fixation, indirect hemagglutination, and bentonite flocculation tests are available, and the results are positive for the majority of patients with echinococcal disease. The most reliable test is an enzyme immunoassay utilizing partially purified hydatid antigen.

Treatment

Surgical removal of the cyst, the treatment of choice, is often not technically feasible, and chronic disease is frequent even after apparently complete extirpation of the cyst. However, despite the persistence of chronic hydatid disease of the lungs or abdomen for many years, the patient may lead a relatively normal life. Secondary infection of the cyst should be treated with appropriate antimicrobial agents and surgical drainage. Medical therapy with mebendazole or albendazole may be effective.

Ascariasis

Ascariasis is a common intestinal nematode infection caused by *A. lumbricoides.* It is worldwide in distribution, and in the United States is found particularly in the southeastern section of the country. After ingestion, the embryonated ova hatch into larvae that penetrate the intestinal wall, reach the circulation, and subsequently arrive in the lungs. During pulmonary migration, fever is commonly of considerable magnitude. Cough, hemoptysis, inspiratory rales, and evidence of focal consolidation are the other common manifestations, but on rare occasions the lesions can be diffuse and produce death either directly or through the development of severe, superimposed bacterial infection. Peripheral eosinophilia is often found during pulmonary migration but may not become evident until late in the course of the pulmonary disease. In addition to pneumonitis with fever, cough, and hemoptysis, there is considerable evidence to suggest that migration of the larvae through the lungs produces a milder illness that is consistent with Loeffler's syndrome.

The diagnosis of pulmonary ascariasis may be established by finding the larvae in the expectorated sputum or in gastric aspirates. The role of *A. lumbricoides* also should be suspected in patients with pneumonitis or Loeffler's syndrome if ova or adult worms are found in the stool. Serologic tests, including agar gel diffusion and immunoelectrophoresis, are available. Treatment of the pulmonary disease is usually not necessary, and in any case it is not known whether any of the currently available antihelminthic agents are beneficial in lung ascariasis. If pulmonary disease persists, a trial of mebendazole might be considered.

Visceral Larva Migrans

Visceral larva migrans results from the ingestion of embryonated ova of the dog or cat roundworm *T. canis* or *T. cati.* The disease occurs predominantly in young children who have close contact with dogs or cats and eat dirt. The larvae hatching from the ova penetrate the intestinal wall and migrate widely. Hepatomegaly is noted frequently. During pulmonary migration, wheezing, cough, cyanosis, or dyspnea may occur in association with roentgenographic evidence of diffuse or focal pneumonitis. The diagnosis can be established best by liver biopsy, with histologic sections of the specimen showing eosinophilic granulomas with larvae. The blood leukocyte count is usually markedly elevated, often reaching 40,000/mm^3 or higher, and eosinophilia of >30% is present in 85% of patients. The available serologic tests, indirect fluorescent antibody and indirect hemagglutination, are sensitive but lack specificity. The prognosis is usually good. Thiabendazole, the present drug of choice, can be given orally in a dosage of 25 mg/kg of body weight twice a day for 5 days (maximal daily dose, 3.0 g).

Strongyloidiasis

An estimated 35 million persons in the world suffer from infection with *Strongyloides stercoralis.* The majority of cases in the United States are confined to the southern parts of the country. Pneumonitis may occur during pulmonary migration of larvae, characterized by fever, wheezes, productive cough, and patchy or diffuse infiltrates on chest roentgenogram. Blood and sputum eosinophilia are found frequently, and typical larvae may be detected in the expectorated sputum.

Pulmonary manifestations are usually transient but may be chronic or recurrent. Recurrence is perhaps related to repeated bouts of endogenous dissemination to the lungs from established foci in the small intestines.

In the normal host, rhabditiform larvae are passed in the stool but can reinvade through the perianal area. This is called *exoautoinfection.* In patients with immunologic defects, in particular resulting from hematologic malignancies, large numbers of filariform larvae may penetrate the intestinal wall and invade various tissues, including the lungs (*endoautoinfection*). In almost all cases, corticosteroids and/or immunosuppressive agents have been administered. As a consequence of the penetration, gram-negative septicemia may occur, involving one or more enteric organisms. Larval meningitis may occur, and the pulmonary involvement varies from small pneumonic patches to massive infiltrates of five lobes. Larvae can usually be seen in expectorated sputum. Findings on stool examination are usually positive but in some cases may be negative, and jejunal intubation is necessary to establish the diagnosis. In the hyperinfection syndrome, eosinophil counts range from normal to markedly elevated. Immunofluorescence, complement fixation, and indirect hemagglutination tests for antibody determination are available, but more data are needed

to define their usefulness.

Thiabendazole is the drug of choice in intestinal strongyloidiasis. Whether it is beneficial in acute or chronic pulmonary disease caused by *S. stercoralis* is unknown.

Paragonimiasis

Pulmonary paragonimiasis is found commonly in Southeast Asia, the Philippines, and less frequently in the South Pacific, Africa, India, and Latin America. The etiologic agent is the oriental lung fluke *Paragonimus westermani.*

The pulmonary manifestations vary considerably and depend on the number of parasites involved. Most patients have little fever or prostration. Cough is usually not marked but may be productive of thin sputum with globules of tenacious gelatinous material, or there may be small amounts of blood-stained sputum. Occasionally, the symptoms may be more severe, consisting of prostration and dyspnea. Pleuritic pain is noted infrequently. In most patients, the only findings are inspiratory rales, sometimes accompanied by dullness to percussion and roughened breath sounds. Less frequently, areas of focal consolidation or pleural effusion or pneumothorax may be detected. Roentgenograms of the chest usually reveal linear or patchy infiltrates in the lower lung fields or nodular densities in which there may be areas of rarefaction. Cystlike lesions may be found and may be as large as several centimeters, and on rare occasions thick- or thin-walled cavities may be present. Pleural effusion and pneumothorax are each observed in <10% of cases.

In most cases of paragonimiasis, the blood leukocyte count is normal and eosinophilia is inconstant. The diagnosis can be made only by finding the characteristic ova, which can usually be seen readily on examination of the sputum or stool.

Paragonimus westermani infection frequently produces chronic disease that is sometimes incapacitating, and occasionally, in patients experiencing very heavy infestation, it is fatal. The treatment of choice is 25 mg of praziquantel per kilogram of body weight, given three times in a 1-day course.

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CHAPTER

25 Hospital-Acquired Pneumonia

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INTRODUCTION

Hospital-acquired pneumonia is the second leading cause of nosocomial infection, accounting for 13%–18% of all nosocomial infections. It is the leading cause of death among patients with hospital-acquired infections, and the cost of therapy for this problem exceeds $2 billion annually. This chapter focuses on the epidemiology, risk factors, pathogenesis, diagnostic strategies, and preventive measures related to hospital-acquired pneumonia. As many of the infective etiologies of pneumonia are reviewed in other chapters, only those organisms and/or features unique to the hospital setting are discussed here. The chapter concludes with a section on pneumonia in the immunocompromised host.

EPIDEMIOLOGY

Lower respiratory tract infection is not a reportable illness, but available data suggest it occurs at a rate of 5 to 10 cases per 1000 hospital admissions. This incidence may be 6 to 20 times higher in patients who are being ventilated mechanically. Nosocomial pneumonia has occurred in as many as 70% of patients with the adult respiratory distress syndrome (ARDS). Crude mortality rates for hospital-acquired pneumonias of 20%–50% have been reported, but they may be as high as 90% when pneumonia occurs in patients with ARDS. Although all these deaths are not the direct result of infection, the attributable mortality of hospital-acquired pneumonia is estimated to account for one third to one half.

RISK FACTORS

Although many of the variables predisposing to the development of hospital-acquired pneumonia are likely to be interrelated, several studies using regression analysis have identified independent risk factors. These include the following: (1) host factors, such as extremes of age and underlying disease; (2) conditions favoring aspiration; (3) surgical procedures, especially thoracic or upper abdominal surgery; (4) colonization of the oropharynx with gram-negative bacilli; and (5) continuous mechanical ventilation. More than 85% of patients in whom a nosocomial pneumonia develops have a serious underlying disease. Patients with chronic lung disease may have altered mucociliary clearance, and those with neurologic disorders may be predisposed to aspiration because of an impaired gag reflex.

Colonization of the oropharynx with gram-negative bacilli is an important risk factor because most cases of nosocomial pneumonia result from aspiration of contaminated oropharyngeal secretions into the tracheobronchial tree. Approximately 45% of healthy adults aspirate during sleep, and aspiration is even more frequent in patients with altered consciousness, abnormal swallowing, depressed gag reflexes, delayed gastric emptying, or decreased gastrointestinal motility. Intubation compromises the natural barrier to aspiration, and the entry of bacteria into the lung may also be facilitated through pooling and leakage of secretions around the endotracheal tube cuff. In the normal respiratory tract, the oropharynx is colonized, but not with enteric gram-negative bacilli. When serious illness of any type is present, enteric gram-negative bacilli can replace the normal flora and become the colonizing bacteria in the oropharynx. Patients receiving antibiotics or acid-neutralizing medications also have a higher incidence of colonization. When the time course of colonization was examined, most patients had acquired gram-negative bacteria by the third hospital day.

Gastric colonization as a source of oropharyngeal and tracheal colonization in mechanically ventilated patients has been suggested by studies dating from 1978 and later. These studies have emphasized gastric overgrowth with aerobic gram-negative bacilli and increased rates of pneumonia in patients who have received agents that alter gastric pH. Several meta-analyses found that administration of sucralfate (which does not increase gastric pH) was associated with a reduced incidence of pneumonia when compared with the use of either antacids alone or in combination with H_2 antagonists. In all studies, gastric colonization has correlated best with gastric pH (increasing as pH exceeds 4.0), and rates of pneumonia increase accordingly.

The lower respiratory tract is ordinarily sterile in healthy nonsmokers. Smoking increases the likelihood that the tracheobronchial tree has lost its sterility, and half of patients with chronic bronchitis have a colonizing tracheobronchial microflora, but enteric gram-negative bacilli are not present. Oropharyngeal and tracheobronchial colonization patterns in intubated patients reveal that gram-negative bacteria usually enter the trachea after first colonizing the oropharynx. The exception to this finding is *Pseudomonas aeruginosa,* which can colonize the tracheobronchial tree as a primary event without first becoming established in the oropharynx. Colonization of gram-negative bacteria in the tracheobronchial tree occurs in 50%–100% of intubated patients, and more than one potential pathogen may be present. The relationship of airway colonization to the subsequent development of pneumonia is well-known, as respiratory infection develops in 13%–23% of colonized patients.

In addition to aspiration and colonization, one of the most important risk factors is tracheal intubation and mechanical ventilation, with the incidence of pneumonia rising as the duration of intubation increases. The risk for pneumonia is seven to 21 times greater in intubated patients than in other hospitalized patients, and pneumonia develops in as many as two thirds of patients with tracheostomy who require mechanical ventilation. The relationship of nosocomial pneumonia to the duration of mechanical ventilation was demonstrated by Fagon and colleagues; the risk for pneumonia was found to be 6.5% after 10 days of ventilation, 19% at 20 days, and 28% at 30 days. The endotracheal tube itself is not routinely changed. In one report, 95% of the tubes examined by scanning electron microscopy had partial bacterial colonization, and 84% were covered by bacteria in a biofilm or glycocalyx. Whether this is clinically relevant remains to be seen.

PATHOGENESIS

Nosocomial pneumonia develops when organisms reach the lung and overcome the pulmonary host defenses. Illness results if the inoculum is sufficiently large, if the organism is virulent, or if host defenses are malfunctioning. Organisms may reach the lung via aspiration of oropharyngeal secretions colonized with pathogenic bacteria, aspiration of esophageal/gastric contents, inhalation of contaminated aerosols, hematogenous spread from a distant infected site, exogenous penetration from a pleural infection, or by direct inoculation into the airways of intubated patients. Not all routes, however, are equally effective in precipitating infection. Of these routes

of entry, aspiration of oropharyngeal flora is recognized as the predominant mechanism in both intubated and nonintubated patients. Although microaspiration is a frequent event, reportedly occurring in as many as 45% of healthy adults during sleep, the critical event is the presence of pathogenic bacteria that are able to overwhelm the lower respiratory tract defenses. If organisms reach the lung as a liquid bolus, fewer organisms are needed to cause infection than if they are delivered as an aerosol. In the mechanically ventilated patient, sources of a liquid bolus of organisms include aspiration from a previously colonized oropharynx, aspiration from a colonized stomach to the oropharynx and then to the lung, leakage of pooled subglottic secretions above the inflated endotracheal tube cuff, or direct instillation of colonized ventilator tubing condensate into the lung via the endotracheal tube.

The aerosol route is an effective method for the spread of *Legionella* species, certain viruses, *Mycobacterium tuberculosis,* and fungi, such as *Aspergillus* species. Hematogenous spread from distant sites of infection is especially noted in postoperative patients and in patients with indwelling intravenous or genitourinary catheters.

The initial step in oropharyngeal colonization is the adherence of bacteria to mucosal cells, an interaction dependent on both host and microbial factors. The usual local respiratory tract chemical (salivary proteases, secretory IgA) and physical (mucociliary escalator) barriers to infection may be overcome by bacteria after tracheal intubation or large-volume aspiration. Systemic illness can result in an increase in the number of airway cell receptors and in a loss of surface fibronectin, thereby promoting bacterial adherence. Mucous glycoproteins that trap bacteria may act as actual surface receptors for these gram-negative organisms if they are not cleared as a result of faulty ciliary function. If the airway has been injured, underlying connective tissue and basement membrane, to which bacteria readily bind, can be exposed. Pili or fimbriae act as bacterial adhesions for many enteric gram-negative bacilli; other bacteria secrete exoproducts that promote airway colonization by impairing ciliary function, degrading fibronectin, stimulating excessive mucin production, or degrading mucin. Bacterial adherence has been shown to mediate tracheobronchial colonization and correlate with the subsequent development of pneumonia in mechanically ventilated patients in the intensive care unit (ICU).

It is unlikely that an increase in adherence by itself leads to colonization and infection unless other host defenses are impaired. However, many of the same clinical factors that can cause a rise in adherence can also impair mucociliary clearance and interfere with the cellular and humoral immune functions of the lung. For instance, malnutrition is associated with airway colonization, and this is likely the result of increased buccal and tracheal cell adherence, impaired cell-mediated immunity, decreased neutrophil migration, impaired recruitment of alveolar macrophages to the lung, complement deficiency, and diminished airway levels of IgA.

DIAGNOSIS

Several criteria have been used to establish a clinical diagnosis of nosocomial lower respiratory tract infection; these include fever, leukocytosis, purulent tracheobronchial secretions, and the radiographic appearance of a new or progressive pulmonary infiltrate. The development of these clinical manifestations in a previously healthy individual without underlying lung disease almost invariably indicates pneumonia. When these criteria have been applied to mechanically ventilated patients, however, they have been quite sensitive but not very specific, as a variety of noninfectious causes may lead to pulmonary infiltrates in this setting. Fagon and colleagues prospectively evaluated 147 consecutive patients suspected of having ventilator-associated pneumonia, and three of the usual clinical criteria were met in 93% of the patients and all four criteria were present in 51%. The diagnosis was definitely excluded in 49% of the patients, and no combination of 16 clinical variables was useful in distinguishing patients with bacterial pneumonias. In studies of patients with ARDS, pneumonia was falsely diagnosed using these clinical criteria in 19%–36% of patients but was unrecognized in up to 62%. Whereas overdiagnosis of pneumonia is the problem in mechanically ventilated patients in general, those with ARDS have not only the problem of overdiagnosis but also that of underdiagnosis. The remainder of this section reviews the diagnostic tools that may be useful in the diagnosis of both hospital- and ventilator-associated pneumonia.

General Evaluation

All patients with suspected hospital-acquired pneumonia require certain diagnostic evaluations. A careful history and physical examination can identify the presence of specific risk factors or conditions that may suggest the likely etiologic pathogens (Table 1). Chest radiography is imperative and can be used to define the presence and location of infiltrates, cavitation, and complications such as pleural effusion, and the severity of the process. Diagnostic thoracocentesis should be performed in individuals with parapneumonic effusions, especially if the effusion is 10 mm thick on a lateral decubitus chest x-ray film, if the individual has had chest trauma, or if a chest tube has been placed previously. A complete blood cell count and serum electrolyte levels should be determined, and arterial blood gas analysis and renal and liver function tests should be routinely performed. Although these do not contribute to the identification of a specific etiology, the tests help to define severity of illness and guide appropriate antimicrobial dosing. Serologic studies are of little use in the initial evaluation and should not be routinely performed.

Organism	Risk factor
Anaerobes	Abdominal surgery, poor dentition, witnessed aspiration
Staphylococcus aureus	Antecedent influenza, coma, head trauma, diabetes mellitus, renal failure
Legionella	Corticosteroids
Pseudomonas aeruginosa, Acinetobacter	Prolonged ICU stay, prior antimicrobial therapy, chronic lung disease

TABLE 1. *Hospital-acquired pneumonia: pathogens associated with specific patient risk factors*

Blood Cultures

Blood cultures can isolate the causative organism in almost one fourth of all cases of hospital-acquired pneumonia. In patients with ARDS, bacteremia has been documented in 27% of those with pneumonia and 67% of those with an abdominal focus of infection. A positive blood culture result in patients with respiratory failure, the appearance of a new pulmonary infiltrate, and the presence of purulent tracheal secretions are not necessarily conclusive evidence of pneumonia, as an additional source of infection may be present in up to 50% of these patients.

Sputum/Tracheal Aspirate

Gram's stain and culture of the respiratory tract secretions are the time-honored methods of microbiologic evaluation but are of limited diagnostic value in ventilator-associated pneumonia. Cultures of expectorated sputum in patients with nosocomial pneumonia in whom the etiologic diagnosis was based on cultures from uncontaminated specimens (blood, transtracheal aspirate, pleural fluid) yielded the implicated bacterial pathogen in up to 80% of patients if *Staphylococcus aureus* was involved. On the other hand, gram-negative bacilli were recovered from sputum in 45% of patients who did not have these organisms as the etiologic agent. The absence of gram-negative bacilli in purulent secretions usually excludes their presence in the lower airways. Quantitative culture of expectorated sputum specimens is of no value diagnostically.

Microscopic examination of respiratory tract secretions is of limited usefulness. Grading of Gram's stains for neutrophils, bacteria, and percentage of intracellular organisms has correlated with quantitative tracheal aspirate colony counts, but overlap with results from patients who do not have infection makes this method less reliable.

The presence of elastin fibers in sputum or tracheal aspirates after digestion with potassium hydroxide is a very reliable indication of the diagnosis of hospital- or ventilator-associated pneumonia (Plate 1). The microscopic finding of elastin fibers is indicative of pulmonary parenchymal destruction or necrosis and was first described in 1846 as pathognomonic for tuberculosis. The demonstration of elastin fibers has subsequently been associated with necrotizing bacterial pneumonia, with a sensitivity of 52% and specificity and positive predictive value of 100% for infection. Recovery of elastin fibers from bronchial aspirates of patients with ARDS has a lower positive predictive value (50%), as noninfectious lung necrosis may occur in that setting. Elastin fibers are more likely to be seen in nosocomial pneumonia caused by gram-negative bacilli than in that caused by gram-positive bacteria, and the presence of elastin fibers may actually precede radiographic evidence of pulmonary infiltrates by a few days.

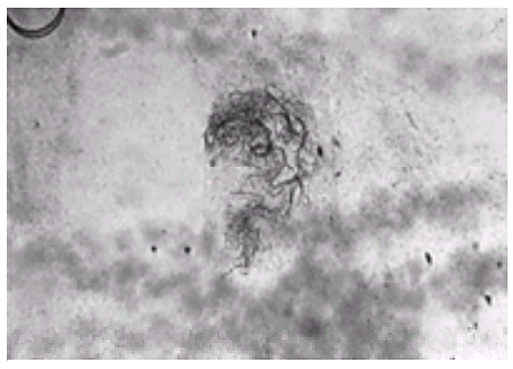


PLATE 1. Elastin fibers in a potassium hydroxide preparation of sputum. *See color plate 14.*

Qualitative cultures of tracheal aspirates have a high false-positive rate, frequently contain more than one potential etiologic pathogen, and are the least reliable method of diagnosis. Studies evaluating quantitative cultures of tracheal aspirates have yielded inconsistent results, with thresholds for the diagnosis of pneumonia ranging from 10^5 to 10^7 colony-forming units (CFU) per milliliter. The specificity of quantitative culture of tracheal aspirates has been best at higher cutoff points, but at the expense of decreasing sensitivity.

Transthoracic Lung Aspiration

Transthoracic lung aspiration for the diagnosis of bacterial pneumonia is of limited applicability for patients in the ICU, and it is contraindicated in patients receiving mechanical ventilation. Sensitivities as high as 79% have been reported in community-acquired pneumonias, but series dealing with more complex pneumonias have revealed sensitivities of 35%–56%. Because of the high incidence of pneumothorax associated with this procedure and its limited sensitivity, transthoracic lung aspiration is not recommended as a diagnostic procedure for patients in the ICU.

Bronchoscopy

Fiberoptic bronchoscopy has become an increasingly valuable tool for the diagnosis of lower respiratory tract infection. To reach the bronchial tree, however, the bronchoscope must traverse the oropharynx or the endotracheal tube, and colonization of these sites with pathogenic bacteria has been reported in up to 90% of patients receiving mechanical ventilation. Bronchoscopic aspirates in patients undergoing bronchoscopy are frequently contaminated by oropharyngeal bacteria, and as a result routine bacterial cultures obtained through the bronchoscope are unreliable for the diagnosis of pneumonia.

Two diagnostic techniques that have been recently described make it possible to acquire lower respiratory tract specimens for bacterial culture without oropharyngeal contamination. One technique uses a double-sheathed protected specimen brush (PSB), and the second involves bronchoalveolar lavage (BAL) of radiographically involved portions of the lung. Both methods rely on quantitative bacterial cultures to differentiate between infection and colonization.

Accordingly to a meta-analysis, the use of a predetermined threshold concentration for either PSB or BAL may not be appropriate in all clinical settings. Quantitative cultures of PSB and BAL specimens should be interpreted according to the pretest likelihood of pneumonia and how information gained from the procedure will influence management. Because pretest probability, risks of therapy, and likelihood of benefit vary widely among patients, a single value that defines an abnormal PSB or BAL culture result for all patients cannot be defined.

Bronchoalveolar Lavage

BAL refers to the sequential instillation and aspiration of a physiologic solution into the lung through a bronchoscope that has been wedged into an airway and so is subject to contamination with oropharyngeal flora. Quantitative cultures of BAL fluid have yielded growth in excess of 10^5 CFU/mL in the majority of patients with pneumonia, and the presence of 1% squamous epithelial cells in the BAL sample accurately predicts the presence of heavy contamination by oropharyngeal flora. A growth of 10^5 CFU/mL in a BAL specimen with at most 1% squamous epithelial cells has a diagnostic sensitivity of 88% and a specificity of 100%. Unprotected BAL, however, does not discriminate pneumonia from acute bacterial bronchitis. More recently, the technique of protected BAL has been described for diagnosing ventilator-associated pneumonia. Using a threshold of 10^4 CFU/mL, quantitative bacterial cultures of protected BAL samples had a sensitivity of 92% and a specificity of 97%, with a positive predictive value of 97% and a negative predictive value of 92%.

Microscopic analysis of cytocentrifuged BAL fluid may be useful in the diagnosis of pneumonia. Whereas total and differential cell counts are not helpful, the presence of intracellular organisms in 7% of cells (sensitivity of 86%, specificity of 96%) and the presence of bacteria on BAL specimen Gram's stain correlate closely with the results of both BAL and PSB quantitative cultures.

Protected Specimen Brush

The feasibility of obtaining uncontaminated specimens from the lower respiratory tract through a contaminated bronchoscope with a double-sheathed catheter was demonstrated in 1979. The technique has been described in detail and requires that a catheter containing a PSB be passed under direct visualization into the area of lung involvement as defined radiographically. Using a cutoff of 10^3 CFU/mL, quantitative cultures of samples obtained by PSB can separate patients with lower respiratory tract infection from those with airway colonization. Quantitative PSB cultures correlate well with histologic and bacteriologic features of tissue obtained at autopsy in mechanically ventilated patients and have a positive predictive value of 75% in ventilated patients who meet the standard clinical criteria for nosocomial pneumonia. Antecedent use of antibiotics diminishes the diagnostic efficacy of PSB cultures. In general, the sensitivity and specificity of PSB quantitative cultures are cited as 70%–90%. Studies comparing the efficacy of PSB and BAL quantitative cultures for the most part support the concept that these techniques are complementary. In patients with clinically suspected pneumonia in whom quantitative culture of PSB samples yields organisms in a concentration of 10^2 CFU/mL but $<10^3$ CFU/mL, PSB sampling should be repeated if pneumonia continues to be suspected clinically. In one third to one half of these patients, follow-up PSB quantitative culture will yield organisms in a concentration exceeding the diagnostic cutoff of 10^3 CFU/mL.

Plugged Telescoping Catheters

Because the routine use of the PSB technique is time-consuming and requires the use of a fiberoptic bronchoscope, an alternative, simpler technique using a plugged telescoping catheter (PTC) has been presented. Blind PTC sampling is as accurate as directed sampling via the bronchoscope, with a sensitivity of 100% and specificity of 82%. The accuracy of undirected PTC sampling is not unexpected. Pathologic examination of the lungs of intubated patients dying with nosocomial pneumonia has shown that bronchopneumonia is predominantly found in the lower and posterior parts of the lung, and chest radiographs taken during blind BAL via PTC have shown that 95% of catheters are lodged in the distal airways of the lower lobes. PTC sampling thus appears to be a useful tool for the diagnosis of ventilator-associated pneumonia as long as the radiographically defined area of involvement is limited to the lower lung fields.

PROPHYLAXIS

Given the fact that nosocomial pneumonia is the most common fatal nosocomial infection, an effective prophylactic regimen could have a significant impact on survival of hospitalized patients. To date, no single specific measure for pneumonia prevention has been proved to be beneficial, but several techniques currently under investigation may emerge as useful in the future.

Conventional Infection Control

Conventional infection control strategies have focused on identifying reservoirs of infection, interrupting transmission among patients, preventing progression from colonization to infection, and improving host defenses. Conventional infection control practices may fail to prevent nosocomial infection in the ICU, because many patients arrive already colonized with nosocomial bacteria; hand washing and barrier precautions are abandoned during crisis situations; and health care personnel may fail to adhere to traditional measures aimed at preventing infection in colonized patients, such as changing intravenous catheters routinely, discontinuing bladder catheters, suctioning with careful aseptic techniques, and removing ventilator circuit tubing condensate frequently to minimize exposure to the patient. The use of gloves by health care workers, as advocated under universal precautions guidelines, can lead to inadvertent transmission of pathogens (*Acinetobacter, Pseudomonas*)

if they are not changed between patients.

Enteral Nutrition

Enteral nutrition is the method of choice for nutrient administration, as it is less invasive, more physiologic, and less expensive than total parenteral nutrition. In one study of patients with abdominal trauma, enteral feeding with a jejunostomy tube was not accompanied by pneumonia in any of the 29 patients treated in this manner, whereas pneumonia occurred in 6 of the 30 patients receiving parenteral nutrition. Although nutrition is an important therapeutic modality used to counteract the adverse effects of malnutrition on lung defense mechanisms, enteral feeding produces a definite risk for infection. The most significant risk of enteral feeding results from gastric colonization and the subsequent transmission of gastric organisms to the trachea, with resultant nosocomial pneumonia. Pingleton and colleagues evaluated simultaneous daily gastric, tracheal, and oropharyngeal cultures in mechanically ventilated patients not receiving antacids or H_2 antagonists, and they demonstrated that the number of gastric gram-negative isolates increased significantly after enteral feeding began. In their study, 36% of patients had gram-negative bacilli recovered first in the stomach that were later recovered in the trachea. The mechanism of transfer of gastric organisms into the trachea appears to be aspiration. Important factors implicated in aspiration associated with enteral feeding are the size and location of the feeding tube. Clinically significant aspiration is infrequent when enteral feeding is administered continuously via a small-bore nasoenteral tube in intubated patients. Feedings delivered directly to the stomach, as opposed to distal enteral feeding, increase the likelihood of aspiration and pneumonia, especially if the patient is being kept supine rather than semi-erect.

Antimicrobial Prophylaxis

Antibiotic prophylaxis of nosocomial pneumonia can be administered systemically, topically, by aerosol, or by a combination of these methods.

Systemic Antibiotic Prophylaxis

Systemic antibiotic prophylaxis has clearly been unsuccessful. In the 1950s, trials of systemic antibiotic prophylaxis involving patients with poliomyelitis who have undergone tracheotomy, comatose patients in the ICU, and patients with congestive heart failure failed to demonstrate a significant reduction in tracheal colonization or frequency of pneumonia. Furthermore, prophylaxis actually increased the risk for resistant gram-negative bacillary pneumonia, cutaneous infection, and bacteremia. Based on data that 50% of pneumonias appear within 4 days of ICU admission, a more recent multicenter survey readdressed the issue of systemic prophylaxis. In that study of 570 patients in 23 ICUs, antibiotic prophylaxis did not result in a statistically significant decline in rates of early-onset pneumonia or death.

Aerosolization

The delivery of aerosolized antibiotics directly into the tracheobronchial tree has had minimal success as prophylaxis for ventilator-associated pneumonia. Polymyxin B was selected in several studies because it is bactericidal against a broad range of gram-negative bacilli, including *P. aeruginosa,* and it adsorbs well to epithelial surfaces without being absorbed systemically. Although aerosol polymyxin B can clearly reduce the occurrence of *P. aeruginosa* colonization and pneumonia when it is administered for prolonged periods, it results in the emergence of resistant organisms, and overall mortality rates have not been improved. Similarly, the endotracheal administration of gentamicin has been shown to decrease the rate of pneumonia, but overall mortality and infection-related mortality were unchanged. In addition, patient colonization with gentamicin-resistant organisms increased.

Selective Decontamination

Selective decontamination of the oropharynx is a prophylactic technique in which nonabsorbable antibiotics are applied directly to the oropharynx, in either a liquid or paste form. Parenteral antimicrobial agents are not administered. Prospective trials comparing topical nonabsorbable antibiotics with placebo have demonstrated decreased incidence of nosocomial pneumonia, but overall mortality rates were unchanged. Despite promising early results of selective oropharyngeal decontamination trials, flaws in study design have made these results largely unreliable.

Selective digestive decontamination as a method of pneumonia prevention was initially investigated in Europe. It is based on the use of orally administered, nonabsorbable antibiotics that eliminate aerobic gram-negative bacteria from the gut while sparing anaerobes. With time, selective digestive decontamination has been gradually modified. Fungal overgrowth often followed prophylaxis with polymyxin E and tobramycin, so amphotericin B became a standard part of the regimen. Because lower respiratory tract infection occurring within 5 days after ICU admission cannot be prevented solely by the topical administration of antibiotics to the oropharynx and stomach, intravenous cefotaxime given for several days was added to the regimen. Early nonblinded trials of selective digestive decontamination demonstrated reductions in rates of pneumonia, but for the most part no improvement in overall mortality or length of stay. More recent prospective, randomized, double-blinded, placebo-controlled studies using invasive methods to define the presence of pneumonia, however, have failed to demonstrate a benefit of selective digestive decontamination in decreasing the incidence of nosocomial infections (including pneumonia), length of stay, duration of mechanical ventilation, or mortality rates.

Gastric pH and Bacterial Overgrowth

Many studies have correlated high levels of gastric pH with logarithmic increases in the concentrations of gram-negative bacteria in the stomach and demonstrated the development of retrograde colonization from the stomach to the oropharynx and trachea. Several investigators reported increased rates of pneumonia in patients who received agents that alter gastric pH. Meta-analysis has consistently demonstrated that sucralfate (which does not alter gastric pH) is associated with a reduced incidence of pneumonia in comparison with antacids alone or combined with H_2 antagonists. There is disagreement, however, about whether the use of H_2 antagonists alone is associated with a higher rate of pneumonia in comparison with sucralfate or placebo. Nevertheless, it is overly simplistic to say that any intervention that raises gastric pH is undesirable. Other factors, especially gastric volume and the route of enteral feeding (gastric vs. distal) influence gastric bacterial growth, and analyses have not consistently considered the impact of these concomitant risk factors.

Management of Equipment Used for Respiratory Therapy

Bacteria can proliferate in the equipment used during respiratory therapy, and the incidence of pneumonia is increased if the tubing is manipulated frequently rather than infrequently. When tubing is handled, the condensate should always be drained away from the patient, as it can contain large concentrations of bacteria. Although many hospitals have a policy to change ventilator tubing every 48 to 72 hrs, there are no data showing that any particular frequency of circuit changes, compared with no circuit changes, lessens the incidence of pneumonia. The use of heat and moisture exchangers to lessen ventilator tubing contamination may decrease bacterial colonization of the circuit but has no effect on the incidence of pneumonia.

Aspiration of subglottic secretions is achieved with the use of a special endotracheal tube, designed with a suction port above the endotracheal tube cuff, in the subglottic area. The removal of contaminated respiratory secretions pooling above the endotracheal tube cuff reduces the incidence of some forms of ventilator-associated pneumonia. Once endotracheal tubes allowing the aspiration of subglottic secretions become more widely available, this approach may be used more regularly.

Continuous Postural Oscillation

Many years ago, it was recognized that prolonged recumbency increases the risk for pulmonary complications after operation, and for that reason early ambulation after surgery has become standard practice. For many critically ill patients in the ICU, however, ambulation is impossible, and the use of oscillating beds has been advocated as a means of avoiding the adverse pulmonary consequences of prolonged immobilization. Continuous postural oscillation (CPO) has been studied in patients bedridden with acute stroke, immobilized head-injured patients in traction, and victims of blunt trauma, and pneumonia occurred in significantly fewer patients randomized to CPO than to a conventional bed. Other studies, however, have not supported the benefit of CPO. Postoperative chest physiotherapy has failed to affect the incidence of pneumonia after gastric bypass surgery, and the use of CPO in medical patients in the ICU did not reduce overall mortality or the incidence of pneumonia. Although CPO may have a valid role in the care of certain critically ill patients, studies to date can be faulted for relying on clinical criteria for the diagnosis of pneumonia, and future trials are warranted.

MICROBIAL ETIOLOGIC AGENTS

Most reported cases of nosocomial pneumonia are caused by bacteria, and the time of onset of pneumonia after hospitalization is related to the bacterial etiology. Early-onset pneumonia, defined as pneumonia developing within 2 to 4 days after admission, occurs in anywhere from 8%–60% of patients requiring prolonged intensive care and accounts for up to 50%–60% of all cases of nosocomial pneumonia in some series. Early-onset pneumonia may be caused by community-acquired flora, including *S. aureus, Streptococcus pneumoniae,* and *Haemophilus influenzae.* After this initial time period, gram-negative bacteria become the major etiologic agents, coinciding with the time frame of oropharyngeal and tracheal colonization described earlier. Gram-negative bacilli account for 50%–80% of all nosocomial

pneumonias, and 10%–20% of cases are polymicrobial.

Among the gram-positive bacteria, *S. aureus* is by far the most common, accounting for at least 10% of all nosocomial pneumonias. *S. aureus* is the gram-positive organism most often responsible for bacteremic nosocomial pneumonia. Staphylococcal pneumonia is more common in individuals with recent influenza, head injury, coma, a history of injecting drug use, chronic renal failure, or diabetes mellitus. Chest radiographs usually reveal multilobar infiltrates, predominantly in the lower lobes, often bilaterally. Pleural involvement is common, but cavitation and abscess formation infrequently occur. Infection caused by methicillin-resistant organisms is more likely in persons who have previously received antibiotics.

Although *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia, it accounts for less than 3% of all nosocomial pneumonias but up to 12% of bacteremic nosocomial pneumonias. Pneumococcal nosocomial pneumonia usually occurs within the first few days of hospitalization. Enterococcal nosocomial pneumonia has been associated with antecedent cephalosporin therapy and enteral alimentation.

Pseudomonas, Klebsiella, Enterobacter, Escherichia coli, and *Serratia* species are the most commonly reported causes of gram-negative bacillary pneumonias. *Pseudomonas* and *Serratia* are the most common pathogens causing bacteremic nosocomial pneumonia, whereas *E. coli, Klebsiella,* and *Enterobacter* are more frequently associated with nonbacteremic cases. Patients with ventilator-associated pneumonias who have received antibiotics before the onset of pneumonia are especially likely to be infected by *P. aeruginosa* or *Acinetobacter* species. Bacteremic nosocomial pneumonia caused by gram-negative bacteria is more likely to occur in elderly patients with debilitating underlying diseases, and mortality rates of 58%–82% are typical. *P. aeruginosa* is the most common pathogen, accounting for almost 17% of all nosocomial pneumonias. Oropharyngeal colonization by the organism with subsequent spread to the lower respiratory tract, as is typical for most gram-negative bacillary pneumonias, commonly occurs with *P. aeruginosa* but is not the sole mechanism of pathogenesis. Primary tracheal colonization with *P. aeruginosa* without antecedent oropharyngeal colonization has been described, and for this reason attempts at topical oropharyngeal decontamination would be unlikely to prevent primary colonization of the lower respiratory tract. In addition, hematogenous or bacteremic *Pseudomonas* pneumonia, with a presentation that mimics cardiogenic pulmonary edema, can occur and is nearly universally fatal.

Bacteremic *Pseudomonas* pneumonia is more common in patients with leukemia, lymphoma, solid tumor neoplasms, or chemotherapy-induced granulocytopenia (Plate 2), whereas nonbacteremic disease is seen more frequently in debilitated elderly patients with underlying cardiopulmonary disease. Radiographically, *Pseudomonas* pneumonia may be focal or diffuse. The focal form characteristically involves a lower lobe, although multilobar involvement has been the usual finding in patients with terminal infection. Infiltrates are usually alveolar, often with radiologic evidence of cavitation or abscess formation. Occasionally, a peculiarly nodular bronchopneumonia of the lower lobes, with multiple small, thin-walled radiolucent cystic lesions, is seen. The diffuse form is a fearsome disease having an early radiographic presentation that mimics cardiogenic pulmonary edema. Bacteremia and leukopenia are common. If the patient survives beyond 48 hours, the chest radiograph demonstrates evolution into a necrotizing bilateral bronchopneumonia, often with pleural effusion and abscess formation. Histologically, this form is characterized by necrotizing pneumonia, vasculitis, pulmonary hemorrhage, and abscess formation. Mortality rates of 30%–60% have been reported for nonbacteremic *Pseudomonas* pneumonia, whereas the bacteremic variety is associated with case fatality rates invariably exceeding 80%. Treatment, which depends on in vitro sensitivities, is ordinarily with ceftazidime, aztreonam, imipenem, ciprofloxacin, or extended-spectrum penicillins plus an aminoglycoside. In many series, mortality has been independent of the effectiveness of the antimicrobial regimen applied, correlating mostly with the underlying disease process and degree of immunosuppression.

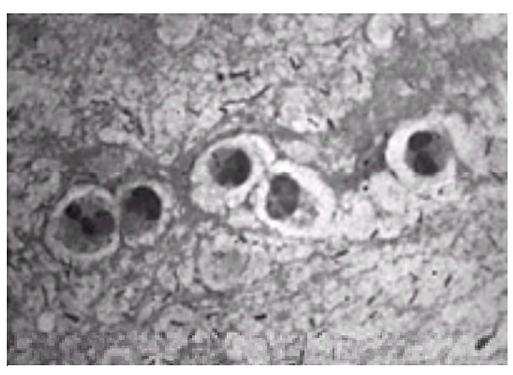


PLATE 2. *Pseudomonas* in sputum of a neutropenic patient. ×900. *See color plate 15.*

E. coli is the third most frequently isolated gram-negative organism responsible for hospital-acquired pneumonia, following *Pseudomonas* and *Klebsiella.* Pneumonia caused by *Klebsiella* is discussed in chapter 24. *E. coli* may colonize the oropharynx and subsequently invade the lower respiratory tract, but bacteremic invasion may occur from a distant focus in the genitourinary or gastrointestinal tract. The presence of serious underlying disease is a major factor leading to *E. coli* pneumonia, and two thirds of the patients have had been receiving broad-spectrum antibiotics, corticosteroids, or cytotoxic chemotherapy before the onset of pneumonia. Multilobar involvement is as common as disease localized to one lobe, and parapneumonic pleural effusion occurs frequently. Bacteremic *E. coli* pneumonia is associated with a normal or elevated white blood cell count, unlike bacteremic *Pseudomonas* pneumonia, in which leukopenia is a major predisposing factor. Mortality rates of 60%–80% are reported, with the worse outcomes associated with bacteremia.

Legionellosis may account for up to 30% of nosocomial pneumonias in hospital settings where potable water is contaminated, but because the diagnosis requires special serologic and microbiologic techniques, the true incidence is unknown. The presentation of nosocomial *Legionella* pneumonia may be sporadic or epidemic. Clinical diagnosis in an outbreak setting is not difficult; however, differentiating *Legionella* pneumonia from other types of pneumonia in a nonepidemic setting can be troublesome. Risk factors for nosocomial legionellosis include malignancy, renal failure, neutropenia, cytotoxic chemotherapy, and corticosteroid therapy. Factors such as altered consciousness, prior antibiotic therapy, and intubation, which are known to be associated with other types of pneumonia, have a negative association with *Legionella* infection. There are no pathognomonic radiologic findings. Initial infiltrates are usually patchy, alveolar, and unilobar, with a predilection for the lower lobes. Generally, the infiltrate spreads locally within a lobe and then to contiguous lobes (Fig. 1). Pleural effusion may occur, and cavitation is seen in 10% of patients, usually in an immunosuppressed host receiving corticosteroids. Diagnosis and therapy are similar to those previously described for community-acquired disease.

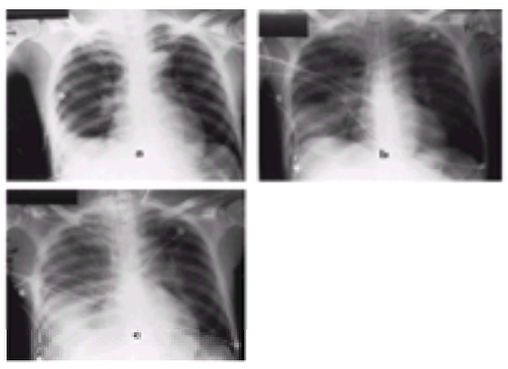


FIG. 1. A,B,C: Nosocomial legionellosis appearing as a patchy infiltrate in the right lower lobe with rapid progression during a period of 4 days.

Nosocomial viral lower respiratory tract infections are particularly common in children, and in one survey viral agents accounted for 20% of all hospital-acquired pneumonias. Respiratory syncytial, influenza, and parainfluenza viruses are important causes of viral nosocomial pneumonia, but only with prospective monitoring using specialized virologic diagnostic methods can the true incidence of nosocomial disease be determined. Nosocomial viral pneumonias are dissimilar to bacterial infections in several respects. Whereas bacterial nosocomial pneumonias tend to reflect the environmental flora of the hospital, nosocomial viral disease generally parallels activity of these agents in the community. Transmission of respiratory viruses involves active infection of hospital personnel in addition to passive transfer of virus on fomites or hands. Finally, whereas nosocomial bacterial infections are most likely to occur in individuals at high risk, viral diseases may occur in any exposed, nonimmune individual.

Herpes simplex virus (HSV) has been identified as a cause of nosocomial lower respiratory tract infection, but because endogenous reactivation is the likely mechanism leading to disease, the term *hospital-acquired* may be inaccurate. Most of the cases reported to date have involved patients with alterations of

cell-mediated immunity, severe underlying disease, or diffuse lung injury, including ARDS. It should be borne in mind, however, that HSV infection of the lower respiratory tract has occurred in apparently normal, immunocompetent hosts. Chronic lung disease and tobacco abuse have been reported by some authors as predisposing factors. Aspiration or contiguous spread from the oropharynx to the respiratory tract is the predominant pathogenic mechanism, but hematogenous seeding may occur in cases characterized with diffuse interstitial infiltrates (Plate 3). Aspiration as a mechanism is supported by the fact that in most patients, HSV infection of the lower respiratory tract is accompanied by oral or pharyngeal sores.

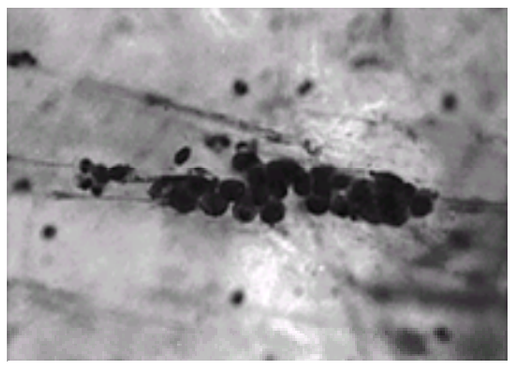


PLATE 3. Giemsa stain of endotracheal secretions showing intranuclear inclusions of HSV. Fever and diffuse interstitial pneumonia developed in this patient after coronary bypass surgery. *See color plate 16.*

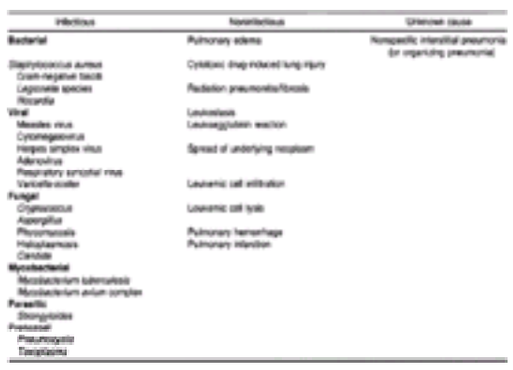
Clinically, the disease process is variable, and in its mildest form nothing more than the extension of an oropharyngitis occurs. HSV infection can be localized to the trachea and large bronchi, or a more generalized tracheobronchitis with extension into the bronchioles and alveoli can occur. HSV tracheobronchitis usually presents acutely with substernal pain, bronchospasm, and bloody respiratory secretions, and it may progress to respiratory failure, with the need for intubation and mechanical ventilation. When HSV tracheobronchitis arises in the intubated patient, it may manifest as bronchospasm, and weaning from mechanical ventilation is difficult. Localized or diffuse pneumonia can also be seen. Bacterial and fungal superinfections occur frequently.

HSV can be cultured from the mouth of 1%–5% of asymptomatic adults, and with any respiratory illness, the carriage rate rises to 2.7%–11.5%. For this reason, viral cultures of respiratory secretions are nondiagnostic unless supported by cytologic or histologic evidence of infection. Cytologic preparations typically reveal multinucleated giant cells and Cowdry type A intranuclear inclusions in patients with HSV infection of the lower respiratory tract. Bronchoscopy has been particularly useful in the diagnosis of HSV tracheobronchitis, as it allows for direct visualization of the characteristic punctate mucosal ulcerations and fibrinopurulent tracheal membrane. Direct immunofluorescent staining of HSV-infected tissue may be useful in obtaining a rapid diagnosis.

Acyclovir is the drug of choice, administered in a dose of 5 mg/kg intravenously every 8 hours for 10 days. In patients who fail to respond, an acyclovir-resistant HSV strain may be present, and intravenous foscarnet should be substituted. Mortality rates of 30%–70% have been reported.

PNEUMONIA IN THE IMMUNOCOMPROMISED PATIENT

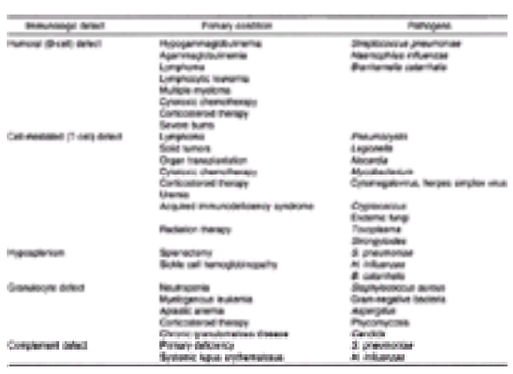
Pulmonary infiltrates occurring in the immunocompromised host may have a myriad of causes, both noninfectious and infectious (Table 2). The differential diagnosis in any given patient can be narrowed by employing a systematic approach in which the clinician categorizes the nature of the underlying immunodeficiency, the onset of disease relative to hospitalization or immunosuppressive therapy, the tempo of the disease process, and the radiographic pattern of involvement. This section focuses on the diagnostic approach to the infectious etiologies, and only those etiologic agents unique to a particular clinical situation are discussed. Pulmonary infections complicating the acquired immunodeficiency syndrome (AIDS) are reviewed in Chapter 26. This chapter concludes with a discussion of the pulmonary infectious complications of transplantation.



Infectious	Noninfectious	Unknown cause
Bacterial	Pulmonary edema	Nonspecific interstitial pneumonia (or organizing pneumonia)
Staphylococcus aureus	Cytotoxic drug-induced lung injury	
Gram-negative bacilli		
Legionella species	Radiation pneumonitis/fibrosis	
Nocardia		
Viral	Leukostasis	
Measles virus	Leukoagglutinin reaction	
Cytomegalovirus		
Herpes simplex virus	Spread of underlying neoplasm	
Adenovirus		
Respiratory syncytial virus		
Varicella-zoster	Leukemic cell infiltration	
Fungal		
Cryptococcus	Leukemic cell lysis	
Aspergillus		
Phycomycosis	Pulmonary hemorrhage	
Histoplasmosis	Pulmonary infarction	
Candida		
Mycobacterial		
Mycobacterium tuberculosis		
Mycobacterium avium complex		
Parasitic		
Strongyloides		
Protozoal		
Pneumocystis		
Toxoplasma		

TABLE 2. *Pulmonary infiltrates in the immunocompromised host*

The differential diagnosis of pulmonary pathogens in a particular patient is influenced in part by the nature of the immunologic defect (Table 3). Patients with abnormalities of immunoglobulin synthesis, hyposplenism, or complement deficiencies are uniquely predisposed to infections with encapsulated bacteria, especially *S. pneumoniae, H. influenzae,* and *Branhamella catarrhalis.* Quantitative or qualitative defects in neutrophil function primarily predispose patients to both bacterial and fungal pathogens, whereas cellular immune dysfunction can lead to infection by a variety of opportunistic organisms. The clinical situation is seldom so easily defined, and coexistent immune defects may be present. For example, although Hodgkin's disease is classically associated with cell-mediated immune dysfunction, both humoral and granulocytic immune dysfunction may also develop in these patients secondary to cytotoxic chemotherapy, radiation therapy, and splenectomy.



Immunologic defect	Primary condition	Pathogens
Humoral (B-cell) defect	Hypogammaglobulinemia	*Streptococcus pneumoniae*
	Agammaglobulinemia	*Haemophilus influenzae*
	Lymphoma	*Branhamella catarrhalis*
	Lymphocytic leukemia	
	Multiple myeloma	
	Cytotoxic chemotherapy	
	Corticosteroid therapy	
	Severe burns	
Cell-mediated (T-cell) defect	Lymphoma	*Pneumocystis*
	Solid tumors	*Legionella*
	Organ transplantation	*Nocardia*
	Cytotoxic chemotherapy	*Mycobacteria*
	Corticosteroid therapy	Cytomegalovirus, herpes simplex virus
	Uremia	
	Acquired immunodeficiency syndrome	*Cryptococcus*
	Radiation therapy	Endemic fungi
		Toxoplasma
		Strongyloides
Hyposplenism	Splenectomy	*S. pneumoniae*
	Sickle cell hemoglobinopathy	*H. influenzae*
		B. catarrhalis
Granulocyte defect	Neutropenia	*Staphylococcus aureus*
	Myelogenous leukemia	Gram-negative bacteria
	Aplastic anemia	*Aspergillus*
	Corticosteroid therapy	Phycomycosis
	Chronic granulomatous disease	*Candida*
Complement defect	Primary deficiency	*S. pneumoniae*
	Systemic lupus erythematosus	*H. influenzae*

TABLE 3. *Immunologic defects and associated pathogens*

The time of onset of the pulmonary illness relative to the underlying immunodeficiency or immunosuppressive therapy may help to focus the differential diagnosis (Table 4). A retrospective review of patients with acute leukemia found that focal infiltrates occurring before initiation of therapy were likely to represent bacterial infections, whereas diffuse infiltrates were never caused by opportunistic pathogens and were usually noninfectious in etiology. In contrast, once patients had received chemotherapy, the occurrence of pulmonary infiltrates was usually secondary to opportunistic infections. Nodular or patchy alveolar infiltrates developing after prolonged periods of granulocytopenia are likely to represent invasive pulmonary aspergillosis. Lastly, pulmonary infectious complications of organ transplantation

commonly follow characteristic temporal patterns, and this is discussed at the end of the chapter.

Before immunosuppressive therapy	Bacterial, viral
	Pulmonary hemorrhage
	Neoplasia
	Primary bronchogenic carcinoma
	Metastatic carcinoma
	Lymphangial spread
	Leukemic cell infiltration
During chemotherapy	Opportunistic pathogen
	Leukoagglutination reactions
	Leukemic cell lysis pneumonopathy
	Pulmonary edema
Late or delayed	Cytomegalovirus
	Radiation pneumonitis/ fibrosis
	Cytotoxic drug-induced

TABLE 4. *Time of onset of pulmonary infiltratein relation to etiology*

The rate of disease progression varies according to etiology and helps in narrowing the differential diagnosis (Table 5). Acute illnesses of 24 hours' duration suggest a bacterial pneumonia, whereas subacute presentations spanning several days are more consistent with infectious processes such as cytomegalovirus (CMV), *Pneumocystis carinii,* nocardiosis, or fungi. Lastly, chronic illnesses occurring during a period of weeks are more typical of mycobacterial or endemic fungal pathogens.

Rapid	Subacute	Insidious
Infectious		
Bacterial	Cytomegalovirus	Nocardia
Gram-negative organisms	Fungi	Fungi
Staphylococcus aureus	Aspergillus	Cryptococcus
Legionella	Cryptococcus	Histoplasmosis
Viral	Phycomycosis	Mycobacterium
Herpes simplex virus	Pneumocystis carinii	
Measles virus		
Noninfectious		
Pulmonary edema	Leukemic cell infiltration	Cytotoxic drug-induced
Leukoagglutination reaction		Radiation pneumonitis/fibrosis
Pulmonary hemorrhage		
Leukemic cell lysis pneumonopathy		

TABLE 5. *Time course of pulmonary disease in immunocompromised patients*

The radiographic pattern of involvement is rarely pathognomonic, but classification into diffuse, nodular, or focal infiltration is useful (Table 6). A definitive diagnosis cannot be established on the basis of the radiographic presentation alone, as more than one etiology may be present and progression of infiltration from a focal to a diffuse pattern may occur. The air-crescent sign, however, is virtually pathognomonic of invasive pulmonary aspergillosis and is perhaps the only diagnostic radiographic pattern (Fig. 2). In addition, a characteristic halo sign, or zone of lower attenuation surrounding a pulmonary mass, has been observed on computed tomography in patients with invasive pulmonary aspergillosis.

Diffuse	Nodular or cavitary	Focal
Common		
Bacteremia	Bacterial lung abscess	Bacteria
Pneumocystis carinii	*Nocardia*	*Nocardia*
Cytomegalovirus	*Staphylococcus aureus*	*Cryptococcus*
Herpes simplex virus	*Cryptococcus*	*Aspergillus*
	Aspergillus	Phycomycosis
Uncommon		
Candidemia	Tuberculosis	Tuberculosis
Miliary tuberculosis	*Legionella*	Histoplasmosis
Disseminated histoplasmosis	*Pneumocystis carinii*	*Legionella*
	Septic emboli	

TABLE 6. *Radiographic patterns of pulmonary infiltrates in immunocompromised patients*

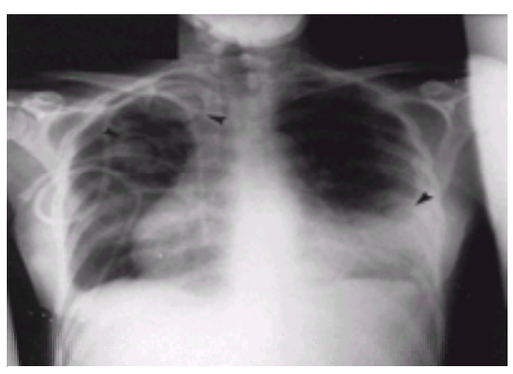


FIG. 2. Multiple air-crescent signs (*arrowheads*) in the lingula, right upper lobe, and right lower lobe in a patient with refractory acute myelogenous leukemia and invasive pulmonary aspergillosis.

Diagnostic techniques, including sputum examination and fiberoptic bronchoscopy with BAL, are similar to those described for the diagnosis of hospital-acquired pneumonia. In addition, transbronchial biopsy may be necessary for the diagnosis of pulmonary infiltrates in the immunocompromised host. Unfortunately, a significant number of transbronchial biopsies fail to establish a definitive diagnosis. For example, a specific diagnosis was made in only 45% of nearly 600 procedures reported in 18 studies. Furthermore, at least 11% of the transbronchial biopsy results in those studies were falsely negative, largely attributable to sampling error. It should also be borne in mind that the addition of transbronchial biopsy to fiberoptic bronchoscopy increases the risk of the procedure 20-fold, with a resultant 14% complication rate. Open lung biopsy remains the definitive diagnostic procedure. In the critically ill immunosuppressed patient, frequently with a bleeding diathesis, it offers the additional advantage of direct control of complications resulting from the tissue biopsy. Complication rates vary from 8%–20%, with 3% of them major. Procedure-related mortality is estimated at 1%. The highest diagnostic yield of open lung biopsy in general is in patients with pulmonary nodules, masses, and cavities. It has been useful in patients with diffuse infiltrates who have had previous bronchoscopic evaluation. Overall diagnostic yields range from 44%–94%, and the incidence of missed diagnoses is about 6%.

Lower respiratory tract infection in the immunocompromised host may be caused by a variety of microbes, including bacteria, *Legionella,* viruses, and opportunistic fungi. The clinical manifestations of these etiologic agents have been reviewed earlier in this chapter, as well as in Chapter 24, Chapter 26, and Chapter 27. The reader

is referred to the respective sections for details. *P. carinii* and CMV, however, are uniquely pathogenic to the immunocompromised host and warrant further discussion.

P. carinii has been recognized as a cause of pneumonia for 30 years, and through the 1970s the majority of cases occurred in patients with lymphocytic leukemia, lymphoma, or congenital T-cell deficiencies, or those receiving chronic corticosteroid therapy. In the 1980s, *P. carinii* emerged as the most common cause of pneumonia in patients with human immunodeficiency virus (HIV) infection, accounting for thousands of cases annually in the United States (Chapter 26). Nevertheless, *P. carinii* continues to cause considerable morbidity and mortality in non-HIV-infected immunocompromised patients, and this discussion focuses on such individuals.

Not all patients with neoplastic disease are at risk for *P. carinii* infection. Attack rates of 20%–40% have been reported in children with acute lymphocytic leukemia, and patients with underlying hematologic neoplasm, especially lymphoma, account for the majority of cases. Cases in patients with underlying solid tumors have become more common, now accounting for approximately 40% of the cases complicating neoplastic disease. Treatment with corticosteroids represents the main chemotherapeutic risk in most series, a risk factor noted in 80%–90% of all cases. Interestingly enough, in 80% of patients, the corticosteroid dose was being tapered at the time of diagnosis.

The clinical presentation is marked by fever, dry cough, and dyspnea of several days' duration. Chest radiographs disclose bilateral interstitial infiltrates, and arterial blood gas determination shows hypoxia. Serum lactate dehydrogenase levels may be elevated. There are dissimilarities in the clinical presentation of *P. carinii* pneumonia between patients with AIDS and those without AIDS (Table 7). The onset of illness is typically more acute in the non-HIV-infected host, and a more fulminant presentation mimicking that of bacterial pneumonia may be seen. The *Pneumocystis* cyst burden seen on microscopic examination of the respiratory tract secretions is generally much lower than that encountered in AIDS patients. Recurrence is rare, as is the development of extrapulmonary pneumocystosis in the non-AIDS host. Although adverse reactions to trimethoprim/sulfamethoxazole are uncommon in patients without AIDS, the overall mortality rate is consistently higher than in patients with AIDS (50% vs. 10%–15%, respectively). The diagnostic methods, therapeutic aspects, and prophylactic strategies are similar to those in AIDS patients (Chapter 26). It should be noted, however, that no trials have assessed the utility of adjunctive corticosteroid therapy for *P. carinii* pneumonia in non-AIDS patients.

Clinical feature	AIDS	Non-AIDS
Mean duration of symptoms, days	28	5
Cyst load in secretions	High	Low
Recurrences	Common	Rare
Side effect to trimethoprim-sulfamethoxazole	Common	Rare
Mortality rate, %	10–15	50

TABLE 7. *Clinical features of Pneumocystis carinii pneumonia: AIDS versus non-AIDS patients*

CMV is ubiquitous among organ transplant recipients and has been referred to as the “troll of transplantation.” CMV infection is associated with increased susceptibility to bacterial, fungal, and protozoal superinfection; increased risk for chronic transplant rejection; and increased overall mortality. CMV-seronegative recipients of marrow or granulocyte infusions or organs from seropositive donors are at the greatest risk for development of serious CMV disease. CMV infection typically occurs 2 to 12 weeks after transplantation, with a mean time to diagnosis of primary disease of 3 to 4 weeks and to discovery of reactivation/reinfection of 6 weeks. Fever occurs in 90% of patients and is frequently prolonged. Headache, arthralgias, myalgias, fatigue, and diarrhea may antedate the onset of pneumonitis. Neutropenia, anemia, and hepatitis are frequent accompanying abnormalities. Diffuse interstitial and/or alveolar infiltrates are the most common radiographic findings, although focal infiltrates, nodules, discoid atelectasis, and normal findings have been reported.

The diagnosis of CMV pneumonitis requires cytologic or histologic confirmation of positive CMV cultures, titers, or antigen detection. Conventional culture of BAL fluid has a high sensitivity and negative predictive value; however, the cultures must be incubated for several weeks, and a positive culture lacks specificity. The BAL fluid may also be cultured in the shell-vial method and stained after 24 to 48 hours of incubation for expression of early CMV antigen. Although more rapid than conventional culture techniques, an analogously high sensitivity and low specificity are expected. Standard cytologic examination of BAL fluid for cells with viral inclusions has had a low sensitivity (21%) but a high specificity (98%). Immunocytochemical staining of BAL cells to detect the presence of CMV antigen has a higher sensitivity (86%), lower specificity (84%), and a good negative predictive value (96%). The sensitivity of transbronchial biopsy for the diagnosis of CMV pneumonia cannot be readily ascertained; it remains the diagnostic procedure of choice, however, and open lung biopsy is rarely necessary. Coinfection with other opportunistic pathogens, particularly *P. carinii,* is common. Ganciclovir or foscarnet is the drug of choice, and outcome is much better in recipients of solid organ transplants than in bone marrow transplant recipients.

ORGAN TRANSPLANTATION

Largely as a result of improvements in immunosuppressive therapy, 1-year survival rates among recipients of livers, kidneys, hearts, and lungs now approach 70%–80%, and in 1990 it was estimated that 9560 kidney, 2656 liver, 2085 heart, 262 lung, 50 heart-lung, and 2200 allogeneic bone marrow transplantations were performed in the United States. Transplantation of any organ is often followed by a variety of complications, prominent among which are pulmonary disorders, both noninfectious and infectious. This section reviews the pulmonary infectious complications as they pertain to the specific organ transplanted.

Liver Transplantation

Orthotopic liver transplantation was first performed by Starzl in 1963, and 1-year survival rates now exceed 70%. The early postoperative course is marked by the development of pleural effusions, atelectasis, and diaphragmatic dysfunction. Infection is the most important postoperative pulmonary complication, and it is the principal source of morbidity and mortality from pulmonary disease in orthotopic liver transplant recipients. Risk factors for infection after transplantation include prolonged operating time, prolonged postoperative antibiotic therapy, renal failure, and gastrointestinal or vascular complications, and overall, the incidence of bacteremia and fungemia is 70%. The critical time period for the development of infection after orthotopic liver transplantation is the first 2 months.

Bacterial pneumonia occurs in 2%–25% of recipients and accounts for almost 50% of all pulmonary infections. The majority of cases of bacterial pneumonia develop in intubated patients and are not usually associated with bacteremia. A decline in the incidence of pneumonia has been reported when selective bowel decontamination is employed, although gram-positive organisms then become more frequent etiologic agents. Case fatality rates approach 40%.

CMV is the most common infectious agent in this patient population, with an incidence 60%. Symptomatic disease occurs in 20%–70% of infected individuals, and augmentation of immunosuppression for treatment of allograft rejection often precedes the onset of CMV disease. In particular, treatment of allograft rejection with OKT3 has been associated with an increased incidence of disseminated disease. Ganciclovir is effective therapy, with complete clearing of virus occurring in 75%–100% of patients.

The majority of fungal pneumonias occur within the first month of transplantation, and are usually caused by *Candida* species and *Aspergillus.* Disseminated infection with these organisms is associated with 70%–100% mortality. *P. carinii* pneumonia usually occurs 3 to 5 months after transplantation, and prophylaxis with trimethoprim/sulfamethoxazole is recommended.

Renal Transplantation

Both patient and renal allograft survival rates have improved during the past decade, such that transplantation now compares favorably with dialysis as a therapeutic modality for end-stage renal disease. More than 95% of renal transplant patients are alive at 1 year, and graft survival rates of 70%–90% are expected. Infections account for 65% of all pulmonary complications after renal transplantation, and the incidence of pneumonia has ranged from 8% to 16% in recent surveys.

Bacterial nosocomial pneumonias usually develop within the first month of transplantation, and the clinical presentation may be quite fulminant. The administration of steroid boluses for the treatment of allograft rejection is associated with an increased risk for hospital-acquired pneumonia. The incidence of fungal pneumonia may be directly related to the number of treated rejection episodes, and fungal infections that are superimposed on CMV infection have an especially poor prognosis.

Aspergillus is the most frequent and most serious of the pulmonary mycoses described, and infection usually occurs within the initial 4 months. Amphotericin B is the treatment of choice, and the response is variable. The presence of copathogens significantly affects outcome. Eighty percent of those with primary *Aspergillus* infection respond to therapy, whereas none of those with *Aspergillus* infection superimposed on another pulmonary infection survive.

The incidence of mycobacterial infection in renal transplant patients is several times higher than that in the general population, occurring in 0.6%–2.3% of patients. Pulmonary involvement is the most frequent clinical manifestation, although an increased incidence of joint and skin disease occurs. The onset of infection is usually late, often developing a year or more after transplantation. Respiratory symptoms are often minimal, and an unexplained fever or abnormal-appearing chest radiograph may be the only clue to the infection. Dissemination is common, and ARDS has occurred. Response to standard antituberculous therapy is good.

The incidence of *P. carinii* pneumonia was 5% in the early experience with renal transplantation, but a striking increase in incidence of disease followed the introduction of cyclosporine. The onset of illness is typically acute, with fever and respiratory symptoms evolving within several days. Illness usually develops 2 to 4 months after transplantation, and prophylaxis with trimethoprim/sulfamethoxazole for 12 months after transplantation is recommended.

CMV infection is the most common infectious complication after renal transplantation, with an incidence of 75% consistently reported. Overall, symptomatic disease develops in 20%–40% of infected patients. The majority of patients have either asymptomatic or mildly symptomatic disease that usually appears within the first 2 months after transplantation. Before the availability of ganciclovir, CMV pneumonia in the renal transplant patient carried a 48% mortality, and 90% of patients requiring mechanical ventilation died. Ganciclovir is effective therapy for CMV pneumonia in renal transplant patients, and the survival rate approaches 78%, including a 39% survival rate in patients requiring mechanical ventilation. Complete virologic clearing is seen in 70%–90% of treated patients.

Bone Marrow Transplantation

Bone marrow transplantation has been successfully applied to a growing list of hematologic and malignant diseases, and 2-year, disease-free survival rates exceed 60% for some forms of leukemias and aplastic anemia. Pulmonary complications occur in 40%–60% of marrow recipients, and particularly prominent among the infectious pulmonary complications are the respiratory viral and fungal infections.

Bacterial pneumonia is infrequently diagnosed during the early period after marrow transplantation, primarily because of the early empiric use of broad-spectrum antibiotics during episodes of fever. Nevertheless, a recent publication reported a 12%–60% incidence of bacterial pneumonia in this population, with gram-negative organisms as the predominant cause. Most of the late bacterial infections occurring after marrow transplantation involve the respiratory tract, are associated with chronic graft-versus-host disease, and are caused predominantly by gram-positive organisms, including *S. pneumoniae.*

The incidence of CMV infection after allogeneic bone marrow transplantation ranges from 50%–70%, and CMV pneumonia develops in one third of infected patients. Overall, CMV pneumonitis occurs in 15% of all bone marrow recipients, and an increased incidence has been observed among older patients, seropositive patients, those who have received total-body irradiation, those with severe graft-versus-host disease, and seronegative recipients of marrow from seropositive donors. The single feature that distinguishes CMV pneumonia in bone marrow recipients from CMV pneumonia in recipients of solid organ transplants is the high mortality. Despite the significant antiviral action of ganciclovir in vitro, its clinical efficacy for CMV pneumonia in bone marrow recipients has been variable. When used alone, ganciclovir has resulted in 17%–48% survival rates. The combination of ganciclovir with high-titer, CMV-specific immune globulin has proved beneficial, with survival rates ranging from 52%–70%. Relapses occur, however, in nearly one third of these patients.

Recent studies have demonstrated the efficacy of antiviral agents for the prophylaxis of CMV infection. In one study, high-dose, intravenously administered acyclovir reduced the incidence of both CMV infection (from 75% to 59%) and pneumonia (from 31% to 19%). In addition, survival was greater in the acyclovir-treated patients. Even better results have been found with ganciclovir. Schmidt and co-workers randomized recipients of allogeneic bone marrow who had CMV detected in BAL fluid at day 35 after transplantation to receive full-dose ganciclovir versus observation. The incidence of CMV pneumonia or death was reduced from 70% in the control group to 25% in the prophylaxis group. Based on these findings, ganciclovir should be considered for prophylaxis in asymptomatic bone marrow recipients shedding CMV in BAL fluid or blood.

In the absence of acyclovir prophylaxis, HSV is excreted by 80% of seropositive bone marrow recipients, usually between the second and third week after transplantation. Most of these infections represent viral reactivation and involve the oropharyngeal mucosa. The clinical features are nonspecific, and two forms of HSV pneumonitis exist. Focal or multifocal pulmonary involvement usually arises from direct, contiguous spread from the oropharynx, whereas diffuse pulmonary involvement represents hematogenous dissemination from oropharyngeal or genital sites. Virtually all patients have mucocutaneous involvement, and copathogens are frequent.

Respiratory syncytial virus may cause interstitial pneumonitis in bone marrow recipients. Patients present with fever, cough, and signs of ear or sinus involvement before the onset of clinical and radiographic pulmonary disease. The majority of cases occur during the winter and spring. Therapy with aerosolized ribavirin and intravenous immunoglobulin has been advocated. Mortality rates exceed 80%.

Although pulmonary infection with *Candida, Cryptococcus, Histoplasma,* and *Coccidioides* are described, *Aspergillus* species are the most common cause of invasive fungal disease in bone marrow transplant recipients. Recipients of bone marrow are the most susceptible of all transplant patients to invasive pulmonary aspergillosis because of the nature of their immunosuppression. The duration of granulocytopenia and the administration of high-dose corticosteroids are well-recognized risk factors for the development of invasive pulmonary aspergillosis, and these factors concomitantly exist in the majority of bone marrow transplant patients. Treatment of invasive pulmonary aspergillosis is unsatisfactory, and outcome is best determined by the recovery of the granulocyte count. Mortality rates are high, approaching 80%–90%.

The incidence of *P. carinii* pneumonia has dropped significantly since the routine introduction of prophylaxis with trimethoprim/sulfamethoxazole, and cases are now limited to those patients who either cannot tolerate sulfa drugs or are noncompliant. The median time to onset of *P. carinii* pneumonia is 2 months after transplantation. Response to therapy is good if it is started early.

Heart Transplantation

In the United States, approximately 2500 heart transplantations are performed annually, with a 5-year actuarial survival rate of 72%. Pulmonary infections are by far the leading infectious complication after heart transplantation, occurring in 40%–60% of patients in the era before cyclosporine and in 24%–40% of patients in recent years. The majority of infections occur within the first 3 to 4 months, and multiple pathogens are present in 20%–25% of patients.

Most episodes of bacterial pneumonia occur within the first few weeks after transplantation and are usually caused by the aerobic gram-negative bacteria present in the hospital environment. *Legionella pneumophila* may cause up to 5% of bacterial pneumonias after heart transplantation, and unlike immunocompetent patients, organ transplant recipients may present with nodular infiltrates that progress to necrotizing pneumonia with cavitation. Treatment with erythromycin is usually successful, but 6 to 12 months of therapy may be required, because relapse is common. The incidence of nocardial pulmonary infection varies from 0–6% following cardiac transplantation. Fever and cough are the most common clinical features, and in 80% of patients the radiographic presentation is a solitary nodular lesion. The lung is the only site of involvement in about 80% of patients; the remainder, with disseminated disease, often exhibit skin or bone involvement. Treatment with trimethoprim/sulfamethoxazole is universally successful.

In approximately 30% of heart transplant recipients, invasive fungal disease develops, and the reported incidence of *Aspergillus* infection ranges from 0–24%. The clinical presentation is similar to that previously described, and mortality rates of 50%–86% are typical.

The use of prophylactic trimethoprim/sulfamethoxazole has reduced the incidence of *P. carinii* infection substantially. Mortality rates of 34% in heart transplant recipients have been reported, but outcome is generally good if the disease is diagnosed and treated early.

CMV infection after heart transplantation occurs in 67%–100% of patients, and CMV pneumonia develops in up to 16% of infected patients. Before the advent of effective antiviral therapy, mortality ranged from 46%–75%. Ganciclovir has proved to be effective in this patient population, and mortality rates have been reduced to 14% with this antiviral agent.

Of special concern to the heart transplant recipient is pulmonary infection by *Toxoplasma gondii.* Twelve percent to 17% of heart transplant recipients have had no previous exposure to this organism and receive a heart from a seropositive donor. A symptomatic primary infection develops in more than half of these patients. The most frequent clinical manifestations include fever, chorioretinitis, encephalitis, myocarditis, and pneumonitis. The diagnosis of toxoplasmosis requires the demonstration of tachyzoites in body fluids or tissues. Serologic studies may be useful, and titers begin to rise 4 to 12 weeks after transplantation. Prophylaxis with pyrimethamine or trimethoprim/sulfamethoxazole is recommended for patients at risk for primary infection.

Heart-Lung Transplantation

Infection is the leading cause of mortality after heart-lung transplantation, accounting for 48% of early postoperative (30 days) deaths and 73% of the late deaths. The lung as an allograft is more vulnerable to infection, as ischemia, handling, preservation, and reimplantation alter local pulmonary defenses. In addition, the normal cough reflex has been ablated by denervation, and mucociliary clearance has been markedly reduced.

Bacterial pneumonia is common after heart-lung transplantation. An overall incidence of 66% during the early experience with heart-lung transplantation has been reduced to only 13% by administering antibacterial prophylaxis with ceftazidime and clindamycin and by promptly adjusting the drug regimen to treat any bacteria isolated from airway secretions during the first 7 to 10 days. As with most hospital-acquired infections, gram-negative organisms, *S. aureus,* and *L. pneumophila* have been the most frequent causes.

CMV pneumonitis poses a special problem, as its clinical presentation is similar to that of acute rejection. Fiberoptic bronchoscopy with BAL and transbronchial biopsy, as described earlier in this chapter, have a good diagnostic yield and a low complication rate in this setting. There are no controlled trials evaluating the efficacy of ganciclovir in such patients; however, other treatment modalities have been disappointing. Therefore, ganciclovir should be considered the treatment of choice, and immune globulin can be considered in refractory or severe cases.

Before the routine administration of prophylactic therapy, *P. carinii* pneumonia developed in 75% of heart-lung transplant recipients at risk, although the majority of cases were subclinical. The diagnosis, therapy, and prophylactic regimen are similar to those already described.

Deep-seated fungal infections have been uncommon following heart-lung transplantation. *Candida* infection has been the most frequent, and these infections are usually disseminated. Although isolation of *Candida* species from respiratory tract specimens is not unusual, true *Candida* pneumonitis occurs infrequently. Only a few cases of *Aspergillus* infection after heart-lung transplantation have been reported, and mortality rates have been high.

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CHAPTER

26 Pulmonary Complications of HIV Infection

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INTRODUCTION

The AIDS epidemic, now in its second decade, is one of the most important global health problems of the twentieth century. In many urban communities in the United States, AIDS-related disorders are the leading causes of death among adults 25 to 44 years of age. By June 1996, 548,000 cases of AIDS had been reported in the United States, about half of them since 1993, and 343,000 had died. The worldwide impact is even more devastating: some sub-Saharan countries could lose a quarter of their adult population to AIDS, and without a cure, an estimated 10 million Asians will die of AIDS-related illnesses before the year 2015.

Since the beginning of the epidemic, lung diseases have been among the most important causes of illness and death. The first cases of AIDS were described in homosexual men in Los Angeles who had *Pneumocystis carinii* pneumonia (PCP) without a known reason for immunodeficiency. Lung diseases were later recognized not only in HIV-infected patients with full-blown AIDS, but in others with less severe immune compromise. Over the years, shifts in the demographics of HIV-infected populations and advances in the prophylaxis of HIV-associated infections have profoundly influenced the types of lung diseases in these patients.

PATHOGENESIS

Human immunodeficiency virus type 1 (HIV-1), the etiologic agent of AIDS, is a cytopathic RNA virus in the lentivirus subfamily of retroviruses. HIV-2, a retrovirus endemic in West Africa, also causes an immunodeficiency syndrome. In almost all cases, the virus is transmitted by sexual contact, by exposure to blood or blood products (most often among injection drug users), or from mother to child during childbirth.

The pathogenesis and immunologic effects of HIV infection involve a complex interplay of persistent viral replication, immune activation, and dysregulation of cytokine secretion. After primary infection, HIV disseminates widely through the blood. The virus is initially contained within follicular dendritic cells in the germinal centers of lymphoid tissue, and the number of $CD8^+$ T lymphocytes increases, opposing the progression of infection. Humoral responses, with antibodies directed against HIV proteins, may also reduce the severity of viremia. However, proinflammatory cytokines (interleukin-1b, interleukin-6, tumor necrosis factor, granulocyte-macrophage colony-stimulating factor) are overexpressed, upregulating HIV expression.

HIV causes disease mainly by infecting cells that express the CD4 molecule. Infection of $CD4^+$ (helper) T lymphocytes usually leads to progressive depletion of this cell line and immunosuppression, but some nonprogressors remain well, with stable CD4 cell counts for at least 10 years. $CD4^+$ T lymphocytes also regulate immune responses mediated by B cells, suppressor T cells, natural killer cells, monocytes, and macrophages, so the effects of HIV infection on immune responses are far more profound than simple T-cell depletion.

HIV may be identified in alveolar macrophages and lymphocytes early in the course of HIV infection, and the function of these cells may become impaired. Initially, the $CD8^+$ alveolitis may protect against immune killing of HIV-infected cells. Release of proinflammatory cytokines may be directly toxic to pulmonary epithelium, activate neutrophils, or facilitate HIV replication.

DEFINITION OF AIDS

In 1983, the Centers for Disease Control (CDC) established a case definition of AIDS to track the epidemic. AIDS was defined by the presence of specific opportunistic infections and neoplasms that occurred with advanced immunosuppression, and PCP was the most common AIDS-defining disorder. Since the purpose of surveillance is to describe the affected populations so as to anticipate trends and guide public health planning and responses, the case definition was revised in 1987, and again in 1993. The current definition includes recurrent pneumonia, pulmonary tuberculosis, and carcinoma of the cervix in HIV-infected persons. Advanced immunosuppression, defined as a CD4 count of 200/μL, was also included in the case definition, even in the absence of opportunistic infections or neoplasms. The expanded case definition of AIDS led to a 111% increase in reported cases from 1992 to 1993, and new case reports increased disproportionately in women, racial/ethnic minorities, and injection drug users.

Knowledge of the types of pulmonary disorders that are associated with HIV infection are reflected in the updated case definitions. In October 1983, the National Heart, Lung, and Blood Institute Workshop on Pulmonary Complications of HIV Infection found that 41% of the 1067 patients in whom AIDS was diagnosed in the participating institutions had serious pulmonary disorders, and PCP was by far the most common, occurring in 85% of the patients with lung disease. For years, PCP was considered the predominant pulmonary disease in HIV-infected patients. However, the early reports of pulmonary disorders associated with HIV infection considered only patients who met the case definition for AIDS, and almost all had advanced immunosuppression. We now recognize that other common respiratory illnesses develop in patients with less severe immunologic impairment, and the full range of pulmonary disorders associated with HIV infection is wide. Table 1 lists the infectious, neoplastic, and inflammatory diseases that occur in patients with HIV infection, and their typical radiographic patterns are summarized in Table 2.

TABLE 1. *HIV-associated respiratory disorders*

Focal opacification	**Mediastinal lymphadenopathy**
Bacteria	*M. tuberculosis*
Mycobacterium tuberculosis	*M. avium-intracellulare*
Pneumocystis carinii	Kaposi's sarcoma
	Lymphoma
	Fungi
Diffuse opacification	**Pleural effusion**
P. carinii	Bacteria (parapneumonic effusion, empyema)
M. tuberculosis	*M. tuberculosis*
Kaposi's sarcoma	Kaposi's sarcoma
Bacteria	Lymphoma
Fungi	Fungi
Cytomegalovirus	Cardiomyopathy
	Hypoproteinemia
Diffuse nodules	**Cavitation**
Kaposi's sarcoma (large nodules)	*M. tuberculosis* (high CD4)
M. tuberculosis (miliary)	*P. carinii* (low CD4)
Fungi (small nodules)	*Pseudomonas aeruginosa* (low CD4)
	Rhodococcus equi
Pneumothorax	Fungi
P. carinii	Lymphoma
	Cytomegalovirus

TABLE 2. *HIV infection: chest radiographic patterns and common etiologies*

RISK FACTORS FOR SPECIFIC PULMONARY DISEASES

The pulmonary disorders associated with HIV infection range from mild abnormalities in pulmonary function unaccompanied by respiratory symptoms to fatal opportunistic infections. The risk for each of these disorders is strongly influenced by the severity of immunosuppression, the patient's demographic characteristics and place of current or prior residence, and whether the patient is using prophylaxis against common HIV-associated infections. Genetic factors are probably also important but less precisely defined.

Influence of Immune Function

The severity of the abnormality in host defense is a primary determinant of the risk for specific pulmonary disorders. Early in the course of HIV infection, when the immune system is not severely compromised, respiratory disorders may occur that are similar to those in the general population; opportunistic infections occur only with severe immunodeficiency. The CD4-lymphocyte count is used most often as a surrogate marker for severity and progression of HIV disease, and the probability of specific diseases developing can be estimated by this measurement. Assessment of HIV load by measurement of the number of HIV-1 viral RNA copies in the blood also correlates strongly with disease progression.

The spectrum of disease in patients with severe immunosuppression was well-described early in the epidemic, but more recent studies have confirmed the relationship of immune function to the risk for common problems like upper respiratory infection, bacterial pneumonia, and pulmonary tuberculosis. In the Pulmonary Complications of HIV Infection Study, 1353 subjects were followed prospectively in six U.S. cities to determine the prevalence, incidence, and types of lung diseases that occur in persons in selected HIV transmission categories. To describe the types of disorders that occur in early HIV infection, patients with an AIDS-defining diagnosis (1987 case definition) were excluded from enrollment. After 18 months of follow-up, the most frequent respiratory diagnoses in the HIV-seropositive subjects were upper respiratory infection (33.4%), acute bronchitis (16%), and acute sinusitis (5.3%). Although these disorders were also common in a control group of HIV-seronegative homosexual men and injection drug users, the incidence of acute bronchitis and sinusitis was significantly higher in the HIV-infected subjects. Surprisingly, upper respiratory infection (defined as a mild, self-limited illness with coryza and sometimes sore throat and cough) occurred less frequently in subjects with a baseline CD4 count of 250/µL than in those with higher lymphocyte counts. The reason for this is not known, but it is possible that patients with severe immunosuppression may have a less vigorous immune response and milder symptoms with this self-limited illness. In the same study, bacterial pneumonia and PCP occurred more frequently in subjects with baseline CD4 lymphocyte counts of 250/µL than in those with higher counts.

The association between reduction in the CD4 lymphocyte count and the risk for specific diseases was explored in a survey of the medical records of more than 18,000 HIV-infected subjects who received care at more than 100 sites in 10 U.S. cities (Table 3). Common disorders like sinusitis, bronchitis, and pharyngitis occurred at all strata of CD4-cell counts. With lower counts, different pulmonary infections occurred with increasing frequency: 80% of cases of bacterial pneumonia and pulmonary tuberculosis occurred with CD4 counts of 400/µL; recurrent pneumonia and nontuberculous pulmonary mycobacterioses at CD4 counts of 300/µL; and PCP, Kaposi's sarcoma (KS), and disseminated *Mycobacterium tuberculosis* infection at CD4 counts of 200/µL. More than 80% of cases of disseminated nontuberculous mycobacteriosis, including *M. avium-intracellulare* infection, disseminated fungal infection, central nervous system toxoplasmosis, and cytomegalovirus (CMV) disease occurred in patients with the most severe immunosuppression (CD4 count of 100/µL).

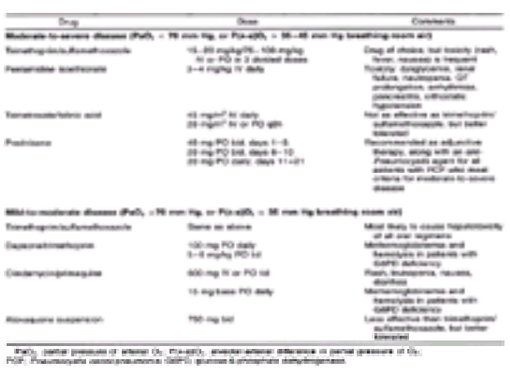

TABLE 3. *Treatment of Pneumocystis carinii pneumonia*

Therefore, common respiratory problems like sinusitis and bronchitis may occur at any CD4 count, and bacterial pneumonia and tuberculosis often occur before AIDS-defining opportunistic infections and neoplasms. Declining immune function increases the risk for all HIV-associated respiratory disease, except for mild upper respiratory tract infections.

Demographic Factors

The demographic characteristics of persons with HIV infection also have a major impact on the incidence of specific pulmonary disorders, and demographic shifts were accompanied by a changing spectrum of disease. Persons who acquired HIV infection through injection drug use and heterosexual contact represent an increasing proportion of new cases of AIDS. From 1981–1987, 64% of cases of AIDS were in homosexual men, compared with 45% of new cases from 1993–1995. In the early

years of the epidemic, most patients with AIDS were white. Now, the majority are black and Hispanic.

These demographic trends are reflected in the recognition of bacterial pneumonia and pulmonary tuberculosis as important HIV-associated infections. CDC surveillance data in the 1980s showed a doubling of mortality rates for pneumonia among persons ages 25 to 44 years in cities with a high prevalence of injection drug use and AIDS. Selwyn et al. found that the incidence of bacterial pneumonia was five times greater in HIV-infected than non-HIV-infected injection drug users, and that bacterial infections accounted for substantial mortality. In the cohort followed in the Pulmonary Complications of HIV Infection Study, bacterial pneumonia occurred more frequently than PCP, and the risk for bacterial pneumonia was significantly higher in injection drug users than in others.

Race and ethnicity may also influence the risk for bacterial pneumonia and tuberculosis, but these associations are confounded by differences in access to health care, the higher prevalence of tuberculosis in minority communities, and the disproportionately high numbers of injection drug users who are black or Hispanic. Nevertheless, the risk for tuberculosis is higher in blacks and Hispanics than in whites, whereas whites have a higher risk for HIV-associated malignancies and CMV disease.

Residence

A person's place of residence strongly influences the risk for acquiring specific infections. The high incidence of PCP in the United States and Europe contrasts sharply with that in Africa, where it is much less common. It is still unknown whether genetic or environmental factors account for the lower incidence of PCP in Africa. In the United States, the incidence of HIV-associated tuberculosis is highest in the Northeast. The geographic distribution of endemic fungi is a strong determinant of risk for those infections; disseminated histoplasmosis and coccidioidomycosis are common in patients with AIDS who live in endemic areas. These infections may also occur as reactivation disease after HIV-infected persons move to other areas and become immunocompromised.

Use of Prophylaxis

The risk for specific opportunistic infections declines with the use of prophylaxis. This is reflected in studies that document a declining incidence and mortality of PCP and a declining case rate for tuberculosis despite the relatively constant number of persons in the United States who are immunocompromised by HIV infection.

PULMONARY FUNCTION TESTS

Pulmonary function tests are usually not performed in the evaluation of patients with suspected HIV-associated pulmonary disorders, as no pattern of abnormality is specific for any disease and precise measurement of severity of physiologic derangements in patients with acute illnesses is usually not helpful in management. The common disorders (PCP, pulmonary KS) may reduce the vital capacity (VC), and they consistently reduce the single-breath carbon monoxide diffusing capacity (D_LCO). Measurement of D_LCO is sometimes used in the diagnostic evaluation of patients with normal chest radiographic findings who are suspected of having PCP; a normal value is interpreted as strong evidence against this infection.

Persons with HIV who have no apparent lung disease may also have abnormalities in pulmonary function. Values for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC are usually normal, but FVC and FEV_1 may be reduced in injection drug users compared with other HIV-infected persons, perhaps related to their high prevalence of cigarette smoking. The D_LCO is often reduced in asymptomatic persons with HIV infection, especially in those with advanced immunosuppression. In the Pulmonary Complications of HIV Infection Study, asymptomatic HIV-infected subjects with CD4-lymphocyte counts of 400/µL and/or HIV-associated symptoms had small but significant reductions in D_LCO compared with HIV-infected persons with higher CD4 counts. Perhaps subclinical inflammatory pulmonary processes such as nonspecific interstitial pneumonitis and lymphocytic interstitial pneumonitis occur in asymptomatic HIV-seropositive patients, reflected by a reduction in D_LCO. In many patients, D_LCO may be reduced by factors unrelated to HIV infection, including race, cigarette smoking, and injection drug use.

PNEUMOCYSTIS CARINII PNEUMONIA

Despite the development of effective prophylaxis against *P. carinii,* PCP remains the most common AIDS-defining infection. Until recently, *P. carinii* was assumed to be a protozoan, but recent molecular studies classify it as a fungus. Whether the organism is acquired from an environmental source or by person-to-person transmission is unknown.

Clinical, Radiographic, and Laboratory Features

The presenting features of PCP are nonspecific; they include dyspnea, dry cough, and fever that usually progress gradually during several weeks. However, it may occasionally present as an acute illness with rapid deterioration within a few days. The chest radiograph usually reveals diffuse granular opacities, which strongly suggests the diagnosis (Fig. 1), but sometimes patients with PCP have nodular densities, lobar consolidation, or normal radiographic findings. All of these radiographic patterns may also occur with other infections and neoplasms. Cystic abnormalities and spontaneous pneumothorax in patients with known or suspected HIV infection are usually caused by PCP (Fig. 2).

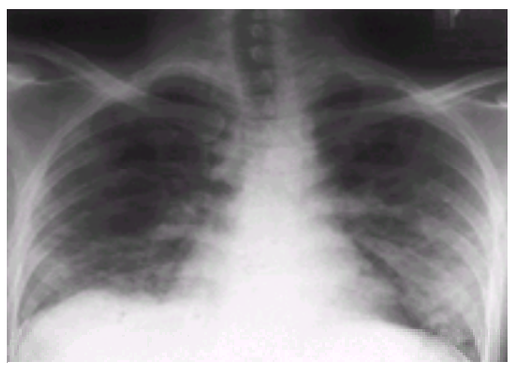

FIG. 1. Typical radiographic appearance of PCP, with diffuse granular opacifications.

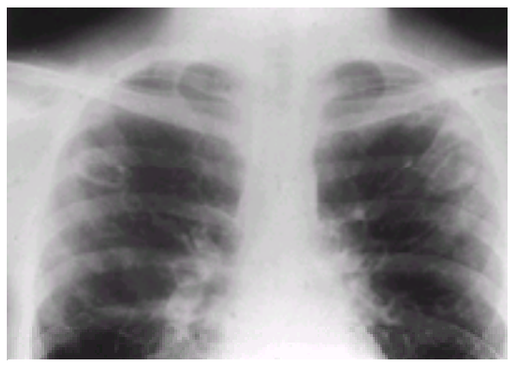

FIG. 2. Chest radiograph of a patient with cystic pulmonary lesions caused by PCP.

The diagnosis of PCP may be supported by adjunctive testing. This infection is unlikely in a patient who had a CD4-cell count of 200/µL in the preceding 2 months in the absence of other HIV-associated symptoms. Approximately 90% of patients with PCP have an elevated serum lactic dehydrogenase level, but this may occur with other pulmonary diseases. Oxygen desaturation with exercise is a relatively sensitive and specific test in patients suspected to have PCP, but it is not diagnostic.

Gallium 67 and indium 111 lung scans are highly sensitive indicators of PCP, but isotope uptake also occurs in other pulmonary infections, so they are seldom useful in a diagnostic algorithm. One of these tests could be used in patients with normal chest radiographic findings in whom an opportunistic infection is suspected. If the scan shows abnormal uptake in the lungs, further diagnostic studies may be appropriate, whereas most patients with a negative scan can be observed. The lesions of KS do not take up gallium 67 or indium 111, and lymphoma does not take up indium 111, so the scans may be useful adjuncts in the noninvasive diagnosis of these malignancies in patients with abnormal chest radiographic findings.

Microbiologic Diagnosis

P. carinii cannot yet be cultured in vitro; therefore, infection and the diagnosis of PCP can be confirmed only by demonstrating organisms in a lung-derived specimen. The least invasive test is the analysis of sputum induced with 3% saline solution delivered by ultrasonic nebulization. By means of modified Giemsa, methenamine silver, or immunofluorescent staining, the organism can be identified in up to 80% of cases, depending on the experience of the laboratory. Other pathogens, especially *M. tuberculosis* and fungi, may also be found in induced sputum by using appropriate staining and culture techniques.

Whether to proceed routinely with fiberoptic bronchoscopy to confirm the diagnosis of PCP in patients suspected of having the disease but whose sputum specimens are nondiagnostic is controversial. Some prefer to treat these patients empirically for PCP and establish a diagnosis only if no clinical response occurs within 5 days. Proponents of empiric therapy hold that a presumptive diagnosis of PCP is usually accurate and that the procedure usually carries unnecessary inconvenience, risk, and discomfort to patients, as well as expense. A decision analysis supporting initial empiric therapy indicated that the expected 1-month survival rate was identical whether patients received early bronchoscopy or whether the procedure was offered only to nonresponders, and that bronchoscopy was associated with greater costs and effort.

Proponents of early bronchoscopy maintain that routinely using an empiric approach subjects many patients to treatment and its attendant toxicity for a disease that they do not have, and nonresponders may be too ill to undergo bronchoscopy after several days of inappropriate therapy. Coinfection with other pathogens is common and may not be diagnosed in patients treated empirically. Also, adjunctive corticosteroid therapy may transiently improve symptoms in patients with other pulmonary disorders and contribute to the emergence of other opportunistic infections, such as aspergillosis and CMV disease.

In any case, fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is the next procedure in the diagnostic algorithm for PCP when sputum specimens are nondiagnostic. The complication rate is very low, and the yield is 90% in most centers. This yield is optimized by performing lavage in more than one lobe, and the yield is higher in the upper lobes than the lower. All lavage specimens should be examined for the presence of acid-fast bacilli, fungi, and viral cellular inclusions, as patients with suspected PCP may have another infection or may be coinfected with other pathogens. The use of BAL in the diagnosis of bacterial pneumonia in HIV-infected persons is not generally indicated.

When bronchoscopy with BAL is carried out in patients with HIV-associated pulmonary disorders, it is also controversial whether to perform bronchoscopic lung biopsies routinely. Because the diagnostic yield of BAL in PCP is so high, some authors recommend that biopsy be omitted initially and performed during a second bronchoscopy if the lavage specimen is nondiagnostic. However, biopsy specimens are occasionally diagnostic of PCP and other pathogens when the lavage result is negative, and it is the least invasive means of diagnosing other pulmonary conditions that require histologic interpretation. Transbronchial biopsies are contraindicated in the presence of bleeding disorders, and the high risk for pneumothorax usually precludes biopsies in patients undergoing mechanical ventilation. Diagnosing PCP by video-assisted thoracoscopy or an open procedure is rarely necessary, as almost all cases are confirmed using sputum induction or bronchoscopy.

Treatment

The drugs used to treat PCP are outlined in Table 3. Trimethoprim/sulfamethoxazole (T/S) is the agent of choice, regardless of the severity of disease. It is consistently the most effective in comparative studies and also inexpensive and available in both oral and intravenous preparations. Although it is usually well tolerated, many patients are unable to tolerate the drug for a full course. The optimal duration of treatment is unknown, but most clinicians treat for 14 to 21 days, followed by prophylaxis for life.

The choice of anti-*Pneumocystis* treatment depends on the severity of disease and how the patient tolerates the medication. Outpatient treatment with oral agents is an option for patients with mild to moderate episodes whose arterial oxygen tension (PaO_2) while breathing room air is 70 mm Hg. In a comparison of oral T/S, trimethoprim/dapsone, and clindamycin/primaquine, all three had similar efficacy and rates of treatment-limiting toxicity. Atovaquone is available as second-line treatment for mild to moderate PCP, defined as a PaO_2 of 60 mm Hg and an alveolar-arterial oxygen difference [$P(A\text{-}a)O_2$] of 45 mm Hg, in patients who cannot tolerate T/S. This drug is administered orally and is associated with fewer adverse reactions than T/S, but it is also less effective.

T/S is the treatment of choice of patients with moderate to severe PCP. However, the high rate of toxicity limits or precludes its use in many. Adverse effects include fever, rash, stomatitis, nausea, vomiting, neutropenia, nephritis, and elevated serum aminotransferase concentrations. For unknown reasons, persons with HIV infection are more likely than others to have adverse reactions to T/S.

Patients with PCP who cannot tolerate T/S are usually given intravenous pentamidine isethionate. This drug is as effective as T/S, but severe adverse effects are also common with pentamidine, including nephrotoxicity, pancreatitis, hyperglycemia, hypoglycemia, leukopenia, hypotension, and ventricular arrhythmias. Trimetrexate/leucovorin is also an alternative for patients who cannot tolerate or who do not respond to T/S. It not as effective as T/S but is associated with fewer side effects. Whether trimetrexate should replace pentamidine as second-line treatment of moderate to severe PCP is unknown, because comparative trials of these two drugs have not been performed.

Adjunctive therapy with corticosteroids at the start of anti-*Pneumocystis* treatment reduces the likelihood of respiratory failure, deterioration of oxygenation, and death in patients with moderate to severe infection. The precise mechanisms of the beneficial effects of corticosteroids in patients with PCP are unknown. An inflammatory response in the lung occurs at the start of anti-*Pneumocystis* treatment in patients who do not receive corticosteroids, probably in response to components of killed organisms and manifested by deteriorating gas exchange. Corticosteroids modify this inflammatory response, prevent the initial worsening of gas oxygenation, and allow the patient to receive more antimicrobial treatment.

The patients with PCP most likely to benefit from adjunctive corticosteroids have a PaO_2 of 70 mm Hg or a $P(A\text{-}a)O_2$ of 35 mm Hg. Patients with less severe abnormalities of gas exchange usually do not benefit, mainly because their outcomes are very good with anti-*Pneumocystis* treatment alone. Benefit is also questionable when corticosteroids are administered 72 hours after anti-*Pneumocystis* treatment has begun.

The optimal dosage and duration of corticosteroid treatment are unknown, but the largest controlled trial that showed benefit used oral prednisone in the following regimen: on days 1 through 5, 40 mg was given twice daily; on days 6 through 10, 40 mg was given daily; on days 11 through 21, 20 mg was given daily. Adverse reactions occur infrequently, and although life-threatening superinfections have been described, they are uncommon. Patients in whom pulmonary disorders develop shortly after apparently successful treatment of PCP should be evaluated for another opportunistic infection, especially CMV disease.

Prophylaxis

The prevention of PCP with drugs has reduced its incidence, and PCP-associated mortality in HIV-infected persons has fallen dramatically (Fig. 3). Although anti-*Pneumocystis* prophylaxis may prevent this infection and prolong life, longevity is usually accompanied by progressive immunosuppression, rendering patients susceptible to other potentially fatal infections. While the percentage of HIV-related deaths in the United States caused by PCP declined, deaths caused by nontuberculous mycobacteriosis, CMV disease, bacterial infections, non-Hodgkin's lymphoma, and tuberculosis increased. In an analysis of 844 HIV-infected homosexual men enrolled in the Multicenter AIDS Cohort Study, those who received prophylaxis for PCP before being given a diagnosis of AIDS had a lower incidence of PCP and lower mean CD4 count at the time of the AIDS diagnosis than those who did not. However, they had a higher incidence of *M. avium* disease (33.4% vs. 24.8%), wasting syndrome (18.4% vs. 6.4%), and esophageal candidiasis (21.3% vs. 12.8%). PCP prophylaxis also appeared to delay the time to the first AIDS-related illness by 6 to 12 months.

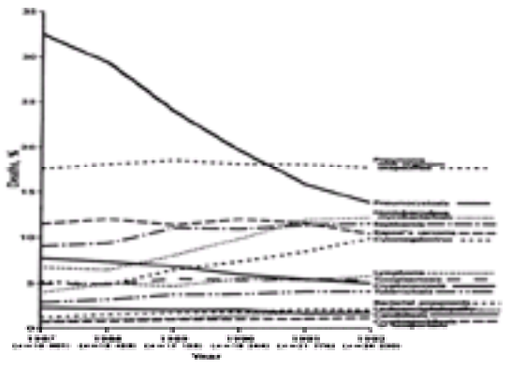

FIG. 3. Trends in the prevalence of infectious diseases and cancers reported among persons dying of HIV infection in the United States from 1987 to 1992. (Reproduced with permission from Selik RM, Chu SY, Ward JW. Trends in infectious diseases and cancers among persons dying of HIV infection in the United States from 1987 to 1992. *Ann Intern Med* 1995;123:933–936.)

Lifelong prophylaxis against *P. carinii* infection is recommended for all HIV-infected persons with CD4-cell counts of 200/µL, and for patients with HIV-related symptoms, including unexplained persistent fever (100°F) for 2 weeks, oropharyngeal candidiasis unrelated to antibiotic or corticosteroid therapy, and unexplained weight loss. Oral T/S, dapsone, and aerosolized pentamidine are the drugs most extensively studied and used.

The preferred regimen is one double-strength tablet of T/S (160 mg trimethoprim, 800 mg sulfamethoxazole) daily. In addition to its superior efficacy against *P. carinii,* this drug may also prevent toxoplasmosis and bacterial infections. However, the high rate of intolerable side effects limits its application. Lower doses (one single-strength tablet daily, or one double-strength tablet thrice weekly) appear to be almost as effective and more likely to be tolerated. Desensitization to T/S may be attempted in patients allergic to the drug who have not had life-threatening reactions. Failure of T/S prophylaxis is associated with noncompliance and with CD4-lymphocyte counts of 50/µL.

Patients who cannot tolerate T/S should take 100 mg of dapsone daily, in single or divided doses. Fifty milligrams of dapsone daily, along with 50 to 75 mg of pyrimethamine weekly and 25 mg of leucovorin weekly, also confers protection against toxoplasmosis. Pentamidine administered by aerosol has the potential advantages of high drug levels in the lung and minimal systemic absorption and toxicity, but it is less effective than T/S and dapsone. The only aerosolized pentamidine regimen recommended by the CDC is 300 mg administered monthly using the Respigard II nebulizer (Marquest, Englewood, Colorado). Other doses and delivery systems are under investigation.

When PCP occurs in patients using aerosolized pentamidine, it is associated with atypical clinical and diagnostic features. Normal regional differences in ventilation deposit the drug preferentially in the lower lung zones, accounting for a higher rate of predominantly upper lobe involvement. These patients are also more likely to have cystic lung lesions and pneumothorax. Extrapulmonary *P. carinii* infection may occur in patients receiving prophylaxis with aerosolized pentamidine, as the drug is delivered only to the lung.

Other agents have been used to prevent PCP in patients who cannot tolerate standard treatments, or in whom PCP develops despite prophylaxis. These include clindamycin/primaquine, atovaquone, pyrimethamine/sulfadoxine, alternative aerosol pentamidine regimens, and intermittent parenteral pentamidine or trimetrexate. Their efficacy is not known, and they should not be used unless recommended drugs cannot be given.

Respiratory Failure Caused by *Pneumocystis carinii* Pneumonia

Despite the use of prophylaxis and declining mortality rates associated with PCP, the infection is still the most common cause of respiratory failure and admission to intensive care units (ICUs) in patients with AIDS. When treatment of PCP is postponed or ineffective, a clinical syndrome develops that resembles the acute respiratory distress syndrome (ARDS), with severe hypoxemia, intrapulmonary shunt, reduced pulmonary compliance, and the radiographic appearance of diffuse opacities. Just as severe PCP clinically resembles ARDS, the supportive treatment, including intubation, mechanical ventilation, and application of positive end-expiratory pressure, is similar. Continuous positive airway pressure (CPAP) delivered by face mask may improve gas exchange without endotracheal intubation, but its usefulness is limited in patients with severe disease. However, it may afford the patient and physician more time to consider whether mechanical ventilation is desirable.

As changes in therapy modified the prognosis, three distinct eras of critical care for patients with PCP and respiratory failure were identified. Initially, the outlook for survival was dismal. In the 1984 National Institutes of Health Workshop, 88 of the 102 patients with AIDS who received mechanical ventilation died, and nearly all had PCP. Other studies from individual centers confirmed that survival after respiratory failure was about 15%. In some centers, ICU utilization declined because physicians did not recommend aggressive interventions, and patients were more likely to decline ICU care. After 1986, mortality rates seemed to decrease to about 50%, with the decline attributed to the selection of patients with a better prognosis and the benefits of adjunctive corticosteroid therapy.

We are now in a third era of outcomes, when patients who require mechanical ventilation for PCP again have a very high mortality rate. At San Francisco General Hospital, mortality increased from 61% in the period from 1986–1988 to 76% in the next 2 years. At the same time, the proportion of patients who were injection drug users and who had recurrent episodes of PCP increased. Mortality was strongly associated with a CD4-lymphocyte count of 50/µL (94%) and with the development of a pneumothorax (100%). Recent patients who require mechanical ventilation for PCP are also more likely to have failed prophylaxis, anti-*Pneumocystis* treatment, or adjunctive corticosteroid therapy and therefore are expected to have a poor prognosis. Recent studies show that when respiratory failure follows several days of appropriate therapy for PCP, the probability of survival is only 10%–20%.

The prospects for long-term survival following PCP and respiratory failure are better than earlier in the epidemic. Prolonged survival is probably related to the selection of patients with a better prognosis for mechanical ventilation, and to improvements in prophylaxis and treatment of subsequent infections.

BACTERIAL PNEUMONIA

The importance of bacteria as HIV-associated pulmonary pathogens was established by investigations in patients who did not have advanced immunosuppression. HIV infection impairs humoral immunity through quantitative and functional defects in CD4 lymphocytes. This increases the risk for bacterial infections, including sinusitis and pneumonia. Although a first episode of bacterial pneumonia usually occurs before the diagnosis of AIDS, the risk for pneumonia increases as the CD4-lymphocyte count declines. Injection drug users are at higher risk than other groups, and neutropenia is an independent risk factor. Prophylaxis with T/S appears to reduce the risk for bacterial pneumonia. Bacterial pneumonia may also accelerate the course of HIV disease, as it is an independent predictor of progression to AIDS and mortality.

In early HIV infection, the pathogens that cause pneumonia are similar to those in the general population. Encapsulated organisms, especially *Streptococcus pneumoniae* and *Haemophilus influenzae,* are the most frequent etiologic agents. Although pneumonia caused by atypical pathogens like *Mycoplasma* and *Legionella* is described, it is relatively uncommon. However, in a careful prospective analysis of 149 episodes of pneumonia in HIV-seropositive former injection drug users, *Chlamydia pneumoniae* was confirmed serologically as the second most common cause of pneumonia (after *S. pneumoniae*), and infection occurred at higher mean CD4-cell counts than infection caused by other pathogens.

Pathogens that rarely cause community-acquired pneumonia in the general population occur more frequently in HIV-infected persons. *Rhodococcus equi,* an aerobic, gram-positive, acid-fast bacillus, may cause focal consolidation, endobronchial disease, and cavitation, usually in patients with advanced HIV disease. Pneumonia caused by *Pseudomonas aeruginosa* was rare in the early years of the AIDS epidemic but is now emerging as an important entity. It usually follows another opportunistic infection or occurs when the CD4-cell count is 50/µL. Although many patients have histories of recent hospitalization, this infection usually presents as community-acquired pneumonia and is not necessarily associated with neutropenia or the use of corticosteroids. Cavitation is common, and the infection is often recurrent or chronic. *Nocardia asteroides* may cause nodules, consolidation, cavitation, pleural effusions, empyema, and intrathoracic lymphadenopathy in patients with HIV infection.

Bacterial pneumonia usually presents in a typical fashion, with fever, chills, productive cough, and localized areas of consolidation on chest radiograph. Although this clinical picture strongly suggests bacterial pneumonia, it may also occur with tuberculosis and fungal infection. Conversely, patients with bacterial pneumonia may have diffuse pulmonary opacities that resemble those of PCP. HIV-infected patients with bacterial pneumonia may be bacteremic and critically ill, but overall mortality is similar to that of HIV-seronegative persons with comparable severity of illness.

The approach to diagnosis and treatment of bacterial pneumonia is the same as that for HIV-negative patients. Because bacterial pneumonia is so common, it should be suspected in any patient with a compatible clinical syndrome and abnormal chest radiographic findings. The routine evaluation includes blood cultures, and if pleural fluid is present, it should be cultured and stained for bacteria, fungi, and mycobacteria. Patients with a productive cough should always have sputum specimens examined for acid-fast bacilli, but the usefulness of sputum Gram's stain and culture in the diagnosis of bacterial infection is controversial.

Empiric coverage for common bacterial pathogens should be started promptly after specimens are obtained. The initial antibiotic regimen should always cover *S. pneumoniae* and *H. influenzae,* and empiric treatment of *P. aeruginosa* should be considered in patients with advanced HIV infection or CD4-lymphocyte counts of 50/µL. Bronchoscopy should be performed in patients who do not respond to empiric therapy without an established diagnosis, to determine whether they have mycobacterial or fungal infection. Occasionally, pulmonary involvement with KS or lymphoma may resemble bacterial infection and can be diagnosed with bronchoscopy.

The polyvalent pneumococcal vaccine is recommended for all HIV-infected people, although persons with low CD4 counts are unlikely to mount an adequate antibody response. A vaccine against *H. influenzae* type b is available, but its usefulness in patients with HIV infection is questionable, as most of these infections are caused by nontypeable strains. Although influenza vaccine is also recommended, there are no data to show that persons with HIV infection are at increased risk for contracting influenza, or that the illness is more severe than in the general population.

TUBERCULOSIS

Modest reductions in cell-mediated immunity increase the risk for reactivation of latent tuberculosis, and the risk increases as CD4-cell counts decline. In HIV-infected persons, tuberculosis often occurs before opportunistic infections, probably because *M. tuberculosis* is more virulent. In patients with mild immunodeficiency, the clinical presentation is similar to that of tuberculosis in HIV-negative patients. Atypical pulmonary presentations, including diffuse infiltrates, miliary patterns, intrathoracic lymphadenopathy, or normal chest radiographic findings, occur more frequently in patients with advanced immunosuppression (Table 3). These patients also have a high incidence of extrapulmonary infection affecting the pleurae, lymph nodes, gastrointestinal tract, bone marrow, and blood.

The diagnosis of tuberculosis may be difficult in HIV-infected persons. Cutaneous anergy is more prevalent as CD4-cell counts decline, making tuberculin skin tests less useful. Radiographic clues to the diagnosis include cavitation, hilar and mediastinal lymphadenopathy, and pleural effusions. When cavitation is present, results of acid-fast smears and cultures of sputum are usually positive. In patients who do not expectorate spontaneously, sputum may be induced with hypertonic saline solution. Results of bronchoscopy with BAL, transbronchial biopsy, and analysis of postbronchoscopy sputum specimens are often diagnostic. Biopsies enhance the immediate diagnostic yield of bronchoscopy in the diagnosis of pulmonary tuberculosis, in comparison with BAL alone.

Despite an appropriate evaluation, results of acid-fast smears of sputum and bronchoscopic specimens may be negative, and cultures may not yield positive results for several weeks. Early treatment of tuberculosis improves the outcome and reduces transmission of the disease to others, so initial empiric therapy is warranted for patients with radiographic abnormalities consistent with tuberculosis unless another disorder is identified.

ATYPICAL MYCOBACTERIAL INFECTION

M. avium-intracellulare causes devastating complications and death in patients with AIDS. In HIV-infected persons with severe immunosuppression, *M. avium-intracellulare* usually causes bacteremia and disseminated infection with fever, weight loss, diarrhea, and anemia. However, *M. avium-intracellulare* is rarely a pulmonary pathogen in patients with AIDS. It is usually isolated from pulmonary specimens in patients with symptomatic pulmonary disease along with another pathogen (such as *P. carinii*) that accounts for the clinical picture. When *M. avium-intracellulare* is isolated from asymptomatic persons, it is strongly predictive of the later development of disseminated infection.

Other nontuberculous mycobacteria may cause pulmonary infection in patients with HIV infection. Like tuberculosis, atypical mycobacterial infections are usually diagnosed first by direct microscopy of smears of any specimen, and the species is then identified by nucleic acid probe or culture. However, if acid-fast bacilli are identified from sputum or bronchoscopic specimens, patients should be treated presumptively for *M. tuberculosis* infection until the species is identified, mainly because tuberculosis is more common and responds better to treatment, and because early treatment of active tuberculosis is an essential public health measure.

CYTOMEGALOVIRUS INFECTION

In patients with CD4-lymphocyte counts of 50/µL, CMV commonly causes retinitis, esophagitis, gastritis, colitis, hepatitis, encephalitis, pneumonia, and death. Patients with AIDS may also have CMV pneumonitis, but uncommonly. Although the virus can often be isolated in cultures of BAL fluid, it is not usually pathogenic. Pulmonary infection can be inferred when typical intranuclear or intracytoplasmic inclusions are found in BAL fluid or biopsy material. The likelihood that CMV is a pulmonary pathogen is also greater when CMV infection is found at other sites.

CMV pneumonitis usually occurs in patients who have had prior AIDS-defining illnesses. They present with a clinical syndrome similar to that of PCP, with dyspnea, nonproductive cough, fever, and diffuse pulmonary opacities. Unilobar radiographic involvement, cavitation, nodules, and pleural effusions are also described. It is treated in the same way as infection in other sites, with intravenous gancyclovir or foscarnet, and the response to therapy is similar to that of CMV retinitis or gastrointestinal disease. As CMV infection occurs only in patients with very severe immunosuppression, the long-term prognosis is very poor.

FUNGAL PNEUMONIA

Life-threatening fungal disease may occur in HIV-infected patients, either by new infection or reactivation of latent disease. The types of fungal infections depend on the severity of immunodeficiency and whether the patient has lived in endemic areas.

Cryptococcosis

Cryptococcus neoformans is distributed throughout the world and is the most common fungus causing life-threatening illness in patients with AIDS. The meninges are the most common site of infection, and cryptococcal meningitis is often the first manifestation of AIDS. With cryptococcal pneumonia, the chest x-ray film usually shows diffuse infiltrates, similar to those of PCP, but localized infiltrates, nodules, cavitation, pleural effusions, miliary patterns, and lymphadenopathy are also seen. Almost all patients with cryptococcal pneumonia have meningitis and disseminated disease, and CD4-lymphocyte counts are typically 100/µL. The diagnosis is established by identification of the organism from sputum, BAL fluid, pleural fluid, or lung biopsy specimens. A high titer of cryptococcal antigen in serum is strongly suggestive, and an antigen titer of 1:8 in BAL fluid is diagnostic of cryptococcal pneumonia.

Because most patients with HIV and cryptococcal pulmonary infection have disseminated disease, 0.5 to 1.0 mg of amphotericin B per kilogram of body weight daily is usually the therapy of first choice. Four hundred milligrams of fluconazole daily is a reasonable alternative in patients who are less ill. After the patient improves and the cerebrospinal fluid is sterilized, lifetime prophylaxis with 200 mg of fluconazole daily is indicated.

Histoplasmosis

Histoplasma capsulatum is endemic in the Ohio and Mississippi River valleys, Central and South America, and the Caribbean Islands. Disseminated disease may develop in patients with HIV infection who come from endemic areas when immunodeficiency permits reactivation of latent infection. The clinical presentation is usually subacute, and the chest roentgenogram typically shows a diffuse or miliary pattern, although localized infiltrates may occur. The diagnosis is established by identification or culture of the organism from blood, lung-derived specimens, bone marrow, or liver.

Amphotericin B is the treatment of choice for most cases of HIV-associated histoplasmosis. An alternative in patients with milder disease is 200 mg of itraconazole daily, and it should be used as suppressive therapy for life after the primary infection has been controlled.

Aspergillosis

Life-threatening pulmonary aspergillosis may develop in patients with advanced immunosuppression. Two common patterns of disease are identified: an invasive parenchymal infection, which is usually fatal, and a predominantly bronchial disease with initial symptoms of dyspnea and airway obstruction. The classic risks for *Aspergillus* infection—namely, prolonged neutropenia and treatment with high-dose corticosteroids—are often absent. Aspergillosis probably develops in patients with advanced AIDS because of defects in neutrophil or alveolar macrophage function. The CD4-lymphocyte count is typically 30/µL, and the prior use of corticosteroids

and neutrophil counts of 500/µL increase the risk. Disseminated disease is common, especially to the brain.

Clues to the diagnosis of invasive pulmonary aspergillosis include upper lobe disease with cavitation and hemoptysis (Fig. 4). Histologic proof has traditionally been required for this diagnosis, because *Aspergillus* is ubiquitous and its presence in nasopharyngeal secretions, sputum, and BAL fluid may represent contamination or colonization. However, recent studies in patients with severe immunosuppression, including AIDS, indicate that the isolation of *Aspergillus* in BAL fluid correlates strongly with histologic proof of tissue invasion.

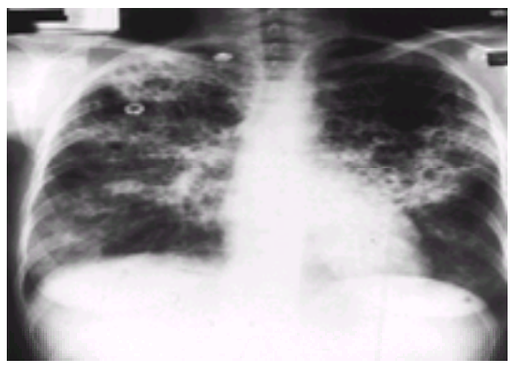

FIG. 4. Chest radiograph of a patient with invasive pulmonary aspergillosis. Diffuse cavitary lesions are present, especially in the upper lung fields.

Invasive aspergillosis is usually treated with amphotericin B, and itraconazole is a reasonable alternative. Despite treatment, most patients die within a few weeks.

Other Fungal Infections

In endemic areas, disseminated coccidioidomycosis and blastomycosis may occur in patients with AIDS, usually as a complication of advanced immunosuppression. In some patients, a prior infection may become reactivated after they have moved from an endemic area. These infections usually involve the lung; the presentation includes cough, fever, dyspnea, and the appearance of nodular, focal, cavitary, or diffuse disease. The diagnosis is established by demonstrating the organism by microscopy or culture in respiratory specimens.

Patients with disseminated disease should be treated with amphotericin B, and if they respond, suppressive treatment is indicated for life. Fluconazole is recommended for coccidioidomycosis, and itraconazole for blastomycosis.

NEOPLASTIC DISEASES OF THE LUNG

Kaposi's Sarcoma

KS is the most common malignancy in persons with HIV infection, and the skin is the major site of involvement. KS is believed to be caused by a herpesvirus that infects many healthy adults and may be isolated commonly in saliva, prostate tissue, and semen. The virus is probably transmitted by sexual contact, and it causes disease when activated during HIV-associated immunosuppression. This hypothesis helps to explain why KS is much more common among HIV-infected homosexual men than in other transmission groups.

KS may involve many organs, including the lung. Patients with pulmonary KS usually have obvious mucocutaneous lesions, but the lung may be the only site of disease in up to 15% of cases. Involvement of the airways, parenchyma, pleurae, and intrathoracic lymph nodes causes a diverse range of symptoms and radiographic findings. The majority of patients with pulmonary KS diagnosed ante mortem have cough, dyspnea, and fever.

In the airways, KS lesions are usually asymptomatic, but sometimes cause obstruction or hemoptysis. The finding of typical lesions on inspection of the airways is usually considered diagnostic. Histologic diagnosis may be difficult, because the yield of forceps biopsy is low. Some authors believe that forceps biopsy of KS lesions places the patient at significant risk for bleeding, but this is controversial.

Parenchymal involvement with KS is suggested by bronchial wall thickening, nodules, Kerley B lines, and coexisting pleural effusions, especially in patients with cutaneous disease (Fig. 5). Bronchoscopy may be performed to determine whether diffuse radiographic opacities are caused by KS or an opportunistic infection. The yield of bronchoscopic lung biopsy in the diagnosis of KS is low, and even open lung biopsy is nondiagnostic in approximately 10% of cases because of the focal distribution of lesions. Therefore, the diagnosis of pulmonary parenchymal KS is usually inferred in patients with cutaneous disease, chest radiographs that suggest this disorder, visual confirmation of airway lesions, and no evidence of opportunistic infection on BAL or bronchoscopic lung biopsy. Patients with parenchymal opacities who have typical lesions in the airways and no identified pulmonary infection are assumed to have parenchymal KS.

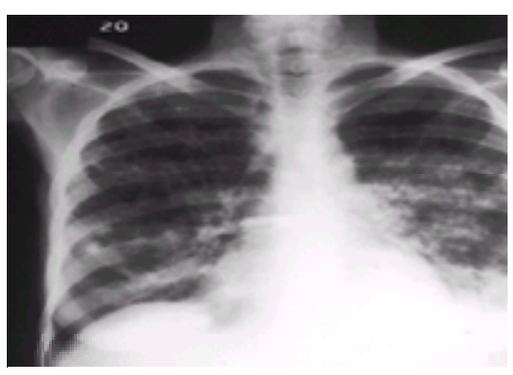

FIG. 5. Chest radiograph of a patient with pulmonary parenchymal KS. The nodular densities suggest this diagnosis, especially in patients with cutaneous disease.

When KS involves the pleurae, effusions are usually exudative and sanguinous, but the cytologic examination is nondiagnostic. Results of closed pleural biopsy are rarely positive because of the focal nature of pleural lesions and predominant involvement of the visceral, rather than parietal, pleura. Because establishing a diagnosis usually necessitates a thoracoscopic or open pleural biopsy, the presence of pleural involvement with KS is usually inferred in a patient with cutaneous disease and a serosanguinous effusion without any reasonable alternative explanation.

Other Malignancies

Non-Hodgkin's B-cell lymphoma is associated with HIV infection. Although pulmonary involvement is usually clinically innocuous, the lung is a common site of extranodal disease. If symptoms occur, they usually do so late in the course of HIV disease and simulate common opportunistic infections. Even in patients with an established diagnosis of lymphoma, lung involvement is usually a late feature of disease. It may present with lobar consolidation, nodules, reticular opacities, and masses. The diagnosis is established by bronchoscopic or open biopsy; BAL has a very low diagnostic yield.

Radiographically, intrathoracic lymph node involvement is manifested by lymphadenopathy, pleural involvement by effusions and pleural thickening, and airway involvement by atelectasis. The diagnosis is established by biopsy or cytologic analysis of pleural fluid.

Carcinoma of the lung has been reported in patients with HIV infection. Although reports emphasize the relatively young age of these patients and aggressive nature of

their disease, it is not established that HIV infection increases the risk for lung cancer.

OTHER PULMONARY DISORDERS

For unknown reasons, patients with advanced HIV infection may have chronic bronchitis and bronchiectasis, even if they do not smoke. These patients usually have CD4 counts of 100/µL. Standard antimicrobial agents are usually effective, but symptoms are likely to recur, especially when *P. aeruginosa* is isolated from the sputum. The role and efficacy of bronchodilators and anti-inflammatory agents in HIV-associated airway disease have not been studied.

Pulmonary disorders without a defined infectious or neoplastic etiology occur in HIV-infected persons. Lymphocytic interstitial pneumonitis and nonspecific interstitial pneumonitis are believed to comprise a spectrum of inflammatory changes in response to HIV infection of the lung itself. Lymphocytic interstitial pneumonitis is most common in HIV-infected children and African-Americans. It may occur as part of a systemic CD8 lymphoproliferative syndrome, with lymphadenopathy, blood lymphocytosis, and involvement of other organs. Nonspecific interstitial pneumonitis is very common in persons with low CD4 counts but is rarely diagnosed because it usually causes no symptoms. When symptomatic, both lymphocytic interstitial pneumonitis and nonspecific interstitial pneumonitis are treated with corticosteroids.

Bronchiolitis obliterans organizing pneumonia is also described in patients with HIV infection, but the reasons for this association are unknown. The manifestations are similar in patients with and without HIV infection. Lung biopsy is necessary for the diagnosis. This disorder often improves dramatically with corticosteroids.

Pulmonary hypertension occurs more commonly in HIV-infected patients than in the general population. It may occur without a prior AIDS diagnosis or severe immunosuppression, and the clinical and histologic features of this disorder are indistinguishable from those of primary pulmonary hypertension. The etiology is unknown, no effective treatment is available, and the prognosis is dismal.

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CHAPTER

27 Pulmonary Fungal Infections

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INTRODUCTION

Infection by fungi generally occurs by inhalation. Thus, the lungs are the organs most frequently encountering these microorganisms and the organs that most often demonstrate the pathologic changes of fungal disease. Generalized dissemination of the fungus may cause spread of the infection from the lungs to the rest of the body as part of a process that has been called *primary infection and postprimary dissemination,* in which the immune system is involved in a complicated series of reactions reflecting innate factors as well as humoral and cell-mediated immunity.

In general, the resistance of the body to infection by fungi characterized as saprogphytic is excellent; in fact, these fungi rarely cause significant infection in healthy humans. A group of more aggressive fungi regularly causes primary infection in healthy human subjects, but this infection is limited and not associated with significant disease, even when postprimary dissemination occurs. In this respect, these fungi behave similarly to *Mycobacterium tuberculosis,* but they are considerably less prone to produce active disease. The fungi making up this group include *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Sporothrix schenckii, Paracoccidioides brasiliensis,* and *Cryptococcus neoformans.* There is also evidence that species of *Nocardia* can cause disease when inhaled.

Special consideration for *Aspergillus* species is warranted, as this genus represents one of the common environmental organisms that rarely, under circumstances not clearly understood, may cause progressive infection in ostensibly normal humans. In addition, this organism may elicit a syndrome of hypersensitivity in the human airways, and it may lodge as a commensal organism in pre-existing cavities and produce a mat of tissue called a *fungus ball* or *mycetoma.* Other fungi have been found to cause fungus balls, but this is rare.

Another special situation relates to organisms normally found within the body, such as *Candida* species and *Actinomyces israelii,* that normally do not produce disease. *Candida* is a normal commensal of the gastrointestinal tract, and it is extremely rare for it to cause progressive systemic disease in immunocompetent persons. *Actinomyces* is likewise a friendly inhabitant of the body but may produce disease in the presence of local trauma to the mouth and throat, where the organism is found, especially in tonsillar crypts and tooth sockets.

When the human immune system is suppressed, any microorganism may cause progressive disease, and fungi are clearly part of this threat. Thus, in any consideration of the impact of fungi on the body in general and the lungs in particular, the state of the immune system must be accounted for.

Although fungi are the subject of this chapter, *Actinomyces* and *Nocardia* species, which are bacteria, are included for two reasons: They have traditionally been dealt with in this manner, and many of the characteristics of diseases caused by these organisms are similar to those of true fungal diseases.

FUNGAL DISEASES

Histoplasmosis (Fig. 1, Fig. 2, Fig. 3, Fig. 4 and Fig. 5)

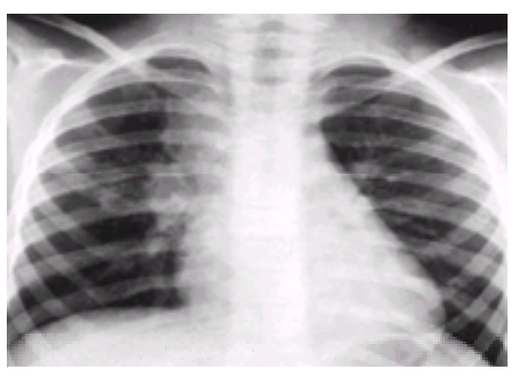

FIG. 1. Primary histoplasmosis with peripheral pneumonia and hilar adenopathy.

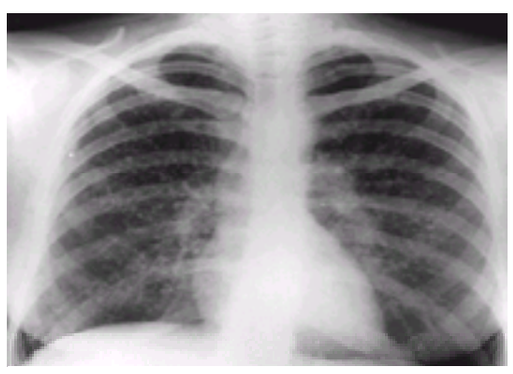

FIG. 2. Multiple primary lesions in acute histoplasmosis simulating hematogenous dissemination.

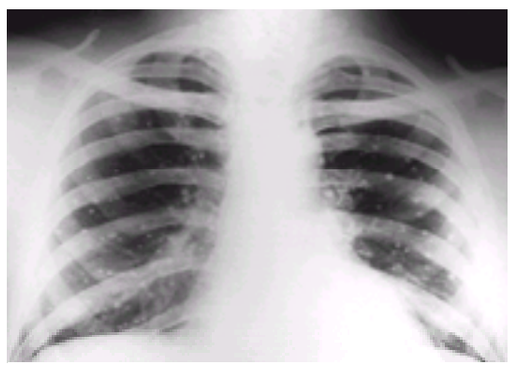

FIG. 3. Healed lesions of pulmonary histoplasmosis.

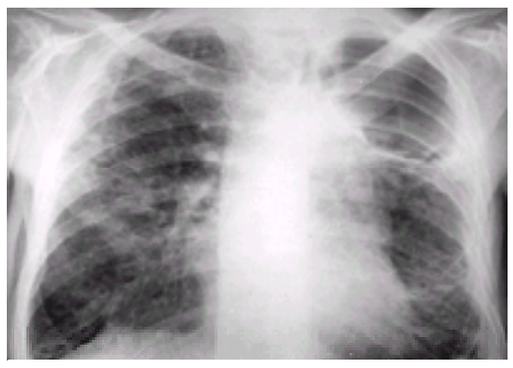

FIG. 4. Large cavity of the left upper lobe resulting from histoplasmosis. Diffuse disease is seen throughout the lung.

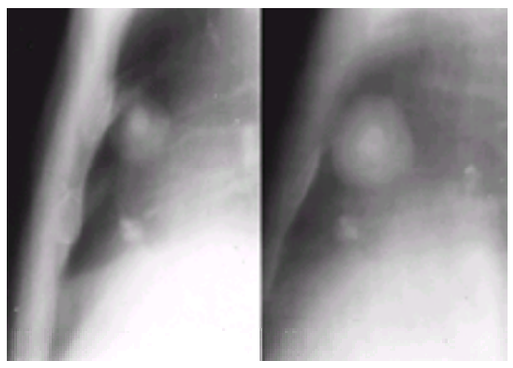

FIG. 5. Enlarging histoplasmoma with central and peripheral laminated calcifications.

Originally thought to be a rare, disseminated, tropical disease, infection with *H. capsulatum* has been found to be very common in endemic areas (the Mississippi and Missouri River valleys in the United States, and isolated areas elsewhere in the world), and sporadic but not rare in other areas. The first patients were found in Panama and described by Darling in 1905. Although he was able to differentiate the organism in tissues from *Leishmania,* which it closely resembles, he nonetheless thought it was a parasite. The fungal nature of the organism was clarified by da Rocha-Lima in 1913. Most infected persons have asymptomatic infections. Humans have excellent resistance to the organism, and despite uniform dissemination in the bloodstream at the time of primary pulmonary infection, progressive disease is uncommon. Healing is associated with massive production of scar tissue and frequently with florid calcification.

Organism

H. capsulatum variety *capsulatum* is a dimorphic fungus that occurs in nature as a mold with septate hyphae bearing tuberculate macroconidia and infectious microconidia. When the microconidia are inhaled, they convert into small budding yeasts (3 to 5 µm) that are found as intracellular pathogens of mononuclear phagocytes.

Pathology

After the microconidia are inhaled and reach the respiratory parenchyma of the lungs, a transient purulent exudate is produced, quickly followed by the sequence of T and B lymphocytes as well as circulating macrophages. This evolution is characteristic of a cell-mediated immune response and is often accompanied by caseous necrosis in the center of the granulomatous focus (or foci) of primary infection. Shortly after infection, a local lymphangitis and lymphadenitis with similar characteristics occur, which may involve the lymph system in progressive fashion until the bloodstream is invaded, with dissemination of the organism throughout the body. The organ most frequently demonstrating foci of infection outside the lungs and thorax is the spleen. This may be a consequence of the large concentration of reticuloendothelial cells found in the spleen. The liver is much less frequently involved. The adrenal glands, bones, gastrointestinal tract, and central nervous system may also host foci of infection. In all, the process is mainly granulomatous in nature.

The healing tendency is remarkable, and the formation of large amounts of scar tissue and calcification, especially in the mediastinal nodes and spleen, may be seen on x-ray films. In fact, scarring and calcification are so prominent that syndromes caused by obstruction and penetration of mediastinal structures, with no evidence of active infection, are part of the clinical spectrum of histoplasmosis. The question of exogenous reinfection occurring in normal hosts is moot, but a few case reports have suggested that it occurs. Much more problematic is whether endogenous reinfection occurs when the primary encounter has ended in clinical healing.

In immunosuppressed humans, primary infection with *H. capsulatum* is associated with much more active dissemination than in immunocompetent hosts. The granulomatous reaction does not develop as well or as typically, and frequently, depending on the degree of lowering of the CD4-lymphocyte count, the reaction to infection may be primarily neutrophilic. Exogenous reinfection almost certainly occurs, and there is evidence to suggest that endogenous reinfection may occur in immunosuppressed hosts.

Immunopathology of *Histoplasma* infection is mainly manifested by activation of the cellular immune system and associated delayed hypersensitivity. The role of humoral immunity is unclear, and the presence of antibodies of both IgG and IgM types appears to be merely a marker of infection.

Epidemiology

The central United States, especially the southern half, is probably the most highly endemic area in the world. Populations of Eastern Europe, South Africa, and parts of

South America and China have shown higher than average rates of skin test positivity. Sporadic cases of infection and disease have been found all over the world, which may reflect the increase in worldwide travel. High concentrations of the organism are found in specific regions outside the endemic areas, and persons who travel to these locales may be subjected to massive exposure. Most dramatically, closed areas, such as caves, abandoned chicken houses, and places where common house bats tend to congregate, may contain very large numbers of infectious conidia in the soil. *H. capsulatum* is a normal inhabitant of the bat colon and is expelled in the feces. Exposure to bat guano is often associated with massive pulmonary infection. Association with starling roosts has been reported.

Clinical Manifestations

Primary histoplasmosis of the lungs is usually clinically silent. If the dose of inhaled conidia is large or if the infection occurs in a young child or weakened adult, there may be flulike symptoms, including fever and chills. These persist for a few days at most unless the host is immunosuppressed from any cause, in which case the symptoms may continue and progress. Cough and scanty sputum production are evanescent. Symptoms clear spontaneously and the diagnosis is usually overlooked. Associated clinical and roentgenographic findings seen in the course of primary infection include pericardial effusion and erythema nodosum. The latter clears spontaneously, as does the former, which rarely persists as chronic constrictive pericarditis. If the infection is massive, the infected person is under 1 1/2 years of age, or immunosuppression is present, blood pancytopenia and more severe signs of systemic organ involvement, affecting the liver and kidneys, may appear. Disseminated infection may be devastating in patients with AIDS, as no effective cell-mediated immunity remains to resist infection.

Healing of the primary infection is almost always associated with massive formation of scar tissue and accompanying calcification. In the lung itself, this leads to a dramatic chest radiographic pattern that has little or no clinical significance. In the mediastinum, however, the results of this process may be devastating. The spectrum includes mild bronchial obstruction (in young patients an enlarged node may cause narrowing from pressure alone); broncholithiasis; esophageal obstruction and formation of diverticula; obstruction of various vascular structures, including the aorta, pulmonary arteries, and most frequently the superior vena cava; bronchiectasis; and lobar or whole-lung collapse. In extreme cases, fibrosing mediastinitis may develop. The signs and symptoms are related only to the anatomic abnormality and usually not to any activity of the infection.

Acute eosinophilic pneumonia caused by *H. capsulatum* has been described with typical clinical characteristics. If indeed this exists, it is a self-limited syndrome; if severe, it responds well to steroid treatment.

Solitary (occasionally multiple) pulmonary nodule may be caused by *H. capsulatum* (histoplasmoma) and appears to be a remnant of the primary focus. It is imperative to differentiate between carcinoma and inactive *Histoplasma* infection as the cause of the nodule. In many instances this requires resection, although the presence on chest x-ray films of a diffuse, “popcorn” kind of calcification in the lesion, especially when the patient is asymptomatic, strongly suggests histoplasmosis as the cause.

Chronic granulomatous disease of the lungs may result from *Histoplasma* infection. There are no clinical or roentgenographic criteria to differentiate between mycobacteria, *Histoplasma,* or for that matter *C. immitis* as a cause of the syndrome, which usually occurs in men of middle age or older and is associated with progression to death if not treated. There is disagreement as to the pathogenesis of this form of histoplasmosis. It would appear to develop in patients with an active cell-mediated immune system, as seen in patients with cavitary tuberculosis. On the other hand, it has been suggested that this form of histoplasmosis represents superinfection of previously existing emphysematous areas in the lung. If this is true, it is hard to explain the very typical pathology of chronic granulomatous infection that is routinely seen. The possibility of endogenous reinfection exists.

Epidemic histoplasmosis is an acute, multifocal bronchopneumonia caused by a massive inhalation of conidia of *H. capsulatum.* Such cases frequently occur in clusters, as numbers of persons may be exposed at the same time or in the same area during a prolonged period of time. Such highly contaminated areas are often inhabited by bats. Roosts of starlings have also been associated with these outbreaks. Exploration of caves containing large quantities of bat guano (spelunkers' disease), use of an abandoned chicken house for storage or playing (chicken house disease), and acute exposure to highly contaminated soil in a central city play area have all been associated with such outbreaks. Patients have an acute febrile illness beginning between 7 and 14 days after exposure, characterized by toxemia, dry cough, and often chest muscular pains. Extensive lung involvement may lead to adult respiratory distress syndrome (ARDS). Only in immunosuppressed patients does the infection progress to extrapulmonary dissemination and death if not treated. In immunocompetent patients, respiratory support may be needed but recovery is almost universal. Of interest is the appearance of multiple parenchymal calcifications in the lungs of persons initially exposed to the fungus. In persons previously infected, the multiple lesions usually heal with no or minimal radiographic findings.

In infants under 1 1/2 years of age or persons over the age of 65 to 70, a first encounter with *H. capsulatum* almost always leads to widely disseminated infection that may be accompanied by miliary pulmonary histoplasmosis. This is potentially fatal and requires treatment. In infants the infection progresses rapidly, whereas in the elderly it may progress slowly and be accompanied by painful mucosal ulcerations.

Cases of typical sarcoidosis have been described from which *H. capsulatum* has been isolated. It is assumed that the fungus triggers the massive granulomatous reaction, noted particularly in the lungs and mediastinal lymph nodes. The principles for treating sarcoidosis are generally adhered to in these cases, and the presence of the organism does not change the therapy.

Diagnosis

Chest x-ray films may show the peripheral focus and enlarged regional and hilar nodes of a typical primary complex. The lymph node enlargement may not be as obvious in adults as in children under the age of 16 years.

Chronic granulomatous disease is associated with characteristic radiographic changes in the lungs, details of which are shown best by computed tomography (CT). Although little used currently, classic tomography is also helpful if CT is not available. Histoplasmomas show solitary or multiple well-circumscribed homogeneous densities anywhere in the lung fields, but most typically in the periphery. The presence of single or multiple calcifications strongly suggests a granulomatous etiology, but a single calcification is not totally reliable. In so-called epidemic cases, multiple, poorly defined densities are seen, usually bilaterally, and there may be associated hilar adenopathy. The parenchymal shadows may simulate miliary disease. Again, the x-ray picture is not specific, but with an appropriate history it can be highly suggestive. In true disseminated disease, miliary lesions may be seen in the lungs, and other organs and systems may be involved by inflammatory changes, including liver, kidneys, bones, and central nervous system.

In epidemiologic surveys, the presence of splenic calcifications, especially more than two, has been found to be a reliable indicator of previous infection with *H. capsulatum.* These may also be seen in patients with active lung disease, but their significance in this setting is no greater than that of any other indicator of previous infection.

Except for pancytopenia, seen in disseminated active infection, and nonspecific signs of inflammatory liver involvement, general laboratory findings are not helpful.

Definitive diagnosis of histoplasmosis is made by isolation of the organism from bronchoalveolar lavage (BAL) fluid, bone marrow, blood, or biopsy material. Although the organism may require 7 to 21 days for initial growth, rapid confirmation may be obtained within 24 hours using a commercially available DNA probe for colony hybridization. A presumptive diagnosis of histoplasmosis is frequently made by direct microscopic examination of clinical material using the Grocott silver stain in tissue or a Giemsa stain of bone marrow or buffy coat. Culture of peripheral blood by the lysis-centrifugation technique has been shown to have equivalent sensitivity to bone marrow culture in HIV-positive patients. Serologic tests for antibody include complement fixation, immunodiffusion, and an enzyme-linked immunosorbent assay (ELISA). In immunocompetent patients, a complement fixation titer ^{3}1:16 is highly suggestive of histoplasmosis. The presence of an M band on immunodiffusion suggests a previous infection with the organism, but the H band is diagnostic of active infection. ELISA has shown promise as a screening test, with greater sensitivity than immunodiffusion. Testing for antigenuria and antigenemia is the serologic procedure of choice in immunocompromised patients; the tests are very sensitive for the diagnosis of disseminated disease, and changes in titer in serial specimens appear to be prognostic. Skin testing with the reagent histoplasmin is useful for epidemiologic investigation, but it is not recommended for diagnosis because of the high incidence of skin test positivity in endemic regions and the propensity of a positive response to modulate antibody responses in subsequent tests using mycelium-derived antigens.

Prognosis and Treatment

In immunocompetent patients over the age of 1 1/2 years who are not elderly or otherwise ill, the prognosis in primary infection is excellent without any specific treatment. This is also true in cases of eosinophilic pneumonia caused by *Histoplasma* and histoplasmoma. The prognosis is grave in chronic granulomatous histoplasmosis and in disseminated active infection. Without treatment, almost all such patients die of their disease.

Thus, antibiotic therapy is indicated in these two forms of histoplasmosis. The antibiotic of choice is amphotericin B. The total dose is between 30 and 40 mg/kg of body weight, given as 1.0 mg/kg/dose intravenously. The dose is smaller at first and increased gradually to the maximum. The drug is administered daily in more acutely ill patients and then continued 2 to 3 times per week. There are many side effects, especially retention of urea and creatinine, which is generally completely reversible if the total dose is 45 to 50 mg/kg. Hypokalemia may also develop, as well as mild hematologic abnormalities. The almost uniform chills, fever, and nausea that occur at

the time of drug infusion are treated symptomatically but are less troublesome if the daily dose is given within 1 1/2 hours. Liposomal/lipid-complexed drug has been used to avoid side effects. The decreased efficacy of these preparations requires the administration of increased total doses to achieve similar clinical results.

Itraconazole is the one azole antibiotic that has shown significant activity in potentially fatal histoplasmosis. It should be considered as an alternative in patients who cannot tolerate amphotericin B therapy. The dose is 200 to 400 mg/day, and the therapy should be continued for 2 months or more. Use of this drug has been recommended for life to prevent recurrences of active infection in HIV-positive patients. The maintenance dose is 200 mg/day.

Coccidiodomycosis (Fig. 6, Fig. 7, Fig. 8 and Fig. 9)

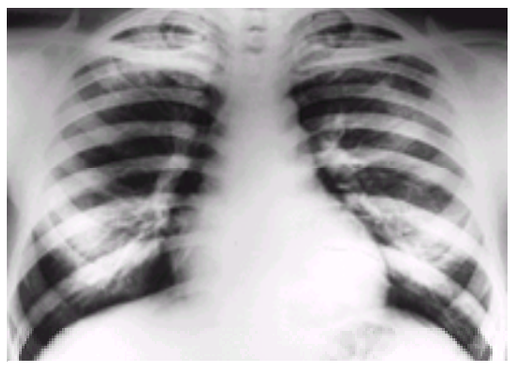

FIG. 6. Acute coccidioidomycosis with bilateral upper lobe infiltrates.

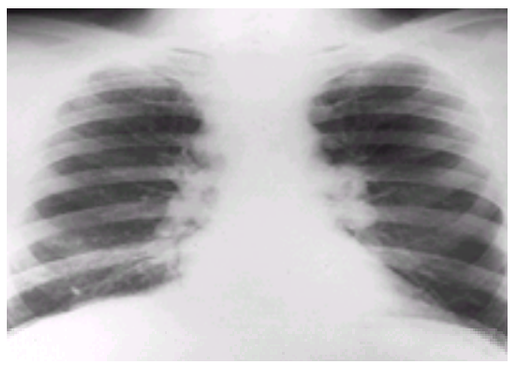

FIG. 7. Acute coccidioidomycosis with bilateral hilar adenopathy.

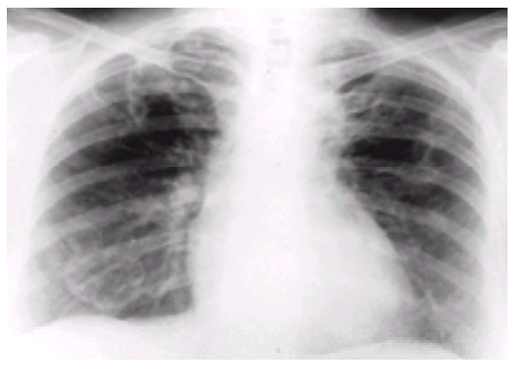

FIG. 8. Thin-walled cavity of the right lower lobe in a patient with chronic coccidioidal infection.

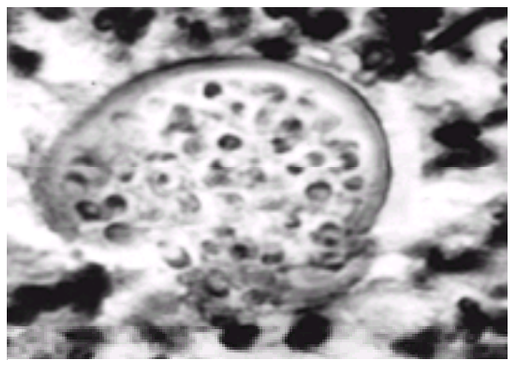

FIG. 9. Spherule of *C. immitis* seen with endospores in tissue section. (Reproduced with permission from Straub M, Schwarz J. Coccidioidomycotic thoracic lesions in dogs in Tucson, Arizona. *Arch Pathol* 1956;62:479. Copyright 1956 by the American Medical Association.)

Described in South America by the young Posadas and his pathologist teacher Wernicke in 1892, this disease was thought to be exclusively a tropical protozoan disease until the work of Dickson and Gifford in the 1930s uncovered a mild pulmonary form of the infection. As with histoplasmosis, natural resistance to the infection is high, but certain ethnic groups appear to have increased susceptibility to the development of active disseminated infection. The clinical spectrum of the disease is broad, and in certain situations curative treatment does not exist.

Organism

C. immitis is another of the dimorphic fungi. It is present in the soil as a mold with septate hyphae that form alternating, barrel-shaped arthroconidia. These arthroconidia are easily aerosolized and highly infectious. Following inhalation, the conidia round up and convert into the tissue form, referred to as *spherules.* Spherules are round, thick-walled structures averaging 30 to 60 µm in diameter. When mature, they are filled with 2- to 5-µm endospores that develop into spherules after being released in the tissue.

Pathology

In most infections, the portal of entry is the lung. After sufficient conidia are inhaled to reach the respiratory tissue, acute inflammation occurs, followed quickly by lymphocyte/macrophage infiltration and the development of a granulomatous process. As in histoplasmosis, caseous necrosis takes place. The lymph system is involved concurrently, with lymphangitis and local lymphadenitis and early dissemination. The pattern is similar to that of other granulomatous infections. The differences are that the degree of scarring and calcification is less than in histoplasmosis, and in a significant fraction of cases the organism clearly remains viable,

even if not actively replicating, after the primary infection has healed. This makes subsequent endogenous reinfection a real possibility. Exogenous reinfection has been seen.

In addition to the T lymphocyte/macrophage-associated delayed hypersensitivity response, antibodies of both the IgG and IgM types develop. They may be demonstrated by a variety of techniques, such as complement fixation, immunodiffusion, and latex agglutination. If the cell-mediated immune system fails to react, active dissemination is common. The active role of the antibodies is unknown at present.

Epidemiology

The endemic areas of infection with *C. immitis* are referred to as the *Lower Sonoran Life Zone,* an area encompassing western Texas, New Mexico, Arizona, southern California, and northwestern Mexico. In addition, the disease has been seen in Central America, Venezuela, Colombia, Paraguay, and Argentina. Other regions have been investigated, but the organism has not been found. Support for this localization has come from widespread skin testing programs using spherulin and coccidioidin. A confounding factor has been the increasing number of people who travel.

Because the organism is present in relatively superficial soil layers in its highly infectious mold form, massive exposure may occur during wind storms in endemic areas, especially during dry weather, or when the infected soil is disturbed by digging. Outbreaks have even occurred after the organism was introduced into an air-conditioning system!

Clinical Manifestations

Primary infection with *C. immitis* is usually silent. Occasionally, nonspecific symptoms of a flulike illness may be accompanied by fever, most often in children. On chest x-ray films, a typical primary complex may be seen that includes both peripheral lung infiltrate(s) and accompanying enlarged regional hilar and/or mediastinal lymph nodes. There may be an associated pleurisy with fluid, an event that usually clears spontaneously. This is almost always a self-limited illness, but in certain ethnic groups (nonwhites in general but especially Filipinos) the likelihood of active disseminated disease developing at the time of primary infection is much higher. If dissemination occurs, it is fatal unless treated.

As in histoplasmosis, there may be dramatic occurrences of widespread bronchopneumonia resulting from exposure to high concentrations of fungus in the soil. Many such events have been described, and the associated syndrome, which has been called *desert fever,* is an acute febrile episode with respiratory symptoms that is usually self-limited. It may be associated with erythema nodosum and other allergic skin manifestations as well as migratory arthopathy, known as *desert rheumatism.* All these symptoms may occur with primary coccidioidomycosis, even if not so dramatically. The symptoms spontaneously resolve. The chest x-ray film shows widespread areas of bronchopneumonia that may simulate miliary lung disease. Potentially, this could cause ARDS. The need to treat with antifungal antibiotics is questionable, but in any case careful clinical follow-up is indicated.

Cavitary coccidioidomycosis is seen both as an asymptomatic surprise finding on chest x-ray films or as part of the syndrome of chronic granulomatous disease of the lungs. Although the so-called typical coccidioidal cavity is described as thin-walled, cavities characteristic of any granulomatous disease are the rule rather than the exception. This form of the disease occurs more frequently in adults than in children and has been ascribed to endogenous or exogenous reinfection. In fact, the pathogenesis is not well understood. Whether asymptomatic individuals require treatment is a controversial point, but currently it is felt that antibiotic therapy is indicated. Clinically, a stable cavitary lesion may not progress and appear to represent localized disease. More frequently, there is true progressive disease. In fact, if the so-called stable lesions are followed long enough, clinical and roentgenologic progression is often noted. Complications of a cavity include hemorrhage, pneumothorax, and the development of a fungus ball. Although fungus balls are usually caused by *Aspergillus* species, there have been rare instances of coccidioidal mycetomas. The presence of the mold form of the fungus within a cavity suggests possible person-to-person transmission of the disease, which does not happen in other forms of active coccidioidomycosis.

Other syndromes may occur. Coccidioidomas are seen, often as a direct result of the primary infection. They are often found on a routine x-ray film. Of importance is that within these lesions as well as within cavitary lesions the organism may remain viable for many years. This is in contrast to the rare positive culture from histoplasmomas. Disseminated disease, which may occur as noted above or in immunosuppressed patients, is rapidly progressive and fatal unless treated, and even then the prognosis is guarded. The most dramatic form of disseminated disease is coccidioidal meningitis, which is a chronic and ultimately fatal disease unless treatment is maintained for life!

Diagnosis

Chest x-ray findings in pulmonary coccidioidomycosis are characteristic of the syndrome but not specific. Radiographic features of primary infection include peripheral foci, hilar node enlargement, and occasionally the accumulation of pleural fluid, findings that in no way differ from those associated with a variety of agents, including mycobacteria or other fungi. The same is true for the cavitary form of the disease, except for the suggestive nature of a thin-walled cavity associated with little or no pericavitary infiltrate. This is usually localized to the upper zones. Fluid levels may be seen. When a fungus ball is present, there are no roentgenologic methods to differentiate between the fungi that can cause this entity.

General laboratory findings include leukocytosis, elevated erythrocyte sedimentation rate, and possible mild liver enzyme abnormalities, but in general they are not pathognomonic for this specific infection.

Microbiologic examinations and immunologic testing are critical in diagnosis and prognosis. The large, endosporulating spherules of *C. immitis* are easily visualized in BAL fluid or biopsy tissue specimens with routine hematoxylin and eosin staining or any of the special stains for fungi. Culture of the organism provides definitive diagnosis; the organism grows relatively rapidly, with most cultures becoming positive within 7 to 10 days, often within 48 hours. Confirmation of the identification of cultures is most rapidly made by utilizing the DNA probe hybridization that is commercially available. Serologic diagnosis of coccidioidomycosis is available as a tube precipitin test for early (IgM) response and as a complement fixation test for IgG response. Immunodiffusion screening tests are available that correlate with both the precipitin and complement fixation tests. The titers of complement-fixing antibodies are prognostic. The diagnosis of coccidioidal meningitis is almost always made by the demonstration of complement-fixing antibodies in cerebrospinal fluid; only in highly immunocompromised patients are spherules seen in or organisms grown from cerebrospinal fluid. Two skin-testing reagents are available, coccidioidin and spherulin, for epidemiologic investigations; the latter is a newer reagent of greater sensitivity and specificity.

Prognosis and Treatment

Most cases of primary coccidioidomycosis clear spontaneously and leave minor residua. Calcification of peripheral foci and hilar and mediastinal lymph nodes is much less pronounced than in histoplasmosis. Chronic cavitary disease may persist with no activity for years and then either slowly progress or, if some associated stress to the body occurs, rapidly disseminate. In cases of progressive cavitary or disseminated disease, only extended treatment prevents mortality. Meningitis may persist with many exacerbations and remissions before causing death, and treatment needs to be lifelong for death to be prevented or significantly delayed.

The drug of choice in serious progressive disease is amphotericin B. Treatment needs to be prolonged, and a total dose of about 60 mg/kg is required. This large dose may cause permanent renal damage. Some cases of meningitis have required even larger doses, but such treatment is rarely permanently effective. As an alternative, up to 50 to 60 mg/kg may be given in one prolonged course of 8 to 12 weeks, after which the drug may be given once a year 3 to 5 times during one week in separate doses of 1 mg/kg. This regimen must continue for the life of the patient. In addition, intrathecal amphotericin B is frequently given. There are numerous side effects, and treatment must be continued intermittently for life.

Alternatively, the drug ketoconazole has been used as extended treatment of pulmonary coccidioidomycosis at a dose of 200 mg/d for as much as a year or more in addition to amphotericin B. More recently, both fluconazole and itraconazole have been found effective and show particular promise for the treatment of coccidioidal meningitis. Amphotericin B, however, remains the major drug for treatment of serious, life-threatening disease.

In cases of skin test-negative coccidioidomycosis, treatment was previously given with transfer factor. This substance, the crude extract of polymorphonuclear leukocytes taken from persons with a strongly positive spherulin skin test, seems to increase the body's immune response, but the effect is temporary and repeated injections of the material are required every 4 to 6 weeks. It is not generally used.

There is increasing experience with a vaccine against *C. immitis* infection, and it may be indicated in persons from nonendemic areas who anticipate exposure for significant periods of time or to possibly high concentrations of the organism.

Blastomycosis (Fig. 10, Fig. 11 and Fig. 12)

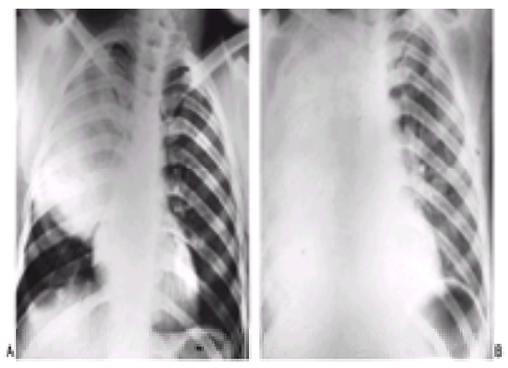

FIG. 10. A,B: Acute blastomycotic pneumonia with consolidation of most of the right upper lobe.

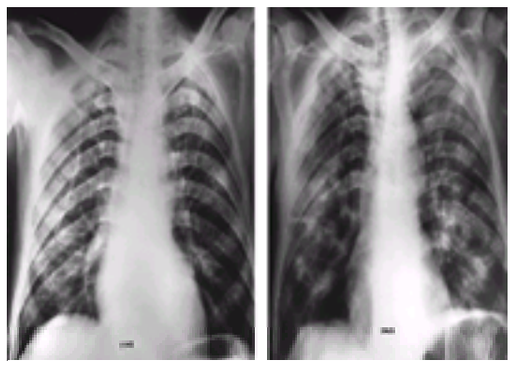

FIG. 11. Chronic pulmonary blastomycosis characterized by linear infiltrates with slow but relentless progression during an 8-year period.

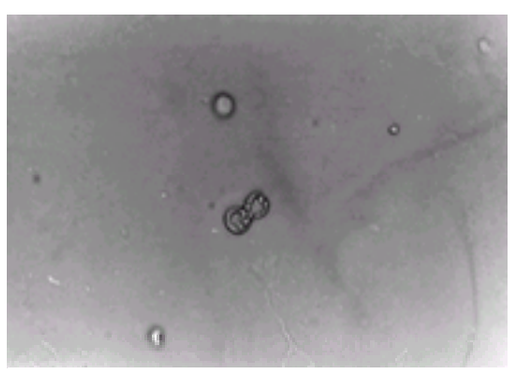

FIG. 12. Yeast-phase *B. dermatitidis* showing characteristic single bud and presenting a “figure 8” appearance.

North American blastomycosis was first described by Gilchrist in 1894 as a disseminated skin disease, and it was considered to be mainly an inoculation infection with ABoccasional instances of dissemination to the lungs and the rest of the body. In the early twentieth century, a group of cases was reported from Chicago, which gave the city's name to the disease. In 1951, it was proposed that the primary infection was almost always pulmonary and that skin lesions represented dissemination of the organism. In the late 1940s, the first effective chemotherapeutic agent for blastomycosis, stilbamidine, was reported, soon to be followed by 2-hydroxy-stilbamidine and subsequently amphotericin B.

Organism

B. dermatitidis is the etiologic agent of North American blastomycosis. The septate hyphae of this dimorphic fungus occur transiently in the soil, where they produce small, round to pyriform conidia, the infectious form of the organism. On inhalation, the conidia are transformed into large (8 to 12 µm), thick-walled, budding yeast cells that are characterized by single buds, separated from the mother cell by a wide isthmus.

Pathology

The classic pathology of blastomycotic lesions of the skin is a combination of pseudoepitheliomatous hyperplasia of the epidermis with microabscess formation in the dermis breaking into the epidermis. In the lung, there may be an acute inflammatory response with primarily polymorphonuclear leukocytes and abscess formation. A granulomatous response is seen in blastomycosis, but almost always in combination with a suppurative reaction. Alternate inflammation and scarring are seen in the same areas of involvement in skin, lung, and other organs. All organs in the body may be involved, but the development of pleural lesions is seldom accompanied by fluid formation. Hilar and mediastinal lymph node enlargement can be found, even in the presence of minimal pulmonary parenchymal involvement. This speaks for the primary pulmonary nature of most infections.

Immunopathology has not been well defined, but the development of delayed skin hypersensitivity suggests that the cell-mediated immune system plays a role. This is supported by the combination of suppuration with granulomatous inflammation seen in most cases. Specific antibody formation is not consistent, and the role of this factor is not clear.

Epidemiology

This infection has been mainly localized to North America, cases having been described in Canada as well as the United States and Mexico. Dogs in these areas have been infected, indicating the localization of the fungus in soil. In the latter part of the twentieth century, cases have been described in natives of central Africa.

Although once known as *Chicago disease,* it is now felt that the endemic area of the infection, if indeed one exists, is in Wisconsin. Outbreaks have been described in other areas as well, but in general the infection has been found east of the Mississippi River. Sporadic cases have been found in the southeastern United States especially. The absence of a reliable skin test or other tools useful in widespread testing for symptomless infection has hindered the collection of accurate epidemiologic data.

Ethnic factors do not appear to influence resistance to the infection or its dissemination. Because of the significantly higher prevalence of the disease in men than in women, there is a question of some genetic determinant of susceptibility. Immunosuppression from any cause favors more malignant dissemination, but blastomycosis is not a special problem of AIDS patients.

Clinical Manifestations

Few cases of clinically diagnosed primary pulmonary infection have been reported. Most of those appear to have been part of so-called mini-epidemics in which acute bronchopneumonia was seen in association with hilar lymph node enlargement. Isolated cases have been reported and support the presence of a definite hilar lymph node component. These cases have been associated with mild flulike symptoms that clear spontaneously within a week to 10 days. Careful history reveals the critical fact of exposure to *B. dermatitidis.* Only if the possibility of the diagnosis is entertained will the critical diagnostic tests be carried out.

ARDS has been described in 10 patients with blastomycotic pneumonia. It was not clear whether these cases were primary infections, but the clinical picture was one of severe acute pneumonia. No underlying immunosuppression was found in any of the patients. Mortality was high despite amphotericin treatment.

Healed primary infection may be encountered, usually on a chest radiograph taken for other reasons. The pulmonary parenchymal and hilar elements of the primary complex are identifiable on x-ray films in such cases, but in contrast to healed primary histoplasmosis, the scarring rarely causes mechanical problems of mediastinal structures. Solitary pulmonary nodules have been described as being caused by *B. dermatitidis,* and almost certainly these are remnants of healed primary pulmonary parenchymal blastomycosis.

Disseminated blastomycosis may present clinically with isolated, chronic skin lesions that exhibit peripheral extension and central scarring, resemble basal cell or even squamous cell carcinomata of the skin, and are associated with peculiarly characteristic microabscesses, typically at the periphery of lesion. This appearance should alert the physician to the possibility of blastomycosis. Patients may present with chronic cough, production of mucopurulent sputum, weight loss, low-grade fever, and many of the symptoms associated with chronic granulomatous disease of any etiology. Chest x-ray findings are nonspecific but indicate a destructive inflammatory process of the lungs. Involvement of the pleurae may occur but is rarely associated with pleural effusion. Lesions may be found in any organ system but rarely in the gastrointestinal tract. The urinary tract in men and women is a common site. Blastomycotic prostatic abscesses have been seen as a cause of urinary obstruction. Occasionally chronic widely disseminated disease is enountered, and such patients are clearly cachectic.

Acute blastomycotic pneumonia has been described in immunosuppressed patients; the only distinguishing characteristic is the presence of the organism in secretions obtained from the tracheobronchial tree or lungs. The clinical picture is that of an acute lower respiratory tract infection modified by the immune suppression of the patient.

Diagnosis

The chest x-ray film in primary pulmonary blastomycosis may show poorly defined infiltrates associated with lymph node enlargement in the hilar/mediastinal areas, or there may be few findings in the pulmonary parenchyma, with nodal enlargement as the only finding. Rarely, bilateral hilar node enlargement may be seen, suggesting the diagnosis of sarcoidosis. In progressive chronic pulmonary disease, most frequently associated with dissemination, typical changes of chronic granulomatous inflammatory disease with cavitation may be seen. There is nothing to distinguish these changes from those caused by *M. tuberculosis* or other fungi.

Results of general laboratory tests add little other than to confirm the debilitating nature of the chronic disseminated infection. Involvement of liver and kidneys may be expressed by abnormalities of function studies.

The diagnosis of blastomycosis is made by the demonstration of the typical, thick-walled, single-budding yeast in sputum, BAL fluid, or tissue. The organism is easily visualized using any of the special stains for fungi. Definitive identification depends on culture of the organism, and confirmation of the morphologic identification may be made by DNA hybridization with the colonies. The organism often requires 7 to 14 days or longer to grow in culture. Serologic testing for blastomycosis rarely is useful. The immunodiffusion test for antigen A is specific but lacks sensitivity. Recent work with an ELISA to detect antibody to an antigen termed *WI-1* shows promise.

Prognosis and Treatment

Based on experience, particularly with epidemics of blastomycosis, prognosis is excellent for spontaneous remission of primary infections in immunocompetent persons. In cases of progressive disease, mortality is high unless the patient is treated with specific antibiotics. Skin lesions tend to recur even after local therapy has been apparently effective. As noted, the mortality in ARDS, even with treatment, is high.

Amphotericin B given intravenously is effective in all types of cases. The total dose is between 20 to 40 mg/kg given as single doses of 1 mg/kg. Therapy is given daily for acutely ill patients, then 2 to 3 times per week according to the clinical situation. Itraconazole (200 to 400 mg/d) may be used as an alternative to amphotericin B in patients not judged to be critically ill.

Paracoccidioidomycosis (South American Blastomycosis)

This disease was first described by Adolfo Lutz in 1908 and has been identified in areas localized to Central and South America. At first thought to be acquired by extrinsic inoculation into the skin and/or mucosae, it is now recognized to be a primary pulmonary infection in almost all cases. Just how common the asymptomatic infection is has not been clarified, but almost certainly the number of active cases seen represents a small fraction of persons infected with *P. brasiliensis.*

Organism

The dimorphic fungus *P. brasiliensis* is found in the soil as a mold with septate hyphae that produce small, round to pyriform conidia, resembling those of *B. dermatitidis.* The yeast cells of *P. brasiliensis* are extremely variable in size, with an average of 10 to 20 µm and a range of 2 to 30 µm. The yeast cells are characterized by multiple buds separated from the mother cell by a narrow isthmus. A specialized form of the budding cells, called a *mariner's wheel,* features a large, 20- to 30- µm mother cell surrounded by many 2- to 3-µm daughter cells.

Pathology

Grossly, the pathology of this infection is most obvious on skin and mucosal surfaces. The cutaneous lesions seen resemble those of blastomycosis and leishmaniasis. Tumorlike growths of granulomatous tissue frequently involve the gastrointestinal tract, as opposed to the lesions of blastomycosis, which are rarely seen in this area. Areas of localized inflammation may be seen in the lungs; interstitial thickening is found in disseminated disease, and cavities may form. This infection involves the lymph system particularly, and nodes are enlarged and necrotic in all areas of the body, but especially in the mediastinum and hilar areas, when the infection is widespread. Histopathology is characterized by the combination of granulomatous inflammation and suppuration, a similarity with blastomycosis. This is noted in all organs involved.

The presence of delayed hypersensitivity skin reactions and the above noted histopathology suggest that the cellular immune system is an important but not the only element in natural resistance to *P. brasiliensis.* There is little information relating to the impact of AIDS or other causes of immune suppression on this infection.

Epidemiology

Paracoccidioidomycosis is encountered almost exclusively in Central and South America but is not seen in areas of rain forest or desert. Up to a few years ago, no cases had been reported from Chile, Guyana, Surinam, or Nicaragua. Southern Brazil is the area of highest prevalence. The definition of the areas in which the organism is found includes elevation of 500 to 1800 m, 800 to 2000 mm annual rainfall, average yearly temperature of 18° to 23°C, and acid soil.

A skin test has been used to identify endemic areas, and to the extent that it has been used the results correlate with the distribution of active cases and with the area defined above.

Clinical Manifestations

This disease is seen mainly in male patients, the estimate being about 90%. Skin test surveys, however, demonstrate a 50:50 relationship between men and women infected with the organism. This is a rare disease in persons under the age of 10 years but may occur in a fulminant form in childhood.

Generally, the disease presents with mucocutaneous lesions, especially in the oropharynx and gingivae, and also in the gastrointestinal tract. The port of entry is the respiratory tract, the extrapulmonary lesions being metastatic, as in blastomycosis.

Pulmonary disease may be localized to the lung parenchyma and the hilar and mediastinal lymph nodes or be part of progressive disseminated disease. The acute

limited disease is manifested by nonspecific symptoms and x-ray findings of multiple foci of infiltrates in both lungs. These may recede spontaneously and the enlarged nodes calcify. The primary infection may occur without symptoms. Minimal parenchymal fibrosis occurs as a residual. Immune factors that determine the outcome of this disease have not been well defined.

A chronic progressive form of the disease seen in adults resembles tuberculosis in all its manifestations. Without effective treatment, it leads to cachexia and death. Cavities are seen in the lungs in only 15% of such cases. Often, extrapulmonary lesions involve the pleurae and all extrathoracic organs.

Diagnosis

A history of residence in the endemic area is the most important diagnostic finding. As the clinical manifestations are nonspecific, awareness of the possibility of this disease is an indication for appropriate diagnostic tests.

Chest x-ray films demonstrate parenchymal infiltrates and hilar node enlargement if the infection is primary. In chronic progressive pulmonary disease, the findings are similar to those of tuberculosis, histoplasmosis, and coccidioidomycosis. Cavities are seen in only 15% of such patients. Geographic prevenience of the patient determines the likelihood of this disease.

Laboratory diagnosis of paracoccidioidomycosis is based on demonstration of the characteristic multiple budding yeast form in respiratory secretions or tissue. The organisms stain readily with any of the special stains for fungi. Confirmation by culture requires patience, as *P. brasiliensis* is one of the most slowly growing of the dimorphic fungi, usually requiring 3 to 6 weeks of incubation. Identification is based on the morphology of the organism and confirmed by in vitro conversion to the yeast forms or an immunologic procedure referred to as the *exoantigen test.* The serologic tests that show the most promise for the diagnosis of paracoccidioidomycosis are the immunodiffusion test for band 1 and an ELISA directed at antigen E2.

Prognosis and Treatment

Most cases of primary pulmonary infection clear spontaneously. Acute pulmonary infection, primary or not, in adults up to about 60 years of age also tends to clear, but chronic pulmonary disease is progressive and fatal unless treated. Disseminated disease, including lesions on skin and mucosae, is progressive and requires treatment; otherwise it progresses, albeit slowly, to a fatal end.

Treatment with sulfadiazine is effective. Other antibiotics have been used also, but sulfadiazine is still considered the drug of choice. Treatment must continue for up to a year at a dosage of 4.0 g/d. Amphotericin B is also effective and used in disseminated cases. The dosage is the same as for chronic histoplasmosis, up to 2 to 3 g per total dose. Ketoconazole has been found effective at a dosage of 200 mg/d for at least 1 year.

Sporotrichosis (Fig. 13)

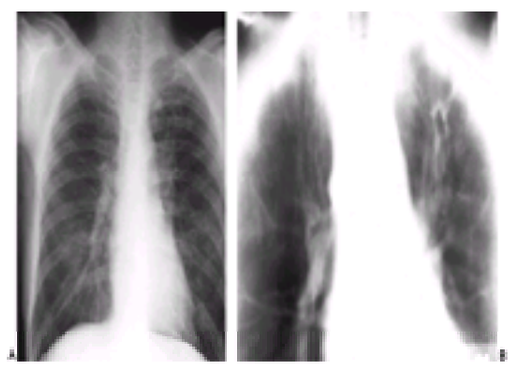

FIG. 13. A: Cavity of the left upper lobe in a young adult with pulmonary sporotrichosis. **B:** Linear tomogram of the cavity. Diagnosis was proved by sputum cultures and by culture of material from resected cavity.

This disease is much better known as a skin disease than as a pulmonary disease, as the majority of cases have localized skin ulcerations and the route of infection is by direct inoculation. The organism was discovered by a medical student, Schenck, in 1898, and the pulmonary form of the infection was recognized much later. Animal infection was noted for the first time in 1907 in Brazil, and since then the presence of the organism in soil has been demonstrated repeatedly.

Organism

S. schenckii is another of the dimorphic fungi. The mold form of the organism features delicate septate hyphae bearing pyriform conidia arranged like petals on a ABdaisy. The yeast cells are small (2 to 5 µm), round to cigar-shaped cells that are difficult to visualize in tissue.

Pathology

Skin lesions appear grossly as induration with or without ulceration, and usually they occur in line with the associated lymphatic channels. Histologically, granulomas and suppuration are seen along with dystrophic changes of the skin that resemble carcinoma. Organisms are rarely demonstrated in tissues, even with the use of special stains.

The lung shows nodular lesions that are occasionally plaquelike and tend to occur in the upper lobes more than in other areas of the lung. Cavities are frequently seen and often are thin-walled. Necrotic lining of the cavities is the best place to look for organisms. Histologically, the lesions are similar to the skin lesions in that both granulomas and purulent exudate are present. The cavities are usually limited by scar tissue, which is also found in the areas of noncavitary pulmonary lesions.

Epidemiology

The organism is found worldwide in soil and on the leaves of a variety of plants. In particular, rose and burberry bushes host the fungus, and it is also found on hedge bark, reeds, potting soil, sphagnum moss, grasses, and tree bark. It has been isolated from timbers used to shore up a mine in South Africa, and this source infected more than 3000 miners in the largest outbreak of the skin disease that has been reported. The skin disease is an occupational risk for gardeners and soil workers.

The distribution of pulmonary cases is sporadic and probably more related to the interest and diagnostic capability of the involved physicians than to the distribution of the fungus! There is no diagnostic skin test to identify asymptomatic infected persons.

Clinical Manifestations

The disease is best known as a skin problem. The distribution of the lesions tends to follow the lymphatic channels, but lymph nodes are involved infrequently.

Pulmonary sporotrichosis appears to be a separate form of the disease, in which the primary encounter with the fungus is through inhalation. Little is known about early events. The patients usually have cough, sputum production, rarely hemoptysis, and occasionally weight loss and weakness, depending on how long they have been ill. There is nothing to differentiate this chronic lung infection from tuberculosis, histoplasmosis, or coccidioidomycosis.

Dissemination is a rare event and is usually associated with immunosuppression. Lesions may appear in any organs and clinically resemble disseminated infection caused by any fungal organism.

Diagnosis

The history of occupational exposure to potential sources of the fungus may be diagnostically important in evaluating the skin lesions, but not in pulmonary sporotrichosis.

Chest x-ray films reveal localized infiltrates, usually in the upper lobes and often associated with cavities, possibly thin-walled. There may be pericavitary spread of the infection. Findings are nonspecific.

In the laboratory, the organism is readily isolated when cultures are held for at least 2 weeks. The morphologic identification of the mold form is confirmed by in vitro conversion of the organism to its yeast form. The organisms are difficult to see in tissue, even when special stains for fungi are used. Although a number of serologic tests for sporotrichosis have been proposed, none is widely used or commercially available.

Prognosis and Treatment

The skin lesions of sporotrichosis progress slowly but inexorably. Dissemination is rare, as is spontaneous cure of the lesions. The pulmonary lesions progress slowly, and all the reported cases have improved only after treatment.

Iodides are the treatment of choice for skin lesions. Why this very old treatment works is a mystery. It is not because of a direct effect on the fungus. Usually, a saturated solution of potassium iodide is used and continued until all lesions have healed. As a matter of interest, this is the only fungal disease in which iodides are effective, although they have been used in the treatment of all.

Pulmonary sporotrichosis is unaffected by iodides; amphotericin B is required for effective treatment. The exact dose is unknown, but if a total of 1 to 2 g is given according to the usual dosage schedule, results are excellent, with disappearance of pulmonary lesions, conversion of sputum to negative, and clinical improvement. Occasionally, surgery may be necessary to eradicate large cavities.

Itraconazole, which has been successfully used for cutaneous sporotrichosis, has been shown to control systemic disease at a dosage of 600 mg/d for a few weeks and then 400 mg/d for up to a year in patients unable to tolerate amphotericin B.

Cryptococcosis (Fig. 14)

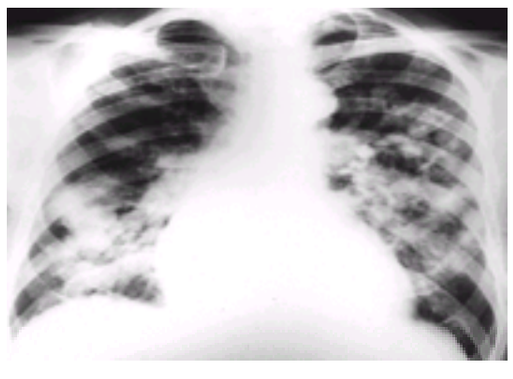

FIG. 14. Chronic pulmonary cryptococcosis in a 66-year-old man with multiple nodular lesions simulating metastatic carcinoma.

This yeast infection was first described in 1894 by Busse and later by Buschke in a patient with involvement of the tibia. Early on, the organism was considered to be a cause of lymphoma, as it was found as a coexisting infection is such patients. A variety of names was given to the organism, but finally it was recognized as a member of a separate genus and the confusion with *B. dermatitidis* was resolved. The major clinical form of the infection, the one most feared because of its high mortality, is meningitis, and to this day the differential diagnosis between cryptococcal and tuberculous meningitis is a challenging one.

Organism

C. neoformans varieties *neoformans* and *gattii* occur as budding yeast cells (2 to 10 µm) with distinctive polysaccharide capsules. The two varieties correspond to the serotypes A/D and B/C, respectively. The yeast cells of variety *neoformans* are typically rounder, whereas those of variety *gattii* tend to be more oval to lemon-shaped. Infrequent isolates of *C. neoformans* have been reported that demonstrate the presence of hyphae in tissue or culture; these are now believed to be the result of failure of haploidization during the sexual reproductive cycle.

Pathology

In humans, this organism may be found in any organ system. Entrance to the body, however, is almost certainly through the respiratory tract. Desiccation of the organism in pigeon fecal material allows for aerosolization of particles of appropriate size to be inhaled and transported to the respiratory areas of the lungs and there cause the initial infection. Dissemination from such primary foci occurs regularly, with special tropism to the central nervous system.

The tissue response to the organism is quite varied, ranging from acute suppuration to practically no response at all. Lesions may display a variety of inflammatory components, including granuloma formation and proliferation of scar tissue. In some cases, significant accumulations of organisms are found with almost no tissue reaction whatsoever. Grossly, such lesions, especially in the skin, look like blisters full of mucus that on microscopic examination demonstrate countless organisms, with the mucinous capsule being responsible for the gross appearance.

The special relationship between infection with *C. neoformans* and immunosuppression, either from lymphomatous disease, AIDS, or immunosuppressive therapy, demonstrates a varied pathology microscopically. There may be a severe, acute, purulent inflammatory response when cell-mediated immunity is suppressed, as in AIDS; there may be granuloma formation (if the T lymphocytes are functional) in lymphomatous disease, or there may be little cellular response in cases in which the immune system has been overwhelmed. Combinations of the above may be seen in a single patient. The clear lack of a granulomatous reaction in patients with AIDS reflects the basic immune pathology of AIDS.

Epidemiology

Infection with *C. neoformans* occurs worldwide, although the occurrence of the various serotypes of the yeast is area-related. Variety *neoformans* is found in Austria, Belgium, Denmark, France, Holland, Switzerland, Italy, and Japan as well as Argentina, Canada, the United Kingdom, and the United States. Variety *gattii* is found in Australia, California, Brazil, Cambodia, Hawaii, Mexico, Paraguay, Thailand, Vietnam, Nepal, and central Africa. The factor that seems to determine the presence of human infection by variety *neoformans* is contamination of the environment by pigeon feces. Variety *gattii* is found in association with the red gum eucalyptus tree.

From early in the history of this infection, clinical disease has been related to the presence of lymphomatous disease, especially Hodgkin's disease. The disease was also described in patients receiving immunosuppressive therapy. Since the early 1980s, cryptococcosis has been identified as the most common life-threatening fungal infection of AIDS patients.

Clinical Manifestations

The most dramatic clinical presentation of cryptococcosis is meningitis, which is very similar in character to tuberculous meningitis. The course is usually protracted in the immunocompetent patient but may be fulminant in the immunosuppressed patient.

Pulmonary cryptococcosis is most frequently encountered as asymptomatic single or multiple pulmonary nodules found by routine chest x-ray examination. The

diagnosis is most often made in these situations by the histology of the resected lesion.

Acute progressive pneumonia may occur, with symptoms of cough, sputum production, fever, and weakness. The clinical picture is not pathognomonic. The progression to abscess formation is more common than in pneumonias caused by bacteria and viruses. Failure of the patient to respond to routine treatment should lead to a search for the causal fungus.

Rapidly progressive infection is most frequently encountered in the immunosuppressed host, especially the AIDS patient. There is often widespread dissemination with involvement of extrathoracic organs. A unique form of the infection consists of multiple superficial mucosal ulcers in the airways, visible on fiberoptic bronchoscopy.

Pleural involvement may occur in all types of pulmonary cryptococcosis, and the resulting pleural exudate is an excellent source for obtaining a culture of the organism. Chronic pleuritis has not been described.

Diagnosis

In the most common clinical presentation of pulmonary cryptococcosis, chest radiography demonstrates single or multiple nodules, well defined and rarely calcified. These may occur in any location. There is nothing to distinguish these nodules from those caused by other fungi, tuberculosis, or tumor. Frequently, only histology is diagnostic. In acute respiratory infection, there may be infiltrates that resemble those of any acute bronchopneumonia. Cavitation may appear, resembling lung abscess. When the lungs are involved as part of a progressive dissemination, there may be multiple foci of infiltration and involvement of lymph nodes in the mediastinum. In all forms of cryptococcosis, CT adds to the exactness of the anatomic diagnosis but not the specificity. It also may reveal enlargement of mediastinal lymph nodes not seen on regular chest x-ray films.

General laboratory findings in all the above presentations are nonspecific and may indicate an underlying lymphomatous process or suggest AIDS. In the asymptomatic syndromes, usually no abnormalities are present.

The diagnostic findings come from the microbiology and pathology laboratories. Culture of bronchoalveolar fluid, cerebrospinal fluid, blood by lysis centrifugation, or tissue readily yields the organism, usually after 24 to 72 hours of incubation. Presumptive identification of *C. neoformans* is obtained within 24 hours by testing for the presence of the enzyme phenoloxidase in any urease-positive yeasts. Although a DNA probe for colony hybridization is commercially available, the sensitivity and specificity of the tests for phenoloxidase render it a less cost-effective procedure than its counterparts for the dimorphic fungi. Confirmation then depends on traditional biochemical testing, using any of the numerous commercially available systems. Rapid diagnosis of *C. neoformans* may also be obtained by the finding of soluble cryptococcal polysaccharide antigen in cerebrospinal fluid or serum, using either a latex agglutination test or an ELISA. Testing of BAL fluid has shown some promise but has a high false-positive rate. Finally, cryptococci are easily visualized in clinical specimens. The India ink preparation is positive in 50%–75% of cerebrospinal fluid specimens from patients with cryptococcal meningitis. The yeasts are stained well by any of the special stains for fungi; cryptococci may be presumptively identified by the intense staining of their polysaccharide capsules by the mucicarmine stain.

Prognosis and Treatment

Asymptomatic pulmonary cryptococcosis appears to be of little threat to an immunocompetent person. This is said with some hesitation, because prolonged follow-up of a significant number of patients in whom the diagnosis was established by resection of a nodule, even a single one, revealed active cryptococcosis in other locations—either the lung or extrathoracic organs, including the meninges—in almost 20% of a total of 60 patients. This included meningitis in almost 10% of them! Thus, the prognosis must be guarded.

In disseminated disease, the outcome is death, but this may not occur until after a long course. If immunosuppression is present, especially if caused by AIDS, the prognosis is for relatively rapid progression to death. All this is without treatment. Of special concern is cryptococcal meningitis. In the days before effective treatment, it was known that exacerbations and remissions could occur spontaneously. This gave rise to stories of spontaneous cures, which merely represented premature conclusions being drawn about remissions in a uniformly fatal disease.

Treatment is now indicated for all cases given a diagnosis of cryptococcosis, even if the diagnosis has been made by resection of a solitary, asymptomatic pulmonary nodule. In the case of an immunocompetent patient with an asymptomatic nodule, the treatment is 2 to 400 mg of fluconazole per day for a minimum of 6 weeks. The basic regimen used for meningitis is applicable to all other cases of pulmonary cryptococcosis. This includes amphotericin B given intravenously at a dose of 0.3 to 0.5 mg/kg per day to a total of 15.0 mg/kg. Initially, treatment is given daily, but if the patient is not seriously ill, this can be quickly reduced to three times per week. Accompanying treatment may be given with 5-fluorocytosine at a dosage of 150 mg/kg daily in four divided doses for a total of 6 weeks. This treatment is 80% effective in meningitis in immunocompetent patients and even more so in pulmonary disease. In immunosuppressed patients, maintenance therapy is required, and this may take the form of 30 mg of amphotericin B every 2 weeks in one intravenous dose. This continues for a year or two, and in the experience of several observers, it is effective on condition that response to the active treatment has been good. In addition to this treatment, it is possible to administer amphotericin B intrathecally in patients with meningitis. The side effects of amphotericin B include decreased clearance of urea and creatinine, anemia, fever, electrolyte abnormalities, and nausea. All these clear when treatment is stopped and can be reduced by giving premedication with antihistamines and antipyretics and by limiting the infusion to no more than 1 1/2 hours. 5-Fluorocytosine is cleared by the kidneys and causes very few side effects. If renal function is already restricted, the amount of 5-fluorocytosine administered each day is reduced in relation to the creatinine clearance.

Liposomes have been used to deliver amphotericin B, but it is necessary to increase the dose to achieve adequate coverage. As of this writing, liposomal treatment is not generally accepted.

Fluconazole is now an accepted treatment alternative, especially for maintenance therapy after completion of amphotericin B treatment of the acute disease. Itraconazole shows promise but is not yet recommended. Two hundred milligrams of either drug daily is continued for a year or more and is well accepted by the patients.

Dosages of fluconazole as high as 800 to 1200 mg/d have been used in the treatment of immunosuppressed patients. The success rate is considerably less than the 80%–90% seen in immunocompetent patients, but it is still significant and worth pursuing. In immunosuppressed patients, maintenance therapy is of critical significance, as the primary treatment is not totally fungicidal and the possibility of a relapse is very high.

Candidiasis

In 1839, the German surgeon Langenbeck described *Candida* in mucosal lesions in a patient with typhus. Actually, the clinical manifestations of candidiasis had been described by both Hippocrates and Galen some 2000 years before. Because the orifices of the body, where the organism normally is found, are readily accessible, *Candida* has been accused of causing many diseases, but as our sophistication has grown it has become clear that even though the surface of the body may suffer insults by *Candida,* the internal organs are extremely well protected by an intact immune system. When the internal milieu of the body is upset by antibiotics, steroids, or other factors, then the normally diminutive organism overgrows and clinical problems ensue.

Organism

Candidiasis is caused by numerous species of *Candida;* the most common include *C. albicans, C. tropicalis, C. parapsilosis, C. krusei,* and *C. (Torulopsis) glabrata.* All species of *Candida* form round to oval budding yeast cells in the size range of 3 to 7 µm. In addition, the first four species listed also form pseudohyphae (elongated yeast cells attached like strings of sausages) in tissue.

Pathology

The normal presence of the yeast *Candida* on mucosal surfaces of healthy persons does not provoke any reaction. When skin surfaces become macerated by moisture or when disease or antibiotic or steroid treatment upsets the ecologic balance of mucosal surfaces, an acute and subacute inflammatory reaction occurs that leads to local irritation. Microscopically, the inflammatory reaction is neutrophilic and lymphocytic. The same basic pathology is found in the esophagus and throat when the infestation progresses to the clinical syndrome of thrush and esophagitis, but a pseudomembrane is added consisting of fungal elements, cell detritus, and fibrin.

Lung involvement almost always occurs in the presence of immunosuppression or cachexia. There may be multiple foci of neutrophilic inflammation with necrosis that may evolve into abscesses. In severely weakened patients, little inflammatory response may be associated with the large collections of yeast cells in lung tissue. Extrathoracic organ tissues are often involved by a similar process, especially the renal cortices. Demonstration of the yeast cells or pseudohyphae of *Candida* is easily

done with regular tissue stains or the special fungal stains.

Special consideration must be given to the possibility of *Candida* pneumonia occurring in otherwise normal hosts. *Candida* may undoubtedly gain entrance to pulmonary tissue via contaminated intravenous needles or tubing, and in such situations blood cultures may well be positive for the yeast. It is highly unlikely, however, that the presence of organisms in the lungs on this basis alone is a threat to an otherwise normal person. The body has excellent defenses against this infection, probably because the organism is normally present on body surfaces. Serum from normal persons inhibits growth of *Candida* in culture. The organisms are subjected to efficient phagocytosis and killing by neutrophils, T lymphocytes and macrophages recognize *Candida* yeast cells, and at least three clones of antibodies are found in serum—IgA, IgM, and IgG. Thus, adequate means are available to control the organism. Entrance of *Candida* to the lungs via aspiration of mouth or nose contents may occur in normal persons, but this is probably quite rare. If it does happen, the same efficient defense takes over, so that finding *Candida* in sputum collected from normal persons almost certainly represents a mouth contaminant of the specimen and not active *Candida* infection of the lungs or airways.

One other expression of altered immune responsiveness is the occurrence of chronic mucocutaneous candidiasis, which is characterized by granulomatous lesions on the skin. This pathologic entity, often associated with various endocrine deficiencies in children, has not been described in the lung.

Epidemiology

The occurrence of systemic candidiasis and candidiasis of the lung as a unique entity is related primarily to immunosuppression and neutropenia. Other factors are associated with a higher incidence of systemic candidal disease are prematurity of infants, chronic cachexia, immunosuppressive therapy for any cause, and long-term steroid therapy. Interestingly, although local candidal involvement of the mouth and esophagus is associated with AIDS, true systemic candidiasis is almost never seen.

Clinical Manifestations

Pulmonary candidiasis occurs for all practical purposes only in immunosuppressed patients, and the only open question is whether the disease is part of a generalized systemic candidiasis. The patients are almost always acutely ill and clearly seriously weakened by their underlying conditions. There may be spiking fever, or in the case of a prolonged underlying illness, the fever may be low-grade. The entire clinical picture is one of overall deterioration. In the most confusing situation, a patient has multiple foci of bronchopneumonia and is unresponsive to antibiotic therapy, and *Candida* is found in the sputum. Even more compelling is the concurrent finding of *Candida* in a blood culture. Clinical judgment is difficult, but careful evaluation of all relevant factors in the case, such as the presence of a long-standing intravenous line or chronic ulcerative skin lesions (foci for dissemination of *Candida*) and the underlying status of the immune system, usually leads to a correct assessment of the need to treat.

Of special concern are patients undergoing bone marrow transplantation. These patients are almost completely depleted immunologically and are extremely susceptible to all types of infections. *Candida* is a significant threat in this situation. It is recommended that preventive therapy be given.

If pulmonary and/or generalized candidiasis has been diagnosed, the clinical situation is grave and treatment is urgently indicated.

If an immunocompetent patient presents with a pneumonia that does not respond to the usual treatment and *Candida* is found in sputum, it is unlikely that the presence of *Candida* is significant.

Diagnosis

The most helpful diagnostic tool is awareness of the overall clinical situation of the patient, especially the immune status, and of whether systemic candidiasis is a likely possibility.

Chest x-ray films demonstrate single or multiple foci of bronchopneumonia, in which radiolucencies often develop. This is a highly suggestive finding, but not specific.

The general laboratory findings are a reflection of the overall clinical situation and not diagnostic.

Specific diagnosis of pulmonary candidiasis depends on the demonstration of yeasts and pseudohyphae consistent with *Candida* in tissue, and the diagnosis is confirmed by the subsequent isolation and identification of the organism from the specimen. Because *Candida* is found as a commensal and a colonizer of mucosal surfaces, identification of the organism from sputum or BAL fluid may be suggestive, but mucosal contamination should always be suspected. The organism is easily cultured from blood, tissue, or respiratory tract specimens; identification depends on demonstration of defined morphologic and biochemical properties. Serologic tests for antibody to *Candida,* such as the immunodiffusion test, lack sensitivity and specificity because of the high prevalence of antibodies in the normal population. Tests for circulating antigen, either mannan or enolase, show promise, but the first generation of commercially available antigen assays has been disappointing.

Prognosis and Treatment

Untreated pulmonary or systemic candidiasis is fatal. In an immunocompetent patient with a positive blood culture resulting from a long-standing intravenous needle or cannula that has become contaminated, the prognosis is excellent if the offending needle or cannula is promptly removed. No other treatment is necessary. Otherwise, serious disease is a possibility, although not a certainty.

Amphotericin B is the treatment for life-threatening candidiasis. The total dose in adults is 15 to 20 mg/kg administered daily (at first) and then three times weekly in intravenous infusions of 0.75 to 1.0 mg/kg per dose. Premedication with antihistamine and antipyretic medication is indicated, and the instillation of 50 mg of hydrocortisone in the infusion helps to minimize side effects. Also, the administration of the entire infusion in 1 1/2 hours is advisable. Almost all species of *Candida* are sensitive to amphotericin B, so that resistance is not a problem. Most cases respond to this treatment. If the immunosuppression that so often underlies the problem can be dealt with, the prognosis is improved. The prognosis is not good for cachectic patients who are deteriorating progressively, even with treatment. In cases of bone marrow transplantation, this treatment should be effective.

Use of the imidazoles and triazoles in life-threatening situations is not recommended at this time. These drugs are effective in various forms of skin and mucosal candidiasis and are indicated as prophylaxis in patients undergoing bone marrow transplantation, but they are not effective in life-threatening candidiasis. Fluconazole has been shown to have the same efficacy in treating candidemia in patients who are not neutropenic as amphotericin B. For preventive therapy, fluconazole is the preferred drug; the dose is 200 mg/d and should be continued until all signs of immunosuppression have disappeared.

Aspergillosis (Fig. 15)

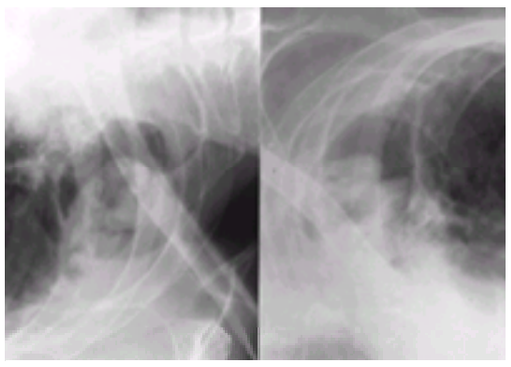

FIG. 15. Cavity in a 68-year-old man containing a fungus ball caused by organisms of a species of *Aspergillus.* Two positions show movement of the ball with change in position of the downward side of the patient.

Aspergillus species have been observed in nature for several hundred years. The name *Aspergillus* is based on the similarity of the spore head of the fungus, first noted by Micheli in 1792, to an aspergillum, the instrument used for sprinkling holy water on supplicants. The fungus was found to cause disease in jays by Mayer and

Emmert in 1815 and was suspected as the cause of human disease later in the nineteenth century. The spectrum of disease caused by this fungus became clear only in the middle of the twentieth century.

Organism

Invasive aspergillosis is caused most frequently by *A. fumigatus* and *A. flavus. A. niger* is often the cause of aspergilloma. Allergic bronchopulmonary aspergillosis (ABPA) is almost always caused by hypersensitivity to *A. fumigatus.* The two species causing invasive disease are heat-tolerant organisms. All species form septate hyphae in tissue; in culture and in nature, millions of conidia, the infectious propagules, are formed on aspergillum-shaped heads produced by the hyphae.

Pathology

The presence of the fungus on the intact skin produces no reaction, and even if there are breaks, there is almost never any inflammatory reaction. On mucous surfaces, the fungus may induce an immediate allergic reaction in persons previously sensitized. The presence of specific IgE seems to be the mediator of the reaction, which is similar to immediate hypersensitivity caused by any allergen. In the airways, there may be an immune response in sensitive individuals that is mediated by IgM and especially IgG antibodies. An acute inflammatory reaction characterized mainly by lymphocytic exudate, edema, and local vasodilation occurs in response to the presence of antigen-antibody complexes lodged in the mucosa at the site of the *Aspergillus* residence. This in turn may result in necrosis locally in the airway, with the development of local bronchiectasis. If the individual colonized with the fungus is allergic, the resulting exudation is characterized by the presence of eosinophils and neutrophils and the hypersecretion of mucus. In such cases, mucous plugs containing inflammatory cells and often hyphae may obstruct airways. The presence of hyperreactive airways and asthma may be suggested pathologically by hypertrophy and hyperplasia of smooth-muscle cells in the bronchial wall.

In the pulmonary parenchyma, *Aspergillus* is seen in at least three circumstances. In the case of hypersensitivity, as described above, in which the lymphocytic infiltrate predominates in the bronchial wall, similar infiltrates may be seen in the pulmonary parenchyma, characterized also by the presence of macrophages and generally similar to those of typical hypersensitivity pneumonitis.

Disseminated aspergillosis may occur in immunosuppressed patients, especially those with leukopenia (granulocytic leukemia, either in an aleukemic phase or being treated with chemotherapy) who are cachectic. This is characterized by widespread dissemination of the fungus in the body, especially in the lung. The pulmonary lesions may demonstrate a lymphocyte/macrophage exudate with few neutrophils associated with necrosis, or in an overwhelmed patient, there may be almost no cellular reaction whatsoever. The fungi may be demonstrated easily by all stains. Similar pathologic changes may occur in all other organs.

It is not clear whether progressive, necrotizing aspergillosis of the lung can occur in patients who are not immunosuppressed. Cases have been reported with localized, acute inflammatory lesions in the lung, suppurative and necrotic in nature, in patients with no obvious underlying disease. This is rare.

In pre-existing cavities with an underlying cause that is usually not active, *Aspergillus* may enter and grow rapidly. The abundance of nutrients in the cavity and the narrow bronchial exit lead to the development of an aspergilloma (fungus ball). Little or no pericavitary invasion by the fungus is seen, but there may be an intense inflammatory reaction caused by the presence of antigen–anti-*Aspergillus* antibody complexes in the wall of the cavity, with associated dilatation of the blood vessels supplying the cavity. As these usually come from the high-pressure bronchial circulation, bleeding into the cavity occurs and may be identified histologically.

Epidemiology

The presence of *Aspergillus* in the environment is the primary factor in determining where various forms of aspergillosis will be encountered. The fungus occurs more frequently in temperate areas of the world, especially if the annual rainfall is more than 25 in (650 mm). The prevalence of the fungus in the air in any given area is relevant in that it increases or reduces the likelihood of contamination of sputum cultures.

Clinical Manifestations

Disseminated aspergillosis is a ravaging disease, seen especially in neutropenic patients and cachectic patients who have leukopenia. Patients with abnormalities of other branches of the immune system seem less prone to the infection. With the advent of treatment for acute leukemia and the use of bone marrow transplantation in a variety of situations, and the associated therapeutic pan-immunosuppression, the physician must be alert for the development of this specific infection.

Acute necrotizing pneumonia has been diagnosed in immunocompetent patients when there has been no response to routine antibiotic therapy and an invasive procedure has been performed that reveals *Aspergillus* species on culture. These cases are similar clinically to any other acute necrotizing pneumonia and are rare.

A fungus ball may first be revealed on chest x-ray films. On the other hand, hemoptysis may be the symptom that calls attention to the mass. Systemic symptoms of fever and muscle aches may be associated with evanescent pulmonary infiltrates in hypersensitive patients. The cavity may have been caused by histoplasmosis, tuberculosis, coccidioidomycosis, or even sarcoidosis, and the underlying process is usually not active at the time the fungus ball is discovered.

ABPA is characterized usually but not always by severe attacks of asthma, fever, cough with scanty sputum and the production of mucous plugs, the appearance of pulmonary infiltrates in varying locations, and proximal bronchiectasis that may be associated with normal bronchi more peripherally in the same bronchial branch. The serologic and skin test findings are described below. The fungus may be found in the sputum of the patient, but this is not essential to the diagnosis. The sedimentation rate is usually greatly elevated, and values for specific anti-*Aspergillus* IgE are high. The active disease waxes and wanes spontaneously but may ultimately lead to localized pulmonary fibrosis.

The above description relates to pure syndromes, but in fact cases are encountered in which a fungus ball may be associated with locally invasive, albeit limited, disease, symptoms of ABPA may be appear in association with a “quiet” fungus ball, and a local necrotizing lesion may be associated with dissemination or aggressive local progression.

In AIDS patients, treatment-induced neutropenia is often the predisposing factor for disseminated aspergillosis with pulmonary manifestations. The use of steroids is also associated with the development of widespread disease. Cavities containing fungus balls tend to bleed and thus pose an added threat to patients.

Patients with cystic fibrosis are at greater risk for ABPA than the general population. The reason for the relationship is not clear. The course and treatment are the same as for patients without cystic fibrosis, and the response to therapy is good. The ultimate impact of ABPA on the course of cystic fibrosis is not clear.

Diagnosis

A clinical picture of periodic worsening of underlying asthma is suggestive of the diagnosis of ABPA. The coming and going of pulmonary infiltrates seemingly not related to other events and without the usual allergic seasonal connection is also suggestive of the diagnosis, especially in asthmatic patients. The sudden onset of hemoptysis in a patient known to have a cavity caused by one of the usual granulomatous infections should arouse suspicion of a fungus ball.

In ABPA, the x-ray film demonstrates the infiltrates as noted. Bronchiectasis proximally located may be seen by high-resolution CT and, in rare cases these days, bronchography. The presence of an intracavitary mass, especially one that moves when the patient changes position, is clear evidence of a fungus ball. CT makes the picture even prettier, but no more accurate. In disseminated aspergillosis, poorly defined focal infiltrates may be seen that are nonspecific. Small radiolucencies may be seen.

Diagnosis of ABPA is aided by the demonstration of elevated titers of anti-*Aspergillus* IgE and IgG and the presence of a wheal-and-flare reaction following skin testing with *Aspergillus* antigen. Specificity of these tests has been improved with the introduction of a purified antigen, Asp f1. In cases of aspergilloma, cultures of sputum and BAL fluid are usually positive, and precipitin tests for IgG antibodies often demonstrate numerous positive bands.

Diagnosis of invasive aspergillosis is the most difficult. Because the organisms are ubiquitous, positive cultures of respiratory secretions do not always indicate the presence of invasive disease. Therefore, definitive diagnosis often depends on the demonstration of septate hyphae in biopsy material (easily seen in tissue stained with any of the fungal stains), with the subsequent isolation of the organism in culture. Isolation of the organism is necessary, as many organisms with the same morphology have been described as opportunistic pathogens of profoundly neutropenic patients. The organism is rapidly growing; cultures are positive in 24 to 72 hours. Identification is based on morphologic criteria. Antibody-based serologic tests are of little value in the diagnosis of invasive aspergillosis. Antigen tests show great promise, but those currently available lack sensitivity, in part because of the transient nature of the antigenemia.

Prognosis and Therapy

Disseminated aspergillosis is a fatal disease unless the underlying immunosuppression and/or cachexia can be reversed. Even with antibiotic treatment, death is almost certain. Fungus ball is a benign syndrome and is not threatening to the life of the patient except when hemoptysis is significant. ABPA is very disturbing to the patient but rarely if ever life-threatening unless the asthma that usually accompanies the syndrome becomes very severe. The syndrome does not spontaneously disappear permanently, but it may be in remission for prolonged periods.

Treatment of disseminated disease is ineffective unless the underlying depression of the immune system is repaired. Amphotericin B, which is the antibiotic most frequently used, is relatively ineffective in this situation. There is still a possibility that one of the newer triazole drugs will prove useful against *Aspergillus* species, although itraconazole at a dosage of 600 mg/d for the first few days and then 400 mg/d continued for months has shown limited effectiveness.

It is not necessary to treat a fungus ball unless hemoptysis or recurrent systemic symptoms that have been proved to be caused by the fungus ball are present. If treatment is required, resection is indicated. Inhaled amphotericin B has been suggested for this condition, but it is ineffective as a systemically administered drug. The reason is that the bleeding and other symptoms are caused by the inflammatory reaction in the wall of the cavity, as a consequence of the large quantity of antigen present. Antifungal therapy has no effect on that.

Treatment of ABPA is aimed at two different aspects of the problem. In the first place, the asthma that so frequently accompanies ABPA is usually severe and thus requires the use of b_2-adrenergic agonists, inhaled steroids, and in certain cases oral theophylline. Systemic steroids, usually oral prednisone, may be required on the basis of the severity of the asthma. The other role of steroids is to reduce the immunologic response to the specific fungal immunogen that is the basis of the syndrome. The dose is about 1.0 mg/kg daily at the outset, with slow tapering of the dose guided by both the clinical condition and the level of specific IgE in the serum. In cases with pulmonary infiltrates only and no asthma, steroids are the only therapy indicated.

PULMONARY DISEASE CAUSED BY ACTINOMYCETACEAE

This group of organisms is identified with fungi, although taxonomically they are bacteria closely related to *Mycobacteria.* In some respects they resemble fungi (e.g., staining and behavior within the body), but they resemble bacteria morphologically and in their characteristics on culture. They have traditionally been considered with the fungi, and we shall do so in this chapter.

Actinomycosis (Fig. 16)

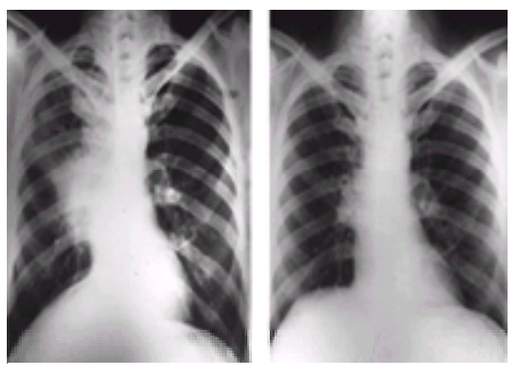

FIG. 16. Acute actinomycosis with focal infiltrates in a 40-year-old man (**A**) before and (**B**) 9 months after initiation of penicillin therapy.

This infection was first recognized in cattle in 1826, and in humans in 1845. The localization of the disease to the mouth in both mammalian species was a frequently observed clinical characteristic. The advent of sulfonamides and antibiotics changed the perception of this disease, and also its frequency.

Organism

The most common cause of actinomycosis in humans is *A. israelii,* an anaerobic, non–spore-forming, gram-positive rod. It is catalase-negative, and succinic acid and lactic acid are its two major metabolic products in culture. Its historical inclusion with the fungi can be attributed to its propensity to form filamentous rods, especially in tissue.

Pathology

This organism is found in the mouth normally, and in otherwise healthy persons there is no reaction to its presence. When local trauma or aspiration of mouth contents containing the organism occurs, the body reacts and disease develops. The response under these conditions is acute inflammation with suppuration and necrosis of tissue. The suppurative process is inexorable in its progression unless treated and has the tendency to cross tissue boundaries that usually limit inflammatory processes caused by bacteria, even mycobacteria. This process leads to fistula formation wherever the infection is found: in the facial tissues, in the lung and pleurae, and in the abdominal organs and peritoneum. Pleurocutaneous fistula (empyema necessitatis) may occur. The disease has been identified in all body organs, implying hematogenous spread.

The characteristic tissue finding in this disease is the so-called sulfur granule, which is a collection of filaments radiating out from a central necrotic core. These may be up to 5.0 mm in diameter and can be recognized grossly in pus. In fact, collections of pus should be routinely examined for sulfur granules. They characterize this disease in tissues, although they are not absolutely pathognomonic, as they may be found in nocardiosis and less frequently in pus associated with staphylococcal infection. In tissues, the sulfur granules take the hematoxylin-eosin stain and are dramatic findings.

A chronic form of this infection is seen in which localized, slowly progressive granulomatous lesions are associated with a plethora of scar tissue. These may be seen on skin, in mediastinal lymph nodes, and in other locations of the body.

Epidemiology

The distribution of cases in the world is related more to clinical awareness of the possibility of the disease than to any external characteristic such as climate, terrain, or living conditions. This is because the organism can be found in the mouths of almost everyone in the world! The wide use of sulfonamides and antibiotics has reduced the incidence of this disease, as this organism is exquisitely sensitive to most of them.

Clinical Manifestations

Actinomycosis most commonly appears in a localized, maxillofacial form. Swellings and distortion of tissues in the maxillofacial area result in fistula formation unless the disease is diagnosed and treated. There is often a history of mouth or face trauma before the development of clinical actinomycosis of this type. In the abdomen, fistula formation is disastrous, and the diagnosis is usually made late in the course of the disease.

Pulmonary actinomycosis is almost certainly secondary to aspiration of mouth contents containing the organism. Also, mouth or facial trauma have frequently occurred before the onset of pulmonary disease. The clinical presentation may be acute and characteristic of pneumonia caused by any organism. It may also be more chronic in onset, with a course similar to the development of aspiration lung abscess of any cause. In fact, a diagnosis of actinomycosis should be considered in any case of lung abscess in which aspiration is a possible factor, and the organism should be specifically looked for. The course of the disease is prolonged and downhill if it is not appropriately treated. Suppuration is extensive, with all the associated toxic systemic signs as well as increasing shortness of breath, cough, production of large quantities of purulent sputum, and chest pain if the pleurae become involved. Empyema may develop, and if untreated it may be complicated by the formation of a

pleurocutaneous fistula.

Lesions of the chronic form of actinomycosis are quite rare in the pulmonary parenchyma. There are usually no acute symptoms; rather, the patient is chronically mildly ill. The course may be many years long before a specific diagnosis is made.

Diagnosis

A history of mouth trauma or of aspiration should arouse suspicion of this disease. Chest radiography is helpful if pulmonary infiltrates cross natural tissue boundaries, such as pleural borders, or chest wall structures. The picture of lung abscess is nonspecific, but again attention should be paid to the anatomic configuration of the lesions.

Laboratory diagnosis begins with clinical suspicion, so that material for culture is collected and transported to maintain anaerobiosis. Collections of pus may be examined for sulfur granules; if found, these should be rinsed in sterile saline solution before culture. Cultures must be incubated anaerobically and held for at least 7 to 10 days; they should be examined every other day for the presence of the characteristic molar tooth colonies. Identification of the organism depends on demonstration of appropriate morphology on Gram's stain and characteristic reactions to a panel of biochemical tests. Direct microscopic examination of sulfur granules or tissue often provides a presumptive diagnosis. The granules are irregular in size (0.1 to 5 mm) and shape and may have a slightly yellow hue. They are made up of filamentous bacteria in a radial array; the exterior ends of the rods are coated with eosinophilic material in hematoxylin and eosin. Serologic testing does not play a role in the diagnosis of actinomycosis.

Prognosis and Treatment

All forms of actinomycosis are rapidly or slowly inexorably progressive and potentially fatal if untreated.

Treatment of actinomycosis is preferably penicillin given in doses of 2 to 10 million units, at first systemically and then continued by mouth. The response is usually prompt, but the treatment must be continued for a minimum of 6 to 9 months, preferably a year. The rationale for this is based, in part at least, on the presence of a great deal of necrotic and fibrotic tissue in the lesions and the persistent viability of the organism residing in this tissue. Results with prolonged treatment are excellent, even in the chronic form of the disease.

If the patient is hypersensitive to penicillin, sulfonamides may be given as well as tetracyclines and many other antibiotics. The emphasis is on length of treatment, regardless of which antibiotic is used.

Treatment of empyema with adequate drainage is mandatory. It is important to prevent the spontaneous formation of a pleurocutaneous fistula, as this increases morbidity significantly.

Nocardiosis (Fig. 17)

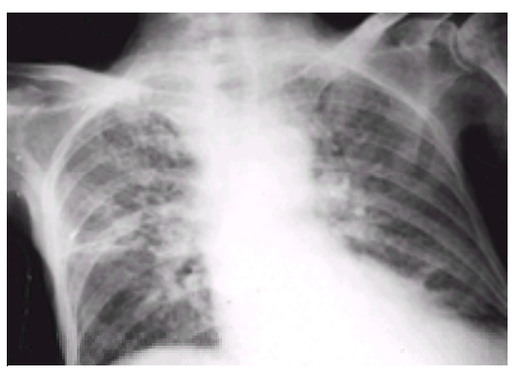

FIG. 17. Acute, fatal pulmonary nocardiosis occurring during steroid therapy in a 73-year-old man with lymphatic leukemia. Note the diffuse infiltrates.

Infection with this organism was first described by Nocard in 1888. Its place in the spectrum of suppurative diseases became clearer in the mid-twentieth century, especially when it was noted to be an accompaniment of alveolar proteinosis. This organism has been found in soil all over the world. There are many confusing elements to this infection, not the least being the weak acid-fast nature of the hyphae and their tendency to fragment and resemble bacilli. The organism has many cousins that cause a variety of serious skin lesions.

Organism

Pulmonary nocardiosis is most commonly caused by *N. asteroides; N. brasiliensis, N. otitidis-caviarum,* and *N. farcinica* represent the etiologic agents of the majority of the remaining cases. All are aerobic, non–spore-forming, gram-positive, branching filamentous bacteria that stain weakly acid-fast. The filaments (1.5 mm) tend to break into coccobacillary forms; aerial filaments are formed in culture. The cell wall of the genus is characterized by the presence of meso-diaminopimelic acid.

Pathology

This is a suppurative disease in whatever organ it is found. The lung is the most common site, as the route of infection appears to be by inhalation of the organism, with primary lesions in the lung. Other sites in which the disease may be found include the central nervous system, skin, and urinary system, especially the kidneys. Histologically, the characteristic inflammation is neutrophilic, and only rarely are granulomatous changes seen. There may be scarring, but it is less pronounced than that seen in actinomycosis. The sulfur granules that may be found in actinomycotic pus may also be found in nocardial suppuration. The tendency for crossing tissue barriers noted in actinomycosis is also present in nocardiosis, although it is less dramatic. The frequency of extrapulmonary suppurative and fibrotic lesions is estimated to be close to 50%, but accurate figures are not available.

Epidemiology

Nocardiosis is found all over the world. In the United States, 90% of cases are caused by *N. asteroides* and the rest by the other *Nocardia* species. There is an association with certain underlying conditions, such as malignant disease, cachexia, alveolar proteinosis, and immunosuppression from diseases or treatment, but about 20% of cases have been found in patients with no identifiable predisposing factor. There appears to be no association with occupation, season, sex, or ethnic origin.

Clinical Manifestations

Pulmonary nocardiosis is almost always an acute or subacute pneumonia that progresses to abscess formation. There is nothing specific about the clinical picture, but the frequency of extrapulmonary lesions is high. There may be pleural involvement with empyema. Of the extrathoracic sites, the central nervous system and the skin are most frequently involved. In fact, the syndrome of multiple subcutaneous abscesses, pulmonary lesions, and possibly pleural effusion is very suggestive of nocardiosis. Cases of chronic brain abscess have been seen. The course of the untreated disease is progressively downhill, and death is inevitable. The disease progresses much more rapidly in patients with immunosuppression.

The association between alveolar proteinosis and nocardiosis was reported in the 1960s, but the reason for the association is not known. The course of the combined diseases is more malignant than the course of either one alone. Treatment of the nocardial infection with antibiotics is not hindered by the proteinosis.

There appears to be a chronic form of nocardiosis that resembles cavitary pulmonary tuberculosis; only the microbiologic findings differentiate between disease caused

by two different agents.

Diagnosis

The clinical syndrome noted above of subcutaneous and pulmonary lesions is suggestive of the diagnosis, as is a complicated course of alveolar proteinosis. In malignant disease with complicating pulmonary, subcutaneous, or central nervous system lesions, nocardiosis must be considered among other opportunistic infections.

Chest radiography shows focal bronchopneumonia frequently associated with abscess formation. Empyema is present in a significant percentage of the patients. None of these findings is specific, however. The typical lesions of proteinosis, widespread alveolar or interstitial shadows, are not modified by the superinfection by *Nocardia.* The brain abscesses that may develop are well demonstrated by standard radiography, CT, and magnetic resonance imaging (MRI), but the lesions are not diagnostic.

Laboratory diagnosis of nocardiosis depends on the isolation of the organism from BAL fluid, pus, or tissue. Clinical suspicion of the diagnosis must be communicated to the laboratory to ensure appropriate handling of the cultures. The organism grows slowly for a bacterium, requiring 5 to 10 days to become positive on culture; because it is sensitive to many antibiotics, it may not grow on the selective media used for routine isolation of fungi. The organism is identified by morphology, staining characteristics, and biochemical profile; analysis of cell wall components by chromatography may also be used. A presumptive diagnosis based on the appearance of filamentous, branching, gram-positive bacteria in clinical material is strengthened if the filaments are determined to be weakly acid-fast (i.e., require the use of dilute mineral rather than acid alcohol for decolorization). In tissue, the filaments may be stained with Brown and Brenn, Grocott, or the Fite modification of the acid-fast stain. Granules are rarely seen in pulmonary disease but may be present in infections acquired by the direct inoculation of the organism into skin.

Prognosis and Therapy

The disease progresses without treatment, with dissemination throughout the body in immunosuppressed cases especially. A fatal outcome occurs in a large fraction of cases. Even with response to therapy, significant scarring may occur.

Effectiveness of therapy varies based on the sensitivity of various strains of *N. asteroides* and other *Nocardia* species to antibiotics, and on the underlying condition of the patient. The most frequently effective antibiotic or chemotherapeutic agent is trimethoprim/sulfamethoxazole. Other effective antibiotics are amikacin and to some extent the tetracyclines. In any case, treatment should be continued for at least half a year and perhaps longer, depending on the clinical course. In the case of brain abscess, surgery may be necessary, and when collections of pus are present subcutaneously, in the pleurae, or elsewhere in the body, adequate drainage is essential.

In the case of a patient who has AIDS or is HIV-positive, it is especially important to test for drug sensitivity, as the organism is more often resistant to the above-mentioned antibiotics in this situation, possibly because of the use of sulfa drugs as chemoprophylaxis against *Pneumocystis.*

MISCELLANEOUS FUNGAL DISEASES

The following infections are rare indeed and almost always associated with some underlying factor that renders the patient more susceptible.

Trichosporonosis

This infection caused by *Trichosporon* species was extremely rare as a cause of human systemic disease until the advent of immunosuppression as a relatively common clinical situation. Involvement of the lungs is seen almost always as part of disseminated disease. There may be superinfection of chronic inflammatory lesions of the lung caused by other conditions. Treatment with a variety of antibiotics, including 5-fluorocytosine and amphotericin, is not very effective but should be tried.

The majority of cases are caused by *T. beigelii.* Regardless of the species involved, infection is characterized the presence of budding yeast cells, hyphae, and arthroconidia in tissue.

Pseudoallescheriasis

Pulmonary involvement includes the formation of a fungus ball, colonization of the tracheobronchial tree, and invasive parenchymal disease. This latter is almost always associated with immunosuppression, and the lesions occur as foci of bronchopneumonia. Treatment is indicated only in the pneumonic form of the infection; the imidazoles have been reported to be effective. Colonization of the airways alone is not a threatening condition, and the fungus ball is dealt with in the same way as an *Aspergillus* fungus ball.

Pseudoallescheria boydii (*Scedosporium apiospermum*) is the most frequent cause of this infection. Rarely, cases are caused by *Scedosporium prolificans.* The organisms appear identical in tissue and must be differentiated in culture.

Zygomycosis

This infection is caused by several fungi belonging to the order Mucorales, including *Mucor, Rhizopus,* and *Absidia* species. Infection with these organisms is associated with diabetes mellitus and neutropenia. Pulmonary disease is rare and is usually seen as a progressive pneumonia that is resistant to usual antibiotic therapy. More frequent is the syndrome of rhinocerebral disease, in which the paranasal sinuses are involved and there may be spread to the major venous sinuses of the head. The pathology in all forms of the infection is acute inflammation associated with a prominent amount of tissue necrosis. Underlying pathology is nonspecific except that the fungi tend to invade blood vessels and thus cause intravascular thrombosis. This phenomenon may be the factor responsible for the prominent necrosis. Treatment is inconsistently effective with amphotericin B. Surgical debridement is often necessary to remove necrotic bone or other tissues.

Rhinocerebral mucormycosis is caused by *Rhizopus* species in 90% of cases. Although *Rhizopus* is also the most common cause of pulmonary disease, species of *Mucor* and *Absidia* are seen more frequently. In tissue, all appear identical, and differentiation is made by identification of the organism in culture.

ABPA Syndrome of Various Causes

Clinically and roentgenographically, typical ABPA has been described infrequently as caused by a variety of fungi, many of them known as saprophytes. These include *Aspergillus* species other than *fumigatus, Candida albicans, Pseudoallescheria boydii, Fusarium vasinfectum, Curvularia lunata, Rhizopus, Helminthosporium, Penicillium, Stemphylium, Candida glabrata, Bipolaris,* and *Drechslera hawaiiensis.* The diagnosis is made only by means of serology, skin tests, and finding the specific fungus in culture, the finding of lesser frequency. The treatment is mainly with steroids using the same criteria for length of treatment as in ABPA.

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CHAPTER

28 Tuberculosis

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INTRODUCTION

Does it not seem reasonable that if a new infectious epidemic were to emerge that annually infected one third of the earth's population (1.7 billion people), causing sickness in 8 million new victims, striking 20 million people at any one time, and killing 3 million, then scientists and policy makers would work overtime to highlight the problem, identify the cause, and find a cure to eliminate this scourge rapidly?

Tuberculosis is an ancient disease that fulfills all the above descriptions regarding its infection prevalence, incidence of morbidity, and mortality. The disease is quite common, its cause is well characterized, and it is by current state of the art both preventable and curable with inexpensive, nontoxic medications.

Yet, embarrassingly, tuberculosis still kills more people than any other infectious disease. Even though its cause and methods of cure are well established, the global health organizations have never put enough political pressure on governments to apply the practical solutions that would eliminate this disease from the world.

By all rights, when the first edition of Baum's *Textbook of Pulmonary Disease* was published, anybody would have predicted that by the sixth edition tuberculosis would have been considered as a rare, historic curiosity. In the sixth edition, however, we are still considering a disease that now affects and kills more people worldwide than at any time in history.

This chapter presents a 1997 view of an ancient killer and includes current information regarding its epidemiology, transmission, pathogenesis, prevention, and treatment. The medical community and world governments merely need to exert the political will necessary to ensure that by later editions, tuberculosis will rightfully have become the curiosity it deserves to be.

EPIDEMIOLOGY

Ever since Robert Koch's remarkable discovery of the tubercle bacillus in 1882, many mycobacterial species have been identified. Pulmonary disease caused by atypical mycobacterial infection, which frequently is clinically indistinguishable from tuberculosis, is now recognized as being caused by several different nontuberculous mycobacteria, most often *M. avium* complex and *M. kansasii*.

Tuberculosis in humans is caused by infection with the *Mycobacterium tuberculosis* complex of organisms. *M. tuberculosis, M. bovis,* and *M. africanum* are mammalian tubercle bacilli that are included in this group.

It is estimated that 1.7 billion persons—one third of the global population—are infected with mammalian tubercle bacilli. Annually, on a worldwide basis, 20 million prevalent active cases occur, including 8 million new cases, with an incidence of approximately 160 cases per 100,000 population. This disease is the leading infectious cause of death in the world, with approximately 3 million people worldwide dying yearly of tuberculosis.

It was estimated in 1990 that 3 million people worldwide are coinfected with the tubercle bacillus and human immunodeficiency virus (HIV). More recent estimates (1994) place this figure closer to 5.5 million. Because of the increased numbers of tuberculosis cases that will likely occur from this cohort of dually infected patients, it is projected that global rates of tuberculosis will rise in the decade ahead, particularly in sub-Saharan Africa and perhaps most seriously in Southeast Asia.

Tuberculosis has re-emerged as a very important public health problem in the United States. It is estimated that 10 to 15 million people are infected with the tubercle bacillus in this country and that most new cases of tuberculosis come from this infected cohort. It should be pointed out, however, that recently there have been increasingly frequent reports, primarily in persons coinfected with the tubercle bacillus and HIV, of clusters of new tuberculosis cases documented by DNA fingerprinting to have resulted from recent infection.

The number of tuberculosis cases declined approximately 5%–6% per year from 84,304 cases in 1953, when nationwide reporting began, to 22,255 cases in 1984 (Fig. 1). However, from 1985, when the number of reported tuberculosis cases reached its lowest point (22,201), through 1992, tuberculosis morbidity in the United States increased by almost 20%, to 26,673 cases (Fig. 1). Since 1992, largely because of an unprecedented expenditure of resources designed to re-establish the public health infrastructure for tuberculosis prevention and control, the number of reported tuberculosis cases has begun once again to show a downward trend, although sustaining this reduction in an era of budget cuts and health care reform may be difficult.

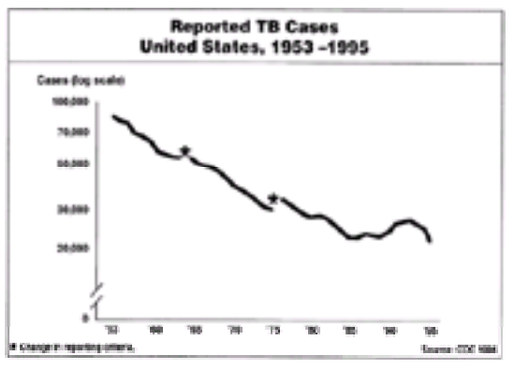

FIG. 1. Reported tuberculosis cases in the United States, 1953–1995.

In 1993 and 1994, and again in 1995, reported tuberculosis cases declined in the United States from 25,287 to 24,361 (3.7% reduction) to 22,812 (6.4% reduction). However, the number of reported cases in 1995 still represents a 2.8% increase over 1985. During the period from 1985 through 1995, it is estimated that >75,000 excess cases of tuberculosis were reported in this country than would have been reported if the trend of a 5%–6% decline per year, as from 1953 to 1984, had continued.

Of the main factors that contributed to the increase in the number of reported tuberculosis cases in the past decade, first and foremost is the deterioration of the infrastructure of the health care system that was allowed to occur. Other contributing factors include coinfection with tubercle bacilli and HIV, transmission of infection in congregate settings, and immigration from countries where tuberculosis is common. The reason that the infrastructure is so important is that all the other factors can be successfully managed in the presence of a proper infrastructure for tuberculosis control.

In 1994, the number of tuberculosis cases reported in persons born in the United States decreased in all age groups except young children (<15 years of age), in whom a 0.4% increase was noted. In foreign-born persons that year, the number of reported tuberculosis cases increased in all age groups except children <15 years of age, in whom a 7.5% decrease was noted. The number and percentage of tuberculosis cases that have been reported in the United States since 1985 in foreign-born persons have progressively increased, and in 1994 they represented almost one third of the cases of tuberculosis reported in this country (Table 1).

Year	Cases, No.	Percentage
1986	4925	22
1987	5025	22
1988	4868	22
1989	5411	23
1990	6262	24
1991	6982	27
1992	7270	27
1993	7354	29
1994	7627	32

TABLE 1. *Reported tuberculosis cases in foreign-born persons in the United States, 1986–1994*

Tuberculosis occurs across racial and ethnic lines and among all age groups. However, case rates are higher among racial and ethnic minorities in the United States than among non-Hispanic whites. In 1994, the risk for tuberculosis was eightfold greater for blacks, sixfold greater for Hispanics, fivefold greater for Native Americans, and 13-fold greater for Asian and Pacific Islanders than for non-Hispanic whites in this country.

Among all age groups, regardless of sex, race, or ethnicity, tuberculosis case rates are highest in the elderly, but they have been declining for several years (Table 2). The largest increase in the number of reported cases of tuberculosis occurred primarily in the younger groups, particularly the 25- to 44-year-old age group; this is in large part a consequence of the increase in tuberculosis morbidity in persons who are coinfected with HIV.

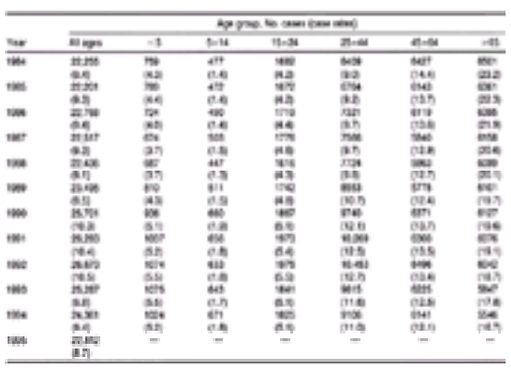

TABLE 2. *Tuberculosis cases and case rates per 100,000 population by age in the United States, 1984–1995*

In a general sense, in the non-Hispanic white population in the United States, tuberculosis is primarily a disease of the elderly (³65 years of age), whereas among minorities, tuberculosis morbidity primarily affects younger age groups (Fig. 2). In 1989, the Centers for Disease Control and Prevention (CDC) reported that the median age of members of minority groups with tuberculosis was 39 years, compared with 61 years in non-Hispanic whites.

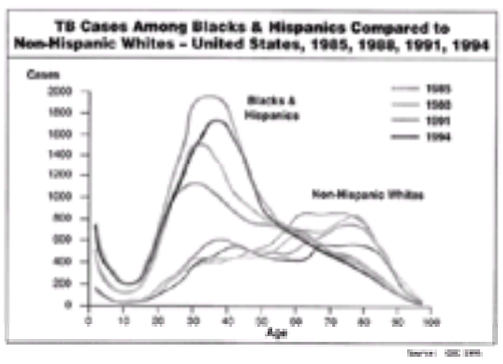

FIG. 2. Cases of tuberculosis among blacks and Hispanics compared with non-Hispanic whites in the United States: 1985, 1988, 1991, and 1994.

Between 1989 and 1992, multiple outbreaks of multidrug-resistant tuberculosis (MDRTB) were reported. These outbreaks were associated with HIV infection, high mortality rates, and evidence of transmission to health care workers. In response to this threat of MDRTB, the CDC began to monitor the number of reported cases of MDRTB each year. For the first quarter of 1991, the percentage of tuberculosis cases that were reported to be resistant to both isoniazid (INH) and rifampin (RIF) was approximately 3.4%. This represented approximately a sevenfold increase over the percentages in 1984, when only 0.5% of reported cases were resistant to both INH and RIF.

One of the most constant aspects of tuberculosis epidemiology has been the dictum that 90% of cases arise in persons previously infected. Recent studies utilizing DNA fingerprinting for tracking infection by the same strain reveal that 33% or more of tuberculosis cases in several areas represent recent infection. By the same technique, HIV-infected patients have been shown to be at high risk for reinfection with new organisms that may be responsible for apparent relapses.

TRANSMISSION AND IMMUNOPATHOGENESIS

Tuberculosis in humans is caused by infection with one of four closely related mycobacterial species that collectively make up the *M. tuberculosis* complex of organisms, which includes *M. tuberculosis, M. bovis, M. africanum,* and the bacillus Calmette-Guérin (BCG), which is a modified strain of *M. bovis. M. microti,* the vole bacillus, is an infrequently encountered mycobacterial species that is also included in the *M. tuberculosis* complex by some mycobacteriologists but does not cause disease in humans.

In the United States, tuberculosis caused by the *M. tuberculosis* complex of mycobacteria is almost always caused by infection with *M. tuberculosis.* However, in this country *M. bovis* has not been completely eliminated as a cause of tuberculosis, and in third world nations, where the pasteurization of milk is less common, *M. bovis* is a prominent source of tuberculosis morbidity. In rare instances, the administration of BCG to victims of bladder cancer and HIV-infected persons has led to reported tuberculosis outbreaks. Cases of tuberculosis in patients from equatorial Africa caused by *M. africanum* were initially reported in 1969 and are presumed to be spread via airborne transmission.

Infection with *M. tuberculosis* is almost exclusively spread from person to person by airborne transmission. The studies of Riley clearly demonstrated airborne transmission of *M. tuberculosis* from humans to guinea pigs, and Houk's studies of an airborne tuberculosis outbreak on the USS Richard E. Byrd strongly support this principle.

Tiny particles containing tubercle bacilli (droplet nuclei), 1 to 5 µm in size and enveloped in an aerosol droplet, are expelled into the air primarily when someone with pulmonary or laryngeal tuberculosis coughs or sneezes. These microscopic infectious particles can remain suspended in air for extended periods of time (several hours). If a new host inhales the air contaminated by these droplet nuclei, transmission may occur. Larger particles fall out of suspension and are deposited on the mucociliary escalator lining the airways and are simply expectorated or swallowed. Smaller droplet nuclei are not deposited on the airway mucosa but are transported by air currents primarily to the periphery of the lower lung zones and deposited on the surfaces of alveoli, where they may be ingested by alveolar macrophages and destroyed, or, as happens in certain instances, the tubercle bacillus may multiply.

Following inhalation, any one of several outcomes is possible. The tubercle bacillus can be eliminated immediately (no infection) or can remain dormant in the host indefinitely (infection without disease), as occurs in the majority (90%) of persons, who are free of disease but remain infected with *M. tuberculosis* for the rest of their lives. The organism can immediately or rapidly cause tuberculosis (primary tuberculosis), as occurs in approximately 5% of persons, in whom tuberculosis develops in the first or second year following infection. Finally, the tubercle bacillus can cause disease many years after infection has occurred (recrudescent tuberculosis), as occurs in approximately 5% of patients. Thus, disease develops at some point during their lifetime in only about 10% of persons infected with *M. tuberculosis.*

Despite recent advances in molecular biology that have greatly increased our knowledge of the immunopathogenesis of tuberculosis, the complex interactions (checks and balances) that occur between the tubercle bacillus and the human immune system remain incompletely understood. Lurie's studies on the histopathology of tuberculosis using immune-competent and immune-incompetent rabbit models were seminal. Dannenberg's subsequent observations, based on Lurie's work, pointed out the importance of the interaction between delayed-type hypersensitivity (DTH) and cell-mediated immunity (CMI) in determining what form tuberculosis takes and greatly aided our understanding of these complex events. Dannenberg proposed that both CMI and DTH inhibit growth of *M. tuberculosis.* CMI enhances the ability of macrophages to destroy tubercle bacilli, causing little tissue damage, whereas DTH destroys nonactivated macrophages that are laden with tubercle bacilli, causing tissue damage. Nardell, in a review of Dannenberg's analysis of the pathogenesis of tuberculosis, outlines four stages (Fig. 3): onset, logarithmic growth, immunologic control, and liquifaction.

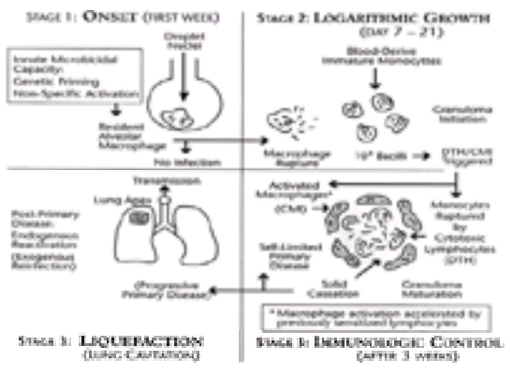

FIG. 3. Four stages in the pathogenesis of tuberculosis in the normal host. See text for detailed description. (From Nardell 1993, with permission. Based on Dannenberg 1991.)

Stage 1: Onset

Following ingestion of droplet nuclei by nonspecifically but highly activated alveolar macrophages, the mycobacterial inoculum is either destroyed (90%) or inhibited or may multiply, depending on the innate mycobactericidal ability of the macrophage and the innate resistance of the tubercle bacilli to the defenses of the host.

Stage 2: Logarithmic Growth

Intracellular multiplication of tubercle bacilli occurs when the innate mycobactericidal ability of the macrophage is inadequate to destroy the initial inoculum of mycobacteria. *M. tuberculosis* organisms not destroyed by alveolar macrophages are released when the macrophages die and lyse, attracting inactivated monocytes from the bloodstream to form an early primary tubercle (initial granuloma formation). Although these monocytes are capable of ingesting the released tubercle bacilli, they do not have the ability to destroy them or inhibit their growth, which increases logarithmically during this stage (7 to 21 days).

Stage 3: Immunologic Control

By 3 weeks, CMI and DTH have developed, as can be demonstrated by intradermal injection of purified protein derivative (PPD), resulting in tuberculin reactivity at 48 to 72 hours. During stage 3, tubercle bacilli have multiplied in many of the inactivated macrophages to a number far in excess of what can be destroyed by immune cellular mechanisms (CMI), and only cytotoxic lymphocytes carrying the CD8 marker (DTH) can limit further logarithmic growth by killing the *M. tuberculosis*-laden macrophages. The destruction of these tubercle bacilli results in the formation of the caseous necrotic center of the granuloma. This necrotic, soft, cheeselike center is surrounded by an accumulation of partially and highly activated macrophages and lymphocytes that have organized to form a granuloma.

The tubercle bacillus is an obligate aerobe and is unable to multiply in solid necrotic granulomas, which contain toxic fatty acids and are very acidic and anoxic. The organism either dies or becomes dormant. Tubercle bacilli that are released from destroyed macrophages within the granuloma are also ingested and destroyed during stage 3 by highly activated macrophages that are specifically activated by helper T lymphocytes (Th1 subset).

Released tubercle bacilli as well as those in infected macrophages are transported via peribronchial lymphatic channels to regional lymph nodes. If infection is not contained (stage 4), ultimately it spreads to the hilar and mediastinal lymph node chains, from which entrance to the systemic circulation via the thoracic duct is

possible.

Stage 4: Liquifaction (Lung Cavitation)

The causes of liquifaction are incompletely understood; however, the release of hydrolytic enzymes that liquefy solid caseum and DTH to tuberculin proteins are thought to be contributing factors. Liquifaction of the solid, necrotic, caseous center of the granuloma kills macrophages but provides a favorable environment for abundant multiplication of tubercle bacilli. The large antigenic load that is created triggers a DTH response, causing extensive tissue damage. Erosion of the liquefied caseous material into adjacent airways, lymphatics, and blood vessels leads to pulmonary spread via the bronchial tree and extrapulmonary spread by lymph and hematogenous dissemination.

Immunologic Mechanisms

Several cell types—including helper (CD4) T cells (subsets Th1 and Th2), cytotoxic (CD8) T cells, and gd T cells as well as natural killer (NK) cells, alveolar macrophages, and monocytes—play an important role in regulating CMI and DTH. However, the actual roles that these cells play in producing and regulating the various cytokines, the most important of which include interleukin-2 (IL-2), tumor necrosis factor (TNF), and interferon-g (INF-g), is not well understood.

DIAGNOSIS

Clinical Presentation

Important components of a complete diagnostic evaluation for tuberculosis are an accurate medical history and physical examination. Particular care should be taken in determining tuberculosis exposure, prior treatment for the disease, concurrent medical problems, including HIV infection, and use of medications that affect host immunity.

The presenting symptoms of tuberculosis may differ depending on the site affected. In most cases—approximately 85%—the lung is the site of disease, and respiratory symptoms predominate. The clinical presentation of pulmonary tuberculosis may include nonspecific cough, chest pain, and hemoptysis. At its onset, the cough is usually nonproductive but persistent, and it may become productive of mucopurulent or blood-streaked sputum; occasionally hemoptysis can be moderate to severe. Chest pain may occur and often is described as dull and aching or pleuritic in nature. The latter may frequently be associated with the presence of a pleural effusion. Dyspnea is an uncommon feature; when present, it is usually caused by extensive parenchymal disease or a large pleural effusion.

Chills, fever, night sweats, fatigue, and loss of appetite and weight are systemic symptoms consistent with both pulmonary and extrapulmonary tuberculosis. Approximately 15% of tuberculosis cases are extrapulmonary (the percentage is higher when coinfection with HIV is present). The clinical symptoms of extrapulmonary tuberculosis also depend on the site affected. Headache, back pain, swelling of the neck, and blood in the urine may be the presenting symptoms in patients with tuberculosis of the central nervous system, spine, lymph nodes, and kidneys, respectively.

Unfortunately, in elderly patients many of the classic clinical features that many physicians rely on to diagnose tuberculosis may be absent. Frequently in this group, symptoms are nonspecific or atypical. The presence of concurrent illnesses, such as chronic obstructive pulmonary disease (COPD) or lung cancer, in an elderly person may obscure the diagnosis of tuberculosis, delaying therapy, or tuberculosis may be completely missed, only to be found at autopsy. The physical examination may provide important information regarding the patient's overall medical condition and guide the physician in choosing appropriate diagnostic and therapeutic approaches.

Tuberculin Skin Testing

The tuberculin skin test is a useful diagnostic test for evaluating persons who have symptoms of tuberculosis or who are suspected of being infected with *M. tuberculosis.* It is the standard test for detecting tuberculosis infection before progression to disease occurs. The tuberculin test may also be of particular assistance in evaluating patients with extrapulmonary tuberculosis, who may have normal findings on chest roentgenograms.

A negative tuberculin skin test reaction *never* excludes the diagnosis of tuberculosis. Normally, a period of 2 to 10 weeks is required after infection for a DTH response to tuberculin to develop. Infants <6 months of age may have a false-negative tuberculin skin test reaction because their immune systems have not yet fully developed. False-negative tuberculin skin test reactions may occur in persons with severe illness, HIV infection, sarcoidosis, and uremia, and in those receiving therapy with immunosuppressive drugs.

Overall, approximately 10%–25% of person with tuberculosis will have a false-negative reaction when given a tuberculin skin test. Although infected with *M. tuberculosis,* 30% of patients who are HIV-seropositive may have false-negative tuberculin skin tests (<5 mm) when tested. Thus, a positive tuberculin skin test reaction supports the diagnostic possibility that a suspected illness is tuberculosis; however, a negative tuberculin skin test reaction by no means excludes the diagnosis of tuberculosis.

Two preparations, purified protein derivative (PPD) and to a much lesser extent old tuberculin (OT), are currently used clinically. Robert Koch in 1890 first used the filtered and concentrated heat-sterilized broth in which tubercle bacilli had been grown as a therapeutic agent, and designated the concentrated extract *old tuberculin.* OT was later adopted as a diagnostic tool but proved to be a crude, nonspecific preparation containing extraneous antigenic substances that caused skin test reactions that were not always diagnostic of infection with *M. tuberculosis.* In the United States, OT is used primarily as an antigen in multiple puncture screening tests, in which the exact antigen dose introduced into the skin cannot be standardized. Therefore, these multiple puncture devices should not be used as diagnostic tests.

In the early 1930s, Florence Siebert isolated a protein from filtrates of OT, which she called *purified protein derivative.* PPD-S (Siebert's lot 49608) has subsequently been adopted as the international standard for purified protein derivative of mammalian tuberculin by the U.S. Public Health Service.

In the United States and Canada, the potency of PPD preparations is measured in tuberculin units (TU); a TU is defined as 0.00002 mg of PPD-S. The dose that best separates true-positives from false-positives is the 5-TU (standard in the United States) dose of prepared PPD, which produces a skin reaction equivalent in size to one produced by using PPD-S, regardless of the actual amount of tuberculin used. Because tuberculin is absorbed by glass and plastics, a detergent, Tween 80, has been added to prevent loss of potency of tuberculin during storage.

The standard for diagnosing infection with mammalian tubercle bacilli is the Mantoux test, performed by the intracutaneous injection of 0.1 mL of Tween-stabilized liquid PPD into the dorsal or volar surface of the forearm. In 48 to 72 hours, the area of induration (not erythema) is measured and recorded in millimeters. If a delay occurs in reading, a positive test reaction, if present, may be valid up to 1 week following placement of a Mantoux test. A negative test reaction must be confirmed by 72 hours.

A Mantoux skin test reaction size of ³5 mm is interpreted as positive in the following cases:

1. Persons having or suspected of having HIV infection
2. Close contacts of a person with infectious tuberculosis
3. Persons with abnormal chest radiographic findings suggestive of old healed tuberculosis who have not been previously appropriately treated
4. Persons who inject drugs and whose HIV status is unknown

A tuberculin skin test reaction size of ³10 mm is considered positive in the following cases:

1. Persons with certain medical conditions, excluding HIV infection
2. Persons who inject drugs (if HIV-negative)
3. Medically underserved, low-income populations, including racial and ethnic groups at high risk
4. Residents of long-term care facilities
5. Children <4 years of age
6. Locally identified high-prevalence groups (e.g., migrant farm workers or homeless persons)

A Mantoux skin test reaction of ³15 mm is considered positive in all persons with no known risk factors for tuberculosis.

Anergy testing, although currently recommended by the U.S. Advisory Council for the Elimination of Tuberculosis (ACET) in the evaluation of immunosuppressed

persons suspected of having tuberculosis but whose tuberculin skin test reaction is negative, is a controversial point. Recent studies suggest that anergy is a complex, unstable process that varies dramatically within short periods. A recent study of anergy in HIV-positive persons found that the degree of anergy was best defined by the helper lymphocyte count. Clearly, to recommend routine evaluation of CD4 counts and placement of antigens, such as mumps virus or *Candida,* in all immunosuppressed patients who are suspected of being anergic, adds substantially to patient care cost without evidence of definite benefit. Anergy testing should not be used for individual patient decisions.

Roentgenographic Examination

Historically, the chest roentgenograph has been an important diagnostic tool in evaluating patients, particularly for pulmonary tuberculosis. The chest x-ray film can be used to rule out tuberculosis in a person with a positive tuberculin skin test reaction and no symptoms of tuberculosis. A posteroanterior projection is the standard view needed for the detection of chest abnormalities. Lateral, lordotic, oblique, and decubitus views may be helpful, depending on the location or nature of the suspected lesion.

In some instances, newer imaging techniques, such as computed tomography (CT), may be helpful. CT of the chest is particularly helpful in evaluating hilar and mediastinal adenopathy, pleural effusion, and calcifications of the visceral and parietal pleural surfaces, and may also be helpful in evaluating patients with extrapulmonary tuberculosis. Tuberculosis involving the vertebrae, with paravertebral abscess formation, and lesions of the central nervous system may be evaluated using CT with or without contrast. Magnetic resonance imaging (MRI) may also be helpful in evaluating tuberculous lesions of the central nervous system.

Although certain abnormalities on chest x-ray films are highly suggestive of tuberculosis, it should be remembered that they are *never* diagnostic. Parenchymal infiltration and cavitation changes involving the apical or posterior segments of the upper lobes and less commonly the superior segments of the lower lobes are compatible with postprimary tuberculosis.

The manifestations of primary tuberculosis of the lungs include hilar and mediastinal adenopathy, pleural effusions, and infiltrates in the lower lung fields. However, the lung changes associated with pulmonary tuberculosis can vary and include consolidation (as occurs in endobronchial spread of disease) and miliary nodules, in addition to the previously described changes. Some elderly patients and those with HIV infection may have unusual chest x-ray findings, which may be normal or compatible with primary tuberculosis (adenopathy, lower lung infiltrates).

It has been reported that 60% of patients with advanced AIDS have hilar or mediastinal adenopathy, compared with 3% of non-AIDS patients; 29% have localized middle or lower lung field infiltrates, compared with 3% of non-AIDS controls; and 12% have normal chest x-ray findings, compared with none of the non-AIDS patients. In one study, none of the AIDS patients had chest cavitary lesions, compared with 67% of the non-AIDS patients, and 97% of the non-AIDS patients had upper lobe disease, compared with 18% of the AIDS patients.

Laboratory Evaluation

Specimen Collection

A joint statement of the American Thoracic Society (ATS), the CDC, and the Infectious Disease Society of America states that an important feature in the diagnostic evaluation for tuberculosis is ". . . to obtain appropriate specimens for bacteriologic and histologic examination." Depending on the location of the disease, sputum, bronchial washings, lung tissue, lymph node tissue, bone marrow, liver, blood, urine, stool, and cerebrospinal fluid may be examined.

Because most cases of tuberculosis are pulmonary, examination of sputum is of primary importance. The yield of positive sputum smears in patients with pulmonary tuberculosis when three sputum specimens are collected has varied from approximately 50%–80%, depending on the study. The specificity of a positive smear has remained high (>99%). Some of the variability in studies reporting the sensitivity of positive sputum smears in patients with pulmonary tuberculosis may be explained by differing clinical presentations. In one review, 52% of patients with cavitary tuberculosis and only 32% of patients with local infiltrates had positive smears; similarly, only 45% of AIDS patients (noncavitary disease) with tuberculosis had positive sputum smears, compared with 81% of non-AIDS patients.

Patients who are suspected of having pulmonary tuberculosis should have 10 mL of an early morning sputum specimen submitted to an appropriate laboratory for smear and culture for tubercle bacilli. Several methods exist for obtaining specimens from patients who have difficulty producing sputum spontaneously (i.e., after inhalation of a saline aerosol). Transmission of tuberculosis, especially in HIV-infected populations, may occur in association with sputum induction, so special precautions should be taken by using portable hoods and sputum induction chambers that are appropriately vented. Gastric lavage fluid may be used for culture of tubercle bacilli but not smears as saprophytic mycobacteria are normally found in the stomach. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and/or biopsy has a high yield and may be useful in such patients or in those whose initial sputum specimens are negative for acid-fast bacilli (AFB) on smear. These procedures also may generate hazardous aerosols. The yield of bronchoscopy specimens in the demonstration of AFB is extremely high.

Invasive procedures beyond bronchoscopy to obtain diagnostic specimens are warranted when other techniques fail. Body fluid specimens should always be analyzed for differential cell count and glucose and protein content. In tuberculosis, lymphocytosis and elevated protein and low glucose levels are usually present in infected body fluid. Tissue biopsy (needle aspiration biopsy, transbronchial biopsy, biopsy of bone marrow, lung, liver) specimens should be divided and a portion sent to the laboratory for culture and another sample placed in formalin for histologic examination. Histologic changes characteristic of tuberculosis include granuloma formation and caseation necrosis.

Acid-Fast Bacillus Stains

Although far less sensitive than culture, the AFB smear is an important diagnostic aid for tuberculosis. AFB stains may be done quickly and provide the physician with the first preliminary confirmation of a clinical diagnosis of tuberculosis. AFB smears do not actually confirm tuberculosis, because nontuberculous mycobacteria and nonmycobacterial organisms such as *Nocardia* and some species of *Legionella* may produce positive stains.

The fluorescent staining technique that utilizes fluorochrome dyes (auramine/rhodamine) is now the preferred staining method for AFB. When the fluorochrome stain is viewed with fluorescence microscopy, AFB stain bright against a dark background and are more easily detected than when conventional AFB staining techniques are used. Because of the shortened amount of time needed to review a slide, fluorescent stains are considered more sensitive for detecting AFB. Until recently, the conventional Ziehl-Neelsen stain or one of its modifications, the Kinyoun stain, viewed under a light microscope were the conventional stains of choice for AFB, and positive smears correlated closely with infectiousness.

Mycobacterial Identification

Digestion and Decontamination

Sputum contains numerous microbes and various types of organic debris that interfere with mycobacterial growth on culture medium. Raw sputum specimens, therefore, must undergo a process of digestion and decontamination before being cultured for mycobacteria. The digestion and decontamination method most widely used in the United States utilizes *N*-acetyl-L-cysteine (NALC) and sodium hydroxide (NaOH). Raw sputum samples contain mucus and other proteinaceous materials that surround microbial contaminants and mycobacteria. NALC is used to liquify the debris that surrounds and protects these microbes from the decontamination effects of NaOH. Liquification of the debris also gives surviving mycobacteria freer access to the nutrients of the medium into which they are subsequently inoculated.

Raw sputum contains numerous bacteria that grow more rapidly (doubling time of <1 h) than tubercle bacilli (doubling time of 18 to 24 h), and these will quickly overgrow the mycobacteria if a raw sputum specimen is inoculated directly onto culture medium. To prevent this occurrence, decontamination of the raw specimen is accomplished by adding NaOH. Because of the high lipid content of the cell wall, mycobacterial growth is less inhibited by NaOH than is the growth of normal bacterial flora. However, some mycobacterial growth is inhibited by the chemical. Normally sterile fluids like blood, cerebrospinal fluid, and pleural fluid should therefore not be decontaminated for fear of further decreasing the small number of mycobacteria present.

Conventional Growth Techniques

Culture of specimens containing tubercle bacilli is a much more sensitive method of detecting mycobacteria than are direct smears. It is estimated that ³10,000 AFB must be present per milliliter of sputum for a sputum smear to give a positive result, whereas a culture of sputum can detect as few as 10 AFB per milliliter of a digested, concentrated specimen. Culture of AFB also allows speciation of the organism and recognition of its drug susceptibility pattern.

Two types of solid media have traditionally been used: an egg-based medium (Lowenstein-Jensen) and an agar-based medium (Middlebrook 7H10 and 7H11). A liquid

medium (Dubos Oleic-Albumin) that requires incubation in 5%–10% carbon dioxide (CO_2) for 3 to 8 weeks is also available. The principal drawback to the use of solid culture media is that cultures grow slowly, and the process requires highly skilled personnel and is labor-intensive.

Because all mycobacterial strains cannot be grown on a single substrate, it is a common laboratory practice to inoculate both egg and agar media to obtain the initial isolate. Following growth of the mycobacteria, colony morphology, growth rate, and pigment production should be determined and tested biochemically to identify the organism completely. When sufficient mycobacterial growth has occurred, evaluation of colony morphology is helpful. Colonies of *M. tuberculosis* are typically rough with irregular edges when viewed on translucent Middlebrook 7H10 agar with a stereo-optic microscope.

Most mycobacteria, including *M. tuberculosis,* require >1 week for growth. Notable exceptions to this observation are the rapid growers, such as *M. fortuitum* complex, which often produces mature colonies on Lowenstein-Jensen media in 3 to 5 days, and *M. marinum* (5 to 7 days). *M. tuberculosis, M. avium* complex, and *M. fortuitum* usually do not have significant pigment and are buff-colored. This contrasts sharply with the highly pigmented (orange) scotochromogens, such as *M. scrofulaceum,* and the highly pigmented photochromogens, such as *M. kansasii* and *M. marinum,* which become bright yellow when exposed to light. The bacteriology of nontuberculous mycobacteria is discussed in Chapter 29.

Nearly 99% of the strains of *M. tuberculosis* are niacin-positive. However, some strains of *M. simiae* and *M. kansasii* may also be niacin-positive. In biochemical testing, the combination of a positive niacin test, positive nitrate reduction test, and negative heat-stable catalase test is diagnostic of *M. tuberculosis.*

The Bactec system is an automated radiometric culture method, introduced in the late 1970s, that can detect the growth of mycobacteria more quickly than can other conventional culture methods using solid media. The system uses a liquid Middlebrook 7H12 medium containing radiometric palmitic acid labeled with radioactive carbon (^{14}C). Growth of mycobacteria within the system is measured as a daily growth index that represents the production of carbon dioxide ($^{14}CO_2$) by the metabolizing organisms. The detection of ($^{14}CO_2$) allows early recognition of mycobacterial growth, even before there is visible evidence of growth. The growth of *M. tuberculosis* complex is inhibited by *p*-nitro-L-acetylamino-b-hydroxypropiophenone (NAP), but NAP does not impede the growth of nontuberculous mycobacteria. When an increase in the growth index indicates that AFB are growing in a Bactec system, confirmation by a positive stain of the specimen is usually carried out. Samples of the specimen can then be subcultured in Bactec bottles with and without NAP. If the growth index value of each Bactec bottle is monitored daily, it is easy to tell whether *M. tuberculosis* complex or nontuberculous bacteria are growing in the sample. Results are usually available in 5 to 7 days.

DNA Probe

A significant advancement in the ability to identify mycobacteria rapidly and precisely occurred in the late 1980s, when nucleic acid hybridization assays were introduced. A complementary DNA (cDNA) probe is labeled with acridinium ester as a detector, and most commonly is directed at ribosomal RNA (rRNA) of the target mycobacteria in the sample. When the cDNA probe reacts with the target rRNA, a DNA-RNA hybrid is formed, producing light (chemiluminescent assay) that can be measured with a luminometer. This detection method is very sensitive; chemiluminescence is 10^6-fold more sensitive than fluorescence. Commercially available probes can react specifically with *M. tuberculosis* complex, *M. avium, M. intracellulare, M. kansasii, M. gordonae,* and *M. avium-intracellulare* complex. The sensitivities and specificities of these assays are >95% for these species.

At least 10^5 to 10^6 organisms must be present for best results; thus, the probes require cultures. A DNA probe can be completed in a matter of hours and can be used in combination with the Bactec system. When an increase in the growth index is noted in a Bactec system, a sample of the broth culture medium is stained, and if AFB are observed, a DNA probe is performed on the medium. It is estimated that by using this method the time required for identification of *M. tuberculosis* can be reduced to 1 to 2 weeks.

Both high-performance liquid chromatography (HPLC) and gas-liquid chromatography are used to identify mycobacterial species, with HPLC perhaps enjoying wider use. However, although HPLC provides a rapid and sensitive means of detecting mycobacteria, this technique has been used preferentially in level III reference laboratories because of its high cost. Because substantial growth of the mycobacteria is required for analysis, HPLC is not applicable for direct detection of mycobacteria in clinical specimens. HPLC is based on the observation that each species of mycobacteria produces specific fatty acids in its cell wall. These mycolic acids are extracted from the cell wall and methylated to form a methyl ester; when analyzed by chromatography, the methyl ester produces a characteristic pattern that can be used to differentiate the various species of mycobacteria. This test provides a specific diagnosis for most species in <4 hours. Detection of tuberculostearic acid by gas-liquid chromatography has proved to be a very sensitive and rapid method of detecting *M. tuberculosis* and may be particularly useful in the diagnosis of tuberculous meningitis. However, this test is still in a developmental stage.

Drug Susceptibility Testing

A drug susceptibility test should be obtained for all initial isolates, and whenever patient response to treatment is inadequate or cultures remain positive for ³2 months after initiation of treatment. Drug susceptibility testing may be performed using the conventional method or Bactec system; both methods have advantages and disadvantages.

Conventional Method

The conventional method for drug susceptibility testing uses solid media (Middlebrook-Cohn 7H10) that can be impregnated with antituberculosis drugs, depending on the desired test. The proportion method is most commonly used in the United States. An isolate of *M. tuberculosis* is considered drug-resistant if the number of colonies on the drug-containing medium is >1% of the number of colonies on the drug-free control plate.

Direct and Indirect Methods

Drug susceptibility tests can be carried out directly or indirectly. A direct test can be performed on a digested and decontaminated specimen with a smear positive for AFB. A direct test provides results faster (21 days) and gives a truer picture of the population of mycobacteria in the isolate.

Indirect tests are usually performed when the smear of the clinical specimen is negative for AFB or when significant contamination with pyogenic bacteria or other non-AFB is present. The inoculum for indirect drug susceptibility tests is obtained from the culture of the initial isolate. When indirect tests are performed, there is a risk of inadvertently selecting a predominant population of susceptible or resistant mycobacteria that are not truly representative of the population of organisms in the isolate that is being subcultured. This bias may be lessened by preparing a dilution of the entire subcultured population of mycobacteria. Because it is more difficult to avoid contamination and adjust the inoculum size when using the Bactec system, conventional drug susceptibility testing using solid media is the suggested method for performing direct drug susceptibility testing. The Bactec system (see above) is more applicable to indirect drug susceptibility testing using solid culture media or Bactec broth media. The Bactec method is best suited for testing first-line drugs and is preferable for pyrazinamide (PZA) testing. PZA susceptibility testing requires a very low pH (5.5) in conventional solid media, which prevents the growth of some strains of *M. tuberculosis.*

Newer Laboratory Methods

Polymerase Chain Reaction

The polymerase chain reaction (PCR) is a laboratory method for amplification of the amount of DNA in a specimen. The technique can be used on raw (uncultured) clinical specimens and theoretically is capable of detecting a single mycobacterium in a biologic sample. The process requires initial denaturation of double-stranded DNA by heating the specimen. Highly specific oligonucleotide primers—synthetic, short, single-stranded DNA probes—are added and attach only to cDNA sequences of the target mycobacteria. A DNA polymerase then enzymatically extends the primers to make a complete strand of cDNA. Multiple cycles of this process repeated sequentially create millions of identical copies of target DNA sequences of mycobacteria. These markers are specific for *M. tuberculosis* complex or other species of mycobacteria and can be detected by gel electrophoresis. If the target mycobacteria are absent from the sample, the primer has nothing to bind to, and amplification of the target DNA sequence does not occur. Although available in many laboratories, PCR is so far not generally used for the routine diagnosis of tuberculosis. It is highly sensitive, and contamination must be rigorously controlled. However, it is a promising tool for the rapid diagnosis of tuberculosis and may prove to be particularly helpful in the diagnosis of smear-negative tuberculosis.

Ligase Chain Reaction

Like PCR, ligase chain reaction (LCR) is a recently developed target amplification system used for the detection of species of mycobacteria. In research laboratories, the test has been demonstrated to have very high sensitivity and specificity and can be performed rapidly. However, it is still in the developmental stage.

Restriction Fragment Length Polymorphism or DNA Fingerprinting

DNA fingerprinting is not a diagnostic test but is a recently developed epidemiologic tool used primarily to evaluate the transmission of tuberculosis and identify cross-contamination of specimens within the laboratory. Restriction fragment length polymorphism (RFLP) subtypes strains of mycobacteria by fragmenting target DNA from *M. tuberculosis* with restriction enzymes (endonucleases) that recognize specific sequences and cut DNA into fragments of varying length. Cloned mycobacterial DNA (IS6110) probes are used to hybridize the fragments, which produce specific electrophoretic patterns and can be compared from strain to strain.

Luciferase Reporter Phages

A functional assay for the rapid assessment of drug-resistant mycobacteria using luciferase reporter phages has been recently developed but has not yet been tested clinically. This system can provide susceptibility results within 18 to 24 hours after a culture containing ³1 million mycobacteria has been obtained.

The assay involves placing the firefly gene for the production of luciferase into mycobacteriophages that then infect *M. tuberculosis,* introducing the firefly luciferase gene into the tubercle bacillus. Luciferin is added to the system and the activity of luciferase is monitored. Luciferase in the presence of adenosine triphosphate oxidizes luciferin to oxyluciferin, resulting in the production of light that can be measured in a luminometer. If an antituberculosis drug is added to the system, drug-resistant strains continue to produce light, whereas drug-susceptible strains do not.

Adenosine Deaminase

Adenosine deaminase is an enzyme produced by macrophages and activated T lymphocytes. Levels of adenosine deaminase have been reported in various studies to be present in increased amounts in several different body fluids infected with *M. tuberculosis.* Clinical value is still not clear.

SCREENING

In the United States, screening is a valuable method for controlling and ultimately eliminating tuberculosis. Screening should be performed only in selected, high-risk populations to identify infected persons who would benefit from therapy to prevent the development of tuberculosis, and to identify persons with active tuberculosis who should be treated to prevent transmission. Table 3 lists high-risk groups of people for whom screening is indicated. Groups not at high risk for tuberculosis should not be routinely screened because of cost and low yield; false-positive reactions may lead to inappropriate preventive treatment.

Persons with or at risk for HIV infection
Close contacts of persons with infectious tuberculosis
Persons with certain medical conditions
Persons who inject drugs
Foreign-born persons from areas where tuberculosis is common
Medically underserved, low-income populations, including high-risk racial and ethnic groups
Residents of long-term care facilities
Locally identified high-prevalence groups (e.g., migrant farm workers or homeless persons)

TABLE 3. *Groups that should be screened with the tuberculosis skin test*

Screening in most instances is carried out by health departments or health care providers affiliated with drug treatment centers, long-term care facilities, correctional institutions, and hospitals. However, all primary health care providers should be aware of the high-risk persons in their practices and should administer skin tests to these patients as part of their routine medical evaluations.

The Mantoux tuberculin skin test is the preferred method of screening for tuberculosis infection. However, to identify tuberculosis in specific settings where the risk of transmission is very high and/or the stay is short (conjugate settings such as homeless shelters, hospitals, and jails), intake screening with chest roentgenograms or sputum smears may be more appropriate. Tuberculin screening in institutional settings provides baseline information on the tuberculin skin test status of clients and staff, identifies candidates for preventive therapy, and detects whether transmission of tuberculosis is occurring within the facility.

Tuberculosis screening is recommended for residents of long-term care facilities. It is also recommended for staff members, who may be exposed to patients with tuberculosis on the job, or who would pose a significant risk to large numbers of susceptible persons if they became infectious with tuberculosis disease (e.g., staff of AIDS wards or child care centers). These people should be screened on entry or beginning of employment and at least yearly thereafter, depending on the risk for transmission in a particular facility. For persons who are screened periodically (e.g., staff of tuberculosis clinics), a two-step Mantoux skin test procedure should be used for initial skin testing.

Two-Step Mantoux Skin Testing

DTH to tuberculin tends to wane with aging. Persons who are given a tuberculin skin test many years after their initial infection with *M. tuberculosis* may have a negative reaction. However, that skin test may boost or recall their DTH response to tuberculin, causing a positive reaction to a subsequent test that may be misinterpreted as a skin test conversion.

A two-step Mantoux skin test should be used for the initial testing of elderly patients and adults who will be retested periodically as follows:

1. If the first test result is negative, give a second test 1 to 3 weeks later.
2. If the second test result is positive, consider that the person is infected with the tubercle bacillus but is not a skin test converter. If the second result is negative, consider the person uninfected with the tubercle bacillus.
3. Any positive reaction to a subsequent test is considered a conversion.

TREATMENT

More than a quarter of a century ago, Dr. Wallace Fox stated that effective chemotherapy and patient cooperation in taking prescribed medications were important factors influencing the success of a tuberculosis treatment program. The passage of time has borne out the accuracy of his observations.

Current principles on which recommendations for treatment are based include (1) the use of multiple drugs to which the tubercle bacilli are sensitive, (2) continuation of treatment for a period of time that is sufficient to control and usually eradicate the disease, and (3) regular ingestion of medications by the patient.

Two-Phase Chemotherapy

Multiple drugs are used to treat primary resistance present at the inception of therapy, or to prevent the emergence of acquired drug resistance. The concept of initiating treatment with multiple drugs is based on the fact that tuberculosis may occur from infection with initially resistant strains of *M. tuberculosis.* In addition, at the initiation of treatment of cavitary pulmonary tuberculosis, a large population ($>10^8$ bacilli) of mycobacteria is present, with the potential for spontaneous emergence of resistant strains. These mutants can be resistant to any of the antituberculosis drugs, but resistance occurs more frequently with some drugs than with others.

It is estimated that the frequency of mutations resistant to INH and streptomycin (SM) in populations of *M. tuberculosis* is approximately 1 in 1 million (1 in 10^6), and for mutations resistant to RIF it is 1 in 100 million bacilli (1 in 10^8). Therefore, mutants resistant to both INH and RIF given at the same time would occur approximately once in a population of 10^{14} organisms. By giving initial chemotherapy with two or more drugs, the likelihood of drug resistant bacilli surviving in the bacterial population

is extremely small.

Drug Treatment

After multiple drug therapy has been started, the second principle of treatment is to ensure that therapy is continued for a sufficient period of time. Prolonged therapy is necessary to eliminate persistent bacilli and prevent relapse of tuberculosis.

Before the introduction of RIF or currently when RIF is not used in a treatment regimen, 18 to 24 months of treatment are required to ensure a cure of tuberculosis. However, using multidrug regimens currently available that contain INH, RIF, and PZA, treatment can be completed in as short a period as 6 months, and trials for even shorter courses of chemotherapy are under way.

Chemotherapy is divided into an initial bactericidal phase, in which INH is the most effective drug, followed by a sterilizing phase, during which RIF and PZA are the most effective drugs. INH has its greatest effect against actively dividing tubercle bacilli, and PZA exhibits its greatest effect on organisms in an acid environment (tubercle bacilli ingested by macrophages). RIF is noted for the speed with which its bactericidal action starts, resulting in the selective killing of organisms that are largely dormant but have occasional short spurts of growth. Completely dormant mycobacteria are not killed by any drugs but may be eliminated by the host immune response.

Studies initiated by the British Medical Research Council and expanded by the U.S. Public Health Service, using 6 months of therapy with INH and RIF supplemented by PZA for the first 2 months, clearly established that short-course treatment regimens are both safe and effective.

Drugs available for the treatment of tuberculosis have been separated into “first-line” (Table 4) and “second-line” (Table 5) agents. The initial regimen for the treatment of tuberculosis consists of four drugs, including INH, RIF, PZA, and either ethambutol (EMB) or SM in communities where INH resistance is >4%. The treatment regimen can be adjusted as soon as drug susceptibility results are known.

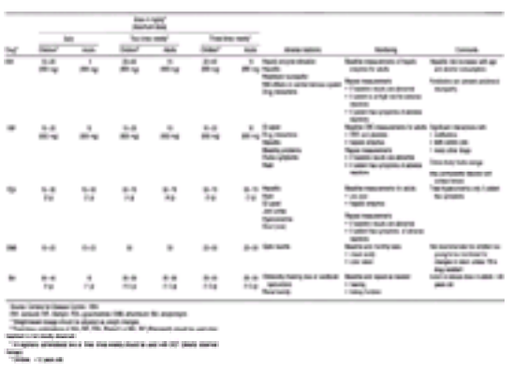

TABLE 4. *First-line drugs for tuberculosis*

TABLE 5. *Second-line drugs for tuberculosis*

In areas where INH resistance is <4%, an initial regimen of INH, RIF, and PZA may be used; alternatively, in very rare instances, a 9-month regimen containing INH and RIF may be used for those who cannot be treated with PZA. EMB or SM should be included in the treatment regimen until the results of drug susceptibility studies are known.

Patient adherence to a prescribed drug regimen is a major determinant of treatment success. The use of bus passes, vouchers, fixed drug combinations of demonstrated bioavailability, and other treatment incentives and enablers enhance patient adherence to a given drug regimen. Recent publications have emphasized the importance of directly observed therapy (DOT) in reducing tuberculosis case rates. DOT is the standard of care in the United States. Whenever possible, all patients should receive DOT. All intermittent regimens should be administered only under direct observation.

CASE 1: TUBERCULOSIS IN AN HIV-NEGATIVE PATIENT WITH SENSITIVE ORGANISMS

A 43-year-old African-American male bookbinder was admitted to the hospital with a productive cough of 3 months' duration, chest pain, fever, night sweats, easy fatigability, and weight loss of 10 lb. He denied having a known tuberculosis contact, had never had a tuberculin skin test, and stated that a findings on a chest roentgenogram taken 2 years previously were normal.

The patient was febrile (102°F), and crackles were heard over the posterior left lung base.

The admission chest x-ray films (Fig. 4) revealed volume loss with associated tracheal deviation and elevation of the left diaphragm, bilateral upper lobe infiltrates, and a large left upper lobe cavity. Laboratory findings included a negative HIV serology, a hemoglobin of 11.3 g/dL, and an erythrocyte sedimentation rate of 59 mm/h; three separate sputum specimens were reported positive on smear for AFB.

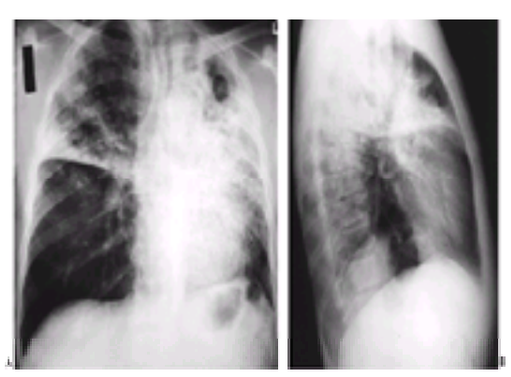

FIG. 4. Admission posteroanterior (**A**) and lateral (**B**) x-ray films of case 1. Note the volume loss and bilateral upper lobe infiltrates with a cavity in the left upper lobe.

The patient was started on daily DOT with a four-drug regimen of 300 mg of INH, 600 mg of RIF, 1500 mg of PZA, and 1200 mg of EMB. He tolerated the regimen well and after 1 week was continued on DOT five times weekly under the supervision of a trained field worker. On weekends he took a fixed-dose combination of INH, RIF, and PZA (Rifater) with EMB. All members of his immediate household (five people) were receiving preventive treatment with INH or therapy for active tuberculosis.

After 8 weeks, *M. tuberculosis* isolated from the patient was reported sensitive to all first-line antituberculosis drugs (INH, RIF, PZA, EMB, and SM). At this point, PZA and EMB were discontinued and he was maintained on twice-weekly oral DOT with 900 mg of INH and 600 mg of RIF for an additional 16 weeks, after which all medications were discontinued. His compliance taking antituberculosis medications approached 100%. On discharge, he noted marked improvement in his symptoms and had regained approximately 25 lb; despite improvement, residual changes persist on his chest roentgenogram (Fig. 5).

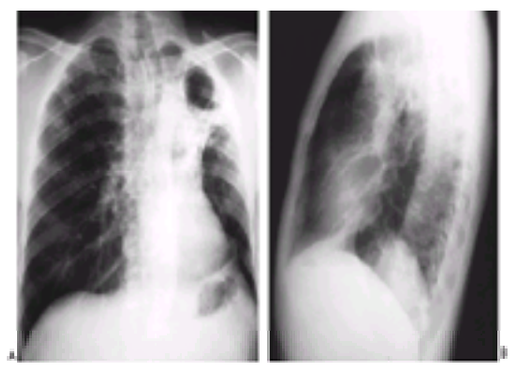

FIG. 5. Posteroanterior (**A**) and lateral (**B**) chest x-ray films of case 1 after the completion of treatment for tuberculosis. Note the clearing of disease in the right lung with residual cavitation and scarring in the left lung with volume loss.

COMMENT: This is a case of recrudescent, drug-sensitive tuberculosis in an HIV-seronegative patient that responded well to treatment. Unfortunately, the tubercle bacilli of this patient were transmitted to two of his children and his spouse, documenting the infectiousness of symptomatic cavitary tuberculosis. Despite appropriate treatment, he has significant residual lung damage.

TREATMENT OF SMEAR-NEGATIVE, CULTURE-NEGATIVE TUBERCULOSIS

Patients with smear- and culture-negative tuberculosis who are from areas where INH resistance is <4% and drug resistance is unlikely should be treated with a 4-month regimen of INH and RIF that is supplemented with PZA for the first 2 months. Patients with smear- and culture-negative tuberculosis who are from areas where INH resistance is ³4% or who have personal risk factors for drug resistance should be treated with a 4-month regimen of 4 drugs including INH, RIF, PZA, and EMB or SM.

TREATMENT OF HIV-SEROPOSITIVE PERSONS

Current recommendations for treatment of tuberculosis in HIV-seropositive patients are the same as those for HIV-seronegative patients, with the caveat that treatment should be prolonged if the response is suboptimal. There have been isolated cases of relapse of tuberculosis in AIDS patients, and when this occurs in AIDS patients with drug-sensitive tuberculosis, malabsorption of medications, new infection with tubercle bacilli, or some other reason for apparent treatment failure should be suspected. We recommend longer treatment and follow-up until clinical studies determine the optimal duration.

TREATMENT OF EXTRAPULMONARY DISEASE

The basic principles that guide the selection and duration of treatment for pulmonary tuberculosis are generally the same as for extrapulmonary tuberculosis, in which 6- to 9-month short-course regimens have proved effective. Some exceptions are miliary tuberculosis, bone and joint tuberculosis, and tuberculous meningitis in infants and children, in whom treatment should be extended for at least 12 months. For diagnostic as well as therapeutic reasons, surgery may be more commonly required in extrapulmonary tuberculosis than in pulmonary tuberculosis. Corticosteroid therapy has also been of benefit in treating some forms of extrapulmonary tuberculosis, and in preventing neurologic problems associated with tuberculous meningitis and cardiac constriction in tuberculous pericarditis.

TREATMENT FAILURE AND RELAPSE

Patients whose sputum remains positive on culture after 4 to 6 months of treatment should be considered treatment failures. Unlike patients undergoing initial treatment, patients requiring retreatment frequently are nonadherent, and their infecting organisms are drug-resistant. Patient motivation to adhere to treatment and selection of effective therapeutic regimens are more difficult to control but extremely important in such a setting. A detailed history, including the duration and frequency of previous treatment and the drugs used, should be obtained, and prior tuberculosis treatment records and chest x-ray films should be reviewed whenever possible.

Most patients who relapse following treatment with short-course chemotherapy have fully sensitive organisms and can be retreated with INH and RIF. However, drug susceptibility testing is of paramount importance when a retreatment program is undertaken. While waiting for results, which are frequently delayed, the original drug regimen may be continued, or new treatment should be started with at least two, but preferably three, drugs to which the patient's organisms have known sensitivity or that the patient has not previously received. *A potentially effective new or previously used single drug should never be added to a failing or failed regimen!* If the susceptibility pattern is known and the addition is highly unlikely to cause resistance, adding a single drug may be considered.

INTERMITTENT TREATMENT

Intermittent therapy is effective and more readily supervised than daily therapy. Several methods of delivering intermittent regimens have been identified and are listed in Table 6. In general, with the exception of the RIF dose, which remains the same, the dose of all the first-line drugs is increased when they are given intermittently.

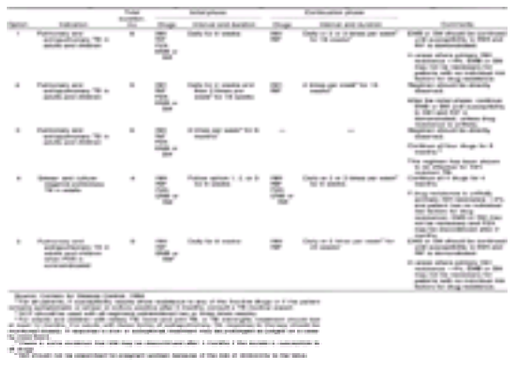

TABLE 6. *Regimen options for treatment*[a]

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

A 6-month regimen of RIF, PZA, and EMB or SM is adequate for treatment of tuberculosis that is known to be only INH-resistant. An acceptable alternative would be to treat with RIF and EMB for a minimum of 12 months. If for any reason RIF cannot be included in a treatment regimen, treatment should be continued for a minimum of 18 months. If resistance to PZA is demonstrated, treatment should be continued for a minimum of 9 months if INH and RIF are included in the regimen. Tuberculosis treatment in the face of resistance to EMB or SM only may not need to be prolonged but may require replacement of these two agents with second-line drugs.

MDRTB (i.e., tuberculosis resistant to at least INH and RIF) may be primary or secondary. Primary resistance is noted particularly in patients who are HIV-positive and have never had antimycobacterial treatment. Secondary resistance occurs in patients who have previously received treatment and whose infecting mycobacteria have acquired resistance to the antituberculosis medications previously given. MDRTB significantly complicates patient management and treatment, and treatment should be individualized based on the results of drug susceptibility tests and the patient's prior medication history.

When treating MDRTB, at least two and preferably three antituberculosis medications to which the organisms are susceptible should be used. Unfortunately, studies are not available that unequivocally establish the effectiveness and duration of various treatment regimens for MDRTB. In general, treatment should be continued with at least two drugs for a minimum of 18 to 24 months following culture conversion. Physicians unfamiliar with treatment of these patients should always seek expert consultation, as these are complicated, perhaps life-threatening situations, often with major significance to public health.

CASE 2: MULTIDRUG-RESISTANT TUBERCULOSIS

A 34-year-old African-American woman came to the hospital with fever and a persistent cough. Four years earlier, she had converted her tuberculin skin test but declined INH preventive treatment. Her chest roentgenogram revealed a left upper lobe pulmonary infiltrate (Fig. 6), and sputum smears were positive for AFB.

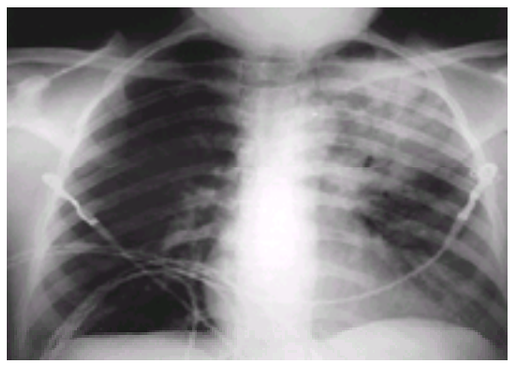

FIG. 6. Posteroanterior chest x-ray film of case 2 reveals a left upper lobe infiltrate.

Treatment with INH, RIF, PZA, and SM was begun while awaiting identification of the AFB and the results of drug susceptibility tests. The patient's symptoms worsened and sputum cultures obtained monthly remained positive at 12 weeks, when the initial sputum studies identified *M. tuberculosis* resistant to INH, RIF, SM, and ethionamide (ETA). Her chest x-ray film taken at that time is seen in Fig. 7.

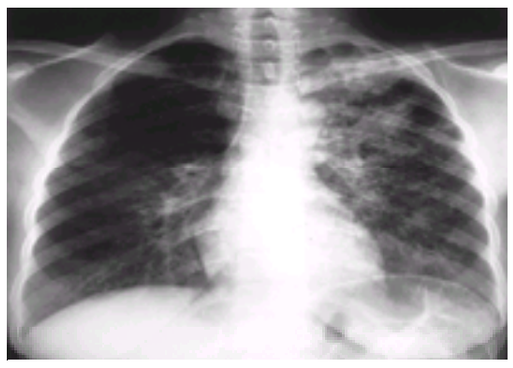

FIG. 7. Posteroanterior chest x-ray film of case 2 shows bilateral infiltrates with worsening of the infiltrate in the left lung.

Directly supervised therapy during the next 9 months with various drug regimens comprising second-line drugs not previously used was not successful. Treatment failure may have been related to side effects of her medications, particularly gastrointestinal intolerance, that often led to discontinuation of one or another of the drugs, thus raising the possibility of monotherapy. Approximately 1 year after starting treatment, the patient remained stable but unimproved, with positive sputum cultures for *M. tuberculosis* on a drug regimen including PZA, EMB, rifabutin (RBT), cycloserine (CS), and capreomycin (CM).

At this point, the patient came to our center, where drug susceptibility tests were repeated and chest roentgenograms were taken. A decision was made to discontinue her treatment regimen and substitute a treatment regimen containing at least three drugs that the patient had not previously received and potentially effective drugs that she had previously taken. This was the approach used pending the results of drug susceptibility studies.

Under direct supervision, the patient was started on the following regimen: kanamycin (KM) (new), para-aminosalicylic acid (PAS) (new), clofazimine (new), RBT (previously received), EMB (previously received), ciprofloxacin (previously received). She tolerated the regimen well after slight modifications were made for gastrointestinal intolerance.

After 12 weeks of therapy with the new regimen, her symptoms improved, sputum smears were negative for AFB, and cultures were negative for *M. tuberculosis.* Drug susceptibility studies revealed resistance to KM, ciprofloxacin, INH, RIF, SM, ETA, and CS. The organism was sensitive to PZA, amikacin, PAS, clofazimine, EMB, and CM.

At this point (12 weeks after starting the new regimen), her treatment regimen was modified. KM and ciprofloxacin were discontinued and replaced with CM and PZA; PAS, RBT, EMB, and clofazimine were continued. Six months after starting this treatment, the patient remained culture-negative for *M. tuberculosis* and CM was discontinued. Eighteen months after initiation of treatment, sputum remained culture-negative and RBT and PZA were discontinued, and 24 months after initiation of treatment and sputum conversion, PAS and EMB were stopped. The patient remains clinically well, her chest x-ray findings are improved (Fig. 8), and she has returned to work full-time.

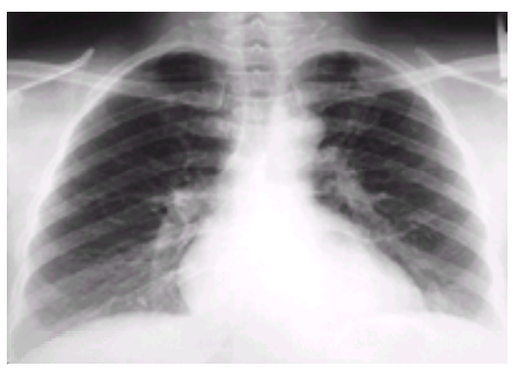

FIG. 8. Posteroanterior chest x-ray film of case 2 reveals residual scarring in the left lung after completion of treatment.

COMMENT: This case illustrates the importance of drug susceptibility tests in the treatment of tuberculosis. The delay in obtaining drug sensitivity information adversely influenced drug selection. It is probable that the drug resistance of the infecting organism was both primary and secondary.

TREATMENT DURING PREGNANCY

Certain precautions must be considered when treating tuberculosis during pregnancy. There is no doubt, however, that untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does any specific treatment.

In general, INH, RIF, EMB, and PAS are drugs that have been used during pregnancy in the United States because they have not been found to have teratogenic effects (Table 7). Although PAS is not associated with teratogenic effects, the frequent associated gastrointestinal side effects preclude its use as a first-line drug either with or without pregnancy.

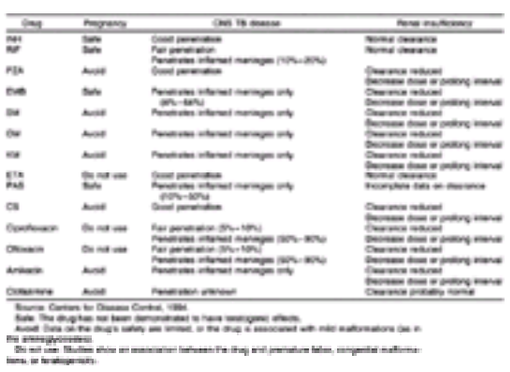

TABLE 7. *Drugs for tuberculosis in special situations*

PZA is approved by international guidelines for routine use during pregnancy; however, in the United States it is not recommended because of insufficient data concerning its teratogenic effects. Therefore, in the United States INH and RIF are the recommended initial treatment regimen. EMB should be included when primary INH resistance in the patient's locale is >4%. If PZA is not included in the initial treatment regimen, a minimum of 9 months of therapy must be given. SM has been demonstrated to have adverse effects on fetal development of the eighth cranial nerve in the third trimester, causing congenital deafness. KM and CM are also aminoglycosides, and all three are not recommended. Because data on the safety of the other second-line drugs and newer antimycobacterial agents, such as the quinolones and macrolides, are limited or suggest toxicity, their use should be avoided if possible during pregnancy.

Breast-feeding should not be discouraged, because the concentrations of drugs in breast milk are not sufficient to cause toxic effects in nursing infants. To prevent peripheral neuropathy, pyridoxine (10 to 50 mg/d) is recommended for pregnant women receiving INH.

TREATMENT OF TUBERCULOSIS IN CHILDREN

Treatment of tuberculosis in infants and children is generally guided by the same basic principles that apply to adults. However, because tuberculosis is more likely to disseminate in infants and younger children (<4 years old), the rapid institution of effective therapy is of the utmost importance. The initial treatment regimens prescribed for the treatment of tuberculosis in adults are also recommended for children (Table 4, Table 5 and Table 6). EMB is less useful in young children because the ocular toxicity that the drug may cause is difficult to monitor. SM or PZA is an acceptable alternative. Because there is less cavitary disease in children, confirmation of the diagnosis on culture is less likely than in adults. When hilar adenopathy or parenchymal infiltrates are present on chest roentgenograms in a child with a positive tuberculin test, the child should be treated as a case of active pulmonary tuberculosis.

Because the results of sputum culture are often negative in children, the results of culture and drug sensitivity studies from the contact case are very helpful in guiding the selection of treatment regimens. When knowledge of drug susceptibility patterns is critical, as in suspected MDRTB, it may be necessary to obtaining early morning gastric aspirates or BAL fluid. Assessing improvement in children depends more on clinical and x-ray findings than on results of sputum cultures, as noted above. Extrapulmonary tuberculosis in children is treated the same as pulmonary tuberculosis, except for tuberculous meningitis, bone and joint tuberculosis, and disseminated tuberculosis, for which a minimum of 12 months of treatment is recommended.

MONITORING TREATMENT

Adults who are treated with INH and RIF should have baseline measurements of hepatic enzyme, bilirubin, and serum creatinine levels, and a complete blood count and platelet count should be obtained. Serum uric acid should be measured if PZA is included in the regimen, and a baseline test of visual acuity and color vision should be obtained in those receiving EMB. Audiometry should be performed in patients receiving SM or other aminoglycosides. The purpose of these tests is to detect abnormalities that may cause complications or require modification of treatment regimens, and to provide a baseline for comparison if abnormalities develop during therapy. Table 4 and Table 5 present guidelines for monitoring during treatment with both first-line and second-line drugs.

All patients should be educated regarding adverse reactions to the medications they are receiving and instructed to stop medications and seek help immediately if these symptoms develop. Patients should be followed by a physician monthly while on treatment and specifically queried regarding symptoms at each visit. Monthly laboratory monitoring for toxicity in adults with normal baseline values is not required. If symptoms develop, laboratory testing should be performed immediately.

PREVENTIVE TREATMENT

INH preventive therapy has been shown to reduce substantially the risk for progression of tuberculous infection to disease. Infected persons at high risk for development of tuberculosis, listed below, should be given INH preventive therapy regardless of their age:

1. Tuberculin-positive reactors (³5 mm) who are HIV-seropositive; included are positive reactors who have risk factors for HIV infection but whose HIV serologic status is unknown. Tuberculin-negative reactors (<5 mm) who are HIV-seropositive and who live in areas with a prevalence of tuberculosis infection of 10% or greater should be given INH preventive therapy regardless of their age.
2. Tuberculin-positive reactors (³5 mm) who are close contacts of infectious tuberculosis cases. Tuberculin-negative (<5 mm) children and adolescents in this category should also be started on INH preventive therapy. The tuberculin skin test should be repeated 12 weeks later; if the result is still negative and contact with the infectious case was interrupted when preventive therapy was started, INH can be discontinued.
3. Tuberculin-positive reactors (³5 mm) who have chest roentgenograms suggestive of old healed tuberculosis and who were inadequately treated or untreated (these individuals can be given INH and RIF for 4 months).
4. Tuberculin-positive persons who have within the past 2 years converted their tuberculin skin test from negative to positive (³10 mm increase if <35 years of age; ³15 mm increase if ³35 years of age).
5. Tuberculin-positive (³10 mm) persons with certain medical conditions that have been reported to increase the risk for tuberculosis, including silicosis, diabetes mellitus, prolonged corticosteroid therapy (>15 mg of prednisone daily for 2 to 3 weeks), other immunosuppressive therapy, some hematologic and reticuloendothelial diseases, injection drug use in a person known to be HIV-seronegative, end-stage renal disease, and conditions associated with weight loss to 10% or more below ideal body weight or chronic undernourishment (head and neck cancer, intestinal bypass surgery or gastrectomy, chronic malabsorption syndromes).

Tuberculin-positive reactors (³10 mm) <35 years of age who remain high-priority candidates for preventive therapy but are at somewhat lower risk for development of

tuberculosis than persons in the above groups should also receive INH preventive treatment; they include the following:

1. Foreign-born persons from regions of the world with a high incidence of tuberculosis, such as Asia, Africa, and Latin America
2. Medically underserved low-income domestic populations, including high-risk ethnic or racial minorities such as blacks, Hispanics, and Asian-Americans
3. Residents of long-term care facilities such as mental institutions, nursing homes, and correctional institutions
4. Other groups, such as migrant farm workers and the homeless that are locally identified as having an increased prevalence of tuberculosis

Tuberculin positive reactors (³15 mm) who are <35 years of age and have no risk factors for tuberculosis should also be considered for INH preventive therapy but should be given a lower priority for preventive treatment than the groups previously discussed.

Because the risk for INH-induced hepatitis outweighs the benefits of preventive therapy, INH is not recommended for tuberculin-positive reactors (³10 mm) who are ³35 years of age and are not at high risk for development of tuberculosis.

To prevent the progression of tuberculous infection to disease, INH is used alone as preventive therapy in a single dose of 5 mg/kg of body weight per day up to 300 mg/d in adults and 10 to 15 mg/kg of body weight per day in children, not to exceed 300 mg/d.

Clinical trials have demonstrated that the greatest reduction (90%) in the risk for development of tuberculosis occurs with daily administration of INH for 12 months. However, 6 months of daily INH preventive therapy also conveys a high degree of protection and reduces the risk for development of tuberculosis by approximately 70%. Administration of daily INH for <6 months has been shown to reduce the level of protection significantly. Administration of INH for >1 year has not been shown to convey additional protection. Therefore, current recommendations are that every effort should be made to ensure continuation of daily INH preventive therapy for at least 6 months. Children should receive therapy for 9 months and individuals with HIV infection for 12 months.

Data on the effectiveness of intermittent INH preventive therapy are limited; however, studies in which INH is given twice weekly during the sterilizing phase of tuberculosis treatment suggest that this would be an effective preventive treatment. For potentially nonadherent treated persons at high risk, supervised intermittent INH preventive therapy has been recommended twice weekly at a dose of 15 mg/kg. Tuberculin-positive adults who have silicosis or abnormalities on chest roentgenograms as noted above with no evidence of current disease should receive 4 months of therapy with INH and RIF, as they are considered to have sputum-negative, active pulmonary tuberculosis. An acceptable alternative is 12 months of INH therapy, provided that infection with INH-resistant organisms is unlikely.

Pregnant women with positive tuberculin skin test results generally should not be started on INH preventive treatment until after delivery. Exceptions are made when recent skin test conversion has occurred or when high-risk medical conditions such as HIV infection exist. Under these circumstances, INH preventive therapy should be given.

No data are currently available that document the clinical efficacy of any drug other than INH for preventive therapy in any setting. Short-course preventive therapy regimens using RIF and PZA for 2 months and RIF alone for 4 months have shown promise in animal models and are being evaluated in humans.

When the source case has INH-resistant organisms or when treatment candidates cannot tolerate INH, preventive treatment with RIF should be considered. The RIF should be given daily in standard doses for at least 6 months in adults and 9 months in children. Guidelines for preventive treatment of individuals who may be infected with INH- and RIF-resistant organisms are based on the likelihood that the infection is recent and the probability that active tuberculosis will develop (i.e., HIV-seropositive patients). If these circumstances are unlikely, then observation of the patient or the administration of standard preventive therapy has been recommended. For patients with an especially high risk for tuberculosis, as in HIV infection or other immunosuppression, preventive therapy with EMB and PZA or PZA and one of the quinolones (ofloxacin or ciprofloxacin) in the usual standard doses should be considered.

Peripheral neuropathy may result from the use of INH but is extremely uncommon at a daily dose of 5 mg/kg of body weight. We give pyridoxine (10 to 50 mg/d) only in the presence of conditions commonly associated with neuropathies, such as diabetes, alcoholism, anemia, malnutrition, seizure disorders, and pregnancy.

Increasing age, chronic liver disease, and alcohol abuse have been associated with an increased incidence of INH-induced hepatitis in patients receiving preventive therapy. Young women, particularly blacks and Hispanics, have been reported to be at increased risk for fatal hepatitis associated with administration of INH. It is recommended that all patients ³35 years of age and younger patients at risk for hepatoxicity have liver function tests (measurements of hepatic transaminase, bilirubin, and alkaline phosphatase) before starting INH preventive therapy. If patients report symptoms of adverse reactions after therapy is begun and hepatic transaminase measurements exceed five times the upper limits of normal, INH should be discontinued. Baseline measurements of liver function parameters are not necessary for persons <35 years of age. Patients should be told what the symptoms of hepatitis are and advised to discontinue INH and report immediately if they occur. Patients should be clinically evaluated monthly while receiving INH preventive therapy.

BCG Vaccination

The bacille Calmette-Guérin (BCG) was developed from an attenuated strain of *M. bovis* in 1919 and serially cultured into several different, variable strains. It is used in many countries as a vaccine to protect against tuberculosis and is the most widely used vaccine in the world. Because the potency of the various strains varies, the protection obtained from the vaccine has been reported from none to 80%. A recently conducted meta-analysis by the Harvard School of Public Health attributes an overall 50% protective effect to the vaccine and a 64% protective effect against tuberculous meningitis. A large number of studies have suggested that it protects infants and young children from the more serious forms of tuberculosis, although its ability to prevent disease in adults is much less clear. Thus, its contribution is epidemiologic control of tuberculosis is not great. (Most cases of tuberculosis in children are sputum-negative and thus not infectious.)

BCG is not generally recommended for use in the United States, where most cases of tuberculosis occur in persons who are already infected with *M. tuberculosis* and would not benefit from BCG. Additionally, the use of BCG vaccination causes tuberculin skin test conversion, thus rendering the tuberculin test, the major indicator of new infection, useless. BCG vaccination of tuberculin-negative infants and children may be warranted when they are at high risk for intense, prolonged exposure to untreated or ineffectively treated cases of infectious tuberculosis, contact with the infectious case cannot be broken, and long-term effective preventive therapy is not possible. BCG is contraindicated in patients who are immunosuppressed.

In the United States, all persons who have a positive tuberculin skin test and who have a history of BCG vaccination should be considered infected with *M. tuberculosis* and evaluated for INH preventive therapy.

INFECTION CONTROL

This section briefly discusses selected public health aspects of tuberculosis control and the importance of coordinating the activities of public health departments and facilities that provide health care for tuberculosis patients. Effective tuberculosis control programs are based on the early detection, isolation, and treatment of infectious tuberculosis patients to reduce the risk for exposure to others. Infection control programs utilize various measures to achieve these goals, including administrative, engineering, and personal respiratory protective measures to prevent the transmission of *M. tuberculosis.*

Administrative Controls

The essential components of administrative infection control consist of detecting infectious tuberculosis cases early, isolating them, and providing rapid, effective therapy to reduce the risk for transmitting the organism to others. This requires a high index of suspicion by health care providers, particularly regarding HIV-infected patients with tuberculosis whose presentation may be unusual. Following diagnosis, all infectious tuberculosis patients should be isolated and started on DOT with an appropriate drug regimen (see above).

All facilities that provide health care to tuberculosis patients should have procedures for reporting cases and for coordinating activities between public health departments and other facilities that are involved in patient care.

Administrative controls should focus principally on reducing the risk of exposing susceptible persons to patients with infectious tuberculosis. Such administrative controls include the following:

1. Developing and implementing effective written policies and protocols to ensure rapid identification, diagnosis, isolation, and treatment of individuals who are likely to have tuberculosis
2. Implementing effective work practices among health care workers within health care facilities
3. Educating, training, and counseling health care workers regarding basic concepts of tuberculosis transmission, pathogenesis, diagnosis, treatment, and infection

control
4. Screening health care workers for tuberculosis infection and disease

The transmission of the tubercle bacillus has long been a recognized risk in health care facilities, and as a result infection control guidelines were developed by the CDC. Unfortunately, a relaxation of infection control practices occurred with time, which led to several outbreaks of tuberculosis.

In the early 1990s, numerous accounts of institutional outbreaks of MDRTB were reported. These outbreaks occurred primarily in HIV-infected persons and were associated with high mortality rates and a rapid progression from diagnosis to death. The outbreaks occurred most often in clinics or wards where HIV-infected patients received care. Not only was patient-to-patient transmission identified, but the spread of infection from patients to health care workers was reported to be common.

Major factors that contributed to these outbreaks included the comingling of highly susceptible immunocompromised patients with infectious tuberculosis patients, delayed recognition and treatment of both drug-sensitive and drug-resistant tuberculosis, delayed initiation and premature discontinuation of isolation, and delayed implementation of existing infection control measures (adequate respiratory protection during cough-induction procedures).

Recently collected data from several of the health care facilities involved in the outbreaks indicates that once implemented, infection control measures significantly limited or entirely stopped the continued transmission of *M. tuberculosis.*

Engineering Controls

Engineering and personal respiratory protective measures used during outbreaks of MDRTB were proved to be important infection control measures for stopping further spread of MDRTB in institutional settings.

In health care facilities, as part of a tuberculosis infection control plan, rooms for isolation and treatment of infectious tuberculosis patients, in addition to facilities for sputum induction and aerosol-generating procedures, should be available.

Ventilation reduces the concentration of droplet nuclei in room air by diluting and removing contaminated air and directing air flow patterns within a room. Two types of general ventilation systems (single-pass and recirculating) are used for dilution and removal of contaminated air. The preferred choice is the single-pass system, in which the air supply (either outside air or clean air from a central reservoir) is passed through a room or area and completely exhausted to the outside.

For optimal air mixing, the air supply source and exhaust should be located at opposite sides of the room, so that clean air flows from areas where health care workers are located across the infectious source (patients) and out through the room exhaust. It is currently recommended that a minimum of six air changes per hour be required for tuberculosis isolation and treatment rooms.

Air normally flows from an area of higher pressure to one of lower (negative) pressure. Negative pressure can be achieved by exhausting air from a room faster than it is being supplied to the room. Thus, the direction of air flow can be controlled. Preferably, the direction of air flow should be from a less contaminated area to a more contaminated area. A minimum pressure difference of 0.001 inch of H_2O is required to create and maintain adequate air flow.

Ideally, potentially infectious tuberculosis patients should be isolated and treated in a negative-pressure room ventilated by a single-pass ventilation system having at least six air changes per hour and exhausted directly to the outside.

As an interim measure, a small exhaust fan placed in a window or an outside wall will exhaust air to the outside and create a negative room pressure, but it will not provide clean air and thus offers suboptimal dilution. Negative room pressure can be checked visually with smoke tubes or by measuring the pressure difference between a room and its surrounding area.

Booths, hoods, and tents (local exhaust ventilation devices) are useful for preventing the introduction of airborne tubercle bacilli into room air by trapping them near their source; this prevents exposure of health care workers in the area. The use of these devices is especially important during sputum induction procedures.

Of the two types of local exhaust ventilation devices (enclosing and exterior) that are available for use, enclosing devices are preferable because they completely enclose the infectious source. Enclosing-type devices should provide adequate air flow to remove at least 99% of airborne tubercle bacilli. All air from booths, hoods, and tents should be exhausted to the outside; however, if it is recirculated, air should be exhausted through a high-efficiency particulate air (HEPA) filter.

HEPA filtration is a method of removing tubercle bacilli from room air that supplements the previously discussed ventilation control measures. HEPA filters have a minimum efficiency of 99.97% for removing particles ³0.3 µm in size from room air. Although their ability to filter tubercle bacilli from room air has not been studied, the droplet nuclei that contain tubercle bacilli are approximately 1 to 5 µm in size. HEPA filtration can be used to remove droplet nuclei from room air before it is exhausted to the outside or recirculated to other areas, in fixed or portable room air filtration units for recirculating air within a room, or, as previously discussed, in the exhaust of ventilation equipment such as booths and hoods.

Ultraviolet germicidal irradiation (UVGI) kills tubercle bacilli under experimental conditions; it has been shown to reduce transmission of other microbes in hospitals and classrooms and has been recommended as an engineering control measure to supplement other infection controls. UVGI probably kills or inactivates airborne tubercle bacilli, but before its role can be unequivocally defined in preventing tuberculosis transmission, further study is required. Germicidal ultraviolet lamps are low-pressure mercury vapor lamps that emit radiant energy at a wavelength of 253.7 nm.

UVGI can be used to inactivate tubercle bacilli from contaminated room air by placing ultraviolet lamps within ventilation ducts that exhaust air before it is recirculated from tuberculosis isolation or treatment rooms or other areas of general use, including waiting rooms, emergency rooms, or patient rooms where air could be contaminated by undiagnosed cases of tuberculosis. The advantage of using UVGI within ventilation ducts is that patients and other persons are protected from its harmful effects.

UVGI is also used to inactivate tubercle bacilli in contaminated upper room air by placing ultraviolet lamps on an upper wall or suspending them from the ceiling. The lamps are constructed to direct the flow of irradiation upward, which minimizes exposure to individuals in the lower part of the room. UVGI of upper room air is used in tuberculosis isolation and treatment rooms, hallways, and patient, waiting, and emergency rooms.

Short-term exposure to UVGI can cause erythema and keratoconjunctivitis, and long-term exposure is associated with an increased risk for squamous and basal cell carcinomas of the skin. Recent studies have reported an increase in HIV replication caused by ultraviolet radiation. However, in places where UVGI has been used properly, there have been no reports of untoward effects.

Personal Respiratory Protection Controls: Particulate Respirators

From a public health perspective, the use of personal respiratory protective equipment is the least efficient and least effective of all infection control methods, because it protects only the user and must fit well to work well. Such equipment is used primarily when it is likely that high concentrations of tubercle bacilli are contaminating room air, as in tuberculosis isolation and treatment rooms during sputum induction and aerosol-generating procedures, or when administrative and engineering controls are inadequate to remove droplet nuclei from room air.

The Occupational Safety and Health Administration (OSHA) standard for respiratory protection requires certification by the National Institute for Occupational Safety and Health (NIOSH) of all respiratory protective devices used in the workplace.

Until recently, the only particulate respirators used for protection against transmission of *M. tuberculosis* that met NIOSH certification criteria were HEPA filter particulate respirators. Recently, NIOSH developed new regulations that are more stringent, under which nine types of particulate respirators are certified. Three different levels of filter efficiency of 95%, 99%, and 99.97% were classified, and three different categories based on the resistance to filter efficiency degradation, labeled *N, R,* and *P,* were outlined. In health care settings, either N, R, or P respirators may be selected.

All nine classes of particulate respirators certified by NIOSH meet or exceed CDC filtration efficiency performance standards. Several of the newer classes of particulate respirators will be less expensive and easier to wear than the HEPA filter respirators previously certified.

The policy of OSHA with respect to particulate respirators currently allows the use of an HEPA filter particulate respirator or any of the nine classes of particulate respirators for protection against *M. tuberculosis.* OSHA requires that all respirators be properly fit-tested. Manufacturers recommend that users of the respirators follow

fit-checking procedures each time the respirator is worn.

Role of the Public Health Department

Tuberculosis is a prime example of the impact that public health policy may have on the diagnosis and treatment of disease. The best trained, most informed clinicians cannot ever hope to have any impact on tuberculosis care and control without dedicated and sustained cooperation from the local public health agency.

Because many tuberculosis patients are beset with a myriad of social problems, a practicing physician cannot treat tuberculosis in isolation. DOT, follow-up of contacts, and investigation of outbreaks are at least three areas in which major interactions are required between the clinician and the public health agency.

In an era of reform of health care delivery strategies, it behooves all treating clinicians not only to forge and sustain relationships with health departments to facilitate a beneficial clinical and public health outcome, but to advocate the proper appreciation and funding of these specialized services.

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CHAPTER

29 Nontuberculous Mycobacterial Pulmonary Disease (NTM)

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BACTERIOLOGY

After the tubercle bacillus (*Mycobacterium tuberculosis*) was identified as a cause of human disease, identification of other mycobacteria affecting various animals, such as livestock, fowl, and marine creatures, followed. Better and more specific bacteriologic techniques allowed microbiologists to separate and identify various mycobacteria pathogenic for humans.

Early on, *Mycobacterium avium,* pathogenic to fowl, was found not to be pathogenic for humans, but subsequently *M. avium* complex (MAC) was described as pathogenic for humans. Seroagglutination has allowed the identification of 28 types of MAC. It is difficult to distinguish *M. avium* from *M. intracellulare* without seroagglutination; Infection/disease by either one is generally referred to as MAC or *Mycobacterium avium-intracellulare* (MAI) disease. *M. avium* includes serotypes 1 through 11 (except 7) and 21; *M. intracellulare* includes serotypes 7, 12 through 20, and 25.

A wider spectrum of mycobacterial lung disease was recognized following the descriptions of *M. fortuitum* in individuals with chronic obstructive lung disease secondary to aspiration, and of *M. kansasii* in individuals without prior lung diseases.

Timpe and Runyon's classification of nontuberculous mycobacteria (NTM) in the 1950s provided a working algorithm; groups were based on pigment production, colony morphology, and growth rates. The schema in Fig. 1 shows temperature growth preferences; the cutaneous mycobacteria grow best at 30°C to 32°C. At 37°C and above, two growth rates are noted: rapidly growing mycobacteria and slowly growing mycobacteria. *M. chelonei* and *M. fortuitum* are rapidly growing organisms, also classified as Runyon group IV. Runyon groups I through III are slowly growing mycobacteria. The organisms included in Runyon group I are photochromogenic mycobacteria; cream-colored colonies grown in the dark turn yellow on exposure to light. Runyon group II organisms are scotochromogens; yellow-colored colonies change to orange in the dark. Runyon group III mycobacteria produce cream-colored colonies that do not change pigment color on exposure to either light or dark. Pigmentation was eventually found to be related to soluble beta carotene found in mycobacteria and controlled by an oxygen-dependent light-activated enzyme. *M. tuberculosis,* MAC, and *Mycobacterium xenopi* belong to Runyon group III and are differentiated by their reaction to niacin (*M. tuberculosis* is niacin-reactive, whereas MAC does not react to niacin). Arylsulfatase activity differentiates MAC from *M. xenopi.*

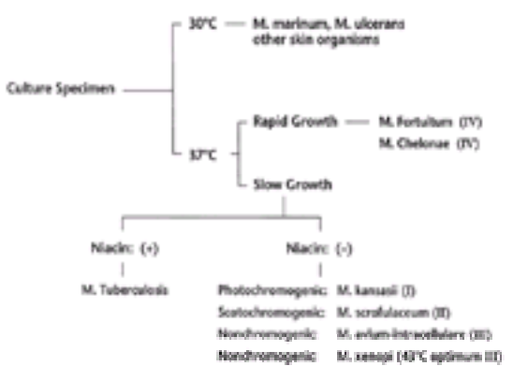

FIG. 1. Temperature growth preferences of NTM (nontubercular myocobacteria).

The tree in Fig. 1 includes some of the important pathogens and highlights the biochemical reaction (niacin) that differentiates *M. tuberculosis* from the rest of the NTM organisms. The laboratory characteristics of pigment production and growth rate have not contributed to clinical diagnostic or therapeutic decision making. The only clinical correlates were that the organisms were easy to treat or difficult to treat (Bailey classification). Standard antimycobacterial drugs had to be juggled to find an appropriate combination.

More modern techniques are currently available to identify specific mycobacteria rapidly. These include thin-layer chromatography, gas-liquid chromatography, high-pressure chromatography, species-specific DNA probes, and the Bactec NAP (*p*-nitro-L-acetylamino-b-hydroxypropiophenone) test. These are sensitive and specific tests that may provide identification of species within 4 hours using isolates from broth or agar.

The geographic distribution of the NTM is wide and variable. Species-specific skin-testing antigens have not been standardized and are not highly specific. Clinically, some patients with NTM disease may have a positive skin test using purified protein derivative-tuberculin (PPD-T), with reactions of <10 mm. The only utility of the tuberculin skin test in the clinical setting in which NTM are suspected is to determine the presence of intact delayed hypersensitivity.

Because many mycobacterial species have similar bacterial wall antigens, cross-reactions are expected and common. However, among a group of patients with cystic fibrosis and documented NTM infection, none responded to PPD-T. All were from the southeastern United States (an endemic area for NTM). The few who reacted to PPD were known to have been exposed to *M. tuberculosis.*

Data from restriction fragment length polymorphic (RFLP) typing, plasmid typing, and serotyping show two populations of *M. avium,* one infecting humans and the other infecting animals. Until more specific skin-testing antigens are available, however, skin-test antigens developed from different geographic locations and strains must be utilized with caution.

The most important NTM pulmonary pathogens are MAC, *M. kansasii, M. fortuitum-M. chelonei,* and *M. xenopi.* Occasional pulmonary pathogens are *M. scrofulaceum, M. szulgai, M. simiae,* and *M. malmoense.* Because NTM disease is not reportable, information regarding its incidence and prevalence is based largely on estimates. In 1979–1980, these diseases were estimated to occur in one third of 32,000 mycobacterial isolates. Of these, 60% were MAC, 19% were *M. fortuitum-M. chelonei,* and 10% *M. kansasii.* The estimated incidence of NTM disease is 1.8 cases per 100,000 in the U.S. population.

SPECIFIC NONTUBERCULOUS MYCOBACTERIAL DISEASES

Mycobacterium avium-intracellulare Complex Disease

MAC occurs in the environment, notably soil, bodies of water, and water systems, and in animals, such as poultry. The epidemiology of disease, however, has no correlation with the distribution of MAC in the environment, as MAC is found throughout the United States, including the western states. Migration of native residents from primary endemic regions to nonedemic areas after primary infection (not unlike what occurs with *M. tuberculosis*) may contribute to the wide distribution. The clinically predominant serovar types are 1, 4, and 8. Serovar 4 is dominant in northern California and the eastern United States, while serovar 8 is dominant in southern California.

MAC is found in geographically warmer environments and in highly acidic brown swamps of the southeastern coastal plains of the United States. MAC isolates from patients differ from environmental isolates. In addition, MAC isolates from patients with acquired immunodeficiency syndrome (AIDS) differ from environmental isolates and those found in patients without AIDS. In San Francisco, for example, environmental contamination does not account for the high prevalence of MAC cultured from AIDS patients.

Next to *M. tuberculosis,* MAC organisms are the most common mycobacteria in human disease. It traditionally occurs in patients with underlying pulmonary conditions, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, old healed tuberculosis, or currently active tuberculosis. Individuals in occupations associated with heavy exposure to dust are also more likely to be infected.

During the last two decades, attention has been directed to other groups of patients infected with pulmonary MAC or other NTM. Infections have been reported in patients with cystic fibrosis and in women without underlying lung diseases. MAC has also been associated with human immunodeficiency virus (HIV) disease, especially in full-blown AIDS; it is a case-defining pathogen in HIV-infected persons. Pulmonary disease and extrapulmonary involvement occur frequently in the latter group when the CD4-cell count falls to <100/µL. MAC infection occurs in from 15%–40% of HIV-infected patients.

Pulmonary MAC disease develops in three major groups of patients (Table 1). There may be overlap of the groups (i.e., patients with AIDS may have underlying COPD).

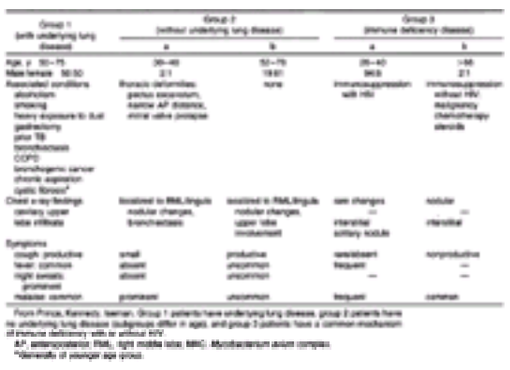

TABLE 1. *Clinical description of groups with pulmonary MAC infection*

In group 1 (patients with underlying lung disease), the most important underlying disease is COPD. It is fairly evenly distributed among men and women, and generally, the patients are older (>50 years). Chronic alcoholism and cigarette smoking are associated conditions in most patients. Eighty-five percent of patients with MAC disease are white. Upper lobe cavitary changes are a common radiologic feature. Symptoms are usually progressive and include productive cough accompanied by fever and night sweats. Malaise is common. When disease is unilateral initially, clinical progression results in bilateral radiologic involvement.

Because of improvements in the care and treatment of patients with cystic fibrosis, they are living longer but are increasingly vulnerable to a multitude of bacterial organisms, including NTM. MAC appears to be the most important NTM pathogen in adult patients with cystic fibrosis. Patients range in age from 18 to 35 years. As with the other chronic lung diseases, diagnosis and treatment may be confounded by the underlying disease. Although some patients with cystic fibrosis have diabetes mellitus resulting from pancreatic insufficiency, they generally do not have immune dysfunction. Their underlying lung disease is obstructive and their nutritional status is often poor. Clinical deterioration resulting from pulmonary bacterial infection is frequent. It is difficult to distinguish colonization from disease, as bacterial infections (*Pseudomonas* and *Staphylococcus aureus*) are particularly common causes of radiologic changes and clinical deterioration. Bacterial contamination (i.e., overgrowth of *Pseudomonas*) has been described, often adding to the clinical dilemma of assessing true disease from colonization.

Patients in group 2 have no underlying lung disease. The majority in this group are women, both young and old. In the younger patients (group 2a), associated thoracic deformities, such as narrowing of the anteroposterior diameter of the chest, pectus excavatum, and scoliosis with mitral valve prolapse, have been observed. These abnormalities may occur singly or in combination. Male patients are less frequently affected. Chest x-ray abnormalities are fairly localized, involving predominantly the right middle lobe or lingula. Nodules and bronchiectasis are usually prominently displayed by computed tomogram (CT) of the chest.

The patients in group 2b are elderly women without underlying lung disease. Radiologic changes in the chest are similarly localized to the right middle lobe and/or lingula. Nodular changes as well as bronchiectasis have been observed. Some patients have upper lobe involvement, most commonly of the anterior segment. Symptoms are similar for both subgroups, including productive cough, malaise, fever, and night sweats. Although the disease course is indolent, it can accelerate and become fatal without treatment.

Group 3 comprises patients with immunosuppression. Group 3a has been fairly recently described as a major part of the AIDS epidemic. The main feature is the presence of infection with HIV. MAC infection has occurred together with *M. tuberculosis* disease; the HIV transmission categories are usually homosexual and bisexual men. Extrapulmonary involvement is a prominent feature in these cases. Disseminated MAC infection is associated with pulmonary involvement in 80% of cases. Patients generally present with gastrointestinal symptoms, fever, weight loss, and fatigue. There are usually no pulmonary symptoms or radiologic evidence of pulmonary disease unless another pulmonary disease is present.

Described radiologic abnormalities have included hilar masses, solitary pulmonary nodules, upper lobe changes, diffuse infiltrates, and cysts, with diffuse infiltrates accounting for 85%. Most of the infiltrates are caused by concomitant *Pneumocystis carinii* pneumonia, tuberculosis, cytomegalovirus infection, and other opportunistic infections.

The patients in group 3b have secondary or acquired immunosuppression resulting from malignancy or blood disorders (leukemia and lymphoma) or from therapeutic interventions, such as chemotherapy and steroid therapy. Immunosuppression is not HIV-related. Pulmonary disease is associated with cavitary infiltrates, as in group 1, and often accompanied by constitutional symptoms, such as productive cough, fever, night sweats, and malaise. The course of the disease is dictated by the underlying malignancy or blood disorder.

Diagnosis of pulmonary MAC infection is made by acid-fast smear of sputum and culture. Diagnostic procedures have included sputum induction, bronchoscopy with lavage, aspiration, and tissue biopsy. Rarely, open lung biopsy is performed. MAC has been identified as a cause of solitary nodules after resection, tissue biopsy, and culture performed as part of the nodule workup. Adenopathy may also require a surgical biopsy (open excision or via mediastinoscopy). CT of the chest has been widely used to detect bronchiectasis and nodules, whereas ventilation-perfusion scan is utilized to determine residual function of a nonresectable lung or the remaining lung.

Treatment

Few clinical trials of the treatment of pulmonary MAC disease were undertaken until 1988, when rifabutin was introduced. Promising responses of combination therapy for MAC infection in AIDS began to be reported. Clearly, monotherapy had no role in MAC disease, because it was associated with rapid relapse, recurrence, and development of bacterial resistance. Treatment results were limited by persistence of MAC and inability to eradicate the infection. The application of this experience using four-drug therapy to treat pulmonary MAC disease has been derived from seemingly successful trials for disseminated MAC infection in AIDS.

Recommendations for the treatment of MAC infection are based on evolving and accumulating experience. Isoniazid and pyrazinamide have no role in the treatment of

MAC disease. Susceptibility testing based on *M. tuberculosis* standards is not applicable in MAC infection. In addition, MAC isolates have a broad range of drug susceptibility, so that a standardized regimen may not be useful. For example, MAC isolates from AIDS patients have shown genetic diversity—that is, individuals may be concurrently infected with more than one strain of MAC. Thus, the choice of antimycobacterial agents should be based on quantitative tests for drug susceptibility.

In the treatment of MAC lung disease, regimens are separated into two treatment phases. During the initial phase, at least four drugs are used: clarithromycin (500 mg orally twice daily), ethambutol (25 mg/kg orally once daily), rifabutin (300 mg orally once daily) or clofazimine (200 mg orally once daily), and streptomycin (10 to 12 mg/kg intramuscularly once daily) or amikacin (12 to 15 mg/kg intravenously three times a week). This regimen is given for 2 months and is followed by a continuation phase. The regimen during the continuation phase is clarithromycin (750 mg orally once daily), ethambutol 15 mg/kg orally once daily), and rifabutin (300 mg orally once daily). Treatment should continue for 24 months or at least 12 to 18 months past the last positive sputum culture. There will likely be instances of relapse. For unresponsive localized disease, surgical resection is often indicated. Commonly used antimycobacterial agents for MAC infection are listed in Table 2, along with some of their adverse effects.

Agents	Dose (adults)	Side effects/toxicity[a]
Azithromycin	250–500 mg PO od	diarrhea, nausea, abdominal pain, elevated liver enzymes
Clarithromycin	500 mg PO bid; 750 mg PO bid	same as above
Ethambutol	25 mg/kg PO od	optic neuritis, soreness, nausea, vomiting
Rifabutin	450 mg PO od	similar to those of rifampin
Ciprofloxacin	500 mg PO bid; 750 mg PO od	GI complaints: nausea, diarrhea
Amikacin	12–15 mg/kg three times a week	cranial nerve (auditory/vestibular)
Rifampin	600 mg PO od; 450 mg for <45 kg	orange discoloration of body secretions, flulike illness, hepatitis, low platelet count
Clofazimine	50–200 mg PO od	skin discoloration, GI complaints
Streptomycin	10–15 mg/kg od	cranial nerve VIII and renal toxicity, low potassium and magnesium levels

Adapted from Masur H, and the Public Health Service Task Force on Prophylaxis and Therapy for MAC. Special report: recommendations on prophylaxis and therapy for disseminated Mycobacterium avium complex disease in patients infected with the human immunodeficiency virus. *N Engl J Med* 329:898–904.

[a] Patients should be monitored for side effects and toxicity.

TABLE 2. *Antimycobacterial agents commonly used in pulmonary MAC infection*

Therapeutic goals may include a reduction in symptoms (fever, night sweats, cough), stabilization or diminution of chest radiologic abnormalities, and improvement in pulmonary function. Adverse reactions should be monitored. An incremental dosing strategy or dose staggering has been recommended for non-HIV patients to reduce discontinuation of treatment because of toxicity and intolerance.

Prophylaxis for MAC Disease in HIV-Infected Persons

Rifabutin was approved by the U.S. Food and Drug Administration for prophylaxis of MAC disease based on two cohort studies. The studies reported significant reduction in bacteremia, clinical symptoms, and laboratory abnormalities when rifabutin was used as a prophylactic agent. The drug was found to be safe, effective, and well tolerated, and adverse effects were infrequent. It improved the quality of life, but there was no overall survival benefit from its use. The current recommendation is 300 mg of rifabutin orally once a day for HIV-infected persons having a CD4-cell count of <100/mm^3, with the treatment to continue for life. In areas with a high prevalence of tuberculosis, the use of rifabutin may preclude the use of rifampin as part of the standard antimycobacterial treatment for tuberculosis because of high levels of cross-resistance. Rifampin-resistant cases of tuberculosis have been documented as a result of rifabutin use for MAC infection. Rifabutin is not recommended as MAC prophylaxis for non-HIV patients.

Drug Interactions

Absorption and efficacy of the drugs may be affected by drug interactions. Clarithromycin interferes with compounds metabolized by the hepatic P_{450} cytochrome system; azithromycin does not interfere with the P_{450} system. Fluoroquinolones are chelated by aluminum compounds, such as antacids. Iron and multivitamin compounds may also reduce their bioavailability. Rifabutin may interact with zidovudine.

M. kansasii Disease

Most isolates of *M. kansasii* have been recovered from tap water in cities known to be endemic for *M. kansasii.* In Texas, where both *M. kansasii* and MAC occur, *M. kansasii* infection and disease were noted to be more frequent in urban dwellers with pulmonary disease, whereas MAC infections were noted in rural dwellers. Almost all strains of *M. kansasii* are susceptible to rifampin and only slightly resistant to isoniazid, ethambutol, and streptomycin. However, rifampin-resistant strains of *M. kansasii* have been reported among patients with and without AIDS. Patients with rifampin-resistant isolates have clinical profiles showing prior use of one or two antimycobacterial drugs and noncompliance. One third of the resistant isolates were from HIV-seropositive patients.

Clinical features of pulmonary *M. kansasii* disease are similar to the features of pulmonary MAC infection. Cavitary lung disease is common; *M. kansasii* disease predominantly occurs in white, middle-aged men; the ratio of men to women affected is 2:1. A greater number of cases are noted among the 30- to 39-year age group in both sexes; upper gastrointestinal disorders, such as prior gastrectomy and peptic ulcer disease, are frequently observed. The majority have previous or existing lung diseases, especially COPD. The presence of underlying lung disease adversely affects the course of treatment and prognosis. Conversely, the absence of prior lung disease portends a more favorable outcome with treatment.

M. kansasii disease in HIV-infected persons has been extensively described. Clinical features include fever, cough, dyspnea, and rarely hemoptysis. Most diagnoses have been made from spontaneously produced sputum specimens, whereas a third have been based on bronchoscopy specimens. Sputum positive for acid-fast bacilli (AFB) is more likely in patients with pulmonary infiltrates, which range from predominantly upper lobe infiltrates to pulmonary cavitary and reticulonodular types. Concomitant organisms such as *P. carinii, S. aureus,* and cytomegalovirus are more frequent when infiltrates are bilateral, diffuse, and interstitial.

Treatment

A better response to treatment with chemotherapy alone has been reported among patients without prior or existing underlying lung disease. Treatment failures are associated with persistence of cavities in association with isoniazid-resistant organisms. Sputum conversion is generally achieved by 92% of drug-treated patients in the first 6 months of treatment. Consideration of surgical resection of cavities was previously suggested if improvement was not observed after 6 months of treatment. The use of rifampin at a higher dose (600 mg to 900 mg) in the initial therapeutic regimen along with ethambutol and isoniazid has changed this situation, with almost a 100% response rate to chemotherapy.

Treatment for *M. kansasii* disease has been suggested using a triple regimen (isoniazid-rifampin-ethambutol). However, in most instances only smears positive for AFB are available at the onset, and the patient is started on four drugs (including pyrazinamide) to treat conventional tuberculosis empirically. When cultures for *M. kansasii* become available, pyrazinamide can be dropped, as it does not have any activity against *M. kansasii.* At the very least, *M. kansasii* is intermediately susceptible to isoniazid; thus, the raised dose of 600 mg is indicated.

A combination regimen of rifampin and ethambutol for 9 months has been used successfully in Great Britain. Relapse rates (8%) were similar to rates in groups who initially started with combinations of four drugs in the first 2 months. A quadruple regimen is recommended for rifampin-resistant cases. Susceptibility testing using the proportion method may not be reliable in predicting resistance, and minimal inhibitory concentrations (MICs) may differ, especially with isoniazid and streptomycin. Clarithromycin is a promising alternative drug.

M. fortuitum-M. chelonei Complex Disease

M. fortuitum complex includes *M. fortuitum* and *M. chelonei* strains. This is the third most prevalent NTM infection in the United States. Men are likely affected by *M. fortuitum,* whereas women are affected by *M. chelonei.* These mycobacteria are generally cutaneous and pulmonary pathogens.

A rapidly growing organism, *M. chelonei* causes a significant number of pulmonary cases. It is not readily isolated from the environment. As is typical in most NTM disease, bronchiectasis, prior mycobacterial disease, and chronic lung disease from aspiration are found in *M. fortuitum-M. chelonei* complex lung disease.

M. fortuitum was first described in cases of chronic aspiration pneumonia and esophageal achalasia. Bilateral patchy infiltrates are frequent; cavitary disease is not common. A slow, progressive course is characteristic, and response to therapy may be observed with amikacin and cefoxitin. Both isolates (*M. fortuitum, M. chelonei*) are often susceptible to amikacin, cefoxitin, and imipenem, and are partially susceptible to doxycycline. Separately, *M. fortuitum* is also susceptible to ciprofloxacin and sulfonamides, whereas *M. chelonei* is susceptible to tobramycin. Some *M. fortuitum-M. chelonei* isolates have been shown to be susceptible to erythromycin. Both *M. fortuitum* and *M. chelonei* are generally resistant to first-line antituberculosis agents.

M. xenopi Disease

Water is a favorite habitat for *M. xenopi;* it is thermophilic, known to grow at 42°C. It has been reported in outbreaks as a pseudoinfection, mostly in nosocomial settings (contaminated bronchoscopy). Pulmonary disease in AIDS has also been reported. The organism is common in Europe, Asia, and Canada. An outbreak of *M. xenopi* pulmonary disease was described in a Veterans Administration hospital in Connecticut. The nosocomial infection was ascribed to the hospital's hot water system. Predisposing factors were pre-existing lung disease and prior hospitalizations in the same environment. Radiographic findings included nodular/mass lesions, thick-walled cavities, and associated apical pleural changes, singly or in combination. Nosocomially acquired infections were indolent and often asymptomatic. In patients not infected with HIV, sporadic cases have been reported to be asymptomatic, with abnormal chest x-ray findings on routine examination. On the other hand, other *M. xenopi* pulmonary disease has been described accompanied by cough, fever, weight loss, and hemoptysis. It has rarely been reported in the United States among AIDS patients presenting with positive findings on sputum smear and negative radiographic findings. It has also been associated with pre-existing conditions such as alcoholism, gastrectomy, cigarette smoking, and lung cancer. Diagnosis has been made from spontaneous sputum, bronchial washing, and resected lung tissue in a workup to exclude neoplasm. The organism is fairly responsive to antituberculosis agents, especially streptomycin, isoniazid, and para-aminosalicylic acid. The initial recommended regimen is isoniazid, rifampin, ethambutol, and pyrazinamide pending cultures for specific mycobacteria.

DIAGNOSIS OF NONTUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE

A general approach to diagnosis in NTM pulmonary disease was recommended in 1990. Some controversies and disagreements still exist, however. A sputum culture positive for NTM must be assessed by determining and defining transient contamination versus true pulmonary disease versus prolonged colonization, usually in the presence of chronic lung disease. Contamination of specimen culture is defined by a single positive culture among several specimen collections and by absence of clinical features or evidence of NTM disease. True pulmonary infection/disease is more difficult to distinguish from NTM colonization. For colonization, bronchial hygiene has been recommended as the first therapeutic step, with or without antimycobacterial drugs. This has been successfully employed with *M. kansasii* and MAC. It has not been studied in other NTM colonization but would be presumed to work as well. In the evaluation of such situations, fungal, neoplastic, and *M. tuberculosis* disease must be considered in the differential diagnosis.

For patients with a radiologic cavitary infiltrate, contamination must be ruled out. Thus, the presence of mycobacteria must be confirmed in two or more sputum or other respiratory specimens on smear and/or by a moderate or heavy growth on culture. Other reasonable diagnoses must have been excluded.

For patients with radiologic noncavitary infiltrate, the criteria are as follows: (1) Two or more sputum or other respiratory specimens (bronchial washings, endotracheal aspirates) must show a positive stain for AFB and/or moderate to heavy growth on culture; (2) after bronchial hygiene has been attempted with or without 2 weeks of antimycobacterial therapy and the NTM does not clear on smear, disease may be presumed when (3) other causes for the infiltrate have been ruled out.

If a sputum evaluation is nondiagnostic in the presence of either a cavitary or noncavitary infiltrate and other diagnoses cannot be excluded, an invasive procedure such as lung biopsy is recommended. True disease is confirmed by the presence of changes consistent with mycobacterial histopathology (i.e., granulomatous inflammation and/or a positive tissue stain for AFB). When two or more sputum specimens are positive for NTM in low numbers and accompanied by the histologic changes described, the diagnosis is presumptive. Clinically, a symptomatic patient with a single culture positive for NTM and a noncavitary infiltrate may require empiric therapy.

Solitary Nodules in Nontuberculous Mycobacterial Infection

Sixty percent of asymptomatic solitary pulmonary nodules are caused by MAC. This entity is generally discovered during routine chest examination. Excellent outcome is observed following resectional surgery in cases treated preoperatively with a standard antituberculosis regimen (two drugs) for positive AFB smears and compatible histology before culture reports become available. There are generally no postoperative complications or dissemination of infection.

Endobronchial Nontuberculous Mycobacterial Infection

Endobronchial mycobacterial disease is infrequently reported, because the ready availability of sputum for diagnosis in most cases of NTM disease precludes bronchoscopy. A few reports have noted that patients having mycobacterial disease may present with normal lungs and a mediastinal mass mimicking malignancy, seen with MAC, *M. kansasii,* and rarely *M. fortuitum.* In the reports, bronchoscopic findings have included ulcerating mass lesion and submucosal masses obstructing bronchial orifices, with resulting segment collapse.

SURGICAL CONSIDERATIONS

The outcome of surgical resection for NTM pulmonary disease is poorer than that of similar resection for multidrug-resistant *M. tuberculosis* pulmonary disease. Complication rates are high, especially in patients with previous chest irradiation or pulmonary resection, perioperative positive sputum cultures, and multimicrobial lung infection. Bronchopleural fistulas, prolonged air leak, and space problems may be frequent, although the use of muscle flaps has reduced these complications. Consideration of early resection for localized disease is still recommended in NTM. Preoperative treatment for at least 3 months and continuation of drug therapy postoperatively are also recommended.

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CHAPTER

30 Embolic Infections of the Lungs and Lipoid Pneumonia

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EMBOLIC INFECTIONS

Embolic infections may result from secondarily infected bland infarcts or from septic emboli. Pulmonary infarction usually arises from thrombotic emboli situated in the deep venous system of the lower extremities (Chapter 66). Secondary infection of the infarcted lung occurs most often as a result of invasion by way of the airway but occasionally via the bloodstream. Autopsy studies indicate that the incidence of secondary infection is between 4.0% and 5.0%, but actual incidence is probably lower, because infection results in a higher case fatality rate. Predisposing factors are cardiac decompensation and oropharyngeal sepsis. Empyema may be the presenting feature.

The diagnosis may be suspected by persistent fever and leukocytosis and the production of purulent or fetid sputum. Chest radiography confirms the presence of an abscess in the previously infarcted area, with or without pleural fluid. Bacteriologic diagnosis is made by the examination of sputum, occasionally from positive blood cultures, and from examination of pleural fluid if it is present. Oropharyngeal anaerobic bacteria are commonly involved, as are *Staphylococcus aureus* and gram-negative bacilli. In the differential diagnosis, cavity formation caused by ischemic necrosis in the center of large infarcts resulting from inadequate bronchial arterial collateral circulation should be considered.

Septic emboli of the lungs most commonly arise in the right side of the heart (endocarditis) or in the peripheral veins, where the underlying process is septic thrombophlebitis. Other, less common sites of origin include the head and neck (postanginal sepsis, mastoiditis, dental infections), the pelvic veins of women post partum (septic pelvic thrombophlebitis), and the central veins when catheters are placed therein for prolonged administration of therapeutic biologic products. The latter site has become more important as the numbers of patients with acquired immunodeficiency syndrome (AIDS) or advanced cancer who require total parenteral nutrition has increased. Similar embolization may accompany suppurative thrombophlebitis of the internal jugular vein from deep infections of the pharynx and tonsils, known as *postanginal sepsis* or *Lemierre's syndrome.*

The presenting clinical picture usually is that of the underlying disease, although occasionally the primary manifestations are related to the lungs. The pulmonary signs are pleuritic pain, cough, and eventually purulent sputum. The radiographic findings have been well characterized. There may be areas of consolidation with subsequent suppuration and necrosis, especially in *S. aureus* infection (Fig. 1). More often, small, localized infiltrates are scattered through both lungs that rapidly break down to form thin-walled cavities (Fig. 2). On occasion, necrosis causes a piece of lung tissue to be sequestered in the centers of such nodules, with the development of an intracavitary loose body simulating a “target.” Computed tomography (CT) is useful in diagnosis. Typical CT appearances include multiple peripheral nodules, a feeding vessel sign, cavitation, wedge-shaped lesions abutting the pleurae, and air bronchograms within the nodules.

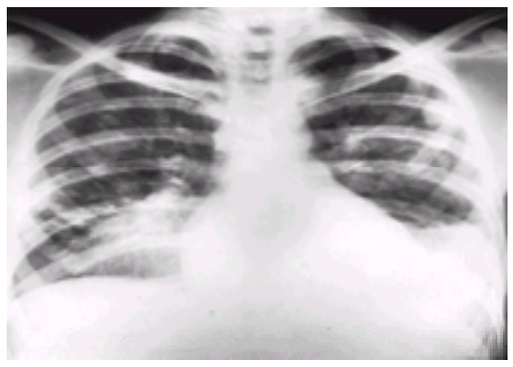

FIG. 1. Embolic lesions of lung associated with submandibular *S. aureus* infection in a 30-year-old man.

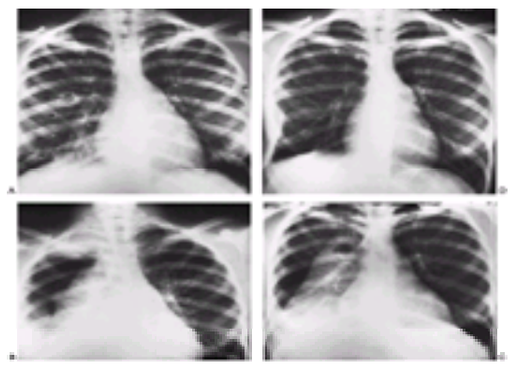

FIG. 2. Serial chest roentgenograms taken during a 6-month period in an 18-year-old girl with pelvic inflammatory disease demonstrate multiple metastatic lung abscesses caused by *Bacteroides* and microaerophilic streptococci (**A**) and paravertebral empyema (**B**) with gas formation (**C**), which eventually resolved following drainage (**D**). Note multiple abscesses (*arrows,* A.)

In Lemierre's syndrome, the common etiologic agent is an anaerobic organism, especially *Fusobacterium.* When pelvic veins are infected, the agent is generally an anaerobe of the *Bacteroides* group. *S. aureus* is the usual culprit from other sites. Treatment should be directed at the underlying condition and may include surgical drainage, removal of infected catheters, and administration of appropriate antibiotics. Progression of the lung disease to empyema requires repeated aspiration, tube drainage, or thoracotomy.

LIPOID PNEUMONIA

The inflammatory reaction associated with the presence of oil or fat in the alveoli is known as *lipoid pneumonia.* The lipid material may originate in the lung itself, or it may be aspirated or inhaled into the lung.

Endogenous Lipoid Pneumonia

In endogenous lipoid pneumonia, the lipid material consists of cholesterol and its esters, released during the breakdown of cell walls in atelectatic pulmonary tissue distal to an obstructed airway. Endogenous lipoid pneumonia may also be seen in association with long-standing tuberculosis, chronic pulmonary abscesses, or bronchiectasis. The usual cause of obstruction in the airway is tumor. In primary or idiopathic endogenous lipoid pneumonia, there is no underlying condition to explain the process. In children, coexisting endogenous lipoid pneumonia and pulmonary alveolar proteinosis have been reported as complicating otherwise benign pulmonary disorders.

The clinical presentation is that of the underlying bronchogenic tumor or chronic infection. Fever, chills, productive cough, and pleuritic chest pain are common. No predisposing conditions that favor aspiration are present, nor is there any history of ingestion of oily substances. The chest radiograph shows a segmental or lobar consolidation with many variations, depending on the underlying condition (Fig. 3). Neither expectorated sputum nor bronchial washings contain lipid-laden macrophages. Only after open lung biopsy or lobectomy is the diagnosis established. The lung is golden-yellow in appearance, and the bronchial lymph nodes often are enlarged. Under the microscope, a dense infiltrate of foamy macrophages containing homogeneously distributed vacuoles of fat can be seen (Fig. 4). The lipid material may form the cleft-like crystals of cholesterol after extrusion into the parenchyma.

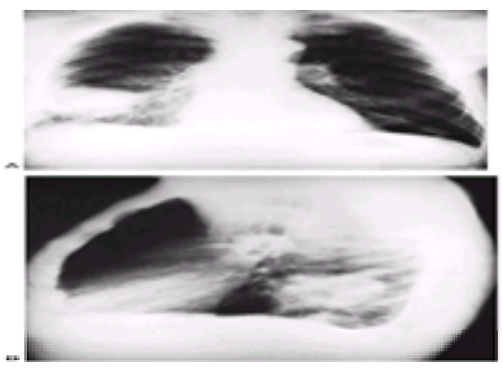

FIG. 3. Posteroanterior (**A**) and lateral (**B**) chest roentgenograms showing a well-circumscribed homogeneous infiltrate in a patient with endogenous lipoid pneumonia. (Courtesy of Dr. Robert Pugatch.)

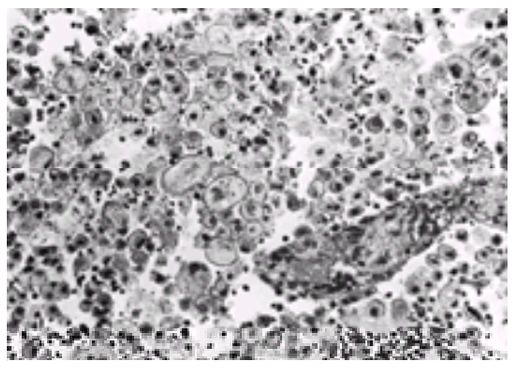

FIG. 4. Microscopic section of lobectomy specimen obtained from patient whose roentgenograms are shown in Fig. 3. Foamy macrophages are consistent with cholesterol pneumonia. (Courtesy of Dr. Y. Jung Legg.)

Exogenous Lipoid Pneumonia

Exogenous lipoid pneumonia is an inflammatory reaction to the aspiration or inhalation of oil or fat. The disease is seen mainly in children, elderly debilitated adults, or individuals with underlying conditions predisposing to aspiration (e.g., altered consciousness, difficulties in swallowing resulting from neurologic disease, or disorders of esophageal motility). There is usually a history of prolonged use of mineral oil in laxatives or nose drops. Undoubtedly, exogenous lipoid pneumonia now is less frequent than in the 1930s, when it was seen during almost 9% of autopsies in children and 1.2% in adults. Retrospective studies since the 1950s, nevertheless, indicate that the disease persists. A survey of 389 chronically ill patients showed that 58 (15%) had exogenous lipoid pneumonia, and 87% of them admitted to the ingestion of mineral oil or oil-containing medication or the use of oily nose drops.

It is reasonable to postulate that the oil reaches the lungs because of an incompetent lower esophageal sphincter and aspiration from the esophagus during the night. Radiopaque oily material instilled into the nose of healthy people during sleep often may be detected in chest radiographs the next morning. When instilled intratracheally, oil fails to provoke two important protective responses of the airway: glottic closure and coughing. In addition, it overcomes another defense mechanism, mucociliary transport. Although mineral oil does not affect ciliary beating, it markedly impairs the movement of the mucous blanket by altering the physical properties of the secretions.

The nature of the oil reaching the alveoli determines the pathologic response. Simple vegetable oils provoke little response and may be cleared from the lung largely by expectoration. Animal oils cause inflammation involving mononuclear and giant cells, proliferation of connective tissue, and variable necrosis. Mineral oil is rapidly emulsified and elicits a brisk outpouring of alveolar macrophages, which ingest oil globules. Later, a foreign-body granulomatous reaction is seen, and with time, a proliferative fibrotic reaction develops. Although most of the oil remains within alveoli, some droplets and lipid-laden macrophages may travel via lymphatic vessels to regional bronchial lymph nodes.

The clinical presentation may be one of chronic cough, wheezing, dyspnea, and low-grade fever. About half of the patients have no symptoms, their disease being evident only because of abnormal findings on a chest radiograph taken for other reasons (Fig. 5). In early disease, the acinar location of oil causes a homogeneous dense consolidation, often with air bronchograms and a “spun glass” appearance. A pattern of reticular markings can develop as emulsified oil enters the interstitium, and Kerley B lines may be visible. Fibrosis may result in nodules or masses. CT may be useful in detecting areas of consolidation with low attenuation values typical of fat. Although early reports of magnetic resonance imaging (MRI) in lipoid pneumonia indicated that the high signal intensity observed on T_1-weighted images (equal to subcutaneous fat) were indistinguishable from findings of hemorrhagic infiltrates, recent studies suggest that the use of chemical-shift MRI can differentiate these two conditions.

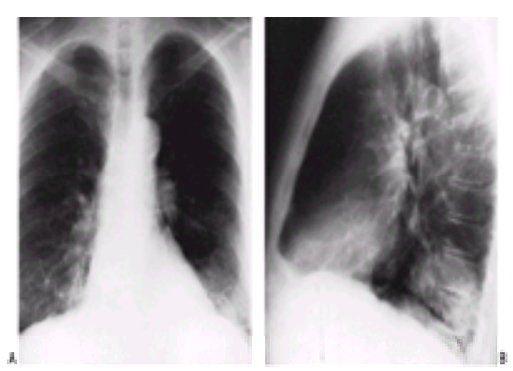

FIG. 5. Posteroanterior (**A**) and lateral (**B**) chest roentgenograms demonstrating a well-circumscribed homogeneous retrocardiac infiltrate in the left lower lobe. The patient was asymptomatic and initially denied taking any medicines. Repeated questioning revealed daily ingestion of mineral oil using a gulping technique. Results of cytology, stain for acid-fast bacilli, and Sudan stain for fat in specimens of expectorated sputum were negative.

The diagnosis may be confirmed by the finding of macrophages containing stainable fat in the sputum, bronchial washings, or bronchoalveolar lavage (BAL) fluid (Fig. 6). BAL fluid may be grossly oily. Transbronchial or open lung biopsy may be necessary for cases in which the diagnosis cannot otherwise be established. Stains for oil in tissue must be performed on frozen sections, because routine preparation for paraffin-embedded samples removes the oil.

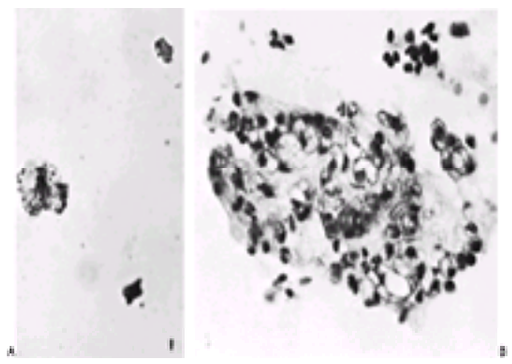

FIG. 6. Bronchial washings from patient whose roentgenograms are shown in Fig. 5. **A:** Hematoxylin and eosin stain shows typical clear areas of lipid-laden macrophages. **B:** Sudan black stain reveals oil. In this setting, such findings are considered diagnostic of exogenous lipoid pneumonia. (Courtesy of Dr. J. Merriam.)

A careful study of BAL fluid from seven patients with mineral oil pneumonia was recently reported. Increased numbers of polymorphonuclear leukocytes, eosinophils, and lymphocytes were indicative of a cell-mediated immune response; the authors postulated that this response accounted for the later appearance of interstitial fibrosis. The alveolar macrophages contained large vacuoles in which liquid paraffin could be identified by thin-layer chromatography and infrared spectroscopy.

Secondary infection may be demonstrable in and around areas of lipoid pneumonia. Especially important is infection with rapidly growing mycobacteria, as discussed in Chapter 29.

The most important aspect of treatment is immediate cessation of use of the oily material. Underlying conditions, such as swallowing dysfunction and disorders of esophageal motility, should be corrected whenever possible. Mycobacterial infection should be treated with appropriate drugs (Chapter 29). Repeated BAL with physical removal of oily material may be helpful in early cases, at least theoretically. Resection may be beneficial for selected patients who have circumscribed areas of disease.

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CHAPTER

31 Aspiration Pneumonia, Lipoid Pneumonia, and Lung Abscess

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ASPIRATION PNEUMONIA

Pathogenic organisms can invade and infect the lung through four pathways: aspiration, inhalation, hematogenous seeding, and contiguous spread. Aspiration of pathogens from a previously colonized oropharynx is the primary pathway by which organisms gain entrance to the lungs, and thus in a broad sense, most pneumonias are aspiration-related. However, when the term *aspiration pneumonia* is used, it is meant to refer to the development of a radiographic infiltrate in the setting of either a witnessed episode of gross aspiration or risk factors for aspiration.

Aspiration pneumonia, like other respiratory tract infections, usually occurs in patients with underlying disease. Although normal adults commonly aspirate while sleeping without any obvious health effects, pneumonia can develop after episodes of aspiration in patients with certain underlying diseases that predispose to host defense impairment. Other factors that modify the risk for pneumonia after aspiration, besides host factors, include certain characteristics of the aspirated material. The pH, tonicity, and volume of the aspirate in addition to the frequency of aspiration all contribute to the development of pneumonia.

Not all infiltrates that follow aspiration represent an infectious process. In some patients, depending on the type of material aspirated, a noninfectious inflammatory response develops that results in pulmonary leukocyte sequestration. Most of these noninfectious infiltrates resolve, but 25%–50% progress to infectious pneumonia or fulminant acute lung injury. In a study by Croghan and colleagues of patients in a nursing home who were evaluated for aspiration with videofluoroscopy, pneumonia developed in 50% of patients with documented aspiration during a 12-month period and in 12.5% of patients without aspiration. In that study, the volume of the aspirate was directly related to the risk for pneumonia; pneumonia developed in 43% of patients with mild aspiration (of thin liquids), and in 67% of patients with severe aspiration (of material of all consistencies at almost every swallow). In a study by Bynum and Pierce, 50 patients with significant aspiration were evaluated. Rapid clearing of infiltrates was noted in 62%, and adult respiratory distress syndrome (ARDS) developed in 12%. Infectious pneumonia developed in the remaining 26% of patients, often after initial improvement.

Risk Factors

Risk factors for aspiration pneumonia are numerous and complex. One general way of categorizing these risks is according to whether they are host factors or characteristics of the aspirated material. Host factors lead to impaired host defenses and/or increased exposure to bacteria because of an increased risk for aspiration. Usually, it is the combination of disease-related immune impairments and exposure to large numbers of aspirated bacteria that leads to pneumonia.

Host Factors

Host factors that predispose to aspiration pneumonia are numerous (Table 1); they either impair host defenses or enhance the risk for aspiration. A number of conditions, such as diabetes mellitus, congestive heart failure, malnutrition, chronic obstructive lung disease, renal failure, and malignancy, can impair host defenses. Diabetes is associated with neutrophil dysfunction, including diminished chemotaxis and impairment of phagocytosis. In patients with congestive heart failure, clearance of pneumococci and staphylococci from the respiratory tract can be impaired as a result of pulmonary edema. If liver disease is complicated by cirrhosis, atelectasis from pleural effusions and/or ascites can result in stagnation of secretions. Cirrhosis is also associated with diminished leukocyte chemotaxis in response to inflammation, depressed levels of complement, and defects in cellular immunity. Renal failure can increase the rate of colonization of the oropharyx by gram-negative bacteria and *Staphylococcus aureus* and can lead to complement deficiency, impaired cellular immunity, and, in animal models, decreased clearance of staphylococci and *Pseudomonas aeruginosa* along with an increase in the binding capacity of buccal cells for gram-negative bacteria. Neoplastic disease can affect host defenses either directly or as a consequence of therapy. For example, neutropenia, endobronchial obstruction, and impaired cough reflex are common in cancer patients and can all predispose to the development of pneumonia.

Host risk factors	Aspirate risk factors
Underlying serious illness	Fluid pH ≤ 2.5
Altered sensorium	Large particles
Stroke	Large volume (1 mL/kg)
Dysphagia	Hypertonic fluid
Gastroesophageal reflux	Bacterial contamination
Postgastrectomy	
Xerostomia	
Feeding tube	
Periodontal disease	

TABLE 1. *Aspiration pneumonia*

Host factors that predispose to aspiration as the result of neurologic, mechanical, and/or contractile dysfunction of the esophagus and upper airway are listed in Table 2. They include stroke, dysphagia, gastroesophageal reflux, altered sensorium, placement of a feeding tube, and the postgastrectomy state. Once material has gained access to the airways, the clinical response depends on the characteristics of the aspirate. If the aspirate is small in volume but highly contaminated with bacteria, then host defenses may be overwhelmed and pneumonia can result. If the aspirate is large in volume but relatively less contaminated, then pneumonia will result only if the aspirated organisms are highly virulent or the host defenses are severely abnormal. Most episodes of aspiration involve oropharyngeal flora, which can achieve extremely high concentrations in the presence of periodontal disease. Whereas normal saliva contains 10^8 organisms/mL, saliva from a patient with gingivitis may contain 10^{11} organisms/mL. In periodontal disease, anaerobes predominate among the oral flora.

Neurologic	Mechanical	Contractile
Unconsciousness	Obesity	Gastroesophageal reflux
Laryngeal nerve damage	Head and neck surgery	Diabetic gastropathy
Advanced age	Bowel obstruction	Critical illness
Acute stroke	Abdominal surgery	Trendelenburg position
Pseudobulbar palsy	Enteral feeding	Protracted vomiting
Seizures	Pregnancy	
Parkinson's disease	Endotracheal intubation	
General anesthesia	Tracheostomy	
Insulin-induced hypoglycemia		
Alcoholism		
Drug abuse		
Cardiac arrest		
Metabolic encephalopathy		

TABLE 2. *Conditions that increase the risk for aspiration*

Xerostomia has recently been shown to predispose to aspiration pneumonia, probably reflecting the fact that normal saliva flushes the oral cavity and maintains a bacterial level of $<7 \times 10^8$ organisms per milliliter. With xerostomia, the normal salivary flow rate is diminished and patients are at risk for gingivitis, and these two factors can result in bacterial counts that are higher than normal. When a patient with xerostomia aspirates, the lower respiratory tract is exposed to larger numbers of bacteria than normal, and aspiration pneumonia can result.

When aspiration develops in the hospitalized patient, many of the same host risk factors prevail. However, for patients in an intensive care unit, particular issues to consider in evaluating aspiration risk include patient position, site of enteral feeding (stomach or small bowel), volume of gastric contents, and size of any feeding tube that is used. Studies have suggested a reduced risk for aspirating gastric contents in patients who are maintained in a semi-erect position, in those whose feeding tubes are placed in the small bowel, and in those with small-bore feeding tubes.

Characteristics of the Aspirate

The characteristics of aspirated material play an important role in the pathogenesis of pneumonia. As only 25%–50% of all cases of aspiration progress to pneumonia, infection is particularly likely if the patient aspirates contaminated material. Pneumonia may also develop in patients who aspirate noninfectious material as a result of the lung injury caused by certain types of material.

Aspiration of very toxic, irritant material with high concentrations of hydrogen ion (pH ≤2.5) results in a chemical pneumonitis. This initial type of lung injury is typically noninfectious and characterized by a predominance of neutrophils. The magnitude of lung injury is directly related to the volume and hydrogen ion concentration of the aspirated material. In animal models of aspiration, acid pneumonitis does not occur unless the pH is <2.5. The resulting damage renders the mucosal barrier of the lower respiratory tract incompetent and places the patient at risk for infectious pneumonia as new sites for bacterial binding are created.

Large-volume and large-particle aspirates predispose to pneumonia by a different mechanism. A number of studies have shown that the majority of large-volume and large-particle aspirates are composed of vegetable matter, which can mechanically obstruct the lower airways and cause atelectasis, stagnation of secretions, and thus an increased risk for infection. In addition, aspirates containing particulate matter can be contaminated by bacteria, as oral secretions are often heavily colonized by potentially pathogenic organisms. In hospitalized patients, the stomach can harbor large numbers of enteric gram-negative bacteria if the gastric pH is >3.5 to 4.0. In patients in the intensive care unit, the risk for development of pneumonia is great when morning gastric pH is high (>3.5). Gastric pH may be elevated by enteral feeding, antacids, or H_2 antagonists. The role of prophylaxis for intestinal bleeding in the pathogenesis of pneumonia is uncertain, with continuing controversy about the role of the stomach in causing pneumonia. In addition, H_2 antagonists have not uniformly led to an increased risk for pneumonia in all studies, and their impact must be considered in relation to gastric volume, patient position, and site of enteral feeding.

Classification of Aspiration Syndromes

The aspiration of material into the tracheobronchial tree can result in a number of clinical consequences, ranging from no evident reaction to respiratory failure, ARDS, and/or death. Three different types of aspiration syndromes can result, depending on the type of material entering the tracheobronchial tree. These syndromes, which are not mutually exclusive and can occur in combination, include the irritant-toxic type, the inert-nontoxic type, and the infectious type.

The irritant-toxic syndrome is caused by aspiration of acidic liquids (pH ≤2.5) and/or fine particulate material; it results in acute pneumonitis or, if severe enough, ARDS. The inert-nontoxic syndrome is caused by aspiration of large particulate matter and/or large volumes of fluid; the clinical response ranges from chronic respiratory symptoms (e.g., cough and wheezing) to atelectasis or, if massive enough, sudden death. Infectious aspiration syndromes result from the entry of potentially pathogenic organisms into the lower airways. Although pneumonia is part of the infectious aspiration syndrome, other infectious syndromes can result, including lung abscess, necrotizing pneumonia, and empyema.

As community-acquired aspiration pneumonia usually involves anaerobic bacteria, aspiration pneumonia should be viewed as part of a continuum that can progress to cavitation (lung abscess) or even development of empyema. If aspiration pneumonia is not treated, necrotizing abscess formation follows in 8 to 14 days, usually in a peripheral location, and is characterized by the expectoration of putrid sputum. When anaerobic lung infection occurs, the pleura is commonly involved, being affected alone or in combination with parenchymal tissue in up to half of all patients.

Mendelson's syndrome (acid pneumonitis) is an example of irritant-toxic lung injury; it usually follows a witnessed episode of aspiration of acidic gastric fluid. Initially, an asthma-like reaction occurs, but within 2 hours a patient may exhibit dyspnea, cough with nonpurulent sputum, bronchospasm, bilateral lower lobe infiltrates, hypoxemia, and decreased lung compliance. In Mendelson's original description of this syndrome, no deaths were documented, although subsequent investigators have reported mortality rates as high as 70%, with some patients progressing to ARDS.

Pathogenesis

Aspiration-induced lung injury is believed to be biphasic, with the volume and pH of the material dictating the severity of the response. The first phase of injury is characterized by an acute localized response to the physical effects of the material aspirated, which, in the case of acid-induced lung injury, is a consequence of the chemical burn. This local response is immediate and limited to the areas of direct contact with the acid; the amount of resulting injury is directly related to the acidity and volume of the aspirated material.

The first-phase response results in local inflammation; this triggers a second phase characterized by a generalized neutrophilic infiltration, occurring within 2 to 6 hrs after aspiration. The initial response, although local in nature, causes cell injury and death secondary to the physical insult of the aspirated material. Pathologically, peribronchial hemorrhage, bronchial epithelial cell death, and pulmonary edema can be seen. This in turn can lead to the release of multiple inflammatory cytokines and proteases. Once released, these inflammatory substances set off a cascade of responses that result in microvascular permeability defects, pulmonary leukocyte sequestration, fibrinous alveolar exudation, tissue hypoxia, and hyaline membrane formation, all of which characterize the acute lung injury.

Neutrophils are thought to be the cells primarily responsible for the second-phase response to injury, and several inflammatory mediators have been identified as potential neutrophil chemoattractant agents. In one animal model, acid-induced lung injury was mediated by a mechanism dependent on interleukin-8 (IL-8). IL-8, a potent chemoattractant for neutrophils, also primes neutrophils for activation and upregulates neutrophil adhesion molecules on endothelial cells. Acid-induced abnormalities of oxygenation and enhanced amounts of extravascular lung water did not develop in animals given anti-IL-8 antibodies, either as pretreatment or 1 hr after acid aspiration.

Aspiration-induced neutrophil sequestration in the pulmonary vasculature can lead to lung injury in several ways. In one study, the complement system was shown to play a role; animals pretreated with a complement-receptor inhibitor had reduced lung edema, decreased alveolar protein accumulation, and improved tissue oxygenation after acid aspiration when compared with untreated animals. There was no effect of complement inhibition on pulmonary leukocyte sequestration, possibly indicating that neutrophils activate the complement system and cause lung injury via this mechanism. Another possible mechanism of lung injury in these patients is the release of high levels of neutrophil-derived serine proteases, which can overcome the normal antiprotease defense mechanisms of the lungs. In one study using a model of acid-induced lung injury, high levels of serine proteases were found in the bronchoalveolar fluid of injured animals. This pathophysiologic response can impair both local and systemic lung defense mechanisms and predispose to pneumonia, even if the aspirated material is sterile.

Bacteriology

The bacteriology of aspiration pneumonia is intimately tied to the flora of the oropharyngeal cavity. Under normal circumstances, the saliva of the oral cavity contains 10^8 organisms/mL, with a predominance of anaerobic organisms. Individuals with poor dental hygiene or gingivitis can have anaerobic bacterial levels of 10^{11}/mL of saliva, and patients with underlying illness who are hospitalized for prolonged periods can become colonized by enteric gram-negative bacilli. The majority of cases of aspiration pneumonia are caused by anaerobic organisms originating in the oropharynx and are usually polymicrobial, with at least two anaerobic organisms and sometimes a mixture of aerobic and anaerobic pathogens.

The bacteriology of aspiration pneumonia has not changed much during the last few decades, although the taxonomy of some of the involved pathogens has. For example, some organisms originally classified in the *Peptostreptococcus* genus have now been reclassified in the *Streptococcus* genus, e.g., *S. intermedius.* With this in mind, many studies in the 1970s and 1980s documented anaerobic streptococci, *Fusobacterium nucleatum,* and *Prevotella melaninogenicus* (formerly classified in the genus *Bacteroides*) as the three major pathogens in aspiration pneumonia. It was once thought that *B. fragilis* was a significant pathogen in anaerobic lung infections, although recent data make this seem less likely.

Aerobic bacteria are found as either primary pathogens (approximately 10% of the time) or as coinfectors (approximately 40%); they include *Streptococcus* species, *S. aureus, Klebsiella pneumoniae, Escherichia coli, E. cloacae,* and *P. aeruginosa.* A more recent study examining early aspiration pneumonia in intensive care unit patients has documented a more virulent profile of aerobic pathogens. In this series, no anaerobes were isolated, but in those patients who had community-acquired early aspiration pneumonia, *Streptococcus pneumoniae, S. aureus, E. coli, E. cloacae, Haemophilus influenzae, Streptococcus viridans,* and *P. aeruginosa* were isolated alone or in combination. In those patients who aspirated in the hospital, *S. aureus, H. influenzae, Serratia marcescens, Morganella morganii, Candida albicans, K. pneumoniae, P. aeruginosa,* and *Proteus mirabilis* were isolated alone or in combination by a protected specimen brush. These data suggest that the bacteriology in severely ill patients with underlying medical diseases may differ from that of patients with aspiration pneumonia that is not severe.

Treatment

The two major modes of therapy for aspiration pneumonia are administration of antibiotics and supportive care. In the setting of a witnessed or suspected aspiration, antibiotics should be started if an infiltrate is present. If the infiltrate clears in 24 to 48 hrs, the pneumonitis was likely noninfectious, and therapy can be discontinued. If no infiltrate is present, therapy can be withheld provided that the patient is followed with serial chest radiographs. Antibiotic therapy for patients with aspiration pneumonia should be based on an assessment of the severity of illness (Table 3), where the infection was acquired (community versus hospital), and the presence or absence of risk factors for gram-negative colonization (Table 4).

Respiratory rate >30 breaths per minute
Need for mechanical ventilation
Chest radiographic findings:
50% increase in the infiltrate in 48 hours
Bilateral multilobar involvement
Presence of shock
SIRS (systemic inflammatory response syndrome) or need for vasopressors to support blood pressure
Severe lung injury (PaO_2/FIO_2 ratio ≤ 250 mmHg)
Urine output <20 mL/h
Acute renal failure requiring dialysis

TABLE 3. *Severe aspiration pneumonia*

Malnutrition
Severe illness
Coma
Intubation
Diabetes
Prior surgery
Lung disease
Renal failure
Prior antibiotic use
Hypotension
Cigarette smoking
Prolonged hospitalization

TABLE 4. *Risk factors for gram-negative colonization*

If pneumonia is acquired in the community, then an anaerobic pathogen is more likely than if the infection was acquired in the hospital. In community-related aspiration pneumonia, the antibiotic regimen should be directed against the oral anaerobes (e.g., anaerobic streptococci, *F. nucleatum,* and *P. melaninogenicus*). Patients should be treated empirically without collection of sputum for culture by expectoration or invasive aspiration. The initial empiric antibiotic used in this case may be clindamycin, penicillin alone, or a combination of penicillin and metronidazole. Some data show a lower failure rate in patients treated with clindamycin compared with penicillin for anaerobic pleuropulmonary infection, suggesting a primary role for clindamycin in this infection. Recent data from patients with community-acquired lung abscess found resistance rates to penicillin, metronidazole, and clindamycin of 21%, 12%, and 5%, respectively, again supporting a primary role for clindamycin in anaerobic lung infections.

Clindamycin is a bacteriostatic antibiotic that binds to the 50S ribosomal subunit of bacteria and inhibits protein synthesis. Clindamycin potentiates opsonization and phagocytosis of bacteria, and has a prolonged effect that suppresses bacterial growth after concentrations fall below the minimal inhibitory concentration for the target organism. Clindamycin has antibacterial activity against most anaerobes, including *Bacteroides, Prevotella, Fusobacterium, Clostridium,* and *Porphyromas* species, and against aerobic gram-positive cocci, such as group A, B, C, and G streptococci, microaerophilic streptococci, *S. viridans,* most pneumococci, and methicillin-sensitive *S. aureus.*

The route of antibiotic administration is determined by the severity of the pneumonia and whether the patient is treated as an outpatient or inpatient. Treatment may be given orally on an outpatient or inpatient basis, depending on the severity of illness, but initial therapy in severely ill and hospitalized patients is usually by the intravenous route.

The above antibiotic regimen needs be modified if the patient has severe infection, hospital-acquired aspiration, or risk factors for gram-negative colonization (Table 4). In this situation, the likelihood of infection with a virulent gram-negative bacillus or an aerobic organism is greater, and therefore additional antibiotic coverage is required. Sputum or tracheal aspirate may be helpful in identifying high-risk pathogens, such as *P. aeruginosa,* in intubated patients. After empiric therapy has been started, culture results can be useful to determine the presence or absence of infection with *P. aeruginosa.* In this patient population, clindamycin plus an antibiotic with activity against gram-negative bacilli is recommended, or a single antibiotic with activity against anaerobes and gram-negative bacteria is adequate (e.g., ampicillin/sulbactam or ticarcillin/clavulonate) (Table 5). If risk factors for infection with *P. aeruginosa* are present, we recommend empiric antibiotic therapy with a dual anti-*Pseudomonas* combination until culture results are known.

Community-acquired infection that is not severe	Hospital-acquired infection or severe community infection
Oral route	**Intravenous route**
Penicillin	Clindamycin plus ciprofloxacin[a]
Penicillin plus metronidazole	Clindamycin plus aminoglycoside[a]
Clindamycin	Ampicillin/sulbactam
Amoxicillin/clavulanate	Cefoxitin
Intravenous route	Piperacillin[a]
Penicillin	Imipenem[a]
Penicillin plus metronidazole	
Clindamycin	
Ampicillin/sulbactam	
Ticarcillin/clavulanate	

[a] If any of the following are present, *P. aeruginosa* infection is possible: prior antibiotic use, prolonged hospital course, and/or severe pneumonia. If *P. aeruginosa* infection is suspected, dual anti-*Pseudomonas* therapy should be initiated with a β-lactam/aminoglycoside or a β-lactam/quinolone combination.

TABLE 5. *Initial antibiotic regimen for aspiration pneumonia*

LUNG ABSCESS

A lung abscess is defined as a localized (usually >2 cm in diameter), suppurative, necrotizing process occurring within the pulmonary parenchyma. Several processes, either respiratory or systemic, can lead to abscess formation. Most abscesses are primary and result from necrosis in an existing parenchymal process, usually an untreated aspiration pneumonia. Among the causes of necrotizing pneumonitis, infections and neoplasms are the most frequent. A secondary abscess is one that complicates either a septic vascular embolus (e.g., right-sided endocarditis) or a bronchial obstruction (e.g., aspirated foreign body).

Classically, anaerobes have been identified as the most common cause of lung abscess, although aerobic bacilli, fungi, parasites, and mycobacteria may also be responsible. Among neoplastic causes, primary squamous carcinoma of the lung is the most common malignancy associated with abscess formation. Between 8% and 18% of lung abscesses have been associated with neoplasms in all age groups, but in patients whose age is >45 years, the association approaches 30%.

The incidence of lung abscess has declined by as much as 10-fold during the last few decades, presumably as a result of improved treatment regimens for pneumonia. Accompanying this decrease in incidence is a decrease in mortality to between 5% and 10%, with a recent series reporting a mortality rate of 2.4% in community-acquired lung abscess and 66.7% in hospital-acquired abscess. Diagnosis and treatment have changed little through the years, as lung abscesses are uncommon and it is difficult to obtain enough patients to perform controlled clinical trials. As will be discussed, administration of antibiotics is the most important treatment, as in aspiration pneumonia. The role of the newer antimicrobial agents remains controversial, although they may represent an advance over traditional therapeutic agents (penicillin), especially as drug-resistant bacteria become more prevalent.

Pathogenesis

Most lung abscesses are caused by infectious agents, such as bacteria, fungi, parasites, and mycobacteria. In the majority of cases, a mixed bacterial flora can be found, with anaerobes being present in up to 90% of cases. Aerobic bacilli may be present in up to 50% of patients, but in most cases they coexist with anaerobes, and in only 10% of cases are they the sole responsible pathogens.

As in aspiration pneumonia, the basis of lung abscess formation is aspiration of infectious oropharygeal material in a host who cannot adequately clear the infectious challenge. Individuals predisposed to lung abscess formation are those with host defense defects in the setting of risk factors for aspiration (Table 1 and Table 2). Aspiration, as described above, is more likely in patients who have neurologic, mechanical, and muscular dysfunction associated with alcoholism, seizure disorders, drug overdose, general anesthesia, protracted vomiting, or neurologic disorders such as cerebrovascular accidents, myasthenia gravis, amyotrophic lateral sclerosis, and other bulbar processes.

In addition to having risk factors for aspiration, patients predisposed to the formation of lung abscess are exposed to large concentrations of potentially pathogenic bacteria, usually orogingival in origin. It appears that the size of the aspirated bacterial inoculum is important, as abscess formation is enhanced by the presence of poor dentition and gingival disease, two conditions that are associated with bacterial counts in saliva in excess of 10^{11}/mL. Approximately 73% of patients with lung abscess have at least one predisposing factor for aspiration, and many have clinically silent gingival disease.

The pathophysiology of lung abscess formation appears to be related to a combination of aspiration, host defense defects, and the size of the infectious inoculum. Experimental data suggest that lung abscess formation occurs 8 to 14 days after aspiration of infectious orogingival material. When aspirated in large amounts, a single species of anaerobic bacteria or a combination of organisms can cause a necrotizing pneumonitis that, if progressive or untreated initially, forms a lung abscess. As expected, the location of the abscess is determined by gravity and body position at the time of aspiration. Lung abscess is typically located in the basal segments of the lower lobes, the superior segment of the lower lobe, or the posterior segments of the upper lobes, analogous to the location of infiltrates found in patients with aspiration pneumonia.

With these pathogenetic principles in mind, it is clear that an abscess arising in an edentulous patient (without oral anaerobes) or in a location other than the ones mentioned should raise suspicion of another pathologic process, involving either a nonanaerobic infection (such as tuberculosis), an esophageal disorder, or an obstructing endobronchial lesion.

Microbiology

Approximately 90% of lung abscesses are associated with anaerobic bacteria, either as the primary pathogens or in combination with aerobic bacteria. This observation may be explained by the fact that anaerobic bacteria commonly cause necrotizing inflammation. Other bacteria associated with lung abscess include *S. aureus, E. coli, K. pneumoniae, P. aeruginosa,* other gram-negative bacilli, *Streptococcus pyogenes, Pseudomonas pseudomallei* (melioidosis), *H. influenzae* (especially type b), *Legionella pneumophila, Nocardia asteroides, Actinomyces* species, and rarely pneumococci. Parasites (*Paragonimus westermani, Entamoeba histolytica*), fungi, and mycobacteria also may cause lung abscess (Table 6).

INFECTIOUS		
Bacterial	**Fungal**	**Parastic**
Anaerobic abscess	Coccidioidomycosis	Echinococcosis
Aerobic abscess	Histoplasmosis	Amebiasis
Infected bulla	Blastomycosis	
Infected pulmonary infarct	Aspergillosis	
Empyema	Cryptococcosis	
Tuberculosis		
Actinomycosis		
NEOPLASTIC	**INFLAMMATORY**	
Bronchogenic carcinoma	Wegener's granulomatosis	
Squamous cell	Sarcoidosis	
Metastatic carcinoma		
Colorectal		
Renal		
Lymphoma		
Hodgkin's disease		

TABLE 6. *Cavitary lung lesions*

Anaerobes are usually part of a polymicrobial flora, with the average number of organisms isolated being three, either strictly anaerobes or a combination of aerobic-anaerobic bacteria. The change in bacterial taxonomy has been referred to in the section on aspiration pneumonia.

Classification

Lung abscesses have been categorized using several methods, but the classification into acute versus chronic appears to have the most clinical utility. This distinction is not absolute but can aid the clinician by helping to formulate treatment regimens and identify patients who may need further diagnostic evaluation, such as

bronchoscopy.

A lung abscess is defined as acute if the patient presents with symptoms of <2 weeks' duration. Patients with an acute lung abscess are less likely to have an underlying neoplasm but are more likely to have an infection caused by a virulent aerobic bacterial agent, such as *S. aureus.* In a recent series of patients with acute community-acquired lung abscess, a mean of 2.3 bacterial species per patient was identified, with anaerobes isolated alone in 44% of cases, aerobes alone in 19%, mixed aerobes and anaerobes in 22%, and the remainder caused by an unidentified pathogen or *Mycobacterium tuberculosis.* The most common anaerobic pathogens identified were from the *Prevotella* species, and the most common aerobic pathogens were *S. viridans* and *Staphylococcus* species.

A chronic lung abscess is defined by symptoms lasting for >4 to 6 weeks; patients are more likely to have an underlying neoplasm or infection with a less virulent, anaerobic agent. There may be some overlap in this classification scheme, because it does not take into account host defense factors or serious comorbidity, but this scheme can be useful during initial patient evaluation.

Clinical Features

Most patients with lung abscess have an insidious presentation, with symptoms lasting at least 2 weeks before evaluation. Signs and symptoms include cough, foul-smelling sputum that forms layers on standing, hemoptysis (25% of patients), fever, chills, night sweats, anorexia, pleuritic chest pain (60% of patients), weight loss, and clubbing. Although most of these signs and symptoms are seen, their specificity for lung abscess is low. On the other hand, putrid sputum is a highly specific sign that is pathognomonic for anaerobic infection, although it is found in only 50%–60% of patients. A history of weight loss is also common, occurring in 60% of patients, with an average loss of between 15 and 20 lb. Historical data usually include risk factors for aspiration, such as alcoholism, drug overdose, seizures, head injury, or stroke, and the absence of such risk factors should prompt a search for a diagnosis other than primary lung abscess.

Laboratory data are also nonspecific. Erythrocyte sedimentation rate is elevated, and anemia of chronic inflammation and leukocytosis are present. Culture and microbiologic information from sputum are generally not helpful unless the abscess is caused by nonanaerobic agents, such as mycobacteria, fungi, or aerobic bacteria. Sputum is contaminated with anaerobes from the oral cavity, so that finding these organisms is not specific. If the abscess is associated with an empyema, as is the case 30% of the time, then culture of the empyema fluid may yield reliable bacteriologic data.

More invasive methods for microbiologic diagnosis (transtracheal aspiration and bronchoscopy) are rarely employed, as the majority of patients are treated empirically. This approach is supported by recent data showing that most lung abscess pathogens are sensitive to conventional antimicrobial therapy. If, on the other hand, the patient presents in an atypical fashion or is not responding to therapy, then invasive techniques are justified (Table 7).

Atypical presentation
Absence of fever
WBC count < 11,000
Absence of systemic symptoms
Fulminant course
Absence of predisposing factors for aspiration
Atypical abscess location
Abscess formation in an edentulous patient
Failure to respond to antibiotics
Presence of mediastinal adenopathy
Suspected underlying malignancy
Suspected foreign body

TABLE 7. *Criteria for fiberoptic bronchoscopy inpatients with lung abscess*

Chest radiography generally shows a solitary cavitary lesion of variable size. Some studies report that the size of the cavity is helpful in distinguishing neoplastic from non-neoplastic lung abscesses, but others have not found such a correlation. A dearth of inflammation seen radiographically surrounding the abscess suggests patients with underlying neoplasm.

Radiographically, empyema and infected bullae are sometimes difficult to distinguish from a lung abscess. Empyema is a purulent infection that in most cases is confined to the pleural space, although it can develop as a complication of, or be a cause of, a lung abscess. An infected bulla is pneumonia within a pre-existing bullous cavity and does not result from tissue necrosis. Both entities can demonstrate air-fluid levels, but one is parenchymal (infected bulla) and the other is extraparenchymal (empyema). If an empyema contains an air-fluid level, then a bronchopleural fistula is present. When the chest radiograph cannot distinguish these two entities from a lung abscess, computed tomography (CT) suggests a lung abscess if a thick, irregular, walled cavity with no associated lung compression is seen (Fig. 1). Empyema and an infected bulla usually have thin, smooth walls with compression of uninvolved lung and, in the case of the infected bulla, minimal surrounding inflammation (Fig. 2). The real difficulty arises when one tries to differentiate between a lung abscess and an empyema with a bronchopleural fistula. Prior pleural fluid on chest radiograph, extension of the air-fluid level toward the chest wall, extension of the air-fluid level across a fissure, and tapering of the air-fluid collection on the radiograph suggest empyema.

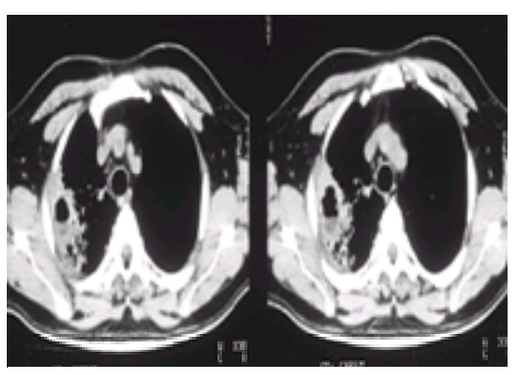

FIG. 1. CT of a patient in whom a lung abscess was diagnosed. Note the cavitary lesion with the characteristic air-fluid level and surrounding inflammation and tissue necrosis.

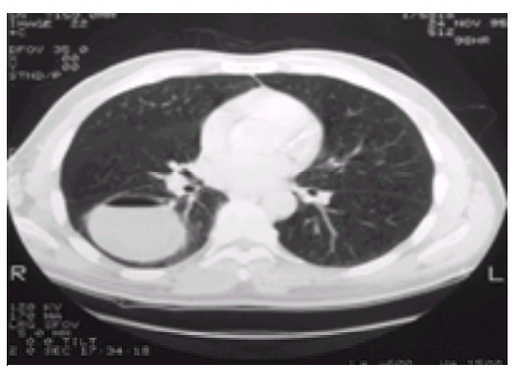

FIG. 2. CT of the chest showing typical findings in an infected bulla. The cavity is thin-walled without surrounding inflammation or necrosis.

If a lung abscess fails to communicate with a bronchus, the characteristic air-fluid level within a cavity will not be seen radiographically. In this case, the radiographic appearance is one of a focal, ground-glass infiltrate with indistinct borders. Given the history of illness and this radiographic picture, the differential diagnosis includes other chronic pulmonary infections, such as postobstructive bacterial pneumonia, nocardiosis, fungal pneumonia, tuberculosis, and actinomycosis. In addition, a variety of noninfectious pulmonary processes can also be confused with a noncavitary lung abscess. These include BOOP (bronchiolitis obliterans organizing pneumonia), radiation pneumonitis, chronic eosinophilic pneumonia, and allergic bronchopulmonary aspergillosis. When a lung abscess presents in this manner, it is usually necessary to perform a further diagnostic workup, such as bronchoscopy and or lung biopsy. This is also the case if multiple cavities are seen on the radiograph, a rare finding in an anaerobic process not complicated by immunosuppression, recurrent aspiration, or virulent anaerobe(s) causing a necrotizing pneumonitis.

Treatment

In the pre-antibiotic era, three treatment modalities were available for lung abscess. These included supportive care, postural drainage with or without bronchoscopy, and surgery. All three modalities led to the same mortality rate of 30%–35%. Currently, the mainstay of therapy for lung abscess is antimicrobial therapy with either intravenous penicillin alone, penicillin plus metronidazole, or clindamycin. Penicillin has historically been the therapy of choice since its first use in the 1950s, with a cure rate of 95%. With the growing concern over penicillin-resistant anaerobes, two trials compared clindamycin with penicillin in a prospective study design. Both studies found that clindamycin therapy was associated with fewer treatment failures and a shorter time to symptom resolution. When metronidazole was evaluated as a single treatment modality, it was found to have a 43% rate of treatment failure and hence is not recommended for single-agent therapy. Metronidazole in combination with penicillin is considered an appropriate treatment regimen for lung abscess, because penicillin has activity against the aerobic and microaerophilic streptococci that are often resistant to metronidazole. Many other antibiotics have *in vitro* activity against oral anaerobes but have never been evaluated in clinical trials to gain FDA approval for use in these infections. These antibiotics include chloramphenicol, imipenem, erythromycin, azithromycin, clarithromycin, and b-lactams with a b-lactamase inhibitor (e.g., ampicillin with sulbactam).

After the appropriate antimicrobial agent has been selected, the next issue is determining the length of therapy. Although there is considerable controversy in the literature, the approach taken by Bartlett seems the most conservative and appropriate. He recommends treating most patients until the pulmonary infiltrates have resolved or until the residual lesion is small and stable. Initially, antibiotics are given intravenously until the patient is afebrile and shows clinical improvement (4 to 8 days). Oral medications are then given, usually for a prolonged period, although the length of time needed varies from patient to patient. Many patients require a total of 6 to 8 weeks of antimicrobial therapy.

In the past, bronchoscopy was part of the standard care of patients with lung abscess. Its uses included helping to promote drainage and ruling out underlying malignancy. Currently, bronchoscopy is reserved for those patients with atypical presentations who are suspected of having an underlying malignancy or foreign body (Table 7). Bronchoscopy is no longer routinely used for abscess drainage, as the majority spontaneously communicate with the airways and drain. There is also a possibility of rupturing an abscess during bronchoscopy and causing contamination of previously uninvolved lung segments.

As for using bronchoscopy to rule out underlying malignancy, several patient characteristics appear to be correlated with underlying carcinoma. Criteria for bronchoscopy in patients with lung cavities are (1) mean oral temperature ≤100°F, (2) absence of systemic symptoms, (3) absence of predisposing factors for aspiration, and (4) mean leukocyte count ≤11,000/mm^3. When more than three of these factors are present in a patient with lung abscess, an underlying carcinoma is likely. Other factors that should prompt bronchoscopic evaluation include an atypical clinical presentation (noncavitary lesion or lesions and fulminant time course), atypical abscess location (especially in the anterior half of the lung), abscess formation in an edentulous patient, failure to respond to antibiotics, and lung abscess associated with mediastinal adenopathy, a finding not commonly found in anaerobic lung infection.

Complications of lung abscess include empyema formation resulting from a bronchopleural fistula, massive hemoptysis, spontaneous rupture into uninvolved lung segments, and failure of the abscess cavity to resolve. Although uncommon, these complications often require prolonged medical therapy as well as surgical intervention, either with tube thoracostomy in the case of empyema or lung resection in the case of massive hemoptysis.

Surgical treatment of lung abscess is usually reserved for cases with complications such as massive hemoptysis, bronchopleural fistula, and empyema. It is also used in the setting of fulminant infection and in those patients who fail medical therapy. Approximately 10% of lung abscesses require surgical intervention. Prognostic factors associated with failure of medical treatment include recurrent aspiration, large cavity size (>6 cm), prolonged symptom complex before presentation, abscess associated with an obstructing lesion, abscess with a thick-walled cavity, advanced age, neoplasm, and other chronic medical conditions (Table 8). An alternative to surgical drainage is percutaneous catheter placement. At this time, percutaneous drainage should be reserved for patients who are unresponsive to medical therapy and have lung abscesses located peripherally. Placement of a percutaneous catheter can obviate the need for surgery in a significant percentage of patients who have failed medical treatment, with a mean time to abscess resolution of 10 to 15 days and improvement in clinical parameters within 48 hours. These patients should also receive intravenous antibiotics during and after percutaneous drainage of a lung abscess.

Recurrent aspiration
Large cavity size (>6 cm)
Prolonged symptom complex before presentation
Abscess associated with an obstructing lesion
Presence of thick-walled cavities
Underlying serious co-morbidity
Development of empyema

TABLE 8. *Factors associated with failure of medical therapy in patients with lung abscess*

LIPOID PNEUMONIA

Lipoid pneumonia is a chronic illness of the lower respiratory tract resulting from the accumulation of lipoid material in the alveoli and/or the interstitium; it is not strictly an infectious syndrome. The clinical characteristics of this disease depend on whether the syndrome is exogenous or endogenous in origin. A noninfectious alveolar filling process causes chronic, nonresolving pneumonia, but lipoid pneumonia can be complicated by secondary infection. An example of this can be seen in patients with postobstructive pneumonia secondary to an endobronchial lesion.

Exogenous lipoid pneumonia, now an uncommon occurrence, was first described by Laughlen in 1925, when he identified lipid deposits in four autopsy specimens from the lungs of patients who had received either oil nose drops or oily laxatives. Experimental studies later confirmed similar findings in animals who had mineral oil artificially instilled in the trachea. Exogenous lipoid pneumonia is the result of aspiration of lipid material such as mineral oil, vegetable oil, and animal fats, with the type of aspirate predicting the underlying pathologic response. As a result of fatty acid production, aspiration of animal fat usually causes a severe inflammatory reaction resulting in hemorrhagic pneumonia. On the other hand, aspiration of vegetable oil results in little to no pathologic response, whereas mineral oils usually cause a foreign body reaction resulting in pulmonary fibrosis. This pathologic response to mineral oil is actually used, in animals, as a model of pulmonary fibrosis.

In exogenous mineral oil lipoid pneumonia (the most common syndrome), the clinical features include cough, dyspnea, sputum production, occasional hemoptysis, and chest radiographic abnormalities consisting of nonspecific infiltrates in the lower lobes, although any pattern can be seen, including cavitary lung lesions. Ordinarily, patients have minimal or no clinical symptoms and seek medical assistance because of abnormal findings on a chest radiograph. Intratracheal aspiration of mineral oil usually occurs subclinically, and patients are usually without cough, other signs associated with liquid aspiration, or acute inflammation.

The typical patient who recurrently aspirates mineral oil-based medicinal aids is an elderly individual who has used oil-based nose drops or an oil-based laxative for several years. The diagnosis can be made by a history of use of mineral oil or other oil in a patient with respiratory symptoms and a chronic nonresolving pneumonia. Not uncommonly, the diagnosis is made on biopsy, as lipoid pneumonia can mimic infectious diseases and lung malignancy. Once the diagnosis of exogenous lipoid pneumonia is made, treatment consists of removal of the cause (e.g., oil-based laxatives) and supportive therapy. Other therapeutic modalities, such as repeated bronchoalveolar lavage and corticosteroids, are available, but their overall clinical usefulness is uncertain.

Endogenous lipoid pneumonia is caused by the accumulation of lipids derived from the breakdown of endogenous products (e.g., cell membranes and surfactant). The

material most often associated with this type of lipoid pneumonia is cholesterol, and thus *cholesterol pneumonia* is another name for this entity. The pathologic process is usually localized and limited to an abnormal region of the lung, in contrast to what occurs in exogenous lipoid pneumonia. The most common underlying abnormality resulting in endogenous lipoid pneumonia is an obstructing endobronchial lesion, either lung cancer or a foreign body.

The clinical presentation of patients with endogenous lipoid pneumonia is typically that of the underlying cause. In the case of an obstructing lesion, it is characterized by cough, fever, chills, and a chest radiograph revealing an underlying mass or segmental lesion with a concomitant postobstructive pneumonia. In sharp contrast to exogenous lipoid pneumonia, there is no predisposition to recurrent aspiration or history of use of an oil-based substance. Like the exogenous type, endogenous lipoid pneumonia is not infectious in origin, but secondary infection from the underlying obstructive process can occur.

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CHAPTER

32 Occupational Lung Diseases Caused by Asbestos, Silica, and Other Silicates

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INTRODUCTION

Lung diseases caused by asbestos, silica, and the other silicates are the most prevalent pneumoconioses. They have produced very significant morbidity and mortality, particularly during the early part of the twentieth century. In the industrialized regions of the world, conditions of exposure increased rapidly during the nineteenth century. Like all major health problems, the pneumoconioses have been easier to recognize in the field at times when exposures of large cohorts of workers have been intense. As the twentieth century draws to an end, the epidemiology of the life-threatening pneumoconioses is undergoing global shifts. Dust-induced diseases are becoming more problematic in emerging nations with rapidly expanding industrial sectors. This has occurred while disease in advanced nations has gradually been reduced through enforcement of strict regulations to control dusts in the workplace.

Typically, cases of pneumoconiosis that continue to accumulate in the advanced nations represent incidental radiographic findings not associated with disability or premature mortality. Under these conditions, the challenge to the diagnostician to recognize subtle but typical radiographic features is more daunting. Characteristic presentations of pneumoconiosis at the end of the twentieth century in nations with effective dust controls in place are complicated by (1) the minimal extent of disease (often apparent only radiographically), (2) a history of multiple dust exposures leading to aberrant radiographic patterns, and (3) the preponderance of cigarette smoke-induced lung disease in the exposed population. Ever increasingly, pneumoconioses are detected as a perplexing radiographic pattern in an elderly patient undergoing evaluation for an unrelated medical problem. When cases of severe pneumoconiosis do occur, they tend to be limited to small groups of employees receiving intense but often brief exposures not appropriately monitored by regulatory agencies.

OCCUPATIONAL HISTORY

The most important step in the diagnosis of unsuspected pneumoconiosis is to question the subject regarding specifics of the actual job and of the minerals or materials involved. Without an adequate occupational history, scientific principles of risk management cannot be implemented. Often, the subject's past or present occupation may not immediately suggest mineral dust exposure. In an era of a mobile work force, it is always important to seek a detailed account of the subject's past employment. Because some pneumoconioses develop after only brief but intense dust exposures, it is important to inquire about part-time employment. Sometimes, the subject's story must be corroborated by reviewing samples of suspected dusts or materials brought from the workplace. Mixed exposure to silica, talc, or other mineral dusts occurs when multiple minerals are mined in a single region or used in a single factory setting. The type of work done may give clues to the severity of exposure. When the interviewer is unfamiliar with the work-related terms (e.g., bagger, miller, weaver, pipe fitter, fettler, tunneler), it may be easier to seek a description of the actual working habits. Many pneumoconioses are now related to exposures outside the workplace; hence, it is of key importance to ask about hobbies and unusual activities in the home. Subjects should be questioned about whether they worked with a respirator or other protective equipment and whether they were alerted to potential hazards. Given the gender composition of the blue collar work force, almost all workers exposed to asbestos have been men. Moreover, because increased regulation of exposure has been a relatively recent development, chronic asbestosis is generally found in the older segment of the work force.

Cigarette smoking can have a particularly devastating impact on workers exposed to mineral dusts. For the clinician/epidemiologist, the coexistence of smoking-related diseases invariably confounds all epidemiologic studies of the pneumoconioses. In those mineral dust diseases causing minimal impairment, the deleterious effects of smoking far overshadow any effects attributable to dust. Rates of smoking as high as 80% have often been recorded among miners and hard rock workers.

ASBESTOS-RELATED DISEASE

Asbestos (from the Greek asbestos, “unquenchable”) is the collective term for a group of fibrous mineral silicates of the serpentine and amphibole groups that break into fibers when crushed rather than into dust. They share the properties of being nearly indestructible, heat- and acid-resistant minerals. Perhaps no mineral has presented more social and political controversy during the past century than asbestos. During the middle of the twentieth century, an epidemic of asbestos-related disease afflicted many heavily exposed workers.

There is no doubt that asbestos continues to be an important health concern. However, as the disorder has abated in prevalence and severity, concern for other than occupational exposures, particularly among groups such as schoolchildren and office workers, has grown, often without sound basis. Many observers feel that this heightened level of concern with asbestos has inappropriately drawn public attention from other, potentially more hazardous features of the environment.

Asbestos exists in multiple forms, all of them fibrous silicate minerals. They are variably resistant to heat and to destruction by acids and other chemicals. All asbestos forms have a fibrous structure, which makes them suitable for use in woven fabric. The main elements present in addition to silicon are magnesium, calcium, iron, and sodium in differing proportions. All forms of asbestos can be divided into one of two mineralogic types, the serpentines and the amphiboles. Commercially, chrysotile is the most important serpentine. Long chrysotile fibers have a curled appearance; the amphiboles have more needle-shaped fibers (Fig. 1). Common amphiboles include crocidolite, amosite, anthophyllite, tremolite, and actinolite (Table 1).

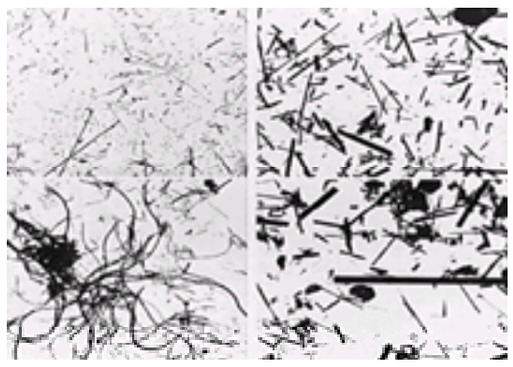

FIG. 1. Various types of asbestos. Anthophyllite (*top left*). Chrysotile (*top right*). Amosite (*bottom left*). Crocidolite (*bottom right*).

Amphiboles	Serpentines
Crocidolite (blue asbestos)	Chrysotile
Amosite (brown asbestos)	
Tremolite	
Actinolite	
Anthophyllite	

TABLE 1. *Mineral forms of asbestos*

Commercial Uses of Asbestos

Chrysotile accounts for the preponderance (>95%) of asbestos mined and used in the world. It has been mined primarily in eastern Canada and New England as well as in Russia. Crocidolite comes primarily from South Africa and was previously mined in western Australia. However, with recognition of its toxicity, demand for crocidolite has greatly decreased.

Asbestos has been widely mined since the end of the nineteenth century. Regulatory efforts by government agencies, such as the Environmental Protection Agency (EPA) in the United States, has greatly cut down on its use. World production of asbestos rose steadily from <0.2 million tons in 1920, peaked at 5 million tons in the late 1970s, and has shown a slight decline since that time. For many years, sheathing and insulation used in the construction of office buildings and houses consisted largely of agents that had been reinforced and rendered heat-resistant with asbestos fibers. Asbestos was used to line furnaces and lag pipes; it was also used as friction material in brakes, as a fire retardant in spray paints, and as a binder and strengthener for cement pipes. It was extensively used in warships as insulation and to prevent fire. In the 1950s, asbestos was even a component of cigarette filters.

Historical Aspects and Effects of Exposure to Asbestos

Asbestos exposure can lead to three serious pulmonary conditions: asbestosis (a diffuse fibrosing disease of the lungs), lung cancer, and mesothelioma. Whereas asbestosis can vary from mild to lethal, the latter two disorders are almost invariably fatal.

Asbestosis was first recognized as a distinct disease entity in 1907 by Murray in the United Kingdom. The magnitude of the hazard and the exposure-response relationship were worked out in the subsequent decades. Recommendations for improved industrial hygiene practices grew out of those seminal studies. The risk to users of the finished asbestos products became more generally apparent by the early 1960s. Before that, sporadic case reports of asbestosis occurring in pipe fitters, welders, and others had been reported. Most such instances suggested that the victim had acquired the condition as a result of an exceptional and unusual exposure. Studies in the 1960s made it clear that a significant risk existed in all users of asbestos. Furthermore, it was clear from those studies that the prevailing regulatory statutes were not protecting the work force from asbestosis.

The role of asbestos as a carcinogen was debated during the 1930s and 1940s. However, the issue remained controversial until 1955, when Doll published a classic article presenting the statistical evidence needed to confirm the association with certainty. Doll's study described the increased risk for lung cancer only in subjects with coexisting asbestosis, and did not consider asbestos exposure in the absence of fibrosis as a potential cause of lung cancer.

In the late 1950s, the association between malignant pleural mesothelioma and prior asbestos exposure was made by clinicians in South Africa. The risk for development of mesothelioma, like that for asbestosis and lung cancer, is concentration-related and depends significantly on the type of asbestos fibers inhaled. The prolonged inhalation of asbestos fibers has been said to be associated with an increased risk for laryngeal, ovarian, gastrointestinal, and renal carcinomas. This association is not clear, however, as some cases of mesothelioma may have been incorrectly diagnosed as primary cancers of other organs.

Standards for Asbestos Exposure

Exposure limits for asbestos have been developed and applied throughout the twentieth century in response to epidemic disease and disability. Precise standards vary somewhat between industrialized nations. In the United States, the regulated standard has progressively been reduced to 0.2 fibers per cubic centimeter. To allow for frequent changes in ambient dust levels in the workplace, this standard refers to an 8-hr time-weighted average (TWA). Asbestos fibers 5 µm and larger are responsible for most of the toxicity and are therefore the focus of regulatory standards. To account for the different toxicities of different fiber types, some jurisdictions apply more rigorous standards for the amphiboles.

For many years, asbestos levels were measured as the number of particles present per cubic centimeter of the ambient air. Asbestos content is usually determined by trapping airborne particles on filters. Fiber size and number are then determined by phase-contrast microscopy. Only fibers >5 µm in length are measured, as smaller fibers are cleared from the lungs and are not likely to lead to pulmonary disease or malignancy. When particles and fibers are counted, asbestos is not distinguished from other substances. Although this does not matter much in asbestos textile factories, where most of the airborne fibers are asbestos, in other occupational settings the percentage of asbestos fibers is much smaller and may be as low as 5%–10%. Under such circumstances, optical counts using a microscope can be misleading, and when it is imperative to separate asbestos fibers from other types of fibers, more definitive techniques, such as transmission or scanning electron microscopy, must be used.

As a result of regulatory efforts in the industrialized nations of the world, the incidence of asbestos-related lung disease has become less common during the past several decades. Subjects with established asbestosis are thus becoming an increasingly elderly population. Moreover, as the ambient levels have fallen in the workplace, the latency time between exposure and appearance of asbestos-related disease has lengthened. For example, a report from 1938 showed that asbestosis was present with exposures as short as 5 years. At that time, dust levels could be as high as 400 particles per cubic centimeter. During and after World War II, the average duration of exposure before the development of asbestosis rose from 10 to 12 years to >20 years. Nonetheless, asbestosis still occurred in certain industries. Since then, the regulations have become considerably more stringent; it is highly likely that no new cases of asbestos-related lung diseases will develop under current standards. The reduction in the use of amphiboles makes this prospect even more likely.

Specific Occupational Risks

It has been estimated that as many as 27 million workers in the United States received a significant exposure to asbestos during the middle four decades of the twentieth century. Environmental exposure to asbestos and other minerals can occur at each stage of production and use: extraction (miners), purification and

production (weavers), and use of the finished product (plumbers, laggers, insulation layers). Workers involved in removal of the used product from buildings, ships, and other sites may be exposed. This statement applies only to those involved in removal efforts in older buildings and equipment in which the risk of asbestos is not apparent. Somewhat surprisingly, miners of asbestos have generally been found to be at lower risk for disease than millers and weavers. Regardless of the context, exposure to chrysotile carries significantly less risk than exposure to crocidolite and the other amphiboles.

Very close contact is a critical determinant of risk. Examples abound of work forces in which certain jobs carried much higher risks than others. Thus, welders working in the same factory with pipe fitters had little or no increase in asbestos-related lung disease, whereas the latter group was at high risk.

Asbestos-related disease as a result of exposure outside the workplace occurs but is infrequent and requires very substantial exposure. Stories of wives washing their husbands' asbestos-laden clothing may be true but are less frequently documented as regulations have been enforced. Low levels of asbestos fibers are found in ambient air in the urban environment. Sources include demolition of equipment and buildings. These levels continue to drop as regulatory measures have been implemented. People who work or live in older buildings containing asbestos are not at significant risk, as the asbestos is largely immobilized in building materials. One recent study has indicated that public buildings contain as few as 0.002 fibers per cubic centimeter, far below the regulated standard. Finally, asbestos occurs as an air and water pollutant in certain regions of the world where surface deposits are a part of the landscape.

Pathogenesis of Asbestos-Related Disease: Inhalation and Deposition

Inhaled asbestos fibers deposit on airway bifurcations of terminal and respiratory bronchioles. Lesser degrees of deposition occur in the alveoli. Somewhat paradoxically, it is the longer fibers that have the potential to reach the distal lung and exert toxicity. Fibers as long as 60 µm, a size not normally considered to be in the respirable range, evade impaction in the large airways. Their exaggerated length-to-width ratio allows them to penetrate into the small airways, from which they migrate into the lung interstitium. Small fibers (<5 µm in length) are removed by the mucociliary escalator mechanisms of the lungs and therefore represent less of a lasting risk.

On ingestion by macrophages, asbestos fibers undergo a process of chemical leaching and partial dissolution. This phenomenon occurs chiefly with chrysotile asbestos; the amphiboles are more resistant to macrophage ingestion and leaching, and once deposited, they have a much longer half-life. As a result of their different half-lives, the longer-lasting amphiboles tend to become predominant with time in subjects exposed to mixed dusts. Clearance cannot be effected if the length of the fiber is >20 µm. Fibers that cannot be cleared via the mucociliary escalator up the airway lumen move into the interstitium, from which they migrate to the regional lymph nodes.

How might asbestos prove toxic to lung cells? Heintz and colleagues have shown that asbestos increases the expression of certain proto-oncogenes (c-*fos,* c-*jun*) in mesothelial cells and tracheal epithelial cells. Asbestos induces increases in protein factors that bind specifically to the DNA sites that mediate gene expression by the AP-1 family of transcription factors. The persistent induction of transcription factors by asbestos suggests a model of asbestos-induced carcinogenesis involving chronic stimulation of cell proliferation through activation of the early-response gene pathway, which includes c-*jun* or c-*fos.* The inflammatory nature of the evolving asbestos lesions can be seen graphically in workers and in experimental animals using gallium scanning. In workers with positive findings on gallium scanning, the intensity of gallium uptake correlates with the activity of the inflammatory process.

Nuclear factor kappa B (NF-kB), a transcription factor regulating expression of genes intrinsic to inflammation and cell proliferation, may be an important intracellular intermediary in initiating asbestos-associated diseases. Crocidolite asbestos causes protracted and dose-responsive increases in proteins binding to nuclear NF-kB-binding DNA elements in airway epithelial cells. NF-kB induction by asbestos may prove to be a key event in the regulation of multiple genes involved in the pathogenesis of asbestos-related fibrosis and lung cancers.

The issue of variability of susceptibility to asbestosis and other pneumoconioses between workers with comparable exposures has long interested investigators. The best available evidence suggests that the retention and accumulation of dust in the lungs is a more important determinant than absolute exposure levels. Lung and airway size correlate with the presence or absence of disease in workers exposed to asbestos, silica, and other dusts. Airway caliber in particular seems to be a major determinant of person-to-person variation.

The weight of evidence suggests that smokers are at greater risk for the development of asbestos-related disease through similar mechanisms. Smoking has the potential to delay the clearance of particles such as asbestos from the lungs by incapacitating the mucociliary escalator. In line with the hypothesis presented above, cigarette smoking enhances fiber retention in the lungs; the longer residence time and greater burden of fibers in the lungs of smokers allows uptake of fibers by epithelial cells and other structural cells.

Asbestosis

Asbestosis is a diffuse interstitial fibrosis of the lungs caused by inhalation of asbestos. It results from heavy exposure to respirable forms of asbestos. The common presenting symptoms of asbestosis are dyspnea and dry cough, which may initially be ascribed by both subject and physician to heavy cigarette use. As with other pulmonary disorders, the victim often does not seek medical advice until the condition is fairly disabling. Weight loss is an early feature. If the original asbestos exposure was intense, disabling symptoms may continue to progress despite removal from further exposure.

Early in the disease process, the clinician can hear middle- to late-inspiratory crackles, which are most prominent in the bases of the lungs. As the disease progresses, these extend from the bases to the middle zones and become more widespread. Tachypnea is almost always present by the time the disease has reached the symptomatic stage. Cyanosis may be visible. Clubbing of the fingers, when present, usually signals advanced disease and a poor prognosis. Signs consistent with failure of the right side of the heart also become apparent later in the course.

Radiographic Features

Asbestosis is characterized by the development of irregular small shadows on chest x-ray films. To assist in standardization of interpretation of chest radiographs, the International Labor Office (ILO) developed a classification based on plain chest radiography. In the ILO system, small irregular shadows are described as *s, t,* and *u* in increasing size. Rounded shadows (such as are seen typically in silicosis) are termed *p, q,* or *r* shadows. The amount or profusion of small round or irregular shadows is graded as either 0, 1, 2, or 3. When the reader is somewhat uncertain about the grading, intermediate grades can be indicated with a slash mark. For example, a reading between grades 1 and 2 would be 1/2, with the first number given being the one the reader believes to be correct and the second one being also possible. In asbestosis, the smaller *s* and *t* shadows predominate over the larger *u* shadows. Scanty irregular shadows are present on chest radiographs in a significant percentage of smokers who have had no asbestos exposure, making their presence less specific. As in other interstitial lung disorders, these small irregular shadows tend to blur the margins of normal anatomic structures such as the diaphragm and the cardiomediastinal and bronchovascular markings (Fig. 2). Initially, the small irregular shadows appear in the lower zones, the site of most intense asbestos inhalation. With progression of disease, the upper lung zones become more obviously involved. Use of computed tomography (CT) to detect disease in exposed workers with normal chest x-ray findings is controversial. In asbestos-exposed subjects who have normal chest x-ray films, high-resolution CT can identify a group with significantly reduced lung function, indicative of restrictive lung disease, in comparison with a group having normal or near-normal CT scans. Pathologic correlation to indicate what early shadows signify are limited. Because the ILO classification system was set up to categorize disease according to plain chest x-ray features, the chest x-ray remains the widely used diagnostic standard.

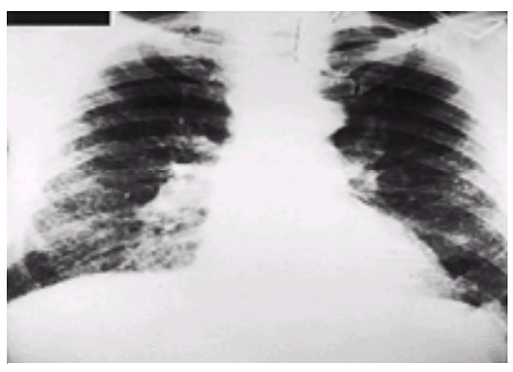

FIG. 2. Radiograph of a worker with category 2/3 asbestosis. He had worked for 30 years as an insulator.

Often, the parenchymal shadows are accompanied by pleural thickening with or without calcification (Fig. 3). In this circumstance, the evaluation of the character and profusion of the irregular parenchymal shadows can be confounded; the pleural changes when viewed *en face* can be mistaken for parenchymal disease. CT is particularly helpful in clarifying this issue. Another clue on the posteroanterior chest x-ray film is that the pleural thickening is most prominent in the middle third of the chest.

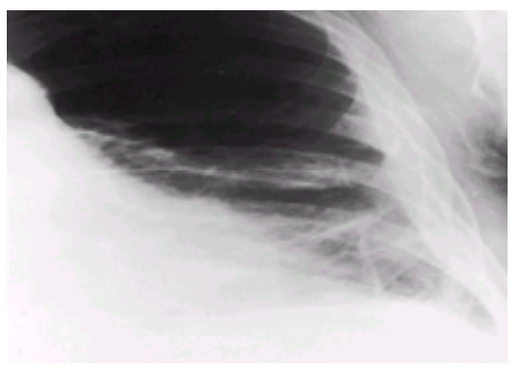

FIG. 3. Lateral wall pleural thickening and pleural plaques. Also evident are calcified pleural plaques viewed *en face.*

With late disease, other radiographic features emerge. As in other forms of interstitial fibrosis, a pattern of honeycombing—radiographically apparent cystic spaces in the lung—develops. In all the interstitial disorders in which it is seen, honeycombing provides incontrovertible evidence of advanced and irreversible lung remodeling and fibrosis. Its appearance, therefore, confirms that the asbestosis is severely disabling. In advanced disease, CT reveals features similar to those of other forms of late interstitial pulmonary fibrosis. Enlargement of the right ventricle and the central pulmonary arteries occurs late in the disease process, when pulmonary hypertension and cor pulmonale develop. Exceptionally large conglomerate masses in upper lung zones, such as are seen in coal workers' pneumoconiosis and silicosis, are rarely seen in asbestosis. These generally occur in subjects with concomitant silica exposure or in conjunction with rheumatoid arthritis (Caplan's syndrome, discussed below).

The presence of irregular shadows in low profusion in the lower zones cannot be considered unique or specific for asbestosis. Exposure to fibrous dusts other than asbestos may cause the appearance of small irregular shadows in the lung bases, particularly in smokers and elderly patients. Irregular shadows are seen in all forms of interstitial fibrosis, after exposure to non-asbestiform fibers, and in cigarette smokers. However, in these circumstances the irregular shadows are usually not profuse. Finally, the ILO classification can be used in predicting life expectancy.

Rounded atelectasis is a distinctive radiographic pattern nearly unique to asbestosis. It probably develops as an exuberant focal pleural reaction that entraps subjacent lung tissue in a swirl of pleural inflammation. It is important to recognize this lesion, as it may be mistaken on the plain chest x-ray film for a peripheral lung mass, an error that often leads to an unnecessary search for a lung tumor (Fig. 4). Rounded atelectasis, when suspected, can easily be confirmed by CT, which shows the characteristic atelectatic lung tissue and distorted bronchovascular markings.

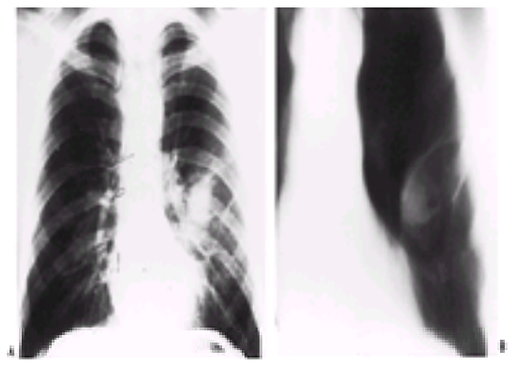

FIG. 4. Rounded atelectasis in a worker who had been an insulator for 15 years. The subject had no chest symptoms and normal lung function. **Panel A:** Posteroanterior film. **Panel B:** Tomographic view.

Pulmonary Function Studies

Symptomatic asbestosis is associated with changes in mechanical properties of the lungs resembling those seen in other forms of interstitial fibrosis. As remodeling progresses and extracellular matrix proteins are deposited in excess amounts, the lungs become regionally less compliant and all lung volumes are reduced. In consequence, there is a marked increase in the respiratory rate, a decrease in the tidal volume, and an absolute increase in the minute volume as the ventilation-perfusion relationship becomes less evenly matched. The diffusing capacity may be reduced before lung volumes are overtly lowered. Tests of regional lung function have shown impaired ventilation of the lower zones. As a result of the altered ventilation-perfusion relationship, hypoxemia and hypercapnia may be severe in advanced disease, particularly during exercise.

A number of attempts have been made to detect the disease at a presymptomatic stage and in the absence of overt chest radiographic abnormalities. Most such efforts have focused on measurements of lung mechanics. It has been possible to show a lower maximal expiratory flow for a given transpulmonary pressure in subjects with normal chest x-ray findings but with significant dust exposure. However, because these approaches require invasive studies with particular attention to calibration and are relatively cumbersome, measurements of lung mechanics are not feasible in field studies of exposed populations.

The potential importance of small-airways disease in asbestos exposure remains unclear. Certainly, the early lesions in asbestos exposure are localized to the terminal and respiratory bronchioles, and tests of small-airways function detect flow limitation in small airways before results of other pulmonary function tests become abnormal. However, asbestos-induced small-airways disease may occur independent of the other abnormalities of asbestosis.

Diagnosis of Asbestosis

The diagnosis of asbestosis is based on four criteria: (1) an appropriate history of exposure, (2) compatible radiographic changes (ILO category >1/1), and (3) diffusing capacity and forced vital capacity below the lower limits of normal. These criteria and the evidence supporting their applicability have been published by the American Thoracic Society. It is particularly difficult to diagnose asbestosis in the absence of changes on the chest x-ray film. Lung biopsy via bronchoscopy, thoracotomy, or video-assisted thoracoscopy are only rarely required or justified in making the diagnosis. Biopsy can be occasionally justified to exclude other causes of interstitial fibrosis but should never be carried out merely to provide evidence for litigation.

Pathology of Asbestosis

Visual inspection of lungs from victims of asbestosis usually demonstrates thickened visceral pleural membranes. The cut surfaces of the shrunken lungs display honeycombing and fibrosis identical to those seen in other forms of diffuse interstitial fibrosis.

The microscopic hallmark of asbestosis is the asbestos is body. Asbestos bodies are elongated, golden-brown structures beaded with proteinaceous material; their lengths correspond to the individual asbestos fibers that form their cores (Fig. 5). Because of their high iron content, they stain particularly well with iron stains. Early in the disease process, asbestos fibers are found intracellularly within macrophages recruited to the area of deposition. Within the macrophage, the fiber may become leached and fragmented to a smaller size. The beading represents biologic modification of the fiber and is composed of proteinaceous material rich in ferritin. After the

death of the macrophage, the acellular coated fiber can be recognized under the microscope as a mature asbestos body.

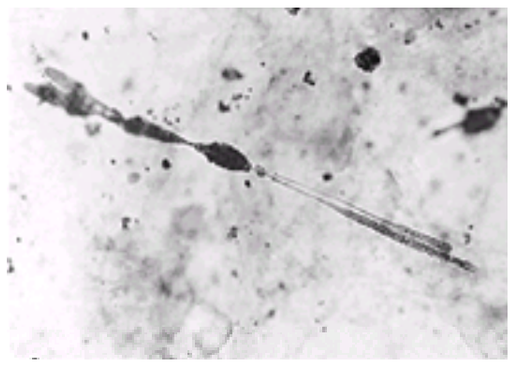

FIG. 5. High-power photomicrograph of asbestos body.

The minimal number of asbestos bodies in lung samples needed for a certain diagnosis of asbestosis remains unclear despite considerable research. One study has shown that lungs of urban dwellers with no occupational exposure to asbestos should contain only one asbestos body for every hundred sections of lung tissue examined. To make the diagnosis of asbestosis, there should be evidence of interstitial inflammation (early) and fibrosis (later) in the presence of asbestos bodies.

With a few notable exceptions, asbestos bodies are found regularly in patients with asbestosis; conversely, the absence of asbestos bodies is a reliable sign that the disease is not present. In any case, large tissue samples are required for certain diagnosis; biopsy material obtained by bronchoscopic biopsy is not adequate to identify the occasional asbestos body.

Inhalation of certain other fibrous minerals, such as glass wool, fibrous alumina, or silicon carbide, may induce formation of similar bodies. Because the core of these structures is composed of fibers other than asbestos, they are more accurately referred to as *ferruginous bodies.* Specific mineralogic identification of the fibers using electron microscopy and x-ray energy spectroscopy may be required to distinguish between asbestos and the other fibrous minerals.

The expectorated sputum of workers exposed to asbestos often contain asbestos and asbestos bodies many years after exposure has ceased. Asbestos bodies can also be found in samples of alveolar lavage fluid recovered by bronchoscopy. These findings confirm the exposure to asbestos but do not indicate the diagnosis of asbestosis. Most residents of industrialized areas have some asbestos bodies in their lungs. However, their presence is not diagnostic of asbestosis in the absence of clinical manifestations of disease.

When ferruginous bodies are detected in lungs or respiratory secretions of subjects who report no occupational exposure, the types of asbestos most often found are chrysotile and tremolite. Tremolite may be inhaled during the use of facial powder composed of talc contaminated with small amounts of the nonasbestiform mineral tremolite.

Chrysotile is particularly susceptible to the leaching process; with time the number and size of chrysotile fibers decline notably. In contrast, amphiboles are more resistant to chemical leaching and tend to persist in the lungs. The intracellular production of asbestos bodies may inacti-vate the fiber and prevent further toxicity. In chrysotile-induced asbestosis, numerous asbestos bodies and uncoated fibers may be found for prolonged periods despite the leaching process.

From the above discussion, it is apparent that the numbers of fibers and ferruginous bodies found in respiratory secretions and lung tissue at postmortem examination can vary considerably, depending on exposure history and other factors. Urban dwellers without specific occupational exposure have relatively few fibers; much greater numbers of fibers are seen in subjects with clear occupational exposure and clinical manifestations of asbestosis.

The hazards of asbestos exposure—namely, asbestosis, pleural thickening and plaques, bronchogenic carcinoma, and mesothelioma—can be related to the extent of exposure. The density of fibers found in the dried lung samples of various population groups depends on the intensity of exposure and shows an enormous range. Although subjects with no occupational exposure have detectable fiber counts, it is important to keep in mind that the numbers of coated and uncoated fibers are hundreds of times lower than in exposed healthy workers and thousands of times lower than in workers with apparent lung disease. Urban dwellers without occupational exposures have <1000 fibers per gram of dry lung tissue. Fiber counts in lung samples from established cases of asbestosis and mesothelioma usually exceed 80 million per gram of dried tissue. In subjects with lung cancer, fiber counts are more difficult to relate to disease risk because of the dominant carcinogenic effect of cigarette smoke.

Measuring Asbestos Fibers in Tissues

Most of the asbestos present in the lungs of exposed workers is in the form of short (<5 µm) translucent fibers that do not take up histologic stains. Hence, most of the asbestos burden in lung tissue is invisible by standard light microscopy but can be seen by phase-contrast or electron microscopy techniques. Only a very small minority of the longer fibers evolve into more conspicuous asbestos bodies. To overcome this problem, standardized scientific approaches for evaluating the asbestos burden have been developed.

The Pneumoconiosis Committee of the American College of Pathologists has specified that the minimal criteria for the histologic diagnosis include the identification of peribronchiolar fibrosis and at least two asbestos bodies in tissue sections. Fiber counting can be done on a digest of tissue. However, enumerating asbestos bodies in tissue sections is the usual approach for general pathologists. Because the segmented coating of asbestos bodies is rich in iron, the use of iron staining is a particularly sensitive method for detecting asbestos bodies. It turns out that agreement is excellent between the numbers of asbestos bodies seen in tissue sections and those present in digests of tissue. An average of two asbestos bodies on 2 × 2-cm sections of lung tissue is equivalent to approximately 200 asbestos bodies per gram of wet fixed tissue.

Pathogenesis of Asbestosis

Little is known about the earliest tissue responses to inhaled asbestos in humans. Experimental studies in animals exposed to asbestos in relatively high concentrations show that the first lesions are inflammatory in nature and are localized to bifurcations of small airways, the sites of most intense deposition of inhaled fibers. With further exposure, a macrophage-dominant inflammatory process involves the lumina of small airways and extends into alveoli. Because the macrophage is central to dust phagocytosis, it can be assumed to modulate many of the subsequent pathologic events. It is important to note that activated macrophages release a number of inflammatory mediators and proinflammatory cytokines. These include chemotactic cytokines and peptides, growth modulators such as insulin-like growth factor-1, platelet-derived growth factor, interleukin-1a, and tumor necrosis factor-a. Also produced are enzymes allowing rapid generation and release of active oxygen species, such as peroxides, hydroxyl radicals, and superoxide anions. These in turn directly oxidize lipids of cellular membranes and damage DNA and proteins. The proteolytic enzymes such as elastases and cathepsins induce injury and death of adjacent structural lung cells, such as epithelial cells, endothelial cells, and interstitial fibroblasts.

A second step in the pathogenesis of asbestos lesions involves fibers interacting directly with epithelial cells and fibroblasts. Undegraded asbestos fibers enter epithelial cells by endocytosis and are transported along the intracellular microtubular network. From the basolateral surfaces of the cells, the fibers migrate into the interstitium and can directly interact with interstitial fibroblasts.

With time, pathologic amounts of extracellular matrix proteins such as collagen, elastin, and proteoglycans are deposited. The lungs lose air space volume and elasticity. The lesions are found more in the lower lung zones, reflecting the proportionally greater ventilation (and hence particle burden).

Clinical Course of Asbestosis

Severe asbestosis advances to physiologic deterioration, disability, and death. Death is the result of respiratory failure, failure of the right side of the heart, and respiratory malignancies. The major reductions in deaths caused by asbestos during recent years can be traced to the relatively milder disease present in the population of aging workers. Efficacious therapy for asbestosis does not exist. Treatment of the symptoms—bronchodilators if obstruction is present, cardiac medications if right-sided heart failure is present—probably have little effect. Whether continuous low-flow oxygen therapy is helpful in hypoxemic patients has not been

proved.

Pleural Effusion and Diffuse Pleural Thickening

Benign pleural effusions often appear during or after asbestos exposure. Effusions usually occur within the first decade of exposure. The chief symptoms are dyspnea and pleuritic pain. The radiographic appearance is no different from that of other effusions. Because the majority of such effusions are not associated with signs of established asbestosis, diagnostic thoracocentesis is often required. Systemic signs of inflammation, including an elevated white blood cell count and elevated sedimentation rate, may be present. The pleural fluid is an exudate and may contain both polymorphonuclear leukocytes and mononuclear cells. Only infrequently is the fluid overtly bloody. Asbestos fibers are hard to find, and usually biopsy of the pleura shows only a chronic, nonspecific reaction. The effusion tends to linger for several months and frequently leads to diffuse pleural thickening and a fibrothorax. In some instances, the fibrothorax leads to appreciable restrictive impairment. When a substantial fibrothorax develops, there is a tendency to consider surgical decortication; however, asbestos-induced pleural thickening and fibrothorax generally improve during the course of several years and should be observed without intervention. Pleural effusions and thickening do not portend the development of mesothelioma.

Pleural Plaques

Pleural plaques are a characteristic feature of prolonged asbestos exposure. Plaques, often calcified, are usually located on the lower lateral chest wall and on the central portion of the diaphragm; radiographically discernible plaques usually do not develop until after more than a decade of exposure. Their pathogenesis is distinct from the development of effusion and fibrothorax. They represent markers of asbestos exposure but do not by themselves constitute a disease process, nor do they portend later pulmonary impairment. In many instances, such plaques may extend around the lateral curvature of the chest. Sometimes they are seen on the anterior or posterior chest wall only. Pleural plaques, usually on the diaphragm, can be found at autopsy in most subjects who have worked for >5 years with asbestos. Although diffuse pleural thickening is often associated with fibrothorax and restrictive ventilatory impairment, pleural plaques probably have no adverse effect on lung function. Plaque formation and calcification may also involve the pericardium (Fig. 6).

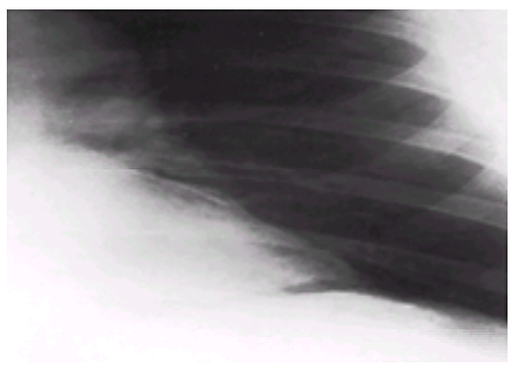

FIG. 6. Calcified plaques of pericardium and left diaphragm.

When viewed *en face* on the posteroanterior chest film, plaques can be mistaken for parenchymal shadows and disease (Fig. 3). In such cases, absence of parenchymal disease on the lateral chest film should alert the interpreter that pleural disease has obscured the interpretation of the posteroanterior film. Also, CT has proved to be a sensitive and definitive method for defining plaques and distinguishing them from parenchymal disease, but it is not required except in complex cases.

It is a mistake to assume that the presence of plaques portends the development of mesothelioma or lung cancer. Pleural plaques are seen more frequently after exposure to the amphiboles than to the serpentine chrysotile. Calcification usually appears in the plaque that has been present for more than a decade. However, calcification is seldom noted on the plain film until two decades after first exposure to asbestos.

Asbestos as a Carcinogen

No aspect of asbestos is more controversial than the issues surrounding its association with malignancy. That there is an association between exposure to asbestos and risk for malignancy has been clear for the past 40 years. Moreover, at intense exposure levels there is an approximately linear dose-response relationship. What remains difficult to pin down is the precise risk of asbestos exposure relative to other carcinogens, and the precise mechanisms of tumor induction. One analysis suggested that lung cancer may account for as many as 26% of deaths in some groups of asbestos workers, a risk three to five times higher than that expected in other workers. The excess mortality is detectable after at least a decade of exposure and climbs progressively thereafter. The risk depends somewhat on the type of industrial exposure, as asbestos textile workers exhibit a higher incidence of lung cancer than cement workers, who in turn have more malignancies than asbestos miners. In most of these studies, the populations were exposed to chrysotile fibers only; the amphiboles are considered more carcinogenic than chrysotile.

With control of asbestos exposure in the workplace, cigarette smoking may be a more important determinant of lung cancer risk in exposed workers than asbestos itself. In this regard, lung cancer has developed in relatively few nonsmoking workers with significant asbestos exposures. Moreover, the very high incidence of smoking among industrial workers increases the risk for lung cancer in nonsmoking co-workers through secondhand exposure to smoke. Certainly, the risk of smoking in the induction of lung cancer was considerably underestimated in early population studies.

The minimal level of asbestos exposure or disease that puts an individual at risk for malignancy remains uncertain. Back extrapolation of the concentration response that applies for workers with heavy exposures cannot be scientifically justified; there are too few reliable data among subjects with lower levels of exposure. One analysis suggested a threshold level of exposure rather than a finite but decreasing risk at low exposure levels. This threshold is close to the threshold for development of asbestosis. Studies in asbestos cement workers in the United States and miners exposed to amosite in South Africa both provide support for the notion of a threshold value for asbestos-induced lung cancer.

Malignant Mesothelioma

Pleural mesotheliomas can occur as either benign or malignant tumors. The benign form, which is not associated with asbestos exposure, is frequently accompanied by hypertrophic pulmonary osteoarthropathy. In contrast, malignant mesothelioma is an aggressive, uniformly fatal, diffuse cancer arising from the pleura and sometimes the peritoneum (Fig. 7, Fig. 8 and Fig. 9). Most malignant mesotheliomas can be traced to previous exposure to asbestos or the non-asbestiform fibrous mineral erionite. As mentioned previously, asbestos-induced mesotheliomas develop only after intense exposure; they do not occur following the minimal exposures experienced by urban dwellers.

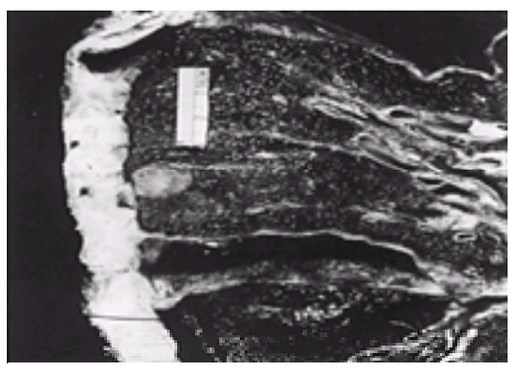

FIG. 7. Whole-lung section of a subject dying of malignant mesothelioma. The lung is encased in white tumor tissue, and a secondary deposit is apparent in the lung parenchyma.

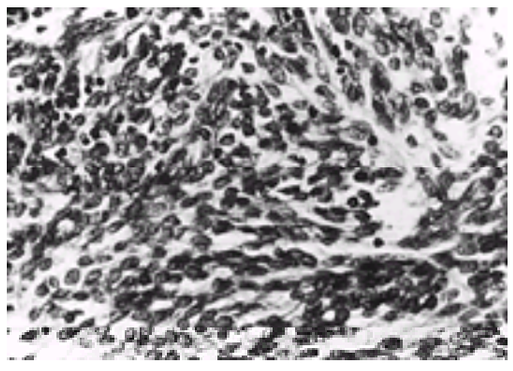

FIG. 8. Photomicrograph showing the histologic features of a sarcomatous type of mesothelioma.

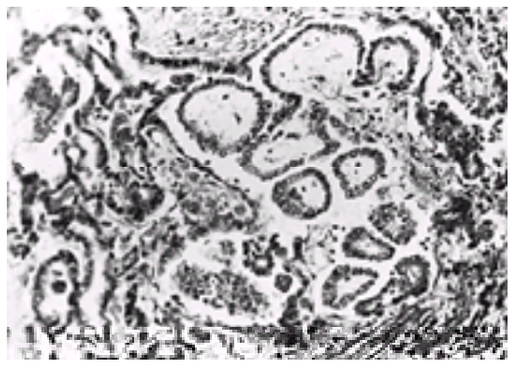

FIG. 9. Photomicrograph of a section of a tubopapillary mesothelioma. This histologic variant bears a close resemblance to a papillary carcinoma of the thyroid.

Malignant mesothelioma remains a rare cancer. It typically appears several decades after the first exposure to asbestos, although shorter incubation periods have been recorded following particularly intense exposures. In certain instances, however, the intense exposure may have ceased several decades before the mesothelioma becomes clinically apparent. Treatment options for this resistant neoplasm, which remain limited, are discussed in Chapter 70.

DISEASES ASSOCIATED WITH EXPOSURE TO SILICA

Silicosis is the disease induced by the inhalation of free crystalline silica (silicon dioxide). Silicon is the second most abundant element and forms the greater part of the earth's crust. It is therefore ubiquitous in the human environment, and some exposure to silicon dioxide and the salts of silicic acid is a fact of life. Silicosis probably occurred in paleolithic times, as soon as humans began to make stone tools. Indeed, the term *silicosis* derives from the Latin word *silex,* meaning “flint.” Intense exposure leading to disease occurs in mining and in those industries in which the mineral is used, such as the manufacture of ceramics, pottery, and bricks. However, as with asbestos, public health regulations have significantly reduced the numbers of silicosis cases in the industrialized world.

Silicon can exist free, that is, not chemically combined with other elements, or it may form silicates by combining with various elements. Silicon dioxide exists in crystalline and amorphous forms, as well as mixed forms. The crystalline forms include cristobalite, tridymite, and quartz. All can produce fibrotic pulmonary disease, with quartz being somewhat less potent in this respect than the others. The amorphous silicas include diatomite, derived from the skeletons of oceanic diatoms, and vitreous silica, a manufactured product of heated silica. The amorphous forms are generally not fibrogenic. Mixed forms, deposits containing crystalline and amorphous features, include chert and flint.

Many of the silicates, salts of silicic acid, are also variably fibrogenic. With the obvious exception of asbestos, the silicates tend to be less toxic than the free crystalline forms of silica. Sandstone and flint are composed of almost pure quartz; granite contains from 15%–70% of free silica by weight, slate 30%–45%, and shales around 10%.

Sources of Exposure

The harmful effects of hard rock mining have been known for millennia. Pliny the Elder wrote about them but may not have associated them with the respirable dusts. In the sixteenth century, Agricola correctly associated most of the lung disease of metal miners with the continued inhalation of mine dust in *De Re Metallica.* Later, Ramazzini pointed out that many diseases originated from workers' occupations and that mining was particularly dangerous. He noted that stone cutters were particularly at risk for the development of lung disease. In the nineteenth century, grinding, the manufacture of pottery, and trades using flint and slate emerged as particularly hazardous.

Definitive regulatory efforts in the industrialized nations have resulted in a major decrease in silicosis during the past half-century. New cases of silicosis tend to be sporadic rather than epidemic. In contrast, the pneumoconioses present a growing problem in the emerging industrial nations. Silicosis persists as a public health menace in coal and metal mines, sandblasting, ceramics refractories, and foundries. Silica flour, finely ground silica used as filler for cosmetics, abrasives, and paint extenders, represents a particularly hazardous form of silica.

Sandblasting is a particularly high-risk occupation, generating large amounts of airborne silica. The use of silica for this purpose has ceased under regulatory pressure in many advanced nations. In nations such as the United States, where its use persists, it remains the most frequent cause of acute silicosis.

Exposure-Response Relationships

As many as a million Americans may be exposed to silica in the workplace. Precise figures of the prevalence and incidence of silicosis are not available. It is certain, however, that the prevalence of silicosis has fallen very significantly in recent decades. This drop has been best documented in the small but well-studied Vermont granite industry.

Although large groups of workers exposed to free silica have undergone surveillance for many years, few attempts have been made to derive an exposure-response relationship. Currently, studies are under way in the United States, South Africa, and Canada to establish the relationship between the development of silicosis and cumulative dust levels. The current evidence suggests that an air quality standard for free silica of 0.1 mg/m^3 should protect the vast majority of the work force. Chronic forms of clinically important silicosis are seldom seen before a decade of moderately intense exposure.

Silicosis

Clinical Features

For clinical purposes, silicosis has traditionally been divided into chronic, subacute, and acute forms (Table 2). Classic or chronic silicosis, the usual type, can be further divided into simple and complicated forms based on the radiographic appearance. Simple silicosis is characterized by the presence of small rounded shadows that usually appear in the upper lobes and later are noted throughout all lung zones (Fig. 10). Complicated silicosis is said to be present when shadows on the chest x-ray film expand to >1 cm in diameter (conglomerate masses).

Chronic silicosis
Simple silicosis
Complicated silicosis
Conglomerate shadows ("progressive massive fibrosis")
Caplan's syndrome (rheumatoid pneumoconiosis)
Acute silicosis (silicoproteinosis)
Other syndromes
Irritant bronchitis
Small-airways disease
Emphysema

TABLE 2. *Clinical classification ofsilica-induced syndromes*

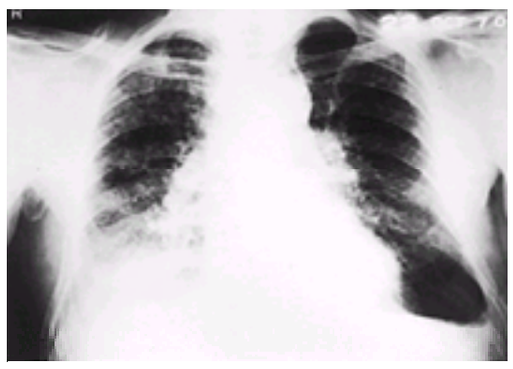

FIG. 10. Chest radiograph of a worker with simple silicosis. Note the evidence of a resolved pleural effusion in the right hemithorax.

Simple silicosis is not associated with respiratory symptoms. Typically, simple silicosis is discovered during radiographic screening. The chest x-ray film shows a striking profusion of small rounded shadows, not associated with symptoms. If any respiratory symptoms, such as cough or dyspnea, are present at this stage, they are more likely the results of an associated respiratory illness other than silicosis. Given the high prevalence of cigarette smoking among workers exposed to mineral dusts, smoking-related lung disorders must also be considered as a cause of symptoms at this stage.

In general, simple silicosis does not progress after cessation of exposure, and the patient can be assured that disability will not occur. In complicated silicosis, however, the large shadows on the chest x-ray film slowly enlarge during a period of years. This can occur even without further exposure. Subjects with massive fibrosis, high relative levels of exposure to dust, or tuberculosis are most likely to progress to complicated silicosis. The earlier the onset of complicated silicosis, the greater the likelihood that the disease will progress and become disabling. When complicated disease reaches more advanced stages, symptoms of breathlessness, cough, and sputum production appear. As the size of the conglomerate masses increases, the symptoms worsen, and pulmonary function tests demonstrate a worsening restrictive pattern. When cor pulmonale develops, it is not related as much to hypoxia as to a generalized decrease in the vascular bed. Thus, pulmonary hypertension and overt cor pulmonale occur late in the disease course.

Irritant Bronchitis and Emphysema in Silicosis

Productive cough in victims of silicosis is usually a consequence of smoking; less frequently, cough may be a result of silica exposure. Silica-induced bronchitis would appear to be limited to severe cases of silicosis. The possibility that it is caused by other substances in the workplace (industrial bronchitis) cannot be ruled out. Pulmonary function tests show somewhat reduced flow rates. Correlation between these abnormalities and the radiographic evidence of advanced silicosis is poor.

The airways obstruction appears to be a result of torsion and distortion of the large airways and is usually associated with some bullous emphysema and marked overdistension. Questions have been raised as to whether silicosis might be associated with an increased incidence of emphysema. This issue has been difficult to study, given the very high incidence of smoking among workers exposed to silica. A recent Canadian study based on CT analysis suggests a significant excess of emphysema in both smokers and nonsmokers working with silica. Radiographically evident emphysema was associated with abnormal pulmonary function both in those with established pneumoconioses and in smokers with silica exposure but no radiographic changes of silicosis. In nonsmokers, radiographic evidence of emphysema was detected by CT only when there was evidence of established pneumoconiosis. Not surprisingly, smokers in this study had emphysema even without evidence of overt pneumoconiosis.

Acute Silicosis

Intense exposure to very high ambient concentrations of silica within a short period leads to the characteristic syndrome of acute silicosis. Because acute silicosis shares pathologic features with alveolar proteinosis, it has also been referred to as *silicolipoproteinosis.* Certain exposed workers, including sandblasters, ceramic workers, and surface coal miners who drill holes to place explosives, are at particular risk for acute silicosis. The production of silica flour may be associated with intense exposure and lead to the development of acute silicosis. The duration of exposure to silica is usually a matter of only months. In the United States, the most notorious epidemic of acute silicosis involved miners constructing a hydroelectric tunnel through a sandstone mountain, the Hawk's Nest Tunnel at Gauley Bridge, West Virginia, in 1933. In what was the United States' worst industrial disaster, nearly 500 miners died of acute silicosis within several years, and many more were severely disabled.

The clinical features of acute silicosis include severe dry cough, fever, intense dyspnea, and weight loss. Hypoxemia may be profound. Pulmonary hypertension and cor pulmonale rapidly develop. The chest x-ray findings may resemble those of classic silicosis; alternately, it may show coalescent shadows in the lower lung zones (Fig. 11). Once acute silicosis becomes established, hypoxic respiratory failure develops inexorably. Patients who survive for more than a few months with acute silicosis have been thought to be particularly susceptible to infection with various intracellular respiratory pathogens, such as mycobacteria and *Histoplasma capsulatum.* Use of antifibrotic and anti-inflammatory drugs such as corticosteroids has proved ineffective; lung transplantation or heart-lung transplantation may prove to be the only effective therapy.

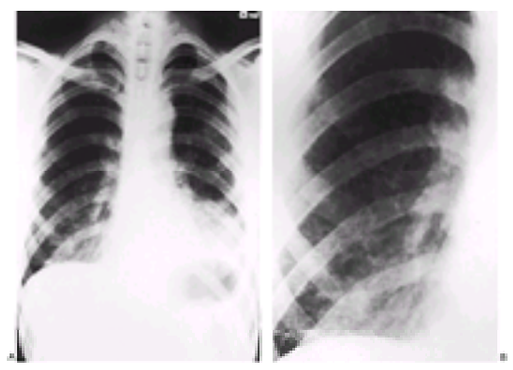

FIG. 11. Chest radiograph of a subject with acute silicosis. **Panel A:** Acinar filling pattern in both lower zones and in the left lateral chest. The extensive soft shadowing seen in acute silicosis is more often seen in the upper zones. **Panel B:** Detail of a right lower lung zone containing an acinar filling pattern with scanty irregular opacities.

Pulmonary Function in Silicosis

Altered pulmonary function accounts for much of the disability and death in severe cases of silicosis. However, in the early stages of simple silicosis, pulmonary function is usually not impaired. Spirometric values, gas exchange, and lung volumes and mechanics are normal or minimally altered. Perhaps because of their focal nature, the silicotic nodules present throughout the lung parenchyma have surprisingly little effect on lung function. The pathways of removal of silica particles into the pulmonary interstitium and regional nodes bypass the distal airways and alveoli, minimizing any deleterious effects on gas flow or mechanics. In this regard, silicosis differs importantly from asbestosis, in which extensive bronchiolar and alveolar inflammation and scarring of the gas exchange surface takes place.

In simple silicosis, a small but statistically significant decrement in the forced vital capacity can be detected when exposed population groups are studied and compared with control subjects without exposure. These changes have no clinical significance and are not associated with symptoms. Because these changes are small, they cannot routinely be detected in individual subjects. The lung volumes in simple silicosis are nearly always normal. Indices of gas exchange, such as the diffusing capacity and arterial oxygen concentration, are generally normal. Pulmonary compliance may be reduced even though spirometric values are normal. The extent of the mechanical changes, although somewhat more sensitive than the spirometric measurements, can only roughly be related to radiographic score.

Studies defining the rate of decrement of pulmonary function among exposed workers have been used to justify current standards for ambient dust levels. Cross-sectional studies of workers in the Vermont granite industry have provided the most comprehensive picture of the impact of any respirable dust on pulmonary function and indicate that granite dust exposure leads to a loss of vital capacity of 2 mL/y. This compares with a decline of 30 mL/y attributable to aging and of 9 mL/y to smoking. This study served as the basis for the National Institute of Safety and Health criteria document recommending that the permissible exposure limit be halved from 0.10 to 0.05 mg/m^3. An additional longitudinal study in the same workers found no difference in the rates of decline in function and no difference in the changes between granite workers and unexposed blue collar workers from the same region. At this time, there is no compelling evidence that exposures to quartz at levels at or below the current standard of 0.1 mg/m^3 result in loss of pulmonary function.

Without a doubt, declines in pulmonary mechanics and volumes occur more rapidly in workers with complicated silicosis. In subjects with simple silicosis in an Asian study, most of whom continued to smoke, the FVC (forced vital capacity) and FEV_1 (forced expiratory volume in 1 second) declined by 59 and 64 mL/y, respectively.

The presentation of the patient with acute silicosis is that of rapidly progressing respiratory insufficiency. Both the lung volumes and the diffusing capacity are markedly reduced. The reduction is generally proportional to the extent of the conglomerate shadows. Lung compliance is markedly reduced, and marked hypoxemia results from ventilation-perfusion mismatch.

Radiographic Features

In uncomplicated early silicosis, the chest x-ray film shows multiple small round shadows, usually developing in the upper zones first. These represent the summation of multiple small silicotic nodules superimposed on one another. High-resolution CT demonstrates the individual nodules.

In complicated silicosis, larger rounded nodules (type *r*) become more profuse than the *p* and *q* shadows. However, these radiographic changes resemble those of many other advanced nodular pneumoconioses, including coal workers' pneumoconiosis (Chapter 33). Eggshell calcification in the hilar nodes occurs fairly frequently, and peripheral shadows themselves may also become calcified. Volume loss in the upper lobes results in overdistension of the lower lobes and retraction upward, with migration of the hila. The conglomerate shadows that form in complicated silicosis are not specific to silicosis and resemble those seen in coal workers' pneumoconiosis. They typically appear in the periphery of the upper lobes first, later appearing to migrate toward the hilum. High-resolution CT allows their detection before they are apparent on the chest x-ray film. However, the prognostic significance of such findings is unknown. Hence, it is rarely necessary to perform CT in the initial evaluation or follow-up of silicosis.

Cavitation of conglomerate shadows may occur and in some cases indicates superinfection with tuberculosis. Pleural plaques can develop in silicosis but are infrequent. Single conglomerate shadows often represent a diagnostic dilemma, as malignancy and tuberculosis must be ruled out. Acute silicosis, as already mentioned, presents as a bilateral alveolar filling process, often in the absence of small rounded shadows.

Pathology

The lungs of silicotic subjects are adherent to the chest wall, and the pleural surfaces are thickened. There may be calcified pleural plaques on the visceral pleural surfaces. The cut surfaces of the lungs are studded with rounded grayish nodules, usually more numerous in the upper lobes; calcification may be present. In some instances, individual nodules may have aggregated into conglomerate masses. These masses may form cavities as a result of ischemic necrosis or superinfection with tuberculosis.

Under the microscope, the hallmark of simple pulmonary silicosis is the silicotic nodule, a pathognomonic feature. The nodule begins as an aggregation of dust-laden macrophages within the interstitium, particularly near respiratory bronchioles, pulmonary vessels, and pleura. The mature nodule has a central area that gradually becomes acellular and is composed of connective tissue arranged in a concentric onion skin pattern. The central area may eventually become necrotic. The periphery is populated with inflammatory cells, particularly lymphocytes and dust-laden macrophages. The nodules may actually assume a granulomatous appearance. Accompanying these changes may be some interstitial thickening in the alveolar wall and a proliferative response of type II pneumocytes in areas of epithelial denudation.

As simple disease progresses to complicated silicosis, the small nodules enlarge and coalesce into large masses of hyalinized tissue. One sees a whorled nodule consisting of an acellular center, through which course fibers of hyalinized collagen. More peripherally, there is granulation tissue and some palisading of epithelioid cells (Fig. 12). The nodules are most prominent around pulmonary arterioles and respiratory bronchioles. The pulmonary vascular bed is slowly obliterated as the nodule increases in size. Smaller vessels become incorporated into the evolving nodule. Expanding conglomerate masses eventually envelop larger segmental and lobar arteries, which then undergo thrombosis and gradually become engulfed by the fibrotic tissue mass. The center of the silicotic nodules, when viewed microscopically under polarized light, contains birefringent silica particles. These tend to be located at the periphery of the nodule, away from the acellular center.

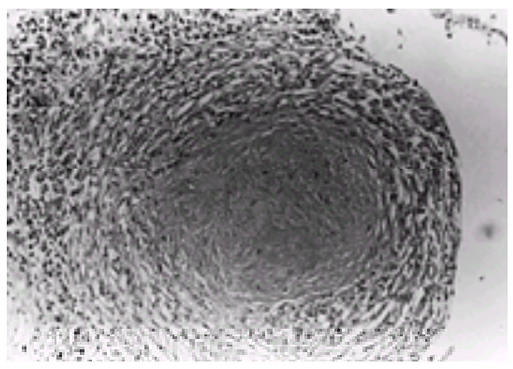

FIG. 12. Photomicrograph of silicotic nodule. Note the typical whorled appearance.

Complicated silicosis usually develops in the upper lobes, which become fibrotic and atelectatic. The lower lobes in turn become overdistended (Fig. 13 and Fig. 14), and the hila shift upward. A variant of the classic conglomerate mass is the even larger rheumatoid silicotic nodule. As its name implies, it is seen in subjects with obvious rheumatoid arthritis or those with high circulating levels of rheumatoid factor.

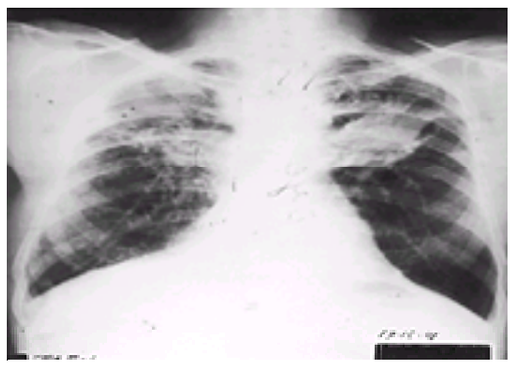

FIG. 13. Chest radiograph of a worker with complicated silicosis. There is a conglomerate shadow in left middle-upper lung zone.

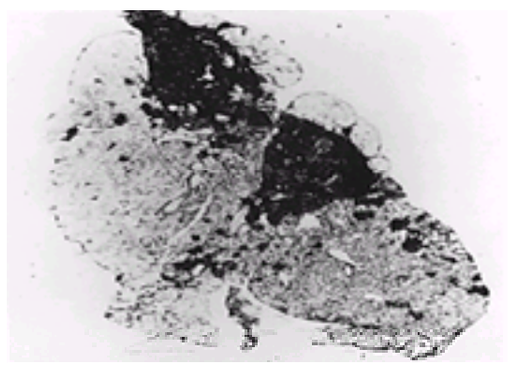

FIG. 14. Whole-lung section of complicated silicosis.

In acute silicosis, the alveoli are diffusely filled with a homogeneous pinkish exudate; the interstitium is infiltrated with mononuclear cells (Fig. 15). The alveoli are lined with degenerating pneumocytes and abundant quantities of birefringent material. The interstitium is thickened and fibrosis is apparent. Mixed pathologic patterns containing features of both acute and chronic silicosis are occasionally seen and have been dubbed *subacute silicosis.*

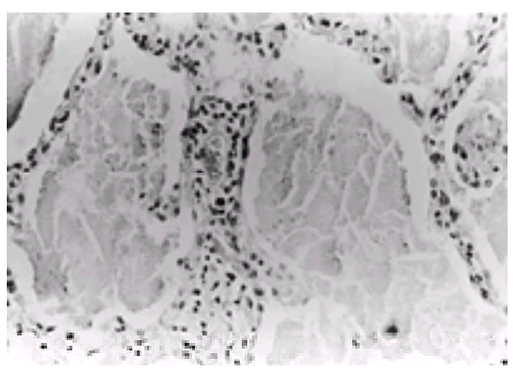

FIG. 15. Photomicrograph showing acute silicosis (silicolipoproteinosis) in the lungs in a sandblaster dying of acute respiratory insufficiency. Proteinaceous (pink) exudate fills all the alveoli. Interstitium is thickened by round-cell infiltration.

Cellular Pathogenesis of Silicosis

Free silica is not biodegradable and presents a toxic burden to a wide variety of lung cells; it is not surprising then that all cellular constituents of the lung may be involved in silicosis. However, the precise mechanisms by which silica exerts its toxic effects are poorly understood. Because ingestion of silica particles by macrophages is such a prominent feature of the disease, their possible role in pathogenesis has been well studied. Ingested silica particles appear in the phagosomes of macrophages; the phagosomes fuse with and damage lysosomal membranes, which then rupture. When this occurs, the macrophage dies and disgorges the silica particles. Along with the released silica particle (which is available to be ingested by another phagocyte), the macrophage releases cytokines, oxidant species, proteolytic enzymes, and other mediators of cellular toxicity.

Alveolar lining cells (type I pneumocytes) are also major targets of silica toxicity. Death of type I cells denudes the alveolar wall, exposing interstitial cells, such as fibroblasts, to contact with fibrogenic mediators, such as growth-promoting cytokines. Proliferation of these cells and their migration into the damaged alveolar space may result in effacement of the distal air spaces by extracellular matrix components.

Plausible and comprehensive hypotheses regarding the exact mechanisms of toxicity of inhaled silica have been put forward by Ghio and colleagues. Biophysical and biochemical interactions between the negatively charged surfaces of silica particles may be a central event. It has been proposed that deposited silicates result in the local generation of oxidants in the lung. The surface of all silicates contains silanol (SiOH) groups. These dissociate, resulting in a net negative charge on the particle surface and allowing adsorption of organic and inorganic cations. In particular, ferric ions react and form complexes with silanol groups. Silanol groups found on silicates have the ability to attract ferric ions, forming silicate-iron complexes.

Reduction of iron in the complex results in the generation of hydroxyl radicals. These in turn oxidize cellular proteins and lipids, presumably resulting in the observed cytotoxicity. Thus, the surface of the ingested silicate particle brings together chelated iron, hydrogen peroxide, and a reductant such as superoxide to allow cytotoxicity to proceed. Experimentally, the toxicity of silica has been mitigated by coating the particles before exposing susceptible cells. In support of this theory, agents such as aluminum or polyvinyl pyridine N oxide, by changing the charge properties of the silica surface, block or markedly reduce the cellular toxicity. This theory also appears to account for the observation that different forms of silica exhibit differing toxicities.

Various inflammatory mediators have been implicated in the development of silicosis. The cytokine tumor necrosis factor (TNF-a) is produced by macrophages in response to exposure to silica in animal models, and antibodies to this particularly toxic cytokine block progression of disease. Some of the effects of silica may represent reparative responses to the ongoing cellular injury. For example, hyperplasia of type II pneumocytes helps to repopulate the alveolar surfaces. This process has been shown to be driven by transforming growth factor-a, a mitogenic cytokine released by macrophages.

The effects of inhaled silica are not limited to the lungs. They affect the immune system, with both cellular and humoral immune responses being markedly altered. Patients with silica exposure and silicosis frequently have elevated levels of circulating autoantibodies, such as antinuclear antibodies. Rheumatoid factor is usually not elevated. This response is thought to represent a systemic response to continued tissue damage and release of nuclear components from dying lung cells. Further studies have shown that there is no reduction in the number or function of circulating T or B lymphocytes. Delayed hypersensitivity remains intact. A postulated decrement in suppressor T-cell function has been invoked to explain the prevalence of autoantibodies in silicosis. To understand genetic factors involved in the development of silicosis, human leukocyte antigen (HLA) phenotyping has been carried out in silica-exposed workers, mostly with inconclusive results. Experimental studies of the immunologic effects of silica delivered as an aerosol or a slurry instilled through the trachea of experimental animals have shown profound changes in immune function.

Diagnosis

The occupational history and radiographic findings almost always suffice to make the correct diagnosis of simple or complex silicosis. The occupational exposure to silica should be appropriately intense and prolonged, and the radiographic and/or CT features should be characteristic. Only in cases of mixed dust exposure might lung biopsy or other invasive studies be required. Isolated cases of acute silicosis may be an exception to this rule, as the disease progresses to respiratory failure so rapidly that lung biopsy may be required to rule out other or coexisting pulmonary disorders. If coexisting infection with *Mycobacterium tuberculosis* is suspected, bronchoscopy may be employed to collect cultures of organisms not found in sputum samples.

Treatment and Prevention

There is no effective treatment for silicosis. Palliative measures are nonspecific and similar to those offered to any patient with other severe restrictive pulmonary disorders and failure of the right side of the heart. Low-flow oxygen is recommended; however, there is no evidence that this prolongs life in patients with silicosis. Steroid therapy is probably of no benefit. Long-term steroid therapy may help patients with silicosis and a second pulmonary disorder that is steroid-responsive. Lung transplantation is offered to patients with end-stage pneumoconioses, including silicosis, and represents approximately 1% of lung transplants done in the United States.

Preventive measures are based on dust control through minimizing generation of respirable dust and providing adequate ventilation at the work site. Respirator masks may be used, but it is far preferable to provide adequate ventilation to remove airborne dust. Sandblasting remains particularly hazardous and has been outlawed in a number of advanced countries. Where allowed, sandblasting should be undertaken only when a positive pressure respirator with its own air supply is used.

Silicotuberculosis

Among the pneumoconioses, silicosis is unique in predisposing to tuberculosis and atypical mycobacterial disease. Miners and other workers with significant exposure to silica have long been known to have a high incidence of tuberculosis. Those parts of the world in which tuberculosis infection and disease rates have declined to low levels have seen a commensurate decline in silicotuberculosis. In contrast, in the emerging industrialized nations, silicotuberculosis remains a significant problem among miners and other exposed workers.

The presenting manifestations of silicotuberculosis are identical to those of tuberculosis and include anorexia and weight loss, fever, and cough. Radiographic features of the infection may be difficult to detect during its early stages, superimposed as they are on the features of silicosis. Later, the appearance is quite similar to that of classic tuberculosis. Silicotuberculosis may progress to cavitation quite rapidly (Fig. 16).

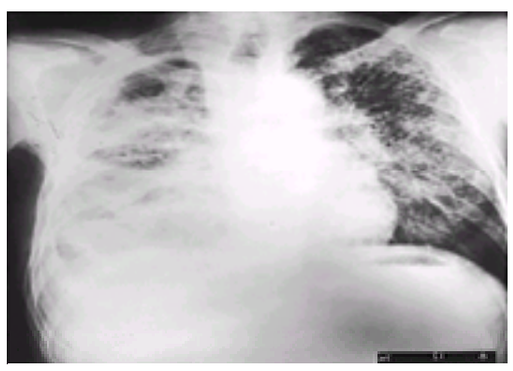

FIG. 16. Simple silicosis (ILO category 3/2) with tuberculous cavities in right middle and lower zones along with pleural effusion. This worker had been a borer and shot firer in a company that sank portals for deep coal mines.

The inhalation of silica has long been recognized to impair the phagocytic functions of macrophages specifically. Because monocytes and macrophages are key effector cells in host defense against *M. tuberculosis* and other intracellular organisms, tuberculous infection tends to progress rapidly in the silicotic lung. Enhanced susceptibility to tuberculosis can be demonstrated in several ways in experimental animals: Initial infection can be established with relatively smaller numbers of organisms than are required to produce disease in control animals; counts of recovered organisms are higher, and there is a greater propensity for spread from subcutaneous inoculation sites to the lungs.

Under conditions of laboratory culture, there is no evidence that silica alters the growth properties or infectivity of the tubercle bacillus itself. Nor does the inhalation and deposition of silica appear to interfere with other components of the immune response. Indeed, greater humoral and cell-mediated immune responses develop in animals exposed to silica than in control animals. Recently, it has been suggested that the increased incidence of tuberculosis in silica workers results from the accumulation of iron that forms complexes with silica dust particles in the lung. According to this hypothesis, silica particles may act as a local reserve of iron, which can be used by dormant mycobacteria as a virulence factor.

Mycobacteria other than *M. tuberculosis* have also been associated with silicosis. *M. avium-intracellulare* and *M. kansasii* have been isolated in subjects with silica exposure, even before overt disease is apparent on the chest x-ray film. When these atypical mycobacteria are detected in sputum samples, efforts must be made to determine whether they represent true pathogens or are simply opportunistic colonizing organisms.

The basic precepts of treatment of silicotuberculosis are the same as for treatment of tuberculosis in the absence of pneumoconiosis (Chapter 28). However, several important distinctions should be made. First, in severe cases of pneumoconiosis, the chest radiographic appearance may be dominated by the silicosis rather than by the tuberculosis. As a result, radiographic improvement during the course of chemotherapy may be minimal. Second, because macrophage phagocytic and killing functions are permanently impaired in silicosis, bacteriologic relapse is common despite the use of appropriate drugs and an adequate duration of therapy. Hence, more vigilance for relapse is in order after a full course of chemotherapy. Finally, disappearance of organisms from the sputum may be somewhat slower than in tuberculosis without accompanying silicosis.

All subjects with silicosis should be monitored with tuberculin skin tests. Those with a positive tuberculin skin test result but no mycobacteria in their sputum should receive routine isoniazid chemoprophylaxis (Chapter 28). Unfortunately, this is probably not as effective a preventive measure as in the general population. Some public health experts have therefore recommended that isoniazid be continued indefinitely in this disease; often, however, side effects preclude this approach.

A recent double-blinded, placebo-controlled trial of antituberculosis chemoprophylaxis was undertaken in 679 silicotic subjects in Hong Kong, where there is a high prevalence of both silicosis and tuberculosis. During the 5-year study, active tuberculosis developed in 27% of the placebo-treated workers and in 13% of those who received any of three chemoprophylaxis regimens. There were no significant differences between the several chemoprophylaxis regimens tested. There was no evidence that chemoprophylaxis led to the development of drug-resistant strains of bacilli. These data support the concept of decreased resistance of silicotic workers to tuberculosis and reaffirm the need for more effective antituberculosis chemoprophylaxis in this population.

Silica as a Potential Carcinogen

In recent years, the long-recognized possibility that silica might be a carcinogen has received renewed attention. Theoretical considerations consistent with this notion are derived from our understanding of the molecular biology of the silica-cell surface interaction. Reactions between silanol groups on the surface of silica particles, ferric iron, and cell surface components might be expected to activate intracellular signaling pathways involved in oncogene expression. However, there is little evidence that even advanced silicosis is associated with lung cancer. Indeed, during the early part of the twentieth century, when complex silicosis was much more prevalent, no association with carcinoma was apparent. Many studies have been unable to separate effects attributable to silica alone from those of other carcinogenic agents in the workplace, such as organic compounds, radon, and cigarette smoke. Animal studies are of limited value in answering these questions, given the relatively short term and high intensity of exposure necessary to elicit malignant responses in target species.

In summary, the evidence for an association between lung cancer and either silicosis or silica exposure remains quite controversial. If such an association exists, it is likely that silica has only a weak carcinogenic potential compared with such notorious carcinogens as cigarette smoke. The public policy consequences of any

abatement projects would be prohibitively expensive. Moreover, the cost of diverting resources away from other more clearly hazardous dusts would be a societal tragedy.

Inflammatory and Immune Disorders Associated with Pneumoconioses

Progressive massive fibrosis seen in conjunction with rheumatoid arthritis is a syndrome described by A. Caplan in 1953 in Welsh coal miners with pneumoconiosis. Caplan's syndrome has occasionally been reported in association with silicosis and rarely with asbestosis. However, in the latter case the association may simply be the result of mixed exposure to silica or coal dust. The majority of reports of Caplan's syndrome come from the United Kingdom; the disorder appears rare in North America. Caplan's syndrome may occur in workers with elevated serum rheumatoid factor who do not have manifestations of arthritis.

Some investigators have suggested that rheumatoid arthritis and other connective tissue disorders are associated with silicosis. This is not surprising, given the regional and systemic alterations of the immune system associated with silicosis. Patients with silicosis often have elevated serum antinuclear activity. However, this activity may simply represent a marker of ongoing tissue damage rather than a sign of rheumatologic disease. It has been suggested that systemic sclerosis develops more frequently following silica exposure, although statistical support is lacking. Despite the possible associations between silica exposure and rheumatologic disorders, the majority of disabled workers have osteoarthritis, not rheumatoid arthritis, as a consequence of the heavy mechanical labor they perform during their careers.

DISEASES CAUSED BY NON-ASBESTOS SILICATES: THE SILICATOSES

In this section, the silicatoses other than asbestosis are discussed. Like silica, the various silicates are ubiquitous on the surface of the earth. As a result of mining and a wide variety of industrial processes, they become airborne and have the potential to be inhaled. The fibrous silicates are relatively long and narrow (i.e., their aspect, or length-to-width, ratio is >3). Both fibrous and nonfibrous silicates induce pneumoconioses but are generally far less fibrogenic than silica. Perhaps as a result of their lesser degrees of toxicity, descriptions of the clinical syndromes induced by the silicates are less clear-cut than those of asbestosis or silicosis. Furthermore, the silicates are often contaminated with more toxic minerals, such as tremolite, that produce effects that tend to dominate radiographic patterns and the course of disease.

Most silicates are nonfibrous (called *phyllosilicates,* based on their leaflike structure). This group includes mica, kaolin, and vermiculite. Wollastonite, zeolite, and fibrous erionite are examples of the fibrous silicates. A number of silicates, such as talc, occur in both fibrous and nonfibrous forms. There is no substantial evidence that the nonfibrous silicates are in any way carcinogenic except when contaminated by asbestos.

Talc Pneumoconiosis (Talcosis)

Talc is a hydrated magnesium silicate having the chemical formula $Mg_6Si_8O_{22}(OH)_4$. It occurs in both fibrous and nonfibrous forms. Talc is mined in a number of parts of the United States, including Vermont, New York, Texas, and Montana. Talc deposits in the United States are contaminated with fibrous silicates such as tremolite, actinolite, and anthophyllite, but these are non-asbestiform variants of these minerals. As much as 40%–50% of some talc deposits may be contaminating minerals. In the United Kingdom, similarly impure talc ore was mined in the Shetland Islands. Talc has also been produced in Canada, Norway, Italy, France, and China.

Talc and mica have a platelike morphology that permits them to slide easily. This property makes them of value as lubricants and as a base for cosmetic powders. Talc is generally mined as soapstone, then milled and calcined. The latter process involves reduction of the milled material to a powder through heating at high temperatures (1200–1400°C). The finished product is used in the production of paints and ceramics, and as a lubricant in the roof-felting industry. It is also important in the production of pharmaceuticals and in the cosmetic industry, where it is used in face powder and talcum powder. High-grade talc from Italy, Vermont, and China is preferred for these uses.

Industrial exposure has been prominent in the rubber industry, where talc is frequently dusted into tire molds so that the finished tire can be more easily removed. Finely ground talc is used in the production of glossy paper. Low-grade talc is important in the fertilizer industry, where it is used for its anticaking properties and as a refractory filler.

Clinical Features of Talc Pneumoconiosis

Talcosis was described at the end of the nineteenth century. Like silicosis, simple talcosis causes few or no symptoms. Dyspnea and productive cough, when present, are usually a consequence of cigarette smoking, industrial bronchitis, or lung disorders other than the talcosis. However, when conglomerate shadows develop, the subject becomes increasingly dyspneic. Although it is clear that the talc itself (rather than its contaminants) is responsible for the pneumoconiosis seen in talc miners, it is far less fibrogenic than silica. Complicated talcosis with conglomerate shadows and disability is now a rare entity in North America, but it is still seen in Europe.

The chest radiographic appearance of chronic talc pneumoconiosis depends on the nature of the talc deposits to which the worker was exposed. When pure talc is involved, there is usually a mixture of rounded *q* and *r* shadows and irregular (*t* and *u*) shadows located in the middle zones, usually in a perihilar distribution. As the disease progresses with time, the shadows extend peripherally from the hila to involve the upper and lower zones. Small irregular shadows in the lower lobes are seen, particularly in cigarette smokers.

When talc deposits contain high concentrations of silica, the radiograph takes on a nodular pattern of shadows involving the middle and upper zones, more reminiscent of silicosis. The shadows are usually of the rounded *q* or *r* types and are located in the upper lobes.

Like asbestos, talc has the capacity to induce pleural plaques, and this can occur in the absence of contamination by asbestos. Pleural thickening is also seen in workers exposed to other silicates, such as sepiolite, wollastonite, kaolin, and zeolite. Such plaques often undergo calcification and are otherwise indistinguishable from those induced by asbestos.

Workers with talc pneumoconiosis who have not smoked have little or no impairment of pulmonary function. With advanced categories of simple talcosis, mild restrictive ventilatory impairment may be found. Only with the appearance of large conglomerate shadows is dyspnea likely to develop in the affected worker. The well-delineated plaques that occur in chronic cases are not associated with significant respiratory impairment. Diffuse pleural fibrosis is occasionally reported, but this is usually a consequence of a prior pleural effusion and so no calcified plaques are noted.

Pathology of Talcosis

Chronic inhalation of talc initially produces a mild alveolar inflammatory process. However, this process seldom progresses to alveolar fibrosis; talc particles are constantly being removed by alveolar macrophages and cleared from the parenchyma by the pulmonary defense mechanisms. With time, dust macules form. These are aggregations of dust-laden macrophages, foreign body giant cells, and epithelioid cells within the walls of the respiratory bronchioles. They resemble foreign body granulomas rather than the typical whorled nodule of silicosis. When these enlarge, small nodules may appear in the interstitial tissue in the same anatomic pattern of distribution as noted with silicotic nodules. Polarizing microscopy easily identifies an abundance of birefringent particles in the nodules. An unusual form of talc granulomatous lung disease occurring in intravenous drug users is associated with a typical vasculitis. Diffuse interstitial fibrosis and massive fibrosis have also been reported in talc pneumoconiosis but are exceedingly uncommon. The potential of talc as a carcinogen is minimal or nonexistent.

Silicatoses Other Than Talcosis

Kaolinosis

Kaolin pneumoconiosis was first reported in 1936 in the United Kingdom. Kaolinite, a complex hydrated aluminum silicate, is used for the manufacture of ceramics (china clay), glossy paper, soap, toothpaste, and medicine. As with silicosis, both simple and complicated pneumoconioses exist. The simple form is characterized by the development of rounded shadows in the lung (Fig. 17). Complicated kaolinosis evolves slowly and mimics silicosis on the chest radiograph (Fig. 18). Although kaolin is usually contaminated with silica, it is clear that the kaolin is responsible for the pneumoconiosis. Deposits of china clay are often heavily contaminated with silica. In the United States, kaolin is mined in the southeastern regions of the country. Intense exposure to kaolin is most likely to occur during the processing stages (drying and bagging). The simple and complicated pneumoconioses noted in shale miners may in part be a consequence of the kaolin content of shale.

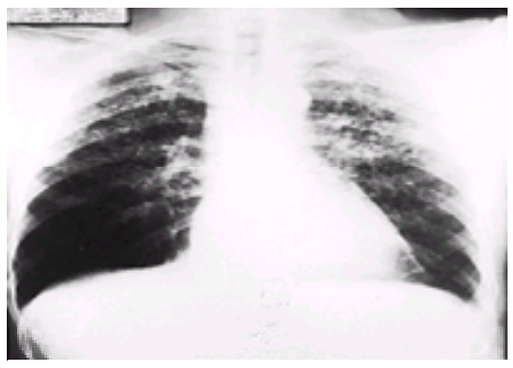

FIG. 17. Chest radiograph of simple kaolinosis. Pneumoconiosis is apparent in upper and middle zones.

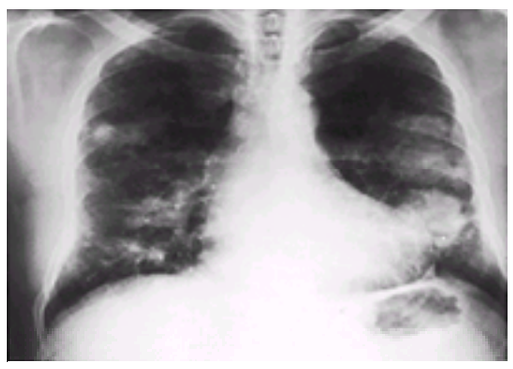

FIG. 18. Complicated kaolinosis in a kaolin worker. Conglomerate shadow appears adjacent to the heart.

The pathologic picture in the lungs varies somewhat from that of silicosis and includes both interstitial and nodular fibrosis as well as mild fibrosis of the alveolar wall. In simple kaolin pneumoconiosis, the lungs show grayish nodular lesions that are less prominent than those seen in silicosis. Simple kaolinosis is usually not associated with symptoms or alterations in pulmonary function parameters. However, as simple kaolinosis progresses to the complicated form, the patient notes the development of dyspnea. In complicated kaolinosis, a restrictive ventilatory pattern is present. Even more so than in silicosis, the profusion of shadowing on chest radiographs is more prominent than the degree of functional impairment.

Fuller's Earth Pneumoconiosis

Fuller's earth is a fine-grained absorbent clay originally used to remove grease and oil from wool (fulling). The highly adsorbent property of Fuller's earth makes it an ideal product to remove unwanted oil and grease. It has found use in oil refining and as a binder in foundry molding sands. It is also occasionally used as a filter and in cosmetic preparations. The various Fuller's earths are fine-grained calcium montmorillonite clays, attapulgite (palygorskite), and bentonite. Contaminating silica may be responsible for the development of disease, as Fuller's earth itself is innocuous. Fuller's earth is obtained by open-cast and underground mining. It is then dried, crushed, and milled. It is produced in the United Kingdom, Germany, and in the United States in the Midwest and Georgia (attapulgite).

Fuller's earth pneumoconiosis is a rare and little-studied clinical entity. It appears to occur in both simple and complicated forms. As with talcosis, only complicated cases appear to lead to impairment and disability. In the few autopsy-based studies available, the lungs contain large, peribronchial, black nodules, usually in the upper zones. Microscopically, there is a relative paucity of cellular reaction around the birefringent particles. The very few reports of Fuller's earth pneumoconioses that have been published suggest a benign course with little risk for symptomatic disease. Secondary users of materials containing Fuller's earths are not at risk for disease.

Bentonite Pneumoconiosis

Bentonite is a fine clay consisting mostly of calcium montmorillonite. It can swell inordinately when hydrated, giving it a high capacity for water absorption. It is this property that makes it so useful as a muddy slurry in oil well drilling and also in the refining of petroleum products. Much of the world mining of bentonite is done in Wyoming, with open-cast methods used, and in the nations of the northern rim of the Mediterranean. Bentonite is variably contaminated with quartz, shale, and sandstone.

Crushing and drying bentonite in ovens is dusty work and presents a hazard to workers. Bentonite pneumoconiosis can develop rapidly, be disabling, and result in fatal respiratory failure. Although bentonite is nonfibrogenic, it induces an abnormal pathologic change: the formation of foamy macrophages containing a periodic-acid-positive material. This pneumoconiosis is in large part a response to the cristobalite content of the product.

Anhydrous Aluminum Silicates

The anhydrous aluminum silicates include sillimanite, kyanite, and andalusite. They find important uses in the manufacture of refractory materials and in porcelain-containing materials such as spark plugs. Dust released during the preparation of these natural minerals can contain contaminating amounts of cristobalite. In general, radiographic changes have been minimal, but interstitial fibrosis appears to have developed in a few subjects. It is generally agreed that contaminating quartz is the underlying cause of the very few cases of mild pneumoconioses reported in sillimanite workers.

Miscellaneous Silicates

Mullite is a rare aluminum silicate that can cause pneumoconiosis. It occurs naturally but is also artificially produced for refractory construction. It also finds use in mortars, kilns, and furnaces. Prolonged exposure to mullite may cause mild pulmonary fibrosis, but probably only when dust exposure has been mixed.

Zeolites

The zeolites, which include fibrous erionite, are a group of hydrated aluminum silicates quarried from deposits of volcanic lava (tuffs). As a result of their marked adsorptive properties, they are used as molecular sieves, in gas chromatography, in the separation of radioactive gases, and as fillers in paper products.

Zeolites do not cause pneumoconiosis. However, during recent decades they have been implicated in the high rates of pleural fibrosis, pleural plaques, calcification, and premature malignant mesotheliomas seen in two villages in Turkey. Approximately half the deaths in this region have been caused by mesothelioma and lung cancer. In addition, pleural plaques, calcification, and fibrosis have been noted but have not resulted in deaths. Although these cases were initially thought to be the result of exposure to asbestos, more recent investigations have shown that ambient levels of fibrous zeolite are responsible for the epidemic. Erionite (a zeolite substance) is composed of long, thin mineral fibers and is extensively used in local building materials and stucco. Fibers of erionite have been found in the lungs of patients from the two villages concerned. Erionite has proved to be a particularly potent inducer of pleural disease in animal exposure studies. Of interest is the observation that many houses in the western United States and southern Mexico contain measurable amounts of locally mined erionite.

OTHER NATURAL FIBROUS MINERALS

Attapulgite

Naturally occurring clays such as attapulgite are composed of small, elongated, fiberlike particles and have not been shown to be harmful. Attapulgite is used as cat litter, in paints, and in fertilizers, and it is also pumped into oil wells to remove moisture during the drilling process. Palygorskite is a chemically related mineral

consisting of longer, thinner fibers. It is quarried mainly in eastern Europe. Animal experiments have shown that palygorskite is capable of inducing mesothelioma in animals, as well as producing other effects induced by the amphiboles or asbestos.

Wollastonite

Wollastonite is a fibrous calcium silicate ($CaSiO_3$) sometimes contaminated with quartz. It is used in ceramics and paints. In recent decades, it has found an expanding market as a substitute for asbestos in insulation, wallboard, and brake linings. It is mined in the United States, Mexico, and Finland. An extensive survey of the wollastonite mines of the Adirondack Mountain region of New York State, one of the major production areas of the world, found no concentration relationship between respiratory symptoms and exposure. There was no evidence of fibrotic pulmonary disease or pleural disease. A follow-up study showed no change of chest radiographic patterns with time.

Vermiculite

Vermiculite is the name of a group of hydrated laminar magnesium aluminum silicates containing iron. More than twenty varieties occur in deposits that are quarried from open-cast mines.

Deposits of vermiculites are often contaminated by silica, talc, tremolite, or actinolite. These, rather than vermiculite itself, account for the pleural effusions and plaques found in vermiculite workers. Several studies have assessed the deleterious respiratory effects of exposure in vermiculite mining. Both positive and negative study results have been reported. Studies suggesting increased morbidity and mortality may reflect the contamination of vermiculite deposits by asbestiform minerals.

Artificial Fibers

During the past several decades, an effort has been made to replace asbestos with fiberglass and other artificial mineral fibers. Fiberglass is a continuous filament and therefore not respirable unless modified. Insulation wool is made from metal slag, igneous rocks, and glass, which are mixed and then melted down and spun into a fibrous mat. Many of the fibers produced in this process are in the respirable range. These ceramic fibers are produced from molten kaolin or from a combination of alumina and silica. Most of these artificial mineral fibers exhibit little or no toxicity.

Although these fibers may induce mesothelioma when implanted directly in the pleural or peritoneal cavity of experimental animals, they do not induce pulmonary fibrosis or tumors when given by inhalation. Moreover, fiberglass has been shown to undergo leaching and fragmentation and can therefore be removed from the lungs. Although a preponderance of evidence speaks against any increased risk from the use of artificial fibers, caution is wise. The mineralogic structure of these agents is fairly similar to that of other fibers known to be pathogenic or carcinogenic. Several factors limit the potential of these fibers to induce pneumoconioses. First, the factories producing these artificial fibers generate relatively few respirable fibers in the workplace environment; second, inhaled and deposited fibers are susceptible to fragmentation and leaching by pulmonary cells.

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CHAPTER

33 Occupational Lung Diseases: Coal Workers', Beryllium, and Other Pneumoconioses

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COAL WORKERS' PNEUMOCONIOSIS AND RELATED CONDITIONS

Coal has been used as a source of fuel for hundreds of years. Initially, it was dug from outcroppings or augered from seams that came to the surface on the slopes of hills. It was the invention of pumps by Savery (1698) and Newcomen (1708) that made it possible to mine coal underground. Until the advent of the pump, there had been no means of controlling underground flooding or of providing adequate ventilation. Coal mining remains a major industry in the United States, Germany, France, Australia, the former U.S.S.R., China, India, and South Africa. Demand, however, has decreased, particularly in the United States and Britain, where the number of miners has been drastically reduced.

Work Force

Coal is mined extensively from both open-cast or surface mines and underground mines. In the United States, open-cast mines are mostly located in the Far West. With this method of mining, dust exposure is relatively limited. A few borers or shot firers who drill their way through rock before placing the explosive charges are exposed to high concentrations of silica, and the rapid development of silicosis has been noted in these workers.

The underground work force is usually subdivided into face workers, persons employed in transportation, workers concerned with the maintenance of machinery, and finally surface workers. Face workers include those who operate continuous miners and the cutting machines (Fig. 1), as well as roof bolters. Face workers have the dustiest jobs. Workers employed in transportation are responsible for moving coal from the face to the portal. They spend a considerable portion of time near the face, and their job is fairly dusty. Silicosis may develop in transportation workers, as they apply sand to the rails to provide traction for the diesel trains frequently used to carry the coal from the face to the portal. Behind and well back from the transportation workers are the miners whose responsibility it is to maintain equipment and carry out other miscellaneous jobs. This group includes electricians, welders, and mechanics. Finally, a few workers are employed in the lamp house and on the coal tipple. The latter is the site where the coal is washed before being transported for use. Surface coal miners, with the exception of drillers, have only very minor exposures to dust, and coal workers' pneumoconiosis is a rare finding in this group of people unless they have previously been employed underground. Drillers bore through rock strata and are subject to development of silicosis unless proper precautions are taken.

FIG. 1. Coal cutter in a U.S. coal mine.

Respiratory Disease in Coal Miners

The hazards of mining were known to Agricola and Paracelsus in the sixteenth century. These early observers noted that Carpathian miners died of what was then known as *miners' phthisis.* It is also now abundantly clear that this term had a generic connotation and included a large number of diseases, ranging from silicosis on the one hand to tuberculosis, bronchitis, bronchiectasis, and probably lung cancer on the other.

Long-term exposure to coal dust leads to three chest diseases: (1) coal workers' pneumoconiosis (CWP), (2) silicosis, and (3) industrial bronchitis. Silicosis is seen uncommonly except in roof bolters, who bore through adjacent rock strata containing silica to place the roof bolts, and in transportation workers, who apply sand to the rails to provide traction.

Earlier in this century, it was noted that radiographic opacities, similar to those seen in silicosis, developed in the lung fields of Welsh coal miners. It was initially presumed that these radiographic features represented silicosis, as it was known that coal mine dust often contains a fair amount of free silica. However, it was observed that radiographic changes identical to those seen in the coal miner also developed in the coal trimmer, a type of stevedore who was responsible for the even distribution of the coal once it had been loaded into the holds of ships. The trimmers handled only coal that had been washed and, as such, contained virtually no free silica. Subsequent analysis of the lungs of some of these coal trimmers showed that they had no more silica in their lungs than did the inhabitants of Cardiff and Swansea. Confirmation that inhalation of pure carbon could induce similar changes was subsequently noted. There is now compelling evidence to indicate that CWP is distinct from silicosis not only epidemiologically but also pathologically and in regard to prognosis.

CWP is best defined as the deposition of coal mine dust in the lung parenchyma and the reaction of tissue to its presence. It is customarily divided into simple and complicated pneumoconiosis, according to the radiographic features.

Simple Coal Workers' Pneumoconiosis

Simple CWP is recognized from its radiographic features plus a suitable history of exposure—that is, >10 years underground. The lung fields show the presence of multiple, small, rounded (regular) opacities. These usually appear first in the upper lobes and gradually spread all over the lung fields. Simple CWP is graded according to the profusion of small opacities on the chest x-ray film. Categories 1, 2, and 3 are recognized. The classification most commonly used was devised by a group of experts from the International Labor Office (ILO) and has received general acceptance. For epidemiologic purposes, a 12-point elaboration of the standard ILO classification was devised. Use of this 12-point elaboration is essential in the assessment of radiographic progression. Small opacities can be subdivided into *p, q,* and *r* types according to size, with *p* (punctate) being <1.5 mm in diameter, *q* (micronodular) being between 1.5 and 3 mm, and *r* being between 3 mm and 1 cm. Although there are occasions when all three types of opacity are present in a single radiograph, in general, a specific type predominates. In the vast majority of radiographs, the appearances tend to be fairly uniform, and one can detect only one type of opacity (Fig. 2 and Fig. 3). Larger nodules (*r*) are more commonly seen in silicosis than in CWP.

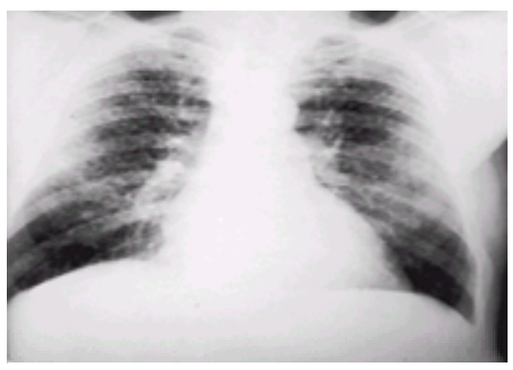

FIG. 2. Radiograph of a subject with category 2/2, *q*/*q* simple CWP.

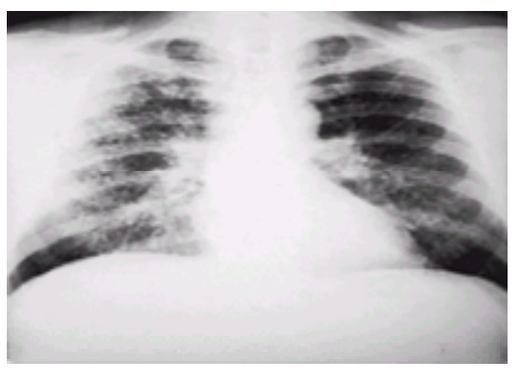

FIG. 3. Radiograph of a subject with category 3/2, *q*/*r* simple CWP.

Symptoms

Simple CWP is not associated with symptoms, although many of those showing the characteristic radiologic features of the condition will admit to bronchitic symptoms—namely, cough and production of sputum. These symptoms are a consequence of either cigarette smoking or industrial bronchitis, should they happen to be present in nonsmokers.

Pathology

Simple CWP is a reaction to dust alone and does not progress in the absence of further exposure. By the same token, it probably never regresses, despite sporadic case reports purporting to demonstrate radiographic improvement. Most such reports are best explained by erroneous diagnoses, such as sarcoidosis or welder's siderosis, which are known to regress, or by changes in technique in taking serial films. The value of the chest radiograph is that it provides an indication of the coal dust present in the lungs. Many investigations have shown that each successively higher category of simple CWP is associated with a comparable increment in the coal dust content of the lung. The mineral content of the lungs also influences the radiographic appearance, and it is of paramount importance to note that radiographic category is a direct reflection of the dust deposited and retained in the lung and an indirect reflection of cumulative dust exposure (Fig. 4). When coal dust particles are deposited in the alveoli, they are taken up by the macrophages, which in turn convey the dust toward the respiratory bronchioles. The exact means whereby the macrophages migrate from the alveoli to the terminal bronchioles and to the interstitial tissue and the source of energy for their translocation are unknown. Provided dust exposure is not intense and prolonged, the clearing mechanisms usually remain effective, but in the face of high and prolonged exposure to coal dust particles, the dust-laden macrophages begin to accumulate at the portion of the respiratory bronchiole that lies adjacent to the pulmonary arteriole. Many subsequently die and liberate dust around the second-order respiratory bronchioles. This engenders a reticulin response and the development of limited fibrosis. Occasionally, with time, a few collagenous fibers are also formed. If the dust contains a high concentration of silica, then the fibrotic response is greater and more collagen is formed. The aggregates of coal pigment appear as small, black spots in large sections of the lungs and are known as *coal macules.*

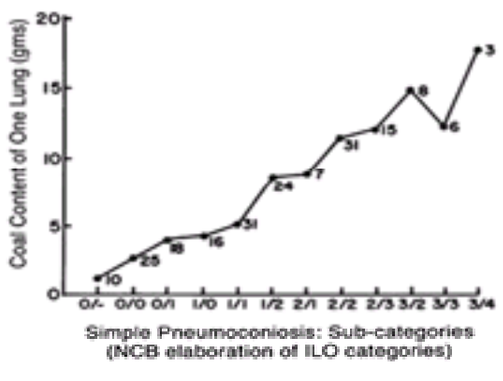

FIG. 4. Relationship between the coal content of one lung and the radiologic category of CWP. The numbers over the points on the graph denote the number of lungs examined within each category of simple CWP.

Initially, the coal macule is small, but with prolonged exposure it slowly increases in size. This increase in size is accompanied by a concomitant increase in the amount of fibrous tissue present. Once this occurs, the smooth muscle in the bronchiolar wall atrophies and, as a result, the bronchiole dilates. It is uncertain what causes the dilatation, but it is probably a consequence of the application of extraluminal forces to the bronchiolar wall. The dilatation eventually becomes large enough to be seen by the naked eye and is then known as *focal emphysema* (Fig. 5). The location of the focal emphysema—namely, in the center of the secondary lobule—is similar to that seen in cigarette smoke-induced centrilobular emphysema. Whereas Gough and Heppleston distinguished focal from centrilobular emphysema and maintained that centrilobular emphysema induced by cigarette smoking is invariably accompanied by bronchiolitis, which is absent in focal emphysema, others maintain that the two pathologic conditions cannot be distinguished.

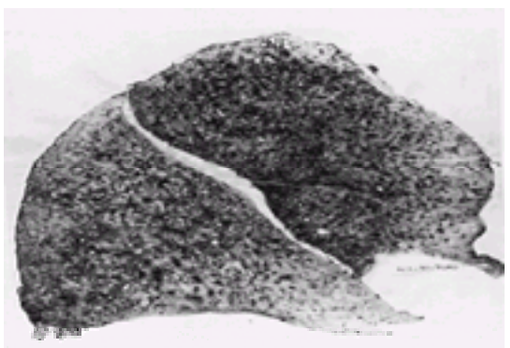

FIG. 5. Large lung section of a subject with CWP showing macules and focal emphysema.

Recent investigations have suggested that the histologic appearance of the macules is affected by the composition and contents of the coal mine dust to which the miner has been exposed.

Lung Function

Although the ventilatory capacity of miners as a whole is decreased in comparison with that of persons of comparable socioeconomic status who are not miners, a higher category of simple CWP is not associated with a larger decrement in ventilatory capacity. If one studies nonsmoking miners with simple CWP, it becomes evident that a variety of pulmonary impairments are present. These impairments include a disturbance in the distribution of inspired gas, which is manifested by a slight increase in the alveolar-arterial pressure gradient, $P(A\text{-}a)O_2$; a minor reduction in the diffusing capacity, especially in subjects with type *p* opacity; and minimal hypoxemia caused by physiologic shunting in categories 2 and 3. With exercise, the $P(A\text{-}a)O_2$ may increase slightly, but in many instances it improves. The focal emphysema that accompanies categories 2 and 3 simple CWP is often associated with a minor loss of elastic recoil and a slight increase in the compliance of the lungs. In addition, an increase in the residual volume often occurs, which is probably related to the same factors mentioned earlier—namely, a change in the elastic properties of the lung (Fig. 6,Fig. 7 and Fig. 8). The increase in residual volume occurs in subjects with and without airways obstruction and cannot be attributed to increased airways resistance.

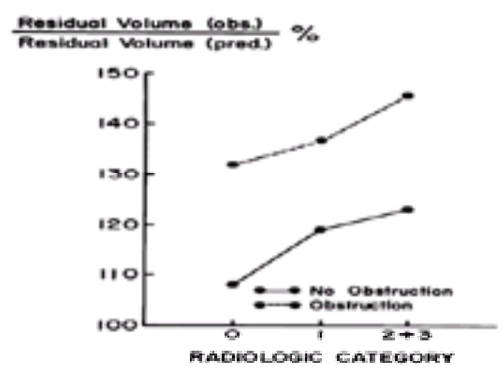

FIG. 6. The relationship of residual volume to radiographic category in coal miners with and without airways obstruction. (Reproduced from Morgan WKC, et al. *Thorax* 1971; 26:585.)

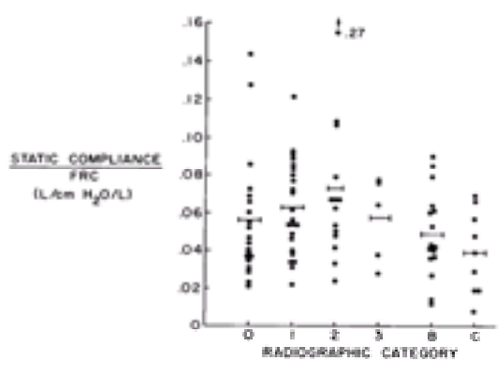

FIG. 7. Static compliance of lungs of coal miners according to radiographic category. *Bars* represent mean values with standard deviation. *FRC,* functional residual capacity.

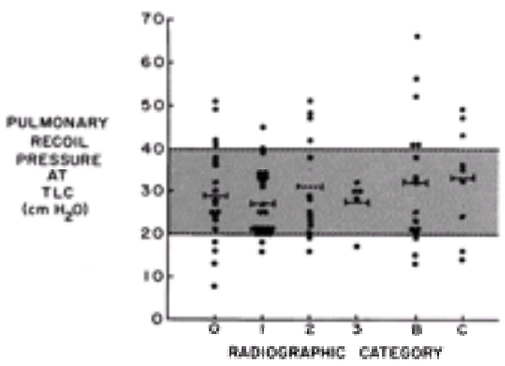

FIG. 8. Pulmonary recoil pressure of coal miners according to radiographic category. *Bars* represent mean values with standard deviation.

In subjects with categories 2 and 3 simple CWP, as mentioned earlier, the diffusing capacity may be mildly reduced (Fig. 9). This is a consequence of ventilation-perfusion mismatching and is mainly present in type *p* opacities. Frans and associates have carried out more detailed studies in which the components of the diffusing capacity have been measured in subjects with simple CWP. They partitioned the diffusing capacity into the capillary blood volume (Vc) and the membrane component (Dm) and found that both were slightly reduced. Although pneumoconiosis had a slight effect on both these components, cigarette smoking had a far greater effect. An extensive study of the effect of CWP on the diffusing capacity was carried out by Kibelstis. He measured the steady-state diffusing capacity (D_LCO_{SS}) at rest and during exercise. The vast majority of nonsmoking miners had a normal D_LCO_{SS}. The effects of cigarette smoking far outweighed those of years spent working underground and the presence of pneumoconiosis.

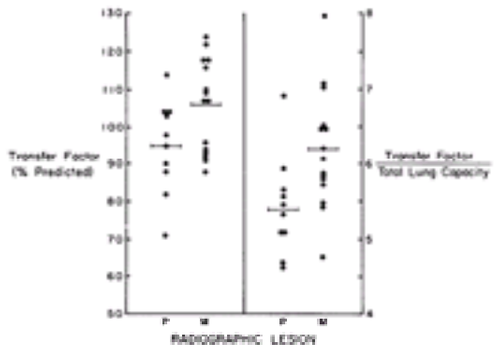

FIG. 9. The diffusing capacity (transfer factor) of a group of nonsmoking coal miners with simple CWP. *P,* punctate or *p*-type opacity. *M,* micronodular or *q*-type opacity. (Reproduced from Seaton A, Lapp NL, Morgan WKC. The relationship of pulmonary impairment in simple coal workers' pneumoconiosis to type of radiographic opacity. *Br J Ind Med* 1972;29:50.)

Evidence of abnormal small-airways function is frequently observed in coal miners and appears to be unrelated to the presence of simple CWP. Abnormalities of closing volume and frequency dependence of dynamic compliance have been noted. It is likely that there is no one simple explanation for these abnormalities, and that small-airways obstruction, regional changes in compliance, and the mechanical properties of the lung all play a role. The presence of these small-airways abnormalities, however, cannot be regarded as disabling or of any clinical significance.

Complicated Pneumoconiosis or Progressive Massive Fibrosis

Unlike simple CWP, complicated pneumoconiosis is associated with symptoms, significant impairment, and decreased longevity. The condition is recognized by a large opacity or opacities 1 cm in diameter occurring on a background of simple CWP (Fig. 10). Although a number of investigators claim that progressive massive fibrosis (PMF) can occur on a background of category 0, the basis for this statement is somewhat suspect, in that other causes of large opacities cannot be excluded. Stage A (i.e., an opacity between 1 and 5 cm in diameter) is seldom if ever associated with either symptoms or a significant decrease in lung function. Stages B and C, however, may be associated with both symptoms and a decrement in lung function. Stage B is defined as an opacity or opacities 5 cm in diameter but not extending over a third of the lung field. Stage C is defined as a large opacity or opacities occupying more than a third of one lung field (Fig. 11).

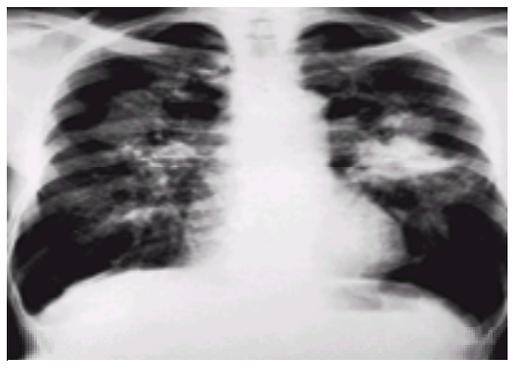

FIG. 10. Radiograph of a subject with stage C complicated CWP.

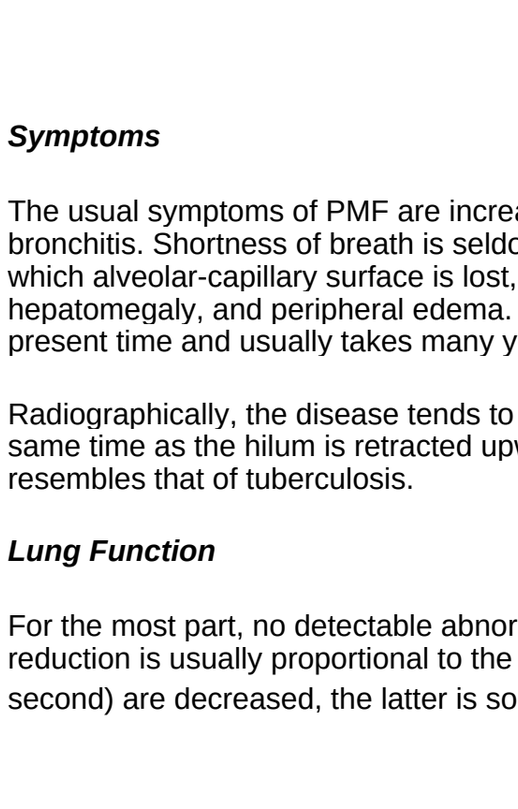

FIG. 11. Stage C complicated CWP with ischemic necrosis in the cavity in the left upper lobe. This subject had worked as a “slave laborer” for 4 years in the Belgian coal mines during the war.

Symptoms

The usual symptoms of PMF are increasing shortness of breath, cough, and production of sputum, but again, the latter is probably a consequence of coincident bronchitis. Shortness of breath is seldom seen until stage B is fairly well advanced, but it becomes more evident as the disease progresses. In far-advanced disease, in which alveolar-capillary surface is lost, non-hypoxemic cor pulmonale often develops. This is associated with a right ventricular heave, the presence of large “a” waves, hepatomegaly, and peripheral edema. It must be stressed that cor pulmonale arising as a result of complicated CWP is an unusual finding in the United States at the present time and usually takes many years to develop.

Radiographically, the disease tends to appear in the axillary region of the posterior segment of either upper lobe. It then often slowly migrates toward the hilum at the same time as the hilum is retracted upward. It also is seen in the superior segment of the lower lobe, and the distribution of the massive fibrosis in this regard closely resembles that of tuberculosis.

Lung Function

For the most part, no detectable abnormalities are present in stage A complicated pneumoconiosis. In stages B and C, the ventilatory capacity is reduced, and the reduction is usually proportional to the size of the conglomerate masses. Although both the FVC (forced vital capacity) and the FEV_1 (forced expiratory volume in one second) are decreased, the latter is sometimes reduced disproportionately. The ratio of FEV_1 to FVC ratio is generally reduced, especially in advanced stage C

disease. The diffusing capacity is likewise affected, and the decrement observed is proportional to the size of the masses. The precise pathophysiologic explanation for the obstruction remains unclear, but it appears to resemble that occurring in far-advanced tuberculosis or widespread end-stage sarcoidosis. Large masses destroy both the vascular bed and many of the airways, and their effects on the former are responsible for non-hypoxemic pulmonary hypertension. Eventually, hypoxemia develops, but it is observed earlier and more frequently in those subjects who happen also to be cigarette smokers.

Pathology

As already mentioned, conglomerate shadows usually develop in the posterior segment of the upper lobes or the superior segment of the lower lobes. Macroscopically, they consist of large, black, amorphous masses that on section tend to liberate a jet-black grumous fluid. They are rubbery in consistency, and occasionally an irregular, thick-walled cavity may be present. The latter represents either ischemic necrosis or tuberculous infection.

Microscopically, the periphery of the masses seems to be composed of dense aggregates of fibrous tissue. Although formerly it was believed to be almost pure collagen, this is now known to be incorrect; the collagen bundles tend to be peripherally situated in the wall of the cavity. Even there, they are often separated by deposits of coal dust. The lung masses gradually encroach on and destroy adjacent airways and blood vessels. Remnants of former internal elastic laminae can be observed on microscopy. The pulmonary arteries, veins, and capillaries are all obliterated.

A rigid separation of simple from complicated pneumoconiosis is probably fallacious, and it is clear that the opacities of <1 cm in size gradually increase in diameter and form a large opacity. It has been shown that the hydroxyproline content of the large masses is only about 3%–4%, implying that the collagen content is about 25%–30%. In an analysis of fresh tissue from the center of conglomerate lesions, there was demonstrated a significant increase in calcium phosphate content and the presence of glycosaminoglycans such as hyaluronic acid and chondroitin sulfate in the mass lesion. These findings are supported by the normal urinary hydroxyproline content in both simple and complicated CWP. It also has been shown that fibronectin is an important component of the masses that characterize PMF.

Necessary for the development of PMF is a suitable dust burden and some factor or factors as yet unknown. Unlike simple CWP, PMF may develop after exposure has ceased, provided category 2 or 3 disease is present at the time the subject stops working. In addition, the disease may progress in the absence of further exposure.

Immunologic Aspects of Coal Workers' Pneumoconiosis

In 1953, Caplan described a syndrome in coal miners characterized by the presence of multiple rounded opacities in the lungs and associated with rheumatoid arthritis. Since then, the condition has been known as *Caplan's syndrome* or *rheumatoid pneumoconiosis.* The opacities differ from those in the usual form of PMF in that they tend to be peripherally situated and often appear in crops during a relatively short period. Moreover, they frequently occur on a background of category 0 or 1 pneumoconiosis. Although most of the patients who were originally observed had rheumatoid arthritis, subsequent studies showed that the condition may appear to antedate the development of rheumatoid arthritis. Typical nodules of Caplan's syndrome and the large opacities of PMF may be present in the same subject. The nodules are often accompanied by the typical rheumatoid nodules found on the Achilles tendon and elbows. Histologically, although the nodules bear some resemblance to the rheumatoid nodules found on the elbows, there are distinct differences. It has been noted that there are concentric layers of dust and granulation tissue with a necrotic area in the center. Beside the necrotic area, there is often a cellular zone infiltrated with mononuclear cells and, in particular, lymphocytes and plasma cells (Fig. 12). Endarteritis is often present. This zone of active inflammation was named the *rheumatoid zone* by Gough and co-workers.

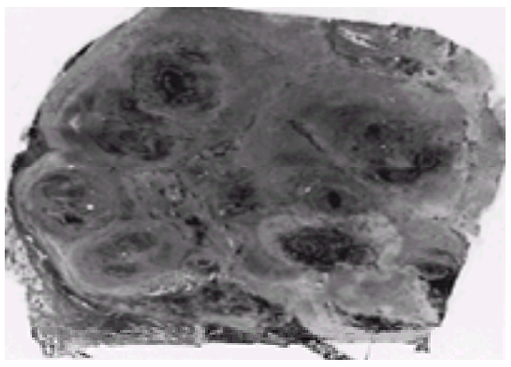

FIG. 12. Cluster of Caplan nodules from a large section of the lung of a deceased coal miner. Note the concentric layers of dust deposition in the nodules. The subject had severe rheumatoid arthritis, but only category 1/0 simple CWP.

Through the years, a number of studies have compared the prevalence of rheumatoid factor in coal miners with that of a comparable referent population. Rheumatoid factor was present in about 70% with typical Caplan's syndrome. This far exceeded the prevalence in subjects with simple CWP. Furthermore, a significant proportion of those subjects with a radiographic appearance of Caplan's syndrome in whom rheumatoid factor was lacking when they were first seen subsequently tested positive for rheumatoid factor. Because of the fact that some subjects with Caplan's syndrome continued to test negative for rheumatoid factor, it was suggested that PMF existed in two forms: one form, much less common, associated with vasculitis, cellular infiltration, and rheumatoid factor in the serum, and a second form, nonspecific and associated with mild inflammation and obliteration of the vascular bed. The evidence in favor of this hypothesis is tenuous. Antinuclear antibody (ANA) is also frequently present in miners who have PMF.

Studies of immunoglobulin levels in miners with and without CWP have shown that the sera of anthracite miners with PMF contain relatively higher levels of complement (C3), a_1-antitrypsin, and immunoglobulins A and G (IgA and IgA) than do comparable sera from bituminous coal miners with PMF. Immunoglobulin levels, however, are normal in miners with simple CWP. Lung reactive antibodies have also been demonstrated in miners with CWP, but their role in the etiology of the condition is not apparent.

Emphysema and Coal Workers' Pneumoconiosis

Although there is no doubt that a form of emphysema usually referred to as *focal emphysema* occurs in coal miners with pneumoconiosis, the effects of this type of emphysema are presently a source of argument. Focal emphysema occurs in the center of the secondary lobule and, in this regard, resembles centrilobular emphysema. Gough and Heppleston maintained that focal emphysema is distinct from centrilobular emphysema as seen in cigarette smokers and does not lead to pulmonary hypertension. They also maintained that centrilobular emphysema of cigarette smokers is always accompanied by a bronchiolitis and in this respect differs from focal dust emphysema.

During the past few years, in a series of articles from South Wales, investigators have proposed that it is the emphysema in the lungs of coal miners that causes airways obstruction. The coal miners chosen for these studies were all disability claimants who had been reviewed by pneumoconiosis panels. As such, they can hardly be regarded as representative of coal miners as a whole. The investigators attempted to show a relationship between lung function in life and the extent of emphysema diagnosed at postmortem examination. They were, however, unable to demonstrate that obstruction increases with higher categories of simple CWP.

There are a number of compelling arguments to refute this hypothesis. It is well accepted that an increasing amount of dust deposited in the lungs is associated with a higher radiographic category. Similarly, it has been shown that the extent of focal emphysema increases in higher categories of simple CWP. If the focal emphysema is responsible for the obstruction, then a decrease in the ventilatory capacity should be noted with a higher category of simple CWP, but it is not. Second, extensive studies in which the hearts and lungs of deceased miners were examined have considered the relationship of antemortem smoking habits and simple and complicated pneumoconiosis. Right ventricular hypertrophy and cor pulmonale do not occur in coal miners if they have not been cigarette smokers or have not had PMF. Similarly, if the emphysema noted in the lungs of miners with simple CWP is truly disabling and leads to a reduction of the alveolar-capillary surface, then a significant reduction in the diffusing capacity should occur, but it does not. The argument has been further developed in the Surgeon General's Report of 1985.

More recently, other investigators have endorsed the concept that the excess emphysema in the lungs of coal miners is responsible for the observed increase in airways obstruction. The proponents of this theory rely on a report of the findings in an autopsy study of the lungs of 1400 coal miners. The prevalence of emphysema was examined in 503 men, and a differentiation was made between panacinar and centriacinar (centrilobular) emphysema. Ninety-five nonsmokers were included, of whom 42 had some emphysema. The presence and type of emphysema were related to dust exposure, age, cigarette smoking, and bronchitis. Thirty-five percent (33 subjects) of the nonsmokers had centriacinar emphysema and 23% had panacinar emphysema. No relationship was found between the presence of panacinar emphysema and coal dust. Only 2 of the 21 nonsmokers who had no coal-induced fibrosis (i.e., no CWP) had centriacinar emphysema. Moreover, emphysema was

regarded as being present when as little as 1/30 of the lung was involved. From this it might be inferred that many of those with emphysema had negligible involvement and were asymptomatic. Elsewhere, it has been shown that at least 20%–25% of the lung must be involved before the subject has symptoms of breathlessness.

The study defined three pathologic groups according to the presence of particular dust lesions. Group M included lungs showing circumscribed dust accumulations with minimal evidence of fibrosis. Most of these did not show radiographic evidence of CWP. Group F showed one or more fibrotic lesions between 1 and 9 mm in diameter. The third group comprised lungs from subjects with PMF having fibrotic lesions ³1 cm in diameter. In a group of 257 miners who had undergone spirometry during life, only two nonsmokers had emphysema in the absence of PMF. Moreover, an exposure-response relationship was lacking between dust and extent of emphysema. Finally, the nonsmokers in the M and F groups, of whom there were almost none, showed no difference in lung function between those with and without emphysema. Thus, the report seems to provide little support for the hypothesis that centriacinar emphysema of nonsmoking coal miners produces airways obstruction, and in smoking coal miners it is clear that cigarettes are the main cause of obstruction.

Bronchitis and Coal Mining

There is no doubt that coal mine dust induces an increase in the size of the mucous glands and an increase in the number of goblet cells. These changes are associated with cough and production of sputum and a small reduction in ventilatory capacity. For the most part, only the large airways are affected. The reduction in ventilatory capacity is unrelated to radiographic category and is present in miners with no radiographic abnormality.

Relative Contributions of Dust Versus Cigarette Smoking and Airways Obstruction in Coal Miners

A number of cross-sectional and longitudinal studies have been carried out in coal miners comparing the effects of dust versus cigarette smoking. Most studies have shown that dust does have an effect, even in the absence of cigarette smoking. Two long-term studies, one carried out in Britain and the other in the United States, have reported that cigarette smoking has about three times the effect of coal dust on the development of airways obstruction. This conclusion is based on a comparison of the mean decrements induced by dust, cigarette smoking, age, and other factors. Unfortunately, such comparisons are misleading. It is well established that significant airways obstruction develops in only about 13%–15% of cigarette smokers. The vast majority of smokers are unaffected. In contrast, most miners who have spent 25 years in the coal mine (and this applies also to nonsmokers) have cough and sputum. Many of them have a small decrement in ventilatory capacity. Thus, when the effects of smoking are compared with those of dust, a significant and occasionally disabling decrement in a small percentage of subjects (13%–15%) is being compared with a much smaller decrement in a far greater proportion of subjects (40%–60%). There seems to be little doubt that coal dust in itself does not lead to disabling obstruction unless PMF is present. Moreover, as mentioned earlier, right ventricular hypertrophy and respiratory failure do not appear to occur in coal miners in the absence of cigarette smoking or PMF.

Lung cancer occurs less frequently in coal miners than it does in the general population. This is probably related to the fact that coal miners are not allowed to smoke in the mines, so that 8 hours of the day are spent in a smoke-free atmosphere. This observation has been made in numerous studies. Similarly, other studies have shown that heart disease occurs less frequently in coal miners than it does in the general population.

Effects of Coal Workers' Pneumoconiosis on Life Expectancy

A number of studies have been carried out showing that simple CWP has no effect on life expectancy, but that PMF is associated with decreased longevity. This has been observed in both Britain and the United States. It also has been noted that coal miners as a group have a normal life expectancy at the present time. Although the death rate from accidents and complicated pneumoconiosis is increased, this is counterbalanced by the decreased death rate from heart disease and lung cancer.

Radiographic Progression

Repeated observations have shown that increasing exposure, as measured by years underground or by cumulative dust exposure, leads to radiographic progression. Originally, this was measured using the standard ILO 3-point scale (categories 1, 2, and 3), but it became apparent that the scale was not sensitive enough. As a result, Liddell and May elaborated their 12-point scale. The adoption of the more accurate gravimetric method of estimating coal mine dust, plus the use of the elaboration of Liddell and May, have made it possible to relate long-term dust exposure to the attack rate of pneumoconiosis and the likelihood that a person with pneumoconiosis will progress from a particular subcategory to another. Using such an approach, a dose-response relationship has been derived, both in Britain, by the National Coal Board, and in Germany. The results obtained in both countries were very similar despite completely different methods of measuring coal dust. Jacobsen has derived a series of curves suggesting that, provided the time-weighted average is kept below 2 mg/m^3, category 2 disease or higher will develop in about 2% of miners who work 8 hours a day, 5 days a week, for a period of 35 years (Fig. 13). Hence, if one can prevent simple CWP, then there is every likelihood that PMF will not develop. The fact that the U.S. coal mines have a standard of 2 mg/m^3 should mean the virtual elimination of CWP by 2005.

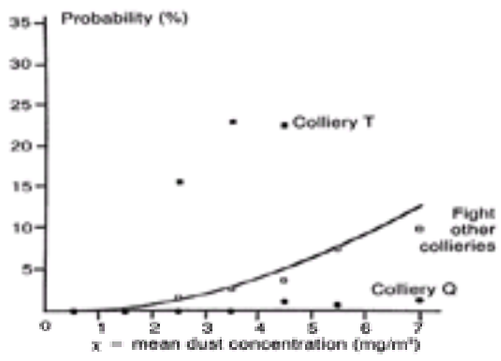

FIG. 13. The percentage of miners with disease evolving to category 2 or higher. This is based on 35 years of exposure for 8 hours a day, 5 days a week. (Reproduced from Jacobsen M. New data on the relationship between simple pneumoconiosis and exposure to coal mine dust. *Chest* 1980;78(Suppl):408.)

Bronchoalveolar Lavage Studies

A number of bronchoalveolar lavage studies of coal miners have recently been performed. Most have been poorly conducted, and the information yielded so far has not been particularly helpful in diagnosing or unraveling the mechanisms involved in the pathogenesis of CWP. There have also been a number of studies of tumor necrosis factor (TNF) in CWP, and it has been shown that in subjects with CWP the level of TNF is increased. Once again, the significance of increased levels of TNF is not understood. Although investigators have related the progression of CWP to increased levels of TNF, the authors of these studies have never been sure what constitutes progression—worsening of the radiograph or a decline in lung function.

OTHER PNEUMOCONIOSES

Several other pneumoconioses have been recognized. Most are relatively uncommon and the existence of some is questionable, but many of those that are well recognized result from the inhalation of metals.

Respiratory Conditions Associated with Exposure to Aluminum

Aluminum is mined as bauxite. Bauxite contains about 40%–50% alumina and other oxides, in particular iron. Deposits of bauxite are found in Jamaica, Australia, Guyana, and France. Metallic aluminum does not occur in a natural state but is found in combination with oxygen, silicon, and fluorine. It is frequently found as combined complex salts of silicic acid. Many minerals, including all types of asbestos, contain aluminum. Cryolite is aluminum fluoride and is found mainly in Greenland.

The production of aluminum involves two steps, the first of which is to convert the bauxite to aluminum oxide. This involves the digestion of bauxite with caustic soda at a high temperature and pressure. The resulting hydrate is then dried and calcined to the oxide. Subsequently, the alumina (Al_2O_3) is reduced by the Hall-Heroult electrolytic process. This takes place in the pot room, where the alumina is mixed with cryolite flux and the mixture placed in large steel pots into which carbon electrodes dip. With the passage of an electric current, the metal accumulates at the bottom of the pot while a crust of alumina and other impurities forms on top. The

metal is subsequently removed from the pot.

A number of respiratory conditions have been attributed to exposure to alumina or metallic aluminum.

Shaver's Disease

This condition was first described in the Niagara Peninsula by Shaver. It was recognized in workers manufacturing the abrasive corundum. The process involves the mixing of bauxite with iron and coke and fusion in large iron pots at a temperature of 2000°C. During the process, dense white fumes are given off containing Al_2O_3 and amorphous silica. Subsequently, it was realized that during fusion some of the free silica had been converted to cristobalite and tridymite.

In a survey of four plants that were manufacturing alumina abrasives, Shaver and Riddell found 23 subjects with radiographic abnormalities. Those affected had shortness of breath and recurrent chest pain. Many also had a cough that was productive of some mucoid sputum. Subsequently, it became evident that the recurrent chest pain was often related to the development of spontaneous pneumothorax. On examination, the subjects were noted to have tachypnea, and cyanosis was present in those with advanced disease. Crackles were present in most, and occasionally signs of consolidation were noted.

The radiologic findings varied considerably. In most cases, both lungs were affected by a diffuse reticulonodular process. The upper lobes were most often involved, and with the passage of time, blebs began to appear and regional honeycombing became evident. In those in whom the condition developed rapidly, the first changes noted were those of an acinous filling pattern. This later resolved, but often only partially, and in doing so left a diffuse interstitial pattern.

Pathology

Macroscopically, the lungs appeared solid and were of a gray-black color, with much pleural thickening and frequent emphysematous bullae at the apex and elsewhere on the pleural surface. In the acute stage, alveolar edema and thickened septa were often present. Interstitial fibrosis developed later, but the classic whorled nodules of silicosis were absent.

Subsequent analysis of the fumes emitted showed that they contained about 70% aluminum and 4%–7% free silica. Initially, it was thought that the free silica occurred as amorphous silica and was probably harmless. However, it became evident later that at the high temperatures, some of the silica had been converted to cristobalite. The latter is one of the more fibrogenic forms of crystalline silica.

Shortly after Shaver described this outbreak, ventilation was improved, and since that time no further outbreaks have occurred. Moreover, numerous surveys of persons exposed to alumina, including those who work in aluminum plants that convert bauxite to alumina, have not revealed any additional cases of Shaver's disease or indeed pulmonary fibrosis. Furthermore, although the intratracheal injection of alumina has successfully induced fibrotic conditions in the lungs of animals, inhalation techniques using high concentrations of aluminum oxide have failed to induce fibrosis.

Aluminum Lung

Molecules of aluminum metal cannot exist in the air for any length of time because they are almost instantaneously oxidized to aluminum oxide. By the same token, larger particles of aluminum metal are invariably coated with aluminum oxide. It is this thin, self-generating coating that gives aluminum its corrosion-resistant properties. Every particle of aluminum is surrounded by a hard coating of alumina that is around 20 ³ thick. When the coating is scratched off the surface of the particle so as to expose the metallic aluminum, it almost instantaneously regenerates.

For commercial use, aluminum particles are prepared in two forms. When fine metallic particles are necessary, aluminum is atomized. This process involves spraying a fine stream of molten metal into a high-velocity air jet, leading to the formation of granular particles with a smooth surface and a shape that is either ovoid or spherical. Granular aluminum particles have a number of uses, especially in the manufacture of pigments. A particular form of aluminum known as *flake* is used in the manufacture of paints and fireworks. This is also known as *stamped aluminum,* and it is processed into fine flakes by ball milling. Whereas granular aluminum particles have a limited surface area, the leaflike flake powder has a much larger surface area. A special type of flake powder known as *pyro* finds a particular use in the manufacture of fireworks and explosives. This is produced by ball milling flake aluminum into exceedingly fine particles that have a large surface area. During the ball milling of pyro, a lubricant is added to prevent impact welding, maintaining separation of the particles during stamping. The lubricant also increases and maintains the large surface area, a prerequisite for the manufacture of aluminum paints, and lessens oxidation. The lubricant that has been used predominantly for this purpose is stearin, a vegetable oil. Its addition during the stamping process causes the pyro flakes to be coated with aluminum stearate. The latter acts as a barrier between the flake surface and the atmospheric oxygen, thereby preventing further oxidation.

In wartime Germany and later in Britain, Sweden, and elsewhere, mineral oil (spindle oil) was substituted for stearin in the manufacture of pyro. The much-quoted reason for the substitution was a shortage of animal fats in Germany during wartime, but it seems that the real reason for the change was that mineral oil allowed more pyro powder to be packed into a cartridge so that the explosive effects were far greater. The latter property was desirable in the manufacture of fireworks.

Just before and during the war, Goralewski noted that pulmonary fibrosis developed in a number of German workers involved in the manufacture of pyro aluminum powder. As a result of Goralewski's experience in Germany, epidemiologic studies were subsequently carried out in Britain. No comparable condition was detected, and no explanation for the difference between the British and German findings was evident. Subsequently, however, a pulmonary fibrosis similar to that described by Goralewski developed in several British subjects who were working with metallic aluminum powder. The various effects of aluminum on the lung and the history of aluminum-induced fibrosis of the lung have been well described.

Clinical Features

These are essentially the same as seen in Shaver's disease, namely, the onset of cough, production of sputum, and anorexia. Basal crackles are noted. As in Shaver's disease, the upper lobes tend to be predominantly involved. In the case of one subject who had pulmonary fibrosis, a diffuse toxic encephalopathy also was present. Radiographs show nodular and flocculent shadows in the upper lobes with an occasional pneumothorax.

Pathology

Macroscopically and microscopically, the changes are similar to those seen in Shaver's disease and most other forms of interstitial fibrosis. There does tend to be somewhat more involvement of the upper lobes than in most other types of interstitial fibrosis. Analysis of the lungs usually reveals a grossly increased aluminum content.

Pathogenesis

Corrin, in a series of in vitro and animal experiments, demonstrated that stamped aluminum powder reacts vigorously with water, whereas granular aluminum is almost entirely inert. The latter form of aluminum, as already mentioned, is coated with aluminum oxide, and this explains its relative inertness. Stamped aluminum, whether in the metallic form or treated with mineral oil, reacts vigorously with water, but the addition of stearin reduces this propensity. As mentioned earlier, during wartime in Germany mineral oil was substituted for stearin, and shortly thereafter Goralewski noticed pulmonary fibrosis developing in pyro workers. He correctly attributed the development of the pulmonary fibrosis to the substitution of mineral oil for stearin. Corrin also noted that it was only after stearin had been replaced by mineral oil that aluminosis began to occur in Britain.

This observation prompted Corrin to conduct a series of experiments in animals, in which he administered intratracheal injections of both granular aluminum and several forms of stamped aluminum, including stamped aluminum with stearin, stamped aluminum coated with mineral oil, and stamped aluminum with both lubricants removed. All three forms of stamped aluminum induced marked pulmonary fibrosis; however, granular aluminum was much less fibrogenic. He therefore concluded that all forms of aluminum powder were fibrogenic, although to differing extents. He still was of the opinion that stamped aluminum, when lubricated with mineral oil, was much more hazardous, but he could not completely exonerate stearin-treated pyro. He likewise realized that intratracheal injection did not necessarily reflect worker exposures, and in this regard he was remarkably prescient. Subsequently, in an attempt to prevent silicosis, metallic aluminum powder was administered by inhalation to many thousands of metal miners in Ontario and elsewhere, with no ill effects.

The patient described by McLaughlin and associates was believed to provide further confirmatory evidence that both stamped and granular aluminum powder could induce aluminosis. At the time this subject was given a diagnosis, he was working with pyro that had been treated with stearin, but it subsequently came to light that he had worked previously in the same factory at the time spindle oil was being used. Thus, it seems that aluminosis has been described only in subjects who have been heavily exposed to pyro treated with mineral oil. Similarly, granular aluminum is fibrogenic only when given by intratracheal injection, and this method of administration

is not physiologic and should not be regarded as a suitable model for human disease.

Other Effects of Aluminum

Development of a granulomatous condition of the lung, attributed to the inhalation of alumina, has been described in two subjects. Once again, there was a lack of evidence to indicate that the disease was related to aluminum, although an increased aluminum content was noted in the lungs of both. As the aluminum content of the lungs is increased in virtually every subject who works with alumina or is involved in the reduction of alumina to metallic aluminum, this finding is of little significance.

A more recent study describes nine workers exposed to Al_2O_3 during the production of abrasives from alundum ore. Most had long-term exposure and all had abnormal chest radiographs (category 1/0 or higher). In three, the respiratory symptoms, prevalence of pulmonary impairment, and radiographic appearances were more significant than in the others, and as a result open lung biopsy was performed. In all three, interstitial fibrosis with honeycombing was seen. The lungs were found to contain a variety of metals, and in one case a significant amount of silica and an increased number of asbestos fibers. All three subjects who underwent biopsy had an increased aluminum burden in the lungs; however, the burden as measured by the number of aluminum particulates varied greatly. Five of the remaining six subjects had radiographs that showed changes of either category 1/0 or 1/1. All five were smokers. The finding of a high concentration of aluminum in the lungs is to be expected with long exposure and cannot be construed as indicating that the aluminum caused the fibrosis. Moreover, in most cross-sectional studies there has been no evidence whatsoever of restrictive impairment, decreased lung compliance, or other changes that indicate pneumoconiosis. All three subjects who underwent biopsy may well have had other forms of interstitial fibrosis, such as fibrosing alveolitis. It should also be borne in mind that radiographic changes have previously been demonstrated in workers exposed to aluminum oxide. The changes noted by these investigators were scanty, irregular opacities ranging from category 0/1 to 1/1 at the most, and predominantly, but not entirely, related to cigarette smoking. The circumstances in which aluminum may cause pulmonary fibrosis have been previously described by Morgan and Dinman and by Abrahamson and associates. The evidence that aluminum oxide produces pulmonary fibrosis is tenuous and unconvincing.

A subject with pulmonary alveolar proteinosis attributed to the inhalation of aluminum dust has also been described. The affected subject was a 44-year-old man seen with shortness of breath, radiographic infiltrates, and restrictive disease. A biopsy showed pulmonary alveolar proteinosis. The affected worker had been employed as an aluminum rail grinder for the prior 6 years. It was suggested that grinding rails generated a large quantity of aluminum particles, many of which were deposited in the lungs. The illustrations left little doubt that the subject had pulmonary alveolar proteinosis; however, the electron micrograph of the aluminum particles showed them to be completely spherical. It seems inconceivable that the particles generated by grinding would be spherical, and indeed the only way in which the aluminum particles could have been spherical is if they were generated as droplets of vapor at a very high temperature. It is well established that pulmonary alveolar proteinosis may develop after high exposure to a number of dusts, but there is no compelling reason to incriminate aluminum in this case report.

Potroom Asthma

An ill-defined and nonspecific form of airways obstruction has been reported in certain groups of potroom workers. This occurs relatively rarely and is completely absent in some aluminum plants. Whether it is a true form of asthma or industrial bronchitis is not definitely known. It has been suggested that the asthmatic symptoms may be a consequence of exposure to fluorides. Nevertheless, there is little doubt of increased evidence of chronic air flow limitation in potroom workers, which tends to worsen with continued exposure, so that by the end of the week a small decrement in lung function is often noted.

Antimony Pneumoconiosis

Antimony is a metal closely related to arsenic that has been used in the manufacture and plating of vases since the time of the Pharaohs. Antimony ore, before it can be used, has to be pulverized into a fine dust. A pneumoconiosis may develop in those workers, particularly at the furnace, who are exposed to the pulverized oxide. Although radiographic changes are present in the lung, pulmonary function does not seem to be affected, and similarly the lungs do not show any fibrosis.

Baritosis

The inhalation of barytes may induce a condition known as *baritosis.* Baritosis also has been described in the manufacture of lithopone, in which barytes is used. Some deposits of barytes are contaminated by significant concentrations of silica, and silicosis may be observed in such workers.

Baritosis is not associated with respiratory symptoms, but the radiographic appearances are quite striking. The deposits of barium appear as multiple, extremely dense, small, rounded opacities. Some radiographic clearing occurs with the passage of time.

Berylliosis

Beryllium is a rare metal. It is found in a number of naturally occurring minerals, of which beryl or beryllium aluminum silicate is the most important. Deposits of beryl are found in Argentina, Brazil, Zimbabwe, and South Africa. Beryllium is in demand as a metal that is often added to other metals to increase their tensile strength. It is nonmagnetic and transmits x-rays. It is frequently used in the manufacture of x-ray tubes as well as in the space program.

Two processes are used to extract beryllium from beryl. These are known as *sulfate* and *fluoride extractions.* The sulfate process involves melting beryl in an arc furnace at about 1700°C and pouring it through a high-velocity water jet to form frit. This is then treated with concentrated sulfuric acid and subsequently ammonia. Later, sodium hydroxide is added to form sodium beryllate, which is hydrolyzed so that beryllium hydroxide is precipitated. Beryllium hydroxide can be easily converted to metallic beryllium.

The fluoride process involves sintering in a rotating furnace a mixture of beryl sodium, silicofluoride, and soda ash. The sintered residue is pulverized, melted, and separated by leaching. Once again, sodium hydroxide is added and beryllium hydroxide is precipitated.

Exposure to beryllium can cause three conditions: dermatitis, acute pneumonitis, and chronic berylliosis.

Acute Berylliosis

The acute syndrome leads to the development of rhinitis, tracheitis, and pulmonary edema. The mucous membranes of the nose are swollen, ulceration may be present in the nasal mucosa, and septal perforation occasionally occurs. Tracheitis and bronchitis associated with a dry, irritative cough are common. When the exposure is severe, a chemical pneumonia develops and the subject becomes acutely short of breath; death is a frequent occurrence. Although many such cases were reported in the 1930s and 1940s, acute berylliosis has not been seen in North America for many years.

The subject with acute berylliosis is noted to be acutely short of breath, often with cyanosis and tachypnea, and in great distress. Crackles may be present all over the lungs. The chest x-ray film shows a bilateral acinous filling process with the appearance of noncardiogenic pulmonary edema. If the subject is capable of carrying out spirometry and other lung function tests, it will be observed that the lungs are stiff and that the patient has severe restrictive disease and a low diffusing capacity.

Treatment consists of giving supplementary oxygen and antibiotics to prevent secondary infection. In many instances, mechanical ventilation becomes necessary. Although steroids are given, usually in high doses, there is no conclusive evidence that they are of any use.

Subacute or Reversible Berylliosis

This entity has been described by Sprince and colleagues, who suggested that interstitial disease may develop in subjects exposed to high concentrations of beryllium that improves after the introduction of better ventilation and adequate industrial hygiene measures. Subacute berylliosis is a nebulous entity, and it remains somewhat unconvincing as a specific form of berylliosis.

Chronic Pulmonary Berylliosis

This condition was first described by Hardy and Tabershaw in 1946. It is a systemic disease associated with the development of granulomas throughout most of the body, but with a particular predilection for the lungs. Those initially affected were mainly involved in the manufacture of fluorescent bulbs for strip lighting; however, beryllium refineries now present the major hazard. Chronic berylliosis mainly develops in those working directly with beryllium, but there have been a few sporadic reports of berylliosis developing in wives of workers, presumably from beryllium dust brought home on their husbands' clothes. There also have been a number of so-called neighborhood cases, but most of these are not convincing. A latent period from first exposure to the development of the condition ranges from 2 or 3 to 15 to

20 years. Berylliosis is now a rare condition, but sporadic cases still occur, mainly resulting from exposure many years ago.

Clinical Features

Although most persons in whom the condition develops are currently working with beryllium, in a few cases it appears many years after exposure has ceased. This emphasizes the need for a detailed occupational history. The presenting symptoms are usually shortness of breath and a dry cough. Both are progressive and unremitting. Occasionally, skin lesions are also present. Physical examination usually reveals tachypnea and a small tidal volume. In the initial stages, few if any crackles are heard. With the passage of time, usually several years, and the development of fibrosis, crackles become evident. Initially, weight loss and fatigue are frequently present.

Berylliosis closely resembles sarcoidosis, and most of the features seen in the latter condition are common to both. Thus, lymphadenopathy occurs in both conditions, although generalized lymphadenopathy is much less frequent in berylliosis. Berylliosis, however, seldom presents without both parenchymal changes and hilar adenopathy. Hilar adenopathy by itself is rare. Granulomatous skin lesions are seen in both berylliosis and sarcoidosis, but the deforming facial rash leading to scarring that occasionally appears in sarcoidosis does not occur in berylliosis. Hepatosplenomegaly is present in both diseases, but parotid enlargement and cystlike bone changes are not seen in berylliosis. Renal involvement, including both nephrocalcinosis and hypocalcemia, occurs in both conditions. In contrast, the development of meningeal symptoms, peripheral neuropathy, and myocarditis indicates that the condition is likely to be sarcoidosis, and this is also true for uveitis and uveoparotid fever. Berylliosis does not seem to affect tuberculin reactivity. Similarly, spontaneous remission, although common in sarcoidosis, is extremely rare in berylliosis. Abnormalities of the plasma proteins occur in both sarcoidosis and berylliosis and do not help to distinguish them. Gamma globulin production is predominantly affected, and the IgG fraction is often elevated. It is also elevated in beryllium workers who have no evidence of berylliosis. As the disease progresses, the patient becomes more and more short of breath, the lungs become increasingly stiff, and the classic signs of cor pulmonale are noted. Pneumothorax may occur from bleb formation, and right ventricular hypertrophy is evident. The disease tends to progress slowly, and survival times of 15 to 20 years are frequent.

Radiographic Features

The most common radiographic presentation is one of miliary mottling, similar to that seen in miliary tuberculosis. Hilar adenopathy is distinctly uncommon. Large, blotchy, coalescent infiltrates resembling those seen in sarcoidosis also occur, and uncommonly, nodular infiltrates similar to those seen in nodular sarcoidosis may be observed. Gradually, the lungs become small, and the typical features of reticulonodulation and interstitial fibrosis develop along with honeycombing.

Pulmonary Function

Abnormalities typical of diffuse fibrosis are found—that is, stiff lungs and restrictive impairment. These abnormalities are entirely nonspecific. Obstruction does not occur except terminally, when minor degrees may be present. It has also been suggested that long-term exposure to beryllium is associated with the gradual reduction in pulmonary function. Such reductions are said to occur in workers who have no radiographic abnormalities. Moreover, it has been suggested that the alveolar-arterial oxygen difference gradually increases with cumulative exposure after controlling for age and smoking. The evidence for this, however, is tenuous and unconvincing.

Other Diagnostic Tests

In 1951, Curtis described a beryllium patch test. Results are usually positive in chronic berylliosis, but there is good evidence that its use may lead to a flare-up of the chronic pulmonary berylliosis. Metallic beryllium cannot be used for skin testing, and the patch test is best carried out by applying to the skin a piece of filter paper soaked in beryllium fluoride, sulfate, or nitrate. The Kveim test result is negative in berylliosis.

Tissue biopsy and spectrographic analysis of specimens for beryllium are not helpful. Increased levels are found in the tissues of most healthy workers in a beryllium refinery. This is true for the lungs only if exposure has been relatively recent, as beryllium is rapidly removed from the lungs and deposited in the bones and liver. It may be present in increased amounts in the urine, but usually only if the subject is currently exposed. Thus, analysis of tissue specimens cannot confirm the presence of disease. On the other hand, a lung biopsy specimen may have a normal beryllium content despite the presence of chronic berylliosis.

Pathology

Chronic berylliosis is characterized by the presence of noncaseating granulomas indistinguishable from those found in sarcoidosis. Eventually, as time goes by, the granulomas become organized and fibrotic. Blebs may develop late in the course of the disease, and these are frequently associated with some pleural thickening.

A number of cellular responses have been described following experimental exposure to beryllium. The alveolar macrophages take up beryllium particles by phagocytosis and in doing so are damaged and release lysosomal enzymes. Any beryllium deposited in the alveoli is cleared relatively slowly. Initially, macrophage activity is decreased, but subsequently activity rebounds and increases. There is also evidence that macrophages sequester beryllium in the lung and in doing so become more active, with resultant damage to the lung.

Treatment

In general, steroids are administered when the condition is diagnosed, but there is no convincing evidence that they have ever produced a cure. Usually, the subject is started on a high dose of prednisone (e.g., 75 mg/d), and this is gradually tapered to a maintenance dose of about 10 to 20 mg. The patient is best followed by serial tests of pulmonary function.

Pathogenesis

All the evidence presently available suggests that berylliosis is a hypersensitivity disease characterized by a cell-mediated immune response to beryllium. Differentiation between sarcoidosis and berylliosis is difficult. Marx and Burrell have suggested that lymphocytotoxins can be demonstrated in the cells of sensitized but not of unsensitized subjects. Production of migration inhibitory factor (MIF) has likewise been noted. The cellular and immune mechanisms of berylliosis were later studied by Deodhar and co-workers. They investigated blast transformation of lymphocytes in subjects with berylliosis. About 60% of their subjects showed this phenomenon, to which severity of disease appeared to be related. They found that the serum IgA level was elevated in about half their subjects, but in this their findings differed from those of Resnick and associates, who noted that the IgG fraction was increased.

A beryllium lymphocyte transformation test has been developed and has been used with some success in the diagnosis of berylliosis. Bronchoalveolar lavage also has been carried out in subjects with berylliosis, and the proportion of bronchoalveolar T cells has been noted to be increased.

The evidence currently available suggests a cell-mediated response to the inhalation of beryllium takes place that includes the following:

1. Microscopic features in the lungs and lymph nodes similar to those seen in other cell-mediated reactions
2. Skin sensitivity reactions
3. Blast transformation and MIF production from lymphocytes
4. Selective stimulation of T lymphocytes
5. Transfer in animal models of cutaneous sensitivity by lymphocytes but not by serum

Prevention

Dust control is of the utmost importance in preventing berylliosis. The present standard recommends that exposure should not exceed 2 g/m^3 of air during an 8-hour period. Whether this is entirely effective in the prevention of chronic berylliosis is unknown, as most of the evidence suggests that the condition is related to hypersensitivity. Although pre-employment and periodic medical examinations, including serial radiography and lung function tests, are recommended, there is no evidence to suggest that they are of any benefit in this disease, as the condition tends to come on rapidly and progress despite separation from exposure. Educating workers about the symptoms of chronic berylliosis and how to avoid exposure would seem to be much more effective methods of prevention.

Graphite and Carbon Pneumoconiosis

Graphite is a form of carbon and is also known as *plumbago* or *black lead.* It is mined or extracted in Austria, the former U.S.S.R., Sri Lanka, Norway, and Korea. Usually, it is found in veins that traverse igneous rocks. It occurs naturally in three forms: lump, amorphous, and flake. The latter is usually extracted by strip mining.

Many deposits of graphite are contaminated by free silica, usually in low concentrations.

Graphite is used in the manufacture of steel and in lubricants, lead pencils, nuclear reactors, and electrodes. Because it also conducts electricity, it is often used in generator brushes. It was at one time used in the printing industry for duplicating plates.

It is now clear that inhalation of pure carbon may induce radiographic and pathologic changes indistinguishable from those associated with inhalation of coal. In some instances, the lung bases have been described as showing a fine reticulation, but more generally this disease appears as the typical nodulation seen in simple CWP. PMF likewise can occur. The pulmonary function abnormalities are similar to those seen in CWP.

Hematite Pneumoconiosis (Silicosiderosis) and Other Mixed-Dust Fibroses

Although iron oxide has been known for many years to produce a condition known as *siderosis,* it is also evident that a lung condition associated with radiographic changes may develop in iron miners. However, iron miners are not exposed to pure iron oxide, but to a mixture of dusts, often with a fair amount of free silica present. The condition that occurs in iron miners is usually known as *silicosiderosis* and has been described in Cumbria in Britain, Germany, Bergamo in Italy, and Alsace-Lorraine. It seldom develops without at least 10 years of exposure.

The best pathologic description of the condition was given by Stewart and Faulds, who noted a diffuse rather than nodular fibrosis, although if the proportion of silica was high, then the latter type of fibrosis often occurred. The whole lung was noted to be brick red in color, with associated areas of focal emphysema. Radiographically, diffuse fibrosis appeared to predominate. Massive fibrotic lesions also were seen and were usually situated in the same regions of the lung in which conglomerate silicosis and PMF occur. As in the other two conditions, these fibrotic masses encroach on the blood and bronchial supply of the affected area. They also may undergo cavitation, either from ischemic necrosis or secondary tuberculous infection. Microscopically, aggregated particles of hematite and silica are seen lying in the alveolar walls. The lesions are situated in the same areas of the acinus that are primarily affected by silicosis, and peribronchiolar and periarteriolar fibrosis are common. Whorled nodules may be seen, especially along the lymphatic vessels. A fair amount of dense collagenous fibrosis is present, usually in association with the typical nodules of silicosis.

There is good evidence that cancer of the lung occurs more frequently in Cumbrian iron miners. Most of the evidence, however, suggests that the increase is related to radon daughters rather than to any inherent carcinogenic property of iron oxide. The symptoms of the condition are very similar to those of silicosis. The presence of iron in the inhaled dust leads to a situation in which, for a given cumulative dust exposure, radiographic abnormalities appear somewhat more rapidly than they would in workers exposed to other dusts containing free silica. A relatively similar condition can also develop in ochre miners.

A mixed-dust fibrosis is commonly seen in foundry welders and burners as well as in boiler scalers. These workers likewise are exposed to a mixture of iron, silica, and other dusts. Iron, with its high atomic number, tends to produce radiographic changes, and such changes are frequent in foundry workers. There is, however, an absence of significant fibrosis. Boiler scalers, on the other hand, are often exposed to dust containing a high content of free silica, and there is a tendency for a condition more closely resembling silicosis to develop.

Labrador Lung

An unusual form of mixed-dust pneumoconiosis known as *Labrador lung* has been described in the iron miners of West Labrador. These miners are exposed to iron, silica, and some anthophyllite. Lung biopsies have demonstrated increased amounts of iron and silica in the lungs and, in addition, a number of ferruginous bodies. The histologic appearances are frequently modified by the presence of anthophyllite.

Polyvinyl Chloride Pneumoconiosis

The manufacture of polyvinyl chloride (PVC) leads to the production of a varying number of respirable dust particles. When administered to animals, PVC may lead to bronchiolitis, some alveolitis, and the formation of granulomas. During the past 10 to 15 years, radiographic changes have developed in a number of subjects working with PVC. Many of these individual case reports have been far from convincing, but a number of epidemiologic surveys have demonstrated that PVC pneumoconiosis indeed exists.

PVC pneumoconiosis was first described in 1970 by Szende and associates. A number of studies have been carried out since Szende's description suggesting that radiographic changes take place. Other studies have indicated that respiratory symptoms and pulmonary impairment may occur. A well-designed study of a large group of workers exposed to PVC was published in 1980, showing a minimal increase in respiratory symptoms in those most heavily exposed and a similar minimal effect on the FVC and FEV_1. The radiographic changes, however, were subtle and consisted of small, scanty, rounded opacities. Pathologic changes in this condition indicated that there may be infiltration of the lung parenchyma with histiocytes and a few multinucleated giant cells, and, rarely, a little collagenous fibrosis may be seen. Macrophages migrate into the tissue and many contain PVC particles.

Shale Pneumoconiosis

Shale deposits are found in many parts of the world, in particular in the Midwest of the United States, Alberta in Canada, and to a lesser extent Scotland. Such deposits are a known source of oil. Shale consists largely of silicates, including a fair proportion of kaolin and mica. Either simple or complicated pneumoconiosis may develop in shale miners. The pathology resembles either CWP or kaolin pneumoconiosis. The simple form of the disease has little effect on lung function, but the complicated pneumoconiosis of shale workers leads to both restrictive and obstructive impairment, as is seen in CWP.

Siderosis (Arc Welders' Lung)

Siderosis was first described by Zenker in the late nineteenth century. Both his subjects had tuberculosis, and the fibrosis he noted was probably related to the infection rather than to the inhaled iron. Siderosis is caused by the deposition of iron in the lungs, usually in the form of iron oxide. It occurs in arc welders, oxyacetylene cutters, silver finishers, and magnetite pulverizers. During oxyacetylene cutting and arc welding, the iron that is being cut or welded melts and then boils from the heat of the arc or torch. This leads to the emission of fine particles of ferrous oxide, which on contact with the air are immediately oxidized to ferric oxide. They appear as bluish-gray fumes. Most of the particles present in these fumes are respirable, with many being submicronic in size. Prolonged inhalation and deposition of welding fumes leads to the development of siderosis, a condition characterized by radiographic changes somewhat similar to those seen in silicosis.

Silver finishers use a preparation (“jeweler's rouge”) to polish their products. Jeweler's rouge consists of iron oxide and is applied to the finished product with a buffer; this creates an aerosol of small iron and silver particles. Prolonged inhalation of such particles leads to a condition known as *argyrosiderosis.*

Welders' Siderosis

Welders' siderosis was first described in 1936 by Doig and McLaughlin. The weight of the evidence suggests that provided only iron oxide is inhaled, the condition is not associated with symptoms and does not lead to fibrosis. Morbidity and mortality statistics from the United States and Britain do not indicate any increased morbidity or mortality among welders other than from lung cancer. However, they do indicate that welders may be more prone to pneumonia and, in addition, frequently have metal fume fever. Nevertheless, sporadic case reports through the years have suggested that welding induces fibrosis and other problems. In certain instances, the welding has been reported to be associated with the development of restrictive impairment and pulmonary fibrosis, whereas in others it has been claimed that it leads to airways obstruction and emphysema. In none of these subjects was there any smoking history or were there any data regarding other exposures. The case reports of Charr described symptomatic welders at the Philadelphia shipyards, and the somewhat inadequate description of the pathology and the few photomicrographs available suggest that these men almost certainly had asbestosis. In fact, in one photomicrograph there appears to be an asbestos body. It must be recalled, however, that at that time it was not known that persons other than miners and millers were at risk for asbestosis. The subject described by Meyer and colleagues, although a nonsmoker, had been a sandblaster, and despite the presence of vast quantities of silica in his lungs, along with massive fibrosis, his disease was attributed to welding. This is not to say that all constituents of welding rods are harmless in all circumstances. The rods and other materials with which welders work contain carbon, manganese, aluminum, silicates, and free silica. Arc welders also may be exposed to ozone, especially if they weld aluminum. Oxyacetylene cutters similarly may cut through cadmium-containing metal and thus be exposed to cadmium fumes.

In regard to the general health of welders, as already mentioned, they seem more prone to pneumonia and metal fume fever. The latter is a well-recognized cause of temporary morbidity. There also seems to be an excess risk for lung cancer that cannot entirely be accounted for by social class and smoking habits. However, many welders, including those studied by Beaumont and Weiss, have worked exclusively or for a long time in shipyards and thereby have had significant exposure to asbestos. Asbestosis is a well-recognized complication of shipyard welding.

Pathology

The pathologic effects of iron on the lung were first described by Harding and colleagues from autopsy findings of four arc welders and an oxyacetylene cutter. One of their subjects had coincident exposure to silica, and there was evidence of a mixed-dust fibrosis. The oxyacetylene cutter, however, showed no fibrosis. When fibrosis was found in the other subjects, it was not related to the deposition of iron oxide but to the other constituents of welding fumes or to other occupational exposures. Similar studies of silver polishers have shown an absence of fibrosis. Experiments in which animals have been exposed to the inhalation of iron have likewise failed to reveal any fibrosis.

The results of lung biopsies in seven welders described by Morgan and Kerr showed that although some of the iron lay free in the alveoli and respiratory bronchioles, most had been taken up by the macrophages and some could be seen in the lymphatic vessels. Fibrosis was entirely absent, except in the one subject who had had a mixed-dust exposure. An analysis of a portion of one subject's lung revealed an iron content 15 times greater than the normal level. Despite this, absolutely no fibrosis was present in the sections (Fig. 14 and Fig. 15).

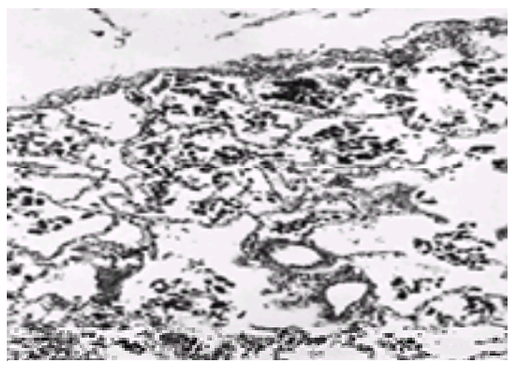

FIG. 14. Photomicrograph of a lung biopsy section taken from a welder. Note the absence of septal thickening and the pigment in the alveoli. Most of the latter is present in alveolar macrophages.

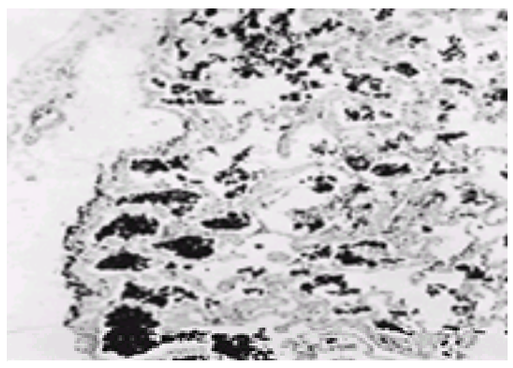

FIG. 15. Photomicrograph of a different section of the same lung as in Fig. 14, but on this occasion stained with Prussian blue. Note again the absence of fibrosis and the heavily stained deposits of iron, which appear intensely blue when viewed under the microscope.

A number of retrospective studies have been published purporting to show that welding fumes cause fibrosis. Of the 3600 cases referred to Liebow, nearly all of which were subjects with pulmonary fibrosis, it was possible to select 29 who were welders and who had fibrosis. No fewer than 14 were reported by Liebow as showing fibrosing alveolitis. Unfortunately, some have assumed that these cases are representative of welders as a whole, and this is clearly not the case. Others have assumed that low concentrations of the oxides of nitrogen induce pulmonary fibrosis, again with no scientific basis.

Radiographic Features

Radiographically, the lungs are characterized by small, rounded opacities widely distributed throughout both lung fields. The preponderance in the upper zones that occurs in silicosis is not usually evident. Moreover, the shadows tend to be somewhat smaller and of the *q* type rather than of the *r* type commonly observed in silicosis. Conglomeration can occur, but when it does, it is usually because of coincident exposure to silica (Fig. 16). Postmortem studies of the contaminants of the lung add little useful information other than giving an idea of the agents to which the welder was exposed during life. Serial observations of welders who have ceased exposure have shown that in certain instances the radiographic appearances tend to improve.

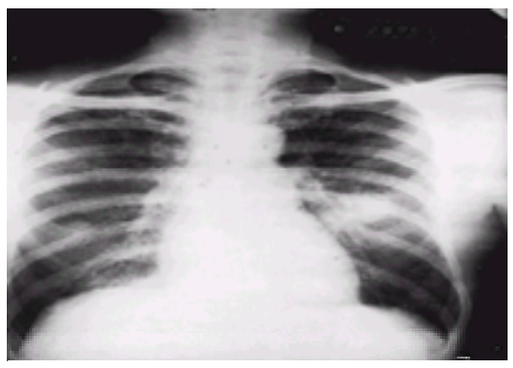

FIG. 16. Chest radiograph of a welder showing welders' siderosis. A large shadow is present in the left middle zone. The subject had a prior exposure to a number of mixed dusts, including some silica.

Pulmonary Function

Siderosis when not associated with the inhalation of other harmful agents is not related to significant pulmonary impairment. This is evident from the studies of Morgan and Kerr, who measured all aspects of pulmonary function except the diffusing capacity. Values obtained during subsequent measurements of the diffusing capacity were within normal limits. Stanescu and co-workers studied the pulmonary mechanics of a group of 16 welders who had abnormal radiographic findings. They were compared with a group of 13 unexposed healthy men. When certain of the more sophisticated parameters of lung mechanics were measured, including static and dynamic compliance of the lungs, values were slightly reduced. The minor abnormalities noted, however, do not cause symptoms.

A number of well-controlled epidemiologic studies of the respiratory status of welders have been carried out. These, for the most part, have shown that welding may be associated with a slight increase in airways obstruction, but this is present only in those welders who are smokers. There is also evidence that welders tend to smoke more often than does the general population.

General Health Effects of Welding

The biologic effects of exposure to welding fumes have generated considerable discussion during the past three to four decades. A fair number of articles have been published purporting to show that welding is a dangerous occupation associated with a number of conditions, ranging from lung cancer to dementia and motor neuron disease. The real and imaginary hazards of welding have been reviewed in detail.

The recognized and accepted hazards of welding can be grouped under (1) acute effects, (2) chronic toxic effects, (3) chronic respiratory effects, and (4) carcinogenic effects.

Acute Effects

A number of agents to which welders are exposed may produce acute effects. These include ozone, the oxides of nitrogen, cadmium fumes, phosgene, and metal fumes. There is little doubt that in exceptional circumstances all can be a respiratory hazard, and the effects of each are described elsewhere. Suffice it to say that exposure to the oxides of nitrogen does occur occasionally in welders working in confined spaces and has been noted in coal mines and elsewhere. Acute exposure to cadmium leading to the development of pulmonary edema and subsequently to emphysema also has been described. Metal fume fever is a recognized complication of welding and oxyacetylene cutting. It is entirely benign.

Chronic Toxic Effects

These occur as a result of exceptional circumstances. Manganese poisoning associated with central nervous system involvement has been described in the former East Germany and eastern Europe, but never in the West. Exposure to fluorides, lead, and various trace elements likewise may occur, but no reports of toxic effects from exposures to these agents have appeared in the last 10 to 15 years.

Chronic Respiratory Effects

A number of chronic respiratory effects may occur as a result of welding. First and of most importance is welders' siderosis. This has already been described in detail.

There is a suggestion that cough and production of sputum are greater in welders than in a comparable general population. Although part of this may be explained by the fact that welders smoke more, little doubt exists that exposure to welding fumes leads to mild chronic bronchitis that is not associated with any significant pulmonary impairment.

Carcinogenic Effects

Evidence is fairly good that welders as a whole have a slightly greater risk for lung cancer than does the general population. Part of this can be explained by the fact that welders smoke more than does the general population; however, a significant proportion of welders have worked or still work in shipyards and have done so for many years. As such, these workers have been exposed to asbestos, and overt asbestosis has developed in many of them. The combination of excess smoking and exposure to asbestos almost certainly accounts for the increased incidence of malignant respiratory disease.

Silver Polishers' Lung

Silver polishers' lung differs from siderosis in that although silver polishers use iron oxide while buffing silver, the buffing tends to aerosolize both silver and iron oxide particles. As a result, inhaled iron and silver are both deposited in the lungs, and the lungs appear black at autopsy because of staining with silver. No physiologic abnormalities occur in this condition.

Magnetite and Limonite Pneumoconiosis

Radiologic changes similar to those seen in siderosis have been described in workers exposed to magnetite and limonite. The appearances radiographically resemble siderosis, and respiratory impairment has not been observed.

Stannosis

Tin is an important metal that is used frequently to form alloys. Both the Phoenicians and the Carthaginians traded with the inhabitants of Cornwall for the tin that was mined there. In the Middle Ages, most of the tin that was mined came from Cornwall, Saxony, and Bohemia, but at the present time, Malaysia, Bolivia, Zaire, and Australia are the main sources. Although some tin is extracted by underground mining, in Malaysia the deposits are on the surface. Most Cornish tin mines are now closed down. Cornish miners, however, were not afflicted with stannosis, but rather with silicosis. The seams were usually located about 1000 ft below the surface, and the adjacent rock that had to be removed before reaching the seam frequently contained large amounts of free silica. Hookworm infection also was a problem. In Malaysia, tin is usually removed by open-cast mining.

The inhalation of tin oxide leads to a benign pneumoconiosis not associated with symptoms or respiratory impairment. Most of the subjects in whom the condition develops are involved in the bagging of concentrated oxide or in the smelting operation. During smelting, hot fumes are emitted that contain submicronic particles of tin. These are inhaled and lead to the development of stannosis.

The radiographic appearances of stannosis are so distinctive that it is difficult to confuse it with other conditions. The high atomic number of tin makes the opacities very dense, even denser than those noted in welders' siderosis and almost as dense as those noted in baritosis (Fig. 17 and Fig. 18).

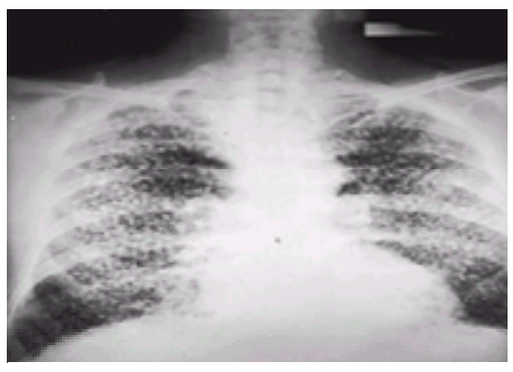

FIG. 17. Chest radiograph of a subject with stannosis. Tin oxide, having a high atomic number, shows up as intensely radiopaque deposits.

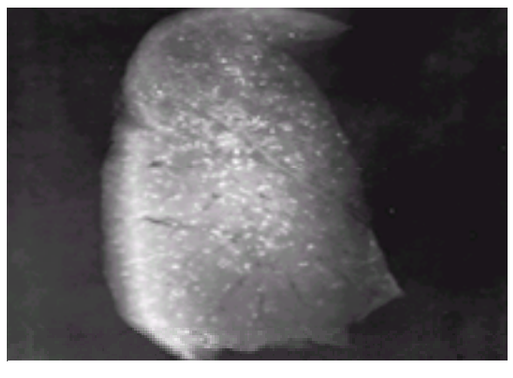

FIG. 18. Radiograph of a large lung section from a subject with stannosis. Death was caused by carcinoma of the prostate, not by stannosis.

Pathologically, blackish or grayish macules are widely distributed throughout the lungs. Gross pigmentation of the interlobular septa is frequent. The foci of dust are composed of dust-laden macrophages containing tin oxide and other agents. Focal emphysema occurs but is not as prominent as in CWP. Fibrosis does not occur.

Thesaurosis

Bergmann and colleagues in 1958 described several subjects with a chronic pulmonary disease that they termed *thesaurosis* or *storage disease.* They were generally young women exposed to hair spray, and Bergmann and associates attributed the condition to the inhalation of polyvinylpyrrolidone (PVP), a major constituent of hair sprays. Following their description, a series of subjects with so-called thesaurosis was described. Unfortunately, those who described thesaurosis seemed unfamiliar with Koch's postulates and certainly did not apply them when they weighed the evidence regarding the existence of this entity. In reality, the subjects described appeared to have sarcoidosis. Subsequent epidemiologic studies have provided absolutely no evidence that cosmetologists are at increased risk for the development of any lung condition other than chronic bronchitis and emphysema. The latter is related to the fact that the prevalence of smoking is exceedingly high in this trade.

Tungsten Carbide Pneumoconiosis (Hard Metal Disease) and Related Syndromes

Although the term *hard metal disease* is in common use, the available evidence at the present time suggests that it is not the tungsten carbide that leads to the respiratory problems seen in hard metal workers, but rather the cobalt that is almost invariably present. Cobalt is frequently added to various alloys to increase their tensile strength. Hard metal is produced by metallurgic compounding of tungsten and carbon, with cobalt being added as a binder. Tungsten carbide, or hard metal, is extremely hard, second only to diamonds, and is used for cutting metals. It is particularly useful in the manufacture of dental drills.

Tungsten carbide is prepared by compounding extremely fine particles of tungsten and carbon. These particles are at the smaller range of the respirable fraction and are about 1 to 2 m in size. The tungsten carbide mixture is then milled with the addition of between 3% and 25% cobalt. The tiny, hard metal crystals are deposited in the cobalt. Paraffin is added to provide body before the metal is pressed into ingots. The ingots are then sintered into hard metal, and the resultant tool is subsequently shaped as desired. Three respiratory diseases are produced by the inhalation of cobalt. These are (1) allergic alveolitis; (2) pulmonary fibrosis, or what is commonly called *hard metal disease;* and (3) a form of asthma.

In 1940, Jobs and Ballhausen noted that in a group of 27 German workers, abnormal chest radiographs developed in eight. A fine reticulonodulation was present. Subsequently, in an examination of 696 hard metal workers, Moschinski and colleagues found a high prevalence of bronchitis. Radiographic evidence of pneumoconiosis was found in a smaller percentage. Fairhall and associates surveyed 2000 tungsten carbide workers shortly after World War II and found that conjunctivitis, rhinitis, tracheitis, and bronchitis were frequent. In addition, pruritus and cobalt sensitivity occurred.

Cobalt-Allergic Alveolitis or Interstitial Pneumonitis

A description by Sjögren and colleagues of a syndrome similar to extrinsic allergic alveolitis in four subjects made it clear that an acute and reversible disease is induced by exposure to cobalt. All of Sjögren's subjects were grinders of hard metal, and symptoms and signs compatible with transient hypersensitivity pneumonitis developed in all. After an absence from work, the symptoms improved, the radiographic changes resolved, and the respiratory impairment decreased or in some instances resolved entirely.

The premonitory symptoms were cough, low-grade fever, muscle aches and pains, and generalized constitutional symptoms. These symptoms would often lead the subject to take several days off from work, during which time the symptoms would improve, only to recur on return to work. Medical examination during the acute phase would reveal basal crackles, low-grade fever, and in some subjects contact dermatitis. Of the four subjects described by Sjögren and colleagues, all had positive patch test results. Of particular interest, it was shown that during the grinding, small particles of cobalt were disseminated in the air and dissolved in the coolants used to cool the metal being ground. Subsequently, when the coolant was applied during the grinding process, it became aerosolized, and the worker would inhale the aerosolized coolant containing large quantities of cobalt. It appears that the cobalt was very soluble in the particular coolants used. The pathology of this condition shows an alveolitis with marked response of type II pneumocytes. Frequently, there is a granulomatous reaction with giant cells present. With repeated exposures, the granulomatous pneumonitis slowly evolves into interstitial fibrosis.

Interstitial Fibrosis (Hard Metal Disease)

An excellent description of the clinical features of hard metal disease is that of Coates and Watson. These workers described 12 subjects with diffuse interstitial lung disease, of whom no fewer than eight died. The symptoms included cough, which was usually dry but occasionally productive of some scanty mucoid symptoms. Later, breathlessness developed that became progressively worse. On examination, the subjects had tachypnea and frequently clubbing of the digits. Basal crackles developed late in the condition. Lung function tests showed restrictive impairment, arterial desaturation, and a low diffusing capacity. With the passage of time, pulmonary hypertension developed, usually on the basis of hypoxemia, and eventually overt cor pulmonale appeared.

The disease was seldom seen without at least 10 years of exposure, but in retrospect, some subjects were found to have had repeated flare-ups of minor constitutional symptoms, suggesting recurrent attacks of interstitial pneumonitis.

Radiographically, the disease presents initially as a fine reticulonodular pattern in the middle and lower zones, with the nodules sometimes being quite large. As the disease progresses, the characteristic features of interstitial fibrosis are noted, and honeycombing may eventually result.

Although the radiograph usually suggests diffuse involvement, on biopsy or at autopsy the fibrosis may be seen to be distributed in a patchy fashion. The interstitial tissue is often infiltrated with histiocytes and plasma cells. The alveolar septa may be thickened. In a few instances, fibrosis may be associated with a granulomatous reaction and the presence of giant cells. The latter are found particularly frequently in this condition, and some believe they are almost pathognomonic. The alveoli contain what are assumed to be desquamated type II alveolar pneumocytes. Electron microscopy reveals the deposition of collagen and elastic tissue in the septa and the presence of multifaceted crystals thought to be tungsten carbide. In one series of subjects with interstitial pneumonitis and hard metal disease, a nongranulomatous process was described characterized by intra-alveolar exudate and some interstitial reaction. Bronchoalveolar lavage showed bizarre giant forms of the alveolar macrophage (Fig. 19).

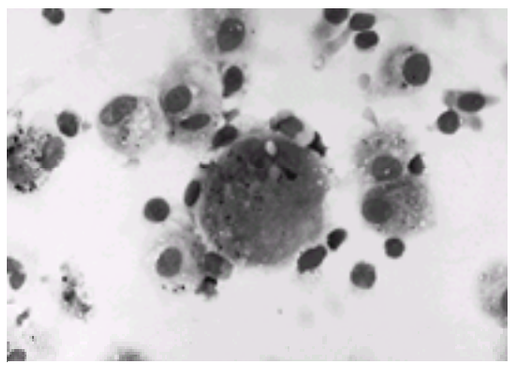

FIG. 19. Photomicrograph of bronchoalveolar lavage fluid showing a characteristic multinucleated giant cell with cytoplasmic vacuoles. Particulate matter is also present along with alveolar macrophages. Patient had hard metal disease.

Airways Obstruction or Asthma

Some subjects with interstitial pneumonitis may also have wheezing, cough, and shortness of breath. Such symptoms also occur in the absence of interstitial pneumonia. The symptoms tend to occur while at work. In most instances, they disappear on the weekends. When subjects return to work on Monday, they remain relatively free of symptoms until late in the afternoon, when symptoms recur. Once the symptoms have appeared, they usually slowly become more severe through the week, only to improve at the weekends. Most subjects with this type of response leave their jobs voluntarily. Those affected also may have itching and skin manifestations resulting from exposure to cobalt. Results of challenge studies with cobalt, but not tungsten, usually are positive, but not invariably so.

Treatment

There is no treatment for established hard metal disease characterized by extensive fibrosis. In contrast, the interstitial pneumonitis usually responds well to steroids and to separation from further exposure to cobalt. It will, however, recur should the subject return to work. Protective devices such as masks are seldom effective.

Etiology

Although a few persons still believe that tungsten carbide rather than cobalt may be responsible, the vast weight of evidence incriminates cobalt. Harding showed that powdered cobalt is toxic in animals, and it did not matter whether it was administered intratracheally or by inhalation. He also demonstrated that the metal was much more soluble in plasma than in saline solution. In contrast, tungsten carbide, when given to animals, is inert. Likewise, Harding was able to induce both an alveolitis and subsequently pulmonary fibrosis. Delahant was able to induce chronic bronchiolitis and metaplastic changes in alveoli with pulverized cobalt, but he failed to do so when he used tungsten carbide, titanium, and tantalum. Single exposures to cobalt during a short period induced granulomatous pneumonitis and bronchiolitis, but if exposures were continued for longer, interstitial fibrosis developed. The fact that cobalt is soluble explains why it may be completely absent in many biopsy specimens obtained from humans. There is little doubt that it is deposited in the lungs, but it is rapidly removed, and lung biopsy 1 month to 6 weeks later may show a normal cobalt content.

Miscellaneous Pneumoconioses

A number of miscellaneous pneumoconioses have been described. Most are of little clinical import. Nonetheless, when faced with a subject who has radiographic abnormalities, it is imperative to take a complete occupational history. Rare earths may induce pneumoconiosis, and cerium oxide is a recognized cause of radiographic abnormalities. Titanium likewise produces radiographic abnormalities, but no associated pulmonary impairment. The same is true of zirconium. Finally, it is important to remember that the esoteric habits of the “lunatic fringe” occasionally lead to the development of radiographic abnormalities and pulmonary impairment. Thus, the development of pulmonary fibrosis in a drug-snorting fire eater who played in a punk rock band serves to emphasize the importance of studying both avocation and vocation.

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CHAPTER

34 Occupational Asthma and Industrial Bronchitis

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OCCUPATIONAL ASTHMA

Occupational asthma may be defined as reversible airways obstruction caused by specific agents in the workplace. It should be distinguished from pre-existing asthma that may be worsened by workplace exposures. The focus of this chapter is primarily on new-onset asthma induced by workplace exposures.

Occupational asthma may be immunologic or nonimmunologic in origin and may be caused by a wide spectrum of low- and high-molecular-weight substances delivered as fumes, gases, or particles. Different classifications are useful when various aspects of occupational asthma are considered (Table 1). One classification divides immunologically mediated occupational asthma into subsets based on type of antigen (high- versus low-molecular-weight agents; Table 2). A second classification divides occupational asthma into subsets based on pathophysiologic mechanisms. Typically, immunologically mediated asthma is associated with a latency period; in contrast, irritant-induced asthma (e.g., reactive airways dysfunction syndrome) occurs without any latency.

Antigens
High-molecular-weight antigens
Protein derived from domestic animals, insets, fungi, or vegetable matter
Dextrans
Low-molecular-weight antigens
Haptens such as platinum and other metal salts
Penicillin and other drugs
Toluene diisocyanate and other reactive chemicals
Pathophysiology
Immunologic—characterized by a latency
IgE-mediated (seen with both high- and low-molecular-weight antigens)
Non-IgE-mediated (seen only with low-molecular-weight antigens)
Nonimmunologic—no latency
Pharmacologic—mast cells, sensory neurons, or smooth muscle as targets
Irritants and toxins (reactive airways dysfunction syndrome)

TABLE 1. *Classification of occupational asthma*

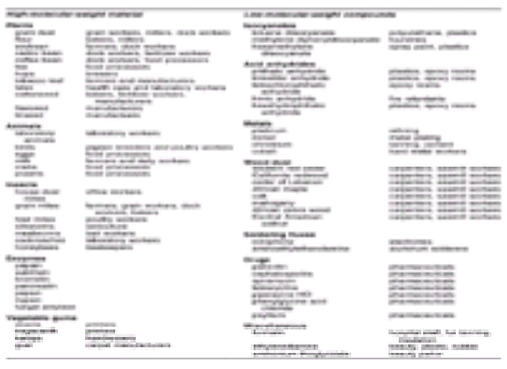

TABLE 2. *Causes of occupational asthma*

Epidemiology and Prevalence

Occupational asthma is now the most common form of occupational lung disease in many industrialized countries. In the United Kingdom and France, the number of claims for occupational asthma exceeds that of pneumoconioses. In the United States, asthma prevalence is increasing, involving approximately 5% of the population; recent studies indicate that 5%–10% of adult asthma is attributable to workplace exposures. However, disease prevalence varies greatly, as does the risk inherent to specific occupational exposures. For example, the prevalence of asthma can be as high as 50% for workers exposed to platinum salts and only 5% among workers exposed to either isocyanates or wood dust from western red cedar. Among 2500 asthmatic subjects ages 20 to 44 years studied in a large young adult Spanish population, the highest risk for occupational asthma was observed among laboratory technicians, spray painters, bakers, plastics and rubber workers, and welders; the risk for asthma attributed to occupational exposures after adjusting for age, sex, residence, and smoking status ranged from 5%–7%, depending on the definition of asthma.

It is difficult to estimate the true incidence or prevalence of occupational asthma. Many surveys have used questionnaire responses only, which may not accurately reflect airways hyperreactivity or its etiology. Cross-sectional studies of workers may underestimate asthma prevalence because of pre-employment screening to exclude sensitive workers and because of dropout of workers who become sensitized at work. Individuals who remain may reflect a healthy worker effect. Other workers may refuse to participate in epidemiologic studies for fear of losing their jobs.

Several risk factors that influence the development of disease have been identified. Genetic factors such as atopy predispose to the development of occupational asthma in industries using high-molecular-weight antigens; the significance of atopy with low-molecular-weight compounds is less clear. In some studies, cigarette smoking has been linked to an increased risk for occupational asthma. The relationship between pre-existing airways hyperreactivity and development of occupational asthma is unclear but is under investigation.

Mechanisms

Asthma is a common disease affecting as many as 20 million individuals in the United States. Workplace exposures may exacerbate symptoms in persons with pre-existing asthma (work-aggravated asthma) or trigger new disease. The mechanisms by which occupational agents induce asthma are similar to those that are operative in non-occupational asthma. Important mechanisms include reflex bronchoconstriction, acute inflammation, and immunologic sensitization. For some agents,

responses may be triggered through several pathways, whereas for others the mechanism by which the material causes asthma is undefined.

Work-Aggravated Asthma: Nonimmunologic Mechanisms

Work-aggravated asthma is defined as concurrent asthma worsened by gaseous or particulate irritants or physical stimuli in the workplace. Exposure to numerous industrial agents can cause reflex bronchoconstriction in asthmatic workers with hyperreactive airways. Sulfur dioxide, acidic aerosols, environmental tobacco smoke, chemicals, and automobile exhaust can precipitate cough or wheezing by stimulating irritant receptors. A striking example of an acute exposure occurs with the gas sulfur dioxide (SO_2), which induces bronchoconstriction in asthmatic individuals at concentrations £1.0 ppm after exposures lasting only 5 min. In contrast, inhalation of SO_2 at concentrations 5 ppm causes only small decrements in airways function in normal subjects. Lung function responses to SO_2 in asthmatic persons are greater when SO_2 exposure is accompanied by increased ventilation, usually stimulated by physical labor or exercise. SO_2-induced bronchoconstriction can be further intensified by breathing cold air and/or dry air. Thus, the irritant response can be enhanced by conditions in the workplace.

At times, it may be difficult to draw a clear distinction between work-aggravated and *de novo* occupational asthma. This is particularly true in the case of atopic individuals who may become sensitized to allergens at work. The pathogenic mechanisms and perhaps even the genetic predisposition are similar for the work-related and non-work-related allergen exposure. For example, the physician may encounter an atopic, asthmatic individual with baker's asthma who is sensitized to aeroallergens outside the workplace, such as house dust mites, and also to aeroallergens encountered at work, such as protein antigens in flour. The severity of disease is determined by a combination of immunologic sensitivity and level of exposure to both work-related and non-work-related aeroallergens. The management of such cases needs to address both exposures or risk the possibility of inappropriate attribution; that is, residual symptoms of house dust mite exposure or other non-occupational allergens may be blamed on responses induced by exposure to flour antigens at work. On the other hand, a specific material may act as both an irritant and immunologically specific antigen. For example, isocyanates can cause cough or irritation to the eyes at high concentrations, but immunologic sensitization can also result, causing asthma at extremely low levels.

A second type of nonimmunologic or irritant-induced asthma is the reactive airways dysfunction syndrome (RADS). In 1981, Brooks and Lockey first used the term in an abstract that described 13 workers in whom symptomatic and physiologic evidence of bronchoconstriction developed within hours after a single toxic inhalation exposure. The symptoms were persistent, lasting at least 3 months and averaging 3 years after the time of initial exposure. A case of RADS was defined in the American College of Chest Physicians Consensus Statement, *Assessment of Asthma in the Workplace,* as meeting the following criteria: (1) a documented absence of preceding respiratory complaints; (2) onset of symptoms after a single exposure incident or accident; (3) exposure to gas, smoke, fume, or vapor with irritant properties present in very high concentrations; (4) onset of symptoms within 24 hours after the exposure with persistence of symptoms of at least 3 months; (5) symptoms consistent with asthma, such as cough, wheeze, and dyspnea; (6) presence of air flow obstruction on pulmonary function tests; (7) presence of nonspecific bronchial hyperresponsiveness; and (8) other pulmonary diseases ruled out.

Histopathologic studies in RADS are limited but have shed light on the pathogenic mechanisms. In general, bronchial biopsy specimens have demonstrated only a mild inflammatory response, with sparse lymphocytes and polymorphonuclear cells and no eosinophils. However, biopsy results are variable depending presumably on type and severity of exposure, type of treatment, and time from injury to biopsy.

Although the acute symptoms following toxic inhalation are related to the resulting airways inflammation, the basis for the persistent bronchial hyperresponsiveness is not well explained. Hypotheses under investigation include altered receptor thresholds in the airways, increased airways permeability, smooth-muscle dysfunction as a result of massive mediator release, and persistent airways inflammation. The treatment of the patient with established RADS is no different from that of any other asthmatic patient.

Immunologically Mediated Occupational Asthma

Two observations suggest that immunologic mechanisms are involved in most cases of occupational asthma. First, there is clinical evidence of sensitization—that is, individuals do not experience respiratory symptoms when first exposed to an antigen, but repeated exposures begin to precipitate symptoms. Moreover, with repeated exposures, symptoms occur at extremely low concentrations. Second, there is immunologic evidence of sensitization. This is most easily seen with agents that induce an IgE response in which specific antibodies can be detected by immediate skin tests or radioallergosorbent test (RAST) and correlated with the development of allergic symptoms such as conjunctivitis and rhinitis in addition to asthma.

Antigens involved in occupational asthma fall into two categories. The first category consists of macromolecular antigens derived from animals, plants, microbes, and even recombinant DNA technology. These antigens resemble those responsible for atopic asthma and are mainly proteins. They are complete antigens containing both T- and B-cell epitopes, and they induce and elicit an immune response by themselves. Asthma secondary to these macromolecular agents is closely related to atopic/extrinsic asthma, as it is IgE-mediated. Indeed, atopy is a risk factor for the development of occupational asthma with at least some of these agents. Allergen-specific IgE is invariably found with occupational asthma caused by exposure to high-molecular-weight allergens. The second category consists of molecules of low molecular weight. These low-molecular-weight antigens are incomplete antigens—that is, they first haptenate macromolecules before they induce an immune response and therefore must themselves be chemically reactive molecules or metabolized to reactive intermediates. Asthma induced by some low-molecular-weight molecules is IgE-mediated. However, atopy is generally not a risk factor. Other risk factors have been sought and include, for example, cigarettes, which increase the risk for both immunologic sensitization to and occupational asthma with platinum salts. It is interesting that some low-molecular-weight molecules induce immunologically mediated asthma in which IgE antibodies appear to play no role. The mechanisms of non-IgE-mediated asthma are poorly understood.

Patterns of Cytokine Production

The importance of bronchial inflammation in asthma has become clear. Eosinophilic and lymphocytic infiltration is present in bronchial biopsy specimens of even mildly asthmatic subjects. A variety of proinflammatory substances are released into the airways tissues of asthmatic subjects, including lipids, proteases, bioamines, neurotransmitters, and cytokines. Of these mediators, cytokines are unique because they are primary effector mechanisms for T cells. The pattern of cytokine secretion appears to differ in the major categories of non-occupational asthma. Studies of cytokine production at the mRNA and protein levels indicate that in extrinsic asthma (allergic asthma) interleukin-4 (IL-4) is produced by mast cells and CD4 lymphocytes; IL-5 is produced by these cells and eosinophils. Intrinsic asthma (non-allergic asthma) has not been as extensively studied. Nonetheless, IL-5 and interferon-g are found, but not IL-4. These patterns of cytokines fit with the immunopathology. IL-5 is essential for eosinophil production in the marrow and additionally is able to attract, activate, and enhance the survival of mature eosinophils. In both intrinsic and extrinsic asthma, IL-5 is produced in the airways mucosa, and both conditions are associated with prominent bronchial tissue eosinophilia. In extrinsic asthma, IL-4 is produced in the airways; in intrinsic asthma, interferon-g is produced instead of IL-4. IL-4 is essential for IgE synthesis, whereas interferon-g inhibits IgE production. Thus, extrinsic or atopic asthma is associated with a pattern of cytokines promoting IgE production, whereas the pattern of cytokines in intrinsic, non-allergic asthma inhibits the production of IgE.

The results of studies of IgE-mediated and non-IgE-mediated occupational asthma are remarkably congruous with those of studies of extrinsic and intrinsic non-occupational asthma (Table 3). In both IgE-mediated and non-IgE-mediated occupational asthma, airways inflammation is a predominant feature, and as in non-occupational asthma, eosinophils and lymphocytes infiltrate the tissue. Analysis of cytokine production in occupational asthma has been limited. In one interesting study, lymphocytes were harvested from bronchoalveolar lavage (BAL) fluid and grown in vitro after exposure to toluene diisocyanate (TDI), an agent that induces non-IgE-mediated occupational asthma. These TDI-elicited T cells were 80% CD8-positive and produced large quantities of IL-5 and interferon-g but no IL-4. Challenge studies with non-occupational agents that induce IgE-mediated asthma elicit predominantly CD4 cells producing IL-5 and IL-4 but no interferon-g. BAL studies have not been done for IgE-mediated occupational asthma but presumably would be similar to those for IgE-mediated nonoccupational asthma. Thus, the two major differences between IgE-mediated and non-IgE-mediated asthma are the T-cell subset involved and the pattern of cytokine induced.

	IgE-mediated	non-IgE-mediated
Eosinophilic bronchitis	++	++
T-cell infiltration of airways	++	++
Predominant T-cell subset	CD4	CD8
MHC presentation	Class II	Class I
Interleukin-5	++	++
Interleukin-6	++	–
Interferon-γ	–	++

MHC, major histocompatibility complex.

TABLE 3. *IgE versus non-IgE immune-mediated occupational asthma*

The preponderance of CD8 cells in BAL fluid after challenge with TDI was surprising, because previous studies of BAL fluid in asthmatic patients reported a predominance of CD4 cells. However, these previous studies used protein antigens, such as house dust mite or pollens. Exogenous protein antigens do not enter the cytoplasm of antigen-presenting cells and are therefore not presented via class I molecules to CD8 T cells. Instead, exogenous protein antigens are taken up into cytoplasmic vesicles, where they become bound to class II molecules and are then returned to the cell surface for presentation to CD4 T cells. Because TDI is not a protein but a reactive chemical, it can form covalent bonds with a variety of macromolecules. These macromolecules include self-proteins in the cytoplasm of the cell and even the class I molecules themselves. TDI-modified self-peptides from cytoplasmic proteins or TDI-modified class I molecules would be presented to CD8 T cells. It is interesting to note that although many low-molecular-weight antigens, such as TDI, western cedar, or colophony, induce asthma by non-IgE-mediated mechanisms, another group of low-molecular-weight antigens, such as platinum salts and acid anhydrides, induce antigen-specific IgE. It is tempting to hypothesize that a crucial difference between the chemicals that induce non-IgE-mediated versus IgE-mediated asthma may be presentation of antigen via class I or class II antigens, respectively.

Pathophysiology of Airway Responses

Classically, inhaled protein allergens such as those from cats (Fel d I) or mites (Der p I) induce an immediate hypersensitivity response with an early- and/or late-phase pulmonary response in patients who have asthma caused by these agents (Fig. 1). Both the early and late phase depend on allergen-specific IgE on the surface of mast cells. The early phase begins within minutes of exposure and typically wanes in an hour. Bronchospasm in the early phase is mediated by soluble factors produced by mast cells. The late-phase response occurs after several hours and then wanes by 12 to 24 hours. It is accompanied by a cellular infiltrate: granulocytes, especially eosinophils, initially and mononuclear cells later. Bronchospasm in the late phase is mediated by soluble factors produced by the infiltrating cells. The vast majority of patients with atopic asthma have an early-phase response, and asthmatic patients with a severe early-phase reaction are more likely to have a late phase. An isolated late-phase response occurs in 10% of atopic persons with asthma. Protein allergens that induce occupational asthma are associated with the same airways changes as protein allergens that cause atopic asthma in the general population; typical IgE-mediated early- and late-phase responses are seen in challenge studies. The pattern of airways response is much more complicated in non-IgE-mediated occupational asthma. Although early- and late-phase responses occur, atypical patterns are also common. These can include isolated late responses, responses that peak early and then persist, responses that begin early and become progressively more severe, and responses that persist for several days (Fig. 1).

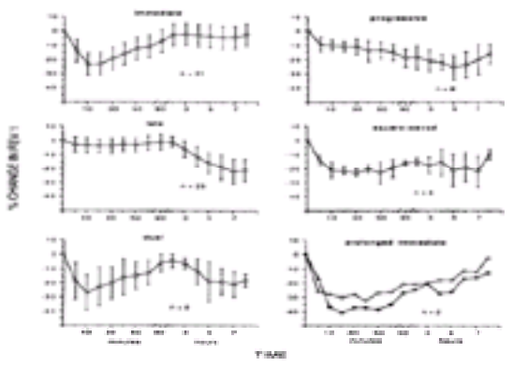

FIG. 1. Patterns of airway response to antigen challenge. (Adapted with permission from Perrin B, et al. Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *J Allergy Clin Immunol* 1991;87:630–639.)

The pathophysiology of acute bronchospasm induced by TDI and similar agents in the absence of antigen-specific IgE is not well understood. TDI has direct biochemical effects, including the induction of substance P secretion. Moreover, TDI can induce the release of histamine-releasing factor by peripheral blood mononuclear cells from sensitized patients. However, neither of these effects provides an adequate explanation for TDI-sensitized patients with immediate bronchospastic responses. The direct effects on substance P or other mediators should not differentiate TDI asthma from asthma of other causes. In addition, histamine-releasing factor is produced slowly and is associated with the late- rather than the early-phase response. Clearly, additional work is needed to clarify the pathophysiology of non-IgE-mediated occupational asthma.

Diagnosis of Occupational Asthma

The two general requirements for a diagnosis of occupational asthma are (1) a diagnosis of asthma, and (2) documentation that the asthma is work-related. Although fulfillment of these criteria is conceptually simple, in practice it is often not straightforward. Several important diagnostic considerations may confound the evaluation of occupational asthma. First, other diagnoses, some of which may also be occupationally related, need to be considered. Second, pulmonary function test results vary considerably depending on whether the patient is currently exposed. Third, many factors in the workplace may act as nonspecific triggers in patients who have hyperreactive airways. Such individuals have work-aggravated asthma, and their management and prognosis differ from those of individuals with true occupational asthma. Finally, the diagnosis has important consequences for both worker and employer. Indeed, patients may either underreport or overreport symptoms for other than medical reasons. Our approach to the workup of occupational asthma is detailed below and illustrated in Fig. 2.

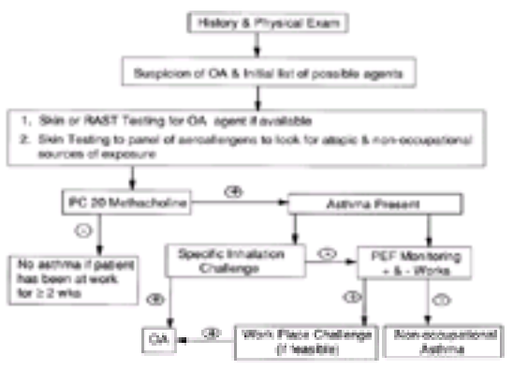

FIG. 2. Algorithm for the workup of occupational asthma. (OA = occupational asthma; PEF = peak expiratory flow)

Defining the Problem

A complete medical history and physical examination are essential in the workup of occupational asthma. The four primary goals are to (1) establish that occupational asthma is sufficiently likely to require further workup, (2) identify alternative diagnoses, (3) assess the severity of illness and the need to eliminate further workplace exposure, and (4) identify likely etiologic agents. In other clinical situations, interventions might be started with just the data provided by the history and physical examination, but in the setting of occupational asthma, additional objective documentation is usually required.

History of the Present Illness

The interview should be open-ended, allowing the patient to raise concerns, and then focus on identified problems. A chronologic history of symptoms should be elicited, including both work-related and unrelated episodes. Particular attention is given to whether symptoms existed before the current job was started. Preceding

asthma is rarely work-related except in the case of a common agent in the environment outside work or a previous work environment. Where and when in the workplace symptoms occur are important in tracking down an etiologic agent; for example, does the patient have problems only in certain areas, or are symptoms associated with a specific process or incidents, such as spills or other accidents? The temporal relationship between work and the occurrence or exacerbation of symptoms should be understood. Do symptoms begin immediately when the patient arrives at work, or do they appear only toward the end of the shift? Do they resolve after the patient has left work? Do they persist during the whole workweek but disappear during weekends or holidays? Are there eye or nasal symptoms, and how do these symptoms change in relationship to work? Are there known precipitants outside the work environment, such as a cat or other animal, damp basements, seasonal exacerbations? The severity and progression of symptoms determine the scope of the workup and whether continued exposure can be tolerated. Evidence of airways hyperreactivity, such as sensitivity to cold air or exercise, and the presence of symptoms that do not support a diagnosis of asthma, such as fever, weight loss, or peripheral edema and orthopnea, are important.

Past Medical History

The past history includes both the personal and occupational medical history. Previous medical records can be especially helpful in ascertaining whether symptoms developed before current workplace exposure. A history of smoking and atopy should be specifically elicited. Childhood respiratory problems such as bronchitis, asthma, frequent colds, hay fever, sinus problems, and allergies point to an atopic predisposition but do not rule out a diagnosis of occupational asthma. A listing of hospitalizations, medical emergencies, and medications should be obtained. Time lost from work and the course of recovery from prior illness may provide insight into how the patient copes with illness. A family history for atopy and other inherited respiratory diseases should be obtained.

Occupational History

Identification of potential etiologic agents for occupational asthma begins with characterization of present and past work-related exposures. This includes a general characterization of the types of potential allergens (chemicals, drugs, metals, animal- or plant-derived proteins, recombinant proteins, or organic dust) and respiratory irritants as well as a general description of the job and the type of job site exposure. Some jobs, such as spray painting or handling animals, necessarily involve exposure to potential allergens. Precautions taken at the workplace, including use of protective gear and ventilation, may mitigate such exposure but can be offset by noncompliance and accidents. The intensity and duration of exposure should be noted. The clinician should also determine if other workers at the same work site have had work-related respiratory illnesses. Problems with ventilation and humidification systems, including contamination with microbes, are common sources of respiratory complaints in the workplace and should be carefully queried. Dampness, particularly when cloth such as carpeting or decaying organic material is involved, may lead to overgrowth of molds or even allergenic mites. Infesting rodents or cockroaches are also potential sources of allergen.

Nonoccupational Environmental History

Environmental factors outside the workplace need to be investigated. The nature and type of housing, type of heating and floor covering, and the presence of any new construction or excessive dampness should be determined. In addition, household pets and rodents or roaches are potential sources of sensitization. Hobbies may involve exposure to chemicals that are sensitizers.

Physical Examination

Normal findings on physical examination are compatible with a diagnosis of occupational asthma. Wheezing and irritation of the conjunctiva or nasal mucosa are the more common positive findings. Nevertheless, determination of vital signs, including the rate and pattern of respiration, examination of the skin, head and neck, heart, extremities, and abdomen, and a screening neurologic examination should be performed in all cases. The primary purpose of this examination is not to make the diagnosis of asthma but instead to exclude other diagnoses.

Confirmation of Asthma

Pulmonary function tests are essential for documenting airways obstruction and reactivity (Table 4). In some cases, the patient will have substantial abnormalities in baseline spirometry, and the diagnosis of asthma can be confirmed by demonstrating a 15% improvement in FEV_1 (forced expiratory volume in 1 second) with inhaled bronchodilators. More commonly, the results of baseline flow studies are normal. In these cases, assessment of bronchial airways hyperreactivity to methacholine, carbachol, or histamine should be undertaken. These tests have not been completely standardized, so the results from different laboratories are difficult to compare. It is therefore important that the individual laboratory have its own database ensuring that normal and asthmatic persons can be discriminated and that results in the same individual are reproducible. In a commonly used protocol in North America, methacholine in doubled concentrations (0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, and 32 mg/mL) is administered as an aerosol via nebulizer for 2 minutes at each dose. A practical problem with this protocol is that the large number of doses requires substantial time in the asthmatic patient with mild or moderate reactivity; often, shorter protocols are used. A major variable in these studies is the nebulizer itself. Use of the same nebulizer in an individual for repeated measurements helps reduce variability.

	Ease	Availability	Sensitivity	Specificity	Comments
Skin prick tests and RAST	++	++	+++	+	Poor correlation with bronchial reactivity. Usefulness and availability depend on antigen.
Spirometry	++++	++++	+	++	Often normal unless illness is severe.
PEFR, serially	++	+++	+++	+++	Very useful with cooperative patient, but compliance is a problem.
Bronchial reactivity (nonspecific)	++	++	++++	+	Very sensitive, standardized. Not specific for etiology.
Bronchial challenge (specific)	+	+	+++	++++	Potentially hazardous. Dose poorly controlled, but reproduces actual exposures.

PEFR, peak expiratory flow rate; RAST, radioallergosorbent test.

TABLE 4. *Confirmation of occupational asthma*

The end point for testing is generally a 20% decrease in FEV_1, and the results are expressed as the PD_{20}. Use of bronchodilators and ingestion of compounds containing bronchodilator agents (e.g., beverages containing caffeine) are stopped before testing. Most inhaled bronchodilators can simply be withheld beginning the evening (12 hours) before, but salmeterol and oral theophyllines should be stopped 24 hours in advance. If the patient is still working (i.e., has been going to work regularly for at least 2 weeks) and is still having work-related symptoms, then an absence of airways hyperreactivity essentially excludes the diagnosis of occupational asthma, and other diagnoses should be entertained. If the worker has been away from the work site for some time or if symptoms have been intermittent (perhaps because of the intermittent presence of the etiologic agent in the workplace), then the absence of bronchial hyperresponsiveness does not exclude asthma, and additional studies are required. One caveat is that the presence of bronchial hyperresponsiveness does not unequivocally mean asthma, because there are asymptomatic individuals with hyperactive airways. In addition, normal individuals may have bronchial hyperreactivity lasting for several months after a respiratory viral infection, such as influenza.

Identification of Potential Agents

Exposure assessment and immunologic testing are the primary tools in identifying potential agents. Exposure assessment begins with a careful history (see above). Additional sources of information include data from an industrial hygiene program, health and safety personnel, material safety data sheets (MSDS), other workers, and in some cases a visit to the work site. When contamination with microbes or mites is suspected, air and/or dust may be sampled for culture, microscopic identification, assays for endotoxin, mycotoxins, and chemicals, or immunoassays for aeroallergens.

Identification of the causative agent occasionally involves an immunologic assessment, because immunologic tests are available for only a few common allergens (Table 4). Asthma with a latency period is immunologically mediated. In immunologically mediated asthma, the immune response induces inflammation in the airways, and this inflammation results in nonspecific airway hyperresponsiveness. In some instances, it has been impossible to demonstrate immune sensitization by skin testing or in vitro assays. This has been particularly difficult with low-molecular-weight antigens, especially those that induce asthma via nonIgE-mediated mechanisms. With both high-molecular-weight antigens and low-molecular-weight antigens that sensitize via IgE, skin testing is still the most sensitive assay for demonstration of immediate hypersensitivity. The problem in many cases is that the skin testing materials for these antigens are not standardized and frequently unavailable

commercially. The investigators may then be faced with the task of manufacturing skin test reagents and/or verifying that they are active.

With some low-molecular-weight sensitizers, manufacture of material for skin testing may involve conjugating haptens to human serum albumin (HSA) and measuring the extent of derivation. Allergen-specific IgE can be measured in vitro using RAST with some allergens. The ability of RAST to quantify results and determine the degree of sensitization may be helpful. False-negatives are more common with RAST, and false-positives may occur in patients with very high total IgE levels. As with airways challenge testing, a database for the individual testing facility can be instrumental in validating skin test or RAST results. Although these tests document immunologic sensitization, sensitization neither proves a diagnosis of occupational asthma nor confirms the test antigen as the cause of symptoms. Generally, more individuals have positive skin test results and no symptoms than have positive skin test results with symptoms. Nevertheless, demonstration of positive immediate skin test results and increased nonspecific bronchial hyperresponsiveness in a patient with both appropriate symptoms and exposure is highly predictive of a positive result on airways challenge with a specific antigen. Moreover, negative skin test results with a valid skin test reagent is strong evidence against involvement of that agent in asthma. For many low-molecular-weight antigens, no skin test reagent has been developed, either because the asthma is not IgE-mediated or because the appropriate carrier or metabolite has not been identified. Skin testing to a limited panel of common non-occupational aeroallergens (in the Northeast a routine panel includes cat, dog, *D. farinae, D. pyterinisinus,* cockroach, mouse, mixed grasses, mixed trees, ragweed, *Alternaria, Helminthosporium, Aspergillus, Penicillium,* and any other pet) can be quite useful in the evaluation of patients suspected to have occupational asthma. Results of this panel are used to define atopic status and determine if non-occupational aeroallergens may play a role. In vitro testing for IgG antibodies may also be done in selected cases, but the presence of IgG antibodies is more helpful in the diagnosis of hypersensitivity pneumonitis than of asthma.

Establishing a Relationship to Work

Monitoring pulmonary function over time and challenges in the laboratory or at the work site are important in relating the workplace exposure to symptoms and physiologic changes and may help to identify the specific agent. Although pulmonary function monitoring to document changes related to work site exposure seems straightforward, there are many potential pitfalls. Perhaps the most significant problem is patient cooperation and compliance. With a highly motivated and reliable individual, useful data can be obtained by measuring peak flows periodically (every 2 hours in most studies, four times a day in some) for 2 weeks. Two studies have evaluated monitoring of peak flows using airways challenge as the gold standard. Peak flow monitoring in these studies was 86% and 87% sensitive and 89% and 84% specific. These results are excellent, but other studies provide evidence that patients are often unreliable and results fabricated up to 25% of the time. The use of computerized meters that record time and results automatically may improve the reliability of peak flow monitoring. Other problems with peak flow monitoring include instances in which exposure may be highly erratic and unpredictable, such as with accidents or equipment failure. In addition, when exposure results in prolonged or delayed respiratory problems, it may be necessary for the worker to be away from the job or on the job for several weeks before a change in function can be seen. Criteria for defining a positive response have often been subjectively based on visual assessment of the record. Objective criteria that have been proposed include (1) diurnal variation in peak flow of 20% or more, (2) occurrence of changes more frequently on days at work than on days not at work, and (3) designation of indeterminate recording when a 20% diurnal change occurs only once or when changes occur over several days rather than daily. By these criteria, 26% of recordings were indeterminate and the specificity and sensitivity of the remaining recordings were 90% and 93%, respectively. However, “subjective” assessment of the record was essentially equivalent to the more “objective” reading.

Airways challenges with specific antigens remain the gold standard for the diagnosis of occupational asthma. Under most circumstances, challenges can be avoided because of good correlation between positive skin test results plus nonspecific airways responsiveness or peak flow monitoring and airways challenges. Nevertheless, challenges are still a necessary tool for some patients. For example, in the patient with a history highly suggestive of sensitivity to a specific agent but in whom monitoring has been indeterminate or unreliable, airways challenge may clarify the issue. Similarly, if the suspected agent has not previously been reported to cause asthma or if the worker has been away from work for a long time, then airways challenge will document sensitization in a physiologically meaningful sense.

The overwhelming consideration in these specific challenges is safety. Laboratory challenges should be performed in specialized centers with trained personnel, often in an investigative setting. An intravenous line should be in place to provide access for medications. Oxygen, inhaled bronchodilators, steroids, and equipment for intubation and resuscitation should be at hand. Laboratory challenge involves several days of observation (Table 5). On the first day, bronchodilator medications are stopped and clinical status, baseline pulmonary function, and fluctuation of FEV_1 during several hours are determined. If the variation in FEV_1 is >10%, then the patient should return when more stable. On the second day, the subject is exposed to aerosolized diluent. Finally, on the third day, exposure to test material is begun. With high-molecular-weight materials, the patient can be exposed to progressively greater amounts of material throughout the course of the day (every 15 to 30 minutes), as isolated late-phase responses are unusual with this type of allergen. During these repeated exposures, FEV_1 should be measured every 10 minutes. With low-molecular-weight materials, isolated late-phase responses and atypical patterns of response are common. Therefore, the patient should be exposed to progressively greater amounts of test material only on successive days. On each of these test days, FEV_1 should be measured every 10 minutes for the first hour after exposure, then every 30 minutes for 2 hours, and finally every hour for the rest of the 8-hour session. The starting dose of test material has to be individualized based on the material to be tested, the severity of the reaction by history, and the patient's nonspecific airways hyperresponsiveness. A 20% fall in FEV_1 is considered a positive response.

Day 1: No exposure
Baseline PFTs
FEV_1 fluctuation <10%
Day 2: Exposure to control material
Day 3: Exposure to specific antigen
For high-molecular-weight material:
Increase doses of antigen every 20 minutes.
Check FEV_1 every 10 minutes.
For low-molecular-weight material:
Increase doses of antigen on successive days.
Check FEV_1 every 10 minutes for 1 hour, then every 30 minutes for another 2 hours, then every 1 hour for the rest of the 8-hour session.

PFT, pulmonary function test; FEV_1, forced expiratory volume in 1 second.

TABLE 5. *Laboratory challenge*

If laboratory challenges are not feasible and peak flow monitoring is unreliable, it may be possible to have the patient return to the work site for progressively longer periods of time, with spirometry, and potential determination of airway responsiveness, performed before and after the exposures. If travel distance permits, these measurements may be made in the pulmonary laboratory, but more often a technician will have to visit the job site.

Although specific challenge tests may be considered the gold standard, false-negative and false-positive interpretations may result. Sources of false-negative results include testing with the wrong material or using an inadequate dose. In addition, nonspecific airways responsiveness decreases with time away from exposure, and a point may be reached at which several exposures are necessary before airway pathology is reinduced and a drop in FEV_1 occurs. Therefore, if there is no change in FEV_1 with exposure, nonspecific airways responsiveness can be measured at the end of the day and the next day to identify subtle changes. Such changes may be an indication for additional exposures. False-positive test results also occur; these may be caused by nonspecific irritation by the test substance or active asthma with a drop in FEV_1 that is independent of exposure. Suggestion may also play a role in airways responses. Indeed, there is some evidence that mast cell degranulation can be conditioned both in animals and humans. Thus, in some circumstances, blinding of both technicians and patient to the test substance may be an important consideration.

Management and Follow-up

The goals of medical treatment of occupational asthma are rapid control of symptoms, reversal of airways hyperresponsiveness, and prevention of irreversible changes to the airways leading to long-term persistence of symptoms.

In the management of occupational asthma, avoidance is the most important intervention. Once a person becomes immunologically sensitized, even infrequent low-level exposure may cause symptoms to persist. Therefore, patient and employer have to be advised that removal from the work site is essential. Interventions short of complete removal should be contemplated only if there is to be close follow-up and documentation of resolution of airways hyperresponsiveness. Such stringent environmental management may not be required in cases of work-aggravated asthma—that is, persons who do not have immunologic sensitization to workplace allergens. For these people, moderate improvements in workplace air quality may be sufficient to control work-related symptoms, especially if their non-occupational asthma is well managed.

Inhaled glucocorticoids are the cornerstone of the pharmacologic treatment of airways inflammation associated with chronic asthma. In a placebo-controlled trial, inhaled steroids have been shown to reverse the airways hyperresponsiveness that otherwise persists for many months after removal from exposure to TDI. It is too early to know whether the benefits of such treatment continue once the drug is stopped. However, if inflammation is the essential process in the development of irreversible changes in the airways, the sooner inflammation is eliminated, the lower the likelihood that permanent damage will result. At this point, it would seem prudent to treat occupational asthma aggressively with inhaled steroid for 6 months and then reassess; it may be reasonable to stop medication at that time and follow symptoms and airways reactivity.

Finally, it needs to be re-emphasized that a large number of diseases may mimic occupational asthma, and these need to be considered whenever the question of occupational asthma is raised. Such illnesses include asthma unrelated to occupational exposures, occupational or non-occupational rhinitis, occupational or nonoccupational bronchitis, RADS, bronchiolitis obliterans, hypersensitivity pneumonitis, sinus disease, adductor spasm of the glottis, and other causes of extrathoracic obstruction. These alternative diagnoses need to be carefully excluded.

Specific Agents of Occupational Asthma

Low-Molecular-Weight Materials

With asthma induced by low-molecular-weight compounds (Table 2), atopy is not a risk factor. In these cases, IgE-mediated sensitization is unpredictable and may or may not be found. Because the antigens are incomplete antigens and need to haptenate a protein carrier, reagents for immunologic testing are often difficult to find. Several examples of asthma resulting from exposure to low-molecular-weight materials are considered below.

Isocyanates

Diisocyanates (TDI, toluene diisocyanate; MDI, diphenylmethane diisocyanate; HDI, hexamethylene diisocyanate; NDI, naphthalene diisocyanate) are used in spray painting, plastic molding, foundry work, and in the manufacture of polyurethane foams. Asthma occurs in 5%–10% of exposed workers. Diisocyanate-induced asthma does not appear to be mediated by IgE. Although RAST or skin testing will detect specific IgE in some workers, these tests do not predict clinical sensitization. Airways hyperresponsiveness to histamine or methacholine and eosinophilic inflammation of the airways are consistently found in sensitized workers. Once airways hyperresponsiveness has been established, it may persist for many years. Early detection of sensitization and removal from exposure are essential to prevent this long-term sequela. In addition to removal from exposure, treatment of sensitized workers with inhaled glucocorticoids accelerates resolution of airways hyperresponsiveness and inflammation. Airways challenge with diisocyanates frequently results in an isolated late-phase response. Atypical delayed and persistent responses are also common. Thus, in contrast to challenges with allergens that induce IgE-mediated sensitization, airway challenges with diisocyanates cannot be immediately repeated with an increased dose when an early-phase response is not observed. Hypersensitivity pneumonitis with pulmonary infiltrates has also been reported with diisocyanates (TDI, HDI, and MDI). In these individuals, specific IgG precipitins can be demonstrated.

Acid Anhydrides

Acid anhydrides (PA, phthalic anhydride; TMA, trimellitic anhydride; HHPA, hexahydrophthalic anhydride; HA, himic anhydride; TCPA, tetrachlorophthalic anhydride) function as hardening agents in the manufacture of epoxy resins used in adhesives, encapsulating agents, surface coatings, and plastics. Workers are exposed to these reactive compounds as fumes from heated resins, dust generated during the grinding of resins, and powdered chemicals added to reaction chambers.

Acid anhydrides are potent irritants that may cause eye, respiratory tract, and skin symptoms; permissible exposure limits for PA have been developed on this basis (6 mg/m^3). IgE-mediated allergic sensitization also occurs, and the permissible exposure level does not account for this. Conjugates of acid anhydride and HSA are sensitive reagents for skin testing, and RAST can also be performed. Results of airways challenge with acid anhydrides are typical of IgE-mediated sensitization; both an early-phase and a late-phase reaction are frequently seen. Specific IgE can persist for years after exposure. Acid anhydrides (TMA) are also associated with a late-onset respiratory systemic syndrome (LRSS) or with a syndrome of pulmonary hemorrhage and hemolytic anemia. These non-asthmatic pulmonary syndromes are associated with elevated levels of specific IgG.

Metals

Platinum salts can induce the production of specific IgE in a high proportion of heavily exposed workers, and this sensitization may lead to the development of skin rashes, eye and nasal symptoms, or asthma. Skin testing with platinum salts can be used to document sensitization, but high concentrations of platinum salts can cause nonspecific mast cell degranulation in unexposed controls. A RAST using malic dehydrogenase as a protein carrier has been developed. Asthma caused by exposure to a number of other metals has also been reported, including nickel, chromium, vanadium, cobalt, and fumes from steel welding and smelting of aluminum. There is evidence for an IgE mechanism with cobalt, chromium, and nickel in some cases, but the mechanisms involving vanadium or fumes from steel or aluminum are unknown.

Wood Dust

A wide variety of woods have been associated with occupational asthma, but the best studied example is red cedar. In red cedar asthma, sensitization is to plicatic acid, a reactive compound found in red and white cedar. Although specific IgE can be found in many workers, asthma appears to be non-IgE-mediated, and bronchial challenge is the only reliable test for immunologic sensitization. Delay in removal from exposure following the development of symptoms, particularly in older workers, has been linked with persistent airways hyperresponsiveness and dyspnea.

Solder

Colophony is used as flux in soldering, and electrical workers can become sensitized to colophony, with development of asthma. Colophony is a derivative of pine tree resin in which several reactive chemicals are found, namely abietic, pimaric, and dihydroabietic acids. As with wood dust, sensitization is not IgE-mediated, and airways challenge is the only reliable test for sensitization. Prolonged symptoms after removal from exposure have also been reported for colophony. Another component of solder flux, aminoethanolamine, can cause isolated late or dual responses.

Drugs

Occupational asthma can develop in workers exposed in the manufacture or use of a number of drugs (e.g., penicillin). Typically, these reactions are IgE-mediated and can be demonstrated with skin testing or RAST.

High-Molecular-Weight Materials

Atopy *is* a risk factor for sensitization to high-molecular-weight materials (Table 2). Typically, the sensitization is IgE-mediated. Because these materials are complete antigens, reagents for skin testing or RAST are usually available.

Foods

Asthma is a frequent occupational disease among bakers. Grain allergens are the usual cause, but sensitization to contaminants such as mold spores or grain mites has also been reported. Other foods causing occupational asthma include coffee beans, tea, soybeans, eggs, snow crabs, and cocoa. Castor beans containing the toxin ricin appear to be a special problem, and epidemics of asthma in nearby residents as well as workers have occurred.

Latex

Latex allergy among health care workers is an emerging problem. Although contact sensitivity is frequently caused by chemicals used in manufacturing, occupational asthma and other IgE-mediated reactions result from sensitization to protein antigens in native latex. Occupational sensitization to latex may have severe consequences for the health care worker who becomes a patient. Sensitized individuals should wear a medical alert bracelet.

Animals

Asthma caused by animal proteins in dander, saliva, or urine frequently develops in laboratory workers, farmers, and other people who handle animals. Such sensitization can occur to any warm-blooded animal.

Insects

Sensitization to the insects used in their work can develop in bee workers and bait workers. Less obvious exposures include sensitization of farmers, grain handlers, or bakers to storage mites, and sensitization of poultry workers to fowl mites.

Vegetable Gums

Vegetable gums represent another, less obvious source of allergens that may cause occupational asthma in workers in a variety of occupations, including printing, carpet manufacturing, and hairdressing.

Enzymes

Proteolytic enzymes used in detergents, meat tenderizer, and various manufacturing processes are potent sensitizers.

Course of Occupational Asthma

Occupational asthma allows investigators to view the entire natural history of asthma in response to a single, clearly defined etiologic agent. This perspective provides insight into the pace and variability of asthma development and also an opportunity to look at the resolution of asthma as workers are removed from exposures. Thus, occupational asthma provides a unique opportunity to study the pathophysiology of asthma. There have been several surprising findings in terms of the natural history of occupational asthma.

The variability in latency—that is, the time from initial exposure to development of symptoms—is well demonstrated in studies of occupational asthma (Fig. 3). The onset of symptoms follows an exponential curve. For example, the latency period for 50% of cases of sensitization to high-molecular-weight antigens is 3 years, but it takes 9 years to get to 75% of cases. There are even cases of occupational asthma developing in some workers after 30 years of exposure.

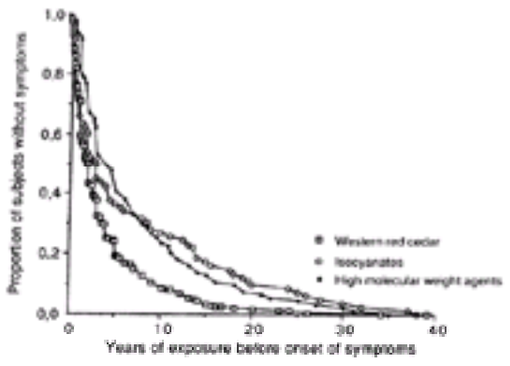

FIG. 3. Proportion of patients without symptoms as a function of exposure interval. (Modified with permission from Malo JL, et al. Natural history of occupation asthma: relevance of type of agent and other factors in the rate of development of symptoms in affected subjects. *J Allergy Clin Immunol* 1992;90:937–944.)

Another unexpected finding in occupational asthma is symptoms are often not reversible when the worker is removed from exposure (Table 6). Even years after removal, airways hyperresponsiveness and inflammation persist in the majority of patients with occupational asthma studied in large series. The prognosis is worse for workers who stay on the job after onset of asthma and better for those workers who leave as soon as symptoms develop. These findings suggest a window of opportunity to remove the worker before irreversible changes take place. Although these results have been criticized because pre-exposure airways responses were often not available, in several workers with normal baseline function before exposure, airways hyperresponsiveness persisted long after removal from exposure. The relationship of inflammation to the irreversible stage of asthma is still controversial. However, an essential component of these irreversible changes may be the development of inflammation in the absence of exogenous antigen. Treatment with inhaled steroids induces resolution of inflammation and the hyperresponsiveness that persists after removal from exposure to TDI. At this point, there is no compelling reason to believe that occupational and non-occupational asthma differ in regard to pathogenesis of chronic effects. The only real difference may be that it is easier to define the long-term effects in occupational asthma because symptoms persist despite removal from ongoing exposure.

Agent	No. of patients	Percentage with residual asthma	Follow-up
TDI	50	82%	>4 y
Red cedar	136	60%	4.3 y
Colophony	20	90%	29 mo
Snow crab	31	61%	1 y

TDI, toluene diisocyanate.

TABLE 6. *Irreversible asthma after occupational exposure*

INDUSTRIAL BRONCHITIS

Chronic bronchitis is defined as a productive cough lasting for >3 months per year for two consecutive years. Chronic bronchitis has been linked to cigarette smoke, which complicates the assessment of industrial bronchitis. Many workplace materials have been implicated as a cause of chronic bronchitis, including a variety of dusts (e.g., cotton dust), fumes, and vapors. The pathology of bronchitis is characterized by mucous gland hypertrophy and goblet cell hyperplasia in the large airways. There is an increase in mucus-secreting glands relative to serous acini, so that secretions tend to be more viscous and have less antibacterial activity. These changes in mucus may predispose to bacterial overgrowth. The role of inflammation in chronic bronchitis is not clear, although it may be important in the induction of mucous membrane metaplasia. In addition, one study indicates that sputum production correlates better with bronchial inflammation than with the structural changes in the mucous glands.

Many of the agents associated with industrial bronchitis have also been linked to an accelerated decline in FEV_1. The pathophysiology of this annual decline in FEV_1 is probably not bronchitis itself, which is a disease of the large airways. Instead, inflammation, mucous membrane metaplasia, and fibrosis in the small airways appear to be the pathologic features that lead to clinical airways obstruction. Thus, bronchitis and the development of small-airways disease with decreased FEV_1 are distinguished by their anatomic localization. They frequently occur together in the same person and often are both caused by exposure to the same agent. An agent inducing chronic bronchitis should alert the investigator to look for a decline in pulmonary function.

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CHAPTER

35 Byssinosis and Respiratory Disease Caused by Vegetable Dusts

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INTRODUCTION

The term *byssinosis* is applied to acute and chronic diseases of the airways occurring in persons exposed to three vegetable textile fibers: cotton, flax (which is woven into linen), and soft hemp (which is used for making rope and net). It is applied both to the acute syndrome of chest tightness, dyspnea, and reversible air flow obstruction that occurs at work within a few hours of exposure to cotton dust, and more broadly to the other respiratory effects of cotton, flax, and hemp dust. Because many more people worldwide are exposed to cotton than to jute and hemp dust, much of the following discussion focuses on cotton dust disease but also applies to the effects of the other vegetable fiber dusts.

With sufficient exposure, dusts from these materials may produce eye and nasal irritation, bronchitis, occupational asthma (with a characteristic pattern of worsening symptoms and air flow obstruction on the first day of exposure after a break from work), fever, chronic air flow obstruction, or combinations of these. The delayed febrile response to these dusts is now known as the *organic dust toxic syndrome* (*ODTS*), which may occur after inhalation of a variety organic materials that have been kept in conditions permitting the profuse growth of contaminating micro-organisms (see below).

Long-term occupational exposure to a variety of vegetable dusts (including some grain and wood dusts) causes airways symptoms of cough, expectoration of mucus, and wheeze, and with sufficient exposure leads to chronic air flow obstruction.

COTTON DUST DISEASE

Cotton is a plant-derived cellulose fiber. The long, thin, flexible cotton fiber consists of glucose units connected by glycosidic linkages containing reactive hydrogen groups. However, it is in large part the dust of the bract (dry, friable materials at the base of the cotton flower), leaf, and stem of the cotton plant, and the micro-organisms that grow on them, that cause disease (Fig. 1). Cotton dust may contain ground-up plant matter, fibers, bacteria, fungi, soil, pesticides, plant matter other than cotton, and other contaminants in varying proportions according to the conditions of plant growth and stage in the processing of cotton.

FIG. 1. The cotton plant, with cotton fibers supported by bract, leaf, and stem. A boll in the process of opening is seen in the *upper right.* In the *center,* the white cotton fibers are surrounded at the base by the brittle cotton bract. Cotton dust is composed mainly of bract, leaf, and stem.

Although the relative importance of the different components of cotton dust in producing disease is controversial, the acute response of byssinosis correlates better with the measured exposure to endotoxin (from the cell walls of contaminating gram-negative bacteria), whereas chronic air flow obstruction correlates better with total cotton dust exposure.

Epidemiology

Cotton growing and production of cotton products are major industries worldwide. Hence, respiratory disease related to cotton dust will continue to be commonplace until dust control in these industries becomes more widespread. Among persons exposed to cotton dust are workers in cotton ginning, cottonseed oil mills, cotton thread and yarn manufacturing, cotton fabric manufacturing, and those working with textile waste used in padding, upholstery, and mattresses. Disease is not usually associated with the harvesting of cotton, flax, or hemp or with exposure only to cleaned cotton fibers once processed into their finished products (Fig. 2). In cotton textile production, where dust exposures are excessive, byssinosis may affect a large proportion of the exposed workers, reflecting a pharmacologic (rather than sensitizing) effect of inhaled materials in the airways. This pattern contrasts with that of typical sensitizing or latency occupational asthma, where fewer than 10% of exposed workers are usually affected.

FIG. 2. Cotton mill worker opening a bale of cotton that has been ginned and shipped to the mill for further processing. Opening bales is one of the dustiest jobs in the

cotton mill. (Photo copyright Earl Dotter, reproduced with permission.)

Cigarette smoking is believed to be associated with an increased susceptibility to the adverse effects of cotton dust.

Clinical Presentation

Airways symptoms of cough, mucous production, or the development of chronic bronchitis are a common response to cotton dust exposure and occur in workers exposed to cotton dust who do not have the chest tightness and reversible air flow limitation of the acute syndrome; they are found in both smokers and nonsmokers. These syndromes have been observed repeatedly in carefully controlled studies of cotton textile workers in the absence of other symptoms of byssinosis.

The cardinal symptoms of the acute byssinosis syndrome are chest tightness and shortness of breath that occur on re-exposure to cotton dust after a weekend or several days away from work. This very common temporal pattern, “Monday chest tightness,” may also occur in previously unexposed persons on first contact with the dust. The temporal relationship of the onset of chest tightness to first exposure at work differs from the latency typical of occupational asthma; it often occurs 2 to 3 hrs after exposure to dust has begun, whereas in occupational asthma the early asthmatic response usually begins within the first hour, and the less common late asthmatic response occurs usually after 6 or more hrs. The chest tightness may be associated with a productive cough. In more severe cases or in older workers, dyspnea on exertion also may occur. Tolerance to cotton dust with a reduction in symptoms on subsequent mornings of the workweek is often seen, with loss of tolerance after 1 day or more away from work. With progression to more severe disease, symptoms of chest tightness and dyspnea may be present each day at work, and eventually at all times. The severity of symptoms is enhanced if symptoms caused by chronic cigarette smoking are present, and both dust exposure and smoking contribute additively to chronic airways disease in cotton textile workers. Those with chronic air flow obstruction have the characteristic symptom of dyspnea on exertion, with reduction in exercise tolerance in proportion to the degree of air flow obstruction.

Thus, persons exposed to cotton dust may seek medical attention with a history of chest tightness occurring at work, intermittent or chronic bronchitis, acute fever occurring several hours after exposure to dust, or chronic dyspnea and exercise intolerance after years of exposure.

Pathogenesis

Byssinosis is a non-allergic airways disease. Bronchoconstriction and inflammation can be induced in previously unexposed persons with a first challenge to cotton dust extract. There are several theories regarding mechanisms, for which some experimental evidence exists. Local release of histamine from airways in contact with dust may result in the acute symptoms and air flow obstruction. A distinct inflammatory airways response to contaminating bacterial endotoxin, other bacteria-derived substances, or other components of cotton dust appears to be important in the chronic bronchitis associated with long-term exposure to cotton dust.

Physical Findings

Findings on chest examination are usually absent or minimal in patients with symptomatic dust disease, although wheezing may be heard. With chronic disease, the findings are chronic air flow limitation, weight loss, use of accessory muscles of respiration, prolonged expiration, and either a quiet chest or wheezing on expiration.

Laboratory Findings

No useful serologic markers have been found for byssinosis. Findings on chest radiographs in patients with byssinosis are usually unremarkable.

Pulmonary Function

In patients with the acute airways form of byssinosis, reversible air flow limitation may be demonstrated by comparing measurements made after a Monday work shift with those made before (Fig. 3). Lung function may be normal between episodes of byssinosis. If spirometry is performed before and after the work shift throughout a week, the FEV_1 (forced expiratory volume in 1 second) and the ratio of FEV_1 to FVC (forced vital capacity) are reduced during the day of exposure in symptomatic workers with byssinosis. The absolute value of the fall in FEV_1 may be greatest on the first day of exposure, and less through the workweek as a result of adaptation. However, the baseline level of FEV_1 at the beginning of the day may be reduced with serial daily exposure through the workweek, only to return to the previously normal baseline on the next Monday morning. The magnitude of the reversible decline in FEV_1 in symptomatic patients may be relatively small (10%–20% during the acute episode) in relation to the degree of chest tightness experienced.

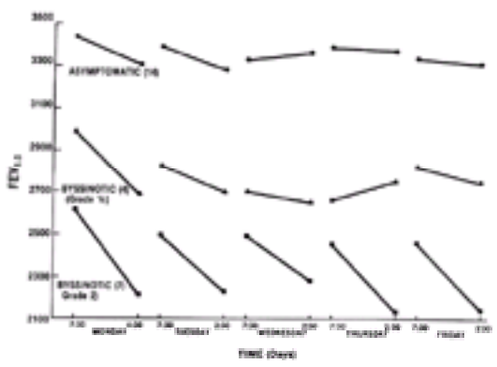

FIG. 3. Correlation of the grade (severity) of byssinosis with FEV_1 on spirometry during a work week in heavily exposed cotton mill carders. Grade 1/2 refers to those with occasional tightness or mild respiratory irritation on the first day of the work week. Grade 2 refers to those with usual chest tightness on the first day and other days of the week. Note that asymptomatic individuals also have work-related decrements in FEV_1. Carders with the higher grade of byssinosis have lower baseline lung function. *Numbers in parentheses* refer to the number of subjects in each group. (Reproduced with permission from Merchant JA, et al. Evaluation before and after exposure—the pattern of physiologic response to cotton dust. *Ann N Y Acad Sci* 1974;221:38–43.)

Patients with byssinosis have greater airways responsiveness to nonspecific challenge than do subjects without byssinosis from the same mill, and airways responsiveness has been demonstrated experimentally to increase across a Monday work shift in mill workers with byssinosis. The role or utility of nonspecific airways challenge in diagnosing byssinosis has not been defined.

Chronic air flow limitation with permanent impairment is seen as a result of long-term exposure to cotton dust through many years. The pattern cannot be distinguished on physiologic grounds from the chronic air flow limitation seen in cigarette smokers, and so the occupational history of exposure to cotton dust is important in establishing a diagnosis. Ascertaining the duration and levels of exposure to cotton dust, a history of acute respiratory symptoms, or a decline in FEV_1 across work shifts, as well as obtaining a complete smoking history, may be useful in determining the degree of chronic air flow limitation attributable to cotton dust versus that attributable to cigarette smoke in a cotton worker who has also smoked.

Treatment

Reduction in total exposure to cotton dust to prevent recurrence is the primary treatment of byssinosis. This can be achieved by control of airborne dust levels—for example, enhancing ventilation in areas with high dust levels. Prewashing of cotton has also been effective in reducing exposure to pathogenic dust.

When acute air flow obstruction is present, treatment with inhaled b-adrenergic agonist bronchodilators has been shown to reverse obstruction, and this treatment is advisable for the symptomatic patient in distress. The diagnosis of byssinosis is a sentinel health event indicating an excessive occupational exposure. Byssinosis is a reportable condition in many states and provinces, and the diagnosis is an indication for intervention in the workplace to reduce dust exposure for the symptomatic patient. Because of the high attack rate in areas of overexposure, the diagnosis of one case indicates that many others are likely to be similarly overexposed and

symptomatic. Occupational standards for dust in cotton-processing workplaces that do not produce acute symptomatic disease have been established and are enforced in many countries.

ORGANIC DUST TOXIC SYNDROME

The syndrome is characterized by prominent, delayed fever and systemic symptoms after an episode of inhalation of organic dust often described as moldy. The illness is self-limiting and without significant radiographic findings. It has been reported in a broad variety of circumstances, including in farmers unloading hay from silos and workers shoveling moldy wood chips. It is categorized among the inhalation fevers, which also include metal fume fever and (Teflon) polymer fume fever. ODTS is not an IgE-mediated allergic response, as it does not require previous sensitization and is characterized by tolerance to similar exposures on subsequent challenge. An acute febrile response to inhaled cotton dust after a period of 2 days or more away from work (“mill fever”) is well described in cotton textile workers with heavier exposure to dust, and cotton dust is now recognized as one cause of ODTS.

GRAIN DUST DISEASES

Epidemiologic studies of agricultural workers exposed to a variety of grain dusts, both in harvesting and in storing, unloading, and transporting grain, have discovered an important association of allergic manifestations, acute and chronic bronchitis, and chronic air flow obstruction related to the levels and duration of dust exposure. A similar pattern has also been observed with at least one kind of wood dust. The clinical picture is often one of an inflammatory bronchitis with mucous gland hyperplasia, chronic hypersecretion of mucus associated with cough and phlegm, and, in cases of prolonged and heavy exposure, accelerated decline in lung function during a period of years. Because of the absence of specific physical, laboratory, or radiographic findings, the occupational history of recurrent exposure to dust (usually at levels that are easily visible in the workplace) may be the most important clue to the underlying cause of the patient's respiratory symptoms. A short course of anti-inflammatory medication, such as an inhaled corticosteroid, may be tried to treat the acute response, and interventions to reduce dust exposure through control technology or the use of respiratory protective masks (still markedly underutilized in agriculture) are necessary to prevent recurrent or progressive disease.

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CHAPTER

36 Occupational Pulmonary Neoplasms

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INTRODUCTION

Although the incidence of lung cancer is increased in certain occupations, the most important cause of this disease remains cigarette smoking. Even if one considers those cancers associated with a particular trade, the occupational risk is small compared with that of smoking. However, in the belief that something can be done to reduce the occupational risk, whereas many smokers seem powerless or too ignorant to help themselves, occupational lung cancer requires further consideration.

HISTORY OF OCCUPATIONAL CANCER

The first neoplasm noted to be related to a particular occupation was cancer of the scrotum. In 1775, Percival Pott observed that the disease characteristically occurred in chimney sweeps and concluded that it seemed to derive from a lodgement of soot in the rugae of the scrotum. Tumors of the skin were later described in cotton workers, shale oil workers, and aniline dye workers.

Harting and Hesse were the first to recognize cancer of the lung as a frequent cause of death in miners of copper, iron, and silver in Schneeberg. It was only later that the cause was found to be radioactive air in the mines. This same problem was identified in uranium mines, where the presence of radon daughters was shown to be associated with bronchogenic carcinoma. In more recent years, the risks associated with several other materials used in industry have been recognized. Lung cancer has been shown to be associated with asbestos, arsenic, chromates, iron ores, coal gas, chloromethyl ethers, beryllium, nickel, and vinyl chloride. Several other substances are suspected, but as yet not proved, to be carcinogens.

EXTENT OF RISK: OCCUPATION VERSUS SMOKING

If the substances involved in producing human cancer can be identified and proved to be causally related, then those substances might be avoided. The portion of blame that can be attached to the various environmental factors thought to be carcinogens has been the topic of considerable debate during the last decade. Most of the work on this subject has been epidemiologic, relying on the incidence of cancers in various populations and countries. It has been suggested by some that environmental factors can account for up to 80% of human cancers. However, this figure is itself an exaggeration and includes not only the toxic materials of industry, but also factors such as diet, numbers of pregnancies, race, and so forth. Nevertheless, the figure of 80% has been used to suggest that exposure to chemicals and toxins such as asbestos is the major cause of cancer in Western society. This view is supported by Epstein, who goes further in stating that a cancer epidemic is in progress as a consequence of occupational and environmental exposures. Not surprisingly, these views have important political implications and have been supported by various governmental agencies. Bridbord and associates, under the auspices of the National Cancer Institute and the National Institute for Occupational Safety and Health (NIOSH), calculated the risk of exposure to six known carcinogens and concluded that occupational cancers comprise 23%–38% of the total number of cancers, with asbestos alone causing up to 18%. To this figure must be added the effects of ionizing radiation and other known carcinogens not included in their calculation.

When these facts, together with the preceding data, were re-examined, basic flaws in the epidemiologic method used by Bridbord and associates were noted. One of the main faults was a disregard for dose and duration of exposure to particular carcinogens, resulting in gross overestimation of the risk. It may well be that the Occupational Safety and Health Administration (OSHA) article was written for political rather than scientific purposes, and that the figure of 38% for cancer deaths caused by occupation should be dismissed. It appears that there is no current cancer epidemic apart from the epidemic of lung cancer, which is largely a consequence of cigarette smoking.

A more realistic view of the situation suggests that 15% of lung cancers in men and 5% in women are attributable to some extent to contact with occupational agents. Of this 15% in men, a third are caused by asbestos, a third by fossil fuels, and the remaining third by other recognized agents, such as chromium, nickel, chloromethyl ethers, and ionizing radiation. Similar estimates of a 10% and 14% excess risk for lung cancer have been suggested. In fact, the figure of 38% of cancers being attributable to industry, noted in the 1978 federal report, has since been acknowledged to be an overestimate.

It is important to note that the results of the above studies are based on exposure to carcinogens in excess of those encountered in industry today. Overall, industrial hygiene has improved, exposure to asbestos is now under strict control, and the introduction of natural gas has, at least in the United Kingdom, decreased the numbers of workers involved with coke ovens. Future studies should show that the excess risk for lung cancer attributable to industry will continue to fall.

A systematic approach was used to examine the proportion of lung and bladder cancers resulting from occupation. An analysis of several large studies of various occupational groups between 1977 and 1988 showed that the proportion of lung cancers attributable to occupation varied by as much as 1%–40%. The main reasons for this large variation are the differences in levels of exposures to carcinogens in the various studies and countries. The criteria used to assess exposure have been improved but are not always precisely defined and may be the origin of any miscalculations.

INTERACTION OF SMOKING AND OCCUPATIONAL CARCINOGENS

A further consideration is the effect of the combination of smoking and exposure to a known carcinogen. The result of such a combination is best documented in the case of asbestos. The risk from exposure to asbestos alone can be demonstrated by examination of asbestos-exposed persons who have never smoked. However, because lung cancer in nonsmokers (including those exposed to asbestos) is rare, large populations are required to produce reliable results. Authors of several studies conclude that the risk for development of carcinoma in a nonsmoker as a result of asbestos exposure is very small, but this risk is approximately five times greater than

that in an unexposed nonsmoker. The risk in a smoker exposed to asbestos is greatly increased, and not just additively; the level of risk can be calculated by multiplying the two separate risk factors. One view of this situation demonstrates that an unexposed nonsmoker has a mortality ratio of 1, a nonsmoking asbestos worker has a ratio of 5.17, and a smoking asbestos worker has a ratio of 53.3. The exposures also were quantified, and in smokers of more than one pack a day the mortality ratio rose to 87.4.

An interaction is also found between radon daughters and cigarette smoking, although it is not as clear as in the case of asbestos. It appears that there are two effects: first, an additive effect of the number of cancers induced by the two agents, and second, a hastening effect, so that the induction-latent period is shorter among smokers than among nonsmokers. Thus, cancers appear earlier in smokers.

Various explanations have been proposed for these interactions between cigarette smoke and carcinogens. Cigarette smoke is toxic to the ciliated epithelium, and the resultant loss of ciliary function with failure to clear sputum means that carcinogens can be in prolonged contact with the mucosa. Cigarette smoke can cause squamous metaplasia, and it also has been suggested that particles in cigarette smoke can absorb carcinogens and carry them farther down the bronchial tree. Conversely, the asbestos fibers may damage cells to allow entry of carcinogens present in cigarette smoke.

The overall conclusion is that no other known single measure would have as great an impact on the number of deaths attributable to cancer as a reduction in the use of tobacco. This view is supported by the Surgeon General of the United States, who stated that cigarette smoking is a greater cause of death and disability than the workplace environment. In occupations in which the worker is exposed to hazardous agents, control of both smoking and the agent itself provides the most effective means of reducing the risk.

INVESTIGATION OF OCCUPATIONAL LUNG CANCER

The investigation of a potential occupational carcinogen can be carried out in two ways: laboratory testing and epidemiologic survey. Under different circumstances, there is a place for both methods, although some agencies tend to give more weight to laboratory testing of animals than to epidemiology. This is a little surprising, as the majority of discoveries relating to occupational lung cancer have been made by astute observation backed up by epidemiologic confirmation. This approach not only led to the description of the first occupational neoplasm, but was also used by others to identify the associations between asbestos and lung cancer, asbestos and mesothelioma, nickel and lung and nasal cancer, and furniture work and nasal cancer.

Laboratory studies also have an important place, particularly when a carcinogen is suspected not because of an increased incidence in a certain trade but because a particular chemical has a structure similar to that of a known carcinogen. The experimental approach was used to identify the carcinogenicity of the chloromethyl ethers.

Laboratory Testing

If suspicion arises concerning a particular substance that physically or chemically resembles a known carcinogen, the approach should be in vitro testing, and if the suspicion is warranted, progression to animal exposure studies is appropriate. In vitro tests are the quickest and cheapest method of examining potential carcinogens. However, their use is limited, because their only function is to show whether or not a particular substance has any effect on DNA. They can be used as a screening test of new materials, or they can be used to show that one carcinogen is more dangerous than another. In *in vitro* testing, the ability of a substance to transform mammalian fibroblasts into particular colonies with malignant characteristics may be detected, or, as in the Ames test, a change in the rate of mutation of a nutritionally deficient strain of *Salmonella typhimurium* may be demonstrated. When such tests are used, known carcinogens will produce positive results nine times in 10. However, false-positive and false-negative results do occur, and no test is yet available that shows whether there is a threshold below which a suspected carcinogen is innocuous in humans.

Animal studies provide data that are more readily applied to humans. However, besides ethical considerations, there are important limitations; the production of tumors in animals remains uncertain and unpredictable and depends not only on variations between species but also on factors such as sex, diet, and age of the animals. Most animal experiments consist of a relatively short exposure of small rodents to substances at inordinately higher concentrations than those encountered in the workplace. Although valuable information can be obtained from animal experiments, as was the case with chloromethyl ethers, the results of carcinogenesis in animals cannot be blindly applied to humans.

The problem with laboratory studies as a determinant of carcinogenic properties lies in the process of carcinogenesis itself. There is evidence that certain compounds act as initiators and induce mutation in the DNA of target cells (irradiation, halo ethers, mustard gas). Others are responsible for the second phase of carcinogenesis and act as promoters, inducing increased cell multiplication (asbestos). Most compounds act directly on DNA. However, nickel interferes with replication, and benzpyrene requires activation by the host before carcinogenic properties develop. It is clear that the basic mechanisms of carcinogenesis are incompletely understood, and for this reason, laboratory testing is, at best, a rough estimate of the risks that might be involved. Laboratory tests should not be used to declare a compound safe or unsafe, but rather should be used as an indicator of whether protection, surveillance, and further research are required.

Epidemiology of Occupational Lung Cancer

The value of epidemiologic study has been emphasized already. Of the known occupational exposures (Table 1) related to cancer of the respiratory tract, 11 were first detected by observation in particular working groups. Only in the case of the halo ethers was carcinogenicity first demonstrated in animal experiments and subsequently confirmed in epidemiologic studies.

Agent	Occupation	Tumor
Asbestos	Mining, weaving, utilization	Lung cancer, mesothelioma
Radioactivity	Uranium metal mining	Lung cancer
Nickel	Refining	Lung, nasal cancer
Chromates	Electroplating, tanning pigments, chemical industry	Lung cancer
Chloromethy ethers	Fungicides, chemical industry	Lung cancer
Arsenic	Metal refining, sheep dip	Lung, skin cancer
Fossil fuels	Coal, coke, gas furnaces	Lung cancer
Mustard gas	Manufacture	Lung cancer
? Vinyl chloride	Manufacture, utilization	Lung cancer
? Beryllium	Utilization	Lung cancer
? Isopropanol	Manufacture	Nasal, ? lung cancer
? Printing ink	Utilization	Lung cancer
? Cadmium	Refining	Lung cancer
? Magnesium	Refining	Lung cancer
? Formaldehyde	Chemical industry	Lung cancer
? Diesel exhaust	Railroad, garage	Lung cancer
? Meat	Processing	Lung cancer

TABLE 1. *Occupational hazards causing respiratory tract cancer*

As shown in the discussion of the relative parts played by occupation and smoking, the epidemiologic method most often used is that of mortality studies of cohorts. A cohort with a particular contact or exposure is identified and examined. Mortality rates and the causes of death of this cohort are then compared with those of the community in general, groups of smokers, and persons of a particular social class, race, and so on. The cohort can be further subdivided with reference to levels of exposure, age, and tobacco consumption, and thus groups within groups can be compared. The main problems encountered with this type of study are that numbers must be large and data, particularly concerning smoking and exposure contact, must be accurate. An alternative epidemiologic method is the case-control approach. In this method, persons with a certain disease are identified and compared in terms of occupational exposure with matched control subjects who do not have the disease in question. Again, numbers must be very large; for example, a study to estimate the proportion of lung cancer caused by occupation would require 10,000 cases and 10,000 controls.

In the study of occupational lung cancer, despite the disadvantages of requiring large numbers and resources and using retrospective information, epidemiologic studies have provided the bulk of information presently available, alerting industry to hazards so that preventative measures can be undertaken to avoid risks.

PREVENTION OF OCCUPATIONAL LUNG CANCER

Prevention is the most effective method of treating lung cancer, and the prevention of occupational pulmonary neoplasia cannot be realistically separated from the prevention of lung cancer as a whole. The majority of cases of pulmonary cancer are avoidable. The way to reduce the incidence of carcinoma of the lung is to avoid exposure to the relevant carcinogens. The link between smoking and carcinoma is well established. The American Cancer Society records a prevalence of lung cancer

of 149,000 cases per year, and although approximately 10%–15% are associated with industry, the majority are caused by smoking. Within this 10%–15% attributable to industry, many cases will represent a combination of occupational exposure and smoking. In any discussion of prevention, these facts must be considered.

The responsibility for reducing the incidence of carcinoma rests with the medical profession, industry, the government, and the work force. The medical profession must make the facts available and educate industry, the government, and workers. It must continue both epidemiologic surveillance and research to identify new hazards. All this must be accomplished within the confines of available financial resources. Industry must accept advice from informed sources and do its utmost to protect the worker. The government must act responsibly, its first priority being the health of the work force.

The most important group, the workers, must be informed of the risks and must use all protective methods necessary. The most important fact, however, is that workers need to be aware of the risk of smoking, especially in the setting of an occupation with a known hazard.

SURVEILLANCE

Although prevention is the best approach to occupational cancer, another, albeit less effective, alternative exists—detection of early cases of disease in the hope that prognosis can be improved. There has been much debate concerning the value of screening for occupational cancer, and although the concept of medical monitoring has been received enthusiastically, it must be remembered that the value of screening programs is based on the assumption that early diagnosis is beneficial. Although this is true for most infections, it is not necessarily the case for occupational lung cancer. For example, is there any point in detecting mesothelioma earlier when no treatment or cure is available?

In 1968, the World Health Organization (WHO) produced guidelines for screening programs that still apply today. Although most of the criteria are relevant to occupational neoplasia, three require special mention. First, there should be an acceptable form of treatment for patients with recognizable disease. Second, the cost of case finding needs to be balanced economically in relation to possible expenditure for medical care as a whole. Finally, the benefits accruing to persons with true-positive findings should outweigh the harm done as a result of false-positive diagnoses. Added to the required standards of the screening program, the tests chosen must be accurate, sensitive, specific, and of predictive value.

The two tests available to screen for occupational lung cancer are the chest radiograph and sputum cytology. Although both these techniques are useful in detecting cancer, in practice many problems arise. Studies using serial radiography have not improved survival or at best have had only a minor effect. A particular problem is the case of patients with positive sputum cytology but no detectable tumor at fiberoptic bronchoscopy. Segmental bronchial lavage can be performed in an attempt to localize the tumor to a particular segment, but malignant cells can be obtained from several sites or even from both lungs, presumably as a result of spillover.

The results of an extensive three-center study on screening for lung cancer were published in 1984. There was little doubt that cancers could be detected earlier. The radiograph was the most sensitive method, with 40% of cancers identified as stage I (American Joint Committee on Cancer), whereas sputum cytology was effective at detecting early squamous cell carcinomas only. However, despite early detection, it was not clear that there was any subsequent decrease in mortality. A long-term study on chest x-ray screening in chromate workers demonstrated a modest improvement in 5-year survival of regular attenders; however, no significant improvement was seen in the 5-year survival when the total worker population was considered.

Finally, the cost of screening needs to be considered. In one reported experience, the cost per person per year was $135, and as the prevalence of detectable lung cancer is very low (1 in 2000 to 3000), the cost-to-benefit ratio becomes prohibitive. In an earlier series using the chest radiograph, the cost of detection of each cancer was $25,000, with no increase in life expectancy.

In view of all these facts, it may be that the money involved in such screening programs would be better used in preventing rather than detecting largely untreatable cancer.

MANAGEMENT

The treatment of occupational lung cancer is no different from that in the non-occupational setting. In general, the disease is incurable, but surgical resection is the treatment of choice and, if successful, affords a 20%–30% chance of surviving 5 years. The prognosis in occupational lung cancer is slightly worse for two reasons. First, there is a preponderance of small-cell and adenocarcinomas, both of which have a worse prognosis than the squamous cell type. Second, many workers have concurrent lung disease, such as fibrosis, which may make surgery less feasible. A relatively new concept is chemoprevention, and although no proven chemopreventative method exists, several substances, including vitamin A and selenium, have been under investigation. In any case, the improvements in prognosis with such methods are likely to be modest compared with the deleterious effect of smoking.

A problem peculiar to occupational cancer is that of medicolegal ramifications in the form of compensation to the worker or, as is sadly more often the case, to the family of the worker. However, such a discussion is beyond the scope of this chapter.

SPECIFIC CAUSES OF OCCUPATIONAL LUNG CANCER

Asbestos

It is quite clear that lung cancer and mesothelioma are associated with exposure to asbestos and that this association is dose-related.

Specific Occupational Risks

There is little doubt that weavers and certain users of the finished product, such as pipe fitters and laggers, are particularly at risk. In contrast, the risks associated with asbestos mining are significantly less, particularly for chrysotile miners in Quebec. This truism applies not only to mesothelioma, but also to asbestosis and lung cancer. One exception is the relatively higher risk in miners of crocidolite who were employed in the Wittenoom mine in West Australia. Shipyard welders and other workers, who may spend a good portion of their time in close proximity to pipe fitters and laggers, have either no increased risk or, at the worst, a slightly increased risk for asbestosis and lung cancer. Much the same can be said for railroad repair shed workers and, to a lesser extent, those who line furnaces. Garage mechanics working with brake linings do not appear to be at increased risk, and neither in general do persons who come in contact with asbestos merely through working in buildings that contain asbestos.

Asbestos as a Carcinogen

Asbestos is a cocarcinogen, and the presence of asbestosis, especially in smokers, is associated with a significantly increased incidence of lung cancer. The evidence suggests that asbestos is a promoter rather than an initiator of cancer. In regard to the excess of lung cancer that occurs in subjects with asbestosis, it is generally accepted that cigarette smoking is the usual initiator.

It has been estimated in the United States that about 430,000 construction workers and 648,000 workers involved in manufacturing have been significantly exposed to asbestos. Based on these estimates, it is calculated that asbestos plays a role in approximately 3% of all lung cancers that occur in the United States (i.e., 2501 deaths per year), but even then, asbestos acts synergistically with smoking, and the latter makes a greater contribution to the induction of the disease.

That lung cancer is a significant risk in asbestos workers is clear from Fig. 1. The relative risk in asbestos workers is said to be increased up to five to six times, irrespective of the smoking habit. It is now clear, however, that the risk of smoking in the induction of lung cancer was previously seriously underestimated. This is apparent from relating the calculated number of patients in whom cancer deaths were attributed to smoking to the number of cigarettes smoked per day. During the past decade, a number of studies have shown that provided the level of asbestos is kept below one fiber per cubic centimeter, the risk for development of asbestosis is negligible and the risk for development of lung cancer is not increased during a 35- to 40-year working life. In most of these studies, however, the population was exposed to chrysotile only. Smoking has now been shown to play the pre-eminent role. In this regard, it must be remembered that lung cancer has been diagnosed in only about 30 or so lifelong nonsmoking workers with asbestosis. If the smoking histories in these subjects were inaccurate, as is often the case when compensation is being claimed, the excess incidence in nonsmokers would completely disappear. Moreover, great differences exist between the calculated relative risks of lung cancer obtained by different investigators. Such differences are to be expected in the absence of uniform and consistent protocols. Thus, the selection of subjects for studies has differed greatly, with some studies including only asbestos workers with prolonged exposure (i.e., 20 years) and others including all exposures of 6 months. In addition, the smoking habits of the various populations studied have varied greatly. Clearly, these variables will greatly influence the incidence of lung cancer. In certain studies, additional clinical, surgical, and autopsy information was collected from the asbestos-exposed group in whom lung and gastrointestinal cancer developed, but not from the control group. Without applying this refinement to both the groups, the introduction of bias is inevitable. Nonetheless, it is clear that the risk for development of lung cancer is related to the cumulative dose of asbestos; the greater the dose, the greater the risk. It is also evident that increased risk for lung cancer

does not appear until the subject has had an exposure of at least 15 years plus asbestosis—that is, there has been a suitable incubation or latent period. The development of lung cancer in a subject who began to work with asbestos only 5 years before symptoms of the tumor appeared indicates that the cancer is unrelated to the asbestos exposure.

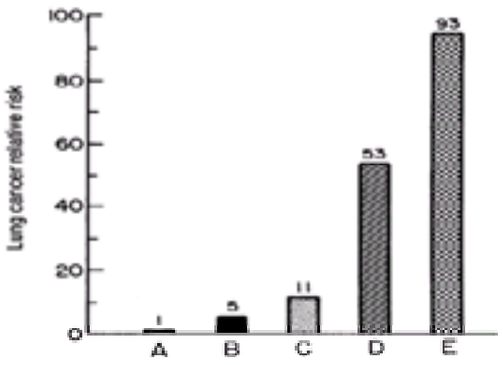

FIG. 1. The relative risk for lung cancer in persons exposed and not exposed to asbestos according to smoking habit. **A:** Unexposed nonsmokers. **B:** Nonsmoking asbestos workers. **C:** Unexposed workers. **D:** Exposed smokers, all. **E:** Exposed heavy smokers (20/d). (Based on data from Hammond EC, Selikoff IJ, Seidman H. Asbestos exposure, cigarette smoking, and death rates. *Ann NY Acad Sci* 1979;330:473.)

In regard to the development of lung cancer in asbestos-exposed workers, the assumption of a linear relationship has received wide but somewhat uncritical acceptance. Such a hypothesis is convenient and simple, but it is not necessarily valid. Deductions based on observations of the risk for lung cancer in subjects with high cumulative exposures cannot, of necessity, be used to predict the response at lower doses. Back extrapolation of the regression line to the intercept at zero is often forced and contrived, as there are usually either no excess deaths or very few deaths occurring at the lower exposures. In many instances, there is just as much mathematical justification for drawing the regression line so that it has either a negative or a positive intercept. Moreover, it is impossible in practice to devise a study that will provide the necessary data to confirm the straight-line, no-threshold hypothesis. Much the same problem exists when the death rate from lung cancer in nonsmoking asbestos workers is considered. In general, the excess death rate in most studies is limited to one or two subjects.

An excellent review of this subject appeared in a supplement to *Thorax* (1996), which examines the article by Williamson et al. (1995) suggesting that excess cancer morbidity occurs without lung fibrosis, and then reviews the subject as a whole. The current evidence indicates that asbestosis (radiographic or histologic) is a prerequisite for excess lung cancer morbidity.

It is true that mining tends to be far less hazardous than weaving. In contrast, users of the finished product are at greater risk. Nevertheless, the apparent safety of mining probably results from the fact that most reliable studies have been carried out on chrysotile miners from Quebec and that chrysotile is less hazardous. There is now fairly compelling evidence to indicate that crocidolite is more carcinogenic than chrysotile, with amosite carcinogenicity in between. This applies not only to mesothelioma, but also to lung cancer. Indeed, it appears that the amphiboles are not only significantly more carcinogenic than chrysotile for a given exposure, but are also more fibrogenic and thus more likely to induce asbestosis. Australian crocidolite miners had a standardized mortality rate (SMR) of 247 for lung cancer after 15 years of exposure, whereas Quebec chrysotile miners with 20 years of exposure had an SMR of only 127. The various dose-response relationships that have been calculated from American studies are shown in Fig. 2.

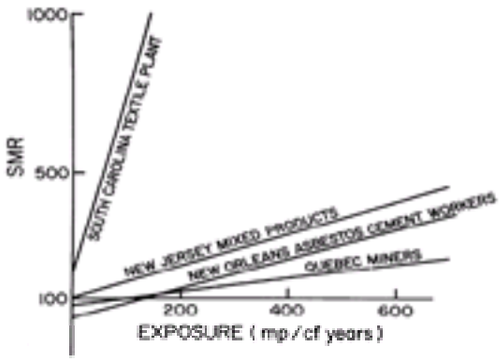

FIG. 2. The SMR for lung cancer in various exposed populations, showing a lesser risk in asbestos miners.

All types of lung cancer are reported to occur in asbestos-exposed populations. The original descriptions suggested that asbestos-associated lung cancer was more likely to be peripherally situated and to be an adenocarcinoma. However, all histologic types are found, and it is impossible to sort out which cancers result from smoking alone, smoking plus asbestos exposure, and asbestos exposure alone (if the latter by itself ever causes lung cancer). Thus, the evidence from pathologic and epidemiologic studies would suggest that fibrosis and epithelial hyperplasia are essential for the induction of cancer. The inability of short fibers to induce fibrosis would explain why such fibers are not associated with the development of lung cancer, and the same is true for fiberglass. From this it can be inferred that the prevention of asbestosis likewise prevents asbestos-induced lung cancer.

Mesothelioma

Mesothelioma occurs either as a benign pedunculated pleural tumor, usually associated with hypertrophic pulmonary osteoarthropathy, or as a diffuse malignant tumor of the pleura or peritoneum. Rarely, the pericardium and tunica vaginalis are affected. Only the diffuse malignant mesothelioma is related to asbestos exposure. Epidemiologic studies would suggest at the present time that about 75%–80% of malignant mesotheliomas are associated with prior asbestos exposure. The tumor also has been associated with exposure to fibrous erionite, a zeolite that is a non-asbestiform mineral. The relationship between asbestos exposure and the development of mesothelioma was established by Wagner and co-workers in 1960.

Malignant mesothelioma usually develops many years after a subject is first exposed to asbestos. The incubation period varies from about 15 to 40 years, with the vast majority of mesotheliomas developing between 25 and 40 years after exposure commenced. In many instances, there has been no exposure to the mineral for 20 to 30 years. There is good evidence that once the lung has been primed by a sufficient dose of asbestos, the development of the tumor is inevitable. However, contrary to previous teaching, mesothelioma does not develop as a sequel to minute or minimal exposures. Although it is true that it may develop after short exposures, in the range of 3 to 24 months, such exposures have usually been intense. Mesothelioma also has been reported in infants and in subjects with no history whatsoever of exposure to asbestos. Although mesothelioma is a rare tumor, it is estimated that it develops in about 1500 to 2000 subjects in the United States every year. In Canada, the figure is probably proportionally somewhat less, mainly because fewer Canadians were exposed to crocidolite in shipyards during World War II.

Mesothelioma and Fiber Type

Early experiments demonstrated that injection of asbestos fibers into the pleural space of animals induced development of mesothelioma. Abestiform fibers such as tremolite caused mesothelioma in the pleural space of rats, but equal doses of non-asbestiform fibers did not. Later, several non-asbestiform fibers, including fiberglass, were found to be capable of inducing mesothelioma provided the diameter of the fibers was 0.5 m, but non-asbestiform actinolite, biotite, and talc failed to produce tumors. The relationship between fiber size and the development of mesothelioma was demonstrated, and it was concluded that fiber structure was a pre-eminent influence in the induction of malignant tumors of the pleura. Later experiments using various forms of asbestiform and non-asbestiform fibers, including fibrous glass and sundry fibrous clays, made it evident that carcinogenicity is related to the dimensional distribution of the fibers, which are longer than 8 m and have a diameter of 0.25 m.

For many years, it has been apparent that the likelihood of mesothelioma developing in chrysotile miners is less than in users of the finished product. It also became apparent that materials made from asbestos contained mixtures of different types, with varying proportions of amosite and crocidolite being added to Canadian

chrysotile before weaving. Epidemiologic studies of the frequency of mesothelioma have shown that the tumor occurs much more frequently in persons exposed to the amphiboles and that crocidolite is particularly dangerous in this regard.

Radioactivity

The excessive mortality of Schneeberg miners was shown by Harting and Hesse in 1879 to be caused by lung cancer, but it had been appreciated three centuries earlier that men working in these mines died prematurely. Lung cancer may have accounted for 40% of deaths in these miners at a time before the introduction of cigarettes to Europe. A similar problem was identified in the uranium miners of Joachimsthal in 1930. The cause of the increased risk for lung cancer in these miners was unknown. However, Kennaway and Lindsey subsequently showed that the air in these mines contained high concentrations of radon and other radioactive elements.

Since that time, radioactive contamination of air or water has been identified not only in uranium mines, such as those in Colorado, but also in several mines concerned with the production of nonradioactive substances, such as fluorspar mines in Canada, hematite and tin mines in the United Kingdom, hard rock mines in the United States, thorotrast mines in Denmark, and iron mines in Sweden.

Uranium

Uranium is mined in Colorado, Canada, Australia, Czechoslovakia, and Central Africa. It is mined on the surface and underground in the form of oxide or pitchblende, or as a compound oxide with vanadium and potassium known as *carnotite.* The ore, of which uranium constitutes 0.5%, also contains 5%–50% silica and hence is associated with a concurrent risk for silicosis.

After ore crushing, the uranium is extracted in the form of uranate known as *yellow cake.* This material is then packed for transport. Uranium is used mainly for the production of atomic energy (peaceful or otherwise), but it also has a minor use in the ceramic and chemical industries. The risk from uranium therefore applies to miners, uranium process workers, and users of the finished product, such as nuclear power plant workers and those who handle uranium in industry.

Mechanisms

Uranium itself is not, from a biologic point of view, dangerous, in that it emits mainly gamma rays, which are of such high energy that they pass through the human body. The problem occurs as uranium decays (Fig. 3). The first step in the decay series is from uranium 238 to radium 226, which in turn decays to radon 222. This element, which is one of the noble gases, decays into its daughters polonium 218 and 214, lead 214, and bismuth 214. Because these radon daughters are ionized metal atoms, they become attached to dust and water vapor. Thus, radon and its daughters can be inhaled into the respiratory tract, where they emit alpha radiation. Particularly important are the radon daughters that have a short half-life and so cannot be cleared from the respiratory tract before their energy is emitted. The alpha particles emitted have a range of 40 to 70 m, sufficient at the site of impaction to damage the mucosal cells and initiate carcinogenesis. This action has been confirmed experimentally when lung cancer has been induced in rats with cesium 14.

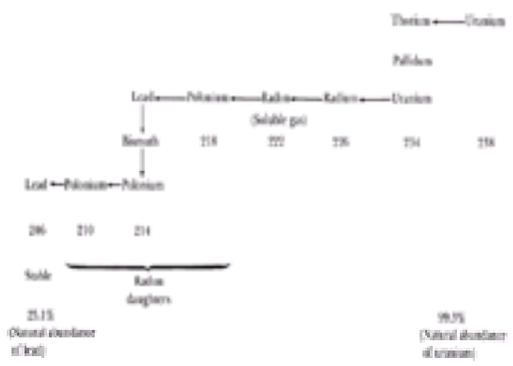

FIG. 3. Simplified natural decay series of uranium.

Epidemiology

Apart from the observations described earlier, several detailed studies have examined the effects of uranium on the lung. Mortality rates of Colorado miners were examined during a 17-year period, and a mortality more than six times greater than expected was demonstrated. Even those miners with low exposure for several years had a fourfold increased risk for lung cancer. A further finding was that the increased total radiation exposure was associated with increasing frequency of undifferentiated small-cell carcinomas.

The interaction between cigarette smoking and radiation is important. Because the incidence of smoking was so high in the initial studies, it was initially believed that smoking was a prerequisite for cancer in uranium miners. However, further studies have shown that although uranium miners who smoke have a higher risk, nonsmoking miners still have an increased risk for lung cancer. From various studies, it is clear that the amount of radiation is important, and for this reason an empiric unit, the *working-level month* (WLM), was derived. This unit is an exposure for 1 working month (170 hours) to a known concentration of radon daughters and thus reflects both intensity and duration of radiation. Risk factors were used to examine the problem in Swedish miners, and if normal nonsmokers had a risk for development of lung cancer of 1, then nonsmoking miners had a risk of 2.4. Smokers with no underground mining exposure had a risk of 6.8, and smoking miners had a risk of 18.2. Another study found that the excess cancer rate in nonsmoking miners was increased (18 observed deaths compared with 1.8 expected), but not as high as in smoking miners (32 actual, 11 expected). These figures suggest that the effects of smoking and exposure to radon daughters are additive. A further effect is the shortening of the induction-latent period, which results in an earlier appearance of cancer. This has been shown to be related to increasing age, increased exposure, and intensity of cigarette smoking, findings that have been confirmed in Sweden.

In summary, there is good epidemiologic evidence that the increased incidence of lung cancer in uranium miners is related to degree of exposure. However, increased incidence is also related to age and cigarette consumption.

Prevention

The atmospheric levels of radon daughters and exposure of workers to them must be kept to a minimum by providing ventilation, sealing off high-risk areas, and controlling water seepage. The work force should be monitored on an individual basis, and exposure should be controlled according to defined standards. In the United States, this is 4 WLM per year, with actual exposure levels being 1 to 2 WLM per year. Because the evidence suggests that the risks of smoking and uranium are at least additive, uranium workers must be strongly advised not to smoke. Some would even suggest that smokers not be employed in such high-risk situations. The question of surveillance is discussed elsewhere.

The preventative measures are not just for miners, but should also be applied to process workers, laboratory workers, and those employed in nuclear power plants.

Fluorspar

Fluorspar, or calcium fluoride, is used in the manufacture of steel and aluminum, in ceramics, and as a source of fluorine. The chief mining area of fluorspar is in Newfoundland, and it was here that the excess of carcinoma of the lung was first demonstrated. The cause of the increased mortality, which was 29 times that expected, was found to be related to radioactivity. Despite the fact that a nonradioactive material was being mined, radioactivity levels were comparable with those in uranium mines. The source was found to be radon daughters dissolved in water that had leaked into the mines.

Metal Mining

Lung cancer has been observed to be more common in certain metal miners. Mortality in hematite miners was found to be in excess compared with mortality in a control population of coal miners, and although initially it was thought that the carcinogens were iron and silica, these hematite mines were later found to be radioactive,

much in the same way as the fluorspar mines in Newfoundland. This same problem has been identified in hard rock miners in the United States, metal miners in Sweden, thorotrast miners in Denmark, and tin miners in Britain.

Nuclear Power Plants

Through the years, the use of nuclear power as a source of energy has been an emotional issue. This is particularly so in respect to possible increased risks for cancers in workers, their families, and surrounding populations. Earlier studies have shown no evidence of an increased risk for carcinoma in nuclear power workers; it should be noted, however, that the data are being amassed for impending court cases concerning the possibility of the development of lymphoma in children of men exposed to radiation at a nuclear power plant in Cumbria, United Kingdom.

Nickel lung cancer was first identified as being related to nickel exposure at the Mond Nickel Works in South Wales in 1958. The findings were later confirmed. These workers also were observed to have an increased incidence of nasal cancer. Their risk was calculated to be increased five times for cancer of the lung and 150 times greater than expected for cancer of the nose. When the study was repeated, the mortality figures had fallen. Studies of other nickel workers also have shown increased risks, especially in smokers.

The agent responsible was thought to be nickel dust, but because the incidence fell as arsenic was eliminated from the process, this also has been implicated. In one autopsy study, however, there was no evidence of arsenic in the lungs of workers who died of cancer. Overall, the evidence suggests that the risk is increased with exposure to several nickel salts, in particular, nickel subsulfide.

Chromates

Chromium is used in the production of alloys, electroplating, pigment production, tanning, and the chemical industry. It is mined chiefly in the former U.S.S.R., Turkey, and South Africa, but it is processed on a much wider scale. A link between chromates and lung cancer was reported early in this century, but epidemiologic study confirmed the association only in the 1940s. A death rate 16 times greater than expected was reported in the United States. The findings were confirmed in the United Kingdom, and the risk was later shown to fall when exposure was reduced.

The risk for carcinoma of the lung and the nose seems to be related to exposure to the salts of chromium, particularly hexavalent compounds such as dichromates and chromium pigments rather than trivalent salts.

Prevention depends on enclosure, extraction, and the use of respirators.

Earlier studies have been updated and have again shown an increased risk for carcinoma of the lung and nose in chromate workers, and the subject has been approached from a different perspective in a later study. When the nickel and chromate content of lung tissues in patients with lung cancer was examined using atomic absorption analysis, significantly higher levels of both metals were shown in the lungs of patients with cancer than in control subjects.

Chloroethers

Chloroethers are compounds encountered in the manufacture of bactericides and fungicides, and two compounds in particular, bischloromethyl and chloromethyl ether, have been shown to be important carcinogens. The other causes of occupational lung cancer were identified by observation and confirmed epidemiologically, but the chloroethers are unique in that their carcinogenic potential was first shown in animal experiments. The effect on humans has since been confirmed, and it has been shown that bischloromethyl ether in particular is associated with oat-cell carcinoma, with risk ratios of 10 to 12 being reported with heavy exposure.

Arsenic

Arsenic has been known as a carcinogen for many years. It was thought to cause scrotal cancer among copper workers as early as 1820, and it was thought that therapeutic arsenic was responsible for skin cancer. Lung and skin cancer were described in 1934 in workers manufacturing arsenical sheep dip. These men were later investigated in detail, and it was found that most workers also showed the clinical manifestations of arsenical poisoning, with hyperpigmentation, warts, and hyperkeratosis.

Nowadays arsenic exposure has been reduced, but a risk still exists in the use and preparation of some pesticides, in metal refining, and in the chemical industry.

Fossil Fuels

The products of fossil fuels, including coal, coke, coal gas, and coal tar, have been shown to be related to an increased incidence of carcinoma. In 1959, lung cancer was shown to be approximately 15 times greater than expected in two studies of Canadian and London gas workers, findings that were supported in a prospective study. Oven top workers in the U.S. steel industry had a 10-fold increase in mortality from carcinoma of the lung, and similar studies have shown this same problem in coke oven workers in the United Kingdom. However, the situation is likely to be improved following the introduction of natural gas. Coke plant workers in the Netherlands were shown to have increased death rates from lung cancer and nonmalignant respiratory disease, but the study failed to examine smoking habits fully. Another study of a cohort of 10,000 foundry workers covering a period of 40 years showed an increased incidence of both lung cancer (SMR 147) and stomach cancer (SMR 137) in comparison with the general population.

Mustard Gas

Mustard gas (bb'-dichlorodiethyl sulfide) has been used as a weapon in warfare. A mortality 10 times greater than expected was shown in Japan, where the gas was manufactured during World War II.

Vinyl Chloride

Vinyl chloride is well-known to produce angiosarcoma of the liver, but it also has been implicated in lung cancer. However, the association is weak, and other studies have attributed the problem to smoking.

Beryllium

Beryllium has not been proved to be a human carcinogen, although the OSHA has recommended that it should be regarded as posing a carcinogenic threat.

Materials Considered Suspect

At the end of any discussion of occupational carcinogens, some compounds should be mentioned that are suspected but not proved to be carcinogens.

Diesel Exhaust

Diesel exhaust fumes have not been proved to cause an excess of lung cancer; however, some studies suggest that exposure to diesel exhaust can increase the risk. A small study showed an increased risk in Swedish garage workers, and a large study of U.S. railroad workers showed increased numbers of deaths from lung cancer in men exposed for 20 years. Further studies have shown a possible association between diesel exhaust fumes and lung cancer, whereas others have failed to demonstrate any increased risk.

Animal studies have also addressed the problem; squamous metaplasia developed in rats exposed to diesel exhaust for 2 years and lung tumors occurred in 16%, compared with no tumors in the control groups. The same study also examined the effect of coal oven flue gas and found a similar increase in the incidence of lung tumors. The possibility that diesel exhaust is associated with lung cancer requires further investigation.

Formaldehyde

Debate is ongoing as to whether formaldehyde causes lung cancer, and the data from a large group of industrial workers exposed to formaldehyde have been

reanalyzed. According to the original interpretation of the data, excess mortality from lung cancer was not related to exposure to formaldehyde, but a repeated analysis suggested an association with formaldehyde. The final conclusion is that formaldehyde should be considered as a possible human carcinogen.

Other Materials

Several studies have examined the effects of silica and possible associations with lung cancer. Although it has been reported that the incidence of lung cancer is lower in miners with silicosis, other studies report increased numbers of deaths from lung cancer in men exposed to silica. Without more and better evidence, however, it is premature to conclude that exposure to crystalline silica has caused lung cancer in humans.

The links of several other compounds and processes with lung cancer remain doubtful. It has been suggested that cadmium is a carcinogen. Also, an increase in cancer has been noted in a group of workers exposed to magnesium.

Increases in lung cancer have been noted in the meat-processing industry and in Swedish bakers and pastry cooks, particularly those who work in small bakeries. Orchardists have been noted to have higher rates of lung cancer, although this is thought to be largely a consequence of cigarette smoking. A cohort of dry cleaners has been found to have a slightly increased incidence of cancer; however, the mortality was less than expected, and no significant increase in the numbers of lung cancers was found.

Isopropanol manufacture is associated with an increase in nasal cancer and possibly lung cancer. The agent suspected from animal studies is isopropyl oil. Suspicion also has been raised in Denmark and the United Kingdom about printing ink, as both printers and newspaper workers have been thought to have an increased incidence of carcinoma of the lung.

An increased risk for lung cancer was found in Swedish and Finish motor mechanics who had high blood levels of lead.

Several materials, such as glass fiber and fertilizers, have been studied and shown not to carry an increased risk for cancer. Cotton workers have been shown to have a decreased risk for lung cancer.

The subject of pulmonary occupational neoplasia is evolving. Further large, long-term studies must be carried out, and the constant review of the situation is necessary.

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CHAPTER

37 Noxious Gases and Fumes

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> “Gas! Gas! Quick, boys! An ecstacy of fumbling, Fitting the clumsy helmets just in time; But someone was still yelling out and stumbling And flound'ring like a man in fire or lime. . . Dim, through the misty panes and thick green light, And under a green sea, I saw him drowning.”
>
> —Wilfred Owen

INTRODUCTION

The deleterious effects of certain gases and fumes have been appreciated for many years. Indeed, several gases have been used specifically for their lethal effects as weapons of warfare. In the industrial setting, 20 or so gases and fumes may be encountered that are capable, after inhalation, of producing serious harm (Table 1 and Table 2).

TABLE 1. *Examples of inhaled chemicals known to cause pulmonary injury*

TABLE 2. *Summary of noxious gases and clinical correlations*

The SWORD (Surveillance of Work-related and Occupational Respiratory Disease) project, a register of cases of occupational lung disease in the United Kingdom, has shown that accidents involving inhalation account for approximately 10% of all industrial lung diseases.

MECHANISMS

The effects of a particular gas or fume can be anticipated by examining its physical and chemical properties. Inert gases cause harm by displacing oxygen, whereas toxic gases produce local irritation. The site of action of a toxic gas depends on its solubility. Soluble gases are absorbed in the upper airways, whereas those that are less soluble cause damage throughout the respiratory tract. Although brownian movement is a major factor in the dispersion of gases, the deposition of particulate matter is influenced more by gravity. Large particles (15 to 20 m) deposit in the nose and upper airways, smaller particles (7 to 15 m) deposit in the trachea and bronchi, and particles between 1 and 7 m may reach the alveoli. Particles <0.5 m are so small that they are influenced by brownian movement, and although deposition is limited, they are still able to cause harm.

The mechanisms by which toxic gases and fumes produce their harmful effects can be divided into four main groups.

1. Displacement asphyxia. The term *asphyxia* is derived from a Greek word that means “stopping the pulse.” The condition is produced by a deficiency of oxygen in respired air, blood, or tissues. Asphyxia resulting from toxic gases or fumes can occur in two ways. In the first mechanism, oxygen is displaced from inspired air by high concentrations of other gases, such as nitrogen, carbon dioxide, and methane.
2. Oxygen-transport asphyxia. The second mechanism involves chemical interference with the process of oxygen transport, preventing either delivery to the vital organs or cellular respiration itself. Carbon monoxide combines with hemoglobin, reducing its oxygen-carrying capability, whereas cyanides block the cytochrome oxidase system, preventing respiration and thereby causing asphyxia at a cellular level.
3. Local irritation. Most toxic gases and fumes cause harm by local irritation. The more soluble substances, such as ammonia, dissolve in the mucus of the nose and

upper airways, whereas the oxides of nitrogen, which are less soluble, exert their effects throughout the respiratory tract.
4. Toxic absorption. Some inhaled substances, in addition to producing immediate effects in the respiratory tract, are absorbed and may damage distant organs. Mercury and manganese damage the nervous system, whereas fluorides can harm the bones. Certain substances can produce long-term effects in the lungs; beryllium causes fibrosis, and cadmium has been associated with emphysema.

Displacement Asphyxia

Carbon Dioxide

Carbon dioxide is an odorless gas that is heavier than air and can be a hazard in any enclosed or ill-ventilated space. It is a particular hazard in coal mines when oxidation of the contaminants of coal occurs at unworked faces, particularly if a face is reopened.

Carbon dioxide was responsible for the deaths of 1700 people in Cameroon when a massive cloud of gas was released from Lake Nyos, a volcanic crater lake.

Inhalation of carbon dioxide causes hyperventilation, sweating, headache, and a bounding pulse with warm peripheries, followed by loss of consciousness. The treatment is to remove the patient from the source of the gas and administer oxygen. Mouth-to-mouth respiration is required if breathing has ceased. Carbon dioxide will extinguish a naked flame, and because of this property, safety lamps can be used to detect carbon dioxide in mines.

Nitrogen

Nitrogen constitutes approximately 80% of air; the remaining 20% is mainly oxygen. If the level of oxygen falls, as in oxidative processes that occur in mines, then the rest of the air is made up of nitrogen and carbon dioxide. If the oxygen level falls to 15%, dyspnea occurs on exertion. As the oxygen falls further to 10%, breathlessness occurs at rest, and at levels below this, collapse and even death may occur on minimal exertion. The way to detect a falling oxygen level again depends on the ability of the atmosphere to support combustion. The treatment is removal, administration of oxygen, and artificial respiration if required.

Methane

Methane, which is without taste or odor, is the product of decaying vegetable matter. It is known to miners as “firedamp” or “marsh gas.” Methane was feared by miners not only because of its asphyxiant properties, but also because of its explosive potential when mixed with air. In the past, methane explosions were the cause of many mining disasters. However, in 1816, Humphrey Davy introduced a lamp that was able to detect methane, which burned with a blue flame.

Methane produces asphyxia by displacement of oxygen, much in the same way as carbon dioxide. The treatment is the same.

Oxygen-Transport Asphyxia

Carbon Monoxide

Carbon monoxide (CO) is the most commonly encountered noxious gas, because it is formed during the incomplete combustion of any carbon-containing material. As well as being an occupational hazard in mines, kitchens, and gas works, around furnaces, and in any situation where high concentrations of motor vehicle exhaust may be present, it is an important cause of death in burning buildings. In the United States, the number of people who die of carbon monoxide poisoning each year is estimated to be above 3,800. In Britain, 1,000 people are estimated to die annually because of the effects of carbon monoxide, which is the most frequent cause of poisoning in children.

The gas is odorless and lighter than air. It causes hypoxia by reducing the oxygen-carrying capacity of the blood and by directly poisoning the cytochrome oxidase systems. The affinity of carbon monoxide for hemoglobin is a 200 times greater than that of oxygen. Carbon monoxide not only forms carboxyhemoglobin and prevents oxygen transport, it also shifts the oxygen dissociation curve to the left, making less oxygen available to the tissue. The tissues most affected by carbon monoxide are those with the highest metabolic rates. Warning symptoms include dizziness and headache, but rapid loss of consciousness without premonitory symptoms often occurs; in fact, it has been estimated that up to 70% of fire-associated deaths in the United States are not caused by smoke or heat of the fire but rather by carbon monoxide poisoning, explaining why individuals with the opportunity to escape fires often fail to do so.

Breathlessness is not necessarily a feature, and physical examination is not particularly helpful. Cyanosis does not occur despite the hypoxia, but a cherry-red coloration of the mucous membranes, caused by carboxyhemoglobin, may be present. The pulse rate is usually elevated.

The chest radiographic findings may be abnormal in acute carbon monoxide poisoning in up to 30% of cases, the usual pattern being diffuse shadowing with a peripheral predominance. If levels of carbon monoxide are insufficient to produce acute carbon monoxide poisoning, then chronic carbon monoxide poisoning can occur. Chronic exposure to carbon monoxide causes headache, muscular weakness, and nausea. If the central nervous system is affected, extrapyramidal or psychiatric symptoms can occur. These features may also be seen in patients who recover from acute poisoning.

The deleterious effects of carbon monoxide are related to its concentration in the inspired air, the duration of inhalation, and the oxygen requirement of the exposed person (and therefore the degree of exertion at the time of exposure). An estimate of the saturation of hemoglobin by carbon monoxide can be obtained for use in, for example, contaminated mines when the concentration is not too high with the formula $b = 4ate/100$, where b is the saturation, a the concentration in parts per million (ppm), t the exposure time in hours, and e the exercise factor (1 for rest, 2 for walking, 3 for working). Even low concentrations of carbon monoxide (0.5%) breathed for 2 hours can cause death. Symptoms begin when the carboxyhemoglobin saturation reaches 20%. Unconsciousness occurs at 60% and death at 80%. High concentrations of carbon monoxide can be produced quickly from vehicle exhaust fumes; a lethal concentration can be reached in a single car garage within 10 minutes. Normal individuals have carboxyhemoglobin saturation levels of 0.5%, whereas smokers have levels of 5%–10%. Nonsmoking London taxi drivers had levels of 0.4%–3%, presumably because of exposure to exhaust fumes.

The traditional means of detecting the presence of carbon monoxide in mines relied on the observation of canaries falling off their perches. Although this method has been largely superseded by detector tubes or infrared analyzers, most mines still keep canaries.

The management of carbon monoxide poisoning is important and consists of prompt administration of the highest concentrations of oxygen available. Normally, this will be 100% oxygen delivered by face mask, but if available, hyperbaric oxygen expedites the dissociation of carboxyhemoglobin. The hyperbaric chamber is undoubtedly the most effective treatment, and such chambers should be available where the risk for carbon monoxide poisoning is high.

The diagnosis of carbon monoxide poisoning is often overlooked (30% in one series). Hence, it is important to measure blood carboxyhemoglobin or breath carbon monoxide in both the industrial setting and in persons who have escaped from fires; this should be followed by prompt treatment with oxygen.

Cyanides

Cyanide poisoning caused by sodium or potassium cyanate can affect persons who are involved in gold extraction and electroplating or who work in chemical and photographic laboratories. The greatest risk, however, occurs with the use of acrylonitrile (vinyl cyanide) in the manufacture of synthetic rubber. The fumes may be inhaled or absorbed through the skin, and workers engaged in loading and unloading or in the industrial process itself are at risk. Cyanides derived from burning seats and furnishings in combination with carbon monoxide were thought to be the cause of death in victims of a recent airplane fire disaster, and elevated levels of cyanide have been identified in persons involved in residential fires.

Cyanide blocks the cytochrome oxidase system. Thus, oxygen can no longer be transferred to the tricarboxylic acid cycle. Asphyxia, therefore, occurs at the cellular level. The symptoms are usually dramatic, with dizziness, nausea, and rapid breathing. This is followed by vomiting, chest and abdominal pain, confusion, and finally coma. Because of the rapid onset of symptoms, the subject is fortunately warned of danger, allowing escape before a fatal dose is absorbed. The saturation of oxygen is not disturbed, and cyanosis is not a feature until respiration is depressed. The diagnosis can be made by the characteristic odor of “bitter almonds” on the breath.

Cyanide poisoning is a medical emergency. Two antidotes are available: nitrites and cobalt. Amyl nitrite, which is inhaled, or sodium nitrite, which is given intravenously, combines with hemoglobin to produce methemoglobin. This combines with cyanide, which in turn combines with thiosulfate to produce the harmless thiocyanate. Thiosulfate is given intravenously with nitrites to augment this conversion. A better alternative therapy is cobalt, which forms stable, inert complexes with cyanide (cobalt cyanides). Hydroxycobalamin can be given intramuscularly, but very high doses are required, so the chelated cobalt dicobalt edetate is the drug of

choice. It should be used only when the diagnosis is certain because of potential serious side effects.

A person poisoned with cyanide should be removed from the area, washed if the skin is contaminated, and given hydroxycobalamin intramuscularly and amyl nitrite to inhale as an immediate first aid measure. If the patient's condition remains severe (i.e., presence of neurotoxicity or depression of respiration), 300 to 600 mg of dicobalt edetate (Kelocyanor) should be given intramuscularly, with a further 300 mg if there is no recovery in 1 minute. Oxygen should be given in high concentration, as this has been shown to have a synergistic antidotal action, particularly when the nitrites are used. If the response is insufficient, then amyl nitrite should be inhaled every 2 minutes, with intravenous administration of sodium nitrite (10 mL of 3% solution) and sodium thiosulfate (25 mL of 50% solution). The patient may require inotropic support, artificial respiration, or even cardiac massage until the antidotes work.

Hydrogen Sulfide

Hydrogen sulfide has a characteristically unpleasant odor that has been used by generations of delighted schoolchildren to make stink bombs. In industry, it is a potential hazard in petroleum refining, the natural gas industry, tanning, the chemical industry, and in the preparation of fish meal.

Exposure to hydrogen sulfide causes conjunctivitis, blurred vision, keratitis, and blepharospasm, together with headache, dizziness, ataxia, nausea, and diarrhea. If the exposure is heavy or if the gas is inhaled, then cyanosis, confusion, pulmonary edema, convulsions, and coma occur. Severe acute exposure causes a greenish coloration of the face and chest. Coma and death result from toxicity of the central nervous system, because the gas binds iron and poisons the cytochrome oxidase system, preventing cellular respiration. Treatment consists of removal from the source with artificial respiration if required. Because the action of hydrogen sulfide is similar to that of cyanide, it would seem logical to give 10 mL of 3% sodium nitrite intravenously, as in cases of cyanide poisoning.

Irritant Gases

Ammonia

Ammonia is a widely used, highly irritant, highly soluble gas. It is utilized in refrigeration, fertilizer production, oil refining, and the manufacture of explosives and plastics. Exposure most commonly occurs as a result of industrial accidents in which tanks or pipes fracture.

The gas is very toxic, and because it is so soluble, its effects are manifested in the skin, conjunctivae, mucous membranes, and upper respiratory tract. Immediately following exposure, intense pain occurs in the eyes, nose, mouth, and throat, accompanied by a sense of suffocation. Stridor and aphonia are followed by cyanosis and ulceration of mouth, nose, and pharynx. Exposure to high concentrations for a minute or less will cause death.

Pathologic examination shows a severe acute inflammatory reaction characterized by edema, ulceration, and desquamation of mucous membranes. Death results from obstruction of the airway caused by edema of the larynx and blockage of the airways with desquamated epithelium. If the gas reaches the lungs, then the alveoli fill with blood and edematous fluid. Survivors have severe airways obstruction that can last for months, although in many cases the epithelial surface completely regenerates. Long-term impairment can occur and has been shown to be caused by bronchitis and bronchiectasis.

The treatment is rapid removal of the patient from the area by rescuers using breathing apparatuses. Weakly acidic mouth washes and eyewashes may help symptoms, but the main objective is to maintain oxygenation. All patients should be given oxygen therapy, and if the case is severe, tracheotomy and artificial respiration may be required. Severe ammonia burns require fluid to treat shock and antibiotics to prevent sepsis. The value of steroids and bronchodilators is unknown, but both tend to be used acutely.

Chlorine

Chlorine is another irritant gas that is widely used in industry in the manufacture of alkalis, bleaches, and disinfectants. It is less soluble than ammonia and is therefore more likely to affect the whole of the respiratory tract rather than just the upper airway. The gas is often stored or transported under pressure, and exposure occurs after accidents such as fracture of tanks or pipes.

Although the gas is less soluble, chlorine exposure still produces conjunctivitis and nasal irritation. However, the most serious effects occur in the lower respiratory tract. Acute exposure causes chest pain and breathlessness. Crackles and wheezes can be heard in the chest, and pulmonary edema with the production of a white or pink sputum can occur immediately or be delayed for several hours.

The degree of parenchymal damage is more severe than that produced by ammonia. Hence, the course of the acute illness is longer, with impairment of gas exchange for several days. Treatment is removal from the source and administration of oxygen, with intermittent positive-pressure ventilation if required. Steroids have been used, although benefit is not proved. Antibiotics are usually given to prevent infection, which may complicate the damaged respiratory mucosa.

Although chronic disability occurred in many victims of World War I gas attacks, this may have been a consequence of the sequelae of infection, as follow-up studies of persons poisoned by chlorine have not revealed permanent impairment of lung function. Nevertheless, there have been several recent isolated reports of persistent bronchial hyperreactivity and asthmatic symptoms (reactive airways dysfunction syndrome, or RADS) following a single large exposure to chlorine gas.

Similar situations have also been reported following a variety of particular smoke inhalations, such as from burning polyvinyl chloride (PVC). Thus, the development of prolonged obstructive airways disease after smoke inhalation is of concern to both fire victims and fire fighters.

Oxides of Nitrogen

Although nitrogen is capable of forming four oxides, the two forms of nitrogen dioxide, NO^2 and N^2O^4, are particularly hazardous. Nitrogen dioxide is a heavy, irritant, brown gas that is relatively insoluble. The gas occurs in several distinct situations in industry: silage production, arc welding, combustion of nitrogenous materials, and manufacture and transport of nitric acid.

Silage is used to feed livestock through the winter. It is produced from fresh green crops, such as grass, alfalfa, and corn, that are stored in a tower or pit at a controlled temperature of ⇀↽38°C. Nitrates derived from the soil or fertilizer are oxidized as a side reaction to the fermentation of vegetable matter, resulting in the production of nitrogen dioxide. The process begins within a few hours of filling the silo, peaks at 2 days, and subsides after a week or two. Farmers and their families are at risk for nitrogen dioxide poisoning at any time in the first week if the silo is entered or even simply approached. Poisoning has occurred up to 6 weeks after filling.

Arc welding, because of the very high temperatures involved, can cause atmospheric oxygen and nitrogen to combine to form nitrogen dioxide and causes a risk when carried out in confined spaces, such as inside tanks or ships' hulls.

Nitrogen dioxide also can be produced when nitrogen-containing materials are burned, as occurs during shot firing in coal and metal mines or the explosion of dynamite. In a particularly notorious episode of nitrogen dioxide poisoning at the Cleveland Clinic, the accidental burning of nitrocellulose radiographic film resulted in >100 deaths. The greatest risk from nitrogen dioxide fumes occurs in the chemicals industry, particularly in the manufacture, transport, and use of nitric acid. The hazard occurs after spills, as nitric acid gives off nitrogen dioxide on contact with organic material. There is also a risk when nitric acid is used to clean metals, in the handling of jet fuels, and in the nitrification of organic compounds.

In agricultural settings, nitrogen dioxide poisoning is known as *silo filler's disease.* However, the clinical features are similar whatever the source of the gas. The gas is not as irritating as ammonia, and low concentrations may produce only mild upper respiratory tract symptoms. The worker may be alerted to the danger by cough or by observing the characteristic brown gas. If the concentration of gas is high, choking and cough will cause the worker to leave the site. Choking and cough are followed by the production of frothy sputum, increasing dyspnea, and within an hour frank pulmonary edema; death may occur at this stage. Alternatively, the onset may be less acute, with cough and dyspnea developing during a few hours, followed by gradual improvement within 2 to 3 weeks. Despite an apparent improvement, there may be a sudden relapse, heralded by fever and chills and followed by cyanosis, dyspnea, and generalized crackles. Death resulting from respiratory failure also may occur in this second stage, but if the patient survives, then recovery is usual, although obstructive defects with impairment of gas transfer have been reported.

Radiographic findings in nitrogen dioxide poisoning are variable. In the acute stage, the radiographic features can be normal or display the appearance of pulmonary edema, which initially may have a nodular component. As the patient recovers, the radiograph clears, but if a second stage occurs, then miliary mottling develops, which at times becomes confluent. In the acute phase, pathologic examination reveals mucosal edema, inflammatory cell exudation, dilated capillaries, and blood in the alveoli. The delayed lesion shows bronchiolitis obliterans.

Management is mainly preventative. Farm workers should be warned of the dangers of recently filled silos, welders should not work in poorly ventilated enclosed spaces, and in addition to the obvious precautions that must be taken in chemical works, even small exposures should be reported and workers observed for late sequelae.

Medical management includes the use of oxygen and ventilation if required. Steroids have been beneficial in case reports, although no controlled trial has proved their benefit. Antibiotics are given to prevent superinfection, but their effectiveness is unproved. Bronchodilators may be of some use in the acute attack.

Ozone

Ozone (O_3) is a constituent of photochemical smog and can be found in the cockpits of aircraft flying above 30,000 feet. It is also produced by high-tension electrical discharges in arc welding.

Serious poisoning by ozone has not been reported, but abundant work in animals has demonstrated that ozone produces structural and functional changes. In humans, low concentrations of the gas (0.3 to 0.9 ppm) produce cough, chest discomfort, and impaired pulmonary function of an obstructive type. Tolerance, however, appears to develop in persons exposed to repeated low levels of ozone, possibly as a result of increased superoxide dismutase.

The evidence that ozone is detrimental to health is increasing. Recent studies have confirmed that ozone causes adverse effects on the pulmonary function of healthy individuals and is particularly harmful to asthmatic patients, potentiating the allergic response even at low concentrations. The subject requires further study.

Phosgene

Phosgene, along with chlorine, was responsible for many of the deaths caused by gassing in World War I. It is a heavy, colorless gas that has a faint odor of newly mown hay. Because it is not particularly irritant, it may be inhaled for long periods without great discomfort. Phosgene is a hazard in the chemical industry, being formed as an intermediate in the synthesis of isocyanates and other organic chemicals. It also occurs when chlorinated hydrocarbons are heated, and cases of phosgene poisoning have been reported following an accident with a carbon tetrachloride fire extinguisher.

Phosgene is toxic to the pulmonary capillaries and causes pulmonary edema (Fig. 1). An exposed worker begins to cough and within an hour becomes breathless. Crackles develop throughout the lungs, and shock follows. Phosgene also appears to cause constriction of the pulmonary vasculature, increasing transudation through the already leaky capillaries and compounding the hypovolemic shock.

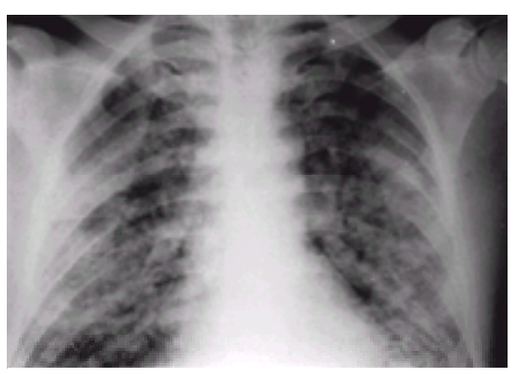

FIG. 1. Posteroanterior radiograph of a 55-year-old man with acute phosgene poisoning. Extensive alveolar shadowing is present, with a normal-sized heart and no evidence of diversion of blood to veins of the upper lobes.

If the patient survives the acute episode, the pulmonary edema gradually subsides during a week. There is no definite evidence of long-term pulmonary damage.

Sulfur Dioxide

Sulfur dioxide occurs in the polluted urban atmosphere, being derived from the combustion of coal and gasoline. In industry, it is encountered in paper production, oil refining, and the manufacture of food preservatives and bleach.

Sulfur dioxide is a heavy, irritating gas with a solubility similar to that of ammonia. The effects are therefore severe irritation of the mouth, eyes, nose, and upper respiratory tract. This is quickly followed by violent paroxysms of coughing. Heavy exposure to sulfur dioxide can cause death from pulmonary edema.

The treatment is much the same as for the other irritant gases, although sodium bicarbonate may provide local symptomatic relief. There is some evidence that sulfur dioxide can exacerbate chronic bronchitis, and long-term complications have included the development of obliterative bronchitis and bronchiectasis. However, a 10-year study of a group of paper workers showed no increase in mortality from either respiratory or other diseases.

Toxic Fumes

Metal Fume Fever

Metal fume fever is an acute febrile illness caused by the inhalation of metal oxides. It is variously known as *brass founders' ague, copper fever, brass fever,* and *Monday morning fever.* The disease is most commonly associated with zinc, copper, and manganese, but it is also seen in persons who work with cadmium, iron, nickel, selenium, tin, and antimony. The industrial situations include ship building, welding, electrical metal furnaces, zinc smelting, and galvanizing.

Metal fume fever is thought to be caused by the inhalation of finely dispersed particles (<1 m in diameter) that are produced by heating the previously mentioned metals. The disease invariably has an acute onset, and repeated bouts are common. Metal fume fever is usually worse on the first day at work, as transient resistance develops after a few days exposure, although this effect quickly wanes—hence the term *Monday morning fever.* Attacks can occur on first exposure to fumes without prior sensitization, indicating that a direct toxic action, possibly involving chemotaxis of neutrophils, rather than an immunologic mechanism is the most likely basis for the condition.

The symptoms begin within 4 hrs of exposure and include sudden onset of thirst with a metallic taste in the mouth. This is followed by rigors, fever, and muscular aches and pains associated with generalized weakness. All the symptoms settle spontaneously within 24 to 36 hours. The diagnosis of metal fume fever is based on clinical findings, as no test is specific, although a leukocytosis is often present. The disease is so common that the diagnosis is often made by the workers, who are well aware of the condition. No medical treatment is available, but drinking milk, for no known reason, provides symptomatic relief.

Polymer Fume Fever

Polymer fume fever is a condition similar to metal fume fever and is known as “the shakes.” It occurs after exposure to the fumes produced during the manufacture of polytetrafluoroethylene (trademarks Teflon and Fluon). The condition, first described in 1951, begins several hours after exposure and is characterized by a sharp attack of chest tightness, choking, and a dry cough. Repeated attacks are common, as with metal fume fevers, and do not lead to permanent problems.

It is thought that inhalation of aliphatic and cyclic fluorocarbons, formed when polytetrafluoroethylene is heated to >250°C, causes leukocytes in the lung to degranulate and release endogenous pyrogens.

The vast majority of cases of polymer fume fever occur in smokers, and the incidence can be reduced if workers wash their hands before smoking. Better still, handlers

of polytetrafluoroethylene should be strongly advised not to smoke.

Osmium

Osmium is a very dense metal that is closely related to platinum. It is found in Russia, Canada, Colombia, Australia, and the United States as the ore osmiridium. Osmium is used as a catalyst, as an alloy with iridium in nibs and compass needles, in photography, and for the staining of histologic sections.

The metal is innocuous, but osmic acid (osmium tetroxide) produces effects similar to those of the halogen gases, including severe conjunctivitis, tracheitis, and bronchitis. Blindness can occur from corneal damage, and prolonged exposure causes nausea and vomiting.

Trimellitic Anhydride

Trimellitic anhydride (TMA) is used in a variety of industrial processes, such as the manufacture of plasticizers, as a constituent of alkyl resins, and as a curing agent for epoxy resins. Asthma and bronchitis were the first problems reported with trimellitic anhydride. However, hemorrhagic pneumonitis also has been described. Workers with pneumonitis were exposed to fumes of trimellitic anhydride when a mixture with epoxy resin was heated; they presented with cough and repeated hemoptysis. Chest radiographs often showed patchy infiltrates consistent with blood in the lung. All patients had hemolytic anemia as well as respiratory problems. Pulmonary function testing showed hypoxemia, and although the diffusing capacity (D_LCO) was occasionally raised initially because of blood in the lung, it was reduced as the anemia became more severe. Histologic examination in these cases showed a hemorrhagic pneumonitis with intravascular hemorrhage and alveolar cell hyperplasia.

Removal from the exposure usually results in resolution of symptoms. Treatment is supportive.

Mercury

The industrial hazard from mercury was appreciated as early as 1703 by Ramazzini, who reported that persons making mirrors became palsied and asthmatic from handling mercury. The inhalation of mercury vapor may cause inflammation throughout the respiratory tract, with tracheitis, bronchitis, bronchiolitis, and a pneumonitis. Exposure to this hazard occurs in extraction of the metal, in the manufacture of thermometers and tungsten-molybdenum wire, in the cleaning of tanks and boilers, and more recently, in the repair of sphygmomanometers.

Symptoms generally begin 1 to 4 hrs after acute exposure, with breathlessness and tightness of the chest. This is followed by development of paroxysmal cough, loss of appetite, fever, restlessness, rigors, and tremor. If the exposure is heavy, dyspnea can be severe and death may occur. If the exposure is small but repeated, the symptoms are of abdominal pain, diarrhea, erosion of the nails, gingivitis, and nonspecific neurologic symptoms such as tremor, irritability, or forgetfulness. Basal crackles may be heard in the lungs. The radiograph may show diffuse, patchy shadowing, and lung function tests show a mixed restrictive and obstructive defect. Mercury levels in the blood may be low, as it is fixed in the tissues. However, chronic exposure can be detected by finding raised levels in the urine. In severe cases, pathologic examination has shown tracheobronchitis and pneumonitis with alveolar edema and hyaline membrane formation. In infants, bronchiolitis and pneumothorax have been known to cause death. Occasionally, patients progress to pulmonary fibrosis. Management of the poisoning is supportive and includes oxygen and corticosteroids.

Manganese

Manganese is used as an alloy to harden steel. It is mined from a black ore containing manganese dioxide (pyrolusite) in Russia, India, Morocco, South Africa, and South America. Exposure to manganese occurs in smelting and the manufacture of dry-cell batteries and glass. The damage to the central nervous system caused by manganese is well-known; its effect on the lungs is not as clear. A high incidence of pneumonia and bronchitis has been observed in workers exposed to manganese, and animal experiments have confirmed its ability to cause pulmonary damage.

Cadmium

Cadmium is a soft, gray metal similar to zinc. It is produced chiefly in the United States, the metal being obtained from its own natural ore, greenockite, or from zinc, lead, and copper ores. Cadmium is also recovered from electrolytic zinc refining and from the fumes of lead and zinc smelting. Because it resists corrosion, cadmium is widely used for electroplating. It is also mixed with nickel and silver to form alloys used in nuclear reactors and batteries, and in the manufacture of jewelry.

Cadmium is toxic to humans. If the salts are ingested, nausea, vomiting, and diarrhea occur within 2 hrs. The most serious effects of cadmium, however, develop after inhalation of the fumes, which can occur at the time of smelting or if cadmium-plated metals are fired or welded. The effects can be either acute or chronic.

Acute exposure to high concentrations of cadmium fumes causes rhinitis, sore throat, cough, a metallic taste in the mouth, and retrosternal discomfort. Later, symptoms similar to those of metal fume fever develop, including malaise, rigors, and muscle pains, and, if the exposure is severe, dyspnea and hemoptysis. Physical signs include fever, tachypnea, cyanosis, and coarse or medium crackles in the chest. The chest radiograph shows vague infiltrates in the middle and lower zones or a pattern similar to that of pulmonary edema.

In fatal cases, pathologic examination shows damage to lung and kidney. The trachea and bronchi are inflamed, and the lungs are edematous. Histologic examination shows congestion with intra-alveolar exudate and hemorrhage. The kidneys are swollen with evidence of cortical necrosis. Glomerular vessels are often occluded by thrombi, and the tubules show widespread damage with proteinaceous and granular casts.

The effects of long-term exposure to cadmium are not as easily delineated. Nonrespiratory problems include anosmia, nasal ulceration, and discoloration of the teeth. Proteinuria occurs in 80% of workers with long-term exposure to cadmium and can be associated with severe tubular degeneration. Liver damage, anemia, and bone marrow depression have all been reported. The effect of long-term exposure to cadmium on the lungs is controversial. Some believe it causes emphysema, and although this may be the case, others argue that cadmium emphysema is in fact caused by cigarette smoking or is the aftereffect of an acute exposure. The situation is further complicated by the fact that cigarettes themselves contain cadmium. The symptoms of cadmium emphysema are much as expected, although there tends to be little in the way of accompanying bronchitis. Pulmonary function tests usually show obstruction, although one study by Smith and associates of heavily exposed workers showed a restrictive defect with evidence of pulmonary fibrosis in a minority of patients. These findings have not been observed by other investigators.

Pathologic examination of the lungs has shown marked emphysema without bronchitis, although there has not been unanimity concerning which type of emphysema is present, both panacinar and centrilobular patterns being reported.

No specific treatment is known for either acute or chronic cadmium poisoning, and both British antilewisite (BAL) and ethylenediamine tetra-acetic acid (EDTA) are thought to be contraindicated.

Vanadium

Vanadium is used to harden certain steels. It has been shown to cause industrial asthma, and after acute exposure, it can produce severe irritation of the eyes, nasal irritation, sore throat, cough, retrosternal discomfort, and bronchitis or a patchy bronchopneumonia.

Metal Fumes and Industrial Asthma

The list of substances that cause industrial asthma continues to increase and includes several metals, such as nickel, chromium, cobalt, and platinum salts. Industrial asthma is reviewed in Chapter 34.

MISCELLANEOUS AGENTS

Various agents are encountered in the workplace that do not necessarily fit into the classification of noxious gases and fumes discussed previously. Nevertheless, they deserve mention.

Diesel Emissions

Diesel emissions have been the subject of a number of investigations because they contain a complex mixture of harmful materials, including carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and nitrogen dioxide. However, despite the potential risks, several studies have failed to demonstrate serious effects. Coal miners showed no decrease in FEV_1 (forced expiratory volume in 1 second) or $FEF_{50\%}$ (forced expiratory flow, midexpiratory phase), railway workers exposed to short-term diesel exhausts showed no adverse effects, and iron ore workers in Sweden had no decrease in lung function after exposure to diesel fumes; an increased incidence of bronchitis was found in underground workers, although this was small compared with the effect of smoking.

Overall, diesel fumes, despite their hazardous potential, have not been proved to have any harmful effects, although surveillance should be maintained and any further complaints investigated. Diesel fumes are also considered in the chapter on occupational pulmonary neoplasms (Chapter 36).

Hexavalent Chromium Compounds

These compounds, used in pigments and tanning, cause nasal ulceration and perforation. In high concentrations they can induce severe tracheobronchitis and pneumonia. Recovery is usually rapid, but secondary infection can occur.

Hydrofluoric Acid

This acid is used in etching, in metal refining, and as a catalyst. It causes severe tracheobronchitis if inhaled.

Zinc Chloride

This compound can be a hazard in the manufacture of dry cells or in galvanizing. Its effects are similar to those of hydrofluoric acid.

Formaldehyde

This is a colorless, inflammable gas that has many industrial uses, including the manufacture of textiles, paper, rubber, adhesives, cosmetics, and insulation materials. It is used as a fixative and preservative in anatomy, in pathology laboratories, and by morticians. Formaldehyde is also present in cigarette smoke and automobile fumes. The irritant effects of formalin are well-known, with exposure causing lacrimation, nasal irritation, sneezing, sore throat, headache, and chest tightness. Evidence is increasing that formalin causes asthma. Formaldehyde has also been linked with cancer; this is discussed in Chapter 36.

Paraquat

This highly efficient herbicide is used worldwide, and although it becomes inactive on contact with soil, it is a serious occupational hazard. The devastating effects of ingestion of paraquat are well-known, producing an often-fatal pulmonary fibrosis. Occupational poisoning has occurred in agricultural workers spraying paraquat, and it is likely that absorption in these cases occurred through the skin. There is a single case report of a patient who survived poisoning by inhalation of aerosol.

Prevention is based on education of workers together with use of protective clothing and respirators. Treatment is supportive, including administration of steroids.

Methyl Isocyanate

Poisoning with methyl isocyanate (MIC) was not recorded until 1984, when a notorious accident occurred at a Union Carbide plant in Bhopal, India. This episode resulted in approximately 1,900 deaths, according to the official estimate of the Indian government; however, the true figure may have been as high as 2,500 to 5,000 deaths. Methyl isocyanate, which is used in the manufacture of pesticides, was thought to have escaped when water entered a tank of the gas. The exothermic reaction that resulted caused a massive escape in a densely populated area (100,000 people within a 1-km radius). The main effects were on the eyes and respiratory tract.

Pulmonary edema was followed by destructive lesions with cavitation, pneumomediastinum, and emphysema in affected individuals. Development of pulmonary hypertension has been reported in survivors, and the possibility of fetal damage and teratogenic effects has been raised. Because of the confusion following the disaster, records and data are incomplete, and many questions about the episode remain unanswered.

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CHAPTER

38 Pulmonary Effects of Radiation

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HISTORY

The discovery of x-rays in 1895 by Roentgen and a practical means of generating them led almost immediately to their use for diagnostic and therapeutic purposes. It also inaugurated the science of radiobiology. The first evidence of effects on the lungs came as early as 1898 in a study of guinea pigs by Bergonie and Teissier. The energy of therapeutic x-rays in the first decade of this century was so low that most was probably absorbed by the chest wall (even of guinea pigs), and the view at that time was that the lungs were relatively resistant to x-rays. During the second decade, however, higher-energy x-rays with more penetration were generated, and radiotherapists began to observe unusual lung reactions in their patients. It was the practice then to irradiate the chest wall of mastectomy patients with opposed anterior and posterior ports. The first suggestion of pulmonary reactions to this treatment was presented by Groover and colleagues in 1921 and described by them in the next 2 years. The same year as their first publication, 1922, Hines reported two cases with autopsy findings, and Tyler and Blackman reported seven cases, including some in which pleural changes were present; these were followed by Evans and Leucutia in 1925. There is some ambiguity in these reports, with early and late effects and pulmonary and pleural reactions being discussed simultaneously under the designation of “pulmonary fibrosis.” However, these were neatly sorted out by Desjardins at the Mayo Clinic in 1926 in the first review article on the subject. His descriptions of the clinical and roentgenographic features and their differential diagnosis leave little room for additions in these areas more than 60 years later. The discoveries of the previous century had clearly resulted in the first lung disorder that was entirely of man's own making.

Subsequent developments can be summarized. The first detailed descriptions of pathologic changes following irradiation were presented by Engelstad and by Warren and Spencer; these were followed by experimental and clinical reports of Jennings and Arden and Smith. Shortly thereafter, in 1966, Phillips suggested that the major change of pathogenetic consequence was the effect on pulmonary capillary endothelial cells, a view that is no longer current.

The physiological effects of pulmonary x-irradiation were investigated by McIntosh and Spitz in 1939 and Freid and Goldberg the next year. But it was not until the era of relative sophistication in pulmonary function testing that a coherent picture of the functional changes emerged.

In the clinical sphere, corticosteroids were first used for treatment of radiation effects on the lungs by Cosgriff and Kligerman and for prophylaxis by Friedenberg and Rubenfeld. Although these and clinical studies by Bluestein and Roemer, Rubin and colleagues, and Whitfield and Bond suggested that corticosteroids might be of benefit, the report by Moss and co-workers appears to have confirmed this experimentally.

RADIOBIOLOGY

The following discussion of the physical and biological effects of ionizing radiation is intended only to provide a superficial background for the understanding of clinical events. For a more detailed and accurate account of the effects of radiation on biological tissues, the reader is referred to any text on radiobiology or radiotherapy.

The two most commonly used forms of ionizing radiation are x- or gamma rays and accelerated particles, of which the only variety of significance for pulmonary effects at present is fast neutrons. (Fast electrons are also in clinical use but, because of their limited penetration, cannot produce effects in the lungs from an external source.) X-rays and neutrons ionize the target by indirect processes. When an x-ray collides with an electron in the target, some of its energy is transferred to the electron, which is accelerated out of its orbit. Neutrons are more likely to accelerate hydrogen nuclei. In either case, fast-charged particles so generated ionize the atoms or molecules they collide with, resulting in ion pairs. These in turn react with adjacent molecules to produce free radicals. In biological tissue, where most of the molecules are water molecules, most of the free radicals will be hydroxy radicals, ·OH, but free radicals also will be generated from more complex molecules. Free radicals,

particularly ·OH, have a great deal of excess energy because of their unpaired valence electrons. They can break covalent bonds to cause some of the biological effects of irradiation. It is in fact the free radical, which is much longer-lived and more energetic than the ion, that does the damage. However, the term *free-radical-forming radiation* is unlikely to displace the conventional term *ionizing radiation.* Although much damage can be rapidly repaired *in vivo,* the presence of oxygen in the target allows some of the free radicals to become oxidized. The result in the case of organic free radicals is an organic peroxide, which is less easily repaired than bond breakage without peroxide formation. Because the molecular injury is “fixed” by oxygen, most forms of radiation are much more damaging if the target is well oxygenated.

What is the target in biological systems? Although all molecules can be affected by the chain of events resulting from the absorption of ionizing radiations, the function of most of them is not important enough or not sufficiently altered to have serious consequences. Thus, a change in the viscosity of a mucopolysaccharide solution or an increase in permeability of a membrane could be corrected by replacement or repair of the damaged molecules. Doses in the range of thousands of rads are required to produce enough damage to nongenetic structures to seriously jeopardize the survival of most cells.

The damage to genetic material, DNA itself, is more important. Although the molecular events in genetic damage are not entirely clear, one can envision a number of points at which mutagenic or subsequently lethal effects could occur: single-strand breaks in DNA could be inadequately repaired, or base substitutions could be made in the repair process. Double-strand breaks could result in fragmentation or misalignment of the ends or cross-links between strands, all of which will occur in a small proportion of the population of irradiated cells. It is unlikely that such damage will be expressed in the cells until their next mitotic attempt. At that time, gross chromosomal damage may make it impossible for the chromatids to separate, resulting in anaphase arrest, or chromosomes may be divided unequally between the daughters, or major chromosomal aberrations such as ring forms, dicentrics, bridges, and fragments may appear. Equally fatal results may occur from deletions and point mutations. Genetic damage from radiation is therefore expressed as a loss of reproductive or clonogenic potential. This can occur at doses of a few hundred rads, in contrast to the thousands of rads needed to cause effects on nongenetic material.

Because ionizing radiations do not distinguish between normal cells and cancer cells, the history of experimental radiotherapy is the story of a search for methods to destroy the tumor cells without destroying the cells that make up the normal tissue around them and that will inevitably be irradiated in the process. This search has been considerably advanced by basic studies of the effects of radiation on cell survival (reproductive capacity). Loss of reproductive capacity is most satisfactorily studied in cultures of continuously dividing cells (i.e., HeLa cells, Chinese hamster cells, and mouse L cells), but similar experiments can be performed on the cells of certain organs *in vivo.*

Repair of Sublethal Damage

Following irradiation of cells *in vitro* or *in vivo* with different single doses of x-rays, a characteristic dose–response curve is generated (Fig. 1). There is an initial shoulder reflecting low doses, followed by a portion in which the fraction of cells that survive (divide) is inversely related to the dose. The initial shoulder indicates that a certain amount of radiation damage must be accumulated by cells for a lethal effect. This phenomenon is known as repair of sublethal damage. Above a certain threshold, reproductive death is a direct function of the dose absorbed. The amount of sublethal damage that can be repaired has been measured for many cell types, and there are techniques by which it can be measured *in vivo.* It has approximately the same value in many tissues and tumors *in vivo* and is equivalent to that produced by a notional dose (Dq) of 300 to 500 rads of x-rays (see Fig. 1); values for lung tissue also lie in this range. Furthermore, the survival curve following a second dose of x-rays given long enough after the first has the same shoulder as the first, indicating that sublethal damage must again be accumulated, and to the same extent, for a lethal effect. The phenomenon can be repeated indefinitely. The molecular mechanism of repair, like the mechanism of damage, is incompletely understood, but experiments in which the second dose follows the first by different times show that repair takes place rather quickly, within the first 4 to 6 hr and certainly within 24 hr. The fact that repair can be partially inhibited—for example, by low temperature—suggests it is a result of the activity of the cell's machinery. The implications of the repair phenomenon in the clinical situation are clear: the smaller the individual fractions, the larger is the total dose that can be administered in the course without destroying the organ, provided the fractions are separated by enough time for repair. Why a larger total dose in many fractions is good for the host cells and bad for the tumor cells may be related to the oxygen effect.

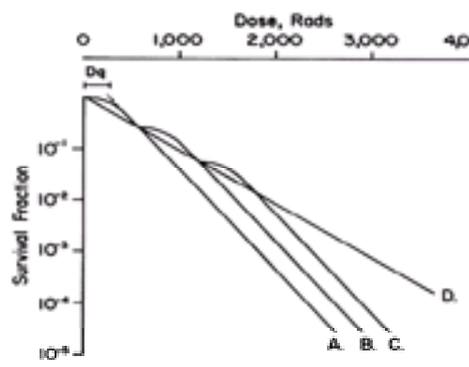

FIG. 1. Typical survival curves of cells in culture. Curve A represents survival (ability to reproduce) following various single doses of x-rays. The initial shoulder is due to sublethal damage, whose amount (Dq) can be calculated by extrapolation to the horizontal axis *(dashed line).* Curve B shows the effect of a second exposure on a culture previously exposed to 600 rads, and curve C the effect of a third such exposure. The line D is the resultant effective survival after successive 600-rad fractions. In this example, a single exposure to 1800 rads would reduce the proportion of surviving cells to less than 10 whereas the same total dose in three equal fractions would reduce the proportion to only 10 - 2, illustrating the sparing effect of dose fractionation.

Oxygen Effect

That ionizing radiations are more damaging to a well-oxygenated target has already been mentioned. This is well demonstrated in survival curves (Fig. 2), which typically show less reduction of reproductive potential of cells *in vitro* that lack oxygen at the time of irradiation. Tumor cells are quite likely to be poorly oxygenated because cells toward the center of the tumor are separated from their blood supply. In fact, tumor cells more than 150 to 200 m from stroma are likely to die of anoxia. Adjacent to the area of necrosis will be many tumor cells that are so poorly oxygenated that they will be relatively radioresistant; only at the periphery of the tumor will the cells have the same radiosensitivity as the surrounding stroma. X-irradiation will destroy the well-oxygenated cells at the periphery of the tumor, thus bringing the hypoxic cells closer to the blood supply at the periphery and rendering them more susceptible in turn. Fractionation of the total dose of x-rays thus “reoxygenates” the more isolated hypoxic tumor cells while minimizing the lethal damage in normal stromal cells. This is particularly important in the lung, which is the best oxygenated of all tissues. It also explains why small tumors (which have a relatively large surface of well-oxygenated cells) are more likely to be amenable to x-ray control than large ones and why there is an interest in pharmacologic agents that sensitize hypoxic cells to x-rays.

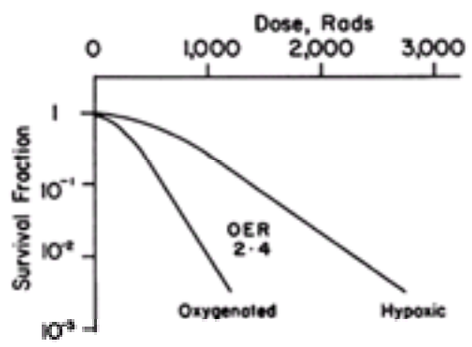

FIG. 2. Survival curves of cells in culture following exposure to various single doses of x-rays under hypoxic and oxygenated conditions. After each dose of x-rays, survival in the culture that was hypoxic at the time of exposure is 2.4 times greater than in the culture that was well oxygenated at the time of exposure. The oxygen enhancement ratio (OER) in this example is 2.4, a typical value for mammalian cells exposed to 250 kVp x-rays.

Radiation Energy and Neutrons

The foregoing discussion assumes that all ionizing radiations have the same energy. X-rays have a wide spectrum of energies, however; most experiments in radiobiology were performed at energies of 250 kV or less, but current radiotherapy is almost universally performed at energies in the megavoltage range. Higher-energy radiation is more penetrating, and the oxygen enhancement effect is in general less. Because penetration and less protection from hypoxia are bad for tumor cells and less bad for normal stromal cells, it is understandable that radiotherapy should move in the direction of higher energies. Fast neutrons, depending on the way in which they are generated, have mean energies up to one order of magnitude greater than conventional x-rays and therefore offer advantages over x-rays in tumor therapy (Fig. 3). Heavier charged particles, such as accelerated nuclei, would be even more advantageous, but for economic reasons, they are most unlikely to make the transition from experimental to therapeutic medicine in the time scale of this or the next edition of this text. For the present, fast neutrons are the only practical alternative to x-rays for deep therapy; experience with them is reviewed by Field. Although they appear to offer advantages in some tumor types, their use in lung tumors has been disappointing.

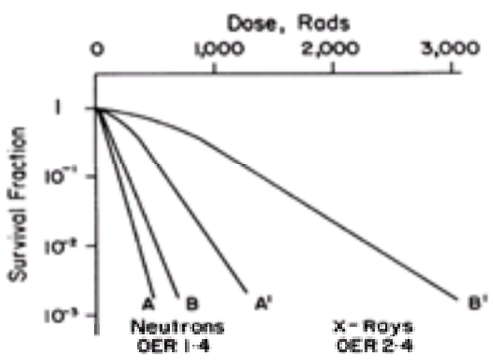

FIG. 3. Survival curves of cells in culture exposed to neutrons and 250 kVp, x-rays under oxygenated (A and A1) and under hypoxic (B and B1) conditions. Not only are neutrons more lethal than x-rays, dose for dose, but there is less sublethal damage (initial shoulder), and the oxygen enhancement ratio (OER) is less.

Units, Time, Dose, and Volume in Radiation Therapy

The unit of radiation exposure is the roentgen (R), but what matters to the patient is the amount of energy absorbed. This is a complex function of many factors, including density and thickness of the exposed tissue as well as energy of the radiation. In the case of x-rays, an exposure of 1 R to solid tissue results in an absorbed dose of approximately 1 rad, the unit of absorbed radiation. It is equal to 100 ergs absorbed energy per gram of tissue and has to be calculated on the basis of certain assumptions, tissue density, thickness, etc. It is important to note that the rad is the amount of energy absorbed per gram of tissue, so that a dose of 700 rads to both lungs is only a fraction of the energy absorbed when 700 rads is received by the whole body. The former would not produce any clinical effects; the latter would almost certainly be fatal. Another common misunderstanding is illustrated by the following: Suppose a patient received 5000 rads to a lung tumor and 5000 rads to the mediastinum. The total dose he or she has received is 5000 rads, not 10,000. The mass of tissue irradiated is thus quite as important as the dose of radiation because it is a determinant of the total energy absorbed. Because the only information that the clinician commonly receives, or takes notice of, is the total dose in rads, a unit, the megagram rad, was proposed. This is a mass integral of absorbed radiation energy and has been used in correlating dose with effect, for example, in pulmonary function. This logical unit enjoyed a brief vogue in previous years but is not widely used now. Radiation scientists and therapists now use a new unit, the Gray (Gy), which is equal to 100 rads, and current reports and treatment plans use this unit instead of the rad.

Important as the total dose is, the way in which it is delivered is as important. As Fig. 1 shows, the phenomenon of repair of sublethal damage indicates that fractionation of the total dose will minimize the damage to normal tissues. The importance of fractionation is well illustrated by a case reported by Whitfield and colleagues of a patient with breast cancer. Following mastectomy, she received 1500 rads in a single dose to the axilla and, inevitably, to the underlying lung. If this dose had been delivered in five to ten fractions, it would have been unlikely to produce any symptoms, even if delivered to the entire volume of both lungs. As a single dose, however, it produced a severe radiation reaction in the underlying lung tissue.

Biological response is thus determined to some extent by the number of fractions a total dose is delivered in. To take account of the effect of fractionation, an isoeffect dose can be expressed as the total dose modified by fractionation factors. Because much of the original work was done by Frank Ellis, the formula that relates tolerance to dose and fractionation is known by his name (the original equation has been rearranged for the purpose of this discussion):

$$\mathrm{NSD} = D \times N^{-0.24} \times T^{-0.11}$$

NSD stands for nominal standard dose; its unit is the ret (rad-equivalent therapy). Hypothetically, it is the number of rads equivalent to treatment as a single dose, but in reality, the formula cannot be extrapolated to fewer than about four fractions. It is the notional dose producing a certain biological effect, traditionally tolerance, resulting from a range of different dose-fractionation schedules. *D* is the total dose in rads, *N* the number of fractions, and *T* the overall treatment time. The Ellis formula (derived from experiments on skin) can be used to estimate the rets for tolerance in a large number of organs, including the lung. Phillips and colleagues reevaluated the exponents of *N* and *T* for the lung; in the equation form given here, they would be -0.377 and -0.058, respectively. (Actually, these will probably differ, if only to a minor extent, from one institution to another.) This formula indicates the importance of the number of fractions and, by comparison, the relatively small effect of the overall treatment time. It is used in treatment planning to calculate the total dose and fractionation to be used in irradiation of the entire lung, on the basis of the likelihood of pneumonitis. Thus, Wara and colleagues calculated that there is a 5% probability of clinical pneumonitis when 510 rets is delivered to the entire lung (Fig. 4). This dose is achieved by a wide range of alternative treatment schedules, for example, 1500 rads in 11 fractions over 20 days, 2000 rads in 24 fractions over 24 days, or 2500 rads in 38 fractions over 40 days. Each of these will have the same biological effect on normal lung but probably different effects on the tumor (because of such factors as reoxygenation). In addition, there may be regional variation in the response to irradiation, with high-grade pneumonitis more frequently being seen after treatment for lower-lobe than upper-lobe tumors in both animal and human models of study. Concomitant therapy with cytotoxic agents (see Contributory Factors) alters radiation sensitivity, adding yet another dimension.

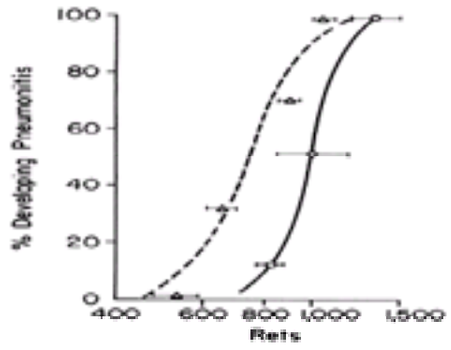

FIG. 4. The probability that pneumonitis will develop following whole lung irradiation at various nominal standard doses (rets) of x-irradiation, with (—D—) and without (-O-) concurrent actinomycin D therapy. (Redrawn from W. M. Wara et al. *Cancer* 1973;32:547. Reproduced from NJ Gross. Pulmonary effects of radiation therapy. *Ann Intern Med* 1977;86:81, with permission.)

The Ellis formula applies, of course, to x-rays. The search for an equivalent formula for neutrons has been reviewed by Field; the exponent of *N* for neutrons is now -0.04. The greatly diminished weighting of the fractionation factor in fast-neutron exposure would be expected from the fact that repair of sublethal damage is much less following neutron exposure (see Fig. 3).

It should be apparent from the foregoing discussion that a great many factors determine the amount of biological damage inflicted on the tumor and the normal

surrounding tissue by ionizing radiation and that all these factors have not been brought together into a single universal expression. There are also a number of assumptions and estimates about individual geometry and tissue density that will have to be made for each patient by each radiotherapist, with inconsistent degrees of success. Such judgments vary with the experience and knowledge of the therapist and must entail a degree of error. Add to these such imponderable factors as errors in localization and field placement, and radiotherapy appears to resemble a thunderbolt with Zeus not completely in control.

PATHOGENESIS OF RADIATION PNEUMONITIS

Histopathologic Cellular Effects

The major clinical effects of lung irradiation are conventionally divided into two stages: radiation pneumonitis and radiation fibrosis. Although the relationship between these is discussed in more detail later (Clinical Syndromes Following Lung Irradiation), we can regard pneumonitis as the episode during which the specific effects of lung damage are expressed, and fibrosis as the subsequent wound-healing phase. Death from radiation of the lungs almost invariably occurs during the time of pneumonitis, 80 to 160 days after treatment. Beyond this time frame, death from radiation itself is uncommon. Moreover, inhibition of collagen synthesis (i.e., fibrosis) does not greatly reduce mortality in irradiated rats, indicating that fibrosis is not a factor in mortality from lung irradiation. Consideration of the pathogenesis of radiation reactions in the lung therefore concentrates on the mechanisms of the acute episode of radiation pneumonitis and the events leading up to it, a process that is probably similar in humans and experimental animals.

One can regard the cellular mechanism of lung damage as being principally a result of genetic damage to lung cells, especially because it is so distant in time from the clinical sequelae. Genetic damage is primarily expressed as a loss of reproductive potential leading to depletion of that cell type in the tissue. The damage sustained by an organ will therefore reflect the reproductive activity of its constituent cells and be expressed when a critical level of certain crucial cell type(s) is reached. In tissues where reproductive activity is minimal, typically highly differentiated tissues such as muscle, a large amount of genetic damage will remain latent; muscle cells have no mitotic future and thus proportionately little likelihood of expressing their genetic damage; such tissues appear to be radioresistant. Rapidly dividing tissues composed of stem cells such as bone marrow and intestinal crypt cells will express their genetic damage as soon as they reveal their incapacity to produce fully functional progeny at the rapid rate required by those organs. Such tissues appear radiosensitive. The principle that radiosensitivity varies directly with the rate of proliferation and the number of future divisions to maturity and inversely with the degree of morphologic and functional differentiation of a cell type was expounded in 1906 by Bergonie and Tribondeau. Much subsequent work has confirmed this general principle.

Discussion of the cellular basis of radiation pneumonitis can begin, therefore, with consideration of the turnover of cell types in the respiratory tract. The data that exist have been reviewed and are quite variable. The cells of the airways make up 10% to 15% of the total lung cell complement if neural, blood, and lymphatic cells are excluded. Turnover rates of individual airway epithelial cell types have not been measured, although these cells are all presumably derived from bronchial basal cells. For the airway epithelium as a whole, a turnover time (100% replacement of the population) has been estimated at 1 to 3 weeks. Bronchiolar epithelium turns over more slowly than bronchial epithelium.

The cells of the lung parenchyma make up 85% to 90% of the total lung complement, of which only a small fraction are alveolar epithelial cells, types I and II pneumocytes. Type I pneumonocytes provide over 90% of the alveolar epithelial layer; their complex three-dimensional structure (a single cell will often form the epithelium of two and possibly more adjacent alveoli) makes it practically certain that they cannot divide. They are fixed postmitotic end cells incapable of mitosis in growth or regeneration. Type II cells, in contrast, undergo mitosis at a slow rate; their turnover time in growing rodents is 4 to 5 weeks, but in response to injury such as exposure to high oxygen concentrations, oxides of nitrogen, or radiation, they can revert to a rapid reproductive cycle, repopulate the alveolar epithelium, and subsequently redifferentiate into type I cells. Thus, in addition to its important and well-known function in the synthesis and secretion of surfactant, the type II cell acts as a stem cell for the alveolar epithelium, capable of replacing alveolar epithelium when type I cells are destroyed.

Capillary endothelial cells comprise about a third of all lung cells. Like type I cells, they have an extended cytoplasm, but unlike type I cells, they are in a continuous process of self-renewal. Their turnover time has been estimated at 8 weeks; however, in regenerating lung they appeared to have the same mitotic activity as type II cells.

Pulmonary mesenchymal cells make up the bulk of total lung parenchymal cells but are themselves a heterogeneous group, at least some of which are fibroblasts and macrophage precursors. No figures are available for their turnover rate. Alveolar macrophages form another small but important sector of the population with interesting origins. The cell type is almost certainly derived from the bone marrow via the circulating monocyte. The monocyte leaves the circulation and enters the interstitial space. There it divides one or more times, possibly even residing as a stem cell, and differentiates into a tissue macrophage. In the lung, this process entails an increase in size as well as the development of an appropriate complement of lysosomal hydrolytic enzymes. The differentiated macrophage leaves the interstitial space and appears fully fledged in the alveolar space. There it performs its important defense functions, ultimately to bow out either via the mucociliary escalator or, less probably, via the pulmonary lymphatics. The turnover rate of macrophage precursors in the interstitium is not known. Their turnover time in the alveolar space is about 1 week, but this is due to traffic through the alveolar space rather than division therein.

Nearly all the preceding data have been derived from small mammals that grow continuously from birth to death. The cytokinetics in adult human lungs may therefore be different. From these data it appears that prime targets for radiation damage would be, in order of reproductive rate, the epithelial cells of the airway, the type II and capillary endothelial cells, and the interstitial macrophage precursors. The histologic and other evidence of radiation damage given below accord to some extent with the reproductive activity of cell types in the lung. However, the disproportionate degree of damage sustained by capillary endothelial and type I alveolar cells suggests that there is considerable nongenetic damage in these cells. This possibly results from their very extended cell processes, regions not richly endowed with organelles and in which repair or replacement of damaged nongenetic macromolecular structures such as cell membrane is limited.

Cytokinetic Studies

In the lung, the long latent interval between irradiation and the occurrence of radiation pneumonitis some months later strongly suggests that critical depletion of a crucial cell type is the mechanism of pneumonitis. Because type II cells and capillary endothelial cells are undergoing constant replication (albeit usually at a slow rate), they are thus both candidates for radiation damage. Endothelial cells have been shown to be sensitive to ionizing radiation; in fact, the radiosensitivity of capillary endothelial cells in an organ has been viewed as the limiting factor in radiation tolerance of that organ. Both capillary endothelial cells and alveolar type II cells perform crucial functions in the lung, the failure of which could conceivably produce the changes associated with radiation pneumonitis. However, a complete explanation of radiation pneumonitis in terms of the depletion of either of these cell types has proved elusive. Relatively little is known about the number of these two cell types following irradiation of the lungs because the systematic morphometric analysis of lung cell types following radiation has not yet been reported in detail. However, recent reports suggest there is a general depletion in all cell types 12 weeks after x-irradiation.

Relevant information also can be obtained by cytokinetic studies. The incorporation of precursors of DNA into the nucleus of a cell is evidence of imminent mitosis, and the proportion of cells in that population that are about to enter mitosis, the labeling index, indicates the replicative activity of that cell type. Cytokinetic studies on lung cells following small doses of radiation to the thorax show mitotic arrest in all cell types in the first week after irradiation. Following this, the labeling index of capillary endothelial cells rises severalfold above control levels for a few weeks and then gradually declines to control levels. The labeling index of type II cells also rises above normal levels after the first week and returns to baseline some 4 weeks later. However, from about 6 weeks on, it begins a steady climb to levels about four- to sixfold above normal throughout the period when pneumonitis is occurring. It is therefore difficult to imagine how significant depletion of either endothelial cells or type II cells could occur unless their loss through death also was accelerated. For the latter, there is no evidence. Thus, an explanation of radiation pneumonitis in terms of classic concepts of radiobiology has not been successful, at least with respect to either type II cells or capillary endothelial cells. Some other crucial cell type may become depleted and be responsible for radiation pneumonitis, but this has neither been suggested nor ruled out.

Nevertheless, there is some radiobiological evidence to implicate type II cells and exonerate endothelial cells as the target in radiation pneumonitis. Butylated hydroxytoluene (BHT) has been used to selectively expose various lung cell types to radiations. Administration of BHT in mice results in a brisk inflammatory response in the lungs, during which type II cells are the predominant proliferative cell at 2 days. At 6 days, the proliferative response resides mainly in the interstitial cells and capillary endothelial cells. Thus, irradiation at either 2 or 6 days should intensify the damage to type II cells or interstitial and capillary endothelial cells, respectively. Irradiation at 2 days only resulted in enhanced radiosensitivity, reducing the mean duration of survival from about 170 days to about 30 days and reducing the median lethal dose (LD_{50}) from 9.5 to 2.7 Gy. Irradiation at 6 days had no such effect and actually increased the LD_{50} as compared to control mice not treated with BHT. This result argues in favor of the type II cell, and not the interstitial cell or capillary endothelial cell, as being the target for radiation pneumonitis, although it is possible that another unidentified cell type may have been stimulated to proliferate at 2 days and therefore was responsible for the enhancement of radiosensitivity following irradiation at that time.

Similarly, corticosteroids have been found to reduce the mortality of radiation pneumonitis (below). As they increase the replicative rate of type II cells in irradiated mice, it may be that their activity is functionally deficient in radiation pneumonitis (in the absence of corticosteroid stimulation). However, corticosteroids have many other effects on the lungs, for example, antiinflammatory effects (see below), and it may be that one of these other effects explains their protective role in radiation pneumonitis.

Biochemical Effects

Lipid studies are of interest because of the superficial resemblance between radiation pneumonitis and adult respiratory distress syndrome (ARDS) and because of histologic abnormalities in alveolar type II cells in the early stages of pneumonitis. Biphasic changes in lung total lipids of rats have been found in the first week after thoracic irradiation. Subsequent changes were not statistically significant, but the dose of x-rays, 800 rads, was well below that required to produce pneumonitis.

A transient increase in the content of lecithin has been noted in both lungs and alveolar fluid between 1 and 8 weeks after irradiation, and incorporation of precursors was probably constant throughout. These changes result from proliferation of type II cells, possibly as part of the regeneration of alveolar epithelium. At the stage of pneumonitis, 16 weeks after irradiation, the content of most phospholipids in the lung was increased up to 50%, and this increase was probably associated with increased phospholipid turnover. These changes were reflected in the alveolar lavage fluid; the degree of saturation of lecithin was normal throughout. These results do not suggest that radiation pneumonitis is associated with an abnormality of the surfactant system. Administration of corticosteroids from 2 to 3 weeks before the expected onset of pneumonitis further increased the phospholipid content of alveolar lavage fluid, increased the rate of incorporation of precursors into phospholipids, and normalized the surface tension properties of alveolar surface lining layer, both *in vitro* and *in situ.*

To identify patients at higher risk for radiation pneumonitis, a model was utilized that evaluated the production of free radicals in lipids after radiation exposure by measuring serum desferrioxamine-chelatable iron (free radical scavenger) and the percentage molar ratio of 9,11-linoleic acid and 9,12-linoleic acid (as an index of oxidation). After one week of radiotherapy, the group of subjects later developing pneumonitis exhibited significantly higher levels of desferrioxamine iron and a greater change in percentage molar ratio. This suggests that these assays might be useful indicators to identify patients more likely to develop radiation pneumonitis at a later time.

Coincident with pneumonitis, there is a five- to tenfold increase in microvascular leakage of plasma proteins into the interstitium and alveolar space, resulting in a chronic form of pulmonary edema. The amount of protein leakage is related to the dose of radiation, and its duration corresponds to that of pneumonitis. This probably explains the fall in lung compliance during pneumonitis. Corticosteroids had almost no effect on the amount of microvascular leakage, but mortality was substantially reduced. One speculates, therefore, that the steroid-mediated increase in surfactant phospholipids described earlier has a protective effect by promoting surfactant synthesis and delivery to the surface lining layer in sufficient amounts to counteract the inactivation or desorption of surfactant by plasma proteins. On the other hand, the beneficial effects of corticosteroids may be unrelated to surfactant production and may instead be secondary to some other action such as their antiinflammatory effect.

A cardinal feature of radiation pneumonitis is a fall in lung compliance that can be attributed to stiffness of the air–fluid interface of the alveolar lining. This may in turn be attributable to the leakage of plasma proteins into the alveoli with deleterious effects on the surfactant system as described above, a feature that radiation pneumonitis shares with any other forms of ARDS. It has now been shown that normal alveolar surfactant exists in several structural subtypes with different surface-active properties. The higher-density surface-active forms evolve into a lower-density form that is not surface active. The distribution of surfactant among these subtypes is greatly altered in radiation pneumonitis. Moreover, the metabolic evolution of surfactant subtypes, which is dependent on a unique serine protease that is secreted by the alveolar epithelium, is delayed in radiation pneumonitis. This may be the result of an 18-fold excess of a_1-antitrypsin (a serine-protease inhibitor) in the alveolar compartment that accompanies the microvascular leakage that characterizes this and other forms of ARDS.

Inflammatory Mechanisms

Following radiation to the lung there is an increase in the synthesis of prostaglandins and thromboxane, whereas in radiation pneumonitis there is an increase in the number of lymphocytes, possibly activated, in the bronchoalveolar lavage fluid. Experimental whole-body radiation results in early effects on cyclooxygenase products.

Phillips and co-workers were the first to show that corticosteroids reduced the mortality of experimental radiation pneumonitis, even when given many weeks after irradiation. Corticosteroids administered continuously to mice from 10 weeks after lethal thoracic irradiation substantially reduced mortality. However, if the corticosteroids were withdrawn during the period when pneumonitis was normally occurring, mortality increased and caught up with the mortality rate in the absence of corticosteroid administration. The protective effect of corticosteroids ceased after the time when pneumonitis normally occurs. Their effect, therefore, coincided with the phase of active radiation pneumonitis.

The inflammatory effects of irradiation can possibly be modulated by g-interferon. Lung lavage fluid cellularity and protein content were monitored in treatment and control groups of animals. After 35 days, animals that were irradiated but did not receive g-interferon had elevated protein and macrophage counts, whereas treated and irradiated animals did not vary significantly from unirradiated controls.

Studies carried out over 6 months after irradiation of rats are relevant to the mechanisms of late radiation damage. Among the findings were that prostacyclin (PGI^2) production by the irradiated lung increased progressively from a normal level at 2 months to a level two to three times higher than normal at 6 months. Coincident with this, there was a reciprocal decrease in perfusion of the irradiated lung. Because PGI^2 is a potent vasodilator and antithrombotic agent, the increase in its production is interpreted as consistent with a homeostatic response to impaired perfusion in the irradiated lung.

An alternative approach has been to study the effect of various antiinflammatory agents on mortality from experimental radiation pneumonitis when given well after irradiation but just before the time when pneumonitis normally occurs. The effect of corticosteroid administration is described above. The effects of a variety of agents that have more specific effects on arachidonate metabolism have been reported. In general, lipoxygenase inhibitors and leukotriene-receptor antagonists were markedly protective, more so indeed than corticosteroids. Cyclooxygenase inhibitors had variable effects; aspirin reduced mortality in a dose-dependent fashion, indomethacin markedly increased mortality, and other cyclooxygenase inhibitors had intermediate effects. These data were interpreted as suggesting that the protective effect of corticosteroids could be attributed to their antiinflammatory effects. They suggest that the mortality of radiation pneumonitis results from activity of the 5-lipoxygenase pathway and raise the possibility that clinical radiation pneumonitis can be mitigated by inhibitors or receptor antagonists of this pathway. This possibility has yet to be clinically tested.

PATHOGENESIS OF RADIATION FIBROSIS

The supposition in the past has been that radiation fibrosis was the natural consequence of lung damage expressed as pneumonitis. This is less clear now because of an apparent dissociation between some of the features of each. The connective tissue of the lung has been studied following x-irradiation both as a model of lung fibrosis and to determine the role of fibrosis in radiation reactions. Although the collagen content of the lungs is probably increased at the time of radiation pneumonitis, the increase at much later times is considerably greater, evidence that fibrosis is unlikely to play a major role in the pathogenetic mechanisms of pneumonitis.

One mechanism for the development of fibrosis is a progressive decrease in plasminogen activator activity that begins 1 to 2 months after lung irradiation. According to this hypothesis, the fibrinogen that leaks into the interstitial space as a result of radiation damage to the capillary endothelium, and is deposited as fibrin, is not adequately lysed by tissue fibrinolytic activity. The fibrin deposits act as foci for fibroblast stimulation and collagen secretion. Intricate cytokine and genetic pathways influencing fibroblast and fibrocyte maturation are well described. The ability of irradiation to induce a rapid and early maturation of fibroblasts as a result of genetic damage along with the enhanced production of cytokines by macrophages and type II pneumocytes has been substantiated. These stimuli together lead to an altered fibroblast-to-fibrocyte ratio, with an excess of fibrocytes favoring an increase in the production of collagen, leading in turn to fibrosis. Reduced fibrinolytic activity has also been demonstrated in irradiated lung and is caused by reduced plasminogen activator activity. Plasminogen activator is a product of both endothelial cells and alveolar macrophages. Either or both of these cells may be implicated in radiation fibrosis because endothelial cells irradiated *in vitro* exhibit impaired release of plasminogen activator and alveolar macrophages lavaged from irradiated rat lungs exhibit a time- and dose-related decrease in plasminogen activator activity.

The development of fibrosis in the lungs has been altered by a number of agents that affect collagen metabolism: triiodothyronine, colchicine, and b-aminopropionitrile. However, the best-studied agent is D-penicillamine, a reversible inhibitor of collagen cross-linking and maturation. Administration of D-penicillamine after irradiation of the rat hemithorax moderated late fibrosis in terms of histopathology, hypoperfusion, collagen accumulation, and lethality after 180 days, the latter being the conventional end of pneumonitis mortality. It also moderates the decrease in both angiotensin-converting enzyme and plasminogen activator activity described earlier. D-Penicillamine has been used in a number of other disorders in humans, but it has not been given prospective trials in patients undergoing radiation therapy to the lungs.

HISTOLOGIC CHANGES

Animals

The nature of radiation reactions in the lungs has been most often studied by microscopy. This is presented in summary form in Table 1. Changes are present at some

time in virtually every structure within the thorax; therefore, only the main features are discussed.

Site	Immediate or early (0–2 months)	Intermediate (2–6 months)	Late (6+ months)
Capillaries	24 hr: Vacuolation of endothelial cells. 2–7 days: Marked endothelial cell changes, separation from basement membrane, sloughing, obstruction of lumen with debris and thrombi, or normal. 1+ month: Many capillaries swollen and obstructed	Marked abnormalities with widespread obstruction by platelets, fibrin, and collagen. Capillary regeneration	Loss of many capillaries and regeneration of new ones
Type I pneumocytes	Early degenerative vacuolation, death, and sloughing, or normal	Decreased number	Further decrease in number
Type II pneumocytes	Early morphologic changes or normal redifferentiating into type I cells	Large increase in size and number, abnormal appearance	Return to normal size and number
Basement membrane	Early swelling, indistinct and later very irregular	Folded and thickened	Folded and thickened
Interstitial space	Edema and debris infiltrated with inflammatory cells and mast cells; slight increase in connective tissue	Infiltrated with mast cells, mononuclear cells, inflammatory cells, and collagen	Few inflammatory cells; large increase in collagen
Alveolar space	Fibrin, hemorrhages, and debris; increased number of alveolar macrophages, morphologically abnormal	Becoming smaller	Small, obliterated in places; distortion in architecture
Airway epithelium	Early transient inflammatory reaction, ciliary paralysis, increase in goblet cells, or normal	Epithelial proliferation	—

TABLE 1. *Pulmonary effects of radiation: Histologic changes in animals*

It seems clear that damage to capillary endothelial cells is a consistent and significant feature. There is some disagreement as to when this first appears, either within hours in the form of vacuolation and blebs in the extended cytoplasmic processes or several weeks later. An early increase in capillary permeability suggests a functional lesion, even if it cannot be seen. Within a few weeks at most, the endothelial cells look definitely sick, raised from the basement membrane in some places and attenuated in others. Some cells are sloughed, leaving a denuded basement membrane and choking the lumen with debris and platelet and fibrin thrombi and, subsequently, collagen. Obstruction of the microvasculature is widespread. Arteriolar and arterial lesions resembling an immune vasculitis may be present. Around the damaged vasculature there is edema, cellular infiltrate, and possibly the beginnings of collagen deposition. Within about 6 to 10 weeks, there is evidence of repair. Some capillaries are recanalized, and new capillaries enter adjacent tissues, although perfusion probably remains reduced and permeability is increased (see Physiological Changes). Endothelial lesions are, in fact, a common feature following x-irradiation in many organs; indeed, many consider the endothelial damage to be the single or most important factor that determines the radiation tolerance of an organ. Evidence of damage to the basement membrane that subtends the vasculature may also be important in view of its role in providing a scaffold on which regeneration occurs and without which architectural reconstruction is abnormal.

Coincident with the endothelial changes are alveolar epithelial changes that may or may not be as functionally significant. Early vacuolation and blebs are seen by some in the type I pneumonocytes, which, like endothelial cells, are probably shed from the basement membrane, cluttering the alveolar space with debris. Infection in experimental rodents may have something to do with these early changes. Unlike endothelium, alveolar epithelium appears to have regenerative potential. Experiments in which damage to type I cells has been inflicted with such diverse agents as NO^2, oxygen, and bleomycin, as well as x-rays, indicate that the alveolar epithelium can be repopulated by type II cells that subsequently redifferentiate into type I cells. The large increase in the size and number of type II cells may reflect their role in regeneration of the alveolar epithelium. These cells appear to be relatively radioresistant by comparison with endothelial and type I cells. Nevertheless, the fact that they are stem cells and have important secretory functions warrants suspicion that they may play a role in the pathogenesis of radiation pneumonitis, as already discussed.

Some other features of the histologic changes are mentioned briefly. Cellular activity in the alveolar septum (interstitial space) is present early after irradiation: increased numbers of mast cells and mononuclear cells. There appears to be a paucity of acute inflammatory cells, although occasionally a brisk inflammatory response has been seen. Fibroblast activity can be seen within the first 2 months, when all the changes previously noted are at their height, but little collagen is laid down until about 6 months. At a later stage, dense fibrosis of alveolar septa dominates the histologic picture.

Little attention has been paid to the airway epithelium. The relatively rapid turnover of its cells, noted previously, would suggest early and extensive damage. This has only rarely been observed, however.

In summary, there are no characteristic histologic features; lesions in all cell types have been reported, but damage to capillary endothelial cells and alveolar epithelial type I cells is fairly consistent. These changes can be found in damage from a wide variety of physical and chemical agents.

Humans

The picture in humans is complicated. Early and serial samples are not, of course, available, but at a late stage the dense fibrosis is entirely nonspecific. Again, material obtained at autopsy is likely to show superimposed changes from terminal heart failure or infection and postmortem artifacts. Changes in virtually all pulmonary structures have been reported in material obtained 4 to 12 weeks after completion of radiotherapy. As in the experimental studies, vascular damage is present. Arteriolar lesions are, however, more commonly mentioned. Changes in the alveolar epithelium are also present. Atypia, hyperplasia, sometimes bizarre, and desquamation into the alveolar space are noted, as well as other debris in the alveolar space and fibrin-rich exudate or hyaline membranes. Some observers considered them to be one of the most common and persistent of the abnormalities seen. Although animal studies frequently indicate abnormalities in the alveolar space, hyaline membranes as such are not reported. Possibly they are a terminal feature or secondary to other pathologic developments in humans.

The interstitial space is frequently thickened by edema and hypercellular because of a mononuclear infiltrate. A variable excess of collagen may be present, but inflammatory cells are usually absent. At 4 to 12 weeks after completion of a course of radiotherapy, abnormalities may be present in the airway walls. These include focal necrosis and squamous metaplasia.

Again, it can be seen that there is little that is characteristic about the histologic appearance in radiation pneumonitis. This is unfortunate because one of the more common clinical problems in diagnosis is the differentiation of a radiation reaction from tumor recurrence and infection. Now that the treatment of each of these alternatives is more aggressive, and lung biopsy by one or another route is so readily available, criteria for their differentiation would be most useful. Some criteria that have been suggested for diagnosis of radiation pneumonitis are (1) the presence within the sample of regions of greatly varying pathologic changes and (2) a combination of atypical alveolar epithelial cells, vascular changes, and widespread hyaline membrane formation. Possibly the absence of much evidence of inflammation and the presence of mast cells adjacent to regions of capillary damage can be added to the preceding features. It is highly unlikely that reactions will be found outside the irradiated regions, although there may be exceptions (see Associated Complications). A precise knowledge of the field placement and biopsy site is thus important.

Six months or more after the completion of a course of irradiation, the major abnormality is the huge amount of fibrosis interspersed with obliteration of alveolar spaces and vasculature, a picture that resembles end-stage lung damage of any etiology.

OCCURRENCE

It is difficult to assess how commonly radiation reactions occur in the lungs. No prospective studies have been performed to our knowledge, although in some studies this complication of treatment had obviously been anticipated in the investigative protocol and is reported in the subsequent publication. Published reports necessarily represent a population of patients highly selected by factors such as interest, awareness, and technique. The evolution of radiation therapy itself accounts for another factor of uncertainty. The trend toward more energetic and penetrating radiation deposits more energy in the lung and less in superficial tissues, but at the same time, dosimetry and field placement have become much more sophisticated. These and other technical factors are constantly evolving. Another difficulty in determining the occurrence of radiation reactions is semantic: some authors, particularly in the radiology literature, use the term radiation pneumonitis to denote a roentgenographic appearance; by others, particularly clinicians, it is used to denote the clinical syndrome, which is probably less common. Occasionally, the term is used without attempt at definition or distinction between pneumonitis and fibrosis. In fact, occurrence rates from 0% to 100% have been reported, raising the question of whether any incidence data are meaningful without definition of technical, clinical, and roentgenographic factors.

The principal conditions for which radiotherapy may expose the lungs to radiation are breast cancer, lung cancer, Hodgkin's disease, and lymphoma. The lungs may be exposed in treatment of other tumors such as cancer of the esophagus, but data are scant. The figures given below are based on selections from the literature that seem to provide some guide to occurrence in the era of megavoltage therapy.

Breast Cancer

The technique of tangential therapy of breast cancer minimizes damage to underlying lung, although wound healing, rib fractures, and chest wall necrosis are

correspondingly more troublesome. The occurrence of roentgenographic changes in the lungs adjusted for numbers in each series is about 45%. The proportion of the total who had symptoms that may have represented radiation pneumonitis was 10%. Fatal reactions were not reported.

Lung Cancer

Although in lung cancer patients the occurrence of each of the radiation reactions is similar to that seen in patients with other malignancies, the incidence of lung cancer is extremely high (about 150,000 new cases per year in the United States). Because the majority receive lung irradiation at some stage, this group forms the largest portion of the population with potential or actual radiation damage.

Hodgkin's Disease and Lymphoma

Close cooperation between clinicians and radiation therapists in a number of large study groups has contributed to technical improvements in the treatment of Hodgkin's disease and lymphoma. A search for factors identifying patients at higher risk for radiation pneumonitis was undertaken by retrospectively evaluating 24 series of patients with over 1900 total subjects. The overall incidence of radiation pneumonitis was found to be 7.8%. Multivariate analysis suggested that fraction sizes greater than 2.67 Gy, once-daily dosing, and the total dose of radiation were associated with an increased risk of radiation pneumonitis. Field shaping (to fit the tumor) and field reduction during the course of treatment minimize the amount of normal lung exposed as it is brought into the field by the rapid reduction in size of the tumor mass.

The three malignancies just discussed contribute nearly all the cases of radiation reactions in the lungs. The figures in Table 2 indicate that roentgenographic changes are common in the early stage. Only a proportion of patients, maybe up to 15%, have clinical radiation pneumonitis, still a very large number. A small percentage of the total will die of radiation pneumonitis. In view of the number of patients who receive lung irradiation, radiation pneumonitis is a clinical problem of considerable size.

Primary diagnosis	Roentgenographic changes[a]	Clinical features[a]	Fatality due to radiation pneumonitis[a]	Roentgenographic changes of fibrosis[a]
Breast cancer	24.5	8		57
	20	13		60
	56	14		
	70	5		
	87			
Lung cancer	13 at 3 months	4.6	5	66 at 12 months
	33 at 6 months	15	2	100 at 30 months
	6	3	0.7	100
	100	5		
Hodgkin's lymphoma	65	0.4–33[b]	0.25–5.9[b]	65
		5		

[a] Figures are percentages of total number of patients in the series.
[b] Higher figures refer to cases with contributory factors, e.g., previous irradiation.

TABLE 2. *Pulmonary effects of radiation: Occurrence of radiation reactions in the lungs (from selected reports)*

Brachytherapy and Interstitial Implantation of Isotopes

There is considerable interest in direct implantation of g-emitting isotopes into the lesion. This innovation offers improved control of the dose and field. The usual isotope is iodine-125, which has a half-life of 60 days and a small volume of irradiation. Multiple sources are inserted directly into the lesion and not removed. Radiation pneumonitis was found in 9% of 46 patients receiving brachytherapy but was attributed to the external beam radiation delivered concomitantly. Experience with this form of radiotherapy is limited, and unfavorable reactions to it are as yet uncertain.

Accidental Irradiation with Isotopes

Intrapleural administration of isotopes with b-emission, such as radioactive gold, produces a local pleural reaction only. Inhalation of dust or particles containing g-emitting isotopes can produce radiation damage. In the event of a nuclear disaster, this could be a long-term consequence. There is also a report of probable radiation pneumonitis, ending fatally, in a worker employed for 3 years in the production of radioactive luminous paint. The treatment with iodine-131 of thyroid malignancy, metastatic to the lungs, also has been associated with fatal radiation pneumonitis.

In patients being treated for inoperable hepatic tumors with intraarterial yttrium-90 microsphere infusions, five of 80 patients developed a syndrome resembling radiation pneumonitis 2 to 4 months after therapy. Technetium-labeled macroaggregated albumin studies were performed before the treatments, and the degree of intrahepatic shunt was quantified. Those who did not develop radiation pneumonitis had shunts of less than 1% to 15% with a median of 6%, whereas five of nine patients with shunts greater than 13% developed radiation pneumonitis. No patients developing radiation pneumonitis demonstrated shunts less than 13%.

CLINICAL SYNDROMES FOLLOWING LUNG IRRADIATION

Radiation Bronchitis

Courses of radiotherapy that typically call for 40 to 60 Gy take several weeks to administer and often include the central airways in the field. Dry irritant cough is very common toward the end of the course or during the next few weeks. From the cytokinetics of bronchial mucosa and the few histologic reports (see Histologic Changes), it seems conceivable that these symptoms are caused by radiation bronchitis. If symptoms are severe, the course of treatment may need to be suspended for a week or two, much as for radiation esophagitis. We are not aware of any detailed investigations into this possibility. No serious complications ensue, and treatment is symptomatic.

Radiation Pneumonitis

Radiation pneumonitis develops insidiously. Although the symptoms can sometimes be traced back to a month or so after the completion of radiation therapy, it is uncommon for the patient to present less than 6 to 8 weeks after completion unless a contributory factor is present (see Contributory Factors). Roentgenographic changes may, however, be detected in advance of this if routine x-ray films are taken (Fig. 5). A useful rule of thumb is that roentgenographic changes can be expected 8 weeks after 40 Gy to a significant volume of lung and 1 week earlier for each 10-Gy increment above 40 Gy. Roentgenographic changes generally precede clinical features but do not, of course, make them inevitable. The early appearance of roentgenographic changes or symptoms, however, generally signifies a particularly severe episode.

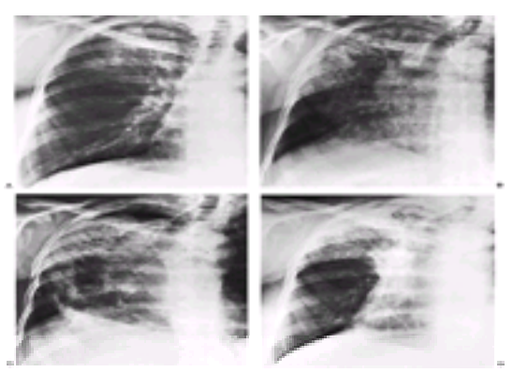

FIG. 5. Roentgenograms of a 54-year-old woman who had a right radical mastectomy for breast cancer and subsequent radiation therapy. **(A)** 3-19-73. Three weeks after completion of radiation therapy **(B)** 4-10-73. More extensive changes in parenchyma with retraction indicated by tracheal deviation, diaphragmatic elevation, and air bronchograms. Patient was symptomatic at this stage. **(C)** 4-30-73. More extensive changes of radiation pneumonitis with pneumothorax at right apex and a fluid level. Pneumothorax resolved spontaneously. **(D)** 12-11-74. Late roentgenographic appearance showing resolution of changes in mid and lower zones, radiation

fibrosis at apex, marked tracheal deviation, and mediastinal shift. (Reproduced from NJ Gross. *Ann Intern Med* 1977;86:81.)

The cardinal symptom of radiation pneumonitis is dyspnea. Mild and occurring only on exertion at first, it may progress in the course of a week or two to severe dyspnea on minimal effort or even at rest. Occasionally, the progression from mild dyspnea to severe respiratory distress may occur in only a few days, particularly if the lesion involves a large volume of lung. In our experience, these patients do badly. Other symptoms coincide with dyspnea but are overshadowed by it. Cough is common and initially dry and harsh. Small amounts of clear or pink sputum may be produced later, but purulent sputum or frank hemoptysis should be attributed to another cause. The sensation of a limitation of inspiratory capacity (doorstop sign) and fever, usually low grade but occasionally high and spiking, may be present. Vague chest pain is common but rarely troublesome unless caused by rib fracture (see Associated Complications).

The dominant physical signs are respiratory distress and tachypnea, particularly on mild effort, with or without central cyanosis. Finger clubbing may have been present because of underlying malignancy but does not develop at this stage. Examination of the chest often fails to elicit any signs. It is worth looking for the tattoo marks on the chest that radiotherapists sometimes use to outline the field and to compare these with the roentgenogram because the close correspondence between these and the roentgenographic changes is highly suggestive of a radiation reaction (see Roentgenographic Changes). However, there is no correlation between the severity of skin reactions such as pigmentation and desquamation and the presence of an underlying lung reaction. Occasionally, a pleural friction rub or rales are present over regions of pneumonitis. In a severe advanced case, features of respiratory distress syndrome with or without right-sided heart failure are present. Acute cor pulmonale is particularly ominous and usually indicates a fatal outcome. The typical course of radiation pneumonitis is protracted over several weeks or months, even if symptoms are mild. Commonly, symptoms persist for a month or more and subside even more gradually than they appeared.

The leukocyte count and red cell sedimentation rate are frequently raised, but not by very much. Blood gas studies are discussed in more detail under Physiological Changes; they commonly show arterial hypoxia and hypocapnia. Other data, such as results of enzyme studies, rheumatoid factor, and complement levels, are lacking. Pulmonary function abnormalities and roentgenographic abnormalities are discussed later; these are very likely to be present at the stage of radiation pneumonitis.

Radiation Fibrosis

Although fibrosis can be diagnosed with certainty only on histologic grounds, the term *radiation fibrosis* has come to be used in situations in which reasonable clinical grounds for it exist. Fibrosis is very likely, if not inevitable, in any region of the lung that has received therapeutic doses of radiation, whether or not radiation pneumonitis has occurred. Histologic (see Table 38-1), biochemical, and physiological evidence (see Physiological Changes) indicates that fibrosis begins as early as 2 months after irradiation and may take several months or years to become fully established. Whether or not pneumonitis was previously present, the roentgenographic features of fibrosis will gradually appear from 6 to 24 months after irradiation and will persist almost without change for the rest of the patient's life.

Clinical features are usually minimal. In a few patients—those with preexisting pulmonary function abnormalities and those who have experienced an episode of severe radiation pneumonitis—the additional burden of pulmonary fibrosis will result in chronic respiratory failure with dyspnea on effort and abnormal gas exchange. Some patients so affected may even develop chronic cor pulmonale, but this is uncommon. More likely than this is a moderate exacerbation of preexisting symptoms such as a decrease in exercise tolerance. The majority will have no symptoms at all. Physical signs, if present, are explained on the basis of contraction of lung tissue in the region of fibrosis, for example, diaphragmatic elevation, mediastinal shift in the case of unilateral fibrosis, and loss of inspiratory excursion. Finger clubbing may develop.

ASSOCIATED COMPLICATIONS

Pleural Effusion

The possibility of pleural reactions following x-irradiation is most frequently suspected when the radiation given for breast cancer, possibly because of the tangential technique. The complication has been noted in 5.5% to 14% of patients so treated.

It is important to distinguish between a malignant effusion and a reaction to radiation. Radiation-induced effusions are invariably associated with and usually appear at the same time as pneumonitis. They may persist for long periods of time. Once they appear, they usually remain stable and rarely increase in size, unlike malignant effusions. The fluid is exudative in character but not blood-stained. Pleural biopsy specimens appear normal apart from a few nonspecific changes.

The mechanism of pleural effusions following radiation is unknown, but they occur with striking regularity in experimental radiation pneumonitis.

Pneumothorax

When pneumothorax occurs, it tends to be a feature of radiation pneumonitis and is found in the same side as pneumonitis. A typical case is illustrated in Figure 5. One would anticipate problems with expansion of the lung, but most reported pneumothoraces have reexpanded spontaneously.

Infection

In addition to its well-known suppressive effects on immunity, radiation impairs clearance mechanisms. In mice there is a transient drastic reduction in the number of alveolar macrophages between 1 and 8 weeks after a single dose of x-rays to the thorax. In addition, impaired phagocytosis and killing of microorganisms have been demonstrated. Although the morphology of macrophages is altered (they become transiently much larger), their individual functional abilities (phagocytosis, etc.) are retained. Thus, increased susceptibility to infection, which is present at this stage, is probably related to the transient reduction in their number.

Data in humans are hard to find. Furthermore, there often are other factors that more potently predispose to opportunistic infection, such as lymphoreticular malignancy or combination chemotherapy. No particular organisms have been associated with infections following irradiation.

Rib Fractures

Rib fractures may occur shortly after completion of the course of irradiation. They are found within the field of irradiation and appear to be more common when radiation is given for breast cancer. Possibly this is because the technique of tangential irradiation of the chest wall delivers more radiation to the rib cage than do opposed anterior and posterior fields. For the same reason, the fractures occur independently of radiation pneumonitis. They may be single or multiple and are usually painful. They heal spontaneously, although slowly if extensive necrosis of the chest wall is present.

Pneumonitis Outside the Field of Irradiation

One of the characteristic features of radiation pneumonitis is that it is confined to the region of lung that was irradiated. Nevertheless, there are a few reports of radiation reactions well outside the field and sometimes in the contralateral lung. This unusual and unexpected occurrence has raised speculations that include obstruction of the lymphatic drainage of the lungs and the induction of autoimmunity to lung tissue. Neither theory explains why the damage should be so widespread in a small number of patients and confined in the vast majority of cases. Hypersensitivity to radiation has been suggested, particularly when a severe reaction follows an apparently small exposure.

Of 17 patients evaluated by bronchoalveolar lavage (BAL) following lung irradiation, 13 (75%) exhibited bilateral lymphocytosis, with two demonstrating a more marked response leading to clinical radiation pneumonitis. In the remaining 25%, no lymphocytosis or immune response was detected. Changes in BAL lymphocyte populations as well as increases in radiolabeled gallium uptake were demonstrated bilaterally. It is proposed that these bilateral findings result from cytokines released from $CD4^-$ helper T lymphocytes recently activated in the irradiated lung exerting their effects in a widened area, which is more consistent with a hypersensitivity pneumonitis pattern. When large numbers of patients are treated according to strictly supervised protocols and closely observed, the number of cases of hypersensitivity diminishes to a fraction of a percent. One rare instance in which abnormal radiosensitivity has been established (ataxia-telangiectasia) is discussed later (see Contributory Factors).

Radiation Carcinogenesis

It is reasonably well established in experimental animals that irradiation of the lungs enhances the formation of pulmonary metastases. The enhancement occurs briefly

and transiently after each exposure and is thought to be related to changes in vascular perfusion or permeability. The phenomenon may be of considerable clinical importance in relation to prophylactic lung irradiation and postoperative irradiation for breast cancer.

An equally important but apparently unrelated phenomenon is the late appearance of a new primary tumor in a previously irradiated lung field. Figure 6 illustrates this phenomenon. If such cases are not coincidental, one can only speculate whether the mechanism involves radiation carcinogenesis, or is related to scar cancer.

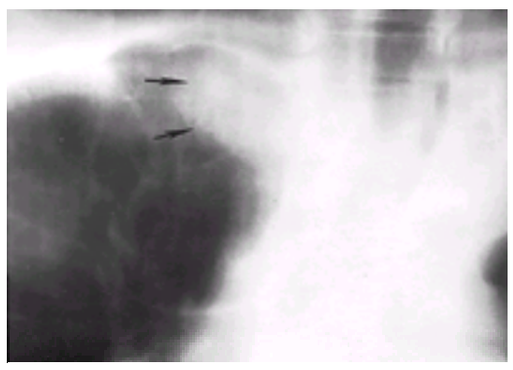

FIG. 6. Radiation carcinogenesis? The patient presented in 1968 with Hodgkin's disease of the right supraclavicular region, for which he received mantle irradiation with x-rays. Details of the treatments are not available, but the field probably resembled that shown in Fig. 8. He returned 8 years later with a lesion in the paramediastinal region of the right upper lobe, shown in this tomogram (*arrows*). The lesion was resected and found to be a primary lung carcinoma within the fibrotic region of previous irradiation. A few months later the patient was also found to have a malignant thymoma, again within the field of previous irradiation.

Miscellaneous Complications

Acute obstruction of a large airway may occur when a tumor that occupies a large portion of its lumen is irradiated. This is because of edema of the tumor and can be prevented by administration of corticosteroids during the first few days of irradiation. Such cases may be mistakenly diagnosed as hyperacute radiation pneumonitis or pneumonia.

Hyperlucency of a lung after unilateral x-irradiation has been reported. Arteriograms show this to be related to hypoplasia of the pulmonary artery without obvious obstruction of its lumen.

Secondary pulmonary effects of cardiac damage from x-rays are, of course, not uncommon, but such a discussion falls outside the scope of this chapter.

Thoracic irradiation given before lung surgical procedures appears to cause few technical problems. In some series, however, there was a much higher incidence of complications related to delayed healing in previously irradiated tissues, i.e., bronchopleural fistula and empyema. At later stages after irradiation, a surgical procedure may be technically difficult because of fibrosis in the chest wall, pleura, and lung.

Phrenic and recurrent laryngeal nerve paralysis and Horner's syndrome do not occur following conventional radiation treatment of the lungs. Spinal cord damage, however, is a complication. Necrosis and cavitation of the lung do not occur except as a result of tumors, although radiation can cause fistulas between hollow viscera. Reactivation of granulomatous disease is rare.

PHYSIOLOGICAL CHANGES

In view of the delicate balance between the structure of the lung and its function, any pathologic condition that involves more than a very small portion will likely produce detectable abnormalities in overall function. Of the considerable number of reports in the literature, those that give the best picture of physiological events in humans concern patients with breast cancer. These patients, unlike those with lung cancer and Hodgkin's disease or lymphoma, can be presumed to have essentially normal lungs before irradiation.

Two principal lesions can be identified, the vascular lesion and the mechanical lesion, with resultant effects on gas transfer.

Vascular Changes

Changes in perfusion of the lungs have been studied by means of isotopes, either ^{131}I-labeled macroaggregates of albumin or xenon-133. A decrease in perfusion has been detected in the first few hours after irradiation, particularly following large single doses. This change appears to be transient and is of questionable clinical relevance (in view of the size of the dose needed to produce it). In the period from a few days to 14 days after irradiation. Some authors reported an increase, whereas others reported a decrease, in pulmonary perfusion. A transient increase in diffusion capacity at this time supports increased perfusion. Permeability changes at this time are quite complex.

All authors have agreed that pulmonary perfusion is decreased from about 14 days on. Hypoperfusion is confined to the irradiated region and persists for a very long period, probably indefinitely. It is more marked following 15-MeV neutrons than g-irradiation. The decrease in perfusion corresponds well with the capillary damage seen histologically and bears on the blood gas changes discussed below. In animals at the stage of pneumonitis there is a marked decrease in perfusion and a marked increase in permeability of the pulmonary vasculature that results in pulmonary edema. The mechanism of this is unclear, but a modest reduction in the perfusion defect can be brought about by long-term administration of the collagen antagonist D-penicillamine.

Mechanical Changes

Studies of pulmonary mechanics in both humans and experimental animals have uniformly shown a dose- and time-related fall in static compliance following irradiation (Fig. 7). This change is first evident at about 40 days, becomes more marked at the time of pneumonitis, and persists for many years. Static compliance of the thorax is the result of the compliance of three parallel elements: the thoracic wall, lung tissue, and lung surface. Studies of excised or exposed lungs of animals showed that the fall in total compliance was related entirely to a fall in the compliance of the lung itself rather than of the thoracic wall. And this in turn was shown to result, at the stage of radiation pneumonitis, in increases in the surface tension of the alveolar surface. In fact, the alveolar fluid obtained by pulmonary lavage of irradiated mice behaves abnormally *in vitro,* and the stability of expressed lung bubbles is impaired. The abnormal behavior of alveolar fluid can be explained by the presence in the alveolar fluid of a large amount of protein of circulatory origin. It is known that extraneous protein, particularly fibrinogen, impairs surface activity. There is an alteration in the distribution of surfactant subtypes in radiation pneumonitis.

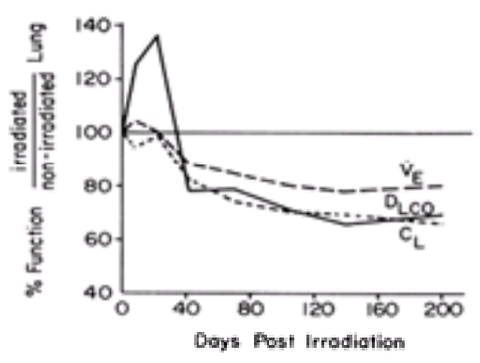

FIG. 7. Physiological effects of irradiation on one lung of dogs. Changes in diffusion capacity (D_LCO, *solid line*) compared with the preirradiation level of that lung. Changes in ventilation (VE, *long-dash line*) and compliance (CL, *short-dash title*) compared with those in the nonirradiated lung. (Redrawn from CD Teates. *J Appl*

Physiol 1965;20:628. Reproduced from NJ Gross. *Ann Intern Med* 1977;86:81.)

At later stages, low lung incompliance appears to result from development of fibrosis and a fall in static compliance of the lung tissue. This change can be regarded as permanent because it is present many years later.

Associated with the fall in lung compliance is a dose-related increase in the respiratory rate and a decrease in lung volumes, again long-lasting. Regional lung studies in patients have shown that volume loss was confined to the region of irradiation, where decreased perfusion also was present. The extent of overall changes in lung function in humans is therefore a function of the amount of lung affected by radiation. Airway resistance is normal or only minimally raised. Consistent with the fall in lung compliance, where present, the elastic work of breathing in humans is raised, and consequently, tidal volume tends to fall, and frequency tends to increase, resulting in a moderate overall increase in minute ventilation. However, decreases in lung volumes may not occur at all despite a successful response to radiation therapy.

Gas Transfer

Overall, gas transfer and blood gas changes again reflect the amount of lung affected. Within the irradiated region, perfusion changes are more severe than ventilatory changes, resulting locally in a high ventilation– perfusion ratio, little change in local gas transfer, and redistribution of pulmonary blood flow to other, unaffected regions. Where the volume of irradiated lung is small and the function of unirradiated lung is normal, overall gas transfer is not impaired, and blood gases are normal. If the volume of affected lung is large and/or the function of unirradiated lung is marginal, some abnormalities of gas transfer are found. In this situation, arterial blood gases typically show mild to moderate arterial hypoxemia with normal or reduced $P^{a}CO^{2}$, a reduced diffusion capacity for carbon monoxide, and an increased alveolar–arterial oxygen gradient. This is the most likely blood gas abnormality in patients with symptomatic radiation pneumonitis. Use of SPECT and CT scanning allows changes in local ventilation and perfusion to be determined relative to the three-dimensional dose distribution of the irradiated lungs. Standard pulmonary function testing noted a 20% decrease in vital capacity and 1-sec forced expiratory volume (FEV_1). The average reduction of local ventilation and perfusion after radiation for all patients was approximately 10% below baseline values and was greater in those with clinically evident radiation pneumonitis. Correlations were demonstrated between decrease in perfusion, decrease in FEV_1, and the presence of radiation pneumonitis. In more severe degrees of radiation pneumonitis, greatly increased stiffness (decreased compliance) of the lungs may superimpose hypoventilation on mismatching, resulting in carbon dioxide retention and severe hypoxia, but this can be regarded as a terminal effect.

Symptoms of radiation pneumonitis are therefore a function of the volume of affected lung and are attributable to changes in the mechanical properties of the lung and associated blood gas abnormalities. Where only the apex of the lung is irradiated, as in postoperative irradiation for breast cancer, the symptomatic and physiological effects will be less because ventilation and perfusion are both lower at the lung apex. It may be possible, using modern refinements of radiation techniques, to ablate the gas exchange effects entirely.

It seems probable that routine clinical tests of pulmonary function such as lung volumes, diffusion capacity, and arterial blood gas tensions could provide early warning of symptomatic radiation pneumonitis, if they were regularly performed in patients at risk.

ROENTGENOGRAPHIC CHANGES

For detailed information on radiation effects in the lungs, the reviews of Rubin and Casarett and Libshitz and colleagues are recommended. As shown in Table 2, roentgenographic changes are very commonly seen following lung irradiation, more commonly than symptoms. They are also present before the clinical episode that may or may not subsequently occur.

The commonly recognized roentgenographic changes are first seen 4 to 8 weeks after completion of radiotherapy, possibly as much as 2 to 3 weeks before symptoms, if the latter should occur (Fig. 8). Initially, the lesion has a ground-glass or soft appearance, and the lung markings are hazy and indistinct. As the lesion evolves, the opacification may become micronodular and harder, with linear branching streaks a centimeter or more in length. These are usually radially oriented and may resemble Kerley B lines if the lesion is peripheral. Symptomatic pneumonitis is very likely to be present if and when these features are present. In the most severe lesions, the affected region may become densely opacified as the nodules and streaks become confluent. Air bronchograms may appear within this region, and pleural and interlobar effusions may occur. The outline of the mediastinum and cardiac shadow becomes indistinct when the lesion is adjacent to these structures. A most striking feature is a marked volume loss in the irradiated region. This is particularly obvious when irradiation was unilateral, as the trachea and mediastinum shift toward the lesion; elevation and tenting of the diaphragm and narrowing of the intercostal spaces are further evidence of contraction of the lesion. Cavitation is not seen in lung tissue, although it may occur in an irradiated tumor.

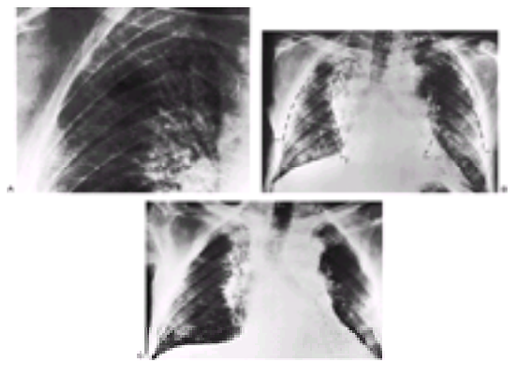

FIG. 8. Roentgenograms of a 64-year-old man with stage IIA Hodgkin's disease. **(A)** 5-15-72. Detail of right apex showing early appearance of radiation pneumonitis 5 weeks after completion of mantle irradiation. **(B)** 5-28-71. The outline of the lung shields from a treatment film (taken supine) has been traced onto a diagnostic roentgenogram (taken erect) to show the close topographic correspondence between roentgenographic changes and the field of irradiation around the lung shields. The patient had dyspnea, cough, and pyrexia at this stage. **(C)** 1-18-73. Roentgenographic changes of radiation fibrosis in the paramediastinal, apical, peripheral, and left basal regions, again corresponding to the irradiated regions of the lung. (Reproduced from NJ Gross. *Ann Intern Med* 1977;86:81.)

A cardinal feature of radiation pneumonitis is that the roentgenographic abnormality is limited sharply by the radiotherapy port (see Fig. 8). Roentgenographic changes outside the port are minor and adjacent to the port; if not caused by uncertainty of the port margins, they may be the result of scattered or oblique irradiation. Because the field of irradiation corresponds to the neoplastic lesion, the roentgenographic abnormality does not usually correspond to anatomic boundaries in the lung. It is therefore of utmost diagnostic value for the clinician to have the treatment films or at least an accurate graphic description of the ports and to observe the skin marks corresponding to the port margins. With this technical information—chronology of treatment and symptoms and evidence of the evolution of lung changes—the diagnosis of radiation pneumonitis can usually be made with confidence. As with the clinical features described, the early appearance and rapid progression of the roentgenographic lesion generally signify a more severe clinical episode.

Like the clinical episode, the roentgenographic features of pneumonitis persist for long periods, possibly months. Depending on the extent and severity of the lesion, the roentgenographic changes gradually resolve and evolve into those of radiation fibrosis. The chest roentgenogram may not stabilize in less than 1 to 2 years. The irradiated region assumes a dense roentgenographic appearance, still limited to the margins of the treatment port but often contracted and further condensed (Fig. 5, Fig. 8, and Fig. 9). There may be linear streaks extending outside the port, but these are centered on the irradiated region, with compensatory hyperinflation in the adjacent or contralateral lung. Irradiated regions may adopt a bronchiectatic, cystic, or even honeycomb appearance and may be mistaken for active pulmonary tuberculosis. Calcification of lymph nodes has been reported, but hilar node enlargement does not occur. Conventional perfusion scans of the lung, whether with ^{131}I aggregates or ^{133}Xe, show decreased perfusion of the irradiated region in the stage of radiation pneumonitis. Hypoperfusion is likely to persist indefinitely.

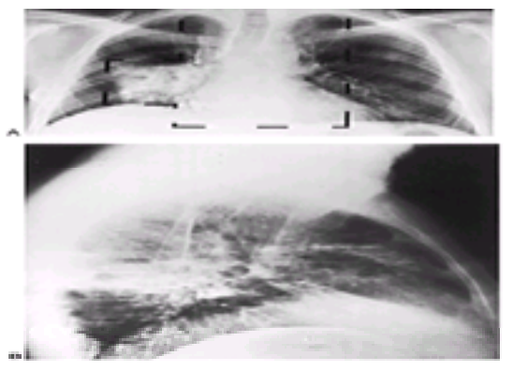

FIG. 9. Posteroanterior **(A)** and lateral **(B)** roentgenograms of a patient who initially presented with inoperable primary carcinoma of the right-lower-lobe bronchus, for which he received radiation therapy. These roentgenograms were taken on routine follow-up 7 months after therapy—the patient was asymptomatic. The outline of roentgenographic changes exactly follows the margin of the port, allowing for contraction due to fibrosis and the fact that treatment films are taken supine. The lateral picture **(B)** shows the opacity running the full depth of the lung, again corresponding to the x-ray beam. The patient received no further treatment and remained asymptomatic without roentgenographic progression of the lesion. Diagnosis: radiation fibrosis.

In summary, roentgenographic changes of some sort are more likely than not to be present following irradiation of the thorax. These are usually strictly limited to the radiotherapeutic port and may or may not be associated with symptoms of pneumonitis. In the great majority, if not all patients, the roentgenographic changes of fibrosis will become evident over the subsequent year.

CONTRIBUTORY FACTORS

The enhancement of the effect of radiation by oxygen has already been mentioned. A number of other factors with similar effect but different actions are also known. Awareness of these is clinically important in modifying treatment planning as well as in recognition of unexpected complications.

Concomitant Chemotherapy

It has been recognized at least since 1959 that administration of actinomycin D enhances the undesirable effects of radiation on the lung. At equivalent radiation doses, pneumonitis is about 30% more likely to occur in patients who receive concomitant actinomycin D therapy (see Fig. 4). In view of the more aggressive current approach to tumor management and, in particular, the combination of multiple drugs with radiation therapy in treatment protocols, the phenomenon of unfavorable interactions has become one of increasing importance.

Lamoureaux reported a small number of lung cancer patients randomized into two groups. One group received mechlorethamine, procarbazine, and vincristine concurrently with radiation therapy; the other received radiation only in the same dose and schedule. All five of the chemotherapy patients had symptomatic radiation pneumonitis as compared to only one of the six patients in the nonchemotherapy group. Which of the three drugs was responsible for enhancing the effects of radiation is uncertain. In the nervous system, vincristine has been implicated, and the experiments of Phillips' group, discussed below, are consistent with such an effect in the lungs. Einhorn and colleagues reported severe radiation pneumonitis in five of 13 patients who received concomitant chemotherapy; three of these cases were fatal. Chemotherapy consisted of bleomycin, doxorubicin (Adriamycin), cyclophosphamide, and vincristine. Patients given chemotherapy alone suffered no pulmonary effects, nor did a further 20 patients who received radiation and the same chemotherapeutic treatment without bleomycin. Einhorn and associates therefore implicated bleomycin as the agent responsible for the extremely common occurrence of pneumonitis, a conclusion not supported by others. Soble and Perry reported a case in which fulminant fatal pneumonitis and bone marrow hypoplasia occurred 4 weeks after a course of 4000 rads to the mantle for Hodgkin's disease. The interesting feature was that the patient had received busulfan (480 mg total) over the previous 6 years. Although both pneumonitis and aplastic anemia can occur following busulfan in this dosage (15% to 20% probability), the sudden appearance of both complications shortly after radiation suggested to the authors that they were induced by interaction with radiation. It is possible that doxorubicin, which has marked effects on the myocardium, also may enhance radiation effects in the lungs. In the foregoing reports, pneumonitis started earlier than usual, was severe, sometimes preceded radiologic changes, and was evident outside the ports of irradiation.

Phillips and co-workers reported that significant enhancement of pulmonary lethality occurred with actinomycin (0.075 mg/kg of body weight), cyclophosphamide (75 mg/kg), and vincristine (0.5 mg/kg) given 2 hr before irradiation, but not with bleomycin, hydroxyurea, or BCNU. With actinomycin D there was significant enhancement of lethality, even when a small dose (0.015 mg/kg) was given 30 days before irradiation but not 30 days after it. Interestingly, the effect of these agents is not consistent between different organs. Nor is the list of drugs that potentiate the effects of radiation the same as the list that can cause pneumonitis in the absence of irradiation.

There is no obvious relationship between the mode of action of these agents and their potentiating effects on lung irradiation. Information on the time of administration of drug in relation to radiation, dose, and fractionation is fragmentary, although of clear clinical importance.

Corticosteroid Withdrawal

There is some controversy about the role of steroids in the treatment of radiation pneumonitis (see Management), and in clinical practice prophylactic steroid therapy is not used. Nevertheless, if steroids are being administered, their inopportune withdrawal appears to be capable of precipitating radiation pneumonitis. Cycles of chemotherapy that included prednisone are likely to be followed by episodes of pneumonitis. Thus, corticosteroids should be administered either continuously or not at all in the period following radiation. In lethally irradiated mice, deaths were markedly reduced by prophylactic prednisolone but occurred rapidly after its withdrawal at 160 days. The phenomenon can be interpreted either as unmasking of steroid-suppressed pneumonitis or, less likely, as precipitation, by the withdrawal itself, of a reaction that would not have been present at all if steroids had not been given.

Previous Radiation Therapy

It has been recognized from the earliest reports that retreatment is likely to precipitate radiation pneumonitis. For example, reirradiation of the mediastinum for inadequately treated Hodgkin's disease resulted in pneumonitis far more frequently than did a first course and that the episode occurred earlier and was more severe. It is not clear whether the phenomenon is a function of the total dose received or whether the lung is more susceptible after the first course.

Ataxia Telangiectasia

The rare disorder, ataxia telangiectasia, appears to be associated with abnormal sensitivity to ionizing radiation. This hereditary syndrome is characterized by cerebellar ataxia, oculocutaneous telangiectasia, immunologic deficiencies, and an increased occurrence of reticuloendothelial malignancy. Increased radiosensitivity can be demonstrated at the molecular, cellular, and clinical levels. Conventional doses of radiotherapy for the malignant complications are likely to be followed by severe radiation reactions. It has been postulated that the radiosensitivity results from defective DNA repair, which also accounts for another feature of the condition: chromosomal instability. This raises the possibility, as yet undemonstrated, of enhanced radiosensitivity in two other disorders characterized by chromosomal instability and predisposition to malignancy, Bloom's syndrome, and Fanconi's syndrome.

Other Contributory Factors

Age has been considered a factor that might modulate a patient's response to radiation. It is mentioned in many reviews but supported by only scant data. Gas transfer appears affected more in older patients. There appears to be an age-related increase in frequency and severity of roentgenographic changes in irradiated breast cancer patients. The grading was made on roentgenograms taken from 7 weeks to 30 months after the end of treatment. Whether atherosclerosis plays a role also has been considered, but data on this are absent. It does seem possible, however, that the lungs of children recover better than those of older adults from the effects of x-rays.

Underlying infection such as that which may be associated with chronic bronchitis also has been considered to be a predisposing factor to radiation intolerance. However, when patients with and without chronic bronchitis were compared, no change in the incidence of minor and major reactions was found, nor were subsequent functional changes different in the two groups. The commonly held view that patients with chronic obstructive lung disease tolerate radiotherapy poorly should be qualified: such patients are not more likely to experience radiation pneumonitis. Radiotherapy will add a certain amount of functional impairment to their already abnormal physiological state, but no more than in normal subjects. It is of interest that radiotherapy has been employed in emphysematous patients without malignancy

as a means of reducing their excessive lung compliance—with only marginal success, but equally without much harm.

DIFFERENTIAL DIAGNOSIS

In a typical clinical setting, the patient who has received radiation therapy for a malignancy and subsequently develops pulmonary problems presents a diagnostic challenge. The differential diagnosis invariably includes radiation reactions, recurrent malignancy, infection, and possibly other entities such as drug-induced lung disease and thromboembolism. In view of the divergent therapeutic requirements of these conditions, their differentiation is of utmost clinical importance. It can often be made on the basis of clinical features and radiologic appearances.

The differentiation of radiation-induced pleural effusion from other effusions has been discussed (see Associated Complications). Differentiation of radiation pneumonitis from tumor recurrence is facilitated by the following criteria: recurrent malignancy is suggested by an interval of more than 4 months between radiation therapy and symptoms; steady progression of the roentgenographic changes, metastases elsewhere, anemia, and hemoptysis. Lymphangitic spread of tumor is usually associated with very severe symptoms, particularly dyspnea, and is more marked at the lung bases, where septal lines and long linear streaks from the hilus to the pleura are seen. Unlike radiation reactions, tumor recurrence is often roentgenographically manifest outside the field of irradiation.

Infections may present a more difficult problem. Criteria for differentiation of radiation reactions from tuberculosis have been suggested but have not been found to be particularly helpful. Usual features of other infections, pyrexia, leukocytosis, and purulent sputum, may or may not be prominent in infected patients who have been compromised by chemotherapy, corticosteroids, and tumors as well as by previous radiation therapy. The diagnosis rests on a combination of immunologic studies, stains, and cultures of bronchopulmonary secretions, and possibly histologic and microbiological studies of lung tissue.

The diagnosis of radiation reactions is greatly simplified by excellent roentgenograms and knowledge of the precise chronology, dose, field margins, and dose schedules in relation to the onset of subsequent problems. Microbiological backup is most helpful, but histologic samples obtained by bronchoscopy or open lung biopsy are particularly important in difficult cases. Even when these are available, differentiation between the various possibilities is not always straightforward.

MANAGEMENT

Because radiation pneumonitis rather than fibrosis is the major life-threatening event, management is principally directed toward this problem. Early recognition is important, as early treatment may affect the course of pneumonitis.

Untoward reactions following radiation could probably be anticipated in a large proportion of patients by roentgenographic monitoring and the more discriminating tests of lung function at the appropriate time. This has been considered impractical for routine purposes because of the extended time over which reactions can occur. Furthermore, the appearance of abnormalities does not necessarily inevitably lead to pneumonitis. Possibly patients who are at increased risk because of an unavoidable contributory factor should be so monitored.

Symptomatic

Patients whose symptoms are not severe or rapidly progressive and develop late (i.e., 10 to 12 weeks after completion of radiotherapy) will probably have a mild clinical course. For these patients, symptomatic therapy is all that is required: restriction of activity, cough suppressants, and observation during the 2- to 4-week period.

If an early reaction occurs and symptoms progress rapidly, additional therapy may be required, as follows.

Corticosteroids

The place of corticosteroids in the management of radiation pneumonitis remains controversial; no controlled clinical trials have been carried out to our knowledge. However, corticosteroids are widely used in clinical practice, and animal studies support their use.

Early clinical studies suggested that relatively small doses might be protective if given prophylactically, before the onset of pneumonitis, or early in its course. They were less beneficial if delayed much beyond the onset of symptoms. Pneumonitis may appear shortly after withdrawal of steroids, but there is a dramatic response of all patients shortly after restitution of prednisone, 20 to 80 mg/day.

Although early animal studies gave divergent views on the use of corticosteroids, it is now fairly clear that when corticosteroids are given before the onset of pneumonitis, mortality is significantly reduced. In a detailed analysis of this phenomenon in lethally irradiated mice, it was found that prednisone (4.0 mg/kg per day starting 10 weeks after irradiation but before deaths from pneumonitis normally occur) significantly reduced the mortality of radiation pneumonitis and was as effective as a larger dose in this respect. However, if steroids were withdrawn during the period when pneumonitis normally occurs, death rapidly occurred and caught up with that of mice that did not receive corticosteroids. But corticosteroids could be withdrawn at 30 weeks (after the usual period of pneumonitis) without resultant mortality. Prednisone had a lesser protective effect when given after the onset of pneumonitis. Steroids, therefore, reduce the mortality of lethally irradiated mice during the period of pneumonitis, even if commenced well after irradiation, a finding that suggests that their beneficial action is related to the suppression of the radiation response. There is evidence that their effect might be a result of suppression of the microvascular leakage that is characteristic of radiation pneumonitis.

The foregoing clinical and experimental data can be synthesized into a hypothesis concerning the place of steroids in radiation pneumonitis: There is a stage, probably following irradiation but preceding established pneumonitis, during which steroid administration prevents the progression of unfavorable cellular or biochemical antecedent(s) or trigger(s) to an abnormal physiological state. The antecedent event remains suppressed or deferred as long as steroids are administered. But once the event occurs, either primarily or because of steroid withdrawal, the physiological and clinical sequelae of radiation pneumonitis follow, and these are not amenable to steroid therapy. However, the antecedent event may occur over a long time span, several weeks, and the physiological sequelae may reverse spontaneously, if slowly. Use of steroids early in the period of emergent physiological derangement prevents further changes from occurring and allows normal repair processes to proceed. This hypothesis would explain the (1) protective effect of steroids, (2) unmasking of latent injury on steroid withdrawal, (3) abrogation of pneumonitis by early use of corticosteroids, and (4) relative inefficacy of steroids in reversing established pneumonitis. Current practice agrees with this hypothesis.

Prophylactic corticosteroids are rarely used in clinical practice. In general, large doses for long periods would be required to abolish all pneumonitis. If and when symptomatic pneumonitis occurs, and especially if early onset and rapid progression suggest a severe reaction, large doses of corticosteroids, for example, prednisone (100 mg/day in an adult), should be instituted as early as possible and maintained for several weeks. When symptoms have been absent or not clinically troublesome for a week or more, the dose can be cautiously reduced, but it must be raised promptly if relapse occurs. Subsequent tapering should be prolonged over several weeks. If respiratory failure ensues, the patient should be maintained by mechanical ventilation and supplemental oxygen in the expectation that the condition will ultimately remit spontaneously, provided the patient can be kept alive. It is, however, unlikely that corticosteroids will be of benefit to the patient who first comes under treatment at the stage of established respiratory failure. There are thus many instances in the literature and in common experience in which even large doses of corticosteroids failed to alter the course of radiation pneumonitis. The ideal would be to recognize pneumonitis early in its course, anticipate its severity, and treat appropriate cases as early as possible with large doses of corticosteroids. Agreement is universal that corticosteroids have no place at the stage of radiation fibrosis.

Other Forms of Therapy

A large number of other agents and procedures have been suggested or exposed to trial in the management of radiation pneumonitis. These are reviewed briefly.

It might have been anticipated that anticoagulants could prevent radiation pneumonitis in view of the prominence of the vascular damage that precedes pneumonitis. Daily injections of heparin given to rats from the time of irradiation did not provide protection against the physiological sequelae. We know of no controlled clinical trial, but oral anticoagulants were given without benefit to one series of patients.

Although there is experimental evidence of transient impairment of lung defense mechanisms, prophylactic antibiotic administration has also proved unable to offer protection against physiological changes or to alter mortality in experimental radiation pneumonitis. Administration of antibiotics to patients also would raise the possibility of superinfection with insensitive opportunistic organisms. When infection occurs as a complication of pneumonitis, it should be treated with the appropriate antibiotic.

Oxyphenbutazone, an antiinflammatory agent, also has been used prophylactically in one prospective double-blind trial on 116 patients receiving cobalt radiation therapy. Patients who received oxyphenbutazone experienced significantly less frequent or severe pneumonitis and fibrosis by roentgenographic criteria. As mentioned above, animal experiments strongly suggest that other antiinflammatory agents, particularly those that inhibit or antagonize the leukotriene pathway, may have a

markedly beneficial effect on the survival from radiation pneumonitis.

L-Triiodothyronine has been given prophylactically to dogs, with small and nonsignificant effects on postirradiation thoracic compliance. b-Aminopropionitrile (BAPN), an inhibitor of collagen maturation, also has been studied as a prophylactic agent in rats. Although an increase in the collagen content of the lungs was prevented as long as BAPN was administered, mortality was not significantly diminished. Another inhibitor of collagen metabolism, D-penicillamine, also moderates the late effects of radiation on the lungs.

Pneumonectomy has been performed for severe unilateral radiation pneumonitis, and single lung transplantation might be considered in the current era.

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CHAPTER

39 Clinical Evaluation of Individuals with Suspected Indoor Air Quality Problems

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INTRODUCTION

The recognition of indoor air pollution as relevant to the practice of pulmonary medicine reflects the increasing time spent indoors, significant contributions of indoor environments to exposures to pollutants, the sealed environments of modern buildings, and the emergence of new clinical syndromes linked to indoor air pollution. Total personal exposure to pollutants represents a weighted average of the exposures received in indoor and outdoor environments, locations having homogeneous characteristics during the time that exposure is received. For many pollutants, indoor microenvironments make dominant contributions, e.g., radon and volatile organic compounds (VOCs). Even for some pollutants regulated in outdoor air, e.g., particles and nitrogen dioxide, exposures in indoor microenvironments may outweigh exposure received outdoors.

The spectrum of adverse respiratory effects of indoor air pollution is broad, ranging from symptoms and exacerbation of preexisting respiratory disease to acute and even fatal conditions that can be readily linked to indoor air pollution. The illnesses directly associated with indoor air pollution can be grouped as specific building-related illnesses and sick-building syndrome. The former includes such well-defined entities as hypersensitivity pneumonitis and Legionnaires' disease. The latter is a nonspecific syndrome, often having both respiratory and nonrespiratory elements. Indoor air is also widely contaminated by respiratory carcinogens: radon, environmental tobacco smoke (the mixture of sidestream smoke and exhaled mainstream smoke), and asbestos. Pulmonary physicians may be consulted concerning the risks posed by these agents and asked for guidance concerning control strategies.

SOURCES OF INDOOR AIR POLLUTION

Indoor air pollution has myriad sources including the materials from which the space is constructed, its furnishings, processes operating within the environment, biological agents, and even the occupants. Outdoor air pollutants can also penetrate indoors, as can soil gas. The broad source headings are combustion, evaporation, abrasion, biological, and radon. The principal combustion sources are gas cooking stoves, burning cigarettes, fireplaces, wood stoves, and unvented space heaters. Evaporation of volatile organic compounds from materials and products leads to ubiquitous contamination by these agents. Abrasion of friable asbestos is a principal source for this indoor contaminant. The biological agents are heterogeneous, extending from infectious organisms to pets and the occupants themselves. Radon comes primarily from soil gas.

The concentration of an indoor contaminant depends on the strength of its source, the rate of removal, the volume of the space, and the rate of exchange of air between the space and outdoors. This “mass-balance” formulation indicates that the concentration of a contaminant might be reduced by limiting source strength, increasing removal rate, or increasing exchange between indoor and outdoor air.

In the typical modern building, the exchange of indoor with outdoor air is accomplished by a central heating, ventilating, and air-conditioning (HVAC) system. These systems are diverse, although all have the same purpose: the delivery of air of acceptable quality to building occupants. The volume of air to be delivered follows the recommendation of standards set by the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE). In the majority of newer buildings, occupants can no longer control the temperature of the work environment, and in most buildings, occupants cannot open windows to increase air exchange. Most residences still rely on natural ventilation.

EVALUATING THE PATIENT

A patient presents to a pulmonary physician with nonspecific complaints, perhaps cough and sore throat. When should indoor air pollution be suspected as a cause? How can the link to indoor air pollution be established? The same questions face the clinician for specific disease entities also caused by indoor air pollution, such as hypersensitivity pneumonitis, Legionnaires' disease, and worsening of asthma. For each, the diagnosis should raise questions about the role of the indoor environment.

For the physician evaluating and treating an individual patient, indoor air pollution often presents unusual challenges. First, the physician needs to think beyond diagnosis and management of the individual, to diagnosis and management of the specific environment. Interaction with other health and safety professionals may be needed to deal with problems of indoor environments. Second, because cases involving indoor air pollution often revolve around a workplace, physicians will frequently find themselves dealing with employers, unions, and other organizational entities and with complex nonmedical issues such as return to work, workers' compensation, risk communication and risk management. In some cases these “nonmedical” issues play a substantial role, and physicians should be familiar with the kinds of questions that will be asked (Fig. 1).

FIG. 1. Evaluation and management of indoor air quality problems.

There is no “typical” presentation for individuals suspected of having health problems related to the indoor environment (Table 1). Patients may report the onset of new symptoms or exacerbation of a preexisting condition. In some cases patients will ask the physician about the possible relationship between symptoms and indoor air. In other cases, the clinician must be alert for diseases or patterns of symptoms that the patient does not necessarily link to a specific exposure or environment. In

managing the patient, the physician's role includes five elements: first, diagnosing the clinical syndrome; second, characterizing the nature and magnitude of any exposures; third, deciding whether the clinical picture is consistent with the likely exposure; fourth, treating the condition; and fifth, managing nonmedical issues such as return to work, compensation, and protection of other potentially affected individuals. Thus, the clinician will often need to consult with industrial hygienists, indoor air quality experts, public health officers, or others who can assist in characterizing indoor environments as well as employers, unions, and regulatory agencies in resolving issues such as return to work and workers' compensation. The physician's role may be complicated by tensions between involved parties such as employee unions and employers and the threat or presence of litigation.

Clinically evident diseases	Diseases for which the usual methods of clinical evaluation can establish a causal link to an indoor air pollutant.
Exacerbation of disease	The clinical status of already established disease is exacerbated by indoor air pollution.
Increased risk for diseases	Diseases for which epidemiologic or other evidence establishes increased risk in exposed individuals. However, the usual clinical methods indicative of injury typically cannot establish the causal link in an individual patient.
Physiological impairment	Transient or persistent effects on a measure of physiological functioning that are of insufficient magnitude to cause clinical disease.
Symptom responses	Subjectively reported responses that can be linked to indoor pollutants or are attributed to indoor pollutants.
Perception of unacceptable indoor air quality	Sensing of indoor air quality as uncomfortable to an unacceptable degree.
Perception of exposure to indoor air pollutants	Awareness of exposure to one or more pollutants with an unacceptable level of concern about exposure.

[a] From Samet JM. Indoor air pollution. A public health perspective. Indoor Air 1993;3:279.

TABLE 1. *Classification of the adverse effects of indoor air pollution*[a]

Although patients may in some cases be convinced not only of the diagnosis but also of its relationship to a specific indoor exposure or environment, the physician should remain a “diagnostic skeptic.” It is especially important to identify specific treatable and preventable conditions, not only for the patient but for others who may be potentially exposed to the same conditions.

A thorough history is the first and most important step in the clinical evaluation. In addition to the symptoms reported by the patient, the physician should elicit the temporal relationship between putative indoor exposure and the onset of symptoms. Do symptoms improve over weekends and vacations? Is there a pattern related to certain activities or locations? An attempt should be made to distinguish between upper and lower respiratory tract symptoms. For example, the presence of lower respiratory tract symptoms points away from sick-building syndrome and toward intrinsic lung disease such as asthma.

Physical examination should focus on the presence or absence of inflamed conjunctivae, sinus tenderness or congestion, signs of allergic rhinitis, nasal polyps, wheezing, and rales. In cases involving possible multiple chemical sensitivity or sick-building syndrome, symptoms may involve many organ systems, and a thorough physical examination is mandatory.

Laboratory testing should focus on the diagnosis of specific conditions, based on the presenting symptoms. Spirometry can be very useful in separating obstructive from restrictive physiology in relation to symptoms that involve only the upper respiratory tract. The presence of an elevated white count may suggest infection or hypersensitivity pneumonitis. Total serum IgE may be elevated in allergic disorders such as asthma and rhinitis. For allergic conditions in which an exposure is well documented or a particular agent is suspected, the use of specific antibody testing through RAST or epicutaneous tests is appropriate. However, the use of broad antigen panels, although they identify individuals with a range of allergies, may not help determine the specific agent to which the person is reacting in the indoor environment.

Because sick-building syndrome and multiple chemical sensitivity are diagnoses of exclusion, when these conditions are being considered there may be a tendency to “exclude everything” and to use tests that have not been adequately validated clinically. Use of appropriate diagnostic testing in sick-building syndrome and multiple chemical sensitivity is considered in more detail below.

Characterizing the responsible exposure will often require consultation with an industrial hygiene professional, an indoor air quality expert, and a heating, ventilation, and air-conditioning (HVAC) engineer. The evaluation of the indoor environment will in most cases involve interviews with the occupants, a walk-through evaluation, and sampling for common indoor pollutants including organics, bioaerosols, and, in some cases, particular substances such as pesticides or combustion products. Measurements of temperature and humidity should be compared with ASHRAE standards. Ventilation rates, including air velocity and air changes per hour, should be measured. The HVAC system should be inspected carefully, including the air supply ducts, air-handling units, cooling towers, and air intakes (which can sometimes inadvertently be located near external sources of pollutants). The building should be examined for water leaks and other defects that often contribute to the development of bioaerosols and other indoor air pollutants. Other potential sources of indoor pollutants include photocopy machines (ozone, toner, VOCs), building construction material such as resin-containing particle boards (formaldehyde), and carpeting. Measurements of indoor air quality are rarely informative by themselves. If the setting is a workplace, and exposure to a particular chemical agent is at issue, the material safety data sheets should be reviewed. These are required under the U.S. Occupational Safety and Health Administration's hazard communication standard. Other factors may also be involved, including lighting of work areas, noise and/or vibration, ergonomics, and, importantly, work organization.

MANAGING INDOOR AIR QUALITY PROBLEMS

There are three aspects to successful management of indoor air quality problems: first, medical management of the affected individual or individuals; second, administrative management of both the individuals and the problem environment; and third, risk communication, a key aspect of medical and administrative management. Medical management depends on the diagnosis.

Whether the patient can return to work is of considerable significance. Patients with multiple chemical sensitivity or sick-building syndrome are often apprehensive that a return to the workplace will exacerbate their symptoms. However, although short-term removal from work may help to reduce symptoms and may also be useful diagnostically in linking symptoms to the workplace, there is a great deal of controversy over whether a return to the offending environment ultimately leads to increased morbidity. Some patients may benefit from supportive counseling or other psychological interventions to facilitate a return to an environment that produced symptoms.

Management of indoor air quality problems often involves more than individual medical therapy. When possible, the diagnosis of a building-related problem should prompt correction of the underlying problem. This generally requires the involvement of building engineers, HVAC professionals, and industrial hygienists. In cases in which a specific causal agent can be identified, the corrective action will usually be apparent. In most cases, however, an iterative approach is required, involving assessment of the design, operation, and maintenance of the HVAC system as well as appropriate decontamination or source control.

Communication is a critical component of successful management of indoor air quality problems. Communication with the patient should address (1) medical issues such as the diagnosis and recommended therapy and (2) administrative issues related to return to work. Although some physicians shy away from advising patients about workers' compensation, the physician should consider whether the employee is aware of workers' compensation and of what he or she should do to gain access to the system. This is particularly important because of the statute of limitations for some compensation claims.

Communication with the employer should include: (1) clear information on the ability of the employee to return to work, including any restrictions and need for follow-up; (2) if the condition is thought to be work-related, any recommendations related to identifying and fixing the source of the problem; and (3) whether there is a need to evaluate other employees who may potentially have been exposed.

The physician should consider not only the individual patient but whether other building occupants may have concerns about their risks. This includes individuals who may not be experiencing symptoms themselves. The communication program should include, at a minimum, disclosure of the findings from the evaluation of the building as well as a discussion of the clinical significance of the findings to the potentially exposed population.

RESPIRATORY HEALTH EFFECTS OF INDOOR AIR POLLUTION

As noted above, the spectrum of clinical responses to indoor air pollution is diverse. Table 2 describes some of the major categories of clinical responses, the responsible agents, and the setting in which they may be found. This section briefly describes these clinical responses, aspects of which are considered in greater

depth elsewhere in this volume.

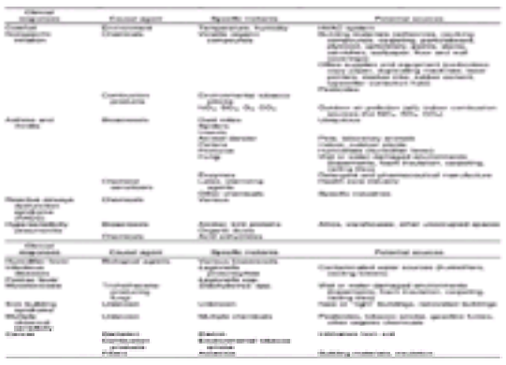

TABLE 2. *Pulmonary responses commonly associated with indoor air pollution*

Asthma

Indoor air pollution both causes and exacerbates asthma. Exposure in the home to house dust mite antigen and to environmental tobacco smoke contributes to asthma. Similar exposures to these and a wide array of other biological agents, antigens from pets, rodents, cockroaches, molds, and fungi, may exacerbate asthma in the workplace. There may be exposure to molds and fungi that have contaminated moist surfaces of heating, ventilating, and air-conditioning systems. Volatile organic compounds, low-molecular-weight agents such as formaldehyde that are released from materials, furnishings, and office processes, may worsen asthma. Smoking adds particles and irritant gases to the air of public and commercial buildings.

Respiratory Infections

Indoor microenvironments are the principal locale for transmission of infectious respiratory diseases, including tuberculosis, influenza, and Legionnaires' disease. Risks reflect occupant density and the level of ventilation provided. Contamination of cooling towers and water systems, which aerosolize bacteria, has been linked to episodes of pneumonia and nonpneumonic disease caused by *Legionella* species. Diagnosis of Legionnaires' disease or Pontiac fever should prompt consideration of the source of the infection. Airborne transmission of tuberculosis has occurred in such diverse enclosed environments as ships, airplanes, and shelters for the homeless.

Lung Cancer

Three agents causally linked to lung cancer may contaminate indoor environments: radon, derived from decay of naturally occurring uranium and entering buildings in soil gas; asbestos fibers released from building materials; and environmental tobacco smoke from the smoking of occupants. Radon is estimated to cause approximately 14,000 lung cancer deaths a year, approximately 6000 to 7000 in never-smokers, and the estimate for mortality from environmental tobacco smoke is 2000 to 3000 lung cancer deaths annually in the United States. Exposures to asbestos in public and commercial buildings are generally low, and the associated cancer risks are likely far lower than for the other carcinogens. As yet, there are no specific markers for lung cancer caused by these agents.

Chronic Rhinitis

Chronic rhinitis related to indoor air pollutants can be a significant cause of morbidity and decreased quality of life for many patients. Causes of chronic rhinitis include annoyance reactions, allergic reactions, chemical irritation, and chemical corrosion. The estimated prevalence rate of allergic rhinitis is between 15% and 20%.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, caused by inhalation of organic dusts and immunologically active chemicals, has usually been associated with building air-handling systems, although room humidifiers have also been implicated in some cases. Humidifier fever has been considered a separate entity because of the absence of chest x-ray findings in the latter condition.

SICK-BUILDING SYNDROME

Sick-building syndrome is a widely used term to describe a constellation of symptoms associated with exposure to an indoor environment, typically a modern office building. The syndrome is characterized by mucous membrane irritation, respiratory complaints, and sometimes skin, central nervous system, or gastrointestinal effects. There is no generally agreed on case definition, and no unifying pathophysiological mechanism has been advanced to account for all of the symptoms (Table 3). Although occupants of buildings where sick-building syndrome (SBS) has occurred often have a very high symptom prevalence, there is no consensus regarding the percentage of occupants who must be symptomatic in order for the building to qualify as a “sick” building. Affected occupants may be only a minority of the total occupants, but they may be clustered geographically in one area of the building.

Component	World Health Organization	American Thoracic Society
Symptoms	1. Sensory irritation in eyes, nose, and throat 2. Neurotoxic or general health problems 3. Skin irritation 4. Nonspecific hypersensitivity reactions 5. Odor and taste sensations	1. Eye irritation 2. Headaches 3. Fatigue 4. Throat irritation 5. Chest burning, cough, sputum production in the absence of exposure to tobacco smoke 6. Wheezing or chest tightness 7. Malaise 8. Rhinitis
Population affected	Majority of occupants	Substantial proportion of a building's occupants, or of the occupants of a particular space within a building

TABLE 3. *Proposed case definitions for sick building syndrome*

The prevalence and incidence of SBS have been studied in a number of different indoor environments. In several studies of office building workers, the prevalence of symptoms was quite high, over 80% for at least one SBS symptom. However, as noted above, there is no agreement that a certain percentage of occupants must be affected in order for the building to qualify as “sick.” Risk factors associated with the development of symptoms consistent with sick-building syndrome include female gender, a history of asthma or rhinitis, occupation (clerical workers are at increased risk compared with managers), high psychosocial stress, and jobs involving use of carbonless copy paper and visual display terminals.

Thus far, the etiology of sick-building syndrome remains uncertain, although volatile organic compounds, bioaerosols such as bacterial endotoxins or b-1,3-glucan, work organization and other psychosocial factors, and unpleasant odors have all been suggested as possible causal or contributing factors (Fig. 2). There is also disagreement whether and under what circumstances the amount of building ventilation affects the development of sick-building syndrome. However, poor maintenance of the HVAC system has been found in many buildings with occupants affected by SBS.

FIG. 2. Contributing factors in sick-building syndrome.

The clinical presentation of SBS is highly variable. Patients may complain only of irritation, or they may have a wide range of symptoms. Sick-building syndrome is characterized by the presence of symptoms in the building and resolution when exposure ceases. The persistence of symptoms outside the suspected building should increase suspicion that another underlying process is involved. In some individuals, symptoms will initially be present only in the building, but over time the symptoms become more generalized, triggered by a variety of chemical exposures. Eventually, some of these patients may become indistinguishable from patients with multiple chemical sensitivity. Individuals with sick-building syndrome usually do not have evidence of any abnormality of respiratory function. The upper respiratory tract has been the focus of considerable attention as a likely target organ. The presence of lower respiratory tract symptoms, particularly cough, wheeze, or dyspnea, should prompt examination for the presence of airways hyperresponsiveness.

Sick-building syndrome is a diagnosis of exclusion. A careful history and physical examination should be conducted. Keys in making the diagnosis are an appropriate relationship between symptoms and occupancy of the building and an appropriate epidemiologic context with similar problems in other persons working in the same building. The physician should be particularly alert for signs or symptoms of allergic disorders because these may be misdiagnosed as SBS and not adequately treated.

There is no specific medical treatment for SBS. Rather, the physician must consider management issues related to the individual patient, the building, and the work environment (including, frequently, psychosocial aspects of the environment). Management of the individual patient often involves some form of reassurance that the problem is being addressed seriously, that there is no long-term health threat, and that, where appropriate, additional therapeutic modalities such as supportive psychological counseling will be available. Symptoms should not be minimized or trivialized, either by the physician or by the building management. Some patients may insist that the cause of the problem be identified and removed, and these patients may require considerable reassurance and support if they are to successfully return to work.

One of the most important aspects of management is effective communication among patient, physician, and employer. Resolution of SBS may require that the physician contact the employer; this needs to be done with the patient's knowledge and approval. If several occupants appear to be affected, and industrial hygiene or building engineering is undertaken to correct a problem, the affected individuals should be kept informed of all findings and corrective actions, along with appropriate interpretations of the probable clinical significance of the findings.

Prevention of SBS requires both proper building design and maintenance, particularly of the HVAC system. Changing uses of the building should prompt careful analysis of the impact on occupants. Overloading of HVAC capacity by increasing occupant density or adding new equipment may lead to SBS, as may failure to address moisture problems, which facilitate microbial growth. Use of low-emission products and allowing emissions from new building materials to dissipate before occupying the building may also reduce the likelihood of SBS. This can be accomplished through a bake-out period before occupancy.

MULTIPLE CHEMICAL SENSITIVITY

The earliest references to multiple chemical sensitivity (MCS) as a distinct clinical entity date to 1987, although some clinicians have for years postulated that there are certain individuals who have a “sensitivity” or “allergy” to environmental chemicals. Other terms for this condition have included “environmental illness” or “chemical hypersensitivity or hypersusceptibility.” The most common clinical and epidemiologic definition used for MCS was developed by Cullen:

> [An] acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms.

Patients with MCS may consult pulmonary physicians because of respiratory symptoms.

There is no scientific consensus regarding the etiology and pathogenesis of MCS. Physiological, psychological, psychophysiological, and sociologic models have been proposed to explain MCS. It has been described as a chemical sensitization of the central nervous or immune system, a conditioned response, a panic attack, or a posttraumatic stress response to odors, as a misdiagnosis of psychological or physical illness, and as an illness “belief system.” Clinical studies of patients diagnosed with MCS have not found any consistent abnormalities in physiological, immunologic, neurologic, or psychological parameters.

The upper respiratory tract has been the focus of considerable attention as a likely site involved in the pathogenesis of MCS. Attention has focused on inflammatory changes detected in some patients by rhinolaryngoscopy and on the possible role of a hypothesized but as yet unconfirmed relationship between inflammation and distant neurophysiological effects.

Typically, a patient will present with symptoms in a number of organ systems that are triggered by exposure to perfumes, cigarette smoke, cleaners, automobile and truck exhaust, and other chemicals with strong odors. Common symptoms include headache, fatigue, confusion, memory problems, shortness of breath, arthralgias/myalgias, and nausea. Symptoms may also be triggered by a particular location such as an office, and it may be difficult to distinguish MCS patients from patients with sick-building syndrome. Although many patients report that their condition was triggered by a specific inciting event, some state that the condition developed gradually.

The evaluation of patients with symptoms characteristic of MCS (Table 4) is often time-consuming, and consultation with a specialist in occupational medicine may be helpful. Because symptoms are by definition multisystem, patients with symptoms in only or primarily one organ system should be carefully evaluated for another diagnosis. The presence of concomitant or explanatory psychiatric diagnoses should be established. Some patients with symptoms characteristic of MCS may also meet many of the criteria for chronic fatigue syndrome, but there is as yet no consensus regarding any relationship between the two entities.

A. History
Detailed exposure history (workplace and other environmental exposures)
Industrial hygiene data (Material Safety Data Sheets, results of exposure monitoring, etc.)
Current and past medical illnesses and results of previous diagnostic workups and treatments
Review of prior medical records
B. Physical examination
Rule out other illnesses in the differential diagnosis
C. Diagnostic testing
There is no established diagnostic testing for MCS
Rule out other illnesses in the differential diagnosis
The following tests are currently not validated for clinical use to confirm the diagnosis of MCS:
Environmental challenge testing (unblinded, uncontrolled)
Quantitative electroencephalography
Brain electrical activity mapping
Evoked potentials (brainstem, visual, sensory)
Positron emission tomography scanning
Single photon emission computed tomography scanning
Immunologic testing
Measurement of trace concentrations of volatile organic compounds or pesticides in blood (parts per billion)
Neuropsychological testing
D. Consultation
Occupational and environmental medicine specialist
Psychiatrist
Other specialists as appropriate to rule out other medical conditions in the differential diagnosis
E. Other
Symptom diary
Short-term removal from exposure

[a] Adapted from Sparks PJ, et al. Multiple chemical sensitivity syndrome: a clinical perspective. In: J Occup Med 1994;36:718–730.

TABLE 4. *Diagnostic evaluation of patients with multiple chemical sensitivity*[a]

Treatment of patients with MCS is typically difficult and best accomplished by a multidisciplinary team that includes a psychologist or psychiatrist. Many patients are

concerned about any possible chemical exposures, and it is not uncommon for patients to resort to increasing social isolation in an attempt to prevent exposure. Just as there is no agreed-on case definition, there is also no agreed-on therapeutic regimen. Most treatment has been aimed at relief of symptoms, which can of itself have a significant salutary effect. The issues that have engendered the greatest controversy over management of patients with MCS are (1) whether to remove patients from exposure, and if so for how long; (2) the use of behavioral therapies; and (3) the role of desensitization or chemical detoxification. In the experience of the authors and of most of the scientific literature, short-term removal from exposure may be helpful both as a diagnostic test and therapeutically, but there is little evidence that long-term removal improves clinical outcome. The use of behavioral therapies has been hotly debated. There have been no controlled trials of behavioral therapy, although case reports suggest that some patients respond favorably to the use of biofeedback or other supportive modalities. No controlled trials have validated the use of chemical desensitization (sometimes termed “neutralization”) therapies.

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CHAPTER

40 Bronchial Asthma

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INTRODUCTION

Asthma is a clinical syndrome defined physiologically by episodic reversible airway narrowing and hyperresponsiveness of the airways to a variety of stimuli (Table 1). It is also defined pathologically by the presence of certain recognizable microscopic features including infiltration of the airways with eosinophils, hypertrophy and hyperplasia of airway smooth muscle, hypertrophy and hyperplasia of mucous secretory apparatus, and overall thickening of the airway wall.

1. Episodic airway obstruction
2. Airway hyperresponsiveness
3. Airway inflammation

TABLE 1. *Characteristics of asthma*

Our current knowledge of the molecular pathogenesis of asthma is minimal. Indeed, our current knowledge of asthma may be likened to our knowledge of anemia before the elucidation of the various molecular events leading to the clinical syndromes that are recognized as distinct forms of anemia. On the basis of our current clinical understanding of asthma, it seems likely that multiple molecular causes for the syndrome will be identified in the future.

Given the uncertainties embodied in the absence of molecular understanding, the Global Initiative for Asthma and the National Asthma Education Program defined asthma as follows: "Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and T lymphocytes." In susceptible individuals, this inflammation is reflected physiologically as recurrent episodes of wheezing, breathlessness, chest tightness, and cough. These symptoms are usually associated with widespread but variable airway narrowing, which causes airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation is also associated with an increase in airway responsiveness to a variety of stimuli.

This is a useful definition for health care professionals interested in asthma, but it lacks the precision needed for use in epidemiologic studies. As a result, many epidemiologists have found it necessary to create their own definition of asthma for use in the populations they wish to study. As methods for quantifying the asthma phenotype become more codified, the definition of asthma from group to group has become more uniform, thus allowing comparisons among various studies. In reviewing asthma studies, it is worthwhile to query whether the definition was based on clinical criteria (for example, the presence of wheeze or a doctor's diagnosis of asthma), on the presence of airway obstruction or hyperresponsiveness, or on pathologic criteria such as analysis of sputum or airway biopsy material. In most circumstances asthma definitions are based on a combination of a characteristic clinical history and physiological evidence of reversible airway obstruction. In cases in which the diagnosis is not clear from these two criteria, airway responsiveness testing is quite often added. Very few clinical studies of asthma have used pathologic characteristics of materials obtained from patients to define asthma.

ASTHMA EPIDEMIOLOGY

Asthma Prevalence

Asthma is a very common disorder that affects approximately 5% of the population of the United States and Europe; it affects men and women equally. It is well established that the prevalence of asthma below age 20 is greater than that above age 20, which suggests a “remission” from asthma some time in the midteen years. Indeed, clinical remission of asthma is common in the peripubertal period, but many adults who develop asthma had a history of asthma in childhood. Worldwide, the prevalence of asthma in children is between 8% and 30% in more affluent countries and on the order of 0% to 5% in less well-developed countries.

There is reason to believe that the prevalence of asthma is increasing. For example, according to data obtained from England and Wales, there has been a doubling of hospital admissions for asthma in individuals of all ages over the past 15 years: in 1990, individuals over age 15 had approximately 12 hospital admissions per 10,000 patients, children aged 5 to 14 approximately 40 admissions per 10,000, and children under age 4 approximately 100 admissions for asthma per 10,000. In comparison, in 1980, the admission rate per 10,000 patients for children under 4 was approximately 40, i.e., 2.5-fold fewer.

Asthma Mortality

Mortality rates from asthma are difficult to estimate because of the difficulty of establishing asthma as the cause of death. For example, evaluation of death certificates indicates that patients with chronic obstructive lung disease may be improperly coded as having asthma. Despite these limitations, most sources indicate that the death rate from asthma in individuals aged 5 to 34 is between 0.2 and 1 per 100,000 population per year, with the lowest rates occurring in the United States, France, Japan, and Canada and the highest rates occurring in Australia, New Zealand, England, and Wales. It is important to note that death rates from asthma, which were very high in New Zealand over the period from 1975 to 1990, have recently fallen to levels consistent with those found in other countries with similar overall socioeconomic status.

“Natural History”

The “natural history” of asthma is not well established. Although we know that asthma is more common in individuals under age 20 than in older individuals, the odds of a given person's having a clinical remission are not established, and new-onset asthma has been documented in every decade of life. What is not known is in what fraction of individuals asthma will progress to chronic airflow obstruction and whether this progression can be altered by appropriate treatment. There is now evidence, from both longitudinal and cross-sectional epidemiologic studies, to suggest that asthmatic individuals with high levels of airway responsiveness lose lung function at a more rapid rate than asthmatic individuals without elevated levels of airway responsiveness. It is not known whether medications that modify airway responsiveness will be associated with a change in the rate of loss of lung function.

PATHOLOGY OF ASTHMA

Morphologic evaluation of endobronchial biopsy specimens from asthmatic volunteers has contributed to understanding the pathobiology of asthma. It is now well established that the airways of patients with even mild asthma are inflamed; some data suggest that asthma severity parallels the degree of inflammation. The airway inflammation in asthma can be classified into three distinct components (Table 2), each of which is considered separately.

Alterations in airway constitutive cells: Cells ordinarily present in the airway wall, such as epithelial cells, smooth muscle cells, and mast cells, are enhanced in number or express a more proinflammatory phenotype than these cell types in normal individuals.
Increased numbers of infiltrating cells: Leukocytes, such as eosinophils, monocytes, TH_2 lymphocytes, and basophils, are found in the airway wall in greater numbers than in normal individuals.
Changes in the noncellular components of the airway wall: The airway wall is thickened beyond that which can be accounted for on the basis of resident and infiltrating cells alone. These noncellular structural alterations in the airway include changes in the epithelial basement membrane and increased amounts of airway wall and luminal liquid.

TABLE 2. *Airway inflammation in asthma*

Alterations in Airway Constitutive Cells

Both hyperplasia and hypertrophy of the airway epithelial cell layer are present in asthma and contribute to the thickening of the airway wall. Within the epithelial layer there are increased numbers of surface secretory cells as well as hypertrophy and hyperplasia of airway mucus glands. Thickening of the airway smooth muscle layer also occurs. In addition, there is reason to believe that mast cells in the asthmatic airway express a more proinflammatory phenotype than those in the normal airway. These changes result not only in thickening of the airway wall, which promotes airway hyperresponsiveness on a simple mechanical basis, but also in an altered phenotype of the resident cells, which produces a microenvironment whereby activating stimuli enhance the production of prophlogistic mediators and cytokines. These mediators and cytokines in turn contribute to the airway obstruction and hyperresponsiveness that characterize asthma.

Infiltration by Inflammatory Cells

The airway wall in asthma is infiltrated by T lymphocytes bearing the T-helper-2 (TH_2) phenotype. These cells can produce a limited panel of cytokines including interleukin (IL)-3, IL-4, IL-5, and granulocyte–macrophage colony-stimulating factor (GM-CSF). Although the primary signals resulting in the infiltration of the asthmatic airways by this lymphocyte subset have not yet been established, the net effect of the cytokines elaborated is to promote the synthesis of immunoglobulin E (IgE) through the actions of IL-4 on immunoglobulin isotype switching and to enhance the differentiation and migration of eosinophils through the actions of IL-5. There is abundant evidence that IgE and the eosinophil are critical elements in the pathobiology of asthma. We are also beginning to appreciate the potential importance of other proinflammatory cytokines and chemokines, such as IL-1, tumor necrosis factor (TNF)-a, and macrophage inhibitory protein (MIP)-1a, in asthma.

Alterations of the Noncellular Component of the Airway Wall

It is well established that the airway wall is thickened in asthma. Although some of the thickening can be ascribed to the cellular components noted above, other components of the thickened airway are not cellular in nature. The basement membrane is increased in thickness and exhibits alterations in the structure of its collagen components; such thickening promotes airway obstruction and hyperresponsiveness. Liquid that infiltrates the airway wall and surrounding tissues as a result of local inflammation further amplifies airway obstruction.

Potential Schema Linking Airway Inflammation and Asthma Pathobiology

Although the anatomic changes in the asthmatic airway wall are now well established, the mechanisms that link airway inflammation and the altered physiology of asthma remain speculative at best; one potential schema linking the known alterations in the airway wall with the clinical changes that occur in asthma is presented in Fig. 1.

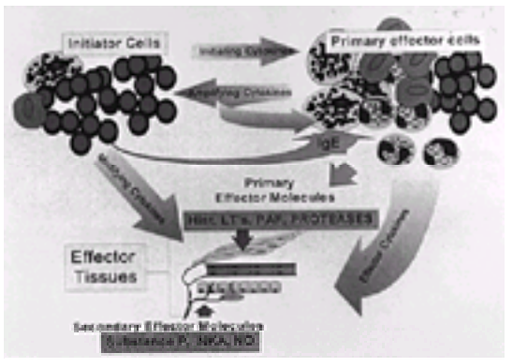

FIG. 1. Schema relating airway inflammation, shown in the top half of the figure, to airway obstruction, shown in the bottom half of the figure. *See Color Plate 17.*

As described above, allergen exposure,[1] via mechanisms that are not fully understood, results in the accumulation in the airway of lymphocytes bearing the TH_2 phenotype. The cytokines elaborated by these cells (and perhaps mast cells, which can also produce IL-4 and other TH_2-type cytokines as well as TNF-a) favor the synthesis of IgE and promote the recruitment of additional T cells, eosinophils, monocytes, and basophils. In addition, the binding of IgE results in immunologically specific sensitization of mast cells, monocytes/macrophages, eosinophils, and basophils. When activated, these cells elaborate mediators of inflammation including histamine, leukotrienes, lipoxins, platelet-activating factor (PAF), and various proteases into the local microenvironment. These molecules, termed *primary effector molecules,* have the capacity to stimulate airway smooth muscle, to alter microvascular permeability, and to promote the release of mucins from airway glands and surface secretory cells. The primary effector cells also secrete cytokines, which amplify the response and perpetuate the asthmatic phenotype by aiding in the recruitment of more inflammatory cells and by having additional proinflammatory effects on smooth muscle and other resident cells. Primary effector molecules can contribute to the inflammatory nature of the lesion (for example, PAF and LTB_4 are potent chemoattractants for eosinophils), and they can also stimulate sensory nerve fibers within the airway, leading to the release of *secondary effector molecules* including substance P and neurokinin A. Nerve stimulation also initiates the release of both vasoactive intestinal peptide and nitric oxide.

The initiation and perpetuation of inflammation in the asthmatic airway thus result in an expansion of the number of primary effector cells and the sensitization of these cells for IgE-dependent mediator release. This process greatly enhances the local production of both primary and secondary effector molecules. Moreover, the effects of some of the products of airway inflammation initiate airway epithelial disruption, which further promotes the asthmatic phenotype.

PATHOGENESIS: LINKS BETWEEN PATHOLOGIC AND PHYSIOLOGICAL FINDINGS

The pathologic changes noted in the airway wall result in the availability in the airway microenvironment of a number of molecules whose presence is thought to be responsible for many of the physiological changes that we recognize as asthma. In general, these molecules fall into three broad categories (Table 3): neurotransmitters, chemical mediators, and cytokines/chemokines. Each of these categories is reviewed separately.

Neural links
Cholinergic neurotransmission via M_3 receptors
Peptidergic nerves
Substance P and neurokinin A: bronchoconstrictor peptides
Vasoactive intestinal peptide: bronchodilator peptides
Nitric oxide
Inflammatory mediators
Histamine
Platelet-activating factor
Leukotrienes
Proteases
Cytokines/chemokines
IL-4
IL-5
TNF-α
Eotaxin
RANTES

TABLE 3. *Molecular links betweeninflammation and asthma*

Neurotransmitters

Cholinergicis

Acetylcholine is released from intrapulmonary motor nerves. The acetylcholine so released can directly stimulate muscarinic receptors of the M_3 subtype found on airway smooth muscle, which cause airway smooth muscle constriction. In addition, it is now established that autonomic ganglia near the airway contain inhibitory autoreceptors, which, when activated, inhibit neurotransmission and thus serve as an endogenous down-regulatory mechanism. Although the specific nature of the human inhibitory autoreceptor is not established on a molecular basis, it is clear that such receptors exist and, if appropriately blocked, may prevent down-regulation of nerve stimulation, hence enhancing airway responses.

Peptidergic Nerves

Peptidergic nerves in the lung are predominantly sensory. Sensory nerve endings contain neuropeptides including substance P and neurokinin A, which, when stimulated by specific action at irritant receptors, result in release of these peptides in the airway microenvironment. At the same time, action potentials are conducted toward the central nervous system to convey the presence of this irritant stimulus. However, as these action potentials cross the terminal ramifications of the airway nerves, antidromic conduction causes the release of the sensory peptides throughout the territory innervated by the specific axon dendrite. This action results in an effective local axon reflex in which sensory nerves serve a motor function. It is well established that both substance P and, to an even greater degree, neurokinin A can constrict airway smooth muscle, thus contributing to the asthmatic diathesis. In addition, these peptides can mediate bronchovascular leak, which may contribute to the pathobiology we recognize as asthma.

In this setting it is important to understand an endogenous down-regulatory mechanism that keeps the physiological effects of these peptides in check. The membrane-bound enzyme neutral metalloendopeptidase (NEP, E.C. 3.4.24.11) is present in the microenvironment where the peptides are released from nerves. It has been shown in both animals and humans that the ability of this enzyme to cleave and inactivate the neuropeptides competes with the ability of neuropeptides to stimulate their specific receptors. It is thought, therefore, that the action of NEP is similar to the action of acetylcholinesterase on acetylcholine; i.e., it is a physiologically important enzyme limiting the expression of the biological actions of neuropeptides. It is of interest to note that conditions such as viral infections and exposure to certain pollutants are associated with decreased NEP activity, which would allow peptides cleaved by NEP not to be cleaved and their “proasthmatic” actions to be amplified.

Vasoactive intestinal peptide (VIP) is a 28-residue peptide found in airway nerves, which can relax airway smooth muscle and may serve as an endogenous bronchodilator. It can be cleaved and inactivated by NEP, which thereby limits its physiological actions. It can also be cleaved by the mast-cell enzyme tryptase, found in enhanced amounts in the asthmatic airway after allergic activation. Inactivation of VIP by tryptase may contribute to enhanced airway responses in the setting of allergic activation.

Nitric Oxide

Nitric oxide is an endogenous molecule with both proinflammatory and bronchodilator actions. It has been shown by a number of groups that nitric oxide can be produced by airway nerves, as indicated by the presence of the neural form of nitric oxide synthase in airway nerves in both normal and asthmatic subjects. However, the role of nitric oxide released from airway nerves in asthma is not known. Nitric oxide can also be produced in large quantities by airway epithelium that has been

stimulated by inflammatory cytokines; nitric oxide released in this setting likely serves a proinflammatory role.

Inflammatory Mediators

Inflammatory mediators are molecules produced by inflammatory cells in the asthmatic lesion that have the capacity to mediate physiological effects consistent with the abnormalities seen in asthma; a mediator is distinct from a hormone in that a mediator's activity occurs near the site of its production or release.

Histamine

Histamine, or b-imidazolylethylamine, is formed by mast cells found in the airway lumen or in the airway wall. Histamine can cause airway narrowing when given by inhalation in normal and asthmatic subjects; patients with asthma are more sensitive to the effects of histamine than normal subjects. Although histamine is present in the airway, agents that inhibit the action of histamine, i.e., antihistamines, have not been very successful in asthma treatment. This observation has been interpreted to indicate that histamine plays a secondary role in the biology of asthma.

Platelet-Activating Factor

Platelet-activating factor is a phospholipid that differs from other phospholipids in that it has an ether rather than an ester link in the *sn*-1 position and an acetyl moiety in the *sn*-2 position; phosphatidylcholine is found in the *sn*-3 position. Experiments in animals and humans have shown that platelet-activating factor is a bronchoconstrictor of modest potency and can sensitize airways to the effects of other bronchoconstrictor mediators. Although a number of clinical trials have been conducted in patients with asthma to determine whether antagonists of the action of platelet-activating factor at its receptor will improve asthma control, none of the trials performed to date has been successful in demonstrating such an effect. Therefore, it remains an open question as to whether platelet-activating factor has a significant role in the biology of asthma.

Leukotrienes

The cysteinyl leukotrienes known as LTC_4, LTD_4, and LTE_4, as well as the dihydroxyleukotriene, LTB_4, are derived by the sequential lipoxygenation of arachidonic acid, which is released from cell membrane phospholipids during cellular activation. 5-Lipoxygenase, a cytosolic protein known as the 5-lipoxygenase activating protein, and LTC_4 synthase are the enzymes required to produce the cysteinyl leukotrienes, whereas LTA_4 hydrolase rather than LTC_4 synthase is needed to produced LTB_4. Mast cells, eosinophils, and alveolar macrophages each have the capacity to produce cysteinyl leukotrienes when appropriately activated. Cysteinyl leukotreines may also be formed by transcellular metabolism in which the first components of the reaction (e.g., LTA_4) are contributed by one cell type, such as polymorphonuclear leukocytes, and other components are provided by other cell types, such as pulmonary epithelial cells.

The major physiological role of LTB_4 is that of a chemotactic factor, whereas the predominant physiological role of the cysteinyl leukotrienes is that of bronchoconstrictor mediators. The cysteinyl leukotrienes are known to play a partial role in mediating the constrictor biology of asthma, and agents that inhibit the synthesis of leukotreines or their action at leukotreine receptors are now established to have a beneficial effect in asthma. These benefits include chronic bronchodilation, improved asthma symptoms, and a decreased need for steroid rescue treatments.

Proteases

A number of proteases are produced by mast cells when activated. Although these enzymes themselves cannot be considered mediators, their biological effect is to cleave active mediators from substrates in the airway microenvironment. Enzymes such as tryptase, chymase, and kallikreins are found in mast cells. Although the endogenous substrates and the molecules formed through cleavage by the action of tryptase and chymase are not known, kallikreins cleave kinins from kininogen. Kinins, such as bradykinin, are potent bronchoconstrictor molecules and can induce microvascular leak. In trials in human subjects, aerosols generated from bradykinin solutions have been shown to induce symptoms consistent with asthma.

Cytokines/Chemokines

The putative role for cytokines and chemokines is to amplify and modify the inflammatory cellular response. These effects are detailed in the previous section. However, there is reason to believe that cytokines may also modify the capacity of effector tissues to respond to stimulation.

PHYSIOLOGICAL ALTERATIONS IN ASTHMA

The predominant physiological effect observed in asthma is airway obstruction, which results from celluar infiltration of the airway wall, thickening of the airway wall by the presence of edema and other liquids, and smooth muscle constriction. When these anatomic events (airway wall stiffening and luminal narrowing) take place, airflow obstruction occurs. From the physics of flow limitation, we know that maximal expiratory airflow rates vary directly with the airway area (smaller areas lead to decreased flows) available for airflow to the third power, whereas increasing airway wall stiffness increases maximal airflow rates to the first power. Therefore, decreasing airway diameter has a much more powerful effect on airflow than increasing airway wall stiffness. The effects of narrowing and stiffening of airways are a decreased forced expiratory volume in the first second (FEV_1) as well as decreased flow rates throughout the vital capacity. Because of the nonhomogeneous nature of airway narrowing, when a maximal expiratory flow–volume maneuver is performed, airflow proceeds first from those units that are least obstructed and then from those that are most obstructed, thus resulting in a characteristic “coved” shape to the flow–volume curve, with the less obstructed units emptying higher in the vital capacity. Administration of a bronchodilator improves flow rates throughout the vital capacity and straightens this expiratory coving. Physiological studies indicate that, during a spontaneous acute asthmatic episode, airway obstruction occurs originally in airways of all sizes, but resolution occurs first in the large airways and later in the peripheral airways. This series of events is reflected in asthma as the airflow rates normalize first high in the vital capacity and later low in the vital capacity. Indeed, it is quite common to find a patient with very mild asthma and a normal FEV_1 whose flow–volume curve will be concave toward the volume axis. In such individuals, the major physiological abnormality is that flow rates low in the vital capacity are substantially depressed; this is reflected by a low maximum midexpiratory flow rate on spirometric tracings.

Because asthma is a disease of the airways, there are no primary changes in the static pressure–volume curve of the lungs. However, during an acute asthmatic episode it is common for airway narrowing to be so severe as to result in complete airway closure. Because individual lung units tend to close at a volume that is close to their maximal volume, this trapped gas results in a change in the static pressure–volume curve of the lung such that for a given volume of gas contained within the thorax, there will be reduced elastic recoil. The physiological consequence of this elastic recoil is to depress expiratory flow rates by reducing the effective driving force for airflow.

Additional factors influence the mechanical behavior of the lungs during an acute attack of asthma. During normal ventilation, as the diaphragm descends, pleural pressure drops from its value of –3 to –5 cm H_2O at functional residual capacity to –5 to –10 cm H_2O at the end of a normal inspiration. However, because there is airflow obstruction in asthma, it is necessary for a larger negative inspiratory pressure to be generated to create airflow. During expiration, as the patient tries to force air from his or her lungs, pleural pressures become quite high. Therefore, the pressure swings, and the subsequent energy that must be expended during a ventilatory cycle, are much greater in patients with asthma than in normal subjects. During acute episodes of asthma, increased respiratory rate, coupled with increased airway resistances, results in a work of breathing that may be more than ten times greater than in normal subjects.

The airway obstruction in asthma causes a maldistribution of ventilation relative to perfusion. Under normal circumstances, most units have a ventilation to perfusion ($\dot{V}/Q$) ratio (when ventilation and blood flow are both measured in liters/min) on the order of unity (i.e., numerically equal to 1). In patients with asthma, many units have $\dot{V}/Q$ ratios far below unity, a maldistribution that results in arterial hypoxemia, which can usually be corrected with small amounts of supplemental oxygen. This is of more than passing therapeutic interest, because administration of oxygen mixtures containing a high F_IO_2 promotes absorption atelectasis. Therefore, only the minimal amount of oxygen required to achieve saturations on the order of 92% to 93% should be administered to such patients.

Irritant stimuli that impinge on the airway in asthma result in tachypnea, which in turn causes hyperpnea out of proportion to that required to maintain normal ventilatory needs. Indeed, most patients with asthma have partial pressures of CO_2 in the arterial blood that are below normal. It has been demonstrated that the P_aCO_2 in patients with asthma decreases in direct proportion to the fraction of the predicted value recorded for the FEV_1 until an FEV_1 on the order of 25% of predicted is achieved. For example, a patient with an FEV_1 45% of predicted will have a lower P_aCO_2 than a patient with an FEV_1 65% of predicted. When the FEV_1 falls below 45% of predicted, the mechanical load to ventilation is so great that the P_aCO_2 increases.

CLINICAL PRESENTATION

A number of the most common distinct clinical presentations of asthma are reviewed separately.

Acute Asthma

During an acute asthmatic episode, the patient experiences airway obstruction that causes symptoms of breathlessness and anxiety, commonly accompanied by wheezing and on occasion cough. The resolution of these symptoms and physical findings usually occurs within 1 to 3 days without specific therapy and may occur within hours if specific therapy is given. During the intervals between episodes of airway obstruction, airflow is normal, and the patient is asymptomatic. A number of distinct conditions associated with airway obstruction are reviewed.

Exercise-Induced Asthma

Individuals who exercise for brief periods of time, on the order of 15 to 20 min, commonly develop airway obstruction after the cessation of exercise. Obstruction usually begins 5 to 10 min after the completion of exercise and resolves in 1 to 4 hrs. Exercise stimuli such as skiing, playing ice hockey, or running in the cold are commonly known to bring on exercise-induced asthma, whereas other forms of exercise such as swimming do not predispose to airway obstruction, probably because of the temperature and high humidity of the air being inspired. Patients with this condition can often prevent exercise-induced asthma symptoms by inhaling a b-adrenergic agonist before exercising.

Cold-Dry-Air-Induced Asthma

This asthma is induced by a change from breathing in a relatively warm atmosphere laden with water to one that is dry and cool. For example, when one exits a heated house into cold dry outdoor air in the winter in northern climates or, conversely, when one goes from warm and humid outdoor air into a dry air-conditioned environment in the summer (mall asthma), asthma attacks may be provoked. In taking a history from a patient with potential asthma, it is worth inquiring whether shortness of breath is induced by this type of environmental change.

Allergen-Induced Asthma

Allergen-induced asthma is one of the best-understood forms of asthma; it likely results from the direct effects of mediators released from inflammatory cells as a consequence of clustering of IgE receptors on the surface of effector cells. Common allergens inducing asthma are cat allergen (Fel D1), house dust mite allergen (der P1), and tree and grass pollens. Because of the high prevalence of cat and house dust mite allergy, specifically asking whether patients develop shortness of breath in the presence of a cat is worthwhile. Furthermore, patients with house dust mite allergy often develop asthmatic symptoms on entering rooms with high concentrations of this allergen, for example, a carpeted bedroom where the humidity is relatively high.

Virus-Induced Asthma

Many individuals with a history of asthma will be relatively asymptomatic until they contract a viral illness, when asthma may occur without other known inciting stimuli. In the absence of therapy, it may take weeks or months for lung function to return to normal.

Occupational or Environmental Asthma Without Simple Allergy Mechanisms

A wide range of conditions can cause asthma in the workplace. The important historical clues relate to the onset of asthma in relationship to workplace exposure. An early response can occur within a few hours, a late response within 8 to 12 hrs. It is important to note that many cases of occupational asthma do not resolve quickly when the patient leaves the workplace environment; therefore, the absence of this finding does not make occupational asthma less likely.

Aspirin-Induced Asthma

Approximately 1% to 10% of patients with moderate-to-severe asthma have aspirin-induced asthma, which consists of symptoms of moderately severe airway obstruction, rhinorrhea, sneezing, tearing, dermal changes, and, in some patients, GI changes (cramping, nausea, or vomiting) after exposure to aspirin or other agents with the capacity to inhibit prostaglandin H synthase type I (PGHS-1 or cyclooxygenase type I). This syndrome has a characteristic onset in the second to third decade of life and is associated with sinusitis and nasal polyposis. Aspirin-induced asthma is an important specific diagnosis to make for two reasons: first, patients may have life-threatening asthma if they take aspirin or even other cyclooxygenase inhibitors; second, there is a relatively specific treatment for this entity, namely inhibition of the 5-lipoxygenase pathway through the use of leukotriene receptor antagonists or synthesis inhibitors.

Acute Severe Asthma

Acute severe asthma is a more severe and prolonged version of an acute asthmatic episode. Quite often individual acute asthmatic episodes will run together, and the patient may give a history of many days to weeks of shortness of breath with diminishing response to therapy. Patients often treat themselves repeatedly with b-adrenergic agonists and finally seek acute medical attention when airway obstruction is so great as to make normal ventilation impossible and collapse and asphyxia are imminent. This syndrome is not pathogenetically distinct from acute asthma but rather represents a more severe prolonged form of acute asthma.

Chronic Stable Asthma

Chronic stable asthma is the name given to the syndrome characterized by episodes of asthmatic symptoms and airflow obstruction that recur. Although there may be one or two severe episodes over the course of many months, most episodes of asthma are of moderate severity. Asthmatic symptoms can be controlled through chronic medication use.

PHYSICAL EXAMINATION

Vital Signs

Patients with asthma have tachypnea, with respiration rates often 25 to 40 breaths/min, accompanied by tachycardia, with pulse rates of about 100 as well as pulsus paradoxus, an exaggerated inspiratory fall in the systolic blood pressure. It is now well established that the magnitude of the fall in systolic blood pressure reflects the magnitude of a negative inspiratory swing in pleural pressure and thus is proportional to the severity of the asthma attack.

Thoracic Examination

During an acute attack of asthma, the chest is hyperinflated, which can be appreciated on inspection. During asthma attacks patients use their accessory muscles of inspiration. Because of the substantially negative pleural pressure generated during inspiration, the skin over the intercostal spaces may be retracted during the inspiratory phase. The expiratory phase is active, with the patient making efforts to expire air from the thorax, which causes expiratory bulging of the skin over the intercostal spaces.

Percussion of the thorax demonstrates hyperresonance, with loss of the normal variation in dullness from diaphragmatic movement.

The cardinal physical finding in asthma is wheezing. Wheezing is commonly heard during both inspiration and expiration; it tends to be louder during expiration. Wheezing is polyphonic (more than one pitch can be heard simultaneously) and is to be distinguished from monophonic wheezing, which suggests airway obstruction by fixed bronchial or tracheal lesions.

It is important to note that not all patients with asthma have wheezing. Some individuals have normal chest examinations even though they may have airflow obstruction. Second, not all wheezing illnesses are asthma (see Table 4). In addition to wheezing, rhonchi may suggest the presence of free secretions in the airway lumen, and rales suggest a condition other than simple asthma, such as localized infection or cardiac failure, and should prompt appropriate diagnostic tests. Absent or

low-intensity breath sounds indicate severe airflow obstruction.

Acute bronchiolitis (infectious, chemical)
Airway obstruction by masses
Central thoracic tumors
Metastatic cancer
Primary lung tumors
Substernal thyroid
Aspiration (foreign body)
Bronchiolitis obliterans organizing pneumonia (BOOP)
Bronchial stenosis
Carcinoid syndrome
Cardiac failure
Chronic bronchitis
Cystic fibrosis
Endobronchial sarcoid
Eosinophilic pneumonia
Pulmonary emboli
Systemic mastocytosis
Systemic vasculitis (polyarteritis nodosa)

TABLE 4. *Differential diagnosis of wheezing illnesses other than asthma*

LABORATORY FINDINGS

Pulmonary Function Testing

Decreased airflow rates throughout the vital capacity are the most common pulmonary function abnormality in mild asthma, as reflected by abnormalities in the peak expiratory flow rate (PEFR), the FEV_1, and the maximum mid-expiratory flow rate (MMEFR; $FEF_{25–75}$). As mentioned previously, when tests of forced expiration are presented in a flow–volume configuration, the curve is characteristically coved (Fig. 2).

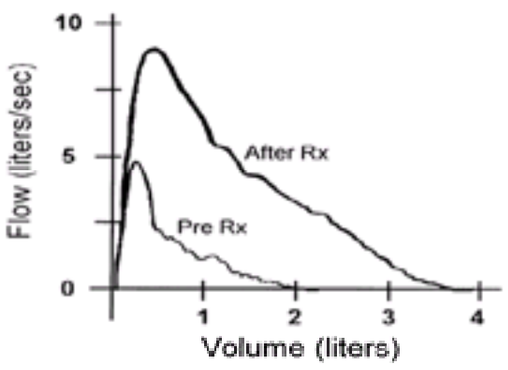

FIG. 2. Actual flow volume curves from a 28-year-old woman with moderate asthma before (pre-Rx) and after (after Rx) treatment with inhaled steroids. Because absolute lung volumes were not measured, curves were “matched” at total lung capacity. Note that treatment increased flows over the entire vital capacity and resulted in a straightening of the curve over the lower 50% of the vital capacity.

The severity of asthma attacks must be assessed by accurate and reproducible objective measures of airflow. Even in the patient who has asthma so severe that an entire spirogram cannot be recorded, a forced expiration of 1-sec duration will allow the FEV_1 to be measured; forced expirations of even shorter durations are all that is required to measure the peak expiratory flow rate. These measures will allow the physician to assess the adequacy of current therapy and the need for further therapy, prolonged attention at an emergency service, or admission to hospital.

As the attack resolves, the peak expiratory flow rate and the FEV_1 both increase while the MMEF usually remains substantially depressed. Even after substantial resolution of the attack leading to normalization of both the FEV_1 and the peak expiratory flow rate, the maximal expiratory flow rate may be depressed to 60% of predicted. Indeed, it may take weeks to months for this index to return to normal.

Airway Responsiveness Testing

Airway responsiveness testing measures the bronchoconstrictor response elicited by a standard stimulus. A schematic diagram of the airway responsiveness test (Fig. 3) shows the response in normal subjects and patients with mild or moderate severe asthma. In this test, the patient is asked to inhale an aerosol generated from solutions containing graded amounts of a bronchoconstrictor agonist, most commonly methacholine and histamine; the FEV_1 response is measured after administration of the agonist. If, after a given dose of agonist, a response of the proposed magnitude is not achieved, the dose is increased by a factor of 2 or 3, and the challenge is repeated. This cycle is repeated until the FEV_1 falls 20%. The interpolated concentration of agonist that would have decreased the FEV by 20% is termed the PC_{20}. The test is used diagnostically when it is not clear from a patient's history or response to medication whether asthma is the correct diagnosis. If the patient's FEV_1 before the test is less than 60% of predicted, the test carries additional risk and should be performed only by laboratories experienced in this testing maneuver. Airway responsiveness is not a fixed entity but rather reflects the inflammatory microenvironment of the airway wall, as noted in the asthma pathology section. Therefore, it will change in response to specific treatment.

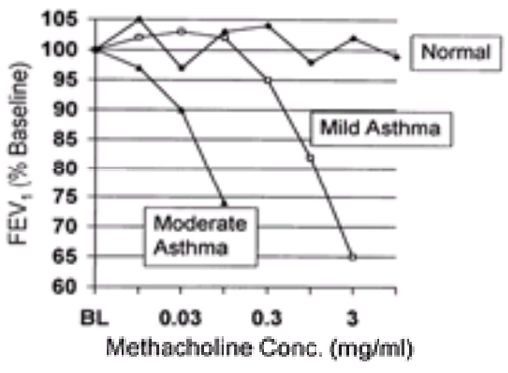

FIG. 3. Schematic methacholine dose–response curves for normal subjects, patients with mild asthma, and patients with moderate asthma. The calculated PC_{20} values for the patients with asthma are approximately 0.08 mg/ml and 1.2 mg/ml. Note that a PC_{20} cannot be calculated for the normal subjects.

Arterial Blood Gases

Analysis of arterial blood carbon dioxide and oxygen tensions need not be undertaken in individuals with mild asthma. However, if the asthma is sufficiently severe to merit prolonged observation, then arterial blood gas analysis is indicated. As noted above, hypoxemia and hypocarbia are the rule. For a patient with a mild attack of asthma, the P_aO_2 is usually between 55 and 75, and the P_aCO_2 between 25 and 35. It is important to note that, if an asthma attack is chronic, the hyperventilation associated with the attack results in a compensatory metabolic acidemia in which the kidneys excrete bicarbonate to normalize pH. Thus, an individual with a prolonged

attack of asthma may have only a slightly alkalotic pH but at the expense of a low serum bicarbonate level. If such a patient deteriorates so that he or she is no longer able to defend a low P_aCO_2, the pH will fall more rapidly than it would in a normal individual. Thus, patients with asthma who show signs of moderately severe airway obstruction but have normal carbon dioxide tensions require very close monitoring.

Other Findings in the Blood

Patients with asthma frequently have atopy; therefore, blood eosinophilia on the order of 4% to 8% is common. In addition, elevated serum levels of IgE are often used as an index of the atopic state. Indeed, epidemiologic studies indicate that asthma is unusual in subjects with low IgE levels. Furthermore, as indicated by the patient's specific history, specific radiooligosorbent tests (RAST) can be conducted to determine the amount of IgE specifically directed against an offending antigen.

Severe cases of asthma can be associated with elevated serum concentrations of aminotransferases, lactate dehydrogenases, muscle creatinine phosphokinase, transcarbamylase, and antidiuretic hormone. Furthermore, therapy with b-adrenergic agonists, may create low serum potassium levels.

Radiographic Findings

In most cases, chest radiographs in patients with asthma are normal. Therefore, unless specifically indicated by adventitious findings on chest examinations or other physical findings suggestive of an infectious illness, or by unusually severe asthma, chest radiography is not indicated. If a patient's asthma is severe enough to merit hospital admission, a chest radiograph is advised. In patients with severe asthma, the x-ray may show hyperinflation, indicated by depression of the diaphragm, and abnormally lucent lung fields. Complications of severe asthma include pneumomediastinum and pneumothorax, which may be detected only radiographically.

Electrocardiographic Findings

In most cases of asthma, the electrocardiogram is remarkable only for sinus tachycardia. In severe attacks right axis deviation, right bundle branch block, P pulmonale, or even ST-T wave abnormalities may occur. If these abnormalities resolve as the asthma attack resolves, they will require no further follow-up. In individuals with substantial cardiac risk factors or a cardiac history, electrocardiographic findings of myocardial infarction should be monitored because of the stress induced by the attack.

Sputum Findings

Between acute asthma attacks, in the absence of infection, the sputum of patients with asthma is usually clear. During an acute asthma attack, even without infection, the sputum may be green to yellow from eosinophil peroxidase. Indeed, the presence of yellow-green sputum does not necessarily indicate infection, and examination of a Gram stain and Wright stain of the sputum is indicated to determine whether the sputum contains asthmatic or infective findings. Asthmatic findings include eosinophils, Charcot-Leyden crystals (crystallized eosinophil lysophospholipase), Curschmann's spirals (bronchiolar casts composed of mucus and goblet cells), or Creola bodies (clusters of airway epithelial cells with identifiable, quite often beating, cilia).

ASTHMA TREATMENT

Asthma treatment is undergoing substantial evolution as we learn how to use most effectively agents that are currently available and those that are being newly introduced. The treatment of asthma is aimed at alleviating asthma symptoms by treating airway obstruction and modifying various aspects of the previously described inflammatory events. It cannot be overemphasized that it is necessary to follow the progress of asthma treatment by using objective measures of airway obstruction; this is critical so that the success or failure of a treatment can be documented. Asthma therapy is best approached by a standard format: first, the severity of the patient's asthma is assessed; second, treatment appropriate for the severity is initiated; third, the response to this therapy is monitored; and fourth, the therapy is modified, if need be, depending on the response. Before specific treatment outlines are reviewed, we will discuss the medications available for use.

Inhaled b-Adrenergic Agonists

Inhaled medium-acting b-adrenergic agonists are the mainstay of bronchodilator treatment for asthma. These agents relax airway smooth muscle, which is constricted as a result of stimuli in the asthmatic microenvironment. b-Adrenergic agents with varying degrees of b_2 selectivity are available for use in inhaled (by metered-dose inhaler or nebulizer), oral, or parental preparations. b-Adrenergic agents, with selective b_2 action are also available in medium-duration and long-duration formulations (Table 5).

Short acting (onset less than 5 min; duration 2–3 hr)
Epinephrine—α and β agonist, not β_2 selective
Isoproterenol—nonselective β agonist
Medium acting (all are β_2 selective; onset 10–15 min; duration 4–6 hr)
Albuterol
Bitolterol
Isoetharine
Metaproterenol
Pirbuterol
Terburtaline
Long acting (onset 1–2 hr; duration 10–14 hr)
Salmeterol

[a] As of June 1, 1995.

TABLE 5. *Inhaled b-agonist for asthma treatment available in the United States*[a]

Because these agents are commonly administered by metered-dose inhaler, it is worthwhile to review the steps required for appropriate use of a metered-dose inhaler. Patients should be instructed to exhale to a comfortable volume in the expiratory reserve volume, to breathe in slowly (approximately 0.5 L/sec), to actuate the inhaler as they inspire, then to complete a slow inspiration to near total lung capacity and hold their breath for 5 sec. Because most individuals have a vital capacity of several liters, this will mean that the inspiratory effort should take 3 to 6 sec; inhaling too rapidly is a common mistake, and care should be taken to ensure that patients inspire slowly. Patients need to have specific instruction in inhaler use and should be asked to demonstrate their technique. Particular attention should be paid to female patients who historically do not use their inhalers as well as male patients. Patients who have difficulty coordinating the onset of inspiration with firing the metered-dose inhaler should be given aerosol “spacers” available from many manufacturers.

The “best” use for long-acting b-agonists has not been established. One use, which is well accepted, is to provide overnight bronchodilation for individuals with nocturnal asthma symptoms. Patients need to be specifically instructed not to use these agents for the relief of acute bronchospasm.

Theophylline

Theophylline and aminophylline are bronchodilators of moderate potency with a long history of use in asthma. The mechanism by which they exert their effect has not been established with great certainty, but it is likely related to the inhibition of certain forms of phosphodiesterase. One of the major difficulties with using theophylline is its relatively low therapeutic-to-toxic ratio because of substantial variations in the rate of its metabolism both in a single individual over time and among individuals in a population. Because of this variability, monitoring of plasma theophylline levels is indicated so that patients who are taking theophylline get adequate medication to achieve a bronchodilator response without excess risk of toxicity. Acceptable plasma levels for therapeutic effects are between 10 and 20 µg/mL; higher levels are associated with gastrointestinal, cardiac, and central nervous system toxicity, including symptoms such as headache, nausea, vomiting, diarrhea, cardiac arrhythmias, and seizures. Because catastrophic complications may occur without any mild adverse effects when plasma levels exceed 20 µg/mL, careful monitoring of plasma level is very important. Indeed, many physicians aim for a steady therapeutic level of 10 to 12 µg/mL, which allows for a decrease in the rate of metabolism without toxicity but does not maximize the therapeutic benefits of theophylline.

Theophylline comes in a variety of preparations, including a number of oral preparations that can be taken only twice a day and preparations for intravenous use. The prior practice of using rectal theophylline suppositories to treat nocturnal asthma has been superseded by longer-acting oral preparations of theophylline as well as

longer-acting b-adrenergic bronchodilators.

Systemic and Inhaled Corticosteroids

Corticosteroids are a widely used and effective treatment for moderate to severe asthma. Although they are effective, their mechanism(s) of action in asthma has not been established but appears to be linked to their ability to inhibit a wide variety of inflammatory processes. Indeed, it may be that the multiple potential mechanisms of steroid therapy account for their effectiveness in many patients with asthma. Despite the effectiveness of steroids during therapy, the disease will usually exacerbate again when treatment is stopped.

There is no consensus on the specific type, dose, or duration of corticosteroids to be used in the treatment of asthma. In nonhospitalized patients with asthma that is not responding to standard treatment, a steroid “pulse” with initial doses of prednisone on the order of 40 to 60 mg/day is indicated. This dose is tapered to zero over the ensuing 1 to 2 weeks. If the patient's asthma reexacerbates during this period, the dose is increased, and the process is restarted. In the occasional rare patient whose asthma is so severe as to require continuous treatment with steroids, it is far superior to find a regimen of treatment on an every-other-day rather than every-day basis, as such alternate-day treatment tends to diminish many of the severe adverse effects of oral steroid therapy.

For patients whose asthma requires in-hospital treatment but is not considered life-threatening, methylprednisolone, 20 mg given every 6 hrs, will have a therapeutic effect observable within the first 12 to 18 hrs. In attacks of asthma that are considered life-threatening, intravenous methylprednisolone, 125 mg every 6 hrs has been advocated. Although the data touting the superiority of this dosage over the smaller dose have not been established through clinical trials, clinical experience suggests that it is effective. In each case, as the patient improves, oral therapy is substituted for intravenous therapy, and the oral dose is tapered over 1 to 3 weeks, with inhaled corticosteroids added to the regimen while oral steroids are being tapered.

Inhaled corticosteroids, which have many fewer systemic adverse effects than oral corticosteroids for a given level of therapeutic effect, are important therapeutic agents in asthma. A large number of clinical trials indicate that inhaled steroids are effective asthma therapy. With the steroids available for asthma treatment in the United States, dosage begins with four “puffs” a day. If the patient fails to respond, the steroid dose may be increased up to 1.5–2.0 mg/day. Although inhaled steroids at the lower doses are highly likely to be safe for long-term asthma therapy, the safety of long-term treatment with high-dose inhaled steroids has not been well established. The major adverse effect of inhaled steroids is oral thrush, which can be prevented by good oral hygiene and the use of aerosol spacers. On the basis of the relative risks of oral and inhaled steroid therapy, there is no question that inhaled steroid therapy is far safer.

Other Nonbronchodilator Antiasthma Drugs

Disodium chromoglycate and nedocromyl sodium are agents whose specific mechanism of action is not yet established. Both are used in the prophylaxis rather than in the acute treatment of asthma. Indeed, both of these agents are most useful when identifiable stimuli such as exercise or allergen exposure can be shown to elicit an asthmatic response; they tend to be more useful in pediatric than in adult populations.

Cyclosporine or methotrexate has been shown in research studies to be useful as adjunct therapy for patients with severe chronic asthma who cannot otherwise discontinue treatment with oral corticosteroids. The use of these agents in asthma is still experimental and should be confined to the asthma specialist with experience in their use.

Receptor Antagonists

Antihistamines

H_1 receptor antagonists such as astenizole, ceterazine, loratidine, and terfenidine have been shown to have a measurable, but not marked, effect on asthma symptoms. These agents are not used in the treatment of asthma directly but are generally reserved for patients with concomitant allergic diathesis.

Anticholinergics

Although atropine can be shown to have a bronchodilator effect in patients with mild to moderate asthma, it is not as effective as a b-adrenergic bronchodilator. The availability of ipratropium bromide by metered-dose inhaler, provides an alternative asthma therapy for those individuals who find b-adrenergic adverse effects intolerable.

Agents Active on the 5-LO Pathway

Agents (montelukast, pranlukast, and zafirlukast) have been developed that can inhibit the action of cysteinyl leukotrienes at their receptor ($CysLT_1$ receptor) or can prevent the synthesis of leukotrienes (zilestun). Studies in patients with chronic stable asthma show that treatment with these agents results in persistent bronchodilation, reduced asthma symptoms, reduced medication use, reduced awakenings from sleep at night, and diminished need for prednisone rescue therapy. Because they have just recently become available by prescription, specific roles in asthma treatment has not been codified; their use is advocated for the treatment of chronic persistent asthma.

SPECIFIC TREATMENT SCENARIOS

These treatment guidelines have been adapted from the National Asthma Education Program and from the Global Initiative on Asthma. They represent a broad overview of the detailed guidelines, which can be found in the specific source documents available from the United States National Institutes of Health or from the World Health Organization.

Management of Mild Intermittent Asthma

Most patients with asthma have mild asthma and require only intermittent therapy. These are patients who usually have up to twice-weekly episodes of dyspnea, cough, and wheezing. They tend to be asymptomatic between exacerbations but may develop symptoms with strenuous physical activity. They are awakened from their sleep less than twice a month by asthmatic symptoms. Such individuals usually have FEV_1 values or peak flow values greater than 80% of predicted when they are asymptomatic; when they are symptomatic, these flow rates may fall. The treatment for these people is one or two puffs of an inhaled b agonist by metered-dose inhaler before participation in events known to precipitate asthma or when asthmatic symptoms have been precipitated. Patients should be instructed to monitor peak flow rates during such attacks to ensure that they return to normal with inhaled agonist use.

Current data indicate that patients with very mild symptoms should be treated with inhaled b-agonists on an “as needed” only basis. If symptoms occur intermittently and lung function can be normalized with intermittent b-agonist this treatment is adequate. Indeed, if asthma can be controlled totally (symptoms and flow rates) by use of a single 200-actuation b-adrenergic agonist each month no additional treatment is warranted.

Management of Mild to Moderate Persistent Asthma

Patients with mild to moderate persistent asthma have symptoms more than twice a week that usually affect their ability to sleep through the night. Patients can perform the more sedentary activities of daily life but are often limited by asthma symptoms in activities requiring higher levels of exertion. These patients have asthma exacerbations that last 2 to 3 days and need to seek emergency care on occasion. Most important, patients in this category will have FEV_1 values of 60% to 80% of predicted when they are only mildly symptomatic and substantially greater decrements in airflow when they are more symptomatic. Primary treatment for this group of individuals should consist of either inhaled corticosteroids or antileukotriene. The starting dose should be that recommended by the package insert for the product to be used. The dose of inhaled steroids may be increased or anti-leukotriene and inhaled steroid therapy combined until the patient has asthma symptoms and lung function more characteristic of mild than of moderate disease. Patients should be instructed to use their b-agonist inhalers on an as-needed basis. If asthma cannot be controlled through the use of inhaled steroids and b-agonists, additional therapy including sustained-release theophylline, or oral b-agonists should be added. Specific evidence based on treatment guidelines indicating which of these agents is most effective have not been drafted, and it is currently a matter of choice for patients and their physicians.

Severe Persistent Asthma

Patients with severe persistent asthma have continuous symptoms; the activities of daily life are always limited by their asthma. These individuals often have difficulty sleeping through the night and have exacerbations with even very mild exercise. Lung function monitoring shows FEV_1 or peak flow values less than 60% of predicted but varying widely depending on the patient's activity and exposure. In addition to the medications used for chronic moderate asthma, oral corticosteroids are often required daily or every other day. Here the goal of treatment is to reduce the patient's asthma severity to that of chronic moderate asthma.

The guidelines given above are for adult patients, and pediatric guidelines are different; the interested reader is referred to source documents for specific treatment scenarios.

Asthma in the Emergency Room

When a patient with asthma presents for acute emergency care, objective measures of the severity of the asthma attack must be obtained, including measurements of airflow such as the peak expiratory flow rate or FEV_1. If this rate is less than 40% of predicted, but the attack does not appear to be life-threatening, inhaled b-agonists (such as albuterol given by nebulizer 2.5 mg every 20 min) should be used. If there fails to be an objective response (FEV_1 or peak flow) to treatment within 60 min, intravenous steroids (40 to 60 mg of methylprednisolone) should be administered. Inhaled treatment should continue at 20- to 30-min intervals until the peak flow rate or FEV_1 rises to more than 50% of predicted values. If this point is not reached within 2 hrs, admission to the hospital for further treatment is strongly advocated.

For the patient who has peak expiratory flow rates and FEV_1 values greater than 60% of predicted on admission to the emergency room, treatment with inhaled b-agonists alone is likely to achieve a salutary therapeutic response. Again, this should be documented by an objective improvement in airflow rates. If significant improvement takes place in the emergency room, these patients can usually be treated as outpatients and given inhaled b-agonists plus inhaled corticosteroids. The dose of inhaled steroids should depend on the severity of the attack and the rapidity of response to treatment; common recommended doses are 200 to 400 µg twice a day for at least 2 weeks following the acute attack. In those patients whose asthma is intermediate in severity between the two scenarios given above, the treatment plan should be intermediate in complexity and duration.

Acute Severe Asthma

The patient with asthma whose FEV_1 or peak flow does not increase to greater than 40% of the predicted value with treatment, whose $PaCO_2$ is within the normal range in the presence of severe airflow obstruction, or who develops life-threatening complications such as pneumothorax or pneumomediastinum should be admitted to the hospital in a setting where they can be closely monitored. These patients should be given frequent treatment with inhaled b-agonists, intravenous amyinophylline at doses yielding maximum safe plasma levels (i.e., 15 to 20 µg/mL), and high-dose intravenous steroids. Oxygen should be titrated to achieve S_pO_2 values between 92% and 94%; higher levels promote absorption atelectasis, which may be detrimental. A search for specific objective evidence for bacterial infection should be made, and appropriate treatment administered only if clear evidence is found. If the patient fails to respond despite intensive inhaled therapy, it may be necessary to institute endotracheal intubation and mechanical ventilation. Remember that asthma is a difficulty of expiratory airflow, and ventilators provide only inspiratory assistance. Because it is quite easy to achieve a state of chronic pulmonary overdistention in the process of mechanical ventilation, one should administer mechanical ventilation just adequate to sustain life and not to normalize arterial blood gases. For example, a PCO_2 of 50 to 70 torr is acceptable in a patient with status asthmaticus; this approach is known as “permissive hypercapnia.” Indeed, in these individuals it is quite often necessary to institute heavy sedation or in extreme cases pharmacologic muscle paralysis to achieve the appropriate stage of relaxation to permit mechanical ventilation.

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[1] Other activation mechanisms such as neural or physical activation of mast cells could initiate the secretion of IL-4, which subsequently could aid in the recruitment of lymphocytes through alteration in the expression of cellular adhesion structures. The details of such mechanisms have not been elucidated.

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CHAPTER

41 Bronchiectasis

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INTRODUCTION

Bronchiectasis is defined as a permanent dilatation of those airways that have a normal diameter of >2 mm. Bronchial dilatation frequently occurs in association with acute pneumonias and with some types of atelectasis, but in these cases the dilatation resolves (90% within 3 months). Bronchiectasis can be localized or generalized, and within an individual segment, the severity of disease affecting individual subsegments may vary widely. Rather than being a single disease process, bronchiectasis is best regarded as the end result of a number of different pathologic processes. Infection is implicated in the majority of cases, and defects in local and systemic host responses can be present.

Postinflammatory bronchiectasis continues to be a common problem in developing countries, but in developed countries the reduction in frequency and duration of childhood pneumonia, through vaccination and antibiotics, has dramatically reduced the incidence of focal bronchiectasis. Cystic fibrosis is now the most common cause of fatal generalized bronchiectasis in Europe and North America. For patients with established bronchiectasis, regardless of etiology, antibiotics have significantly altered prognosis and life expectancy.

PATHOLOGY AND PATHOPHYSIOLOGY

In addition to the pathognomonic remodeling of the airways that characterizes bronchiectasis, there are, in the majority of cases, two associated pathologic developments that may account for the major clinical features of the disease. First, an anatomic and functional derangement of the mucociliary apparatus causes a self-perpetuating cycle of infection and inflammation. Second, marked hypertrophy of the bronchial circulation may be associated with the development of systemic-pulmonary shunts that impair gas exchange and are prone to rupture, with consequent life-threatening hemorrhage.

Remodeling of the Airway

A condition resembling bronchiectasis occurs in association with most cases of acute bacterial pneumonia wherein the airways dilate as the surrounding airless tissue retracts. This dilatation of the airways is temporary and in the majority of cases resolves within 3 months. True bronchiectasis, on the other hand, is generally a permanent condition. The remodeling of the airways was classified by Reid into grades of increasing severity that correlate with the severity of bronchographic abnormality (Fig. 1):

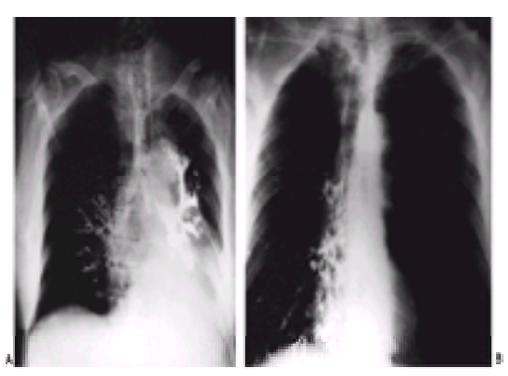

FIG. 1. A: Bronchogram showing normal anatomy of right lung and cylindrical bronchiectasis (left lung). **B:** Saccular bronchiectasis of right lung. (Reproduced courtesy of Manuel Viamonte, M.D., Department of Radiology, Mount Sinai Medical Center, Miami Beach, Florida.)

Grade 1. Cylindrical bronchiectasis: uniform dilatations that end abruptly (Fig. 1A and Fig. 2A)

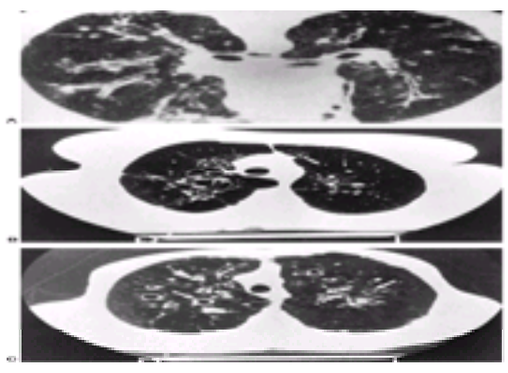

FIG. 2. CT demonstrating cylindrical bronchiectasis with thickened bronchial walls (“tram lines”) in a patient with cystic fibrosis. **B:** Proximal varicose and cystic bronchiectasis in a patient with ABPA. **C:** Two examples of a “signet ring” sign. (Reproduced with permission from Hansell and Strickland. High-resolution computed tomography in pulmonary cystic fibrosis. *Br J Radiol* 1989;62:1–5.)

Grade 2. Varicose bronchiectasis: dilatations that have an irregular contour (Fig. 2B)

Grade 3. Saccular or cystic bronchiectasis: dilated segments that are pus-filled cavities, with destruction of the distal airways (Fig. 1B and Fig. 2B)

The pathophysiology of bronchial dilatation is not understood, but several mechanisms are believed to be involved. The wall of the bronchus becomes weakened with loss of its muscular and elastic elements. The catalyst for this weakening appears to be related either to infection or the host response to infection (inflammation). In most cases, there appears to be a factor that prolongs either the infection or the inflammatory process. For example, regional clearance of infected secretions can be inhibited by an obstructing lesion. Alternatively, the cilia may be abnormal (e.g., primary ciliary dyskinesia) or the secretions may be abnormal (e.g., cystic fibrosis). Immune deficiency can impair the ability to kill micro-organisms and thus prolong the infective process. In contrast, tuberculosis is a chronic condition that in an immunocompetent host can provoke an intense local inflammatory response that can impair airway integrity. The inflammatory products produced by micro-organisms and host defenses include proteases, collagenases, and free radicals. All these substances are capable of impairing the integrity of the airway wall. Further, many inflammatory mediators may impair local mucociliary clearance by inhibiting ciliary beating and altering the composition of secretions. Impaired mucociliary clearance prolongs and aggravates local inflammatory processes. With the progression of bronchiectasis and the attendant loss of airway wall muscle mass and elasticity, medium-sized bronchi (>2 mm in diameter) dilate because of the elastic recoil of surrounding lung.

In addition to weakening of the airway wall, three other mechanisms may contribute to airway distention. First, loss of volume in adjoining lung parenchyma, caused by both impaction with secretions and inflammatory bronchiolar obliteration, may contribute to increased elastic recoil. Second, scarring that may develop in the parenchyma surrounding the airways may contribute to a further increase in elastic recoil pressures. Third, local obstruction may give rise to a mucocele that distends the airway. However, provided the mucus does not become infected, this is reversible.

Mucociliary Dysfunction

Most patients with bronchiectasis have a productive cough. Their sputum is commonly both purulent and copious. Examination of the lungs at necroscopy or at open lung biopsy reveals dilatation and hypertrophy of the bronchial glands. Goblet cell metaplasia of bronchiolar epithelium develops. (Goblet cells are found only in the central airways in normal subjects.) Squamous metaplasia is frequently seen.

Studies in which the clearance of radiolabeled airway mucus was used as an index of tracheobronchial mucociliary function have found that clearance is reduced in patients with bronchiectasis compared with normal volunteers. Several factors are likely to cause the mucociliary impairment that occurs in bronchiectatic airways. The frequency of the ciliary beat, and the composition and rheologic features of lower airway secretions, can be affected by bacterial products or by the host response to infection, especially the response of neutrophils, which are the predominant cell type found in bronchiectatic sputum. Neutrophil elastase, which is present in increased amounts, has been reported to inhibit ciliary function in vitro and is also a potent secretagogue and chemotactic agent. Bacterial and inflammatory cell products may also have a detrimental effect on the mucociliary apparatus. Soluble bacterial and leukocyte products disrupt mucociliary interaction and clearance. For example, in an isolated human nasal cilia preparation, investigators have found that supernatants obtained from *Pseudomonas aeruginosa* and *Haemophilus influenzae* cause a decrease in the frequency of the ciliary beat. Animal data suggest that bacterial products, such as pyocyanin and 1-hydroxyphenazine, inhibit mucociliary function by activating phagocytes and other cells and releasing reactive oxygen species. Furthermore, mucosal biopsy specimens taken from the airways of patients with purulent respiratory infection have revealed impaired ciliary beating in vitro, with a return of ciliary function to normal after antibiotic therapy. Recurrent episodes of bacterial pneumonia can also induce secretory changes in the airways that are characterized by an increase in the quantity and a change in the glycoprotein content of mucus and augmented ion secretion.

Remodeling of the Vasculature

The bronchial circulation is part of the systemic circulation and supplies the bronchi. The pulmonary circulation supplies the lung parenchyma, and anastomoses between the two circulations account for a small physiologic (1%) shunt. However, in bronchiectasis, the bronchial vessels become hypertrophied and flow increases through both existing and newly formed anastomoses (Fig. 3). At the same time that flow through the bronchial circulation is increasing, flow through the pulmonary circulation is decreasing as a response to alveolar hypoxia. The reduction in pulmonary vascular cross-section and the equilibration of pulmonary and systemic pressures have been implicated in the development of right ventricular overload and cor pulmonale. The tortuous, hypertrophied bronchial vessels are prone to hemorrhage, especially in the setting of acute exacerbations of bronchial infection, and hemorrhage is a frequent occurrence in advanced bronchiectasis.

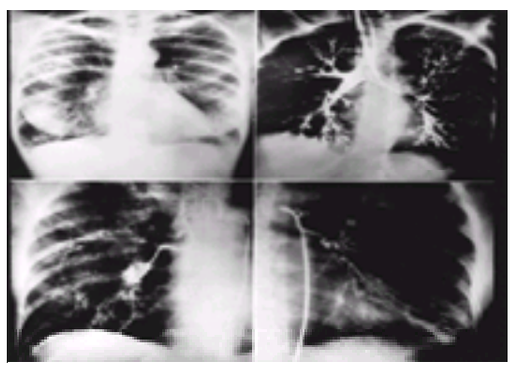

FIG. 3. Plain chest radiograph showing right-sided infiltrate (*upper left panel*) and bronchiectasis confirmed by bronchography (*upper right panel*) in a patient presenting with severe hemoptysis. Bronchial angiography (*lower panels*) demonstrates bilateral tortuous and hypertrophied bronchial circulation, significantly more severe in the right lung, suggesting that this was the source of hemorrhage. (Reproduced courtesy of Manuel Viamonte, M.D., Department of Radiology, Mount Sinai Medical Center, Miami Beach, Florida.)

Anatomic Distribution of Bronchiectasis

In a series of 3000 patients with bronchiectasis reported from South Africa (which excluded patients with prior tuberculosis), the anatomic distribution of bronchiectasis was, in order of decreasing frequency, as follows: (1) left lower lobe, (2) middle lobe, (3) lingula, (4) entire left lung, (5) right lower lobe, and (6) entire right lung. Interestingly, left lower lobe bronchiectasis was twice as common as right lower lobe bronchiectasis, whereas right upper lobe bronchiectasis was four times more common than left upper lobe bronchiectasis (excluding the lingula). Isolated basal segment bronchiectasis was rare but was most common in the right medial basal segment.

The reasons for this pattern of distribution are speculative and may relate in part to relative risks for aspiration and the role of gravity in clearing aspirated material or excessive secretions. In the erect position, the right medial basal segment is the most likely site for deposition of aspirated material. During sleep, in either lateral position, the right upper lobe and the lingula are the most likely repositories for aspirate. In the supine position, the apical segments of the lower lobes are the most likely sites.

When pneumonia develops, there is a tendency for the lung parenchyma to shrink, with consequent distortion of the bronchi. In some cases, this distortion may facilitate clearance by gravity (e.g., left upper lobe), but in others, the distortion may make clearance more difficult (left lower lobe). Additional factors in the various bronchi can predispose to the development of bronchiectasis. For example, the right middle lobe bronchus is not only long and narrow, but also susceptible to compression by lymph modes at its orifice. Although the left main bronchus is less likely to be a receptacle for aspirated material than the right, its angulation, greater length, and smaller diameter may make clearance of aspirated material more difficult.

In contrast to nontubercular postinflammatory bronchiectasis, posttubercular bronchiectasis predominantly involves the upper lobes (Fig. 4). Allergic bronchopulmonary aspergillosis (ABPA) tends to affect the central airways of the upper lobes. Cystic fibrosis usually causes generalized bronchiectasis, but the upper lobes tend to be more severely affected.

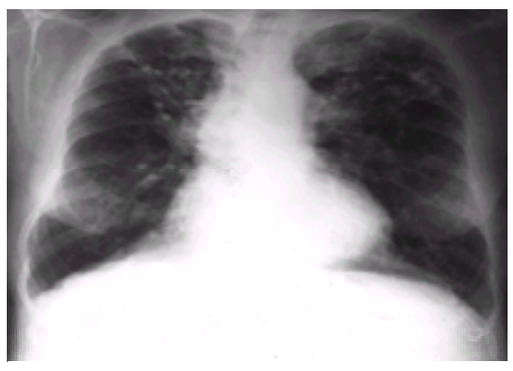

FIG. 4. Bronchiectasis and fibrosis of upper lobes. The most common cause of bilateral upper lobe bronchiectasis is tuberculosis. (Reproduced courtesy of Manuel Viamonte, M.D., Department of Radiology, Mount Sinai Medical Center, Miami Beach, Florida.)

CONDITIONS ASSOCIATED WITH BRONCHIECTASIS

Bronchial Obstruction

Bronchial obstruction can be caused by intraluminal, intramural, or extramural factors. Obstruction by an aspirated foreign body or a benign tumor has been described as a cause of bronchiectasis. Malignant tumors of the lung are not a common cause of bronchiectasis, probably because of the relatively short duration of the obstruction. Other causes include bronchial stricture resulting from prior tuberculosis and extrinsic compression of the right middle lobe bronchus by lymphadenopathy.

Childhood Pneumonia

The incidence of childhood infections, especially measles and pertussis, has been dramatically reduced in developed countries by vaccination. These infections can lead to severe pneumonia, complicated by bronchiectasis, in a significant minority of cases. Why bronchiectasis develops in some patients and not others subjected to the same insult is not known. Clearly, shortening the course of a bacterial superinfection with antibiotics may prevent bronchiectasis. Failure to provide antibiotic therapy, together with impairment of host defenses through malnutrition, may be among the reasons why bronchiectasis is more common in regions with poor access to health care. The reporting of clusters of patients with bronchiectasis in areas with a high frequency of intermarriage may suggest a role for genetic impairment of host defenses. Finally, others have speculated that cofactors may be involved in the development of bronchiectasis in certain settings. For example, it has been suggested that coinfection with herpesvirus or adenovirus may predispose to bronchiectasis in children with rubeola pneumonia.

Antibiotic therapy has reduced the incidence and duration of complicated pneumonia induced by necrotizing organisms such as *Staphylococcus aureus* and *Klebsiella,* with a concomitant reduction in postinflammatory bronchiectasis.

Aspiration and Inhalation of Irritants

A severe chemical pneumonia resulting from aspiration, with or without bacterial superinfection, can cause bronchiectasis, most frequently in the dependent segments of the lung. A similar syndrome has been described in patients who have been exposed to certain toxic fumes (e.g., ammonia). Although chronic microaspiration can cause asthma, it has not been established that this condition causes bronchiectasis. Aspiration of a foreign body should always be considered in the differential diagnosis of localized bronchiectasis.

Tuberculosis and Other Granulomatous Infections

Tuberculosis, active or inactive, is a common cause of bronchiectasis, typically in the upper lobes (Fig. 4). It is frequently described as being a “dry” bronchiectasis, because sputum may be produced only during acute infective exacerbations. Hemoptysis is frequent and thought to be related to infection in many instances. When a patient with a radiograph suggestive of previous tuberculosis presents with hemoptysis, the differential diagnosis includes reactivation of tuberculosis, exacerbation of bronchiectasis with aerobic bacteria or atypical mycobacteria, mycetoma, broncholith, and scar carcinoma.

Identical presentations can occur with other granulomatous infections, including those caused by fungi (histoplasmosis, coccidioidomycosis) and *Nocardia.* Atypical mycobacteria can colonize existing areas of bronchiectasis. Whereas these organisms used to be thought of as innocent commensals, it has recently become apparent that they can play a pathogenic role and also perpetuate the bronchiectatic process.

Cystic Fibrosis

In developed countries, cystic fibrosis is now the most common cause of generalized fatal bronchiectasis. Cystic fibrosis is associated with a defect in the cystic fibrosis transmembrane receptor (CFTR) gene, which is transmitted by a mendelian recessive mode of inheritance. However, although specific genetic defects have been identified, the mechanism by which these genetic defects lead to clinical disease remains a matter of speculation. This gene codes for a chloride channel that is present on a wide variety of cells. In the airway, this defect leads to decreased chloride secretion into the lumen and increased sodium and water reabsorption from the lumen. A similar defect in chloride secretion may lead to impaired acidification of glycoprotein in the Golgi apparatus of glandular mucous cells. These abnormalities may result in the production of dehydrated mucus that is suboptimally cleared and prone to bacterial colonization and infection.

The morphology of the lungs in cystic fibrosis is normal at birth. Recent studies, however, show that even when lung function is still normal, marked inflammation may be present in the airways of infants. The earliest pathologic lesions are dilatation and hypertrophy of the bronchial glands and goblet cell metaplasia of bronchiolar epithelium. The ensuing recurrent infections of airway mucus are thought to be responsible for the development of progressive bronchiectasis. The earliest infections are usually caused by *S. aureus,* but eventually the airways become permanently colonized by various strains of *P. aeruginosa.*

Radioaerosol studies show impairment of mucociliary clearance in patients with cystic fibrosis. Rheologic studies of the sputum reveal increased viscosity. The

predominant cell in the sputum of patients with cystic fibrosis is the neutrophil, and neutrophil elastase is present in increased amounts. Elastase inhibits ciliary function and is a potent secretagogue. Some of the mucociliary impairment in cystic fibrosis is caused by bacterial products that impair ciliary function and change the volume and composition of secretions. If the condition is suspected, a sweat test should be performed. The radiologic features of cystic fibrosis (Fig. 2A) are similar to those of other types of severe bronchiectasis. However, upper lobe predominance can be seen, and the lungs in early disease show radiologic features, and evidence on pulmonary function testing of hyperinflation.

Primary Ciliary Dyskinesia

The cilia of normal respiratory epithelial cells are approximately 6 µm in length and beat at 10 to 15 Hz, with a fast forward stroke and a slower recovery stroke. Their internal structure consists of nine pairs of microtubules surrounding two central tubules. Dynein, a protein with adenosine triphosphatase activity, mediates the sliding of ciliary tubules that causes ciliary bending. Ciliary dysfunction can be a primary defect or it can be secondary to the effects of inflammation, infection, or toxins. In the primary ciliary dyskinesia syndrome, characteristic ciliary defects have been noted that are believed to result in impaired clearance of mucus by ciliated epithelia and the development of bronchiectasis, sinusitis, and otitis media. In addition, male infertility occurs as a consequence of sperm tail immotility; sperm tails contain the same microtubules as cilia. The most common defect in ciliary structure is the absence of the outer dynein arms of the cilia. Approximately 20 other abnormalities of ciliary structure have been described, and these appear to produce identical clinical presentations. The condition occurs worldwide, with a prevalence of 1/20,000 in Europe and North America. The syndrome has been found to cluster in remote populations with a tendency to inbreed. It is thought to be transmitted by a mendelian recessive mode of inheritance.

Dextrocardia or situs inversus (Fig. 5) is associated with the dyskinesia in 50% of cases. The combination of bronchiectasis, sinusitis, and situs inversus is called *Kartagener's syndrome.* There is an infrequent association with congenital heart disease.

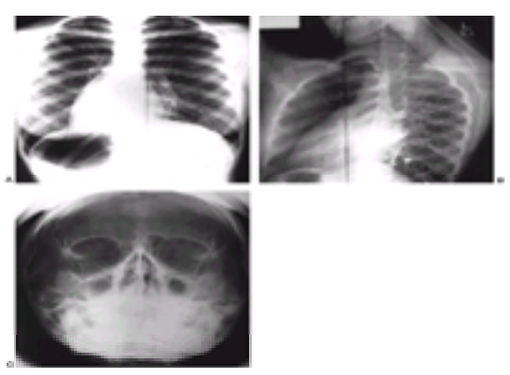

FIG. 5. Primary ciliary dyskinesia in a female patient with situs inversus, bronchiectasis, and sinusitis. **A:** Plain radiograph shows that the cardiac silhouette and stomach bubble are on the right side. An infiltrate silhouettes the left border of the heart. **B:** Bronchogram of left lung confirms bronchiectasis. **C:** Sinus radiograph is consistent with sinusitis. (Reproduced courtesy of Manuel Viamonte, M.D., Department of Radiology, Mount Sinai Medical Center, Miami Beach, Florida.)

Mucociliary clearance is markedly reduced in these patients, and clearance of mucus from the airway is primarily mediated by cough. Primary ciliary dyskinesia is associated with much slower rates of mucociliary clearance than is cystic fibrosis. Nevertheless, patients with primary ciliary dyskinesia, on average, have less severe pulmonary disease than patients with cystic fibrosis.

Young's Syndrome

Young's syndrome is characterized by bronchiectasis, sinusitis, and obstructive azoospermia. The latter affects the tail rather than the head of the epididymis. The converse is the case with obstruction caused by sexually transmitted infection. There is no association with dextrocardia or situs inversus. Radioaerosol mucociliary clearance is markedly impaired. Although the syndrome mimics primary ciliary dyskinesia, the cilia reveal no structural abnormality. The condition has been most frequently reported in the United Kingdom, France, and Australia; it has not been reported in the United States. It has been suggested that the condition may be a sequela of childhood mercury poisoning from teething powders, a suggestion based on epidemiologic data regarding mercury poisoning in the United Kingdom. Mercury-containing teething powders were banned the United Kingdom in 1955, and the incidence of acute mercury poisoning, and apparently of Young's syndrome, subsequently decreased.

Allergic Bronchopulmonary Aspergillosis

The clinical syndrome of ABPA is presumed to be caused by an intense inflammatory response to the presence of noninvasive *Aspergillus fumigatus* in the airways. Similar syndromes have been described much less frequently with other fungal species. The lung parenchyma surrounding the involved bronchi may demonstrate patchy areas of eosinophilic pneumonia. The condition has a predilection for segmental and subsegmental bronchi, the lumina of which may become occluded with inspissated mucus, with resultant segmental atelectasis that gives rise to the distinctive radiologic abnormalities of this condition.

Acute clinical exacerbations of the syndrome are characterized by chest radiographic infiltrates, asthmatic symptoms, peripheral blood eosinophilia (>1000/mm^3), very high levels of serum IgE (>1000 ng/mL), immediate cutaneous hypersensitivity to *Aspergillus* antigen, the presence of fungal elements in sputum, and proximal bronchiectasis (Fig. 2B). The bronchiectasis may progress, if untreated, to respiratory failure and cor pulmonale.

Diffuse bronchospasm frequently but not invariably accompanies acute exacerbations. The asthmatic symptomatology may be of new onset or predate the development of ABPA. However, the asthmatic symptoms usually worsen with the onset of ABPA. In some patients, a form of chronic, glucocorticosteroid-dependent asthma can develop.

Between exacerbations, the radiographic infiltrates resolve and the peripheral blood eosinophilia and serum IgE levels decrease. IgE levels may be the most clinically useful indicator of disease activity. ABPA responds readily to large doses of systemic glucocorticosteroids, but relapse is common once steroids have been discontinued.

Immunoglobulin Deficiency

Immune deficiency syndromes are discussed in detail in Chapter 53. IgA deficiency is common (1/500 individuals) but rarely associated with significant pulmonary disease. However, if a deficiency of IgA is associated with a deficiency of an IgG subclass, sinopulmonary infection, including bronchiectasis, may occur. Immunoglobulins of the IgG2 subclass are involved in opsonization and phagocytosis of encapsulated organisms, such as *Streptococcus pneumoniae* and *H. influenzae.* Deficiency of an IgG subclass can also occur in the presence of normal IgA levels. If total IgG levels are within normal range in the presence of severe infection, when elevated levels would be expected, deficiency of an IgG subclass should be suspected.

The relatives of patients with IgA deficiency have an increased incidence of a much rarer and more serious condition, called *common variable immune deficiency,* that is characterized by a deficiency of all major immunoglobulins. Because the same major histocompatibility complex (MHC) haplotypes are involved in both IgA deficiency and common variable immune deficiency, it has been suggested that these two conditions may represent extremes of the same spectrum of disease. In addition to recurrent, severe bacterial infection and chronic sinopulmonary disease, fever and lymphadenopathy may be presenting manifestations of common variable immune deficiency.

Secondary immunoglobulin deficiency, which can lead to a predisposition to severe pulmonary infection, can be the initial manifestation of lymphoma and multiple myeloma. Bronchiectasis may develop if the course of the underlying disease is prolonged.

Human Immunodeficiency Viral Infection

There have recently been a series of reports of bronchiectasis in patients with acquired immunodeficiency syndrome (AIDS). Most of these patients had advanced

disease and low $CD4^+$-lymphocyte counts. Bronchorrhea was a frequent finding, and the diagnosis was made by computed tomography (CT).

a_1-Protease Inhibitor Deficiency

a_1-Protease inhibitor deficiency is the the second most common fatal inherited lung disease, after cystic fibrosis. In a_1-protease inhibitor deficiency, which is inherited by a mendelian recessive mechanism, the hepatic synthesis and/or secretion of a_1-protease inhibitor is impaired. Although the typical clinical manifestation is emphysema, a significant minority of patients have coexisting bronchitis and bronchiectasis. Smoking may be a predisposing factor for bronchiectasis in this population, as may be a history of childhood respiratory tract infection. Experimental data may provide a rational basis for the development of bronchiectasis. Elastase, which is inhibited by a_1-protease inhibitor, is a potent secretagogue and may also have a role in the impairment of mucociliary transport. Replacement of a_1-protease inhibitor is indicated for certain patients with emphysema, but bronchiectasis is not an approved indication for replacement therapy at the present time.

Yellow Nail Syndrome

Yellow nail syndrome is characterized by yellow discoloration of the nails and lymphedema, most likely caused by lymphatic hypoplasia. Although the most prominent pulmonary manifestation of the syndrome is recurrent pleural effusion, associations with bronchiectasis and chronic sinusitis have been reported.

Rheumatoid Disease

Rheumatoid disease is associated with pulmonary fibrosis, pulmonary nodules, pleural effusion, Kaplan's syndrome (severe fibrosis in rheumatoid patients who worked as coal miners), and bronchiectasis. There is an association between rheumatoid arthritis and bronchiectasis, but the histocompatibility leukocyte antigen (HLA) associations are different from the HLA markers associated with other types of rheumatoid-associated lung disease. The cause of the association is not known. See Chapter 53.

Structural Abnormalities of the Tracheobronchial Tree

In Macleod's syndrome (unilateral hyperlucent lung), hypoplasia of the pulmonary arterial branches leads to hypoperfusion, hyperaeration, and hypoventilation of the involved area. Bronchiectasis of central airways that taper abruptly is seen. However, purulent infections are rare. This condition can develop at any age and the etiology is unknown.

Bronchial cartilage deficiency (Williams-Campbell syndrome) is a rare congenital condition that leads to expiratory collapse of airways. Bronchiectasis develops in most cases. Symptoms usually begin in infancy.

Mounier-Kuhn syndrome is characterized by dilatation of the trachea (diameter 20 mm) and large bronchi, with folds of redundant mucosa and fibromuscular tissues that resemble diverticula. The syndrome is associated with recurrent respiratory tract infections. The cause of the condition is unknown, but it is thought to be most likely of congenital origin.

Bronchopulmonary sequestration is a congenital anomaly in which a portion of the lung is supplied by the systemic circulation alone. The terminal bronchioles do not develop and the proximal airways become dilated. If the sequestered area communicates with the rest of the bronchial tree, bronchiectasis usually develops.

CLINICAL FEATURES

The classic symptom of bronchiectasis is a cough productive of large quantities of mucopurulent sputum, less frequently mucoid sputum (occasionally 200 mL in 24 hrs). However, sputum production is not invariably present or necessary to make the diagnosis. Patients with prior tuberculosis and residual upper lobe bronchiectasis may produce little or no sputum and may exhibit instead intermittent hemoptysis. Chronic bronchitis and bronchiectasis frequently coexist in the same patient, especially in cigarette smokers.

Hemoptysis is a common presentation of bronchiectasis. Usually, small amounts of blood-streaked mucopurulent sputum are expectorated, often heralding the onset of an infective exacerbation. Larger amounts, sometimes resulting from hemorrhage of a bronchopulmonary anastomosis, can be produced in advanced localized or generalized bronchiectasis. Hemoptysis can be chronic and intermittent or occur as a single massive and potentially fatal event.

Pleuritic chest pain is a frequent symptom, especially during exacerbations. Patients may have intermittent wheezing, particularly in ABPA, cystic fibrosis, and IgA deficiency. Dyspnea on mild to moderate exertion occurs with advanced disease.

Symptoms of sinusitis are frequently found in patients with bronchiectasis. There are a number of reasons for this association. First, the ciliated epithelia of the nose and the lung can be affected by the same disease process (e.g., ciliary dyskinesia or cystic fibrosis). Second, the incidence of atopy is increased in certain bronchiectatic populations (cystic fibrosis, ABPA). Third, aspiration of nasopharyngeal secretions can contribute to recurrent or chronic respiratory tract infection, including bronchiectasis.

Patients may offer a history of “recurrent pneumonia,” childhood pneumonia, or tuberculosis, or a family history of cystic fibrosis or other sinopulmonary symptoms. Patients with cystic fibrosis may have symptoms of malabsorption or recurrent cramping abdominal pain.

Physical examination in advanced cases typically reveals cachexia, cyanosis, clubbing, cor pulmonale, and diffuse rales and wheezes on chest examination. Milder cases may have no physical findings. Inspiratory rales may be noted on auscultation of the chest. Primary ciliary dyskinesia may be associated with situs inversus, dextrocardia, and rarely congenital heart disease.

COMPLICATIONS OF BRONCHIECTASIS

The complications of bronchiectasis include recurrent pneumonia, lung abscess, empyema, hemoptysis, pneumothorax, cor pulmonale, and metastatic intracranial infection (cerebral abscess or ventriculitis). Amyloidosis may occur in longstanding, extensive disease.

RADIOLOGIC STUDIES

Plain Chest Radiograph

The plain chest radiographic findings are rarely normal in advanced disease, but the plain chest radiograph is not a reliable screening test in milder cases. The number of bronchial vascular markings may be increased. Parenchymal shrinkage leads to crowding of bronchial markings. Occasionally, the thickened walls of a dilated airway, resembling “tram lines,” can be seen. Advanced end-stage bronchiectasis may reveal honeycombing and cystic changes (Fig. 6). The plain chest radiograph is not reliable in assessing the extent of disease.

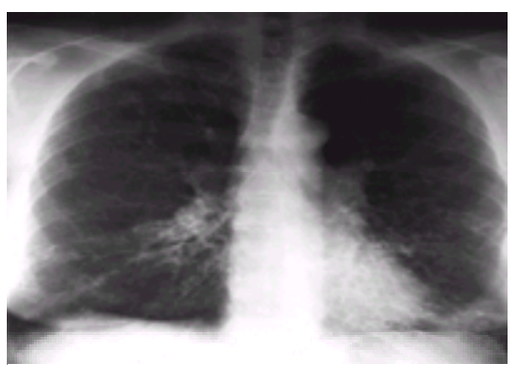

FIG. 6. Advanced generalized bronchiectasis with cystic changes and honeycombing. (Reproduced courtesy of Manuel Viamonte, M.D., Department of Radiology,

Mount Sinai Medical Center, Miami Beach, Florida.)

Bronchography

Until the advent of CT, bronchography was the definitive investigation in cases of suspected bronchiectasis. With the decline in the incidence of bronchiectasis and the advent of CT, the procedure is now rarely performed, except perhaps as a preoperative assessment in candidates for lung resection. Bronchography can be performed either with a fiberoptic or rigid bronchoscope. The procedure is unpleasant—hence the preference by some investigators for general anesthesia. Endobronchial examination is performed to define anatomy and to look for aspirated foreign bodies or other cause of bronchial obstruction. This is followed by aspiration of excess secretions. Generous local anesthesia is required to prevent coughing. Up to 20 mL of an oily contrast material is injected through a catheter advanced over a guide wire placed by fiberoptic bronchoscopy or through a rigid bronchoscope with the patient lying in a lateral position (side to be studied is dependent). Viscous contrast material may cause ventilation-perfusion mismatch, but this is usually transient. An attempt is made to remove the contrast material at the end of the examination. Some investigators then study the contralateral side at the same sitting. Others defer the second examination to another day. Complications are very rare with experienced investigators but include pneumothorax, bronchial rupture, and allergic reaction to the contrast materials.

Computed Tomography

High-resolution CT has in recent years replaced bronchography as the radiologic procedure of choice for the investigation of suspected bronchiectasis. Cylindrical bronchiectasis appears on high-resolution CT as dilated bronchi with thickened walls that extend to the lung periphery; these are sometimes described as resembling “tram lines” (Fig. 2A). On cross-section, the diameter of the bronchus is larger than that of the accompanying branch of the pulmonary artery. (In normal subjects, the diameter of the bronchus and that of the artery should be similar.) On cross-section, the juxtaposition of a dilated bronchus and pulmonary artery is referred to as a “signet ring” (Fig. 2C). In varicose bronchiectasis, the walls of the bronchus show irregular “varicosities” (Fig. 2B). In cystic bronchiectasis (Fig. 2B), the bronchi are grossly dilated and can be thin-walled. Changes on high-resolution CT are specific, but sensitivity varies with the thickness and intervals of cuts. The use of 4-mm contiguous cuts has been recommended. Other authors recommend 1.5-mm cuts at 10-mm intervals.

LABORATORY INVESTIGATIONS

In seeking to determine the cause of localized bronchiectasis confined to the upper lobes, sputum should be induced, stained, and cultured, not just for *Mycobacterium tuberculosis* but also for atypical mycobacteria, *Nocardia,* and fungi. If *Aspergillus* is found in sputum, it may represent saprophytic mycetoma, ABPA, or, if the patient is immunosuppressed, the possibility of invasive disease. The characteristic appearances of a saprophytic fungus ball on chest radiograph or CT should differentiate this entity from ABPA. If ABPA is suspected, serum IgE, eosinophil count in peripheral blood, skin testing with *Aspergillus* antigen, and sputum culture for *Aspergillus* may be indicated.

In patients <50 years of age with unexplained diffuse bronchiectasis or with sputum culture revealing mucoid strains of *P. aeruginosa,* iontophoresis (“sweat test”) is indicated to rule out cystic fibrosis. A sweat chloride level of 60 mEq/L in a child or 80 mEq/L in an adult is highly suggestive of cystic fibrosis.

Serum protein electrophoresis should be considered in patients with unexplained bronchiectasis and in patients with lymphoma or multiple myeloma in whom recurrent respiratory tract infections develop. As discussed earlier, quantification of IgG subclasses may be indicated in some patients.

If primary ciliary dyskinesia is suspected, biopsy of the nasal mucosa and electron microscopic assessment of ciliary morphology are indicated.

Other investigations that are not routinely ordered but that may be indicated in an individual patient include serology for human immunodeficiency virus (HIV) and rheumatoid factor, and a_1-protease inhibitor quantification and phenotyping.

PULMONARY FUNCTION STUDIES

Parameters of pulmonary function may be normal or show a restrictive pattern, an obstructive pattern, or a combination of both. In advanced bronchiectasis, restriction is often the dominant finding. In cystic fibrosis, obstruction and hyperinflation predominate. In early bronchiectasis, obstruction is often partially reversible. Diffusing capacity for carbon monoxide tends to decrease as disease progresses. Results of arterial blood gas analysis should be normal in mild to moderate disease. Respiratory acidosis and hypoxemia develop in the terminal phase of the disease.

Pulmonary function testing may of value in predicting long-term survival. For example, in cystic fibrosis, an FEV_1 (forced expiratory volume in 1 second) value that is 25% of predicted has been reported to herald a 50% mortality within 2 years and constitute an indication for lung transplantation.

FIBEROPTIC BRONCHOSCOPY

Endobronchial examination with a fiberoptic bronchoscope should be considered in cases of localized bronchiectasis. Obstruction by an aspirated foreign body or a benign tumor has been described as a cause of bronchiectasis. Bronchial strictures from prior tuberculosis are an important cause of localized bronchiectasis in some populations. Malignant tumors of the lung are not a common cause of bronchiectasis because of the relatively short duration of the obstruction.

TREATMENT

Antibiotics

Antibiotic therapy is the mainstay of the management of bronchiectasis. Initial therapy should include intermittent antibiotic therapy for infective exacerbations. Empiric therapy should be ideally based on results of previous sputum cultures, even though cultures do not always predict clinical response. Ampicillin/sulbactam or amoxicillin/clavulanate, second- and third-generation cephalosporins, the newer macrolides (azithromycin or clarithromycin), or trimethroprim/sulfamethoxazole will cover most strains of *H. influenzae, S. pneumoniae,* and *Branhamella catarrhalis.* For patients with *Pseudomonas* colonization, the oral quinolones (ciprofloxacin, olfloxacin) permit outpatient therapy. Another outpatient alternative is the use of aerosolized antibiotics; these are of proven efficacy in mild exacerbations of cystic fibrosis, but the data for other types of bronchiectasis are unclear. For the intravenous treatment of *Pseudomonas* bronchiectasis, the ideal regimen is a combination of a broad-spectrum anti-*Pseudomonas* penicillin (e.g., mezlocillin or piperacillin) and an aminoglycoside. The combination is synergistic and may help to prevent the development of drug resistance. Eradication of colonization with *Pseudomonas* may not be possible. Nevertheless, antibiotic therapy has been shown to reduce clinical symptoms and improve pulmonary function.

The use of antibiotics to prevent exacerbations is more controversial. “Rotating” courses of prophylactic oral antibiotics in relatively asymptomatic patients are empirically prescribed by some physicians, although the efficacy of this strategy has not been documented. In patients with severe generalized disease, especially those with cystic fibrosis, who have established chronic infection that cannot be eradicated, long-term administration of oral or aerosolized antibiotics has an established role in diminishing daily symptomatology.

Atypical mycobacteria may require prolonged therapy (several years with combinations of potentially toxic drugs). Therefore, the decision to initiate therapy is not taken lightly. Accepted treatment practices would be to seek out and treat other potential pathogens (*M. tuberculosis,* gram-negative aerobic or anaerobic bacteria) as causes of a patient's symptoms before initiating therapy for atypical mycobacteria, to document the presence of atypical mycobacteria in at least three sputum samples, and to follow objective clinical or radiologic markers of disease progression and response to therapy.

Bronchodilators

In addition to their bronchodilator effects, b-adrenergic agonists and methylxanthines stimulate mucociliary clearance in patients with chronic airways disease. The mechanism of action by which these agents increase mucociliary clearance could include an increase in frequency of the ciliary beat, a change in airway secretion, or both.

Glucocorticosteroids

The role of systemic or inhaled glucocorticosteroids in most forms of bronchiectasis is controversial. Glucocorticosteroids, especially when combined with bronchodilators, may be useful as an adjunct to antimicrobial therapy in patients with partially reversible obstruction of air flow or acute exacerbations.

Systemic glucocorticosteroids are particularly important in the management of bronchiectasis caused by ABPA. A staging system has been proposed to guide treatment: stage 1, acute; 2, remission; 3, exacerbation; 4, corticosteroid-dependent asthma; 5, fibrotic end-stage disease. Stages 1 and 3 require high doses of oral glucocorticosteroids (0.5 mg of prednisone per kilogram daily for at least 2 weeks, followed by the same dose on alternate days for 3 months), whereas stage 4 usually requires lower doses of oral steroids that need to be determined on an individual basis.

Mucolytics and Agents Altering the Composition and Volume of Secretions

The rheologic properties of expectorated sputum in patients with bronchiectasis are often abnormal. Many agents have been evaluated with the intent of optimizing the rheologic properties of lower airway mucus. Unfortunately, most of the agents that exhibit in vitro activity tend to be ineffective in vivo. One reason for the disappointing *in vivo* data may be the lack of objective tests to assess drug efficacy clinically. The ideal test should be able to quantify and define the distribution of secretions in the lower airways before and after drug administration, as the goal of mucolytic therapy is to facilitate ciliary and cough clearance of excessive lower airway secretions. Such a test is currently not available. Therefore, drug effects are evaluated indirectly by sputum volume, mucociliary clearance, pulmonary function, and symptom scores. These yield incomplete, nonspecific, or subjective information.

N-acetylcysteine and *S*-carboxymethylcysteine break disulfide bonds, thereby depolymerizing the glycoconjugate molecule and changing the rheologic properties of sputum, especially by reducing its viscosity. These compounds effectively liquify sputum *in vitro.* Aerosolized *N*-acetylcysteine has been used for more than three decades. Although several authors report that it is an effective mucolytic agent in clinical practice, there are no controlled studies showing that administration of *N*-acetylcysteine improves mucociliary clearance in humans. The clinical usefulness of *N*-acetylcysteine is limited because it can provoke significant bronchospasm in patients with airways disease—a complication that can be prevented by pretreatment with a b-adrenergic agonist. Because of the irritating effects of inhaled *N*-acetylcysteine, oral formulations were developed for long-term maintenance therapy. Their clinical usefulness has been difficult to establish, and studies in bronchitic patients have yielded conflicting results.

Deoxyribonucleic acid (DNA) released from degenerating neutrophils accumulates in the sputum of patients with cystic fibrosis and bronchiectasis. DNA can induce significant changes in the rheologic properties of sputum. Bovine pancreatic DNase was introduced for inhalation 30 years ago but was discontinued because it causes bronchospasm. Recently, human DNase has been manufactured using recombinant DNA technology. In vitro testing of DNase demonstrates a significant reduction in the viscosity of expectorated purulent sputum. The drug appears to be well tolerated compared with inhaled *N*-acetylcysteine. Clinical studies with DNase have revealed symptomatic improvement, as demonstrated by results of questionnaires and a modest improvement in spirometric values that persists for a few weeks after the drug is started. There is as yet no evidence that mucociliary clearance is improved by DNase. Evidence that the number of respiratory tract infections is decreased with this therapy in cystic fibrosis has been reported. Data on the use of this agent in other types of bronchiectasis are currently not available.

A recent study suggested that bromhexine, an oral agent that fragments acid mucopolysaccharide but not deoxyribonuclease fibers, may be useful in patients with exacerbations of bronchiectasis in combination with antibiotic therapy.

Iodinated glycerol produces subjective symptomatic improvement in patients with chronic bronchitis, but no controlled data are available for bronchiectasis. Guaifenesin (glycerol guaicolate) has been used as an expectorant for many years, but clinical studies have not demonstrated consistent objective or subjective improvement in chronic bronchitis or bronchiectasis.

Amiloride, a drug used systemically for many years as a potassium-sparing diuretic, selectively blocks sodium absorption in the airway when administered topically, thus increasing the hydration of mucus. Aerosolized amiloride increases radioaerosol mucociliary clearance. Preliminary clinical data suggest that when administered by aerosol, amiloride may slow the decline in pulmonary function in patients with cystic fibrosis. Data in other types of bronchiectasis are lacking. Hypertonic saline increases mucociliary clearance of radiolabeled mucus in patients with chronic bronchitis and is used to induce sputum in patients who do not have a productive cough. However, hypotonic or hypertonic aerosols can provoke bronchospasm in patients with airway disease. There are no controlled studies demonstrating that sustained use of hypertonic saline improves lung function in patients with obstruction of air flow. Although saline aerosol therapy is commonly used to treat children with upper airway infection, there is no evidence that aerosol therapy is superior to humidification. Despite the fact that patients with bronchitis and bronchiectasis are often exhorted to drink more fluid to facilitate expectoration, a controlled clinical study demonstrated no benefit.

Aerosolized indomethacin has been reported to reduce sputum volume in patients with bronchorrhea. Preliminary data suggest that systemically administered ibuprofen may reduce the rate of decline in pulmonary function in patients with relatively mild lung disease associated with cystic fibrosis.

Intravenous Immunoglobulin Replacement

Therapy of documented IgG deficiency is with intravenous immunoglobulin replacement. IgG subclass deficiency may require treatment with intravenous immunoglobulin. However, an associated IgA deficiency may complicate the administration of IgG because of an increased risk for immune reactions. Furthermore, it is not clear whether replacement is appropriate for all patients with an IgG subclass deficiency or only for those who have been shown to be unable to mount a normal response to specific bacterial antigens.

Physical Therapy

The objective of physical therapy is to move excessive secretions, either directly or by augmenting cough mechanisms. Some of these maneuvers may also have an effect on mucociliary clearance, but this is probably of lesser importance. Physical therapy protocols involve one or a combination of the following: gravity (postural drainage); forced breathing maneuvers, including directed cough; and external oscillation (vibration, either manual or with external devices). Most published studies have been performed in patients with chronic bronchitis or cystic fibrosis, but the findings are probably applicable to bronchiectasis.

Directed Cough

In patients with chronic bronchitis and bronchiectasis, spontaneous expectoration of secretions is an important adjunct to mucociliary clearance. It has been suggested that directed cough, in which patients are trained and encouraged to perform deep coughs, is just as efficacious and more cost-effective than a more complex regimen of postural drainage and percussion administered by a therapist.

Postural Drainage

In patients who produce at least 25 mL of sputum per day, postural drainage alone will improve clearance of secretions by moving secretions to the central airways, where cough clearance is more effective. Although postural drainage adds significantly to the efficacy of other methods of physical therapy (forced expiration, cough, vibration), it is not particularly successful by itself and should be combined with another method.

Forced Expiration Technique

The maneuver involves repetitive, forced exhalation from middle to low lung volumes. It is believed to clear mucus by gas-liquid interaction. In patients with chronic bronchitis (with or without bronchiectasis) who produced a large amount of sputum, mucous clearance was found to improve with a combination of forced expiration and postural drainage. It was also demonstrated that sputum volume and clearance of radiolabeled mucus improved with forced expiration and postural drainage in comparison with cough alone and with postural drainage alone.

Simple devices that facilitate positive airway pressure expiration during spontaneous breathing seem to augment expectoration in patients with cystic fibrosis. Commercial devices include both fixed and variable resistor valves against which patients exhale. The mechanism of action of these maneuvers may be that they cause the equal pressure point (at which expiratory dynamic airways collapse takes place) to move more distally. The fluttering motion that occurs in these areas as the airways transiently but repetitively collapse may mobilize mucus that is adherent to the airway walls.

External Oscillation

The role of manual chest percussion and vibration has been questioned by several investigators. For patients with cystic fibrosis and chronic bronchitis whose disease is stable, there appears to be no additional advantage over the forced expiration and postural drainage combination as assessed by radioaerosol studies or sputum production. The inconvenient requirement for an assistant to perform this service makes the equivalent results of forced expiration and postural drainage seem more attractive.

The failure of manual percussion may be a consequence of the relatively low frequencies achieved with this technique. Mechanical devices can significantly increase frequency. These systems can be subdivided into methods that involve the application of forces to the chest wall and those that provide oscillations at the airway opening. In the case of the latter, animal studies suggest that the use of asymmetric expiratory and inspiratory flow rates may be optimal. In short-term studies, mechanical vibrators appear to be equivalent in efficacy to standard chest physical therapy. However, one long-term study found that whereas FEV_l declined gradually during a period of traditional chest physical therapy, FEV_1 stabilized during a period of high-frequency chest compressions.

Nutrition

With the advent of antibiotic therapy and improved survival of patients with postinfectious bronchiectasis, malnutrition is seen much less frequently. Nevertheless, severe malnutrition can develop in patients with advanced disease. Malnutrition can directly compromise host immune responses and also lead to respiratory muscle dysfunction. Patients who are candidates for lung resection should have their nutritional status optimized to reduce postoperative morbidity. Patients with cystic fibrosis may require pancreatic enzyme supplements to treat malabsorption.

Bronchial Arterial Embolization

Massive hemoptysis (500 mL in 24 h) is a frequent complication of advanced bronchiectasis. If hemopytsis does not resolve with conservative management, including parenteral antibiotics, fiberoptic bronchoscopy may be helpful in localizing the site of bleeding. However, definitive therapy requires either surgery or bronchial arterial embolization. The development of isotonic contrast material has made angiographic assessment less hazardous. The availability of increasingly fine-bore catheters makes localization more precise, and the development of nonirritating embolization materials has also reduced complications. Complications of embolization include spinal arterial embolization and subsequent quadriplegia, necrosis of the chest wall, and necrosis of multiple segments of the lung. Frequently, a site of bleeding is not identified and empiric embolization of suspected vessels is performed. Serial procedures may be required to control a single episode of bleeding. Serial embolization of several small vessels is preferable to embolization of a single large vessel, which is associated with a risk for extensive necrosis.

Surgical Resection

Recent studies suggest that with careful selection, the majority of patients who undergo surgical resection of bronchiectatic tissue experience significant symptomatic improvement, and many are cured. Indications for surgery in a patient who according to pulmonary functional status can tolerate resection include the following: (1) localized disease with severe symptomatology, (2) resectable disease with severe hemoptysis from a segmental or lobar source, (3) resectable disease causing recurrent acute episodes of infection. The main determinant of resectability is the predicted postoperative pulmonary function. Ideally, all affected segments should be resected, because even mildly affected segments tend to deteriorate with time. However, in patients with more generalized disease, resection of the more severely affected regions may convey significant symptomatic relief. When the major portion of a lung needs to be removed, it is desirable to leave a few healthy segments behind. If these segments expand to fill the hemithorax postoperatively, the risk for infection of the hemithorax will be significantly reduced. In the majority of bronchiectatic patients, the lower lobes, middle lobe, and lingula are most often involved, and it may be possible to preserve the unaffected upper lobes and (more controversially) the apical segments of the lower lobes. Extensive resection is usually performed only if the affected lobes are shrunken and if the remaining lung tissue has expanded to fill each hemithorax. The resected lobes in such cases were likely to be making a negligible contribution to pulmonary function. The risks of surgery are much increased if the resected lobes are aerated, as the loss of pulmonary function then could be significant.

In selecting candidates for surgery and planning the extent of resection, meticulous radiologic staging is essential. Bronchogram remains the gold standard in the characterization of bronchiectasis. However, recent studies suggest that high-resolution CT may be an acceptable substitute. Surgery should not be performed in asymptomatic individuals, even if extensive bronchiectasis has been documented radiologically. In preparing a patient for surgery, antibiotics and physical therapy should be employed to reduce the level of infection and volume of lower airway secretions. Nutritional status should be optimized. Spirometry and quantitative perfusion lung scanning are useful in determining the patient's ability to withstand resection.

Bilateral resections are sometimes performed as a two-stage procedure. Some surgeons prefer to operate initially on the more severely affected side, because the reduction in symptoms may obviate the need for a second operation. Other surgeons prefer the converse, operating on the less affected side first so as to be in a better position to evaluate the patient's pulmonary status and ability to withstand the more extensive second resection.

A further consideration in selecting candidates for surgery is the need to ensure that the segments being considered for resection are permanently bronchiectatic. Two circumstances require special consideration. First, in children <3 years old, normal lung tissue surrounding the bronchiectatic area may significantly increase in size to replace shrunken regions lost to bronchiectasis; thus, surgery should be deferred to beyond the age of 3 years. Second, in patients who have undergone a necrotizing pneumonia, the radiologic abnormalities may resemble those of bronchiectasis. However, as this is a transient defect, some investigators recommend that serial high-quality bronchograms, several months apart, should be performed before surgery is undertaken.

Transplantation

The dramatic improvement in survival rates following lung transplantation during the past decade now means that patients with advanced generalized bronchiectasis should be considered for transplantation. The most extensive experience in bronchiectatic patients has been with cystic fibrosis. Fears that complication rates would be higher in patients with cystic fibrosis because of pre-existing pleural disease (predisposing to hemorrhage during cardiopulmonary bypass) and pre-existing infection (predisposing to tracheal anastomotic breakdown) than in other patients have not been realized to date with the exception of those patients colonized with *B. cepacia.*

In contrast to most other lung diseases, which can be treated with single lung allografts, purulent lung disease requires a double lung transplant to reduce the risk for contamination of the allograft. Heart-lung transplantation was the initial treatment of choice. A shortage of donor organs and the risks for cardiac rejection prompted the development of bilateral lung transplants. However, this procedure also requires cardiopulmonary bypass and carries the risk for pleural hemorrhage. Bilateral sequential transplantation avoids the need for bypass, and initial results are promising.

Candidates for lung transplantation should be at significant risk of dying within 2 years without transplantation. Evidence of such a risk includes an FEV_1 value that is 30% of predicted, a 12-minute walking distance of 500 m, a Schwachman-Kulczycki score (a rating scale based on chest radiograph, physical examination, physical activity, and nutrition) of 40/100 in children, hypoxemia, and signs of failure of the right side of the heart. Poor nutritional status is associated with increased postoperative mortality. The current survival rates for adult patients with cystic fibrosis after lung transplant are approximately 70% at 1 year and 50% at 3 years, with somewhat worse results in children.

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CHAPTER

42 Anatomic and Pathophysiological Correlations in COPD

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized functionally by a decrease in maximal expiratory flow rates. In addition, patients with COPD have uneven ventilation, which results in arterial hypoxemia and hypercapnia. These functional abnormalities can be detected and quantified by relatively simple pulmonary function tests. Similarly, pathologic lesions in lungs of patients with COPD have been described in some detail, and efforts have been made to quantify the severity of the lesions observed. Structure–function relationships in COPD are imperfectly understood. Optimally, a pathologist could accurately predict the nature and severity of dysfunction from gross and microscopic examination of lung tissue. Unfortunately, this ideal has not been realized because there may be striking discrepancies between the extent of disease as determined by the pathologist and the severity of dysfunction as measured by physiological tests. These disparities can partly be attributed to the formidable methodologic problems that one faces in studying a structurally complex organ such as the lung. It also indicates that the pathophysiological mechanisms occurring in COPD are simply not well understood. This chapter reviews the basic pathology of COPD; it describes the functional and roentgenographic abnormalities associated with this disease; and it attempts to show how the pathology and physiology are interrelated.

PATHOLOGY

Emphysema

Emphysema is defined by expert committees as “a condition characterized by abnormal enlargement of the air spaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis.” Air space enlargement may be secondary to actual departitioning of alveolar walls or to destructive changes that result in simple rearrangement of acinar shapes without fenestration. Air space enlargement is also observed in conditions other than emphysema, and distinctions are not always possible. For example, the aging lung is characterized by progressive enlargement of the alveolar ducts with effacement of adjacent alveoli. The enlarged alveolar ducts in aged lungs can be readily identified on whole-lung sections, and this condition has at times been termed “senile emphysema.” It is probably best to view this condition as a normal aging process, but because destructive emphysema is primarily a disease of older persons, the two conditions frequently merge imperceptibly.

Two principal subtypes of emphysema are recognized (Fig. 1 and Fig. 2). Centriacinar emphysema is characterized grossly by discrete, enlarged air spaces, usually measuring 1 to 10 mm in diameter. At the microscopic level, these lesions are seen to involve the respiratory bronchioles, the partly alveolated structures immediately distal to the terminal bronchiole. The structure of more distal alveoli within an acinar unit is largely preserved, though with advanced disease an enlarged air space may encompass much of the acinus. It is not uncommon to observe focal areas of inflammation, fibrosis, and black pigment in the structures bordering the emphysema lesion. The earliest centriacinar emphysema lesions tend to occur in the more cephalad lung regions, but they may be seen throughout the lung with severe disease.

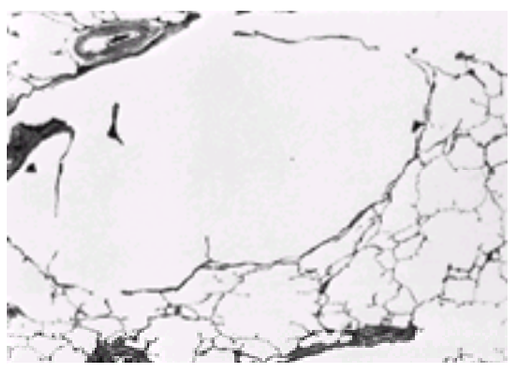

FIG. 1. Centriacinar emphysema. Air-space enlargement is centered about the proximal respiratory bronchiole. More distal lung parenchyma is normal.

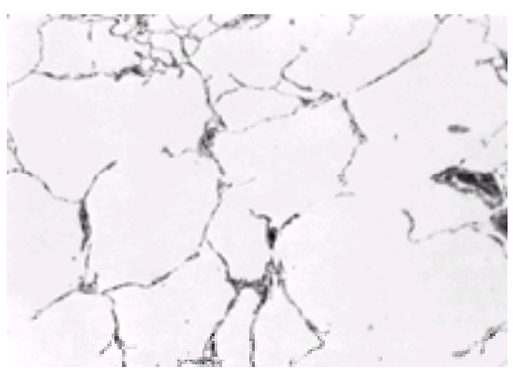

FIG. 2. Panacinar emphysema. The pattern is of diffuse air-space enlargement involving the entire acinus. A small region of normal alveoli is visible at top center.

Panacinar emphysema, as the name implies, more uniformly involves the entire acinar structure. Viewed grossly, mild panacinar emphysema consists of nothing more than a subtle, relatively diffuse enlargement of air spaces. In more advanced disease, single lesions may measure up to several millimeters in diameter. Microscopically, the alveolar architecture is distorted such that alveolar ducts appear enlarged, and it may be difficult to identify individual alveoli. In contrast to centriacinar emphysema, early panacinar emphysema may involve any portion of the lung with some disposition to involve lung bases more severely.

The lung contains abundant quantities of elastin, and this protein is instrumental in maintaining normal alveolar architecture and in conferring organ elasticity. It is now widely accepted that emphysema develops because of damage to the elastic fiber network and that this is caused by an elastase–antielastase imbalance within the distal structures of the lung. The two most powerful arguments in favor of this hypothesis are: (1) proteases with activity against native elastin produce emphysema-like lesions when instilled into the lungs of experimental animals, and (2) many persons with inherited, severe forms of a_1-antiprotease deficiency develop advanced, predominantly panacinar emphysema at a relatively young age. a_1-Antiprotease has a high level of activity against neutrophil elastase as well as other related enzymes, and it is the most abundant antiprotease within the lower airways of the lung. Severe forms of a_1-antiprotease deficiency are relatively uncommon, being found in only a few percent of patients with COPD. The most common known cause of emphysema, cigarette smoking, may upset the normal elastase–antielastase balance in a variety of ways. Most notably, regular cigarette smoking causes a low-grade inflammatory reaction in the distal airways, and the principal cells involved in this reaction, alveolar macrophages and polymorphonuclear leukocytes, are both rich sources of elastases. It is also possible that cigarette smoke may exert its effects by suppressing normal antielastase activity, by inhibiting the production of connective tissue proteins, and by other unknown actions.

Mucus Hypersecretion

One proposed definition of chronic bronchitis is a “clinical disorder characterized by excessive mucus secretion in the bronchial tree, manifested by chronic or recurrent productive cough on most days for a minimum of 3 months per year for not less than two successive years.” Experts arrived at this definition when excessive mucus secretion was thought to play a central role in the development of airflow obstruction in COPD. This is now known not to be true, but the definition continues in use. Many patients with COPD do have mucus expectoration, and the pathologic correlates of this symptom have been well described.

Mucus lines the lumina of the bronchial tree, and it serves an important role in host defense against the environment. Seromucous glands are found within airway walls throughout the central bronchial tree, and their mucus products empty into the bronchial lumen through ducts. In addition, mucus-secreting goblet cells are present as specialized epithelial cells throughout the bronchial tree. Both mucus-secreting elements may become enlarged in disease states. The volume of bronchial mucous gland may increase by 50% to 100% in severe cases of chronic bronchitis (Fig. 3). The population of epithelial goblet cells may also expand, particularly in the more distal airways, where few goblet cells are normally seen. In addition to enlargement of the mucus-secreting elements, it is not uncommon to see a low-grade inflammatory response, smooth muscle enlargement, and squamous metaplasia.

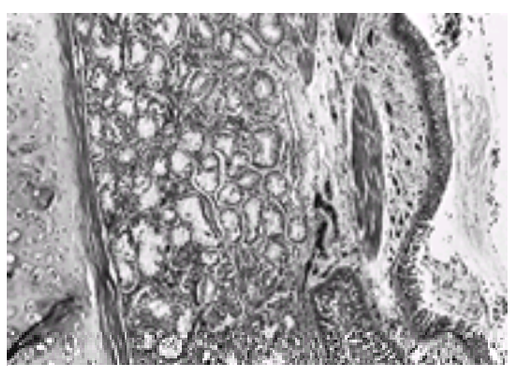

FIG. 3. Bronchial mucous gland enlargement. The markedly enlarged mucous glands from a case of chronic bronchitis occupy about twice their normal volume. Some mucus is visible in the bronchial lumen.

Peripheral Airways Disease

Descriptive changes in the peripheral airways of patients with COPD date back to Laennec's treatise in the 19th century. In the modern era, greater attention has been paid to this element of disease in COPD, as there has been a better appreciation of the functional impact. The abnormalities seen in COPD are multiple and nonspecific in nature (Fig. 4, Fig. 5, and Fig. 6). These include collections of brown-pigmented macrophages within the walls and air spaces of the distal lung passages, a low-grade inflammatory and fibrotic response involving the walls of the terminal bronchiole, goblet cell and squamous cell metaplasia of the lining epithelium, smooth muscle hypertrophy, and increased amounts of luminal mucus. These abnormalities are caused in part by cigarette smoke, but they are also observed to some extent in the lungs of elderly nonsmokers. Little is known concerning the specific pathogenetic mechanisms.

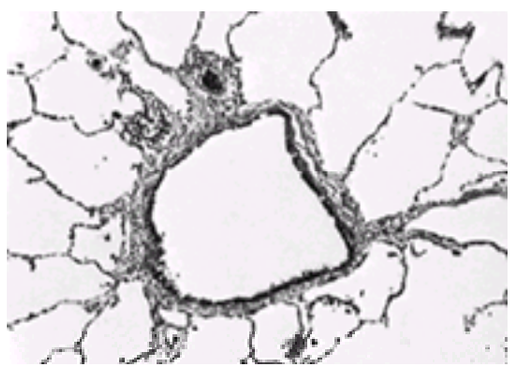

FIG. 4. Normal peripheral bronchiole. The airway lumen is only about 0.5 mm in diameter, and its patency is dependent on the tethering effect of surrounding lung parenchyma.

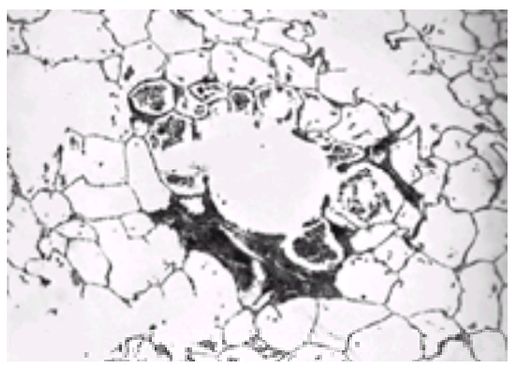

FIG. 5. Section through the junction of a terminal and respiratory bronchiole in a lung from a youthful cigarette smoker. Clusters of pigmented macrophages are visible in the respiratory bronchiole. There is also a mild inflammatory reaction in the wall of the bronchiole and in the adjacent alveoli.

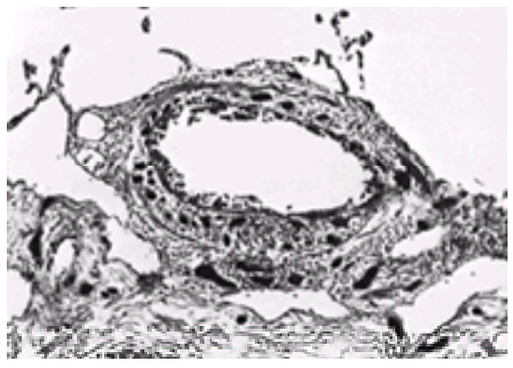

FIG. 6. Severely diseased bronchiole from a patient with COPD. The airway wall is thickened from edema, fibrosis, and smooth muscle enlargement, and a low-grade inflammatory response is visible throughout.

PHYSIOLOGICAL ABNORMALITIES

Lung Mechanics

The most practical and useful physiological test of airflow obstruction is spirometry, in which maximal expiratory flow rates are measured as a function of time. This information can be displayed as either the volume–time or the flow–volume relationship (Fig. 7). Both plots contain the identical information. Conventional parameters of maximal expiratory airflow include the forced expiratory volume at 1 sec (FEV_1), the expiratory flow rate between 200 and 1200 mL of the forced vital capacity ($FEF_{200–1200}$), the midexpiratory forced expiratory flow rate ($FEF_{25–75}$), and other less frequently used indices. Maximal breathing capacity (MBC), or maximal voluntary ventilation (MVV), is an older technique for demonstrating airflow obstruction that has now fallen out of favor. Airflow obstruction also may be evaluated by measurement of total pulmonary resistance or airway resistance. These measurements require more sophisticated instrumentation than does spirometry, and although they may be useful for some clinical investigations, they provide little practical information in the clinical management of patients with COPD. For most purposes, the FEV_1 (particularly when expressed as the percentage of predicted) or the ratio of the FEV_1 to the forced vital capacity (FEV_1/FVC) provide the best quantitative measures of airflow obstruction.

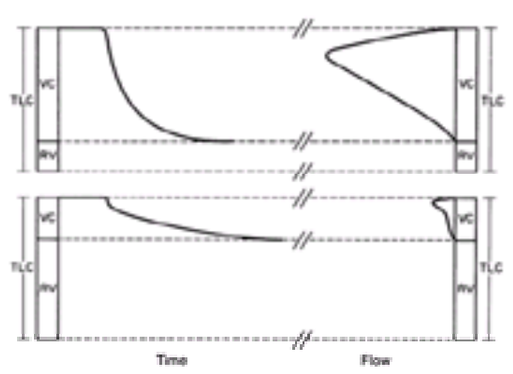

FIG. 7. Characteristic spirometric and lung volume abnormalities in a patient with severe COPD (*lower panel*). Spirometry is shown on the left as a volume–time relationship and on the right as a flow–volume relationship. In comparison with the normal subject (*upper panel*), the patient with COPD has a reduction in expiratory flow rates, a decrease in the forced expiratory vital capacity (FVC), and a corresponding increase in the residual volume (RV). TLC, total lung capacity.

Lung volume abnormalities are also characteristic of COPD and they include (1) a decrease in the forced vital capacity (FVC), (2) an increase in the residual volume (RV) and in the residual volume–total lung capacity (RV/TLC) ratio, (3) an increase in the functional residual capacity (FRC), and (4) a variable increase in the TLC (Fig. 7). Lung volumes are measured either by the washin or the washout of tracer gases such as helium or by plethysmography. Because tracer-gas methods require long equilibration times in the presence of severe COPD, plethysmography is the more accurate method. Surprisingly accurate estimates of TLC can also be made from the standard chest roentgenogram. The measurement of lung volumes may sometimes be useful in differentiating interstitial fibrosis and other forms of restrictive lung disease from COPD. However, these distinctions are usually evident from other clinical and roentgenographic findings, and in most patients with COPD, the determination of lung volumes adds little useful information. Increases in the RV/TLC ratio are observed relatively early in the natural history of COPD, and the magnitude of these changes continues to parallel spirometric abnormalities in more advanced stages of the disease.

Mechanisms of Maximal Expiratory Airflow Limitation

The interaction of air molecules with each other and with the internal surface of a cylinder impedes their movement, so that energy in the form of a pressure difference is necessary to cause flow through the cylinder. Flow resistance is defined as the ratio of the longitudinal pressure difference to the flow rate that pressure differential produces ($R = P/V$). The magnitude of flow resistance depends on the physical properties of the gas and on the length and diameter of the cylinder. The bronchial tree has many generations of branching, and each airway can be viewed as a resistive element existing in series and in parallel with tens of thousands of similar elements.

The energy necessary to move air through this resistive network is provided by the bellows action of the thoracic cage. For a constant resistance, flow through the conducting airways is proportional to applied pressure. In Fig. 8, transairway (alveolar–airway opening) pressure is plotted against flow rate at a constant lung volume in a normal subject. With inspiration, the relationship of flow to pressure is nearly linear, meaning that resistance is relatively constant over a wide range of applied pressures. Therefore, inspiratory flow is limited only by the magnitude of the applied pressure, which is largely dependent on respiratory muscle strength. However, the relationship is quite different during expiration. At low values for flow and pressure, the relationship is nearly linear, but beyond a certain critical point, flow remains constant despite further increases in pressure. This phenomenon is described as flow limitation, which indicates that expiratory airflow resistance increases dynamically as greater effort is expended.

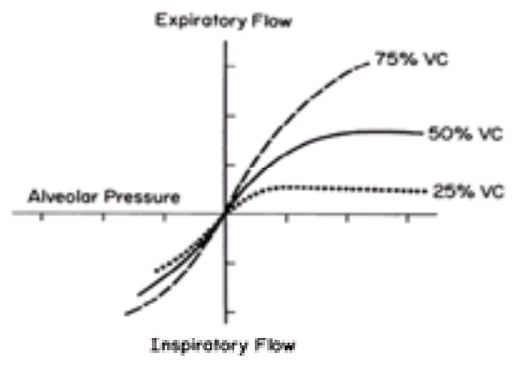

FIG. 8. Inspiratory and expiratory airflow as a function of alveolar pressure at various lung volumes. With inspiration, flow increases as the driving pressure between airway opening and alveolus increases. With expiration, flow increases with pressure only to a point beyond which flow remains constant despite further increases in pressure. This is called flow limitation, and the effect is most marked at small lung volumes. VC, vital capacity.

Flow limitation can be demonstrated by a simple experiment utilizing flow–volume curves. Figure 9 shows a series of flow–volume tracings in a normal subject who was instructed to expire repeatedly from total lung capacity (TLC) to residual volume (RV) with progressively greater efforts. With minimal effort (A), flow rates are low and relatively constant over much of the vital capacity. With increasing efforts (B through D), flow rates at large lung volumes increase correspondingly. However, the tracing from each submaximal effort contains an inflection, and below that volume the flow tracing superimposes on those from previous, lesser efforts. In other words, flow rates at any particular volume over the lower two-thirds of the vital capacity have a maximum that is relatively independent of the effort applied. As will be described, this phenomenon is largely determined by the intrinsic mechanical properties of the lung.

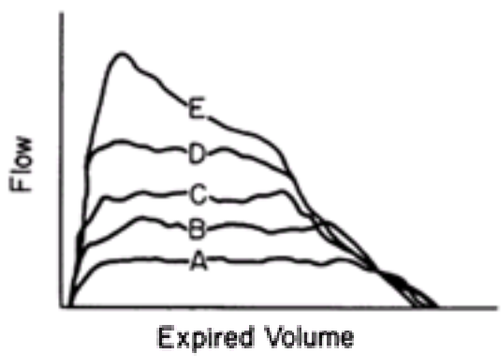

FIG. 9. Flow–volume relationships in a normal subject who expired from total lung capacity to residual volume with progressively greater effort (*A*–*E*). The latter portion of the maximal effort is superimposed on the tracings from lesser efforts, demonstrating flow limitations at smaller lung volumes.

The clinical significance of flow limitation can be appreciated by comparing flow–volume curves in a normal subject to those in a patient with COPD. Figure 10 shows inspiratory and expiratory flow–volume relationships during tidal ventilation and during maximal efforts. In the normal subject, minute ventilation can be increased severalfold in response to increased metabolic demands so that ventilatory capacity is not a limiting factor, even with vigorous exercise. In contrast, the maximal inspiratory and expiratory flow rates are greatly diminished in the patient with COPD, with expiration being more severely affected than inspiration. With severe disease, tidal expiration may be nearly superimposed on the tracing from a maximal forced effort. Such an individual has little ventilatory reserve and can increase total ventilation only marginally in response to exercise demands. This largely accounts for the cardinal symptoms of dyspnea and diminished exercise capacity in patients with COPD.

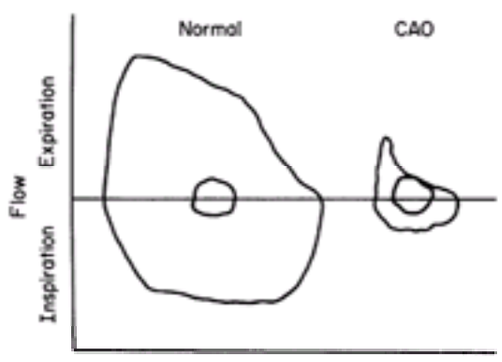

FIG. 10. Expiratory and inspiratory flow rates as a function of lung volume in a normal subject and in a patient with severe COPD. The outer envelopes represent maximal efforts; the inner tracings represent tidal breathing. The patient with COPD has very limited ability to increase ventilation with exercise.

The decrease in ventilatory capacity results not from decreased expiratory effort but rather from abnormal lung mechanics. Models of graded complexity have been used to analyze the physical behavior of the lung during forced expiratory maneuvers. A simple model, shown in Fig. 11, consists of a distensible balloon, representing the gas-exchanging regions of the lung, contained within a box, representing the thoracic cage. The balloon is connected to the environment by a compliant tube (conducting airways) and is surrounded by a space between the balloon and box (intrapleural space). Respiratory muscles, which actively alter intrapleural pressures, are represented by a bellows situated at the bottom of the box. If the lung is inflated above its resting volume, it will deflate to its original volume unless this tendency to recoil is opposed by an outward-acting transpleural pressure difference. The transpleural pressure required to keep the lung statically inflated at a particular volume is referred to as elastic recoil pressure (P_{el}). Alveolar pressure (P_{alv}) is at all times greater than intrapleural pressure (P_{pl}) by the amount of P_{el}; $P_{alv} = P_{el} – P_{pl}$. For air to flow through the conducting airway, there must be a pressure gradient between the alveolus and the airway opening (P_{ao}). With no flow, P_{alv} is equal to P_{ao}, and P_{pl} is negative, equal in magnitude but opposite in sign to P_{el}, in order to keep the lung distended. At functional residual capacity in normal subjects, P_{pl} is typically 4 to 3 cm H_2O less than ambient pressure. Inspiration creates a more negative P_{pl}. Because P_{alv} is the algebraic sum of P_{pl} and P_{el}, P_{alv} becomes negative with respect to P_{ao}, and air is drawn into the lung. Expiration reverses this process: P_{pl} becomes less negative, P_{alv} becomes positive with respect to P_{ao}, and air flows out of the lung. During the normal breathing cycle, pressure fluctuations in the pleural space are only a few centimeters of water, and during expiration, P_{pl} ordinarily remains negative with respect to ambient pressure. During expiration, pressure at all points within the conducting airways is positive with respect to ambient pressure. Hence, during tidal expiration, there is a net pressure gradient acting outward on those conducting airways that are exposed to pleural pressure. However, with forced expiration, this transmural pressure gradient may be reversed; it is these compressive pressures acting on compliant bronchi that narrow the airway lumen and limit maximal expiratory flow rates.

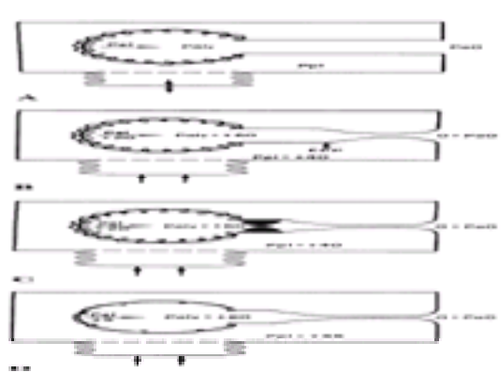

FIG. 11. Model of forced expiratory airflow. See text for explanation. **A** and **B** represent the normal relationships. **C** illustrates the effects of intrinsic airways obstruction on forced expiratory airflow. **D** demonstrates the effects of decreased lung elastic recoil, as might occur with emphysema. P_{el}, elastic recoil pressure; P_{alv}, alveolar pressure; P_{ao}, airway opening pressure; P_{pl}, intrapleural pressure; EPP, equal-pressure point.

Representative pressure relationships during a forced expiration are shown in Fig. 11B. Assume that P_{el} is –20 cm H_2O, P_{pl} is –40 cm H_2O, and P_{alv} is –60 cm H_2O. The alveolar driving pressure is dissipated by flow resistance along the length of the airway so that intraairway pressure progressively decreases to that of ambient pressure at the airway opening. Because P_{pl} is –40 cm H_2O, and intraairway pressure varies from –60 to 0 cm H_2O, there is a point at which intraairway pressure is equal to P_{pl}, and the transmural pressure gradient is zero. Distal (meaning in the direction of the alveolus) to this “equal-pressure point,” pressures within the airway are positive with

respect to P_{pl}, and this outward-acting force distends the airway lumen. Proximal to the equal-pressure point, intraluminal pressures are negative with respect to P_{pl}, creating a compressive force. Because bronchi are not rigid tubes, inward-acting transmural pressure gradients tend to compress the airway lumen, which in turn increases flow resistance. As P_{pl} increases, $P_{alv} - P_{ao}$ increases by the same amount and would, for a constant resistance, cause an increase in expiratory flow. However, increases in P_{pl} subject the proximal bronchi to greater compressive pressures, which narrow their lumina even more. The increase in driving pressure between alveolus and airway opening is balanced by the increase in flow resistance so that flow rates remain relatively constant. Thus, it is the flow-limiting segment of the conducting airways, usually located in the more proximal bronchi, that sets an upper limit to expiratory flow rates.

From this simple model several factors are recognized that might affect the mechanical behavior of the flow-limiting segment and in turn set the magnitude of maximal expiratory flow rates. One factor relates to the intrinsic elastic behavior of the flow-limiting segment itself. It is evident that the same compressive pressure might cause greater flow resistance in a highly compliant airway than in an airway with relatively rigid walls. Experimental studies support this suggestion, but whether such changes play a significant role in COPD is unclear.

The mechanical behavior of the flow-limiting segment is also influenced by flow resistance in more distal portions of the conducting airways. This is illustrated in Fig. 11C, which shows narrowing of the distal airway. Under these conditions, a relatively greater portion of the alveolar driving pressure, $P_{alv} - P_{ao}$, is dissipated over the obstructed segment of airway. Compared to the conditions presented in Fig. 11B, intraairway pressures at each point between the obstruction and the airway opening are necessarily less positive, and the compressive pressures must be correspondingly greater. Because a longer segment of normal airway is exposed to larger compressive forces, airflow resistance would be greater, and maximal expiratory flow rates would be less. Intrinsic airway narrowing may occur from pathologic conditions such as inflammation and fibrosis in airway walls and from excessive luminal mucus, all of which are frequently seen in lungs from patients with COPD. As discussed below, lesions are thought to be a significant cause of airflow obstruction in this disease.

The pathologic condition that may be most important in causing airflow obstruction, emphysema, involves the lung parenchyma and not the conducting airways. How do abnormalities of the lung parenchyma give rise to expiratory airflow obstruction? Emphysema is characterized by destruction of alveolar walls and disruption of the normal parenchymal architecture. These morphologic changes are associated with a loss of lung elastic recoil, which may be viewed as the primary functional defect in emphysema. The loss of elastic recoil affects both the dimension of intrapulmonary airways and the behavior of the flow-limiting segment. Intrapulmonary airways are surrounded by lung parenchyma and are intimately connected to the elastic and collagen fibers in the alveolar walls. As the lung is inflated, alveolar walls become increasingly stressed, and this creates a tethering effect on airways at their points of attachment. As lung volume increases, so do the lengths and diameters of the intraparenchymal airways. This mechanism accounts for the volume dependence of airflow resistance in the lung, the resistance being greater at small volumes and less at large volumes. With loss of lung elastic recoil, the distending forces acting on the airway at any particular volume would diminish, and airflow resistance would increase correspondingly.

Lung elastic recoil also influences maximal expiratory flow rates through an indirect effect on the mechanical behavior of the flow-limiting segment. This mechanism can best be appreciated by again considering the model. In Fig. 11D, the effect of emphysema has been simulated with a decrease in P_{el} from +20 cm H_2O to +5 cm H_2O. For the sake of the argument, let P_{pl} increase from +40 cm H_2O to +55 cm H_2O, a change that could be realized simply by more forceful chest constriction. The sum of P_{el} and P_{pl} in this example provides the same driving pressure between alveolus and airway opening, +60 cm H_2O, as in Fig. 11B. Although the driving pressure is the same, pressure relationships across the airway wall are different. Because P_{pl} has increased by 15 cm H_2O, external pressures at each point on the airway in Fig. 11D are necessarily increased by the same amount. The larger compressive forces on the flow-limiting airways would, in comparison with Fig. 11B, cause greater luminal narrowing, resulting in decreased maximal expiratory flow rates. Thus, P_{el} may be viewed as effectively opposing the compressive forces of P_{pl} on intrathoracic airways. In experimental models of emphysema, it has been demonstrated that the decrease in maximal expiratory flow rates is nearly proportional to the decrease in P_{el}.

Ventilation Distribution and Gas Exchange

An early and characteristic physiological abnormality in COPD is arterial hypoxemia. Mild hypoxemia may be detected in the early stages of COPD, when spirometric values are normal or nearly normal. As COPD worsens, hypoxemia also tends to worsen, although the severity of COPD and the degree of hypoxemia are imperfectly concordant. Some degree of hypercapnia is also usually present in more advanced disease, and there may be sustained elevations of the P_{CO_2} to 70 mm Hg or more in the most severe cases. It is believed that the principal mechanism underlying arterial blood gas derangements in COPD is the mismatching of ventilation and perfusion in regional lung units. As described below, the uneven distribution of inspired ventilation is thought to be the primary event, with alterations in pulmonary blood flow being secondary.

Uneven ventilation in COPD can be demonstrated by several techniques. The single-breath oxygen test is one such method (Fig. 12). The subject inspires a single breath of pure oxygen and then slowly exhales while nitrogen concentration at the mouth is plotted as a function of expired volume. A positive slope in phase III, the “alveolar plateau,” indicates that different portions of the lung with different concentrations of residual nitrogen empty asynchronously. In normal subjects, the slope of phase III is usually no more than a 2% rise in nitrogen concentration per liter of expired volume, but this value may rise to as much as 10% to 15%/L in patients with COPD. A variety of techniques to measure the washin or washout of tracer gases also detect inhomogeneous ventilation. Though difficult to quantify, external scanning after inhalation of radioactive xenon may allow the best visual appreciation of disordered ventilation distribution in COPD.

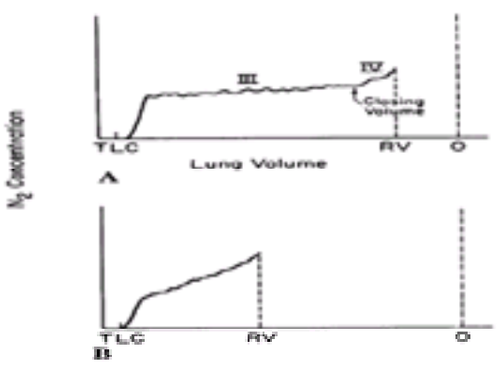

FIG. 12. Representative tracings from the single-breath oxygen test in a normal subject **(A)** and a patient with COPD **(B)**. In normal subjects, the slope of phase III (the “alveolar plateau”) is no more than a 2% change in nitrogen fraction for each liter of expired air. Phase III is delineated from phase IV by an inflection point, the “closing volume.” In the patient with COPD, the slope of phase III is much steeper, suggesting less even ventilation, and frequently the closing volume can not be identified. TLC, total lung capacity; RV, residual volume.

Mechanisms of Deranged Gas Exchange

In patients with COPD, ventilatory capacity may be a limiting factor in determining oxygen uptake and carbon dioxide excretion during exercise. However, even at rest, most patients with COPD have evidence of impaired gas exchange. With mild COPD, impaired gas exchange may be manifest only as mild arterial hypoxemia. However, with severe disease, hypoxemia may be profound, and it, along with hypercapnia, contributes to the clinical signs and symptoms of this disorder. Certain of the mechanisms that impair gas exchange in COPD are intuitively obvious. For example, widespread emphysema is associated with a substantial loss of alveolar capillary surface area. With extensive destruction of parenchyma, the lung simply does not function effectively in exchanging oxygen and carbon dioxide.

However, current thinking suggests that mechanisms other than a simple loss of surface area are more important as a cause of hypoxemia and hypercapnia. These other mechanisms relate principally to the distribution of ventilation and perfusion within the lung. Gas exchange is most efficient when the ratio of ventilation to perfusion ($\dot{V}/\dot{Q}$) is uniform. To the extent that regional $\dot{V}/\dot{Q}$ deviates from unity, the exchange of both oxygen and carbon dioxide is impaired.

If an alveolar region is ventilated but not perfused ($\dot{V}/\dot{Q}$ = ¥), no gas exchange occurs. Relatively overventilated alveolar regions that receive some blood flow behave functionally as though a portion of that region were normally perfused and the remainder received no blood flow. The excess ventilation in both situations is wasted, a condition that is described as a high $\dot{V}/\dot{Q}$ abnormality or “alveolar dead space.” High $\dot{V}/\dot{Q}$ abnormalities are detected as an increase in the dead space to tidal volume ratio (V_D/V_T). In normal subjects, V_D/V_T is no more than 0.3 to 0.4, but in patients with severe COPD, it may be as high as 0.7 to 0.8. In such patients, the major portion of each inspired breath contributes nothing to gas exchange. Alveolar regions that are perfused but not ventilated ($\dot{V}/\dot{Q}$ = 0) also do not participate in gas exchange.

The proportion of the cardiac output that passes through unventilated lung zones is termed the shunt fraction, and the admixture of shunted blood with other pulmonary venous blood results in arterial hypoxemia. If an alveolar region receives some ventilation but is underventilated relative to its blood supply, arterial oxygen desaturation will also ensue. Underventilated alveolar regions, termed low $\dot{V}/\dot{Q}$ abnormalities, are thought to be the principal cause of hypoxemia in COPD. Theoretically, pathologic states affecting the pattern of either ventilation or perfusion may cause the regional $\dot{V}/\dot{Q}$ to deviate from unity.

Abnormal ventilation and perfusion patterns in COPD are readily demonstrated by radioactive scanning and by other methods. Regional hypoperfusion to some extent may be directly attributed to loss of the capillary bed accompanying emphysema. However, abnormal perfusion patterns in COPD also may represent normal homeostasis in the pulmonary vasculature. According to this concept, pathologic changes in COPD create regions of hyperventilation and hypoventilation. Regions that are underventilated develop relative hypoxia, which in turn initiates a local vasoconstrictor response. The reduction in blood flow tends to restore the regional $\dot{V}/\dot{Q}$ ratio toward unity. Over long periods of time, hypoxic vasoconstriction may induce permanent histopathologic changes in the pulmonary arteries, leading to irreversible pulmonary hypertension and cor pulmonale. Because changes in the pulmonary vascular bed may be regarded as secondary, attention in this discussion is directed at those pathologic mechanisms that alter the distribution of ventilation.

Ventilation is the process by which ambient air is transported to the alveolar–capillary interface and alveolar air is removed to the environment. Regional ventilation may be defined as the volume of ambient air that reaches a given lung region relative to the volume of gas that resided in that same region at the beginning of the breath. Regional ventilation is determined by the relative volume expansion of that region and by the manner in which inspired air mixes with resident gas. Expansion of alveolated zones depends on both the elastic behavior of that region and external forces acting on it. Distending forces are closely equated to transpleural pressure. For the same change in transpleural pressure, compliant regions expand more than do noncompliant regions and, other things being equal, receive more ventilation. Therefore, any pathologic state causing nonhomogeneous elastic behavior in various lung regions might be expected to cause uneven ventilation.

Emphysema is the prototype of diseases that alter lung elastic behavior. In most instances, emphysematous involvement is not uniform; severely diseased regions lie adjacent to histologically normal lung tissue. Therefore, one would anticipate abnormal ventilation patterns in emphysematous lungs, and this is observed. Whether emphysematous regions are overventilated or underventilated is not so apparent. This statement may seem surprising in view of the fact that emphysematous lungs are generally said to be overly compliant and that compliant lungs should theoretically receive more ventilation. This seeming paradox can be understood by comparing pressure–volume curves in normal and emphysematous lungs (Fig. 13). With emphysema, there is a loss of lung elasticity with a consequent upward and leftward shift of the pressure–volume curve. At low volumes, the emphysematous lung undergoes a greater volume change for any transpleural pressure change than does the normal lung. However, at large volumes, the emphysematous lung is less compliant than the normal lung and undergoes less volume change for the same change in transpleural pressure. Thus, relative differences in the pressure–volume relationships and in the magnitude of external forces acting on each region would determine the distribution of ventilation between normal and emphysematous zones. Existing evidence suggests that emphysematous areas are usually underventilated compared with normal lung parenchyma. However, if perfusion were even more severely impaired than ventilation, emphysematous regions might still represent high-$\dot{V}/\dot{Q}$ zones.

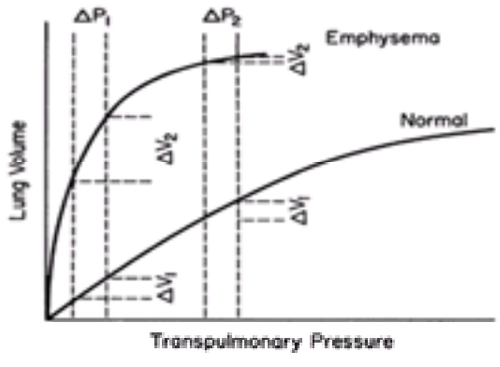

FIG. 13. Pressure–volume relationships in normal and emphysematous lungs. At small lung volumes, the emphysematous lung is more compliant than the normal lung, but the reverse is true at large lung volumes. D*P*, change in pressure; D*V*, change in volume.

The volume change that a lung region undergoes during the respiratory cycle exceeds the volume of effective ventilation. At the end of expiration, all gas-transport pathways contain alveolar gas. With the next inspiration, the “dead space” gas within the conducting airways precedes ambient air into the gas-exchanging zones. Dead-space gas represents a significant portion of each tidal breath, so its distribution and mixing with ambient air may have pronounced effects on gas exchange. Gas is transported from the airway opening to the alveolar–capillary interface by two mechanisms: convection and diffusion. Gas is thought to move through the proximal airways principally by convection, but in the distal alveolated zones diffusion predominates. At the beginning of inspiration, one can imagine a front forming at the airway opening with ambient air on the proximal side and resident gas on the distal side. If no mixing occurs across the interface, the front would migrate distally as inspiration proceeds. The location of this front at the end of inspiration marks the limit of convective flow, and beyond this point gas transport is solely dependent on diffusion. (In reality, of course, mixing between ambient air and residual gas begins at the airway opening, but the notion of a convective front is conceptually useful.) Calculations based on known dimensions of the respiratory tract suggest that, with tidal breathing, this imaginary convective front penetrates to the level of the alveolar ducts. From there gas diffuses radially into the alveoli and axially into more distal alveolar ducts and alveoli. Because distances are short, radial mixing between the alveolar duct and alveoli probably is complete within a fraction of a second. However, axial pathways are much longer. Theoretical studies suggest that because distal pathways are of uneven lengths, mixing between gases in the proximal and distal alveolar ducts may not be complete within the span of a single breathing cycle, even in the normal lung. If so, proximal alveolated regions would represent high-$\dot{V}/\dot{Q}$ zones, whereas more distal regions would represent low-$\dot{V}/\dot{Q}$ abnormalities. Transport pathways within the alveolated zones of the lung may be a critical factor in gas-mixing efficiency, and any pathologic state that alters the dimensions of those airways might have profound effects on overall gas exchange.

Two examples illustrate how these functional abnormalities might occur. Centriacinar emphysema primarily involves the respiratory bronchiole, leaving more distal portions of the acinus intact (Fig. 14). To reach normal alveoli, gas molecules must pass through the increased dead-space volume of the pathologically enlarged respiratory bronchiole. With inspiration, ambient gas preferentially fills the proximal emphysema lesion, while distal regions tend to be filled by resident dead-space gas. This creates a region of relative alveolar hypoxia in the distal acinus but a high-$\dot{V}/\dot{Q}$ zone within the emphysema lesion itself.

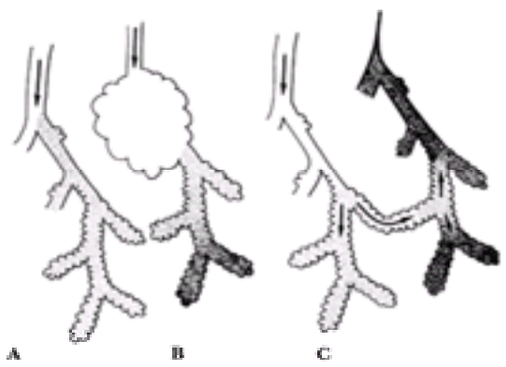

FIG. 14. Postulated mechanisms of uneven ventilation in COPD. (*Shading* represents resident dead-space gas.) **(A)** Normally inspired air is mixed evenly with resident gas throughout the acinus. **(B)** A disproportionate amount of inspired air remains within a proximally located centriacinar emphysema lesion, while the distal acinus contains relatively more dead-space gas. **(C)** Alveolated regions distal to an obstructed bronchiole are ventilated through a collateral channel. Because the pathway for gas transport is longer, mixing between inspired air and resident gas is incomplete.

Another mechanism by which a specific structural abnormality might impair gas exchange is depicted in Fig. 14C. Adjacent acini are shown; one is ventilated through a normal bronchiole, but the other bronchiole is occluded by a mucus plug. If the latter bronchiole remained occluded throughout the respiratory cycle, and if no other

bronchial connections existed, the distal acinus would become atelectatic as gas was absorbed. Atelectasis probably does not occur because some ventilation is supplied to the obstructed acinus via collateral channels. However, the collateral pathways are likely to be longer than normal, with a corresponding increase in the dead-space volume. In the example shown, alveolated regions behind the obstructed bronchiole would function as a low-$\dot{V}/\dot{Q}$ abnormality, whereas portions of the unobstructed acinus might represent regions with a high $\dot{V}/\dot{Q}$ ratio.

These examples illustrate how specific anatomic abnormalities might give rise to abnormal ventilation distribution. Other examples might also be cited, but the relative importance of specific pathologic lesions as causes of $\dot{V}/\dot{Q}$ disturbances in COPD is simply not known. Gas exchange may also be dependent on factors relating to the distribution of pulmonary blood flow, to neural control of breathing, to chest wall mechanics, to systemic hemodynamics, to systemic metabolic demands, and to respiratory muscle function. The final common expression of disordered gas exchange in COPD, arterial hypoxemia and hypercapnia, represents the summation of multiple, complex mechanisms.

PHYSIOLOGICAL CORRELATES OF EMPHYSEMA

Emphysema is by definition an anatomic entity, and its presence and severity can best be directly determined only in specimens obtained at surgery or autopsy. Accurate quantification of emphysema severity requires that lungs be fixed in an inflated state. Assessments of emphysema severity can be made either from whole-lung slices or from histologic sections. The paper mounting of whole-lung slices is one of the more common methods employed. Specimens to be graded are compared to a standard picture panel depicting progressively more severe grades of emphysema. This method is fairly reproducible, and it is also quite sensitive in detecting mild grades of emphysema. Some investigators have assessed emphysema by variations of this method and by point-counting techniques. Emphysema severity also can be assessed by more direct measurements of air-space size from histologic sections. A test line of known length, contained within the eyepiece reticule, is superimposed over lung parenchyma at multiple sites. The number of intersections of the test line with alveolar walls is counted, and from this is calculated the average distance between alveolar walls (mean linear intercept). Provided that adequate attention is given to sampling considerations, the mean linear intercept can be reproducibly determined with an error of only a few percent. The correlations between estimates of severity from the panel-scoring method and from the mean linear intercept are reasonably good in lungs involved by moderate to severe grades of emphysema, but the histologic method lacks sensitivity when estimating milder grades of emphysema. Milder forms of emphysema are usually focal in their distribution, and although these abnormalities can be recognized from visualization of whole-lung slices, these abnormalities may be difficult to detect against the normal background variability of the mean linear intercept.

The problem in assessing emphysema presence and severity is further compounded by the presence of morphologic subtypes, the most important of which are centriacinar and panacinar. The panacinar form of emphysema predominates in the severe a_1-antiprotease deficiency state, whereas centriacinar emphysema appears more closely linked to cigarette smoking by etiology. In their earlier stages, these two forms of emphysema can usually be distinguished, but mixed forms are the rule in most cases of advanced COPD, and the relative proportion of each is difficult to quantify. In most studies, assessment of emphysema has been made without reference to morphologic subtype, and it remains unclear whether either form of the disease is associated with any distinguishing clinical or physiological features.

Patients with physical impairment from COPD nearly always have emphysema, but severity varies widely. Occasionally, emphysema may be absent or present in only trace amounts. Advanced grades of emphysema may be suspected from certain types of pulmonary function abnormalities, but it bears emphasizing that none of the available pulmonary function tests is capable of predicting emphysema severity with a high degree of precision. The enlargement of the air spaces in emphysema is accompanied by loss of alveolar and capillary surface areas available for gas exchange. This factor, coupled with ventilation and perfusion inhomogeneities, might impair oxygen and carbon dioxide exchange between ambient air and capillary blood. However, anatomic emphysema correlates poorly with abnormalities in arterial blood gas measurements. It appears to correlate somewhat better with decreases in the diffusing capacity for carbon monoxide (D_LCO), but even in this case, the literature contains conflicting results. Some studies found correlation coefficients as high as –0.70 (meaning that about 50% of the variance in the D_LCO could be explained by emphysema), whereas other investigators found no significant relationship between emphysema severity and decreases in the D_LCO. These discrepant results might partly be explained by selection biases and by the generally small sizes of the studies. One may reasonably conclude that emphysema probably does cause some reduction in the D_LCO but that the predictive power of the test was too weak to allow valid judgments about the extent of emphysema in the individual patient.

Severe emphysema is also associated with characteristic abnormalities in the lung pressure–volume relationships, which include an increase in maximal lung capacity and a decrease in lung elastic recoil pressure at each lung volume. Efforts have been made to use the pressure–volume relationship and parameters derived from it as tests for emphysema severity. When pressure–volume relationships have been measured in excised human lungs, correlations with emphysema grade and or the mean linear intercept have been fairly close in some studies. Similarly high-order relationships have been shown in animal models of emphysema. Unfortunately, these relationships have been less consistent when the pressure–volume relationships have been measured in live humans and compared to emphysema severity in excised lungs. Correlations generally were found to be of a low magnitude, and they were not always statistically significant. These disappointing results are in part caused by the inherent variability of pressure–volume relationships in live subjects. Additionally, human disease frequently contains mixed elements of panacinar and centriacinar emphysema, and these two subtypes of emphysema may have different effects on lung elasticity. It has also been suggested that loss of lung elastic recoil may relate only indirectly to air-space enlargement and more directly to other, more subtle abnormalities in the lung's connective-tissue skeleton.

In a preceding section it was pointed out that emphysema would be expected to cause a reduction in maximal expiratory flow rates both because of a loss of lung elastic recoil and because of the loss of intraparenchymal airway tethers. Several correlative studies have shown that with increasing emphysema severity, maximal expiratory flow rates do decrease. Spirometric variables usually distinguish those patients with severe emphysema from those with no or trivial air-space enlargement, but in general, the correlation coefficients are surprisingly poor, so that spirometric abnormalities are not a good predictor of emphysema severity.

Total lung capacity is increased on average in patients with severe COPD, as are the vital capacity, functional residual capacity, and residual volume. The hyperinflation that is so characteristic a clinical and physiological feature of COPD is frequently attributed to emphysema. However, correlative studies have again proved disappointing in that none has shown a close correlation between any of the lung volumes and emphysema severity.

Thus, the principal conclusion to be drawn is that no currently available physiological test provides an accurate estimate of emphysema severity. In most studies, emphysema severity has been shown to correlate most closely with the D_LCO and less well with spirometric variables, lung volumes, and parameters of the pressure–volume relationships.

PHYSIOLOGICAL CORRELATES OF AIRWAYS DISEASE

The diverse pathologic conditions that affect the conducting airways in COPD are frequently lumped together as chronic bronchitis. Because not all of these lesions can be described as bronchial inflammation, and because chronic bronchitis has another, clinical definition, the practice of using this term to describe a variety of histopathologic changes in the conducting airways is not entirely logical. In this discussion we describe the entire complex of lesions affecting the conducting airways in COPD airways disease or, to clearly distinguish this category of disease from emphysema, intrinsic airways disease.

As discussed in the previous section, the importance of emphysema as one morphologic cause of airflow obstruction is well established even though the extent of anatomic emphysema does not correlate closely with any single pulmonary function test. Occasionally, patients with well-documented, severe COPD are found to have little emphysema when the lungs are examined at autopsy. Conversely, widespread emphysema is sometimes an incidental finding at autopsy in persons without known respiratory symptoms. Had careful pulmonary function testing been carried out in these individuals, some impairment of lung function might well have been found. Yet it is clear that the same amount of emphysema may be associated with severe disability and death in one person and cause few, if any, symptoms in the next.

This indicates that other morphologic factors must act in concert with emphysema to determine the severity of airflow obstruction. It has long been suspected that the most important of these other factors is the presence and severity of intrinsic airways disease. Earlier descriptions emphasized hypertrophy and hyperplasia of the mucus-secreting elements (i.e., bronchial mucous glands and epithelial goblet cells) as being an essential pathologic feature of COPD. It was suggested that excessive mucus predisposed to recurrent infection and that other pathologic changes, such as inflammation and fibrosis, were secondary phenomena. Because mucus hypersecretion was considered of paramount importance in the pathogenesis of COPD, chronic bronchitis was defined by the clinician as the presence of a productive cough, and to the pathologist it became virtually synonymous with bronchial mucous gland enlargement.

Other investigators described abnormalities in the peripheral airways of patients with COPD. These abnormalities included mural thickening and inflammation in many noncartilaginous bronchioles of lungs from patients with COPD. Morphometric and radiographic methods were employed to show that the peripheral airways from diseased lungs contained regions that were tortuous and modestly narrowed. It was also noted that inflammation and fibrosis of the membranous and respiratory bronchioles were more prevalent in lungs with centriacinar emphysema than with panacinar emphysema. It was suggested that lesions in the peripheral airways might contribute to the airflow obstruction and air trapping observed in COPD, but their mere presence gave no clue to their functional significance.

Earlier efforts to correlate the extent of intrinsic airways disease with the severity of airflow obstruction in COPD proved largely unsuccessful. The relationship between ventilatory dysfunction and mucous gland enlargement was most thoroughly investigated. In most such studies, the extent of mucous gland enlargement was assessed at autopsy by the Reid index or by other quantitative methods and was compared to pulmonary function measured within 1 or 2 years before death. Many such studies failed to show a consistent and compelling relationship between ventilatory function and the extent of mucous gland enlargement. This conclusion is further substantiated by studies of lung mechanics and morphology in postmortem lungs where no relationship was found between bronchial gland volume and any of the flow-resistive properties of the conducting airways. Also, epidemiologic studies demonstrated no significant relationship between excessive sputum production, the clinical correlate of mucous gland enlargement, and long-term changes in spirometric function. Correlative studies were similarly unsuccessful in showing that other disease features, including inflammation, fibrosis, and goblet cell metaplasia, involving either the large or small airways significantly related to antemortem spirometric abnormalities. Although these largely negative studies suggested that airways disease played only a small role in the causation of airflow obstruction, it is important to keep in mind that pathologic features such as inflammation and fibrosis do not lend themselves readily to quantitative assessment. Sampling is another potential problem because a single lung may contain as many as 30,000 separate airways. Hence, the results of these earlier studies should be regarded as inconclusive.

With tidal breathing, most patients with COPD have an elevated pulmonary resistance. The increase in airflow resistance, particularly when measured on inspiration, correlates with clinical status but not with the extent of anatomic emphysema. This measurement is thought to reflect more directly intrinsic airways disease than does spirometry, which, for reasons previously outlined, is also closely dependent on lung elastic recoil. An important clue to the site and nature of increased airflow resistance in COPD was provided by studies in which a retrograde catheter was positioned in the bronchial tree of postmortem lungs. This catheter then permitted airflow resistance to be partitioned between central airways and those peripheral airways of less than 2 mm internal diameter. The measurements obtained suggested that in normal lungs, peripheral resistance was negligible in comparison with the central component. However, in lungs from patients with COPD, central airways resistance was on average increased only slightly, but the peripheral component was increased between ten- and 20-fold. These observations added enormously to our understanding of the pathophysiology of COPD. Contrary to the opinion prevailing at that time, these studies indicated that it was disease in the distal airways and not the large bronchi that was principally responsible for increased flow resistance in COPD.

In addition, novel ideas were introduced concerning the natural history and pathophysiology of COPD. If peripheral resistance was negligible in the normal lung but predominated in severe COPD, quiescent disease might exist in the distal airways for many years before clinical symptoms of airflow obstruction became manifest. It was further suggested that routine spirometric tests may not be sufficiently sensitive to detect early disease in the distal airways. This premise provided the impetus to develop and evaluate a variety of so-called tests of small airways disease, such as the frequency dependence of dynamic compliance and the closing volume. Whether any of these newer tests offer any advantages over spirometry for either clinical or investigational purposes remains conjectural. Available evidence from epidemiologic and correlative studies indicates that standard spirometric tests, such as the FEV_1, are as sensitive as the specialized tests for detecting both early COPD and small airways disease.

This appears to be true because it is now known that the component of peripheral resistance in the normal lung is substantially greater than was suggested by the original retrograde catheter studies. In a population of largely normal lungs, it was found that pulmonary resistance and maximal expiratory flow rates correlated closely with the diameter of the membranous bronchioles and not with any other morphologic variable. For example, pulmonary resistance was correlated to average bronchiole diameter with a coefficient of –0.85, whereas the correlations between pulmonary resistance and both bronchial gland mass (r = –0.10) and large airways diameter (r = –0.21) were not statistically significant. Subsequent studies with the same retrograde catheter technique confirmed that the peripheral component of airways resistance in normal lungs was seriously underestimated in the original study.

This finding has important implications concerning the pathophysiology of COPD. If the peripheral airways are an important determinant of ventilatory function in the normal lung, it logically follows that lung function may be critically vulnerable to minor degrees of pathologic narrowing in those same airways. The sensitivity of ventilatory function to minor degrees of bronchiolar narrowing can be appreciated in Fig. 15, which shows the frequency distribution of internal bronchiole diameters in two normal adult lungs from persons of the same age. The average diameter in one lung is nearly twice that in the other. Because airflow resistance through cylinders varies with the fourth power or greater of diameter, seemingly modest differences in average bronchiole diameter are associated with pronounced functional differences. Pulmonary resistance in the second lung is more than five times greater than that in the first lung, and maximal expiratory flow rates are correspondingly less. Subtle pathologic changes that diffusely affect the distal air passages may have profound functional consequences.

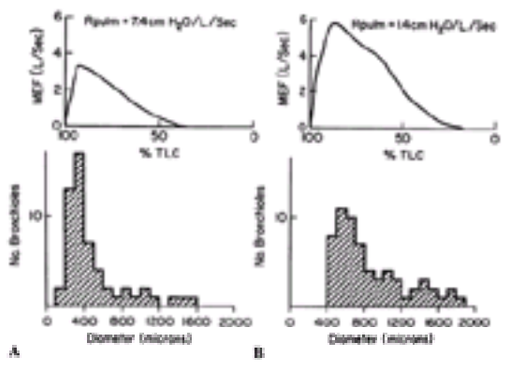

FIG. 15. Ventilatory function is sensitive to minor degrees of narrowing in the membranous bronchioles. Postmortem flow–volume loops and pulmonary resistance (R_{pulm}) were measured in two normal lungs **(A,B)** from men 40 years old. The *lower panel* shows the distribution of internal bronchiole diameters in the same two lungs. Note that R_{pulm} is substantially higher, and MEF is lower, in the lung with slightly smaller bronchioles. TLC, total lung capacity; MEF, maximum expiratory flow.

The suggestion that disease in the peripheral airways might antedate the clinical manifestations of COPD has been largely substantiated by physiological and pathologic studies. Most such studies have been directed at young smokers, a logical choice because cigarette smoking causes COPD, but usually only after at least 20 years of habitual consumption. Subtle ventilatory dysfunction in young smokers has been detected by a variety of pulmonary function tests. The pathologic lesions thought to be responsible for these minimal physiological abnormalities have been identified in studies of lungs from youthful victims of sudden death. The characteristic lesion in cigarette smokers (Fig. 5) is located in the respiratory bronchiole and consists of clumps of brown-pigmented macrophages lying within the air spaces while edema, epithelial hyperplasia, and minimal fibrosis involve the adjacent alveolar and bronchiolar walls. Frequently, a sparse mononuclear inflammatory infiltrate is seen within the walls of the terminal membranous bronchioles. These lesions are present in all lungs from cigarette smokers, but they are noted only occasionally in the lungs of nonsmokers.

Functional and morphologic correlative studies provide additional direct evidence linking peripheral airways disease with airflow obstruction in COPD. Lung tissue was obtained from patients undergoing thoracotomy in whom extensive pulmonary function tests had been performed immediately before surgery. A few subjects had normal pulmonary function, but most had mild to moderate COPD. Emphysema was quantified from thick lung slices, and the extent of small airways disease was assessed on multiple histologic sections from each lung. Each bronchiole was individually evaluated and assigned a score appropriate to the severity of each morphologic abnormality, including luminal mucus, squamous and goblet cell metaplasia involving the epithelium, and inflammation, fibrosis, pigment, and smooth muscle hypertrophy in the airway wall. A weak but consistent relationship was found between composite scores for small airways disease and the severity of airflow obstruction as assessed by various physiological tests. Functional disturbances related most closely to fibrosis and inflammation within the walls of the bronchioles, and they correlated less well with epithelial abnormalities and with the amount of intraluminal mucus. Other studies in which postmortem pathology was compared to antemortem pulmonary function tests yielded similar results.

RELATIVE IMPORTANCE OF EMPHYSEMA AND AIRWAYS DISEASE

From the foregoing discussion it is reasonable to conclude that both emphysema and small airways disease play significant roles as causes of airflow obstruction in COPD. Both are clearly more important than chronic bronchitis and mucus hypersecretion. Lungs from patients with COPD usually contain elements of both emphysema and peripheral airways disease, but numerous studies have yielded conflicting results as to which component might be the more important. This might be a function of case selection and the severity of the clinical disease. When pathologic studies were performed on autopsied lungs, emphysema has generally emerged as the single closest correlate of airflow obstruction. When pathologic studies were performed on lungs resected at surgery, peripheral airways disease has usually appeared to be somewhat more important. Patients undergoing thoracotomy clearly have less severe disease than those patients who are subjected to autopsy. On the basis of such studies, it has been suggested that peripheral airways disease might dominate during the earlier clinical stages of COPD but that emphysema might play a greater role in those patients who are severely incapacitated and who eventually die of respiratory insufficiency. No firm conclusions can be drawn until more complete information becomes available. A summary of the principal pathologic changes found in COPD and their relationship to clinical and physiological

abnormalities is provided in Table 1.

	Symptoms	Pathology	Physiology
Chronic bronchitis	Cough and sputum expectoration	Inflammation and enlargement of mucus-secreting elements in central airways	Little or no effect on spirometry
Emphysema	Dyspnea and exercise intolerance when severe	Air space enlargement with destruction of alveolar walls	Adverse effects on spirometry and arterial blood gases Loss of elastic recoil Decrease in DLCO
Small airways disease	Dyspnea and exercise intolerance when severe	Inflammation, goblet cell metaplasia, fibrosis, and smooth muscle enlargement in distal airways	Subtle spirometric abnormalities in young smokers Contributes to airflow obstruction and blood gas abnormalities in severe COPD

TABLE 1. *Pathologic features of COPD and their relationship to symptoms and pulmonary function abnormalities*

CLINICAL AND PATHOLOGIC SUBTYPES

Patients having in common irreversible airflow obstruction may exhibit otherwise variable clinical and physiological features. Based on clinical, roentgenographic, and physiological criteria, two contrasting categories of disease, the so-called emphysematous and bronchial subtypes of COPD, were described. As implied by the descriptive terms applied to each subgroup, it was presumed that extensive anatomic emphysema provided the principal morphologic basis for dysfunction in the first group, whereas enlargement of the mucus-secreting elements was the major pathologic lesion in patients with bronchial disease. There is general agreement as to the basic clinical and physiological features of each syndrome; whether distinguishable patterns of lung pathology underlie these subtypes of COPD is somewhat less clear.

The patient thought to have predominant emphysema (type A disease) has been described in rather vivid terms as a “pink puffer.” He is said to be a cachectic, elderly man who relates a long history of progressive and unrelenting breathlessness. Sputum production and recurrent chest infections are notable by their absence and, except in the preterminal stages of the disease, heart failure (cor pulmonale) is not clinically evident. The chest roentgenogram reveals a small cardiac silhouette along with the roentgenographic signs of advanced emphysema: lung hyperinflation, attenuated peripheral lung markings, and frequently the thin ring shadows pathognomonic of bullae. At rest, arterial blood gas values reveal mild hypoxemia with little elevation in the arterial carbon dioxide tension. The hematocrit is seldom greater than 45% to 50%, reflecting the relative absence of arterial oxygen desaturation. In addition to the decrease in expiratory flow rates, pulmonary function studies show large lung volumes, with TLC being 130% or more of the predicted value. Because of the loss of alveolar tissue, lung elastic recoil is decreased, and the D_LCO is severely impaired. Pulmonary resistance measured during tidal breathing is normal or only slightly elevated.

The patient considered to have predominant bronchial disease (type B patient) was described as a “blue bloater.” In contrast to the asthenic appearance of the pink puffer, this patient is described as a stocky and sometimes overweight individual with a plethoric facies and pronounced cyanosis. Because enlargement of the mucus-secreting elements has been thought the principal cause of airflow obstruction in these individuals, the presence of chronic cough and sputum production has been considered an essential feature of type B disease. The other essential feature is cor pulmonale, which appears early and remains a prominent feature throughout the course of the disease. Cor pulmonale is manifest clinically as peripheral edema, cardiac enlargement, and classic electrocardiographic signs of right ventricular enlargement. Arterial blood gas values show evidence of severe arterial oxygen desaturation and a strong tendency to carbon dioxide retention. Secondary polycythemia with a hematocrit in excess of 55% commonly develops as a consequence of severe, chronic hypoxemia. As with the type A patient, spirometry shows severe airflow obstruction, but there is less hyperinflation of the lung. Because alveolar tissue is thought to be preserved, lung elastic recoil is normal, as is the D_LCO.

The clinical features that distinguish COPD subtypes can be recognized in some patients, but most patients with COPD appear to have features of both groups and cannot be categorized. It has been proposed that the population of COPD patients represents a spectrum, with the type A patients at one end and the type B patients at the other. Because of extensive overlap between the two groups, clinical investigations have compared only those patients at the extreme ends of the spectrum.

In general, type A patients were found to have larger lung volumes, more nearly normal arterial blood gases, and a larger volume of total ventilation per unit of oxygen uptake. Consistent differences were noted between the two groups with regard to pulmonary vascular hemodynamics and systemic oxygen transport. In the type A patients, cardiac output was subnormal both at rest and with exercise, whereas this physiological variable was normal under both conditions in the blue bloaters. Calculated pulmonary vascular resistance was not significantly different in the two groups, but because cardiac output was higher in the type B group, mean pulmonary artery pressures also were greater. Pulmonary hypertension developed in the type A patients only in response to exercise. Despite a greater degree of arterial oxygen desaturation, systemic oxygen transport was better preserved among the type B patients because of their secondary polycythemia and because of their higher cardiac output. With exercise, minute ventilation in relation to oxygen consumption and to carbon dioxide excretion was higher in the type A patient than in the type B patient. Maximum work load and the exercise level associated with anaerobic metabolism tended to be less in the type A patient.

Ventilation–perfusion relationships have also been compared in patients with type A and type B disease. In general, patients with type A disease had predominantly high abnormalities with relatively few areas of low-$\dot{V}/\dot{Q}$ abnormalities. There was a greater tendency for low-$\dot{V}/\dot{Q}$ patterns to be found in type B disease, but most patients with this clinical syndrome had mixed patterns of both high- and low-$\dot{V}/\dot{Q}$ disturbances.

Though type A and type B patients are recognized clinically, much less is known about the causes and mechanisms of those differences. It is emphasized that subgroup distinctions have usually been made on clinical and physiological grounds, and the pathology has only been inferred. Where efforts have been made to correlate lung pathology with the clinical subtype of COPD, the findings have been contradictory and inconclusive. Many of the criteria used to categorize clinical subtypes are descriptive and not quantitative. It is evident that selection criteria are not uniform among different studies, and sometimes not even among the same groups of investigators at different times. These factors may partly explain the relative lack of success in correlating clinical COPD subtypes with pathology.

Cor pulmonale is generally considered an essential feature of the type B patient but not the type A patient. Clinical right-sided heart failure relates closely to right ventricular enlargement, and this morphologic feature can be accurately assessed at autopsy. One can conclude from the available evidence that the presence of emphysema alone is not the predominant factor in the pathogenesis of cor pulmonale. Numerous autopsy studies compared right ventricular size with emphysema severity. The correlation was variously reported as positive, negative, or not statistically significant. However, even with a positive correlation, only about 25% of the total variance in right ventricular weight could be explained by emphysema severity. The methods for assessing emphysema and right ventricular size are reproducible, so that the poor correlations cannot be attributed to measurement error. It also has been suggested that right ventricular enlargement might be more closely related to the morphologic type of emphysema. Even here the evidence is conflicting; some reports show that right ventricular size is related to centriacinar emphysema, but others report an association with panacinar emphysema. Estimation of emphysema severity by CT also bears no significant relationship to arterial blood gas abnormalities, cardiac output, mean pulmonary artery pressure, or pulmonary vascular resistance.

The dissociation between the severity of emphysema and right ventricular size supports the idea that type A patients have little tendency to develop cor pulmonale. However, a number of earlier efforts to relate bronchial mucous gland enlargement, thought to be the essential pathologic feature in type B patients, with pulmonary hypertension and cor pulmonale were equally unsuccessful. These negative findings are not surprising in light of the previously cited evidence that bronchial mucous gland enlargement is also unrelated to airflow obstruction.

Peripheral airways disease might be more closely associated with cor pulmonale than is either emphysema or mucous gland enlargement. The severity of peripheral airways disease, as assessed from histologic studies, from bronchial casts, or from bronchography, has been compared to right ventricular weights or to the characteristic changes of hypertension in the pulmonary arterioles. Although the association was not strong, and it varied from study to study, a reasonably consistent relationship has been found between indices of peripheral airways disease and the development of pulmonary hypertension.

Certain patients with COPD do have a greater predisposition toward developing hypoxemia, hypercapnia, and pulmonary hypertension, so that the terms pink puffer and blue bloater may have some validity as clinical descriptive terms. However, it is largely unknown why these differences exist. Because they have no clearly defined anatomic basis, there is no justification for describing such patients as having either the emphysematous or bronchitic type of COPD.

ROENTGENOGRAPHIC CORRELATES

A chest roentgenogram is an essential part of the initial medical evaluation of all patients with an undiagnosed complaint of dyspnea. However, its chief diagnostic value may lie in what it does not reveal, namely, roentgenographic signs that suggest some cause for dyspnea other than COPD. The chest roentgenogram is a relatively insensitive test for COPD, and it may appear normal or near-normal in the face of severe airflow obstruction. The criteria for the roentgenographic diagnosis of COPD fall into two main categories: lung hyperinflation and irregular radiolucencies of the lung fields.

Lung Hyperinflation

The standard chest roentgenogram in a patient with severe COPD reveals a diaphragm that is depressed with an altered contour (Fig. 16). The diaphragm is abnormally low if the dome is at the level of the anterior aspect of the seventh rib or below, and it is considered flattened if the maximum curvature is less than 1.5 cm. It has also been suggested that the sternodiaphragmatic angle on the lateral chest film may be a useful sign. In normal subjects, this angle is acute, but in patients with COPD, it is frequently greater than 90°. Lung hyperinflation is also indicated by an increase in the retrosternal clear space. This distance is measured horizontally between the posterior edge of the sternum and the most anterior portion of the ascending aorta. Some experts consider a distance of 2.5 cm or more to be abnormal, but others believe a value of 4.5 cm to be a more specific criterion for COPD.

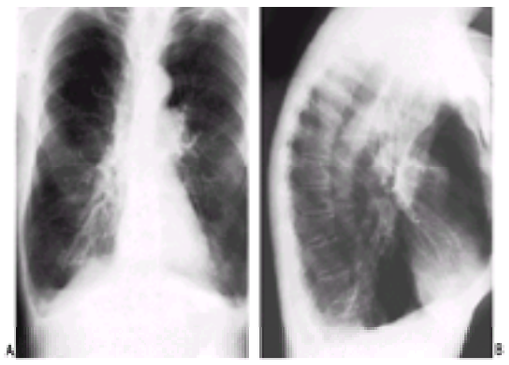

FIG. 16. Chest roentgenogram from a patient with severe COPD. In the posteroanterior projection (*left*), the lungs appear hyperinflated with attenuation of the peripheral lung markings. The lateral projection (*right*) shows loss of the normal contour of the hemidiaphragms and an increase in the retrosternal clear space.

Irregular Radiolucencies of Lung Fields

Emphysema results in a loss of alveolar tissue and a diminution in the number of blood vessels. As a consequence, affected areas are less dense, and these abnormalities can be appreciated roentgenographically as areas of radiolucencies in the peripheral lung fields. On the standard chest roentgenogram, these changes may be quite subtle, and the presence of radiolucencies can be appreciated only by comparison against more normal-appearing regions. The edges of bullae can frequently be identified by the presence of thin, curved lines on the plain chest roentgenogram, and these changes are pathognomonic for bullous emphysema.

The irregular radiolucencies associated with emphysema are much better seen with tomography, particularly with the superior resolution provided by computed tomography (CT). When regional variations in lung tissue density are quantified by CT scans, remarkably good correlations with the extent of anatomic emphysema have been demonstrated. Precise information concerning the anatomic distribution and severity of emphysema has no clinical implications except in those few patients where consideration is given to surgical ablative therapy.

VARIANT FORMS OF COPD

Bullous Emphysema

Bullous emphysema is considered separately because it has certain distinctive pathologic and roentgenographic features and because surgery may be of benefit to the patient. Bullae are abnormally enlarged air spaces, measuring more than 1 cm in diameter, resulting from destruction of alveolar walls. Bullae are thought to represent a variant form of emphysema in which the destructive changes are exaggerated within focal areas. Most patients with bullae have some emphysema in other lung regions, but extensive bullous disease may be present with little pathologic change in other lung regions. Small bullae, occurring singly or in clusters, are sometimes seen at the apices of otherwise normal lungs, particularly in tall young adults. They may spontaneously rupture into the pleural space and cause a pneumothorax. Whether these small apical bullae are the forerunners of more extensive bullous disease in older patients is not known. Giant bullae may occur singly, but they are more commonly multiple, and they frequently involve both lungs. They are located immediately below the pleural surface and occur most commonly in the upper portions of the lung. The predilection for bullae to occur in lung apices might be explained by gravitational effects, which result in greater tissue stresses in the more cephalad lung regions. However, bullae occur in all parts of the lung, and a basal location is more frequently observed in patients with severe a_1-antiprotease deficiency.

Bullous disease, when extensive, can usually be recognized on the plain chest roentgenogram as regions of absent or decreased vascular markings demarcated by curving hair-thin shadows. These thin lines represent the walls of the bullae and, when visible, are virtually pathognomonic. Bullae are visualized much better with the CT scan, and this is the preferred method if there is need to define location and extent. The displacement of the pulmonary vasculature away from areas of bullous involvement can be demonstrated elegantly by pulmonary angiography, but this procedure is rarely necessary. Radioisotope scanning can also be utilized to assess the location and severity of bullous disease, as the involved areas have markedly diminished ventilation and perfusion.

Patients with bullae frequently have reduced maximal expiratory flow rates, an increase in TLC, FRC, and RV, and a decrease in the D_LCO. The extent to which bullous disease is responsible for these functional disturbances is uncertain because patients usually have coexisting diffuse emphysema and airways disease. Bullae are largely avascular, and because they also are underventilated, they contribute little to overall gas exchange. Bullae are frequently viewed as enclosed air spaces that, because of pressure differentials, particularly during expiration, compress and impair function in more normal adjacent lung regions. However, most bullae have some communications with surrounding air spaces, and it therefore seems improbable that large pressure differentials could exist across the walls of the bullae during tidal breathing. Bullae probably impair lung function merely as space-occupying structures that do not permit more normal areas of the lung to expand fully.

The suspicion that bullae may contribute directly to impaired lung function has guided surgical efforts for their removal or ablation. Overall, these efforts have not yielded encouraging results, and as might be anticipated, surgery in this group of patients has a high attendant morbidity and mortality. Despite the generally disappointing results, surgery does confer substantial objective and subjective benefits for a few selected patients. The problem is in knowing how to identify those individuals who are most likely to benefit. Based on the case analysis of published reports, only general guidelines can be offered to predict the response to surgery. The larger and more localized the bullae, the more likely there will be a favorable result from surgical ablation. Patients with the worst preoperative pulmonary function have the poorest chance of appreciable objective improvement. The presence of diffuse severe emphysema, as indicated by a very low D_LCO, is associated with a particularly poor surgical success rate. However, if bullae are localized, if they involve at least one-third to one-half of a hemithorax, if the patient is severely disabled from dyspnea, and if overall lung function is reasonably well preserved, then consideration should be given to surgical ablation.

Unilateral Hyperlucent Lung Syndrome

Swyer and James first described the unilateral hyperlucent lung syndrome in 1953; this report was followed shortly by descriptions of similar cases by MacLeod. Hence, the condition is sometimes described as the Swyer–James or MacLeod syndrome. The diagnosis is principally a roentgenographic one, and many cases are first recognized from routine chest roentgenograms in asymptomatic persons. The principal feature is an abnormal degree of radiolucency involving one lung or one lobe within a lung that results from attenuated vascular markings and not from overexpansion. In addition, there is usually a smaller-than-normal hilar shadow on the affected side. Severe airflow obstruction is present on the affected side, and this is evident with fluoroscopy or with inspiratory and expiratory chest roentgenograms. With inspiration, the mediastinum shifts toward the affected lung, and there is only minimal movement of the rib cage and diaphragm on the involved side. With expiration, the mediastinum shifts toward the normal lung as it empties, while the volume of the affected lung changes little if at all. Pulmonary angiograms show a relatively small pulmonary artery on the affected side, with marked attenuation in the number and size of the smaller arterial branches. The decrease in ventilation and

perfusion in the radiolucent lung can also be readily appreciated from external radioisotope scans.

Originally it was thought that this syndrome represented a congenital or acquired vascular abnormality similar to hypoplastic pulmonary artery, but it is now known that diffuse obstruction in the peripheral airways is the primary lesion, and the vascular changes are secondary. Roentgenographic and pathologic studies demonstrate severe bronchiolar disease, which is responsible for airflow obstruction and air trapping. Bronchograms of affected lungs show largely normal proximal bronchi but dilation and beading of the more distal airways. Many of the terminal airways fail to fill completely with contrast material. The clubbed and tapered peripheral airways are described as having a “broken bough” appearance. Pathologic studies of these same lungs reveal widespread inflammation and fibrosis of the nonalveolated bronchioles with narrowing or complete obliteration of their lumina. Emphysema of varying severity is present in the parenchyma of some of the affected lungs. Small pulmonary arterioles are narrowed, but they are not occluded by thrombi, and they are not involved by an endarteritis. The large pulmonary arteries are normal by histologic examination.

Many patients with the unilateral hyperlucent lung syndrome have a history of severe childhood pneumonia, and other cases have been described following *Mycoplasma pneumoniae* infection, measles, pertussis, tuberculosis, radiation, foreign-body aspiration, and hydrocarbon exposure. The clinical and pathologic observations are consistent with the idea that severe inflammation in the small airways, induced by infection or toxin, causes severe airflow obstruction. Hypoperfusion occurs secondarily because of relative alveolar hypoxia, and over time these vascular changes become irreversible.

The affected lung receives some ventilation (atelectasis would occur if it did not), but minute volume and oxygen uptake on the affected side are usually less than 25% of the total and may be much less. Mixing time for inert gases is greatly prolonged because of the marked disparities in the amounts of ventilation received by the two lungs. Because perfusion is reduced roughly in proportion to ventilation, the $\dot{V}/\dot{Q}$ of the involved lung remains near unity so that severe arterial oxygen desaturation does not usually occur unless the patient exercises. Spirometry characteristically shows a modest reduction in the forced vital capacity and mild airflow obstruction. If the opposite lung is relatively free of disease, pulmonary function test results may be surprisingly normal.

Unilateral hyperlucent lung syndrome usually presents few difficulties in differential diagnosis provided that fluoroscopy or inspiratory and expiratory roentgenograms are obtained. Most patients have no symptoms directly attributable to the disorder, so that no specific treatment is required. If the opposite lung is also involved to a lesser degree, severe airflow obstruction and a clinical picture indistinguishable from COPD may be present. Rarely, recurrent infections in the affected lung may be an indication for surgical removal.

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CHAPTER

43 Clinical Aspects of Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has recently been defined by the American Thoracic Society (ATS) as a disease state characterized by the presence of airflow obstruction secondary to chronic bronchitis (airways disease) or emphysema (parenchymal destruction with air-space enlargement). The airflow obstruction is generally progressive, may be accompanied by hyperactivity, and may be potentially reversible. This definition is very similar to that expressed by other international respiratory societies in similar statements. Inherent to the definition is the acknowledgment that many patients with COPD may show a significant reversible component in their airflow obstruction and that patients with asthma may go on to develop irreversible airflow obstruction indistinguishable from COPD.

Chronic bronchitis is defined in clinical terms as the presence of chronic cough with phlegm production for 3 months in each of two consecutive years, without other specific causes of cough (asthma, bronchiectasis, cystic fibrosis, etc.). Emphysema, on the other hand, is defined pathologically as abnormal air-space enlargement as has been discussed in the previous chapter. Figure 1 graphically represents the interrelation of the different nosologic components that lead to COPD and helps the reader to better understand the concepts. Most patients with asthma have significant reversible airways constriction and respond well to inhaled and systemic antiinflammatory therapy and therefore do not have COPD. As stated before, a small minority of asthmatics go on to develop minimally reversible airflow limitation indistinguishable from COPD. This group of patients do have COPD and are treated as such.

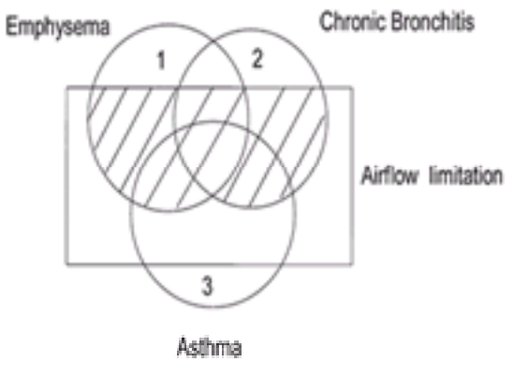

FIG. 1. Nonproportional Venn diagram. Each *circle* represents a nosologic entity. The *rectangle* represents airflow limitation as documented in a forced spirometry. The *shaded area* corresponds to patients diagnosed as having COPD. Notice that a patient (subset 1) may present with emphysema without COPD (patient with bullae on chest roentgenogram without airflow limitation). Similarly, he or she may present with sputum production and normal spirometry (subset 2, with simple bronchitis). Finally, an asthmatic may present without airflow limitation (subset 3) and will be diagnosed only after a bronchoprovocation test.

EPIDEMIOLOGY OF COPD AND RISK FACTORS

It is estimated that in the United States, close to 14 million people suffer from COPD. This number has increased 42% since 1982. Although between 1979 and 1986 the prevalence varied from 4% to 6% of adult men and 1% to 3% of women, it had increased more for the women than for men. There were 85,544 deaths from COPD in 1991 (death rate of 18 per 100,000 persons); COPD ranks as the fourth leading cause of death, but it was the fastest rising one (33%) between 1979 and 1991. When adjusted by age, the death rate from COPD rose 72% between 1966 and 1986. This is particularly important when death rate for all causes decreased 22% and rates from heart and cerebrovascular disease declined 45% and 85%, respectively. Fortunately, there has been a progressive decline in the percentage of the population who smoke (Fig. 2). This should result in decreased mortality from COPD in the near future. It is interesting that most of the decrease is attributable to

smoking cessation in men and not in women. Even greater efforts must be devoted to smoking cessation because the habit is still practiced by 75 million citizens in the United States alone. If the same prevalence exists around the world (there is evidence that it may actually be more), there is an astonishing total of 1.2 billion human beings exposed to the ravages of cigarettes.

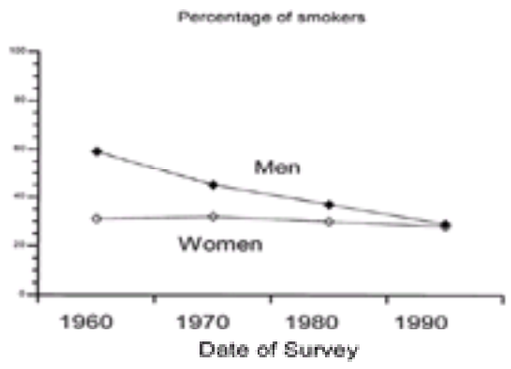

FIG. 2. Prevalence by decade of smoking habit in the general population of the United States.

As shown in Table 1, the most important cause of COPD is cigarette smoking. Other possible causes may act as independent risk factors in its genesis, but their importance dwarfs in comparison with the role of cigarette smoking. The only other risk factor comparable to the importance of smoking for an individual is a_1-antitrypsin (AAT) deficiency, but AAT accounts for fewer than 1% of COPD cases.

Established	Probable	Possible
Cigarette smoking	Air pollution	Low birth weight
Occupational exposure (work smoke)	Poverty	Childhood respiratory infections
α_1-Antitrypsin	Childhood exposure to smoke	Family history
	Alcohol	Atopy
	Hyperreactive airways	IgA nonsecretor
		Blood group A

TABLE 1. *Risk factors for the development of COPD*

Children exposed to cigarette smoke manifest a higher prevalence of respiratory symptoms and diseases than do children of nonsmokers. They also show a measurable decrease in pulmonary function tests. Whether this leads to COPD remains unclear, but it is very possible. Air pollution is harmful to patients with heart and lung disease and may be an important factor in certain areas. Studies in nonsmoking persons who use solid fuels for indoor cooking and lack adequate ventilation have shown presence of COPD in some of the patients studied. This evidence does support some role for pollutants in the genesis of COPD, but it would be small in comparison to cigarette smoking in countries with better pollution control. Expoto polluting agents in the environment may probably operate in the same way and may certainly worsen the function of patients with airflow obstruction. Morbidity and mortality rates from COPD are higher for whites than for nonwhites and in blue-collar than white-collar workers; COPD also aggregates in families independent of a_1-antitrypsin deficiency.

Atopy, hyperresponsive airways, and asthma may play a role in the genesis of COPD. Since it was first proposed by researchers in The Netherlands, the Dutch hypothesis has been the subject of interesting analyses. It has been shown that airway hyperactivity is inversely related to FEV_1 and that it is predictive of an accelerated rate of decline of lung function in smokers. In the Lung Health Study of COPD, there was a rather significant proportion of men (59%) and even more women (81%) who manifested airways hyperactivity. This suggests that hyperactive airways may be an important factor contributing to FEV_1 decline in some patients with COPD, but its true importance remains to be determined.

The only host factor proven to lead to COPD is deficiency of a_1-antitrypsin. This serum protein is made by the liver, and its main role is the inhibition of neutrophil elastase. It is a glycoprotein coded for by a single gene on chromosome 14. The normal value of AAT is 150 to 350 mg/dl (commercial standard) or 20 to 48 mg/dl (laboratory standard). There are rare instances of patients with normal levels of dysfunctional AAT. Most of the persons with severe deficiency are homozygotic for the Z allele (PiZZ) and have very low levels of AAT (mean 18% of the value seen in normals). The threshold protective level of AAT is around 80 mg/dl (35% normal), and heterozygotes (PiSZ) with these levels rarely develop emphysema. Severe AAT deficiency leads to premature emphysema, often with chronic bronchitis, nonspecific airway hyperactivity, and occasionally with bronchiectasis. The onset of disease is accelerated by smoking, and dyspnea begins at the median age of 40 in smokers and 50 in nonsmokers. Not all patients with AAT deficiency will develop emphysema, especially if not exposed to cigarettes or pollution. Patients should be screened for AAT deficiency if they present with premature onset of COPD (before age 50), predominance of basilar emphysema (by x-rays), presence of nonremitting asthma in a young person, and liver cirrhosis without apparent risk factors.

NATURAL HISTORY OF COPD

The decline in lung function with time is shown in Fig. 3. Normal nonsmokers lose between 25 and 35 mL of their FEV_1 yearly. The rate of decline is steeper for smokers than for nonsmokers. The heavier the smoking, the steeper the decline; likewise, the lower the initial FEV_1, the faster will FEV_1 drop. The FEV_1 of patients with COPD decreases around 90 mL a year. The Lung Health Study showed that patients who stopped smoking had a mean postbronchodilator FEV_1 increase of 57 mL at the first annual visit compared with a mean FEV_1 decline of 38 mL for those who continued to smoke. This indicates not only that the decline will decrease but that lung function may actually improve after smoking cessation. The natural rate of decline accelerates dramatically in susceptible smokers. The rate of decline returns toward normal soon after smoking cessation in most of the patients, whereas the development of symptoms with minimal activities will occur much earlier in current than in ex-smokers.

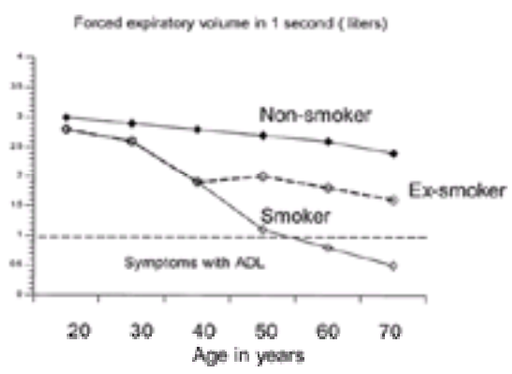

FIG. 3. Rate of decline of lung function according to smoking habit. Notice that the rate of decline is steeper for current smokers and tends to return to the normal rate after smoking cessation. The onset of symptoms related to COPD will be delayed whenever smoking stops.

CLINICAL FEATURES

History

The typical patient with COPD has smoked more than 20 pack/years before symptoms develop. They commonly present with productive cough or an acute chest illness at around the fifth decade. Dyspnea usually begins around the sixth or seventh decade, but it may become the dominant feature. Dyspnea may become crippling and lead to deconditioning as ever less intense exercise precipitates worsening of the symptom. This vicious cycle is one of the most important problems in patients with advanced COPD. Breaking the cycle leads to improvement in the functional status of the patient.

Sputum initially occurs only in the morning and is usually mucoid. During exacerbations, it may become purulent. Acute chest illnesses characterized by increased cough, purulent sputum, wheezing, dyspnea, and occasionally fever may occur intermittently. The history of wheezing and dyspnea may lead to the erroneous diagnosis of asthma. As the disease progresses, the intervals between exacerbations shorten. Late in the course, the patient may develop hypoxemia, which, if severe enough, may result in clinical cyanosis; this is accentuated by erythrocytosis. Development of morning headache suggests hypercapnia. Weight loss occurs in some patients, and cor pulmonale with right heart failure and edema may develop in patients with hypoxemia and hypercapnia. Most episodes of hemoptysis result from mucosal erosion and not carcinoma. However, because bronchogenic carcinoma occurs with increased frequency in smokers with COPD, an episode of hemoptysis raises the possibility that a carcinoma has developed, and it should prompt an evaluation to rule out this possibility.

Physical Examination

Initially, the chest exam may show wheezes only on forced expiration. As obstruction progresses, hyperinflation becomes evident, and the anteroposterior diameter of the chest increases. The diaphragm is depressed and limited in its motion. Breath sounds are decreased at this stage, and heart sounds often become distant. Coarse crackles are often heard at the lung bases. An excessively prolonged forced expiratory time (over 4 sec with the stethoscope over the trachea) may be seen in patients with a significant degree of airflow limitation. The patient with end-stage COPD may adopt positions that relieve dyspnea, such as leaning forward with weight supported on the arms. The accessory respiratory muscles of the neck and shoulder girdle are in full use. Expiration often takes place through pursed lips and with forced contractions of the abdominal muscles. Paradoxic indrawing of the lower costal interspace with inspiration is a classic finding first described by William Stokes in 1837. An enlarged tender liver indicates heart failure. Neck vein distention, especially during expiration, may be observed in the absence of heart failure because of increased intrathoracic pressure. Cyanosis may be present, and asterixis may be seen with severe hypoxemia and hypercapnia.

LABORATORY FINDINGS

Chest Radiography

Because emphysema is defined in anatomic terms, posteroanterior and lateral chest roentgenograms provide evidence of its presence. Hyperinflation is indicated by a low, flat diaphragm, an increased retrosternal air space, and a long, narrow heart shadow. Rapid tapering of the vascular shadows accompanied by hypertransparency of the lungs is a sign of emphysema; bullae, presenting as radiolucent areas larger than 1 cm in diameter and surrounded by arcuate hairline shadows, suggest its presence. However, bullae reflect only locally severe disease and are not necessarily indicative of widespread emphysema. Studies correlating lung structure and the chest radiograph show that emphysema is consistently diagnosed when the disease is severe but that diagnosis is not as accurate when the disease is mild or even moderate. Right ventricular hypertrophy does not result in cardiomegaly in COPD. Comparison with previous chest radiographs may show the enlargement. The hilar vascular shadows are prominent, and the heart shadow encroaches on the retrosternal space as the right ventricle enlarges anteriorly. Lung cancer and heart disease are associated with the same risk factor as COPD, namely, smoking. Therefore, a chest roentgenogram is indicated, not only to find evidence of emphysema but, equally important, to rule out the presence of any of the diseases that may present with similar symptoms.

Computed Tomography

Computed tomography, especially a high-resolution CT scan (collimation of 1 to 2 mm), has much greater sensitivity and specificity than standard chest radiography. However, because this rarely alters therapy, CT has no place in the routine care of patients with COPD. It is the main imaging tool for evaluating the benefit of pulmonary resection for giant bullous disease and for diagnosing bronchiectasis. It also is gaining ground as a good tool to evaluate potential candidates for lung volume reduction surgery.

Pulmonary Function Tests

Determination of a forced vital capacity is necessary for the diagnosis and assessment of the severity of disease and helpful in following its progress. The FEV_1 is easily measurable, has less variability than other measurements of airways dynamics, and is more accurately predictable from age, race, gender, and height. Roughly comparable information can be obtained from the peak flow measurement or from the forced expiratory flow–volume curve. None of these tests can distinguish between chronic bronchitis and emphysema. The FEV_1 and the FEV_1/FVC ratio fall progressively as the severity of COPD increases. In the laboratory, about 30% of patients have an increase of 20% or more in their FEV_1 following a b-agonist or ipratropium bromide treatment.

Lung volume measurements show an increase in total lung capacity, functional residual capacity, and residual volume. The vital capacity may be decreased. The single-breath carbon monoxide diffusing capacity (D_LCO_{sb}) is decreased in proportion to the severity of emphysema because of the loss of alveolar capillary bed. The test is not specific, nor can it detect mild emphysema. If the D_LCO_{sb} is disproportionally low in comparison with changes in other function tests, emphysema is more likely to be the cause of the obstruction. The presence of a low D_LCO_{sb} has correlated with exercise oxygen desaturation in patients with COPD.

Arterial blood gases reveal hypoxemia without hypercapnia in the early stages. As the disease progresses, hypoxemia becomes more severe, and hypercapnia supervenes. Hypercapnia is observed with increasing frequency as the FEV_1 falls below 1 liter. Blood gas abnormalities worsen during acute exacerbations and may worsen during exercise and sleep. Erythrocytosis is infrequently observed in patients living at sea level who have P_aO_2 levels of >55 mmHg; the frequency of erythrocytosis increases as P_aO_2 levels fall below 55 mmHg.

Sputum Examination

In stable chronic bronchitis, sputum is mucoid, and the predominant cell is the macrophage. With an exacerbation, sputum usually becomes purulent with an influx of neutrophils. The Gram stain usually shows a mixture of organisms. The most frequent pathogens cultured from the sputum are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* However, cultures and even Gram stains are rarely necessary before antimicrobial therapy is instituted in the outpatient setting.

DIAGNOSIS AND MONITORING

In patients suspected of COPD, a forced spirometry provides the basic physiologic assessment needed to quantify obstruction. Arterial blood gases in patients with severe COPD (stage III) help to identify the presence and severity of hypoxemia and hypercapnia. The effect of inhaling a b-agonist or ipratropium on the FEV_1 should be determined. Bronchodilators should not be withheld on the basis of this test. Measurements of lung volumes, diffusing capacity, or physiological responses to exercise usually add little unless the diagnosis is in doubt or an assessment of operative risk is being made. Arterial blood gas measurements are not needed with mild or moderate disease unless symptoms or specific clinical findings suggest a need for them. With severe disease (FEV_1 < 1 L), serial measurements of FEV_1 become relatively unimportant because of the difficulty of interpreting small changes. Serial blood gas measurements become the major test for monitoring the course of the disease.

STAGING OF COPD

There is no well-accepted staging or severity scoring system for patients with COPD. An ideal system would allow categorization of patients with COPD for epidemiologic and clinical studies, health resource planning, and prognosis. It would also facilitate communication between professionals. As discussed before, the strongest prognostic indicators for mortality are the age of the patients and FEV_1, followed by the presence of hypoxemia and hypercapnia. Obviously, death is not the only morbidity attributable to COPD. At present, we are limited to grade the severity of COPD on the basis of some objective physiological measure of pulmonary

function, usually the FEV_1. However, the impact of COPD on the ability of patients to perform the normal activities of daily living is incompletely described by the FEV_1. The cardinal symptom of COPD is dyspnea, which often limits functional activity and ability to exercise and frequently causes the patient to seek medical attention. Because COPD is a chronic disorder that limits the patient's ability to work and in severe cases impairs the activities of daily living, a staging system that includes some attribute of this limitation is highly desirable. Therefore, an ideal classification would include elements of all three factors (FEV_1, capacity to perform ADL or capacity to exercise, and dyspnea); unfortunately, this tool has yet to be developed. The current staging system as suggested by the ATS attempts to classify patients according to the degree of FEV_1 value (Table 2). This staging system is designed to help the clinician and health care provider identify the possible level of care and complexity of the patient. It also provides a rough estimate of the patient's prognosis.

	Stage I	Stage II	Stage III
FEV_1 (predicted)	≥50%	30% to 49%	≤30%
Usual findings	Most of the patients May be symptomatic Small impact on health-related quality-of-life issues Usually managed by primary care physicians	Minority of patients Symptomatic Moderate impact on health-related quality-of-life issues May be hypoxemic May be helped by evaluation by specialist	Small minority of patients Severe symptoms Large impact on health-related quality of life Hypoxemic, may show hypercapnia Best managed by professionals familiar with COPD

TABLE 2. *Staging of COPD*

QUALITY OF LIFE

Not all the problems associated with the development of COPD are described by physiological variables (FEV_1 or arterial blood gases). Furthermore, only weak associations have been described for FEV_1 and quality of life or FEV_1 and dyspnea. Because of the capacity of certain questionnaires to provide an accurate estimation of a patient's quality of life in chronic diseases, there has been a recent interest in adding this dimension to the evaluation of patients with COPD. These tools acquire particular importance in the comprehensive evaluation of different forms of treatment because there need not be an association between physiological results and how patients perceive the effect of the intervention. A typical example is that of pulmonary rehabilitation. Several controlled trials have shown significant improvement in patient's perceived quality of life without demonstrable evidence of changes in lung function. Table 3 shows different quality-of-life questionnaires that have been validated and are widely used. Some are generic in nature and are applicable to all forms of chronic diseases. They may not be sensitive enough to detect changes that may arise from improvement secondary to benefits in the respiratory domain. For this reason, there has been recent interest in the development of disease-specific quality-of-life questionnaires. In particular, the ones shown in Table 3 have been validated and proven to be of use when evaluating patients with COPD. They have proven useful in research and may find a role in the everyday management of patients.

Quality-of-life assessment tools	
General	Disease specific (pulmonary)
Quality of Well-Being Scale	The St. George's Respiratory Questionnaire (SGRQ)
Sickness Impact Profile	Chronic Respiratory Disease Questionnaire (CRQ)
Nottingham Health Profile	Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ)
Medical Outcomes Study—Short Form (MOS SF-36)	
Dyspnea assessment tools	
Functional	Exercise related
Baseline Dyspnea Index (BDI)	Borg Scale
Transitional Dyspnea Index (TDI)	Visual Analog Scale (VAS)
Physiological tools	
Complex	Simple
Cardiopulmonary Exercise Test	6- and 12-min walk test
Pulmonary Function Testing	Walk up stairs
Graded Exercise Test	

TABLE 3. *Tools to assess outcomes*

COMPREHENSIVE MANAGEMENT OF COPD

The airflow obstruction of COPD is largely irreversible. This physiological fact has generated an unjustified nihilistic therapeutic attitude in many health care providers. The evidence accumulated suggests otherwise, and an optimistic attitude toward these patients goes a long way in relieving patient fears and misconceptions. In contrast to many other diseases, some forms of interventions significantly prolong life (Table 4), and others improve symptoms and the quality of a patient's life once the diagnosis has been established. The overall goals of treatment are to prevent further deterioration in lung function, to alleviate symptoms, and to treat complications as they arise. Once diagnosed, the patient should be encouraged to participate actively in the management. This concept of collaborative management may improve self-reliance and esteem. Although not proven, it may also help improve compliance with treatment. All patients should be encouraged to lead a healthy life and exercise regularly. Preventive care is extremely important at this time, and all patients should receive immunizations including pneumococcal vaccine and yearly influenza vaccines. An algorithm detailing this comprehensive approach is shown in Fig. 4.

Interventions that improve survival	Interventions that improve symptoms
Smoking cessation	Pharmacotherapy
Oxygen therapy if hypoxemic	Rehabilitation
	Education
	Training and exercise
	Psychological support
	Nutrition
	Surgery (pneumoplasty)

TABLE 4. *Therapy of patients with symptomatic COPD*

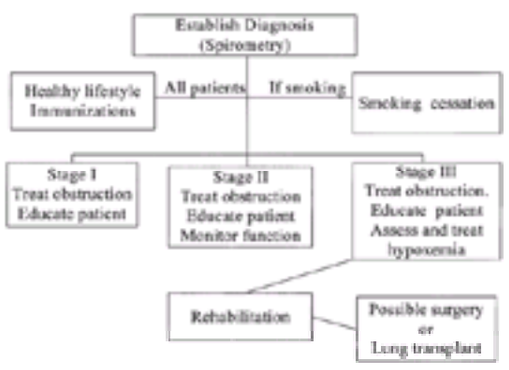

FIG. 4. Algorithm that shows the overall management of patients with COPD.

SMOKING CESSATION

Because smoking is the major cause of COPD, smoking cessation is the most important component of therapy for patients who still smoke. It should become part of our counseling for any patient who smokes. Because secondary smoking is known to damage lung function, limitation of exposure to involuntary smoke, particularly in children, should be encouraged. Although most patients agree that smoking is risky, they seem unaware of its true significance. Continuous abstinence in pulmonary patients who have participated in smoking cessation programs may be as low as 27% in follow-up periods ranging from 6 months to 7 years. The factors that cause patients to smoke include the addicting potential of nicotine, conditional response to stimuli surrounding smoking, psychosocial problems such as depression, poor education, and low income, and forceful advertising campaigns. Because the causes that drive the patient to smoke are multifactorial, the solutions for smoking cessation should also involve multiple interventions. Elements of successful smoking cessation programs are summarized in Table 5.

1. Physician or health care worker should initiate quitting.
   Explain risks of cigarette smoking.
   Offer strong admonition to quit; encourage a quit date; offer referral for self-help or group program.
2. Physician or health care worker may arrange telephone follow-up.
   Call 3 to 5 days after quit date. Review progress. Counsel regarding quitting and recruitment of support individual. Call 1 to 2 weeks after quit date.
   Repeat above as needed.
3. Physician or health care worker should arrange follow-up. Next regular visit should be <2 months after initiating quitting. May assess the progress with CO and expired air and/or continine in urine, blood, or saliva. If abstinent, should review and reward success. Continue follow-up at increasing intervals for 12 months postquitting.
4. If not abstinent, physician or health care worker should review and emphasize elements of success. Identify circumstances of failure. The physician usually offers nicotine replacement to control the withdrawal symptoms; infrequently, other pharmacologic therapy can be considered such as clonidine or buspirone.

TABLE 5. *Protocol for smoking cessation*

The clinician should always express strong interest in smoking cessation, for a physician's advice to quit smoking discriminates successful from unsuccessful results. A strong social support system, including professionals, family, and friends, is associated with cessation and long-term abstinence. The smoker should avoid circumstances likely to prompt relapse, including coping with personal and interpersonal stress. It is helpful for the physician to plan a quit date, because setting a quit date to stop “cold turkey” usually holds an advantage over gradual withdrawal. It may be helpful to make a telephone call to the patient at follow-up intervals to encourage cessation of smoking. This call may be made by the physician or a health care worker. Group smoking cessation clinics are offered by many hospitals and in may work sites as well as by voluntary agencies. They include programs such as the American Lung Association through its Freedom from Smoking clinics. Such programs may have an important role in the support of patients who attempt to quit smoking because they effectively integrate behavioral therapy, counseling, and adjunctive pharmacologic treatment.

Nicotine is the ingredient in cigarettes that is primarily responsible for the addiction of smoking. With each cigarette smoked, between 1 and 2 mg of nicotine is delivered to the lungs. Because of rapid absorption into the blood and a half-life of 2 hr, regular daytime smoking can cause nicotine accumulation for an entire 24-hr period. Nicotine is metabolized by the liver. Cotinine, a primary metabolite of nicotine, has a longer half-life and can be searched for in the urine to detect those patients who continue to smoke. Withdrawal from cigarettes causes anxiety, irritability, difficulty concentrating, anger, fatigue, drowsiness, depression, and sleep disruption, especially during the first week of cessation. In a dose-dependent relationship, nicotine replacement following cessation reduces withdrawal symptoms and enhances abstinence. Highly dependent nicotine smokers can be identified as those who smoke over one pack of cigarettes per day and who require their first cigarette within 30 min of arising and find it difficult to refrain from smoking in places where it is forbidden. Physical dependence can also be assessed by a formal questionnaire such as the Fagerstrom tolerance questionnaire. Nicotine polacrilex gum (2 mg per piece) is effective when compared to placebo, especially in self-referred smokers who are highly addicted to cigarettes. Transdermal nicotine patches are more readily available and may be prescribed for the patient who failed smoking cessation efforts in the past or whose smoking cessation has been troubled by withdrawal symptoms. Short-term success rates have varied widely (between 18% and 77%), but in general nicotine patches are about two times as effective as placebo. Long-term success rates (6 months and longer) are considerably lower (22% to 42%) but are consistently better than those obtained with a placebo patch (2% to 26%).

Adjuvant programs such as individual counseling and group therapy produce a higher success rate when added to pharmacologic intervention. The smoking status (abstinence or continued smoking) during the first 2 weeks of nicotine patch therapy can serve as a predictor of smoking cessation because smoking during this period is a powerful predictor of failure at the end of a 6-month trial. Patients who fail during the first 2 weeks of therapy should be offered more intense pharmacologic or adjuvant therapy. The ideal time of therapy for each dose has not been established. Recently, it has been recommended that nicotine patch therapy beyond 6 to 8 weeks may not be necessary. Although nicotine patches are well tolerated, mild erythema or other local skin reactions may be seen in up to 50% of patients; however, they can be minimized by rotating the patch to different sites on the skin.

Clonidine, an a_2-adrenergic agonist, may enhance abstinence in the short term, but its enduring effects have not been documented. The anxiolytic agent buspirone reduced withdrawal symptoms and may show some benefit on abstinence. Hypnosis may be an effective adjunct but is of little value when offered as a single-session cure. Acupuncture should not be done, as there is little evidence that it contributes to smoking cessation beyond its placebo effect.

PHARMACOLOGIC THERAPY

The pharmacologic therapy of COPD should be organized according to the severity of the disease and the tolerance of the patient for specific drugs. In the outpatient setting, a stepwise approach (Table 6 and Fig. 5), as has been developed for asthma and systemic hypertension, may be helpful. The most common drugs and dosages that are in current use, and the precautions to be taken when indicated are listed in Table 6. There is no current evidence that the regular use of any of these drugs alters the progression of COPD. Nevertheless, they alleviate symptoms, improve exercise tolerance, and improve quality of life, all worthwhile goals in COPD. It is important to remember that most COPD patients are older and thus particularly susceptible to the side effect of some of these medications and that dose adjustments must be made according to each individual circumstance.

TABLE 6. *Pharmacologic step care of COPD*

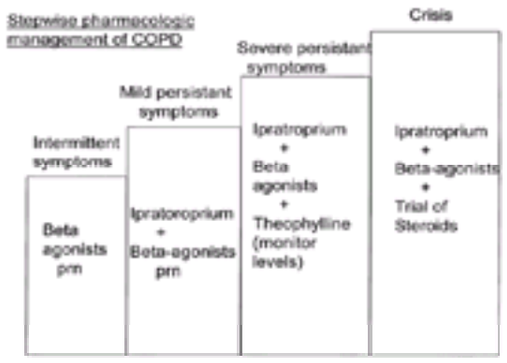

FIG. 5. Stepwise pharmacologic management of patients with COPD.

Bronchodilators

The bronchodilators used in COPD are similar to those used in asthma, but some differences are noteworthy. The b-agonists produce less bronchodilation in COPD, and in some patients the spirometric changes may be insignificant, although symptomatic benefit may be experienced, perhaps through other mechanisms such as decreased dynamic hyperinflation. However, the older age of patients with COPD may result in less tolerance for sympathomimetic-induced tremor, nervousness, and cardiac side effects. Likewise, many older COPD patients cannot effectively activate metered dose inhalers (MDI), and health providers should recognize this limitation and work with the patient to achieve mastery of the MDI. If this is not possible, use of a spacer to facilitate inhalation of the medication will help achieve the desired results. Mucosal deposition in the mouth will result in local side effects (i.e., thrush with inhaled steroids) or general absorption and its consequences (i.e., tremor after b-agonists).

b-Agonists

In patients with intermittent symptoms, it is reasonable to initiate drug therapy with an MDI of a b-agonist as needed for relief of symptoms. Albuterol, pirbuterol, metaproterenol, terbutaline, or isoetharine (each of which is preferable to the less-selective drugs epinephrine, isoproterenol, and ephedrine) should be taken up to a maximum of three or four times a day or as prophylaxis before exercise. The rapid onset of action of b-agonist aerosols may lead to dyspneic patients favoring them for regular use. b-Agonist therapy decreases dyspnea and improves exercise tolerance in COPD. The potential for arrhythmias necessitates careful dosing in patients with probable or known cardiac disease, although serious cardiac complications are rare with conventional doses. In more advanced disease, it may be reasonable to use slow-release oral albuterol, but the value and acceptability of such formulations has not been established. Similarly, the new, long-acting aerosol drug salmeterol has been shown to prevent nocturnal bronchospasm. These agents may improve compliance, which can result in an improved outcome in selected patients.

Anticholinergic Agents

Once the patient suffers from persistent symptoms, regular use of ipratropium MDI is recommended. The drug has a slower onset and longer action than b_2-agonists such as albuterol and thus is less suitable for as-needed use. The appropriate dosage is two to four puffs three or four times a day, but some patients require and tolerate larger dosages. It has been shown that ipratropium is effective in increasing exercise tolerance and decreasing dyspnea. A recent multicenter controlled trial of therapy with ipratropium bromide documented a significant bronchodilator effect, but there was no alteration in the rate of decline in lung function in the patients receiving the medication. As is true for b-agonists, there is no substantial evidence to suggest that regular use of anticholinergic therapy, with or without a b_2-agonist, leads to a worsening of spirometry or to exacerbation of premature death in COPD. Thus, it is appropriate to use regular therapy with ipratropium and to add a b_2-agonist as often as needed for up to four treatments a day.

Theophylline

This currently represents a third-line agent in the therapy of COPD. The potential for toxicity has led to a decline in its popularity. It is of particular value for less compliant or less capable patients who cannot use aerosol therapy optimally because they can readily take theophylline once or twice a day. Theophylline has been shown to improve the function of the respiratory muscles, to stimulate the respiratory center, to enhance activities of daily living, and to decrease dyspnea. It also improves cardiac output, reduces pulmonary vascular resistance, and improves the perfusion of ischemic myocardial muscle. Recent evidence suggests an antiinflammatory role for this drug, thereby expanding its potential indications. It follows that there are several advantages to theophylline therapy in patients with cardiac disease or cor pulmonale, but its use should be carefully followed, and intermittent serum levels should be used. The previously recommended therapeutic serum levels of 15 to 20 mg/dl are too close to the toxic range and are frequently associated with side effects. Therefore, a lower target range of 9 to 14 mg/dl is safer and still therapeutic in nature. The regular use of theophylline has not been shown to have a detrimental effect on the course of COPD. Combination of theophylline, albuterol, and ipratropium can result in maximum benefit in stable COPD.

Antiinflammatory Therapy

In contrast to their value in asthma management, antiinflammatory drugs have not been documented to have a significant role in the routine treatment of COPD. Cromolyn and nedocromil have not been established as useful agents, although they could possibly be helpful if the patient has associated respiratory tract allergy. Corticosteroids may merit more careful evaluation in individual patients on adequate bronchodilator therapy who fail to improve. In outpatients, exacerbations may necessitate a course of oral steroids, but it is important to wean patients quickly because the older COPD population is susceptible to complications such as skin damage, cataracts, diabetes, osteoporosis, and secondary infection. These risks do not accompany standard doses of steroid aerosols, which may cause thrush, but pose a negligible risk for causing pulmonary infection. Most studies suggest that only 10% to 30% of patients with COPD improve if given chronic oral steroid therapy. The dangers of steroids require careful documentation of the effectiveness of such therapy before a patient is put on prolonged daily or alternate-day dosing. The latter regimen may be safer, but its effectiveness has not been adequately evaluated in COPD. Based on preliminary results, two large multicenter trials are being conducted to evaluate the role of inhaled corticosteroids in preventing or slowing the progressive course of patients with symptomatic COPD. Until the results are analyzed, the concurrent use of inhaled steroids with albuterol and ipratropium has to be evaluated on an individual basis.

Mucokinetic Agents

The only controlled study in the United States suggesting a value for these drugs in the chronic management of bronchitis was a multicenter evaluation of organic iodide. This study demonstrated symptomatic benefits. The values of other agents, including water, have not been clearly demonstrated, although some agents (such as oral acetylcysteine) are favored in Europe for their antioxidant effects in addition to their mucokinetic properties. Genetically engineered ribonuclease may prove to be useful in cystic fibrosis but seems to be of little practical value in COPD.

Antibiotics

They are of unproven value in the prevention or treatment of exacerbations of COPD unless there is evidence of infection, such as fever, leukocytosis, and a change in the chest radiograph. If recurrent infections occur, particularly in winter, continuous or intermittent prolonged courses of antibiotics may be useful. When an acute bacterial infection is believed to be present, antibiotic therapy may be justified, but the decision is usually made clinically because culture of sputum is not cost-effective. In prescribing treatment, fiscal concerns should be a consideration, because older less costly agents are often effective, e.g., tetracycline, doxycycline, amoxicillin, erythromycin, trimethoprim–sulfamethoxazole, or cefaclor. The major bacteria to be considered are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* The antibiotic choice will depend on local experience supported by sputum culture and sensitivities if the patient is moderately ill or needs to be admitted to hospital.

a_1-Antitrypsin

Although replacement with this enzyme may be indicated in nonsmoking, younger patients with genetically determined emphysema, in practice such therapy is difficult to initiate. There is evidence that the administration of a_1-antitrypsin is relatively safe, but the appropriate selection of the candidate for such therapy is not clear. Patients with very severe and crippling COPD, or those with good lung function, are not good candidates for therapy. Likewise, deficient nonsmoker patients are at low risk to develop airflow obstruction. Therefore, the most likely candidates for replacement therapy would be smoking patients with mild COPD. The cost of therapy is

such that its use is debatable because its safety and long-term effects remain unknown.

Respiratory Stimulants

These drugs are currently not favored, although they are used in some countries. Psychoactive drugs are often sought by older patients to treat depression, anxiety, insomnia, or pain. In general, these agents can be given with appropriate care and with particular awareness of their depressant effect on the respiratory center. Benzodiazepines do not have a marked effect on respiration in mild or moderate COPD but can be suppressive in severe disease, particularly during sleep. The safer hypnotics for use in insomnia include sedating antihistamines and chloral hydrate. Antidepressants may also have the advantage of improving sleep. Concomitant use of cardiovascular drugs may be needed in severe COPD and cor pulmonale, e.g., diuretics, angiotensin-converting enzyme inhibitors, or calcium channel blockers. Digoxin is occasionally useful, but b-adrenergic blockers are generally contraindicated. These drugs must be used cautiously to avoid dehydration, hypotension, myocardial ischemia, and arrhythmias. Because most patients requiring such therapy are elderly or have impaired drug clearance, all potential side effects must be carefully sought and responded to by modifying the drug regimen.

Vaccination

Ideally, infectious complications of the respiratory tract should be prevented in patients with COPD by using effective vaccines. Although the currently available vaccines are not totally effective and are not utilized widely, there is evidence that COPD patients benefit from their use, and thus, routine prophylaxis with pneumococcal and influenza vaccines is recommended.

MANAGEMENT OF ACUTE EXACERBATION

In the case of an acute exacerbation, the pharmacologic therapy is initiated with the same therapeutic agents available for chronic management. As described later in this chapter, care must be taken to rule out heart failure, myocardial infarction, arrhythmias, and pulmonary embolism, all of which may present with clinical signs and symptoms similar to exacerbation of COPD.

The most important components of therapy for acute exacerbation of COPD are anticholinergic and b-agonist aerosols. Ipratropium may be administered via a metered dose inhaler (MDI), sometimes with a spacer if the administration is erratic, or as an inhalant solution by nebulization. Although the upper limit of dosage has not been established, the drug is safe, and higher dosages than usual can be given to a poorly responsive patient. However, the prolonged half-life means that repeat doses should not be given more often than every 4 to 8 hr. b_2-Agonists should also be administered using the same inhaled techniques. These drugs have a reduced functional half-life in exacerbations of COPD and thus may be given every 30 to 60 min if tolerated. The safety and value of continuous nebulization have not been established, but in selected cases it may be worth a trial. Subcutaneous or intramuscular dosing are recommended only if aerosol use is not feasible; intravenous administration is not an acceptable practice. Careful administration of theophylline may be useful; the drug can be given as intravenous aminophylline in a severe exacerbation. Serum levels are needed as a guide to avoid toxicity, and in most patients a serum level of 8 to 12 mg/ml is appropriate. When the patient improves, oral long-acting theophylline can be substituted, using 80% of the daily dose of aminophylline.

Combination therapy is often needed, and systemic corticosteroids may then be added to the regimen. Corticosteroids can be very effective in a patient who demonstrates inadequate responsiveness to b-agonist or ipatroprium therapy. It is important to avoid prolonged or high-dose therapy in those patients who show little improvement, because older patients are susceptible to severe complications such as psychosis, fluid retention, and a vascular necrosis of bones. Rapid weaning must be accomplished as soon as possible.

Antibiotics such as amoxicillin, trimethoprim–sulfamethoxazole, doxycycline, or erythromycin have been helpful in exacerbations of COPD. Mucokinetic agents, such as iodides, given systemically have not been shown to be effective in exacerbations of COPD, although some patients report subjective improvement when given these agents.

HOME OXYGEN THERAPY

Therapeutic oxygen has been used systematically since Barach and then Petty et al. recognized the association between hypoxemia and right heart failure and appreciated the benefit of continuous oxygen delivery to patients with severe COPD. Since them, much has been learned about the effects of oxygen and hypoxemia, and progress has been made in the area of mechanical oxygen delivery devices.

The results of the Nocturnal Oxygen Therapy Trial (NOTT) and Medical Research Council (MRC) studies have established that continuous home oxygen improves survival in hypoxemic COPD and that survival is related to the number of hours of supplemental oxygen per day. Other beneficial effects of long-term oxygen include reduction in polycythemia, perhaps related more to lowered carboxyhemoglobin levels than to improved arterial saturation, reduction in pulmonary artery pressures, dyspnea, and rapid-eye-movement-related hypoxemia during sleep. Oxygen also improves sleep and may reduce nocturnal arrhythmias. Importantly, oxygen can also improve neuropsychiatric testing and exercise tolerance. This has been attributed to central mechanisms causing reduced minute ventilation at the same workload, thereby delaying the time until ventilatory limitation is reached; improved arterial oxygenation, enabling greater oxygen delivery and reversal of hypoxemia-induced bronchoconstriction; and the effect of oxygen on respiratory muscle recruitment.

Prescribing Home Oxygen

Patients are evaluated for long-term oxygen treatment (LTOT) by measuring the P_aO_2. It is therefore recommended that measurement of P_aO_2, not pulse oximetry (S_aO_2), be the clinical standard for initiating LTOT, particularly during rest. Oximetry S_aO_2 may be used to adjust oxygen flow settings over time. If hypercapnia or acidosis is suspected, an arterial blood gas measurement (ABG) must be performed. Some COPD patients who were not hypoxemic before the events leading to their exacerbation will eventually recover to the point that they will no longer need oxygen. It is therefore recommended that the need for long-term oxygen be reassessed in 30 to 90 days, when the patient is clinically stable and receiving adequate medical management. Oxygen therapy can be discontinued if the patient does not meet blood gas criteria. To prescribe long-term oxygen therapy, a certificate of medical necessity (HCFA form 484) must be completed. The HCFA form 484 evolved in an attempt to insure that the physician, not the home medical equipment (HME) supplier, was in charge of decisions concerning therapy. The HCFA requires the physician or an employee of the physician, rather than the HME supplier, to complete form 484.

Like any drug, oxygen has potential deleterious effects that may be particularly relevant to older patients. The hazardous effects of oxygen therapy can be considered under three broad headings. First, there are physical risks such as fire hazard or tank explosion, trauma from catheters or masks, and drying of mucous membranes as a result of high flow rates and inadequate humidification. Second, there are functional effects related to increased carbon dioxide retention and absorptive atelectasis. Elevated PCO_2 in response to supplemental oxygen is a well-recognized complication in a minority of patients. The mechanism has traditionally been ascribed to reductions in hypoxic ventilatory drive. However, in many patients the decrease in minute ventilation is minimal. The most consistent finding is a worsening of the pulmonary ventilation-to-perfusion distribution with an increase in the dead-space-to-tidal-volume ratio. This presumably results from oxygen blockage of local hypoxic vasoconstriction, thereby increasing perfusion of poorly ventilated areas. Third, although possible, cytotoxic and atelectatic effects have not clearly been demonstrated with the low flow rates (1 to 5 L/min, F_IO_2 24% to 36%) typically used for chronic home oxygen therapy in COPD.

Oxygen Delivery Systems

Long-term home oxygen is available from three different delivery systems: oxygen concentrators, liquid systems, and compressed gas. Each system has advantages and disadvantages, and the correct system for each patient depends on patient limitations and clinical application. Oxygen systems were recently compared on the basis of weight, cost, portability, ease of refilling, and availability. The former three factors may be of particular importance in elderly, often debilitated patients. Compressed gas is stored in variably sized steel or aluminum cylinders that weigh 200, 16, 9, and 4 lb and last 2.4 days, 5.2 hr, 2 hr, and 1.2 hr at 2 L/min flow. The advantages of compressed gas oxygen are its low price, availability, and capacity to be stored for long periods. Disadvantages are its weight (with the large cylinders), short oxygen supply time (with the smaller cylinders), potential hazard of a torpedo-like effect if the valve becomes suddenly disconnected from a compressed gas cylinder, and inferior transfilability. Liquid oxygen is stored at very low temperatures that reduce the volume to less than 1% of the room-temperature equivalent. Portable containers weigh up to 10 lb and last 4 to 8 hr at 2 L/min flow. A wheel-mounted, 140-lb stationary unit is also available that can last up to 7 days at 1 L/min. Advantages of this system are its relative portability and ease of transfilability. Disadvantages are its higher cost and requirements for intermittent pressure venting, resulting in oxygen consumption even when the system is not being used. Oxygen concentrators are electric devices that extract oxygen by passing air through a molecular sieve. The oxygen is delivered to the patient, and the nitrogen is returned to the atmosphere. The devices weigh about 35 lb and are not very portable. They are typically used in a stationary capacity such as in the car or a room, and liquid or gas is used to provide portability. The major advantage of the oxygen concentrator is its relative cost effectiveness; the disadvantages are its need for a power source, regular servicing, and relative lack of portability.

Administration Devices

Oxygen is typically administered with continuous flow by nasal cannula; however, because alveolar delivery occurs during a small portion of a spontaneous respiratory cycle (approximately the first one-sixth), the rest of the cycle being used to fill dead space and for exhalation, the majority of continuously flowing oxygen is not used by the patient and is wasted into the atmosphere. To improve efficiency and increase patient mobility, several devices are available that focus on oxygen conservation and delivery during early inspiration. These devices include reservoir cannulas, demand-type systems, and transtracheal catheters.

Reservoir nasal cannulas and pendants store oxygen during expiration and deliver a 20-mL bolus during early inspiration. Because more alveolar oxygen is delivered, flows may be reduced proportionally. This has been shown to result in a 2:1 to 4:1 oxygen savings at rest and with exercise. Cosmetic considerations have traditionally limited patient acceptance of these devices.

Demand valve systems have an electronic sensor that delivers oxygen only during early inspiration or provides an additional pulse early in inspiration as an adjuvant to the continuous flow. By restricting or accentuating oxygen during inspiration, wasted delivery into dead space or during exhalation is minimized. This results in a 2:1 to 7:1 oxygen savings. The effect of mouth breathing on efficacy is not yet clear. Transtracheal oxygen (TTO) therapy employs a thin flexible catheter placed into the lower trachea for delivery of continuous (or pulsed) oxygen. Because oxygen is delivered directly into the trachea, dead space is reduced, and the upper trachea serves as a reservoir of undiluted oxygen. This provides a 2:1 to 3:1 oxygen savings over a nasal cannula. Other benefits of TTO include its relative inconspicuousness; lack of nasal, auricular, or facial skin irritation; stationary position with ambulation or during sleep; and its purported efficacy in providing adequate oxygenation where a nasal cannula cannot. Transtracheal oxygen therapy has also been reported to reduce minute volume and dyspnea and to improve exercise tolerance by mechanisms related solely to improvements in oxygenation. Thus, TTO appears to reduce dyspnea and improve exercise tolerance through mechanisms that include decreased dead space and decreased minute ventilation.

Complication rates tend to be lower in the larger series and higher in the smaller series. The most frequent complications are dislodged catheters (up to 33%, average 10%), subcutaneous emphysema (up to 10%, average 6.5%), stomal infection requiring antibiotics (up to 25%, average 6.5%), and the formation of symptomatic mucus balls at the tip of the catheter (up to 25%, average 10%). The latter complication may be potentially serious or even fatal. Other complications of TTO therapy include migration of the catheter into the mediastinum, broken catheter tips in the airways, pneumonia, hemoptysis, keloid formation, hoarseness, cardiac arrhythmias, and tracheal stricture. Overall, the TTO catheter offers several potential advantages over more conventional continuous oxygen administration devices, but it requires a motivated dexterous patient for routine care and daily cleaning, and it has a modest rate of usually minor, but potentially serious, complications.

HOSPITALIZATION AND DISCHARGE CRITERIA

Although acute exacerbations are difficult to define, and their pathogenesis is poorly understood, impaired lung function can lead to respiratory failure requiring intubation and mechanical ventilation. The purpose of acute treatment is to manage the patient's acute decompensation and comorbid conditions in order to prevent further deterioration and readmission. Table 7 lists the components of the history, physical examination, and laboratory evaluation that should be obtained during a moderate to severe acute exacerbation to assist the formulation of therapy and the decision for hospital admission.

History	Baseline respiratory status, sputum volume and characteristics, duration and progression of symptoms. Dyspnea severity, exercise limitations, sleep and eating difficulties, home care resources, home therapeutic regimen, symptoms of comorbid acute or chronic conditions.
Physical	Evidence of cor pulmonale, tachypnea, bronchospasm, pneumonia. Hemodynamic instability, altered mentation, respiratory muscle fatigue, excessive work of breathing; acute comorbid conditions.
Laboratory[a]	ABG, chest radiograph (PA, Lat), ECG, theophylline level (if outpatient theophylline used). Pulse oximetry monitoring, ECG monitoring. Post-ER treatment spirometry (if FEV_1, changes from baseline to be used as admission criteria), additional studies as clinically indicated.

[a] Abbreviations: FEV_1, forced expiratory volume in 1 sec; ECG, electrocardiogram; ER, emergency room; ABG, arterial blood gas; PA, posterior–anterior; Lat, lateral.

TABLE 7. *Emergency room evaluation of exacerbations of COPD*

Traditionally, the decision to admit derives from subjective interpretation of clinical features such as the severity of dyspnea, determination of respiratory failure, short-term response to emergency room therapy, degree of cor pulmonale, and the presence of complicating features such as severe bronchitis, pneumonia, or other comorbid conditions. This approach to decision making is less than ideal in that up to 28% of patients with an acute exacerbation of COPD discharged from an ER have recurrent symptoms within 14 days. Additionally, 17% of patients discharged after ER management of COPD will relapse and require hospitalization. Few clinical studies have investigated patient-specific objective clinical and laboratory features that identify patients with COPD who require hospitalization. General consensus supports the need for hospitalization in patients with severe acute hypoxemia or acute hypercarbia. Less extreme arterial blood gas abnormalities, however, do not assist decision analysis. The posttreatment FEV_1 as a percentage of predicted, combined with clinical assessment, identifies patients in need of admission. Asymptomatic patients with posttreatment FEV_1 less than 40% of predicted were successfully discharged from the ER; patients with a posttreatment FEV_1 less than 40% of predicted, accompanied by persistent respiratory symptoms, require admission.

Other factors that identify “high-risk” patients include a previous emergency room visit within 7 days, the number of doses of nebulized bronchodilators, use of home oxygen, previous relapse rate, administration of aminophylline, and the use of corticosteroids and antibiotics at the time of ER discharge.

The pharmacologic treatment of acute exacerbations is similar to that available for chronic management. Inhaled administration is preferred, although intravenous treatment may be reserved for certain drugs such as corticosteroids and theophylline. Once stable, the patient may be switched to oral and inhaled medications. Once the patient has improved, clinical assessment plans for modifying drug regimens, utilization of home oxygen, or potential benefits from pulmonary rehabilitation programs should be prepared. Duration of hospitalization in COPD depends at least partially on the existence of a multidisciplinary team that directs respiratory management.

Because of the complex management issues in caring for COPD patients with impending or frank respiratory failure, physician specialists with extensive experience in and knowledge of COPD should participate in the care of hospitalized patients who present with underlying severe disease or who require invasive or noninvasive modes of mechanical ventilation, develop hypoxemia unresponsive to F_IO_2 0.50 or new-onset hypercarbia, require steroids for more than 48 hr to maintain adequate respiratory function, undergo thoracoabdominal surgery, or require specialized techniques to manage copious airway secretions.

The indications for hospital admission are summarized in Table 8. Based on experts' consensus, they consider the severity of the underlying respiratory dysfunction, progression of symptoms, response to outpatient therapies, existence of comorbid conditions, necessity of surgical interventions that may affect pulmonary function, and the availability of adequate home care. The severity of respiratory dysfunction dictates the need for admission to an ICU (Table 9). Depending on the resources available within an institution, admission of patients with severe exacerbations of COPD to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully. Limited data support the discharge criteria listed in Table 10.

1. The patient has an acute exacerbation of COPD characterized by increase dyspnea, cough, and sputum production with one or more of the following features:
   - Symptoms that do not adequately respond to outpatient management.
   - Inability of a previously mobile patient to walk between rooms.
   - Inability to eat or sleep because of dyspnea.
   - Family and/or physician assessment that the patient can not manage at home, and supplementary home care resources are not immediately available.
   - Presence of high-risk comorbid pulmonary (e.g., pneumonia) or nonpulmonary conditions.
   - Prolonged, progressive symptoms before emergency room visit.
   - Presence of worsening hypoxemia, new or worsening hypercarbia, or new or worsening cor pulmonale.
2. Acute respiratory failure characterized by severe respiratory distress, uncompensated hypercarbia, or severe hypoxemia.
3. New or worsening cor pulmonale unresponsive to outpatient management.
4. Plans for invasive surgical or diagnostic procedures requiring analgesics or sedatives that may worsen pulmonary function.
5. Comorbid conditions, such as severe steroid myopathy or acute vertebral compression fractures with severe pain, have worsened pulmonary function.

TABLE 8. *Indications for hospitalization in COPD*

A patient with severe dyspnea does not respond to initial Emergency Room therapy.
A patient demonstrates confusion, lethargy, or respiratory muscle fatigue characterized by paradoxic diaphragmatic motion.
Laboratory evidence demonstrates persistent/worsening hypoxemia despite supplemental oxygen or severe/ worsening respiratory acidosis (e.g., pH < 7.30).
A patient requires assisted mechanical ventilation by means of an endotracheal tube or noninvasive technique.

TABLE 9. *Indications for ICU admission of patients with acute exacerbations of COPD*

Inhaled β-agonist therapy is required no more frequently than every 4 hr.
Previously ambulatory patient is able to walk across the room.
The patient is able to sleep without frequent awakening by dyspnea.
Any component of reactive airway disease is under stable control.
The patient is stable off of parenteral therapy for 12 to 24 hr.
The patient or home caregiver is educated as to correct use of medications.
Arrangements for follow-up care and home care (e.g., visiting nurse, home oxygen delivery, meal provisions) are completed.

[a] Patients who do not yet fulfill criteria for discharge to home may be successfully managed at non-acute care placement sites for observation during the final resolution of symptoms.

TABLE 10. *Discharge criteria after treatment for acute exacerbations of COPD*[a]

ASSISTED VENTILATION

Progressive airflow obstruction may impair gas exchange to the degree that assisted ventilation will be required. In this clinical context, the therapeutic goals are to support the patient over the short term during the course of acute respiratory failure and to enhance gas exchange and functional status in patients with chronically impaired ventilation.

Assisted ventilation should be considered for patients with acute exacerbations of COPD when pharmacologic and other nonventilatory treatments fail to reverse clinically significant respiratory failure. Indications for initiating assisted ventilation during acute COPD exacerbations include signs of respiratory muscle fatigue, worsening respiratory acidosis, and/or deteriorating mental status. Although several investigators have reported success with negative-pressure ventilation, most studies advocate positive-pressure inflation for acute exacerbations of COPD.

Also, because negative-pressure ventilation may cause upper airway obstruction and arterial oxygen desaturation (when upper airway muscle activation is asynchronous with negative-pressure breaths), its role in managing patients with COPD has been questioned.

The goals of assisted positive-pressure ventilation in acute respiratory failure complicating COPD are (1) resting of ventilatory muscles and restoration of gas exchange to a stable baseline, (2) avoidance of complications associated with mechanical ventilation, and (3) facilitation of weaning and discontinuation of mechanical ventilation as soon as possible.

Major complications associated with assisted positive-pressure ventilation include risks of ventilator-associated pneumonia, pulmonary barotrauma, and laryngotracheal complications associated with intubation and/or tracheotomy. In addition to these general hazards, specific pitfalls in ventilating patients with COPD include overventilation, resulting in acute respiratory alkalemia, especially in patients with chronic hypercapnia; creation of auto-PEEP (or intrinsic PEEP), especially when expiratory time is inadequate; and initiation of complex pulmonary and cardiovascular interactions that result in systemic hypotension. Auto-PEEP has been reported to occur in up to 39% of mechanically ventilated patients, for which one must decrease the respiratory rate, increase inspiratory flow rates to avoid a disadvantageous inspiratory:expiratory (I:E) ratio, use a large-caliber endotracheal tube, and reduce the compressible volume in the ventilator circuit.

Modes of Ventilation

Invasive Ventilation

The three ventilatory modes most widely used for managing COPD patients are assist-control (AC), intermittent mandatory ventilation (IMV), and pressure-support (PS) ventilation. Because some (but not all) clinical reports indicate that PS ventilation provides increased patient comfort, promotes patient synchrony with the ventilator, and may accelerate weaning, it may be a particularly valuable mode of ventilatory support for stabilized patients with COPD and acute respiratory failure who maintain adequate ventilatory drive. No direct evidence exists, however, that patient outcome is improved with the use of PS compared to volume-cycled modes of mechanical ventilation in patients with COPD.

Noninvasive Ventilation

Translaryngeal intubation presents risks of nosocomial pneumonia, laryngotracheal injury, and bacterial sinusitis and also interferes with the patient's capacity for verbal communication. The advent of noninvasive positive-pressure-assisted ventilation modes offers an alternative to intubation in some patients with COPD and acute respiratory failure. Noninvasive positive-pressure ventilation for acute exacerbations of COPD has been examined in several studies, using both facial and nasal masks in conjunction with volume-cycled ventilation, bilevel positive-airway-pressure, and pressure-support modes. Although available studies suggest a significant success rate in patients with acute respiratory failure complicating COPD, the reported experience is still limited, and failure rates up to 40% have been reported in some studies. Primary use of noninvasive techniques for respiratory failure in patients with COPD should be reserved for centers with adequate expertise and supervision to allow safe implementation. Patient features that should discourage considering noninvasive ventilation for acute COPD exacerbations include hemodynamic instability, copious secretions, inability to defend the airway, poor cooperation with the technique, or impaired mental status.

Weaning from Mechanical Ventilation

Many COPD patients who undergo mechanical ventilation for acute bronchospasm, fluid overload, oversedation, or inadvertent hyperoxygenation may experience successful extubation without going through a period of weaning. Some patients with COPD intubated for respiratory failure require gradual weaning. Available techniques for weaning COPD patients from mechanical ventilation include assist-control ventilation with T-piece trials, IMV, and PS ventilation. Theoretical advantages exist to using IMV and PS modes because they provide partial support when the patient is connected to the ventilator and present less opportunity for barotrauma. Insufficient investigations exist to establish that weaning is accelerated or outcomes improved with any of the available weaning techniques.

ETHICAL ISSUES REGARDING INITIATING AND WITHDRAWING MECHANICAL VENTILATION

Because COPD affects patients at more advanced ages, frequently progresses, and may require highly expensive and prolonged life-saving medical technology, affected patients frequently present ethical dilemmas in their management and care. Deliberations in individual patients require a careful analysis of COPD survival statistics, quality of life, community health care resources, and economic aspects of care. Clinicians commonly attempt to determine the value of mechanical ventilation in individual patients with COPD by subjectively estimating the likelihood of survival after intubation. Unfortunately, subjective bedside assessment is extremely inaccurate to predict the survival of COPD patients. The predictive accuracy does not correlate with physicians' experience or level of training.

No correlation exists, for instance, between short-term survival and admission arterial blood gas results, spirometric values, hematocrit, patient age, or number of previous admissions for exacerbations of COPD. Scoring systems such as the Simplified Acute Physiology Score are weak predictors of short-term outcome in patients with COPD and respiratory failure. Nonpulmonary comorbid conditions, such as gastrointestinal hemorrhage, pulmonary embolism, or coronary heart disease, present at the onset of respiratory decompensation contribute to poor patient outcome. Housebound patients with severe, end-stage lung disease and comorbid conditions, therefore, have a worse short-term prognosis than more active patients with less severe underlying pulmonary impairment during episodes of respiratory failure of similar severity. Close to 80% of patients with COPD who require mechanical ventilation for acute respiratory failure survive to hospital discharge. Patients followed from the onset of an episode of acute respiratory failure have a 2-year survival between 28% and 70%. In contrast to common belief, patients with COPD have the highest survival rate among patients with various causes of acute respiratory failure. Finally, the long-term prognosis of patients surviving mechanical ventilation is similar to that of patients with the same degree of underlying respiratory impairment who have not required mechanical ventilation.

It follows that patients with COPD complicated by acute respiratory failure requiring life-support measures do not have an overall grim prognosis. Consequently, no fundamental ethical dilemma exists in considering all patients with COPD for intubation and mechanical ventilation. However, patients who have poor baseline function, marginal nutritional status, severely restricted activity levels, and inexorable deterioration of their late-stage pulmonary dysfunction may elect to forgo intubation when, in their and their physician's judgment, it will only temporarily interrupt the terminal phases of the disease.

Physicians have an obligation to assist their patients with COPD in formulating advance directives before respiratory decompensation occurs. In counseling patients regarding the value of intubation and mechanical ventilation and considerations of forgoing life-support measures, the physician has the responsibility to ensure that (1) the patient has decision-making capacity; (2) the patient has been informed regarding his or her diagnosis and prognosis and of the risks, benefits, and consequences for the full range of available medical interventions including the option of no therapy; (3) the patient has received from the physician professional recommendations regarding the medical choices available, including the use of life-sustaining therapy, based on knowledge of both the medical situation and the values and goals of the patient.

Decisions regarding limitations of care are best made during stable periods before respiratory failure or other life-threatening conditions occur. Patients who choose to forgo life-support measures should be encouraged to outline their wishes as specifically as possible in an instrument of advance directive such as a living will. Patients with COPD should specifically define their health care preferences for several clinical situations likely to be encountered, such as intubation, mechanical ventilation, cardiopulmonary resuscitation, tracheotomy, and long-term life support with difficult weaning. The patient should be encouraged to share these preferences with a trusted family member, friend, or other person who can be designated as a surrogate decision maker through a durable power of attorney for health care.

Once these advance directives are properly established or the wishes of an informed patient with decision-making capacity are known, respect for patient autonomy requires physicians in charge of the patient's care to honor the patient's right to forgo medical intervention. This is considered distinct from participating in assisted suicide or active euthanasia. Physicians faced with a critically ill patient should determine, however, that requests to forgo care are reasonable under the clinical circumstances and derive from deep-seated values and appropriate responses to the severity of underlying disease rather than endogenous depression or temporary conditions of pain, fear, depression, or anxiety during episodes of acute respiratory failure. Physicians who have personal ethical or religious values that do not allow them to comply with a patient's well-conceived request to forgo support should transfer the patient's care to another physician who can honor the patient's directives.

It should be recognized that there is no ethical difference between withholding and withdrawing life-support measures in patients with acute respiratory failure. Ethical principles underlying the decision to withhold intubation and mechanical ventilation apply equally when patients or proxies request a discontinuance of care for patients with terminal disease or a progressive degenerative condition who have no hope for an acceptable and meaningful recovery. Patients electing to have ventilatory support withdrawn may request and receive adequate sedation and analgesia to extinguish all pain and suffering during the dying process even if such treatment accelerates their imminent death.

SURGICAL OPTIONS FOR EMPHYSEMA

In 1959, Otto Brantigan postulated that the tethering forces that tend to keep the intrathoracic airways open were lost in emphysema and that by resecting the most affected parts of the lungs in patients with the most severe form of the disease, the force could be partially restored. Indeed, he developed an operation to resect wedges of hyperinflated lungs. In spite of a significant morbidity and mortality (16%), 75% of his patients manifested clinical improvement for up to 5 years. Because of the lack of some of the technical material now available (pericardial strips) and the need for bilateral thoracotomy, the procedure was abandoned. Recently, Cooper et al. have reported the results of surgical resection of emphysematous lungs of patients with very severe COPD. Using the technique developed by Brantigan, but doing both lungs in the same sitting through a median sternotomy, they have reported a 1-year 45% increase in FEV_1, a 25% decrease in TLC, and a significant improvement in exercise performance.

Although the results are preliminary, several groups have shown improvement in lung function, dyspnea, and quality of life. It is difficult to delineate clearly the factors responsible for this improvement, but recent reports indicate a postoperative increase in lung elastic recoil as one likely explanation. The decrease in lung volume lengthens the diaphragm and other respiratory muscles, placing them in a better contractile position on the length–tension curve. This should result in less effort to produce the same ventilatory pressure. Perhaps this decreases respiratory drive and hence reverses some of the factor associated with dyspnea in these patients. More studies are needed to be able to recommend this procedure to most patients with emphysema. Little is known about the factors that help select the best candidates for surgery. More needs to be learned about the best surgical technique and the optimal timing of the surgery. Nevertheless, for a disease with few therapeutic choices when it is advanced, this revival of an old operation seems to offer a possible and reasonable alternative to lung transplant.

SLEEP AND COPD

Patients with COPD seen to have a higher prevalence of insomnia, excessive daytime sleepiness, and nightmares than the general population. This is not a result of the bronchodilators because studies with these agents have failed to demonstrate any adverse effects on sleep staging or sleep efficiency. Oxygen desaturation during sleep, especially in REM sleep, has long been recognized in patients with COPD. Clinical parameters that have been associated with the presence of nocturnal desaturation include daytime hypoxemia, blunted awake chemosensitivity, severe dysfunction on pulmonary function testing, and chronic CO_2 retention. None of these characteristics has been useful in predicting individual REM desaturators. The mechanisms leading to hypoxemia include ventilation, which is reduced in all stages of sleep, especially in REM sleep. It has also been postulated that it may be related to ventilation–perfusion imbalance, though this has been difficult to prove. REM-associated falls in S_aO_2 are associated with increases in pulmonary artery pressures. It is not clear whether isolated increases in pulmonary artery pressures during sleep can lead to sustained pulmonary hypertension. However, recent studies of COPD patients with nocturnal desaturation and daytime PO_2 levels over 60 mmHg have demonstrated higher daytime resting and exercise-induced pulmonary artery pressures in these patients than in a similar group of patients who did not desaturate at night.

Patients with COPD have increased premature ventricular contractions during sleep, and there is a tendency for these to decrease in frequency when these patients are given supplemental oxygen. The effect of nocturnal oxygen saturation on survival has recently been reported. Both the mean nocturnal S_aO_2 and the S_aO_2 nadir during sleep were significantly related to survival. However, neither measure improved the prediction of survival over measurements of vital capacity or awake S_aO_2. The measurement of nocturnal S_aO_2 during sleep therefore cannot be recommended in the routine clinical management of COPD patients. Several studies have demonstrated that COPD and OSA can coexist, but there is no evidence that this coexistence is more common than would be expected from the relative frequencies of these two conditions. The significance of the association seems to be that patients with both disease processes seem more likely to develop pulmonary hypertension and right-sided heart failure than do patients who have either condition alone. Full polysomnography, however, would be beneficial in those COPD patients with symptoms suggestive of coexistent OSA.

AIR TRAVEL

Commercial airline travel exposes passengers to hypobaric hypoxia because aircraft cabins are not routinely pressurized to sea level. In patients who have compensated COPD at sea level, lowering the partial pressure of oxygen in the aircraft cabin can produce severe hypoxemia. Physical exertion during the flight can increase the risk of an exacerbation of symptoms. It is unknown what proportion of patients who suffer cardiac events during air travel have COPD as a comorbid

condition. Aircraft are usually pressurized to between 5000 and 7000 feet (1500 to 2100 m). For the preflight evaluation of most patients, clinicians should consider 8000 feet (2438 m) of altitude above sea levels as a realistic “worst-case scenario.”

Preflight assessment can be accomplished by estimating the expected degree of hypoxemia at altitude, identifying comorbid disease conditions, and providing an oxygen prescription if necessary. Documentation of the recent clinical condition and laboratory tests, particularly if the patient is traveling abroad, and counseling are also desirable elements of the preflight patient care. The two means of estimating the degree of hypoxia at altitude are the hypoxia inhalation test (HIT) and the use of regression formulas. The HIT is not performed in many clinical laboratories in the United States. Regression equations offer the opportunity to compare a patient with a group of patients with similar clinical characteristics who have been previously studied during exposure to hypoxia. Although regression equations may provide a more physiological basis for the effects of high altitude than the HIT, the regression approach does not assess the individual's susceptibility to the development of symptoms or electrocardiographic changes during hypoxia. The A–a O_2 gradient generally has no advantages over regression equations. Currently it is recommended that the P_aO_2 during air travel be maintained above 50 mmHg. Although 2 to 3 L of oxygen by nasal cannula will replace the inspired oxygen lost at 8000 feet compared to sea level, lesser increments of oxygen will maintain the P_aO_2 above 50 mmHg in many patients, and a 1- to 2-L increment may be sufficient.

Patients with COPD receiving continuous oxygen at home will require supplementation during air flight. Such patients should receive greater oxygen supplementation during the flight than at sea level. Increments equivalent to 1 to 2 L of oxygen by nasal cannula during flight should suffice for most patients. Patients will also require additional oxygen supplementation if the elevation at the destination is significantly greater than at home. The Federal Aviation Administration requires a physician's statement of oxygen need in order for a patient to receive continuous oxygen during flight. There is no uniform airline request form, so each airline must be contacted by the patient to determine what is required. Because the airlines do not provide oxygen for ground use in the airline terminal, patients who require continuous oxygen should be advised to make plans for such locations. The American Lung Association provides patient education materials, including a booklet entitled *Airline Travel with Oxygen,* for individuals who travel with oxygen.

NUTRITION

As many as 25% of outpatients with COPD may be malnourished, and almost 50% of those patients admitted to the hospital have evidence of malnutrition. Sixty percent of critically ill COPD patients with acute respiratory failure are malnourished. The exact cause is not clear, but factors such as increased work of breathing, decreased food intake because of dyspnea, and secretion of cytokines such as tumor necrosis factor may combine to generate the malnutrition state. Malnutrition is associated with wasting of respiratory muscles, causing respiratory muscle weakness.

Assessment

The nutritional assessment of COPD patients includes body weight (loss in excess of 10% ideal body weight), but presence of edema limits the utility of body weight. Hepatic secretory proteins such as albumin, transferrin, retinol-binding protein, and prealbumin are markers of visceral protein stores and proposed as methods of nutritional assessment. Unfortunately, all are influenced by numerous factors in addition to the nutritional state. Anthropometry involves application of simple measurements of skin folds and circumferences to divide the body into compartments of fat, muscle tissue, and skeletal mass. This is used with limited success. Depression of cellular immunity is consistently associated with malnutrition, and nutritional repletion is associated with improved immunocompetence. The utility of skin testing is limited by multiple factors, which include technical application and interpretation of skin tests. Tests of muscle function are also used as markers of nutritional status. Unfortunately, no simple recommendation can be given regarding the “best” test for nutritional assessment. Utilization of any of these methods can be appropriate, providing the limitations are clearly understood.

Nutritional Support

Aggressive oral nutritional supplementation of COPD patients does result in improvement of respiratory strength, but it is laborious, time intensive, and often cannot be maintained by the patient. It has been suggested that COPD patients might benefit from a high-lipid, low-carbohydrate diet because of the reduced RQ when the latter substrates are fed. However, the clinical benefits of altering fat-to-carbohydrate ratios in COPD patients when calories supplied are appropriate remains unproven. Overfeeding should be avoided. Electrolyte disturbances are common in COPD patients and have potential for significant adverse outcomes. Hypophosphatemia, hyperkalemia, hypocalcemia, and hypomagnesemia are associated with decreased respiratory muscle function while repletion of these abnormalities results in improved function. Hypophosphatemia can develop as a consequence of refeeding. Although these complications apply to all patients receiving nutritional support, COPD patients may be at increased risk relative to decreased respiratory muscle function secondary to their prior lung disease. Monitoring electrolyte levels and providing supplemental electrolytes, especially phosphorus in malnourished patients, should be routine in COPD patients with respiratory failure. Patients with COPD should be instructed on good dietary habits. Their weight should approximate ideal body weight. If they are malnourished, attempts should be made to restore nutritional balance. Several smaller meals a day may help maintain caloric needs but avoid undue dyspnea. Forced nutrition or special diets are not recommended at the present time. The use of hormones to improve muscle functions remains experimental.

CONCLUSION

Over the years, our knowledge about COPD has increased significantly. Smoking cessation campaigns have resulted in a significant decrease in smoking prevalence in the United States. Similar efforts in the rest of the world should have the same impact. The consequence should be a drop in incidence of COPD in the years to come. The widespread application of long-term oxygen therapy for hypoxemic patients has resulted in increased survival. During this time we have expanded our drug therapy armamentarium and have used them to effectively improve dyspnea and quality of life. Recent studies have documented the benefits of pulmonary rehabilitation (Chapter 51). Noninvasive ventilation has offered new alternatives for the patient with acute failure. The revival of surgery for emphysema, although still experimental, may serve as an alternative to lung transplant for those patients with severe COPD who are still symptomatic on maximal medical therapy. With all these options, a nihilistic attitude toward these patients is not justified.

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CHAPTER

44 Sleep Apnea Syndrome and Sleep-Disordered Breathing

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INTRODUCTION

Sleep-disordered breathing comprises a collection of syndromes characterized by breathing abnormalities during sleep, by intermittent disruptions in gas exchange, and by sleep interruption. According to cross-sectional studies, sleep apnea is common in the population, and 2% to 4% of the population could be candidates for treatment on the basis of excessive daytime sleepiness, cardiac arrhythmias, cognitive abnormalities, and/or behavioral abnormalities. In addition, there are epidemiologic data to suggest that snoring (partial upper airway obstruction during sleep) is associated with systemic hypertension and stroke and, possibly, myocardial infarction and premature sudden death. Finally, a positive association between sleep apnea and motor vehicle accidents exists. Clearly, sleep-disordered breathing has a medical and social impact on the community.

The purpose of this chapter is to describe the pathophysiology and clinical management issues for respiratory disorders of sleep.

DEFINITIONS USED IN DESCRIBING SLEEP-DISORDERED BREATHING

Sleep apnea syndrome is a disorder characterized by the association of apnea and/or hypoventilation during sleep with a constellation of symptoms and signs related to sleep fragmentation and hypoxic exposure. The syndrome will resolve when the sleep-induced respiratory disturbance is eliminated.

Three patterns of apnea, i.e., cessation of breathing, can be observed during sleep. These are schematically shown in Fig. 1. A central apnea occurs when both airflow and respiratory efforts are absent. Other terms used in the literature that are equivalent to central apnea are diaphragmatic or arrhythmic apnea. These terms imply that there is a cessation of respiratory effort. During an obstructive apnea, respiratory efforts persist, although airflow is absent at the nose and mouth. Other terms for obstructive apnea are upper airway and peripheral apnea. Obstructive and central apneas are not necessarily unrelated. Many adult patients exhibit apneas in which both central and obstructive patterns occur, which are termed mixed apneas. In a single apneic episode there may be a period in which no efforts occur, followed by the appearance of respiratory efforts, also without airflow. In addition, in the same night, patients may have central, mixed, and obstructive apneas.

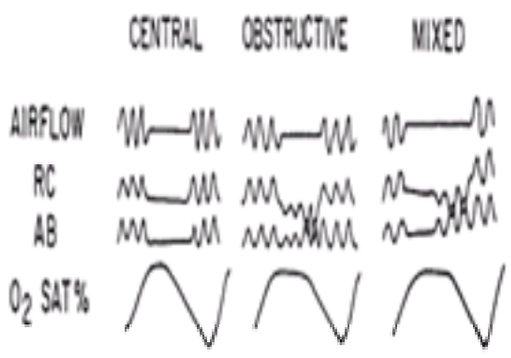

FIG. 1. Shown in diagrammatic form are the three patterns of apnea identified during sleep in human subjects. In each, airflow at the nose and mouth is absent, indicating apnea. In central apnea, respiratory efforts, indicated in this instance by rib cage (RC) and abdominal (AB) displacement, are absent. During an obstructive apnea, efforts by the chest-wall muscles are present throughout the entire episode of apnea. In mixed apneas, both central and obstructive patterns are present in the same apnea. Oxygen saturation (02 SAT %) will fall according to the general level of oxygen saturation and the length of the apnea. (Reproduced from KP Strohl et al. Physiologic basis for therapy of sleep apnea. *Am Rev Respir Dis* 134:791, 1986.)

Hypopneas or hypoventilation during sleep may arise by mechanisms similar to that producing apnea. Hypoventilation (hypopnea) leads to increased carbon dioxide and decreased oxygen levels in arterial blood and arousals from sleep; like apneas, hypopneas result from reduction in respiratory efforts or partial upper airway obstruction. Snoring is a form of partial airway obstruction. Although in most instances snoring is of mild severity, patients who snore heavily may present with symptomatic features of sleep apnea syndrome even if complete cessation of airflow (apnea) never occurs during sleep; moreover, these patients may exhibit abnormal sleep and cardiorespiratory changes as well.

There are certain summary measures used to describe respiratory disturbances during sleep. The *apnea–hypopnea index* (AHI) is the total number of apneas and hypopneas during sleep divided by the hours of sleep time. Values of AHI can be computed for the different stages of sleep. Another term used is the *respiratory*

disturbance index (RDI), which is equivalent to AHI. The term *desaturation index* (DI) refers to the number of times per hour that oxygen saturation falls by more than 4%. Finally, if formal sleep measures are performed, an *arousal index* (AI) is computed. The number or arousals per hour of sleep may not be equivalent to AHI or RDI because many (approximately 20%) apneas or hypopneas are not accompanied by arousals and/or other causes for arousals are present.

EPIDEMIOLOGY OF SLEEP-DISORDERED BREATHING

Subjects without clinical problems may exhibit obstructive or central apneas at sleep onset or during periods of rapid eye movement (REM) sleep. Apneic episodes are usually less than 10 to 15 sec in duration and are not repetitive. Occasionally, longer periods of apnea lasting up to 30 sec are seen in normal subjects, particularly during REM sleep. These episodes are not usually accompanied by arousal or sleep-state changes. Whether there are gender differences in the appearance of sleep apneas in healthy subjects is unclear. In healthy young subjects, some studies have shown that more boys than girls have frequent apneas during sleep, but others report little gender difference in the occurrence of apneas. Study differences may be confounded by small numbers of subjects, subject selection, and the effect of obesity. After the sixth decade, however, respiratory disturbances during sleep seem to increase in number and occur with equal frequency in men and women. Patients with a clinically important sleep apnea may be distinguished from normal by the existence of *repetitive* apneas greater than 10 sec in duration during stages I and II and REM sleep and by improvement in daytime symptoms and general performance with treatment of sleep-disordered breathing. Unfortunately, the number of respiratory disturbances *per se* is not a good indicator of disease, and symptoms of sleepiness are better predictors of treatment success, as experienced by the patient and by objective testing.

A recent epidemiologic study estimated that 9% of women and 27% of men in the U.S. population may have an AHI > 5, a number often quoted as a “threshold value” for normality; however, many people with an AHI > 5 have no symptoms or apparent illness. In a sample of 1500 factory workers, it was found that at least 2% had symptomatic sleep apnea. These studies also suggest that these subjects have higher accident rates and substantial disability. This prevalence rate of symptomatic people with AHI > 5 was confirmed in the U.S. population.

Snoring is believed to be a predisposing feature in the development of disease. Snoring increases markedly with age, so that approximately 45% of men and 30% of women 65 are said to snore. Hypertension is twice as common among persons who snore, even after age and obesity are taken into account.

Reports from sleep clinics suggest that sleep apnea should be considered in any patient referred for problems of initiating and maintaining sleep or excessive somnolence. The incidence of sleep apnea in patients presenting to sleep centers ranges from 7% to 33% and is increasing as there occurs greater recognition of sleep apnea and its sequella by primary care providers.

There is increasing evidence that sleep apnea has a familial component. Symptoms relating to apnea are present with two to six times greater frequency in family members of affected patients than in a control population. Sleep apneic activity itself is present more often in first-degree relatives of patients than in age-, sex-, and socioeconomic-matched control families. These family studies also suggest that the frequency of sleep apnea is underestimated in the community and that the symptomatic sequelae of multiple apneas are quite variable. Furthermore, this effect is not sufficient to recommend screening of asymptomatic family members.

CLINICAL FEATURES OF SLEEP APNEA

Patients will often have five or more of the traits listed in Table 1. Signs and symptoms in a particular patient may be associated with central, obstructive, or mixed apneas during sleep.

Historical data	Clinical signs
Altered sleep; snoring, thrashing	Cardiac arrhythmias
Excessive daytime sleepiness	Systemic hypertension
Dyspnea, especially on exercise	Edema
Morning headaches	Polycythemia
Insomnia	Pulmonary hypertension
Fatigue	Reduced sleep latency by EEG
Intellectual deterioration	
Personality changes	
Hallucinations, automatic behavior	Reddened uvula; pharyngeal crowding
Family history of sleep apnea	

TABLE 1. *Clinical problems associated with sleep-disordered breathing*

Patients with obstructive sleep apnea may be obese and physically resemble patients described as suffering with pickwickian syndrome, exhibiting obesity, cardiopulmonary failure, polycythemia, and hypersomnolence. Yet nearly half of patients with the sleep apnea syndrome are not obese, and the suspicion that the syndrome is present should not be limited to the fat patient or to those with characteristics previously called the pickwickian syndrome.

Restless sleep and observed apneas are sensitive and specific indications of the recurrent apneas. Sleep complaints include either excessive daytime sleepiness or insomnia. Both are related to the number and type of nocturnal arousals. It is said that patients with insomnia generally have fewer and shorter, primarily central, apneas with little hypoxemia, whereas patients with excessive daytime sleepiness have more and longer, primarily mixed and obstructive, apneas with greater hypoxemia.

Bradyarrhythmias during sleep are found in patients with sleep apnea, and cardiac monitoring in the course of workup for heart disease can be a clue to the presence of apneas during sleep. An example of bradyarrhythmia during sleep apnea is shown in Fig. 2. During obstructive apneas, the depressive effects of the carotid body on heart rate predominate, while quickening of heart rate occurs when ventilation occurs. Patients with sleep apnea who exhibit bradycardia during sleep may have normal findings on His bundle studies and otherwise normal cardiac function during wakefulness. Other cardiac arrhythmias include ventricular ectopy and escape rhythms, but in addition, reflexes elicited by forceful respiratory efforts against a closed airway and the resulting swings in pleural pressure probably have significant effects on circulatory function. Arrhythmias in patients with sleep apnea disappear when the apneas are relieved. Holter monitoring is not sensitive or specific enough for use in screening.

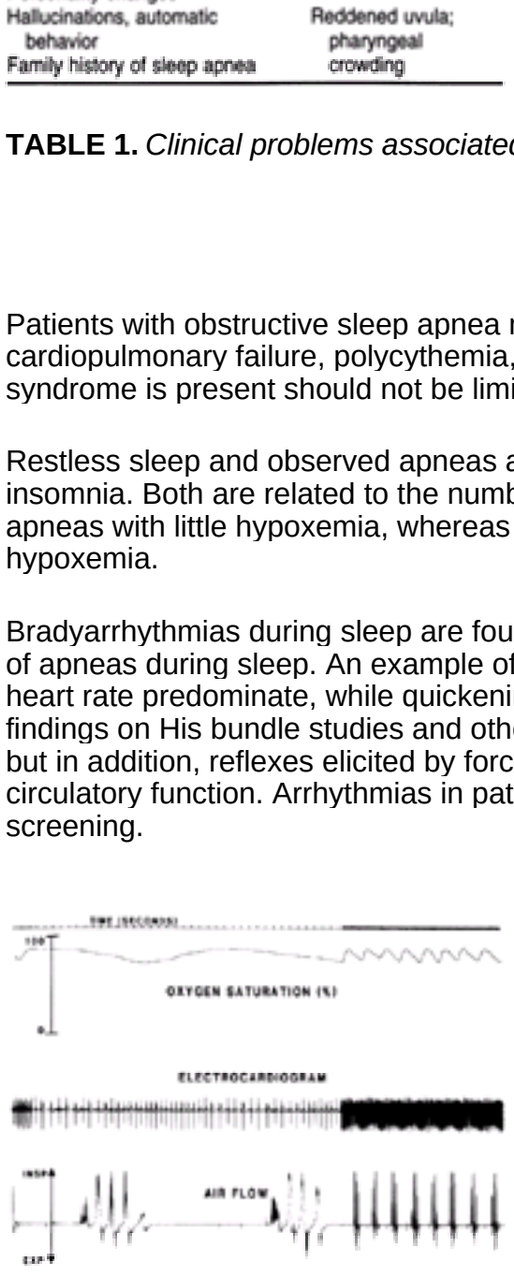

FIG. 2. Shown is the relationship between oxygen saturation, heart rate (indicated by an ECG rhythm strip), and ventilation (measured from a face mask). Cyclic changes in heart rate found on Holter monitoring of a patient can indicate the presence of apneas during sleep. INSP = inspiration; EXP = expiration.

Often it is the family members, rather than the patient, who first recognize the sleep disturbance, e.g., periods of absent breathing, loud snoring, or thrashing movements during sleep. The symptoms of sleepiness develop over many years. These are the most common constellation of presenting symptoms. Patients occasionally present with complaints of fatigue or decreased alertness or with apparently unexplained polycythemia. Sleep apnea is part of the differential diagnosis of

sexual dysfunction, personality changes, and morning headache.

Routine laboratory examinations are not helpful screening tools. Likewise, pulmonary function tests also may reveal no abnormality except those caused by associated obesity (somewhat diminished lung capacities, with greater reduction in the expiratory reserve volume). Although patients with lung diseases also may have the sleep apnea syndrome, there is no evidence that sleep apnea occurs more frequently in patients with pulmonary impairment.

The sleep apnea syndrome should be considered in patients with hypercapnia that is disproportionate to abnormalities in mechanical function of the lungs. Hypercapnia rarely occurs with obstructive lung disease unless forced expiratory volume in 1 sec (FEV_1) is reduced to less than 50% of the predicted value. Carbon dioxide elevation occurs in patients with asthma and fibrotic pulmonary disease only with even more severe reduction in the FEV_1. Patients with unexplained right-sided heart failure or pulmonary hypertension likewise should be questioned for the presence of sleep-disordered breathing. Finally, some patients with the sleep apnea syndrome may be mistakenly treated for primary heart disease because cardiac arrhythmias have been detected during sleep but respiratory disturbances have not.

LABORATORY DIAGNOSTIC SLEEP STUDIES

A definitive diagnosis can be made by polysomnography, in which continuous measurements of several physiological variables are made to assess sleep stages, breathing, and gas exchange. Figure 3 shows the elements of sleep and breathing that can be monitored in patients.

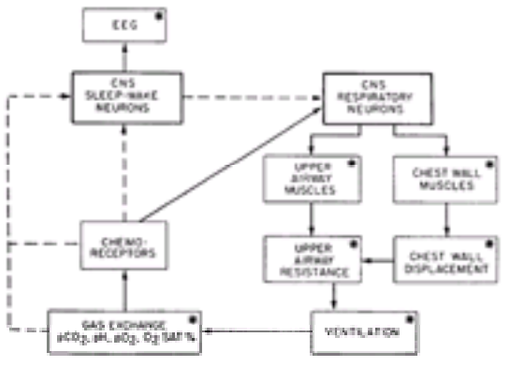

FIG. 3. This schematic diagram shows the general relationships between the respiratory system (CNS respiratory neurons, upper airway and chest-wall muscles, ventilation, chemoreceptors, etc.). And the CNS sleep-wake process. The boxes designated by the asterisks indicate the respiratory variables and the electroencephalogram (EEG) that can be measured in human subjects and are used in the diagnosis and assessment of treatment in patients with sleep apnea. Note that the basic mechanisms in respiration or sleep can be measured only indirectly. (Reproduced from KP Strohl et al. Physiologic basis for therapy of sleep apnea. *Am Rev Respir Dis* 134:791, 1986.)

Sleep staging requires monitoring of the electroencephalogram (EEG) (usually with two or three leads), the chin electromyogram (activity decreases in REM), and the electrooculogram (EOG) to detect REM. It is also useful to record the electrocardiogram (ECG) to see if arrhythmias occur with the apneic episodes.

To distinguish central from obstructive apneas, both respiratory efforts and some index of airflow must be measured.

Noninvasive oximeters that spectrophotometrically and continuously measure the level of oxygenated hemoglobin are ideal for use in sleep studies. These instruments are reliable and accurate for trending of oxygen saturations from 70% to 99%. Issues concerning artifact, sampling time, averaging routines, and sensor placement must be considered in their use and interpretation.

Gas exchange can be assessed by sampling from indwelling arterial catheters. However, intermittent sampling may miss the rapid falls in oxygen tension and saturation that occur during apneas. P_{CO_2} can be sampled by transcutaneous methods and can provide a reasonable alternative for assessment of alveolar ventilation. P_{O_2} can be assessed transcutaneously using electrodes applied to the skin, which is heated to increase blood flow; these electrodes probably have too long a response time to be useful in sleep apnea.

NONPOLYSOMNOGRAPHIC MONITORING TECHNIQUES

Because of the expense and time commitment involved in performing polysomnography, there have been three approaches to reduce the cost or performance of this diagnostic procedure. First, questionnaires have been proposed that could serve to screen individuals, thereby improving the prediagnostic probability and reducing the number of subjects who need polysomnography. Second, equipment has been developed to allow performance of a study equivalent to polysomnography in the home setting. In some instances, a van brings equipment and a technician to the patient. Third, simplified monitoring of selected, crucial variables could be used to assess therapeutic efficacy. In this instance, monitoring devices are carried around by the patient, as is done in Holter monitoring.

For the last purpose, a number of approaches have been suggested. Some include use of tracheal sound recordings, monitoring of position, and oximetry. No single channel of data alone can be used to detect apneas and hypopneas associated with desaturations, but the predictive value with respect to apneas is improved by experienced interpretation of a combination of measures. However, the added value of these abbreviated studies compared to the determination of probability by history and physical is low. Indeed, the absence of abnormalities in such tests does not prove that the patient is free of sleep apnea, that the amount and quality of sleep are adequate, or that other sleep disorders that can produce similar symptoms are not present.

Screening studies that combine continuous measurement of arterial oxygen saturation, airflow sounds, and/or ventilatory effort may be adequate for the follow-up of treatment for sleep apnea if cyclic saturation, breathing, and effort abnormalities were previously detected and then abolished by the application of nasal continuous positive airway pressure (CPAP).

Several approaches to unattended simultaneous monitoring of several variables have been developed recently, using both digital and analog recording techniques. Such devices are being continuously upgraded, as is the detection of respiratory events. Many devices employ signals from the chest and abdomen to detect apneas and hypopneas. In some instances, tidal volume changes can be estimated from the phase relationship between the rib cage and abdomen motion. Simultaneous with the respiratory measurements, recordings are made of other important variables, for example, ear oximetry, heart rate determined by the R-R interval of the ECG, tibialis electromyogram, and body movement with an activity monitor strapped to subject's wrist. The latter is used in an attempt to estimate sleep time.

At the present stage of development, the number of apneas detected by these instruments shows a good correlation with those detected by simultaneous polysomnography. Thus, in general, the instruments correctly identify persons who have sleep apnea. However, the devices are not as proficient in classifying apneas as being obstructive or central. In particular, with current digital systems, central apneas are frequently misclassified as obstructive or mixed. Improvements to obviate these and other problems will be made because the costs of center-based polysomnography limit access to diagnosis and management.

INTERPRETATION OF POLYSOMNOGRAPHIC MEASUREMENTS

Sleep apnea is often considered to be present if there are at least 30 apneas or hypopneas (each more than 10 sec) occurring in both non-REM (NREM) and REM sleep in a sleep recording lasting 6 hours. This is a very difficult number to defend as a classification of disease. There are reports of people who have more than 200 apneas per night yet are relatively asymptomatic, and many otherwise normal, healthy aging subjects would be classified as having sleep apnea syndrome based on currently used criteria, which depend on numbers of apneas. Definitive prospective longitudinal data on the risks associated with only the number of respiratory events during sleep are currently being collected. Retrospective studies suggest mortality increases as the apneic index (number of apneas per hour of sleep) increases. Controversy on the predictive value of polysomnography still exists. Treatment effect is still part of the disease definition.

Levels of oxygen saturation during wakefulness and sleep could be clinically more important than the number of abnormal respiratory events, however defined. With continuous monitoring of oxygen saturation, the fraction of the sleep period spent at each level of oxygen saturation can be determined to quantify hypoxemic exposure (Fig. 4). Minimum levels of oxygen saturation are important because severe hypoxia can trigger cardiac arrhythmias, but mean levels may be even more important. Recently, methods of quantitatively describing the profile of oxygen saturation throughout sleep and wakefulness have been developed and should prove valuable in

diagnosis and in evaluating the effects of treatment.

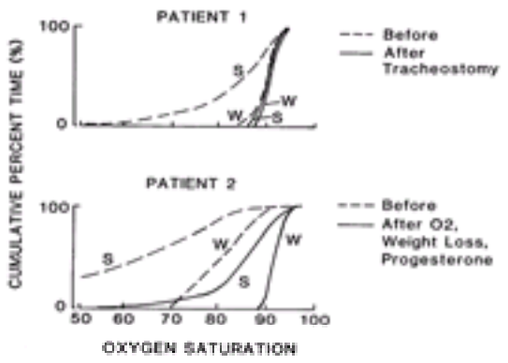

FIG. 4. The effect of treatment on oxygen saturation over time in two patients, one treated with tracheostomy and one with oxygen, progesterone, and associated weight loss. Studies in both patients were performed on room air. Treatment in both cases reversed hypersomnolence, and increased hematocrit, pedal edema, and signs of right-sided heart failure. S = sleep; W = wakefulness.

Some sleep investigators believe that sleep studies should be performed on at least two nights, because it has been shown that the distribution of sleep stages may be altered by unfamiliar surroundings. In patients with lung disease, however, ventilatory changes within a given sleep stage usually can be accurately assessed during a single night's examination. Because all-night studies are costly, attempts have been made to diagnose sleep apnea and its severity with shorter examinations of sleep. The specificity and sensitivity of such studies may improve as our ability to distinguish those patients most likely to benefit from noninvasive or rapid treatment of sleep apnea from those requiring more detailed assessment for other sleep disorders.

It is proposed that any diagnostic study for sleep apnea should include periods of both NREM and REM sleep for the reason that it is during REM sleep that severe changes in respiration often occur. Although this approach is reasonable, correlation of sleep events with clinical symptoms is currently imprecise, and furthermore, the relative importance of abnormal respiration occurring in REM and NREM sleep is unknown.

Figure 5) typifies the spectrum of disease from a personal perspective. Those with severe disease could be defined as individuals who have active daytime sleepiness interfering with normal daily activities and associated with signs of cardiopulmonary failure, polycythemia, and cor pulmonale. Such an individual would now be easily recognized as having a treatable disease. Once the apneic episodes during sleep are eliminated, excessive daytime sleepiness would resolve, and signs of hypoxic stress, such as polycythemia and cor pulmonale, would resolve or not progress. Noted is a correlation among the number of arousals, the number of respiratory events during sleep, and sleepiness as measured by multiple sleep latency testing. Patients fall asleep during the day, in a sitting posture, and are at extreme risk for accidental injury. Clinical studies have shown that reversal of sleep-related hypoxemia can improve sleepiness, hypertension, and abnormalities associated with hypoxemia, such as reversal of the polycythemic state and resolution of edematous states associated with cor pulmonale. The category of severe disease includes patients with more than 30 apneas per hour of sleep and hypoxemia that exceeds lower thresholds of 85% saturation for at least 15% of the time during sleep.

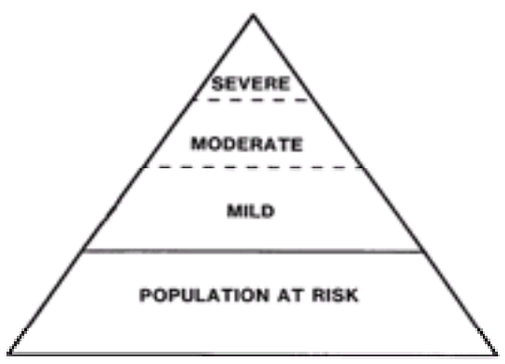

FIG. 5. Degrees of pathophysiology that exist in sleep apnea syndrome. Although this figure illustrates the spectrum of disease, it should be considered a hypothesis. For instance, the population at risk is presumed to be those who snore heavily, somewhere in the vicinity of 50 percent of males and 30 percent of females. Also, the natural progression of the disease is not known.

A second category would be that of moderate disease. This zone would include daytime sleepiness of which the patient is aware and takes steps to avoid falling asleep at times that might be inappropriate. One example might be the patient who often takes a nap in the middle of the day or avoids driving for fear of falling asleep. These individuals are less disabled by their daytime sleepiness than those with severe disease and often are able to continue their daily activities, but at reduced levels. These individuals do not often have daytime signs and symptoms of cor pulmonale; however, they often have hypertension. Detailed studies of pulmonary vascular resistance or of cognitive studies in these individuals have not been performed; however, this group appears to have an increased incidence of motor vehicle violations or accidents. Generally in these patients the apneic/hypopneic index is between 15 and 30, but positionally induced or positionally altered apneic indices could be common, and a high hypopneic index may be present. Sleep fragmentation is observed, but the progression of sleep stages is apparent. This category is distinguished from severe disease by the absence of disabling sleepiness, of cor pulmonale, and of hypercapnic respiratory failure.

A third category is that of mild disease. In these individuals, there is sleepiness that is manifested by a regular tendency to fall asleep under circumstances of inactivity such as reading the newspaper, going to movies, or watching television shows. This “passive” sleepiness may not be recognized by the patient, and the patient does not take steps to avoid activities that might make him or her sleepy. Indeed, sleepiness may be recognized only by family members and be noticed only in retrospect after direct treatment of apnea or of improvement by weight loss or alcohol abstinence. Respiratory disturbance indices in these individuals are generally in the range of 5 to 15 per hour. There may be no signs of hypoxic stress, and oxygen saturation levels during sleep are generally confined to less than 90% for only 5% of the time. Sleep stages and stretches of stage III and IV sleep are preserved. These individuals are distinguished from those with moderate disease to the extent that their sleepiness does not intrude on daily activity or behavior and by the absence of problems ascribed to hypoxic stress.

The substrate for development of disease related to sleep apnea is considered to be those individuals who snore on a regular basis and do not have observed apneas. People with simple snoring generally are not sleepy, although perhaps more susceptible to behavioral influences and morbidity from alcohol or sedatives than individuals who do not snore at all. This group would comprise half of the male and a third of the female population. Respiratory disturbance indices are usually low, and a positional component to snoring and apnea may be present. Aspects of the association between snoring and other common diseases and the distinction between heavy snoring and mild snoring have been reviewed in other sections of this chapter. The major epidemiologic associations with hypertension, cardiovascular disease, myocardial infarction, and stroke possibly include these individuals as well as those with mild or moderate disease severity.

It is clear that in the case of the excessively sleepy individual with cor pulmonale, carbon dioxide retention, and polycythemia, elimination of apneas during sleep by tracheostomy or by nasal CPAP is desirable, leads to clinical remission, and, as indicated by retrospective studies, reduces mortality. The same studies suggest that elimination of apneas in those with moderate disease can reduce mortality; perhaps more importantly, therapy will improve symptoms of sleepiness to the extent that there may be less morbidity from complications such as automobile or industrial accidents.

It is not clear what to do for patients with mild disease or those who snore heavily. The natural history is unclear, and therapy is not well developed. However, this is a large population, and untried and unproved therapies abound. These include antisnoring pillows, devices that attach to the glasses that keep one alert, dental prostheses, external nasal dilators, nasal decogestants, and steroid sprays. Some may have merit. However, prospective randomized trials are needed to assess beneficial effect not only in terms of patient and/or bed partner satisfaction but also in terms of physiological and objective criteria that may relate to morbidity and mortality.

The diagram shown in Fig. 5 really relates to that individual with uncomplicated obstructive sleep apnea, that is, the individual who does not have other concomitant

illness. It is known that sleep apnea can complicate other diseases, as outlined in other chapters; hence, distinguishing the effects of sleep apnea from other sorts of diseases that promote sleepiness and/or hypoxic complications is one major task of the clinician.

STUDIES DURING WAKEFULNESS

The patient with sleep-disordered breathing should undergo a complete clinical examination specifically looking for the presence of cardiovascular, respiratory, or metabolic disturbances that may predispose the patient to or cause repetitive apneas during sleep. Drug addiction or depression may masquerade as sleep apnea, especially in the elderly subject in whom a number of apneas during sleep may be considered “normal.” In addition, some patients with sleep apnea (approximately 10%) may have concomitant narcolepsy, as suggested by family history, and/or evidence for cataplexy or periodic limb movements or restless legs. A careful history is the key to recognizing these diseases. Certain diagnostic tests, such as arterial blood gases, thyroid function testing, pulmonary function tests, the ECG, echocardiogram, and chest roentgenogram, are electively indicated if signs of hypoxic exposure are present.

If the predominant pattern of apnea during sleep consists of repetitive obstructive or mixed apneas, a more detailed physical examination is indicated to determine the presence of anatomic or pathologic narrowing of the upper airway. Physical examination will exclude pathologic processes. In the patient without upper airway or respiratory complaints, the flow–volume loop is unhelpful. A pattern consistent with variable extrathoracic obstruction, that is, a decreased inspiratory flow relative to expiratory flow at 50% of vital capacity, has been described in sleep apnea but is not predictive of the illness nor by itself helpful in directing therapy.

Specialized assessment of upper airway structure or function can be performed in the patient without obvious anatomic or pathologic narrowing of the pharynx but cannot be recommended in routine testing of patients. Computed tomography has shown nasopharyngeal and pharyngeal narrowing in obese patients; of interest, this narrowing does not appear to be caused by fat deposition. Measurements of the bony structures and alignment of the jaw to the head and neck (cephalometrics) have revealed individual and familial traits of a relatively shortened mandible; the degree of such trait correlates with the development of sleep apnea. Electromyography of upper airway muscles has shown a correlation between a decrease in muscle activation and the onset of apnea, yet this finding is universal in patients. The usefulness of nasoendoscopy during wakefulness and sleep is currently being explored as a way of selecting patients for surgical therapy directed at enlarging the airway. Preliminary studies suggest that those patients who exhibit the tendency to obstruct at the level of the nasopharynx, as opposed to the oropharynx, have a greater likelihood of success with uvulopalatopharyngoplasty. Acoustic imaging of the extrathoracic airway has shown that patients with sleep apnea have a smaller and more compliant pharyngeal airway than age- and weight-matched controls. Although all these special studies have given insight into potential mechanisms causing sleep apnea, none has shown sufficient specificity or reliability to dictate one or another therapeutic approach.

Multiple sleep latency testing consists of repetitive, bi-hourly observations of the time to sleep onset and REM. Healthy subjects will generally be unable to reproducibly initiate sleep or exhibit REM sleep at hourly intervals during periods of usual wakefulness. Patients with sleep apnea or narcolepsy will fall asleep and even exhibit REMs within 10 min of each hourly trial. This test is useful in the laboratory documentation of excessive daytime sleepiness, but its specificity and ability to predict daytime performance in the workplace have not been systematically demonstrated.

NATURAL HISTORY OF SLEEP APNEA

The natural history of the sleep apnea syndrome is largely unknown. Although there appear to be clinical categories of disease such as mild, moderate, and severe (see Interpretation of Polysomnographic Studies and Fig. 4), there is little evidence that progression from health to severe disease occurs according to these categories. There are few longitudinal studies in untreated patients with sleep apnea syndromes; those available have one or two subjects studied 4 to 8 years apart and show little change in the quantitative determination of breathing patterns during sleep. If this is the case, the disease progression is either slower than this time interval or sporadic.

It is proposed that snoring in early life leads to the insidious development of hypersomnolence and cardiovascular disease in patients with obstructive sleep apnea. In support of these suggestions are the findings that a history of heavy snoring is reported in more than 70% of adult patients with obstructive sleep apnea syndrome. Patients and family members often report minor symptoms of hypersomnolence occurring 10 to 20 years before diagnosis. Most clinical reports have emphasized the recognition of sleep apnea syndrome in the middle-aged man, and little is known about the natural history of these disorders in women, in the elderly, or in children. However, it is likely that in all groups, symptoms will increase abruptly with the appearance of increased hypoxemia and cardiopulmonary complications.

Death and sleep apnea are associated, but the nature of the association and extent of causality have not been satisfactorily explained. Early reports of patients with the pickwickian syndrome noted a high in-hospital mortality from cardiorespiratory failure, pulmonary embolus, and renal failure. Death has been reported to result from sedative drug use, particularly preoperative medications. However, it is the impression of some that automobile accidents related to excessive daytime sleepiness may have a greater impact on morbidity and mortality than cardiovascular complications or other nonaccidental sudden death.

PATHOPHYSIOLOGY

In most patients a variety of functional and anatomic factors can interact and produce repetitive apneas during sleep. These include sleep state, changes in respiratory control or mechanics with sleep, body habitus, body position, circulation time and cardiac output, and hereditary factors of respiratory control and upper airway morphology. Certain diseases of the cardiovascular and respiratory system are associated with respiratory disturbances during sleep, but in these instances, it is the disease rather than sleep-disordered breathing that dominates the clinical picture.

NEUROPHYSIOLOGY

The rhythmic cycle of a breath depends on interactions between groups of neurons located in the medulla: a dorsal group located in the vicinity of the nucleus tractus solitarius and a ventral group consisting of neurons in the nucleus retro- and paraambigualis, the nucleus retrofacialis, and nucleus ambigualis (NA). Efferent activity of the cranial nerves that supply upper airway muscles is adjusted by NA activity and the neural discharge to the chest-wall muscles by dorsal medullary nuclei. The activity of these medullary groups of respiratory neurons can be altered by descending pathways from pontine and suprapontine areas and can be affected by the sleep–wake cycle, in particular the waxing and waning of the meadian raphe, or reticular activating system.

It is difficult to produce apnea by hyperventilation in awake humans, but in anesthetized and sleeping animals and humans there seems to be some threshold level of carbon dioxide that is required to initiate breathing. This threshold level of P_{CO_2} is decreased by hypoxia in certain subjects, possibly by excitation caused by miscellaneous nonchemical stimuli.

The respiratory controller will influence the activity of the upper airway as well as the muscles of the chest wall. The electric activity of upper airway muscles often seems to be entrained to the respiratory rhythm, and phasic increases and decreases in the activity of many upper airway muscles can be discerned. The amplitude of these phasic changes can be altered by the same chemical stimuli (carbon dioxide and hypoxia) that affect diaphragm and intercostal muscle activity. Sleep may depress the sensitivity of upper airway muscles to chemical stimulation even more than the diaphragm.

The cardinal feature of sleep apnea syndrome in adults is the presence of recurrent apneas during sleep. Apneas may be central, obstructive, or mixed but are repetitively present. Theoretically, the causes of an apneic event include reduced excitatory stimulation, active suppression of breathing from inhibitory reflexes arising from the cardiovascular system, the lungs, and the chest wall or via other somatic and visceral afferents; and loss of reflexes that normally ensure the maintenance of ventilation and do not depend on chemical drive.

Two other explanations for repetitive apneas during sleep are (1) that sleep apnea patients have more pronounced ventilatory oscillations during wakefulness and sleep, and (2) that these oscillations have the same amplitude as in normal individuals, but nonspecific excitatory stimuli contribute to a larger extent to sleep apnea patients' total respiratory drive. Apnea occurs rather than just swings in ventilation during sleep because sleep, in addition to reducing the respiratory stimulatory effects of hypoxia and hypercapnia, also depresses metabolic rate and the overall level of respiratory excitatory input.

An alternative idea is that recurrent apneas result from instability in the feedback control of breathing, which causes ventilation to cycle rather than maintain a constant level. Instability of feedback control or a spontaneous oscillatory phenomenon could cause central, obstructive, or mixed apneas if, in response to the cyclic changes in drive, the mechanical outputs of chest-wall muscles and upper airway muscles are not identical either in phase or in amplitude.

MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Significant changes occur in chest-wall and lung mechanics during sleep and can affect ventilation and later the efficiency of gas exchange, and upper airway resistance increases during sleep. For instance, in NREM sleep the ratio of rib cage to abdominal displacement is greater than during wakefulness, whereas in REM sleep it is less. These changes in movement may affect the distribution of ventilation in the lungs, increasing ventilation–perfusion mismatching, and so contribute to

hypoxia, necessitating changes in respiratory output and possibly initiating an unstable breathing pattern.

Negative pressures produced by the chest-wall muscles during inspiration tend to collapse the semirigid structure of the tissues forming the neck and pharynx. The degree of upper airway rigidity can depend on the long structures supporting the airway, on the soft tissue features of the upper airway, and on the level of activity in upper airway muscles. Studies suggest that the mechanical features of small airstream size and collapsible airway wall are essential in the pathogenesis of obstructive apneas. Furthermore, the spectrum of disease could relate to graded differences in these mechanical properties.

OBESITY

Several factors could predispose the obese patient to apneas during sleep. Hypoxemia occurs in the supine posture as a result of decreased functional residual capacity. Patients with obesity can show a decreased ability to respond with increased respiratory muscle output to added loading of the respiratory system. Another factor could be narrowing of the upper airway. Yet the fact remains that many obese people do not have sleep apnea or a history of snoring; neither can it be shown that sleep apneas cause obesity. Thus, the association between obesity and sleep apnea is quite indirect.

HEREDITY

Sleep apnea syndrome has been shown to exhibit familial clustering, and if snoring is considered as a variant of sleep apnea, the familial incidence of snoring and sleep apnea is quite striking. There is some evidence from cephalometric measurements that the arrangement of the jaw to the head and neck is familially determined. Conceivably, individuals with a certain structural framework would be predisposed to apneas. It is also known that there are familial traits in hypercapnic and hypoxic sensitivity; these could relate to the tendency to breathe periodically during sleep. It is not known if there is a familial trait involving the respiratory coordination of muscles of the chest wall and upper airway. In addition, obesity and alcoholism can be family traits and, to the extent that these factors are causally related to apneas, are bases for familial clustering of sleep apnea. However, this association is not strong enough for routine assessment of asymptomatic family members.

RESPIRATORY DEPRESSANTS: EXOGENOUS OR ENDOGENOUS

Patients with unrecognized sleep apnea may already be given hypnotic medications on the basis of their sleep complaint. However, studies using flurazepam on breathing during sleep have produced conflicting results on whether or not these agents produce apneas in healthy subjects. No study has shown that these drugs produce a syndrome of sleep apnea with associated daytime symptoms, yet it is best to avoid prescribing these medications to patients with sleep apnea.

On the other hand, in physiologic studies, alcohol has consistently been shown to promote apnea and, in particular, obstructive apneas during sleep in asymptomatic subjects and in patients. In one study it was shown that the number of episodes of respiratory disturbance during sleep doubled and that the effect of alcohol ingestion may even persist to the subsequent night's sleep. The mechanism by which alcohol promotes apneas may be through a relatively selective reduction in the respiratory output to the genioglossus muscle. What role alcohol has in the development of sleep apnea syndrome is unclear, but patients can benefit from abstinence from alcohol as a therapeutic intervention.

Do endogenous substances produce this syndrome? Naloxone has been given to patients with sleep apnea on the basis of speculation that opiate-like substances produce the problem, yet opiate receptor blockade does not affect apneas during sleep. There are sleep-promoting substances, but their role in sleep apnea has not been defined.

TREATMENT OF SLEEP APNEA: GENERAL MEASURES

Therapy is directed at sleep fragmentation and hypoxic exposure. Simple measures may be efficacious in many patients with sleep apnea. Initially, there should be a review of the patient for the presence of anatomic or medical conditions that, if reversed, would ameliorate or eliminate breathing disturbances during sleep. Because respiratory depressants seem to increase the appearance of respiratory disturbances during sleep, perhaps by elevating the P_{CO_2} threshold, withdrawal of respiratory depressants such as major tranquilizers, antihistamine, or alcohol is indicated. There are prophylactic measures on which to advise the patient. Preoperative sedation has been reported to be accompanied by some risk of lethal respiratory disturbances, so the patient should be advised to inform the anesthesiologist of his or her diagnosis before any elective surgical procedure. In addition, the excessively sleepy patient should not operate a motor vehicle or engage in activities during which sleep attacks would be hazardous. The risk of serious injury or death from accidents is possibly greater than that of the disease itself.

Metabolic diseases such as hypothyroidism may be associated with sleep apnea syndrome. Treatment with replacement hormones reverses the sleep apnea and clinical symptoms. Patients with sleep apnea and heart or respiratory disease, such as congestive heart failure or asthma, should be placed on maximal therapy for the concomitant disease. Of interest, treatment of hypertension will decrease apneic activity somewhat. Decreased circulation time and/or increased oxygenation may reduce the tendency for periodic behavior during sleep and decrease the incidence or severity of respiratory disturbances during sleep. Consequently, therapy is indicated for renal failure or congestive heart failure. In the patient with recent stroke or cerebrovascular disease, time may be all that is needed before respiratory stability will be restored. Treatment should be tailored to the individual patient and to the degree to which he or she is disabled by the breathing disturbances during sleep.

SURGICAL PROCEDURES

Tracheostomy

Tracheostomy bypasses the site of obstruction during sleep and is the most effective therapeutic maneuver for obstructive apnea. The procedure of choice is a semipermanent tracheal stoma, using skin flaps leading down to the edges of the tracheal fenestration. However, the tracheostomy may be technically difficult because of morphologic features such as obesity, a short neck, or a short mandible. Problems with stomal infection and granulation tissue often occur, and it may take a year or more before the tracheal site is well healed.

Tracheostomy is often not well tolerated because it can interfere with speech, exercise, and social interactions. Chronic cough, irritation from cold dry air, and positional pain or dyspnea are also common complaints. In some patients, revision of the tracheal stoma or custom-fit tracheostomy tubes are needed. Considerable education and counseling are advised both before and after the operation.

Plastic Procedures

Surgical correction of pathologic narrowing of the upper airway caused by enlarged tonsils, nasal polyps, macroglossia, or micrognathia is reported to improve signs and symptoms of sleep apnea. In prospective studies in which tonsillectomy has been performed for sleep apnea, it has been shown that obstructive apneas may persist, but their frequency is greatly diminished.

There are case reports to suggest that surgical intervention for a deviated nasal septum or for redundant nasal mucosa will reduce the symptoms and signs of sleep apnea. The rationale for these procedures lies in the association between increased nasal resistance and inspiratory pharyngeal occlusion. It should be noted that surgical manipulation of the posterior nasal cavity at the level of the velopharyngeal sphincter may in fact result in airway narrowing and precipitate the development of sleep apnea.

Extensive excision of soft tissue in the oropharynx, termed uvulopalatopharyngoplasty, may improve pharyngeal function during sleep. The procedure involves a submucosal resection of redundant tissue from the tonsillar pillars to the arytenoepiglottic folds. The indications for the procedure are the same as for a tracheostomy. In the series of patients reported in the literature, the success rate was approximately 60%, but success varied considerably from center to center. Most patients report symptomatic improvement; however, objective improvement of a reduction in the number or magnitude of respiratory disturbances during sleep is often absent. Patients with massive obesity or with anatomic narrowing of the airway may not show success with uvulopalatopharyngoplasty, whereas patients who snore but do not have frank obstructive apneas may do well. Potential complications of the procedure include speech and swallowing difficulties, in particular regurgitation of food. Some patients may have an increased number of respiratory disturbances during sleep after the procedure, but their recognition is obscured because snoring is absent. These “silent obstructions” may be as severe as apneas before surgical intervention.

Recently, new surgical procedures directed at increasing the size of the hypopharynx have been developed. Expansion hyoidplasty is a procedure directed at moving the hyoid arch forward by placing a prosthetic device in the hyoid arch. Other procedures include mandibular advancement, mandibular osteotomy, sectioning the hyoid, attaching the hyoid to thyroid cartilage, and midline glossectomy. With all these procedures, success in large series of patients remains to be determined.

MEDICAL TREATMENT

Nasal Sprays

There are case reports of successful treatment of obstructive apneas during sleep using nasal vasoconstrictive sprays. Apneas and arousals during sleep are more frequent when the nasal passage is occluded than when it is unoccluded. It is probable that an increase in baseline nasal resistance increases negative pharyngeal pressure on inspiration, thus magnifying the collapsing forces on oropharyngeal soft-tissue structures and promoting pharyngeal obstruction. Consequently, a trial of nasal (vasoconstrictive and antiinflammatory) decongestants is warranted in the patient in whom nasal obstruction is present.

Weight Loss

Even a 5% to 10% decrease in body weight can be accompanied by clinical and objective remission of sleep apnea syndrome in obese subjects. Few investigators, however, are enthusiastic about the long-term efficacy of dietary strategies, perhaps because adherence to dietary restrictions is difficult in the hypersomnolent patient.

Studies have documented that major surgical intervention (ileal bypass or gastric partitioning) for weight loss in obesity can reduce the number and severity of apneas and alleviate signs and symptoms of sleep apnea syndrome. It is interesting that with surgical treatment, large amounts of weight loss, on the order of 150 to 200 lb, was needed before a beneficial effect of weight loss can be demonstrated. Better treatments for obesity would have an immediate and major impact on the management and prevention of sleep apnea.

Oxygen Therapy

Studies of oxygen therapy in sleep apnea show inconsistent results. Certainly, in the patient with resting hypoxemia and cor pulmonale, 24-hr oxygen therapy can improve symptoms and cardiovascular performance, alleviating heart failure. Oxygen therapy appears to be effective in reducing or eliminating central apneas and hypopneic events. This relatively selective effect on central apneas occurs with oxygen therapy in patients who also have obstructive apneas. However, a beneficial effect of oxygen on upper airway obstruction during sleep cannot be found in every patient. Indeed, in some patients with obstructive sleep apnea syndrome, oxygen administration provokes respiratory acidosis. At the present time, one cannot predict which patient will respond to oxygen therapy.

Drug Therapy

General

Various drugs have been used in an attempt to specifically stimulate upper airway muscles in order to prevent obstructive apneas or to increase respiratory neural drive in general in order to alleviate central apneas or increase both upper airway and chest-wall muscle activation. Although this kind of therapy would seem optimal, it has had the least success and surprisingly has generated little interest in organized research. The efficacy of most proposed medical therapies has not been demonstrated. However, certain classes of medications have been used with some success.

Respiratory Stimulants

Good results have been reported in clinical demonstrations with acetazolamide and progesterone in patients with central apneas during sleep. Studies have shown that respiratory rhythmogenesis may be restored to some degree, thereby eliminating a need for other therapeutic measures. Patients who present with primarily central apneas during sleep are, however, in the minority of adult patients with sleep apnea syndromes. As a consequence, few large series have employed adequate clinical drug trials.

Agents with a progesterone-like activity have been tried in obstructive sleep apnea because of their apparent effectiveness in improving daytime sleepiness, cor pulmonale, and polycythemia in patients presenting with obesity, hypoventilation syndromes, and chronic mountain sickness. It is still unclear how progesterone specifically stimulates breathing. The two clinical demonstrations of progesterone usefulness in sleep apnea have suggested that if patients are considered as a group, progesterone has little effect on obstructive sleep apnea. Yet each study has shown that certain patients may respond with a reduction in obstructive apneas and an amelioration of symptoms. This subclass of patients appears to be those who present with hypercapnic respiratory failure. Both studies, however, lacked adequate control trials and were not intended to be adequate clinical trials of efficacy.

There are reports of the use of nicotine, acting both as a central and as a peripheral respiratory stimulant, in the management of obstructive apneas during sleep. Although effective, nicotine has a very short half-life, and it is probably not a clinically practical drug. Drugs directed solely at stimulation of the carotid body have met with only partial success. These drugs include the dopamine-blocking agent prochlorperazine and the orally administered almitrine. A third medication, strychnine, a glycine antagonist, reduces the threshold for activation of the motor neuron and has been tried in selected patients with obstructive sleep apnea. This report suggested that the beneficial effects of strychnine were produced by elevating tonic activity in upper airway muscles rather than by altering their respiratory-related activation. In summary, respiratory stimulants appear to be more efficacious in patients with primarily central apneas, and use in patients with obstructive sleep apnea may be restricted to those with hypercapnic respiratory failure. A most likely candidate for a trial of progesterone, for instance, would be a patient who presents with obesity hypoventilation syndrome, in whom the drug might be given solely on the basis of daytime signs of polycythemia and cardiopulmonary failure.

Antidepressants

The tricyclic medications protriptyline and clomipramine have been used in the therapy of obstructive sleep apnea. The rationale for their use is that they suppress REM sleep, a sleep stage in which apneas occur frequently and the stage of sleep in which there is often intermittent inhibition of chronic activity in postural muscles, including those of the upper airway. Several uncontrolled trials with protriptyline have suggested that it may have some use in diminishing the number of apneas or in improving oxygenation. The one double-blind trial in the literature found that both 2-week and 6-month administrations were associated with a mild reduction in daytime sleepiness and an unexplained increase in oxygenation associated with a diminished time in REM sleep. Side effects of the drug include drying of the mouth, urine retention, and increased cardiac arrhythmias, including ventricular arrhythmias, and these may limit its use.

More recently, more specific agents, such as the serotonin receptor antagonist fluoxetine, have been shown to reduce apneic activity. The precise role of these agents in the management of sleep apnea remains to be determined.

Hypnotic Drugs

Although it may seem odd to suggest that sleep-apneic patients be given a drug that promotes sleep, the argument could be made that these agents might increase the tendency for sleep and could, at least theoretically, reduce arousals and sleep fragmentation. It is known that apneas infrequently occur at deep stages of sleep (stages III to IV) and that in healthy subjects apneas appear only in early sleep stages I or II or in the transition between light and deep sleep. There is one report that found that the sleep-promoting substance L-tryptophan can decrease the number of obstructive, but not central, apneas during sleep. A mechanism of action of this drug was presumed to depend on central neural serotonergic transmitters and was related to its ability to promote sleep. There are no large clinical trials of this medication.

Other Agents

A variety of other agents have been tried without success. Bromocriptine, theophylline, and naloxone are three that have been tried in a small number of patients with sleep apnea and have not shown immediate success; therefore, they cannot be recommended even for clinical trials.

The enthusiasm for medical therapy is thus quite moderate at this particular time. It is hoped that with greater understanding of the neurophysiological basis of respiration in sleep, newer pharmacologic agents can be developed. It should be noted that perhaps one of the reasons for the mixed success of respiratory stimulant drugs in the treatment of apneas in general could be their relative unselectiveness in stimulating muscles. For instance, an increase in chest-wall muscle activity without a corresponding increase in upper airway muscle activity might actually worsen obstructive apneas. Indeed, in some of the clinical trials with progesterone, this actually may have occurred.

MECHANICAL DEVICES

Neural Stimulation

Electric pacing of the phrenic nerve can achieve adequate ventilation in the absence of spontaneous respiration in the patients with cervical injuries. Phrenic nerve pacing at the level of the thoracic inlet also has been successfully attempted in treating patients with only central sleep apnea. Yet stimulation of the diaphragm without upper airway muscle activation may lead to inward collapse of the upper airway and chest wall, producing upper airway obstruction and hypoventilation. Hence, a tracheostomy is necessary when the phrenic nerves are paced. Problems inherent with phrenic pacing result from the direct damage to the phrenic nerve occurring with operative handling or with postoperative infection or inflammation around the electrode. Experience and careful surgical technique will minimize these complications. Pacing with electrodes placed directly in the muscle may achieve equal or greater respiratory output in the diaphragm than phrenic pacing.

Ventilatory support also can be achieved by placing the patient with central apneas on mechanical ventilation during sleep. A ventilator attached to a tracheostomy is tolerated well by both children and adults. Other measures such as rocking beds, the iron lung, or a cuirass can effectively accomplish adequate gas exchange in patients with central apneas. However, the creation of negative pressures in the chest by an iron lung or cuirass may cause upper airway obstruction by a mechanism identical to that occurring with phrenic nerve pacing. Pacing can be applied to treat obstructive apneas. Initial reports suggested that transdermal pacing of the protrusor muscles of the tongue could shorten obstructive apneas. Devices were constructed that identified an apnea from the absence of oronasal flow and delivered electric stimulation to electrodes placed under the chin. A second generation of electric stimulators is being developed, one of which uses an implanted electrode on the hypoglossal nerve. It will be some time before a role for these devices in the routine care of patients is established.

Dental Devices

Intraoral appliances are gaining wider acceptance in the treatment of obstructive apneas. Some devices are designed to tug the tongue forward; others to protrude the mandible or, at the very least, prevent the mandible from retruding with sleep. There are anecdotal reports and reports of collections of patients that attest to the potential usefulness of oral appliances. At the present time there is an ongoing randomized trial comparing an oral device to nasal CPAP (see below) in the treatment of mild to moderate obstructive sleep apnea.

Experience with this therapy is limited; however, common sense suggests that it may be an attractive alternative if CPAP is not tolerated. Certainly, there must be close cooperation between dental and medical professionals when this therapy is chosen; however, indications and cost-effectiveness are not developed at present to the degree that this form of treatment can be considered routine medical practice.

Nasal CPAP

Continuous positive pressure applied to the nose (nasal CPAP) may eliminate obstructive apneas during sleep in adult patients with sleep apnea syndrome. Nasal CPAP seems to act as a pneumatic splint, preventing airway collapse.

Nasal CPAP is effective in the long-term treatment of obstructive sleep apnea and in the prevention of snoring. The effect is dependent on the level of positive pressure applied to the upper airway, and the optimal levels of pressure differ among patients. In general, though, at lower levels of pressure (3 to 6 cm H_2O), apneas are eliminated, but episodes of partial upper airway obstruction (snoring) persist. At higher levels of pressure (5 to 15 cm H_2O), regular breathing tends to be restored. An example of the effect of nasal CPAP in eliminating apneas is shown in Fig. 6. The effect of different levels of nasal CPAP on oxygenation over time is shown in Fig. 7. Most reports suggest that positive pressures must be present over the entire respiratory cycle for nasal CPAP to be effective.

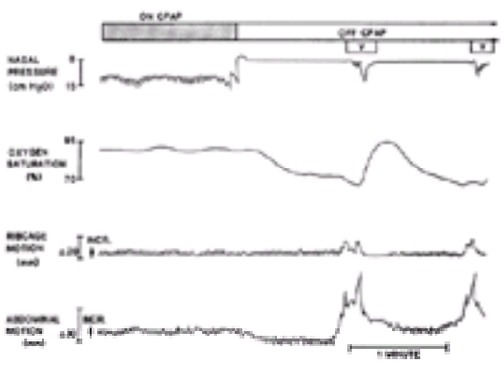

FIG. 6. The effects of approximately 14 cm H_2O positive pressure applied to the nose (nasal CPAP) on oxygen saturation and rib cage and abdominal motion during sleep. On CPAP, oxygen saturation was stable and approximately 90 percent. Respiratory efforts by the rib cage and abdomen were regular. When CPAP was abruptly discontinued, episodic upper airway obstruction interrupted by periods of ventilation (V) occurred, accompanied by hypoxemia. The patient is in REM sleep.

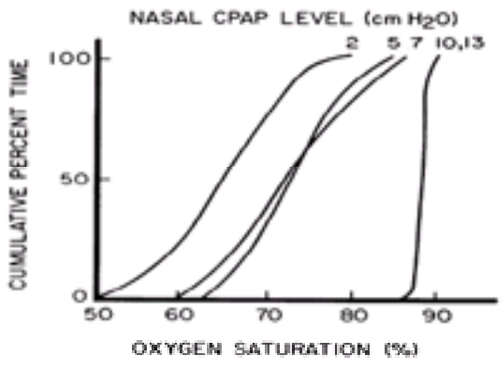

FIG. 7. The changes in oxygen saturation over time in one patient in different levels of nasal CPAP during a single study. Levels of 2 and 5 or 7 cm H_2O were accompanied by repetitive obstructive apneas and partial upper airway obstruction, respectively. At 10 or 13 cm H_2O, apneas and upper airway obstruction were eliminated.

Some patients can use their device every second or third night and remain free of apnea on the intervening nights. Symptoms always recur if CPAP is completely withdrawn, but this may take several days and occurs gradually, so that short interruptions of therapy for surgery or acute medical illnesses are usually well tolerated. Late failures of nasal CPAP occur occasionally. Some are caused by poor application of the mask, so that pressure is lost; some result from too low a pressure being initially prescribed; and some are caused by an increase in the pressure required to prevent apnea. Factors such as alcohol use, hypothyroidism, and obesity may worsen airway stability.

Bilevel ventilation for obstructive apneas is the application of an inspiratory assist over and above the expiratory pressure required to keep the pharyngeal airway open. The medical indications for this approach appear to include the concomitant finding of chronic hypoventilation in addition to obstructive apnea. Titration and chronic use of bilevel ventilation are facilitated by the common patient perception that the inspiratory assist is more comfortable, perhaps because with bilevel pressure, pressures in expiration are generally lower than those with CPAP. There are no direct comparisons of these interventions despite reports that application of CPAP alone over time improves alveolar ventilation. Clinical trials will be needed to determine the balance between patient comfort and medical necessity.

Absolute contraindications to nasal CPAP therapy are complete nasal obstruction and a communicating fracture of the base of the skull. Patients generally accept CPAP therapy fairly well, but in most large series there are some patients (30% or so) who do not. Side effects of therapy include feelings of suffocation, nasal drying or rhinitis, ear pain, and conjunctivitis. Inner ear and eye problems are said to resolve spontaneously and do not recur with continued CPAP therapy. Pulmonary

function does not deteriorate with nasal CPAP, and in patients with lung disease there have been no adverse effects.

PSYCHOSOCIAL FACTORS IN TREATMENT

Sleep apnea has a profound effect on the personal and family life of the patient because excessive sleepiness compromises the patient's ability to solve problems at work or at home or to perform even simple tasks. Family members may suffer injury from automobile accidents caused by the patient falling asleep at the wheel. In some instances, chronic delinquency may result from absent parental authority. Patients who are excessively sleepy limit social activities out of embarrassment. These and other family conflicts may result in personal and financial losses before a diagnosis is sought or made.

Treatment of the respiratory disturbance during sleep also entails psychological and social adjustments. Tracheostomy may change a patient's body image. Fears of inviting social ridicule or limitations in sexual activity are frequently present in patients facing the possibility of a tracheostomy. If the patient and family feel reasonably informed of therapeutic alternatives, they will be better able to cope with a tracheostomy. Supervised meetings of the patient and family with other patients and their families who have faced the same problem may be of help in this process.

Also, after effective treatment, changes in family dynamics may occur as the patient becomes a more active person. The health team can be helpful in assessing how both the patient and the family are adapting to treatment. Furthermore, employer education is often necessary before the patient can return fully to work.

NEED FOR RESEARCH

Sleep apnea is no longer a rare disease, and those with sleep apnea have a chronic illness, much like asthma or diabetes. The incidence of those meeting minimal criteria for clinical illness is 2% to 5%; yet many, perhaps one in 20, are unrecognized. Several efforts are under way to determine whether the lack of recognition results from ignorance of the medical profession or lack of impact of sleep apnea on human health, or both. Research defining the relationship of sleep apnea to cardiovascular risk is perhaps a high priority. One problem is that studies of sleep apnea have been either clinic-based or cross-sectional, and little information is available regarding the natural history of sleep apnea or symptoms attributable to sleep apnea. This information is crucial in areas of both treatment and prevention. Compared to information on the adult male, little is known of the prevalence in women or children.

Formal approaches to decision making in the management of sleep apnea are needed. Professional societies are beginning to see the need for standardized assessment; such criteria would provide a uniform method for recruitment of patients into clinical trials. There are few studies of the impact of sleep apnea from a patient's point of view. Indeed, for some patients with mild to moderate illness, the problems of current therapy are not worth the perceived benefit; recognizing this may prevent unwanted and perhaps unnecessary therapeutic adventures. Furthermore, there has been little formal assessment of ways to improve treatment acceptance and in the manner in which the patient and his or her physician decide on what treatment to use. Finally, primary care physicians will need to be involved in the design of recognition and treatment strategies.

Another new consideration is how sleep apnea might affect utilization of health care resources and costs to society. The Report of the National Commission on Sleep Disorders estimated that between 7 and 18 million people in the United States may meet minimal criteria for OSA, using a definition of an AHI > 5; 1.8 to 4 million people have higher levels (AHI > 15). Cost estimates related to diagnosis and treatment in 1991 are between $3 million (for the most severely affected) and $40 billion (for subjects with only heavy snoring and low levels of apnea), so there is an immediate need to establish thresholds for treatment. If current cardiovascular risks for OSA are correct, untreated OSA may contribute to 38,000 excess deaths per annum, and that $3 million to $2 billion of the health care costs associated with the treatment of vascular diseases may be attributable to untreated illness.

Behavioral and performance deficits associated with OSA could carry hidden costs from morbidity and mortality for motor vehicle crashes and industrial accidents; reports utilizing a variety of indirect sources and assumptions estimated an indirect cost in the billions of dollars. Obstructive sleep apnea is the most common medical cause for sleepiness, suggesting that it may play a significant role in these accidents of sleepiness or inattention. There must be increased educational efforts about the importance of adequate sleep and the perils of sleepiness to permit greater recognition of disorders of sleep by the medical community.

VARIANT PRESENTATIONS OF SLEEP-DISORDERED BREATHING/UPPER AIRWAY DISEASE

Patients with disease of the nose, larynx, and pharynx present with two major classes of sleep problems, sleep apnea and aspiration. Aspiration of secretions may occur because of excessive production of mucus, as exemplified by chronic allergic rhinitis, or because of inadequate neuromuscular tone, as in bilateral recurrent laryngeal nerve paralysis. In both instances, there occur frequent arousals from sleep associated with cough and/or a choking sensation. In sleep, and, in particular, in REM sleep, the cough response is less than during wakefulness. As a result, greater amounts of secretions are tolerated before a cough ensues. After awakening, this larger amount of material may precipitate paroxysmal cough. It is important to recognize that in these cases the disturbed sleep and what might sound like apnea result from problems with secretions or aspiration. Treatment with hypnotic medications may be particularly harmful because greater amounts of secretions may be tolerated before arousal from sleep, increasing the likelihood of aspiration injury to the lungs. In the patient with allergic rhinitis, nasal decongestants given before bedtime may be helpful. In the patient with neuromuscular impairment, elevation of the bed may diminish the tendency to aspirate pharyngeal contents.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with chronic obstructive pulmonary disease (COPD) may present with a variety of sleep problems. Nocturnal cough can be related to bronchitis. Insomnia may be the consequence of therapy with drugs such as aminophylline. Hypoxemia during sleep may occur as a consequence of mechanical impairment of the airways already present during wakefulness but exacerbated by the normal changes in gas exchange during sleep. There seems to be an association between the occurrence of hypoxemia only during sleep and the development of cor pulmonale in the patient with moderately severe COPD. Recognition of these individuals occurs when it is noticed that features of hypoxemia and hypercapnia are not associated with a severe mechanical defect on pulmonary function testing. Certainly other diagnostic entities such as recurrent pulmonary emboli or chest-wall muscle weakness also should be explored. Hypoventilation will occur during sleep not only because of sleep apnea but also because of changes in ventilation–perfusion matching and a decrease in respiratory drive, especially during REM sleep. If the problem is sleep apnea, there is usually historical evidence for snoring and restless sleep, and the patient should be treated appropriately (see above). If apneas are not the problem, treatment with supplemental oxygen only during sleep may be indicated.

ASTHMA

The most common sleep problem associated with asthma is cough. Cough and arousals from sleep with cough may be the presenting complaints of the patient with asthma and increased airway reactivity. Cough may result from changes in airway smooth-muscle tone during sleep and of bronchoconstriction during REM sleep. There is some indication that gastroesophageal reflux may precipitate bronchoconstriction; however, patients with reflux are usually symptomatic during wakefulness as well as sleep. Cough occurring in the patient with uncomplicated asthma may indicate inadequate therapeutic effect of medication throughout the night or exacerbation of airway disease.

A related clinical problem is that of “morning dipping,” which refers to the fall in lung function that occurs in the early morning hours. Morning dipping has been reported in severe asthmatic attacks and has been held somewhat responsible for deaths from asthma. Morning dipping represents an extreme form of diurnal variation in lung function present in most patients with airway reactivity. Reports describing morning dipping emphasize that lung function measured some hours later during the day may be normal, whereas values during the night may show moderately severe airway obstruction. Symptoms suggestive of morning dipping are an indication that additional treatment is needed. If nocturnal symptoms are persistently bothersome, instruction of the patient in the use of a peak-flow measurement device and in the frequent recording of values of peak flow at night may be helpful in identifying changes in lung function throughout the day and in monitoring the effectiveness of medications over the course of a night's sleep.

NEUROMUSCULAR DISORDERS

Respiratory disturbances caused by obstructive apneas during sleep may occur because upper airway muscles such as the genioglossus are affected by the underlying disease process. Inadequate respiratory activation of upper airway muscles makes the upper airway vulnerable to collapse during inspiratory efforts by the muscles of the chest wall. Indeed, respiratory failure in the patient with neuromuscular disease may be related to upper airway muscle disease and not have as dire prognostic consequences as primary involvement of the chest-wall muscles such as the diaphragm.

Disturbances of sleep and respiration during sleep may be the first indication of involvement of the respiratory system in the patient with neuromuscular disease. Occasionally, sleep fragmentation and the effects of sleep deprivation dominate the clinical presentation of the patient with neuromuscular disease. After treatment for sleep-disordered breathing, the clinical manifestations of the primary neuromuscular disorder may not appear so severe.

KYPHOSCOLIOSIS

Severe kyphoscoliosis is associated with restrictive lung disease and cor pulmonale; however, recently it has been shown that treatment of hypercapnic respiratory failure by tracheostomy with or without positive-pressure ventilator support during sleep can reverse cor pulmonale and improve the appearance of the chest roentgenogram.

INTERSTITIAL DISEASES

Restrictive lung disease also can be associated with respiratory disturbances during sleep because of cough or hypoxemia. Patients also may have a concomitant sleep apnea. Sleep hypoxemia may be a factor in the development of pulmonary hypertension. Treatment of sleep hypoxemia is directed at apneas, or if apneas are not present, a trial of oxygen therapy may be indicated.

A restrictive defect on pulmonary function testing and interstitial fibrosis on the chest roentgenogram can reflect a history of chronic aspiration. There are ongoing investigations on aspiration during sleep and its acute and chronic effect on lung function. During sleep, the tone of the gastroesophageal junction relaxes, allowing stomach contents to regurgitate to the level of the pharynx. In patients in whom such a phenomenon is suspected, it may be useful to measure pH levels in the pharynx and esophagus during sleep in order to document gastroesophageal reflux during sleep as a potential cause for aspiration pneumonitis.

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CHAPTER

45 Adaptation and Maladaptation to High Altitude

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INTRODUCTION

Oxygen delivery to the tissues depends on an adequate supply of oxygen at each step of the oxygen transport chain from the inspired air to the mitochondria. The inspired partial pressure of oxygen is approximately 21% of the atmospheric pressure, which decreases predictably at altitudes above sea level (Table 1). Humans at high altitude, therefore, must overcome the disadvantage of ambient hypoxia by making a number of adaptations to optimize the availability of oxygen to the tissues.

Altitude		Barometric pressure (mm Hg)	Inspired P_{O_2} (mm Hg)
Meters	Feet		
0	0	760.0	159.1
1000	3,280	674.4	141.2
2000	6,560	596.3	124.9
3000	9,840	525.8	110.1
4000	13,120	462.8	96.9
5000	16,400	405.0	84.8
6000	19,680	354.0	79.1
8000	26,240	267.8	56.1
8848	29,028	253.0	43.1

[a] Values except 8848 are taken for midlatitude (45°N). There is greater variation at higher latitudes. Modified from Altman PL, Dittmer DS, eds., *Respiration and Circulation*. Bethesda, MD: Federation of American Societies for Experimental Biology, 1971; 12–13.

TABLE 1. *U.S. standard atmosphere: Altitude, barometric pressure, and inspired partialpressure of oxygen*[a]

For the sojourner, easy access to high altitude for work or recreation requires that the body must undergo rapid changes to overcome the disadvantage of hypoxia; for the nearly 30 million people who live at a high altitude in Asia, Africa, and North and South America, their bodies have had generations to adapt to the hypoxic stress. A large majority of travelers and high-altitude dwellers are successful in overcoming this stress, but some do not adapt well and suffer from acute and chronic altitude illness. This chapter, therefore, first reviews what is known about both acute and chronic adaptation to high altitude and then reviews the illnesses that occur when the body maladapts.

ADAPTATION

Abrupt exposure to high altitude (more than 3000 m) can result in illness and even death. This lesson was tragically learned in 1875 when two of three scientists died while exploring altitudes of over 8000 m in their hot-air balloon, the Zenith. Gradual ascent to these same heights, on the other hand, permits a number of physiological adaptations to take place that allow some exceptional humans to function quite well. Populations have lived for centuries as high as 5000 m, and brief forays above 8000 m, where the atmospheric pressure is a third that at sea level, are well documented and are a tribute to the resiliency of human physiology.

In order to optimize oxygen delivery, important compensations take place at each step of the oxygen cascade, which has a number of components: ventilation, matching of ventilation with blood flow, diffusion of oxygen from the air to the blood, circulation of the blood, diffusion of oxygen from the red blood cell to the tissue, and oxidative metabolism in the cell. The first portion of this chapter reviews each of these steps, beginning with the lung.

Pulmonary Adaptation

Ventilation

Acute Ventilatory Response

An increase in alveolar ventilation occurs immediately on ascent to a high altitude. The partial pressures of oxygen and carbon dioxide in the alveolus reflect the degree of hyperventilation that attempts to preserve oxygen partial pressure. For instance, at an extreme altitude (summit of Mt. Everest, 8848 m, 253 mmHg), alveolar ventilation in a climber increases to maintain an alveolar partial pressure of oxygen of about 32 mmHg and of carbon dioxide of about 8 to 10 mmHg. Lower altitudes have a proportionately lower degree of ventilation.

The increase in ventilation is a result of a complex interaction of physiological events, mediated largely by the hypoxic stimulus to the carotid body. The course of the ventilatory response is what constitutes ventilatory acclimatization. There is individual variation in this response, but essentially the pattern of any given level of high altitude is one of an abrupt increase in ventilation followed by a more gradual increase over the next 10 to 14 days to a plateau (Fig. 1). The carotid body plays a primary role in this acute ventilatory response, which may be blunted in part by the resulting alkalosis. The classic explanation for the subsequent ventilatory events goes as follows: Excretion of bicarbonate by the kidneys over days in compensation for the respiratory alkalosis partially restores the acid–base status, resulting in further respiratory stimulation.

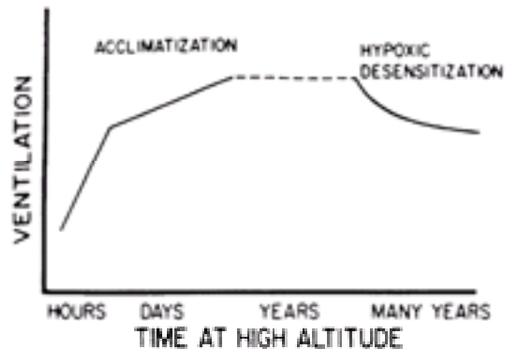

FIG. 1. The time course of ventilatory adaptation to high-altitude exposure. (From Weil JV. Ventilatory control at high altitude. In *Handbook of Physiology: The Respiratory System, Vol 2, Control of Breathing, Part 2.* Bethesda, MD: American Physiological Society, 1986.)

An arterial alkalemia is still present, however, and Severinghaus and colleagues presented data showing a cerebrospinal fluid (CSF) acidosis, which they claimed was the central stimulus for ventilation. Subsequent investigators at altitudes from 3000 to 4000 m documented that in humans and animals, both blood and CSF alkalosis developed in parallel during acclimatization. Additionally, a lower but persistent hyperventilation continued on descent. In light of the loss of hypoxic stimulus on descent and the blood and CSF alkalosis, a further explanation was sought.

The CSF may not reflect the actual milieu around the chemosensors. Data from brain interstitial and intercellular fluid in animals show an acidosis during hypoxic exposure, which may account for stimulation of ventilation. Recent data may shed light on the ongoing respiratory stimulation in the face of blood and CSF alkalosis. Ventilation is stimulated by hypoxia, leading to a degree of hypocapnia that is proportional to the magnitude of ventilation. Hypocapnia decreases cerebral blood flow, which, in addition to a leftward shift of the oxygen–hemoglobin dissociation curve by the respiratory alkalemia, may result in a decreased delivery of oxygen to the brain and subsequent anaerobic metabolism and tissue acidosis. A study in humans that used nuclear magnetic resonance (NMR) spectroscopy before and after a 7-day exposure to a simulated 4300-m altitude in a hypobaric chamber, however, failed to document brain tissue acidosis.

A further increase in ventilation is inhibited by a central suppression of ventilation. After 15 to 25 min of acute hypoxic exposure, ventilation decreases 25% to 30%, which is thought to be secondary to the action of neurotransmitters and a decrease in the metabolic rate in the brain, even though ventilation is elevated to a greater degree than the decrease in the metabolic rate alone would dictate. Acutely, however, true depression of ventilation with hypoxia does not occur when the partial pressure of arterial oxygen falls below 20 mmHg. A full understanding of the ventilatory adaptation to altitude is clearly lacking. A further stay at a high altitude for the sojourner results in an improvement in arterial oxygen saturation secondary to a gradual increase in ventilation over a fortnight or so. At extreme altitude, ventilatory adaptation may take weeks or months or may never be complete. The mechanism of this subsequent adaptation is not understood, but an increased sensitivity of the carotid body has been observed in humans and animals and must play an important role in the progressive hyperventilation. Carbon dioxide sensitivity, which is mediated primarily in the central chemosensors, has also been shown to increase with time at a high altitude and may, therefore, interact with input from the carotid body to effect an increase in ventilation.

On descent, even after the hypoxic stimulus has been removed, ventilation is greater for at least a couple of days than it was before the ascent. This phenomenon may be secondary to the rise in carbon dioxide that occurs as the hypoxic stimulus is removed.

Chronic Ventilatory Response

Alveolar ventilation and hypoxic chemosensitivity decrease in most lifelong residents of high-altitude regions (see Fig. 1). This decrease in hypoxic drive occurs in spite of a hypertrophy of the carotid bodies and is proportional to both the altitude and the duration of habitation. Because the mechanics of breathing entail a metabolic cost, it is conceivable that well-adapted high-altitude natives have invoked other mechanisms to improve oxygen transport to the mitochondrion while minimizing the metabolic cost with lower alveolar ventilation. The relative hypoventilation of the high-altitude native compared to sojourners may predispose some populations to chronic mountain sickness (CMS), which involves excessive hypoxemia and hypoventilation, pulmonary hypertension, polycythemia, and decreased cerebral function (see Chronic Mountain Sickness). Natives of the Tibetan and Nepalese Himalayas, in whom CMS is very rare, are reported to have less blunted alveolar ventilation and hypoxic chemosensitivity than other high-altitude dwellers, especially those in the Andes of South America, where CMS is much more common, but this issue is not fully resolved. This intriguing difference suggests an evolutionary influence wherein the Tibetans who have lived at a high altitude much longer than the South Americans have physiological characteristics that have led to more successful tolerance of high altitude. A genetic factor is also theoretically possible.

Functional and Structural Changes

Lung mechanics are affected at least transiently on ascent to a high altitude. Increased blood flow and central blood volume and a possible increase in interstitial fluid may lead to a decreased vital capacity, an increased residual volume, and decreased lung compliance. This explanation remains speculative. More recent observations in a high-altitude chamber during a 40-day simulated ascent of Mt. Everest showed that vital capacity began to decrease at 4572 m (P_B 429 torr) and was down 14% on the summit (P_B 250 torr). Increased lung water, which usually resolves on acclimatization, also has been noted. High-altitude dwellers in South America, on the other hand, have large chests on physical examination, accompanied by larger vital capacities, in comparison to low-altitude dwellers. These volumes remain increased in natives who descend to lower altitudes. The younger the age that the subjects begin living at a high altitude, the more pronounced is this characteristic. Similar augmentation of lung growth has been induced in rats exposed to hypobaric hypoxia.

Gas Exchange

The increased ventilation on ascent to a high altitude results in an increased alveolar partial pressure of oxygen, but the arterial oxygen content depends on the transfer of oxygen from the alveolus to the capillary and red blood cells. This step requires matching of ventilation ($\dot{V}_A$) to perfusion ($\dot{Q}$) and the diffusion of oxygen to hemoglobin in the red blood cell.

The increase in ventilation is matched in part by an increase in cardiac output and pulmonary blood flow. Alveolar hypoxia leads to pulmonary vasoconstriction, which at rest improves the $\dot{V}_A/\dot{Q}$ match primarily by increasing blood flow to the underperfused portions of the lung, which are usually areas of high $\dot{V}_A/\dot{Q}$. This redistribution of blood flow results in greater homogeneity of $\dot{V}_A/\dot{Q}$.

The next step in gas exchange relies on diffusion of oxygen to the blood. This transfer depends on a pressure gradient for oxygen from the alveolus to the capillary, diffusion capacity of the alveolar–capillary interface (D_M), capillary blood volume (V_C), and the surface area for gas exchange. A true diffusion limitation for oxygen transfer exists at high altitudes. This phenomenon occurs for several reasons. With increasing altitude, the lower alveolar partial pressure of oxygen results in a lower alveolar–capillary oxygen pressure gradient. Full equilibration of oxygen to the blood is also dependent on the transit time of the red blood cell across the pulmonary capillary, usually requiring at sea level about 0.25 sec, one-third of the estimated 0.75-sec normal transit time. At high altitude, this estimated resting pulmonary transit time may not allow enough time for full equilibration. This problem is accentuated during exercise, when an increased cardiac output shortens transit time. For example, the circumstances at the summit of Mt. Everest, where the barometric pressure is about 250 mmHg, are expressed by a model for this diffusion limitation with given values for hemoglobin concentration, oxygen face area consumption ($\dot{V}_{O_2}$), diffusion capacity (D_M), acid–base status, and capillary transit time as shown in Fig. 2.

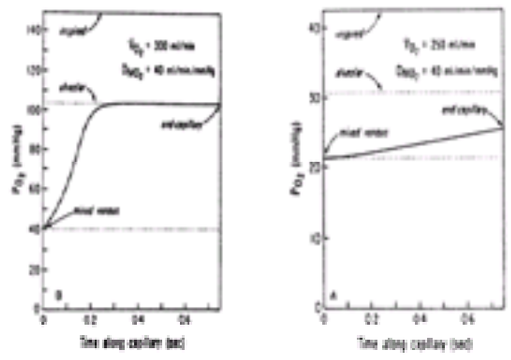

FIG. 2. Comparison of the calculated time course of partial pressure of oxygen in the pulmonary capillary of a climber at rest at sea level **(left)** (P_B = 760 mm Hg) and the summit of Mt. Everest **(right)** (P_B = 250 mm Hg). Adequate time for equilibration is available at sea level, whereas at 8848 m full equilibration is not possible. P_B, barometric pressure; $\dot{V}O_2$, oxygen consumption; D_MO_2, diffusion capacity of oxygen at the alveolar–capillary interface. (From West JB, Wagner PD. Predicted gas exchange on the summit of Mt. Everest. *Respir Physiol* 1980;42:1.)

An important factor in this process at extreme altitude may be relatively high oxygen–hemoglobin affinity secondary to respiratory alkalosis found in some high-altitude animals and in climbers at extreme altitudes. The diffusion capacity of the lung (D_L) may be more optimal in high-altitude natives secondary to either an increased capillary surface area (D_M) or pulmonary blood volume (V_C), which may compensate for the slightly lower level of ventilation at rest and during exercise.

Cardiovascular Adaptation

Cardiac Response

The cardiac response to high altitude also counteracts the stress of hypoxia and optimizes oxygen transport. To maintain a viable oxygen consumption in light of a decreased arterial oxygen content at a high altitude, heart rate increases, which results in a greater cardiac output. An accompanying elevation of catecholamines suggests that they mediate the increase in chronotropic effect on the heart. Subsequently, over the next few days, resting heart rate decreases as other compensatory mechanisms are invoked. Stroke volume decreases secondary to either a lower plasma volume or an increased pulmonary vascular resistance.

During exercise at high altitudes, the relationship between cardiac output and work is maintained, but both maximal work rates and cardiac output achieved at sea level are not reached at high altitudes. Both stroke volume and maximal heart rate are lower at high altitudes. There may be an impairment of stroke volume secondary to increased pulmonary vascular resistance, a decrease in left ventricular volumes secondary to right-to-left septal deviation from pulmonary hypertension, a decrease in myocardial contractility, or general constriction from the pericardium. The lower maximal heart rate is more marked in sojourners; may be secondary to hypervagal tone, hypoxic myocardial depression, or dysfunction of electrical conduction; and may be a major factor in the decrease in maximal exercise at high altitude. There are, however, few data in sojourners to support these possibilities, and it is now generally thought that the cardiac response is appropriate for the amount of work that is being done, which is limited by other factors. Studies in a few high-altitude natives suggest that they may not have a limitation to maximal heart rate at high levels of exercise, but further work is needed to elucidate this question.

Acute exposure to high altitudes results in an increase in systemic blood pressure and systemic vascular resistance both at rest and during exercise, whereas the dweller at a high altitude may actually develop a lower systemic blood pressure, perhaps secondary to microcirculatory vasodilation.

Pulmonary Vascular Response

Pulmonary artery pressure and pulmonary vascular resistance increase acutely at high altitudes, and this is secondary to the hypoxic pulmonary vascular response (HPVR). This initially results in improved $\dot{V}_A/\dot{Q}$ matching but may progress to $\dot{V}_A/\dot{Q}$ heterogeneity and possible interstitial edema.

The HPVR does not become marked until an alveolar partial pressure of oxygen (PO_2) of 60 mmHg or less is reached, and as with the ventilatory response to hypoxia, there is individual and interspecies variation of HPVR. Prolonged exposure to hypoxia may lead to pulmonary hypertension. Sojourners may have a more reactive HPVR than high-altitude natives. Smooth muscle hypertrophy occurs at the pulmonary arteriolar level and may be the mechanism of HPVR. Fibrosis of the intima, which may not be reversible, was found in high-altitude dwellers, suggesting a more fixed pulmonary vascular resistance. There is evidence that some high-altitude natives who have adapted well to the high altitude may have normal pulmonary artery pressures and no hypertrophy of the smooth muscle of the pulmonary arterioles.

Hematologic Adaptations

The purpose of optimizing $\dot{V}_A/\dot{Q}$ matching is to make oxygen available to hemoglobin in the red blood cell, which then carries oxygen in the vascular compartment to tissues where it is consumed. At high altitudes, two major adaptations of the carrier mechanism take place to facilitate delivery: (1) The number of red blood cells is increased by the process of erythropoiesis, and (2) the configuration of the hemoglobin molecule changes to alter the affinity of hemoglobin for oxygen in order to optimize the loading and unloading of oxygen.

Erythropoiesis

The decrease in arterial oxygen partial pressure and subsequently in oxygen content that occurs with progressive hypobaria at high altitude is counterbalanced in part by an increase in hemoglobin concentration and subsequent oxygen-carrying capacity. The rise over the first day or so is secondary to hemoconcentration from a diuresis, whereas the continued rise over the ensuing 2 to 3 weeks is a result of increased red blood cell production, which is stimulated by a humoral substance secreted in the kidney cell, erythropoietin. Erythropoietin levels increase rapidly according to the hypoxic stimulus and then decline a bit in the face of a continued rise in hemoglobin. Erythropoiesis stops abruptly on descent, and hemoglobin concentrations return to sea-level values in approximately 3 weeks.

A striking feature of the erythropoietic response is the variability between individuals and between different highland populations, which may reflect less-than-optimal adaptations to comparable hypoxic stress. For instance, in the Himalayas at 3600 m, hemoglobin levels of 16.1 ± 1.2 g/dl have been documented, whereas in the Andes at the same altitude, the values are 18.2 to 19.0 g/dl. Although the increase in hemoglobin concentration augments arterial oxygen content, an actual decrease in oxygen delivery may ensue if hyperviscosity of the blood limits perfusion to the microvasculature of the exercising muscle. Climbers on Mt. Everest undergoing isovolemic phlebotomy to decrease their hematocrits from 60% to 50% had an increase in psychometric function while not experiencing a decrease in aerobic capacity. Hemodilution in high-altitude natives of the Andes, achieved by decreasing the hematocrit 20%, resulted in an improved exercise performance. Excessive polycythemia in the highland dweller is discussed later.

Oxygen–Hemoglobin Affinity

The role of oxygen–hemoglobin affinity in oxygen delivery is not fully understood. Conditions of stress, such as fever and acidemia, are associated with a rightward shift of the oxygen–hemoglobin dissociation curve, or low oxygen and hemoglobin affinity, presumably to facilitate the unloading of oxygen to the tissues, whereas conditions such as hypothermia and alkalosis have opposite effects. At sea level, where there is an excess of oxygen in healthy individuals, shifts in the oxygen–hemoglobin curve make little difference in oxygen delivery, but at a high altitude, shifts in the curve may have a significant effect.

On acute ascent to a high altitude, hypoxia and the resultant hypocapnic alkalosis stimulate production of 2,3-diphosphoglycerate (2,3-DPG) within the red blood cell, which shifts the curve to the right. At the tissue level, production of carbon dioxide and hydrogen ions also improves the unloading of oxygen from hemoglobin, the Bohr effect. This shift was thought to be an advantage to acute high-altitude adaptation, but in subjects at 4300 m who had the curve shifted experimentally to the right, performance was not improved. Andean high-altitude natives both with and without evidence of polycythemia and pulmonary hypertension also were found to have right-shifted curves.

At moderate altitude, the rightward shifts may be an advantage, but the ease of unloading oxygen must be weighed against the potential disadvantage at higher

altitudes of loading oxygen onto hemoglobin at the pulmonary capillary level. A leftward shift would theoretically convey an advantage to loading oxygen at altitudes where the partial pressure of the inspired oxygen is so low that the diffusion gradient from air to blood is also very low. High-altitude animals and birds, such as the bar-headed goose, that migrate over the Himalayas have left-shifted curves, presumably from the marked hypocapnic alkalosis. Other experimental animal models bear out the advantage of a leftward shift during acute exposure. An optimal model may exist in the llamas and alpacas of the Andes, who have a left-shifted curve at the lung level and a right-shifted curve at the peripheral tissues.

Humans, on the other hand, have not lived long enough at high altitudes to evolve a characteristic hemoglobin that would be most suitable for high-altitude survival. A number of workers have found a modest leftward shift of the curve in humans living at high altitudes. Increased levels of 2,3-DPG have been found in these humans, but a leftward shift of the oxygen–hemoglobin curve was found probably because of the countereffect of the respiratory alkalosis. A group of climbers after 2 months at 6300 m or higher on Mt. Everest was found to have respiratory alkalosis, a modest polycythemic response (mean hematocrit of 54.4 ± 4.01%), and a persistently left-shifted curve despite an increased level of 2,3-DPG (Fig. 3). The advantages of a left-shifted curve at extreme altitudes, therefore, are at least suggested by the preceding data, but further work is necessary to elucidate the underlying mechanisms.

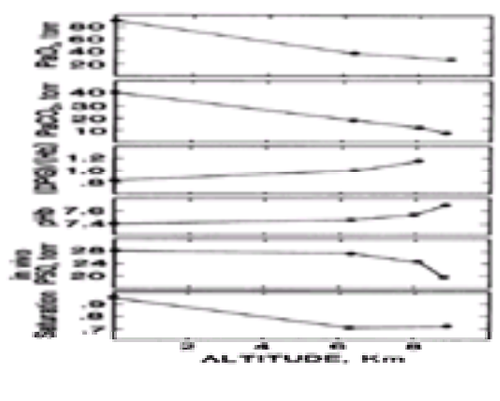

FIG. 3. Effect of altitude on oxygen–hemoglobin affinity. P_{50}, oxygen half-saturation pressure of hemoglobin; DPG, diphosphoglycerate. (From Winslow RM. Red cell function at extreme altitude. In West JB, Lahiri S, eds. *High Altitude and Man.* Bethesda, MD: American Physiological Society, 1984;59–72.)

Tissue Alterations

The final stages of oxygen delivery involve the diffusion of oxygen from the blood across the muscle capillary and muscle cell membrane to the cytoplasm and ultimately to the mitochondrion, where oxidative phosphorylation takes place. This process depends on a critical pressure gradient and radial distance for diffusion of oxygen from the blood to the cell. The critical pressure gradient is probably about 10 to 12 mm Hg, and certain adaptations that may optimize cellular transport and metabolism of oxygen take place.

Morphologic Changes

The purpose of structural changes is presumably to decrease the distance for diffusion of oxygen from the blood to the mitochondrion. Formation of new capillaries and a recruitment of preexisting capillaries in response to a hypoxic stimulus are strategies that can achieve that goal. Experimental animals exposed to hypoxia and guinea pigs native to high altitudes had an increased capillary density in the lung. Quantification of this response is difficult because muscle cell atrophy also occurs during prolonged (weeks, months) stays at high altitudes. In mice exposed to high altitude and exercise, capillary tortuosity and density were thought not to change when muscle fiber size and contractile state were considered.

The adaptation of the mitochondria to hypoxia is not well defined. Mitochondria have been found to be increased as well as unchanged or decreased at high altitudes. Human studies at very high altitudes, on the other hand, have shown a decrease in mitochondrial concentration. Whatever the final verdict, theoretically, an increase in both capillary and mitochondrial density would result in a facilitation of oxygen transport by decreasing the diffusion distance for oxygen from the blood to the mitochondria.

Biochemical Adaptations

Several biochemical mechanisms occur and improve oxygen metabolism. Myoglobin, an intracellular protein that binds oxygen at a very low tissue partial pressure of oxygen, facilitates diffusion of oxygen to muscle mitochondria and is increased in animals exposed to and native to hypoxia. The enzymes of oxidative metabolism also upgrade their function in response to exposure to and living at high altitudes. Succinic and lactate dehydrogenase, part of the glycolytic pathway, increase at high altitudes, but the changes in these studies were not consistent and depended on the degree of exposure, the tissue involved, and the stress itself. In human studies, the results suggest that fatty acid metabolism, which contributes to exercise endurance, is enhanced while glycolytic metabolism, which is responsible for high levels of aerobic work, is decreased. Further work is necessary to clarify this area of cellular adaptation to hypoxia.

Central Nervous System

The brain is the organ most sensitive to hypoxic stress. The historic flight of the Zenith in 1875, a hot-air balloon that carried three Italian scientists to over 8000 m, during which two of the scientists died, is a testament to the catastrophic effects of acute severe hypoxia on the brain. Less vivid but impressive examples of the effect of hypoxia on the brain are found throughout the medical and mountaineering literature.

The brain's defenses to the stress of hypoxia are both acute and chronic. The initial decrease in cerebral blood flow that occurs with hypocapnia secondary to hypoxia secondary to the respiratory alkalosis is outweighed by the increase in cerebral blood flow from the hypoxic stimulus. Blood flow increased 33% after 12 hr at 3800 m and decreased as respiratory adaptation continued but still was 13% greater than control values after 5 days. The net result is that oxygen supply to the brain is probably well preserved despite profound hypoxemia. Tibetans, a well-adapted high-altitude population, maintain cerebral blood flow during exercise better than sojourners.

In spite of augmented blood flow, varying degrees of cerebral dysfunction occur, depending on the acuity, duration, and degree of hypoxic stress. The higher one goes, the more that motor, sensory, and complex cognitive abilities are affected. Learning is impaired at 3000 m, and at 6000 m sensation, perception, and motor skills are diminished.

Acute elevation to 3500 m results in cortical depression of the electroencephalographic (EEG) pattern that is not apparent in inhabitants of that altitude. Correlation of the changes in the EEG with the symptoms of acute mountain sickness (AMS) at 4300 m was noted.

Several studies have addressed the question of prolonged or permanent effects of hypoxic exposure on central nervous system function. Some investigators found no residual psychometric deficits in climbers who had been above 5100 m in the Himalayas, but two other studies of individuals who had been at a high altitude for 10 months found residual motor incoordination and impaired speech, which resolved within a year. There was individual variation in these findings, which was also documented in a study of Polish alpinists who had climbed to 5500 m. All had some impairment noted by psychological testing, and 11 of 30 had EEG abnormalities. A later study showed transient deficits in learning, memory, and verbal expression in two groups of individuals, one of which had been on an expedition to Mt. Everest while the other had been exposed to a simulated similar altitude for 40 days in a hypobaric chamber. Fine-motor skills remained abnormal for up to 1 year in many. Unexpectedly, individuals with a high ventilatory response to hypoxia who are better oxygenated and who usually perform better physically had the greatest deficits. The authors speculated that those who hyperventilated more had greater hypocapnic cerebral vasoconstriction and thus lower oxygen delivery to the brain.

Sleep

Periodic breathing, which was described as far back as 1886, occurs during early exposure to high altitudes but decreases as acclimatization ensues. The degree of periodic breathing varies among individuals and may be a function of individual hypoxic chemosensitivity. Findings in both sojourners and high-altitude natives during sleep, when cortical input is minimized, suggest that individuals with high hypoxic chemosensitivity have ventilatory overshoot, resulting in hypocapnic alkalosis, suppression of ventilation, and periodicity of respiration. These oscillations persist throughout sleep and can result in profound arterial oxygen desaturation during the

hypopneic and apneic phases. The resulting hypoxemia may contribute to some of the aspects of altitude illness.

Carbonic anhydrase inhibitors eradicate periodic breathing, which may be a result of drug-induced tissue acidosis and subsequent ventilatory stimulation. Discussion of their therapeutic efficacy follows in the section on altitude illness.

Exercise

Although a number of observations of the effect of hypoxia on oxygen transport during exercise have been made, an understanding of exercise limitation at high altitudes remains elusive. One thing is certain: oxygen consumption and, subsequently, exercise performance predictably decrease with ascent to high altitudes (Fig. 4).

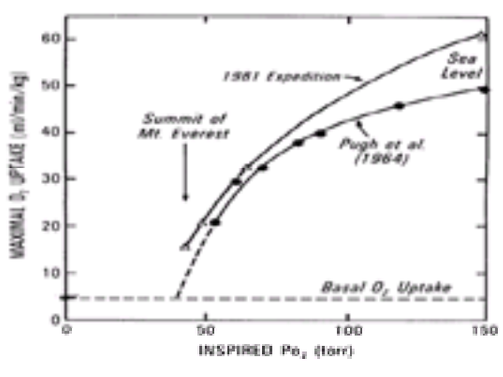

FIG. 4. Maximal oxygen consumption ($\dot{V}O_{2max}$) against inspired partial pressure of oxygen. There is a predictable decrease in $\dot{V}O_{2max}$ at higher altitudes. The more recent data demonstrate that a low amount of work is possible on the summit of Mt. Everest. (From West JB, et al. Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol* 1983;55:688.)

Ventilation

The increased metabolic rate of exercise and hypoxia of high altitude interact synergistically to augment exercise hyperpnea. The increase in exercise ventilation is proportional to the degree of hypoxia (Fig. 5). The degree of exercise hyperpnea is also influenced by the individual's hypoxic ventilatory response, measured at sea level or a high altitude, and extraordinary levels of exercise ventilation may be augmented by the lower gas density. The study on Mt. Everest demonstrated that climbers with higher hypoxic chemosensitivity had greater exercise ventilation, less arterial oxygen desaturation, and better climbing performance. These data supported studies suggesting that climbers to extreme altitudes (higher than 7500 m) benefited from a brisk high ventilatory response. It is, therefore, the ventilatory response at high altitudes that is primarily responsible for the preservation of alveolar and arterial oxygen partial pressure. On the other hand, in the high-altitude dweller, a lower exercise ventilation is accompanied by a lower alveolar–arterial gradient, suggesting a genetic or adaptive increase in diffusion capacity of the lungs for oxygen that results in improved oxygen transport from the air to the blood.

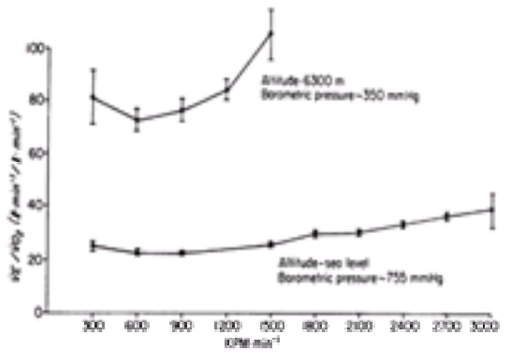

FIG. 5. The ventilatory equivalent ($\dot{V}_E/\dot{V}O_2$) for given workloads in a group of climbers at sea level *(lower line)* an at 6300 m *(upper line).* The data demonstrate the stimulation of ventilation by hypoxia. (From Schoene RB. Hypoxic ventilatory response and exercise ventilation at sea level and high altitude. In West JB, Lahiri S, eds. *Man at High Altitude.* Bethesda, MD: American Physiological Society, 1984; 19–30.)

Gas Exchange

Arterial oxygen saturation in sojourners decreases with exercise at high altitude. This desaturation is largely secondary to a diffusion limitation for oxygen from the air to the blood, but some $\dot{V}/\dot{Q}$ heterogeneity contributes to this phenomenon. This $\dot{V}/\dot{Q}$ heterogeneity may be secondary to interstitial lung water, whereas the diffusion limitation is a result of a decreased driving pressure of oxygen from air to blood compounded by a decrease in transit time of blood across the alveolar–capillary membrane.

Cardiac Response

At submaximal work loads during acute exposure, cardiac output is moderately higher than at sea level, but after prolonged exposure, heart rate and cardiac output are matched for comparable sea-level work loads. On acute high-altitude exposure, maximum cardiac output is the same as at sea level, but it decreases 20% to 30% after 2 months above 4300 m. This decrease is a result of a decrease in both maximum heart rate and stroke volume. The decrease in maximum heart rate is more pronounced in sojourners than high-altitude natives. On the other hand, cardiac output remains appropriate for oxygen consumption, and myocardial contractility, as measured by echocardiography, is preserved even at extreme altitudes. Although pulmonary artery pressures are very high during exercise at extreme altitudes, the increase in pulmonary vascular resistance is not a limiting factor.

Hematologic Changes

A modest increase in hemoglobin secondary to the erythropoietic response may improve oxygen transport, but polycythemia and its accompanying hyperviscosity may result in a decrease in microperfusion of the muscle tissue and a subsequent decrease in oxygen extraction. A study on Mt. Everest showed that isovolemic hemodilution of mountaineers from hematocrits of 60% to the low 50% range did not decrease maximum exercise capabilities. In fact, data from Himalayan highlanders suggest that the optimal hematocrit may be somewhat lower than previously thought.

Tissue

Muscle tissue undergoes some morphologic and chemical changes, the net result of which is that oxidative capacities are reduced. For instance, in climbers returning from 2 months at an extreme altitude, muscle mass decreased, capillary density was unchanged, mitochondrial density increased, and muscle succinic dehydrogenase (a marker for aerobic metabolism) decreased—all of which resulted in impaired aerobic functioning. It is not clear from other studies what effect a decrease in muscle fiber size has on the relationship of capillary and mitochondrial density and subsequent oxygen extraction.

In summary, exercise at modest altitude results in a number of cardiopulmonary changes that optimize gas exchange, while the blood and peripheral vasculature also undergo certain changes that may improve oxygen transport. At extreme altitude, on the other hand, the tissue adaptations may impose limitations on both submaximal

and maximal exercise.

Athletic Performance and Training at High Altitudes

Much of the work on athletic performance at high altitudes was done during the Mexico City Olympic middle-distance running events (at 2270-m elevation). Times were about 8% slower on arrival and approached but did not reach previous best sea-level performances. These findings correlated with measurements of maximum oxygen consumption. Performances in short-distance events (less than 2 min) are not impaired and in fact may be better than at sea level because of decreased air resistance. On the other hand, for prolonged work activities, endurance is improved by training and living at high altitude.

There is controversy over the benefits of training for athletic events at moderate altitudes. After the success in the Mexico City Olympics of the Africans who lived at an altitude of approximately 2000 m, it became quite fashionable for middle- and long-distance athletes to live and train at these altitudes. The results of studies to document this presumed benefit were mixed. The benefits of living at these altitudes (e.g., increased level of hemoglobin) may be outweighed by the fact that training schedules cannot be as intense. A recent study tried to address this controversy by studying four groups of athletes: individuals living and training at a low altitude, ones living and training at a high altitude (3000 m), those living at a high altitude and training at a low altitude, and a final group living at a low altitude and training at a high altitude. The results were not striking but suggested that those who lived at a high altitude and trained at a low altitude had a slight edge over the others. These findings may be explained by the slight elevation in hemoglobin.

MALADAPTATION

Overview

Modern travel and recreation permit rapid ascent to high altitudes, which is the major cause of acute mountain illnesses. On the other hand, millions of people reside at altitudes above 2500 m, and a certain percentage of those individuals develop chronic altitude disorders. In both of these groups, mounting evidence suggests that failure of the body to respond to hypoxic stress with an adequate ventilatory response results in greater hypoxemia, pulmonary hypertension, increased intracranial pressure, fluid retention, and erythropoietic response, all of which may lead to clinical illnesses at high altitudes. Hypoventilation, therefore, may be one of the crucial factors underlying all altitude illnesses. With the previous notes on formal adaptation as a guide, it therefore is the purpose of this section to deal with both acute and chronic mountain sicknesses.

Illnesses of Sojourners to High Altitudes

As was so tragically demonstrated by 19th-century balloonists, acute ascent above 8000 m can lead to death, whereas, as has been repeatedly achieved in the 20th century, climbers can gradually ascend to these altitudes and live and work for short periods of time quite effectively. Failure of the body to adapt to the hypoxic stress leads to acute mountain illnesses that can be fatal. These disorders are classified as AMS, high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). Although there is a great deal of individual variability and overlap in these disorders, this section deals with them separately.

Acute Mountain Sickness

Clinical Picture

Historically, AMS was described many centuries ago, and one consistently described symptom is headache. The headache usually begins shortly after ascent, is more severe in the morning, and is usually treatable with mild analgesics. Other symptoms can include anorexia, lassitude, insomnia, nausea, and vomiting, and some subjects show signs of fluid retention. Sojourners with AMS may be tachycardic and tachypneic but are not febrile. All these signs and symptoms usually abate over several days as acclimatization ensues and rarely requires more than rest, hydration, and mild analgesics. The severity and duration of AMS are a function of the altitude and the rapidity of ascent. For instance, on Mt. Rainier (4400 m), nearly two-thirds of climbers who routinely ascend from sea level over 1 to 3 days develop AMS, and in Summit County, Colorado (2880 m), 25% of travelers from low altitude have AMS. In both of these cases, the symptoms usually resolve in 1 to 3 days without sequelae. However, AMS can progress to HAPE and/or HACE, which can be life-threatening.

In many subjects with AMS, hypoventilation, gas-exchange abnormalities, and pulmonary mechanical dysfunction occur. Fluid retention, weight gain, proteinuria, and increased CSF pressure and brain swelling also have been documented. Individuals who are susceptible to AMS have an exaggerated aldosterone and antidiuretic hormone (ADH) response on ascent that is different from well-acclimatizing individuals who have low ADH and a diuresis. A shift of fluid from the extracellular space to the interstitial and intracellular compartments occurs normally during the initial few days at high altitude, but it may be accentuated and prolonged in persons with hypoventilation and AMS. Fluid shifts also may explain the pulmonary dysfunctions of relative hypoxemia and mechanical dysfunction, which may be precursors of overt HAPE. Evidence that dexamethasone, a medication commonly used for the treatment of many forms of edema, is effective in preventing and treating AMS supports the concept that extravascular fluid extravasation plays a role in altitude illnesses.

Why do some individuals get AMS and others not? Although the answer is not known, mounting evidence suggests that individuals with a blunted hypoxic ventilatory response are more predisposed to AMS and fluid retention. It is probably safe to say that the individual who does not mount a sufficient ventilatory response is more hypoxemic and susceptible to the ill effects and will, therefore, be predisposed to all forms of altitude illness, the first of which is AMS.

Treatment

Successful management of AMS involves recognition and appropriate treatment. If the awareness of and suspicion for AMS are keen enough, then AMS usually will not progress and can be treated with conservative measures, such as rest and mild analgesics (aspirin, acetaminophen, codeine, prochlorperazine). Sedatives, narcotics, and alcohol should be avoided because they may suppress ventilation and mask worsening symptoms. If the subject seems more ill with worsening headache or any other clear neurologic signs, especially ataxia, then this situation should be considered serious, and the patient should descend as quickly as possible. Even a few hundred meters may be helpful. If conditions do not permit descent, then oxygen, if available, is a good temporizing measure.

Few medications have been found to be helpful in either the prevention or the treatment of AMS. Acetazolamide, a carbonic anhydrase inhibitor, is effective in preventing and treating AMS, although its mechanism of action is unknown. Acetazolamide eradicates periodic breathing and arterial oxygen desaturation during sleep at high altitudes, which may improve overall oxygen delivery. The drug also stimulates ventilation at rest and during exercise; induces a renal excretion of bicarbonate, which may facilitate acclimatization; and lowers CSF pressure by decreasing CSF formation. Which of these effects is responsible for the drug's efficacy is not known, but it is effective and safe. Its side effects are minimal and include peripheral, self-limited paresthesias and mild gastrointestinal upset. The present recommendations are that sojourners who frequently get AMS should take acetazolamide (125 mg p.o. b.i.d.) on ascent to minimize the chances of illness; otherwise, those who go high quickly should begin therapy only after the first signs of illness. Individuals who are allergic to sulfa drugs should not take acetazolamide.

Dexamethasone has been shown to be effective in treating and preventing AMS and should be used in situations where treatment is imperative to aid a sojourner's descent. Because there are no data to suggest that the drug facilitates acclimatization, a person who stops taking the drug while still at a high altitude may suffer a rebound of altitude illness. Individuals progressing to more severe signs suggestive of cerebral edema should use dexamethasone immediately.

Recently, a portable hyperbaric chamber has been used for treatment of altitude illnesses in the field. This equipment is lightweight and is effective in treating illness. This manually operated chamber can lower the altitude by 1500 m with a pressure of 2 psi, which, after several hours, is enough to improve symptoms such that a victim can descend under his or her own power. In remote areas, the hyperbaric bag provides an excellent, reusable alternative to oxygen. Whether it is more effective than oxygen alone has not been established.

The best treatment is prevention, and slow, gradual ascent is still the best preventive measure. Maintenance of fluids to ensure a normal urine output and adequate calories in carbohydrates are time-honored tactics. A number of other drugs (morphine, furosemide, spironolactone, phenytoin) have been used, but none is effective, and most have potentially deleterious side effects.

High-Altitude Pulmonary Edema

Clinical Picture

High-altitude pulmonary edema (HAPE) was thought for many years to be pneumonia or heart failure at a high altitude. It was not until the 1960s that HAPE was described as a noncardiogenic form of pulmonary edema. The syndrome affects healthy sojourners of all ages, usually within several days of ascent above 3000 m, although it can occur later and at lower altitudes. It also is more common at higher altitudes with quick ascent. Symptoms and signs of AMS may precede those of

HAPE, and often HAPE and HACE occur simultaneously with varying degrees of each. Dyspnea on exertion, fatigue, and dry cough are early symptoms, with cyanosis, tachypnea, and tachycardia as accompanying signs. Crackles are universally present, although pink frothy sputum is present only in severe cases. Many victims have a low-grade fever, and all will have fluffy infiltrates without cardiomegaly on chest radiograph (Fig. 6). If symptoms are recognized early enough, while the patient is still ambulatory, descent is very effective as a treatment. Most patients recover fully, and many have been able to reascend to very high altitude within a fortnight. This observation is important, as it implies that the lung architecture is preserved.

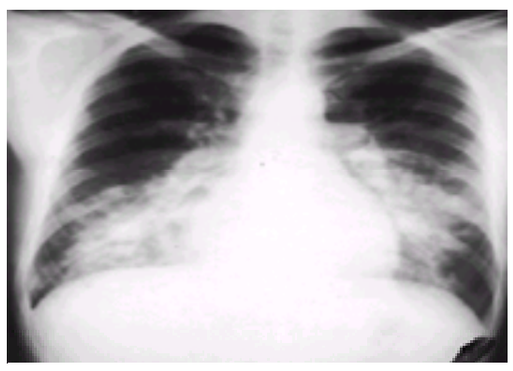

FIG. 6. Chest x-ray film from a victim of high-altitude pulmonary edema with bilateral infiltrates and normal cardiac silhouette. (Hackett PH. *personal communication,* 1987.)

High-altitude pulmonary edema may be an extension of the normal process of accumulation of lung water that occurs on acute ascent to altitude. Additionally, many asymptomatic individuals have crackles on chest auscultation that resolve with further acclimatization. These findings suggest either that those who go on to develop HAPE are not able to compensate for the normal fluid accumulation or that their fluid shift is overwhelming.

Pathophysiology

Both autopsy and bronchoalveolar lavage (BAL) data demonstrate that HAPE is a high-protein/high-permeability leak (Fig. 7). Over 20 autopsies demonstrated a proteinaceous alveolar exudate with hyaline membrane formation. Neutrophils were present, and capillary and arteriolar thrombi and fibrin deposition were found. These data are from those individuals who did not survive and thus are not representative of the early pathophysiological process.

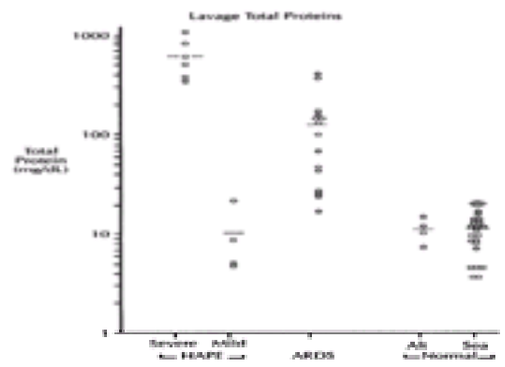

FIG. 7. Protein concentration in bronchoalveolar lavage fluid in patients with **(left to right)** high-altitude pulmonary edema (HAPE), acute mountain sickness with mild arterial oxygen saturation, adult respiratory distress syndrome (ARDS), and two control populations. (From Schoene RB, et al. The lung at high altitude: Bronchoalveolar lavage in acute mountain sickness and pulmonary edema. *J Appl Physiol* 1988;64:2605.)

Bronchoalveolar lavage at 4400 m on Mt. McKinley characterized the cellular and biochemical responses in subjects with HAPE. The protein content was higher than that of patients with adult respiratory distress syndrome (ARDS), and the fluid also was very cellular, but unlike the fluid found in ARDS, which contains primarily neutrophils, BAL fluid from subjects with HAPE consisted largely of alveolar macrophages. Additionally, there was evidence of inflammation with complement activation and leukotriene B_4 production, but inhibition of neutrophil chemotaxis was present, suggesting a mechanism protecting against parenchymal destruction. Thromboxane B_2 also was present, suggesting a vasoactive process. These findings provide important insight into the underlying mechanism of HAPE, although the picture is not complete.

Other physiological observations may provide further understanding of this high-permeability lung leak. A number of subjects with HAPE have a blunted ventilatory response to hypoxia that presumably leads to a more profound degree of hypoxemia, especially during sleep, and subsequent higher pulmonary artery pressures mediated by the HPVR. In addition, studies have shown that subjects with HAPE had very elevated pulmonary artery pressures. Decreasing these pressures with nitric oxide, which vasodilates the pulmonary vasculature, improves gas exchange in victims of HAPE. In a number of patients with HAPE, congenital absence of a pulmonary artery has also been demonstrated. These findings suggest that the pulmonary vascular endothelium undergoes extraordinary stress from an increased cardiac output during exercise at high altitudes, which is being directed through an either globally or patchily vasoconstricted and compromised pulmonary vascular bed. An animal model for capillary stress and failure has been described. Could high shear forces lead to a mechanical stretching of endothelial pores and subsequent permeability leak, or are other biochemical mechanisms responsible? Clearly, high intravascular pressures play a role in the development of HAPE but are not the entire story.

The BAL data showed that biochemical mediators are present. These findings suggest that stress on the endothelium may lead to release of inflammatory mediators, which may affect permeability. It would seem reasonable, therefore, not to classify pulmonary edema as caused by either pure increased permeability or pure increased hydrostatic pressure. This arbitrary division has led to some misunderstanding of some clinical illnesses, which may have a number of contributory factors. It is conceivable that the pathophysiologic process in HAPE begins with high hydrostatic forces, which may lead to leak of protein into the interstitial and alveolar spaces and/or to release of biochemical mediators that affect pulmonary vascular integrity. This latter scenario suggests mechanisms that would violate the traditional separation of causes of lung leak but that may be more realistic.

Treatment

The guidelines for field treatment that have been outlined for AMS are applicable to HAPE, except that it is important to emphasize that HAPE can be fatal. Early recognition is essential to avoid catastrophe. Descent, especially from remote areas where medical help is not available, is still the most important step, and avoidance of any medications that may suppress ventilation, especially sleeping pills, is mandatory. Oxygen, if available, is very effective, but it should be regarded only as a temporizing measure. However, if mild to moderate cases of HAPE are seen in areas where medical help is available, and if the patient's S_aO_2 can be increased to ^{3}90% on low-flow oxygen, then he or she can remain at altitude on oxygen under the overnight observation of family or friends and be seen in follow-up. This approach is reasonable, especially in recreational areas where evacuation is an expensive and logistically unnecessary overreaction. Because HAPE and HACE often occur together to varying degrees, the victim may be more or less incapacitated, and rescue units should have oxygen and/or a portable hyperbaric bag available, as these improve oxygenation and decrease pulmonary artery pressure. Victims usually improve enough within 12 to 24 hr of descent to safer altitudes. Recent studies have shown end-positive airway pressure (EPAP) masks to be effective in improving oxygenation, and these may be useful until the victim can descend or be evacuated.

A number of medications have been used, but no data are available to validate their efficacy. The low incidence of HAPE and the lack of an animal model make a drug trial very difficult. Acetazolamide is certainly safe and may be effective in preventing or treating HAPE, but no studies have been done to prove this point. Potent diuretics are potentially dangerous. Morphine sulfate may improve symptoms, but it suppresses ventilation. Drugs that decrease pulmonary artery pressures have been shown to be efficacious. In a field study in the Alps, Bartsch and colleagues pretreated HAPE-susceptible climbers with nifedipine and placebo. There was a decrease in pulmonary artery pressure and no HAPE occurred in the nifedipine group. Therefore, in HAPE-susceptible individuals who return to high altitude, prophylactic

treatment with nifedipine XL, 30 mg p.o. q.d. or b.i.d., is appropriate.

High-Altitude Cerebral Edema

Because the symptoms of AMS are similar yet milder than those of HACE, it is reasonable to assume that HACE is merely an extension of AMS. High-altitude cerebral edema usually, but not always, follows AMS and is marked by severe headache and papilledema with deterioration of mental status in the presence of objective neurologic signs, especially ataxia. This usually is seen after a recent ascent. The symptoms may rapidly progress to coma and death. Usually HACE occurs at higher altitudes (higher than 4000 m) and is less common than HAPE (approximately 1%). If a severe headache cannot be relieved by analgesics, then HACE should be suspected, especially if other neurologic signs or symptoms develop. Both HAPE and HACE often occur simultaneously with differing degrees of severity.

Autopsies have shown gross cerebral edema with herniation and small petechial hemorrhages in seven of eight HACE victims. The underlying pathophysiological mechanism is unclear, but it probably involves high cerebral vascular pressures with filtration of plasma proteins and water into the interstitial spaces.

Recognition is absolutely essential because HACE, more than any other altitude illness, can progress rapidly to death. Recovery occurs with descent, although oxygen and dexamethasone (10 mg i.m. or 8 mg p.o. immediately and 4 mg p.o. q6h until symptoms resolve) may give symptomatic relief until descent can be achieved. Hyperbaric therapy may also be helpful but should never delay descent if the patient is ambulatory or transportable.

Ophthalmologic Syndromes

A number of ophthalmologic changes have been noted at high altitudes. As the window of the brain, the retina may offer some interesting insight into the effect of altitude on the brain. Retinal hemorrhages are common (more than 50%) in sojourners above 4500 m and were recently observed in all eight subjects who underwent a 40-day simulated ascent of Mt. Everest. Rarely are visual changes encountered, and the hemorrhages resolve within a fortnight and deserve no treatment *per se.* Other funduscopic changes include papilledema, vitreous hemorrhages, and vascular tortuosity and engorgement. The hemorrhages are similar to those found in necropsies of the brain at high altitude, and one can only speculate if these are concomitant processes in the eye and brain.

Visual changes, including visual blurring and intermittent blindness, also occur. This latter phenomenon is probably cortical in origin secondary to global hypoxia and/or decreased perfusion secondary to hypocapnic vasospasm. Visual field impairment also has been described and is vascular in origin.

Illnesses of High-Altitude Residents

Subacute Mountain Sickness

Recently, a syndrome has been found in Indian soldiers who lived for longer than 3 months at an altitude of 5800 m. It is characterized by fluid retention, cor pulmonale, polycythemia, and left ventricular dysfunction. The mortality rate was high in these individuals unless they moved to a low altitude. An infantile counterpart has been observed in Han Chinese infants who have moved to Lhasa, Tibet. Investigators are presently trying to understand the underlying mechanisms of this newly described entity.

Chronic Mountain Sickness

Human habitation at high altitudes is limited both by prolonged hypoxic stress and by the harsh nature of the environment. Nevertheless, millions of people live between 3000 and 5000 m. Some environments might permit living at higher altitudes, but anecdotally, civilizations have settled below 5000 m, suggesting that chronic deterioration occurs above this altitude such that populations tend not to thrive.

Some insight into this phenomenon can be gained by observing some individuals in populations residing at high altitudes who develop deleterious manifestations of chronic hypoxic stress—polycythemia, pulmonary hypertension, mental slowing, and cor pulmonale. This disease is termed *chronic mountain sickness* (CMS) and was first described by Monge in 1928, who noted the sickness in high-altitude natives of the South American Andes. Interestingly, although CMS has been observed in all mountain ranges, some populations, especially inhabitants of the Tibetan plateau and women, do not seem very susceptible to CMS. Populations of lowland natives who move to high altitudes develop CMS over the ensuing years. An interesting study on the Tibetan plateau showed a 13% incidence of CMS in relocated Chinese men, a 1.6% incidence in Chinese women, and a 1% incidence in Tibetan men. One could speculate that the Tibetans, who have lived at high altitudes for over 250,000 years, have evolved more successful mechanisms to improve oxygen transport and cope with the hypoxic stress than have Andean natives, who have lived at high altitudes for less than 30,000 years.

Clinical Picture

Andean villages have many individuals suffering from CMS. The plethoric, sometimes obese male with both mental and physical torpor is classic. Neurologic findings include mental dullness, lethargy, and poor memory. The subjects have polycythemia and cyanosis and resemble in many respects the sea-level dweller with cor pulmonale, polycythemia, and sleep disorders with marked nocturnal oxygen desaturation. There may be underlying lung disease as well.

Most of the clinical manifestations can be attributed to hypoventilation, which is associated with a blunted hypoxic chemosensitivity and subsequent relatively greater hypoxemia. Worse pulmonary hypertension may lead to right-sided heart failure and cor pulmonale. A high-frequency, low-tidal-volume pattern of ventilation may contribute to a low $\dot{V}/\dot{Q}$ ratio, contributing further to the hypoxemia. An increase in red cell mass relative to plasma volume results in a true hyperviscous polycythemia. Hematocrit levels as high as 80% have been described. Hypoventilation, therefore, may be one of the key factors that allows CMS to develop. Other underlying problems, such as lung disease and an inordinate erythropoietic response, may contribute to the development of CMS.

Treatment

The mainstay of treatment is improvement of arterial oxygenation, which should decrease the polycythemia, improve pulmonary hypertension, and improve cerebral function. If possible, the individual should move to a lower altitude and stop cigarette smoking. Often a relocation is not logistically or culturally possible, and most victims of CMS languish away in remote high-altitude villages. On the other hand, some therapeutic interventions are beneficial. Phlebotomy improves cor pulmonale and increases cardiac output and oxygen transport, but the erythropoiesis eventually returns. Low-flow oxygen, especially at night, is also helpful but not always logistically feasible. Medications that stimulate ventilation and result in a marked improvement in nocturnal oxygen saturation are also beneficial. Acetazolamide is particularly effective, as is medroxyprogesterone acetate, although to a lesser degree. Other respiratory stimulants have not been tried.

Reentry Pulmonary Edema

Long-time residents at high altitudes may be more susceptible to high-altitude pulmonary edema if they descend to a low altitude and reascend. Young people (children and teenagers) may be more susceptible, especially if descent and ascent are rapid. Cases have been reported from South America (6.4% incidence) and Leadville, Colorado, but none from Asia. The reasons for this difference are not clear, but it may be secondary to the logistic imposition of a slower ascent in the Himalayas or to the overall better adaptive capabilities of the Tibetan descendants. The cause of reentry HAPE is not known, but it may be secondary to a hypermuscularization and subsequent hyperreactivity of the pulmonary vasculature to hypoxia on reascent.

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CHAPTER

46 Near-Drowning and Diving Accidents*

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INTRODUCTION

Near-drowning and diving accidents have a special importance for pulmonologists and intensivists. These aquatic injuries often cause acute respiratory distress syndrome and other respiratory complications, which usually respond to careful management. The treatment of near-drowning may require the full spectrum of pulmonary and critical care medicine.

Diving accidents may also require specialized intervention such as surface decompression in a hyperbaric chamber. Because of the millions of recreational diving enthusiasts in the United States, pulmonary and critical care providers should maintain familiarity with medical management of diving accidents. Emergency medical services at virtually any location may refer divers with acute injuries for further care.

This chapter considers clinical aspects of near-drowning and diving accidents from the point of view of pulmonologists and intensivists. The chapter begins with a presentation of definitions and incidence of these entities. Near-drowning is considered using a problem oriented, organ systems approach to manifestations and treatment, followed by a similar review of diving accidents. A brief consideration of fitness for diving follows thereafter.

DEFINITIONS

Drowning consists of death from asphyxiation as a result of submersion in a fluid medium. Although aspiration occurs in the vast majority of cases, the definition of drowning does not inherently require significant aspiration of fluid into the lower respiratory tract. Mechanisms of drowning without aspiration are considered below.

Near-drowning consists of survival for a period of time despite illness or soft-tissue injuries resulting from submersion in a fluid medium. The definition usually implies anoxic injury or aspiration. Death may follow at a later time. For cases surviving less than 24 hrs, the distinction between drowning and near-drowning becomes somewhat arbitrary.

Immersion of the face without total body submersion can produce near-drowning in some circumstances. Minimal aspiration associated with momentary submersion and without sequelae constitutes the mildest form of near-drowning and differs little from any simple aspiration. Partial submersion without facial immersion or aspiration may not justify diagnosis of near-drowning.

Diving accidents defy a single definition and consist of several different complications in divers. These include decompression sickness, arterial gas embolism, nitrogen narcosis, oxygen-induced seizures, and other complications. Each can also cause drowning or near-drowning. These are addressed in the section on diving accidents.

INCIDENCE

National mortality statistics have reported 4000 to 5000 accidental drowning deaths per year in the United States during the 1990s. The reported mortality rate from accidental drowning has averaged 1.8 per 100,000 population during these years. This compares favorably with a mortality rate of 3.7 per 100,000 from accidental drowning during the mid-1970s.

Recent medical reviews have typically estimated a greater number of drownings, usually 7000 to 9000 victims per year in the United States and over 100,000 victims worldwide. The difference may reflect the fact that drowning often complicates other types of accidents such as motor vehicle and boating accidents. Statistical summaries that classify by primary accident alone would not reflect the role of drowning as a contributory cause of death.

Near-drowning exceeds drownings five- to tenfold based on emergency room visits and two- to sevenfold based on hospitalizations. Rough estimates place the number of people seeking medical attention for near-drowning at 50,000 or more every year. Submersions not resulting in medical encounters outnumber actual drownings by several hundredfold. Age distributions of drownings reveal two modal peaks: young children below 5 years of age and a broader peak between 14 and 24 years of age. The risk of drowning and near-drowning for boys and men exceeds that for girls and women by up to 4:1. By age and sex distributions, young adult and adolescent boys have the greatest risk. The tendency for risk-taking behavior in boys and the greater likelihood of intoxication in male adolescents and young adults contribute to this gender difference in incidence.

Diving accidents contribute to the annual toll of drowning victims. Fatalities among divers occur in approximately 100 cases per year. The most common causes of death among self-contained underwater breathing apparatus (SCUBA) divers consist of depletion of oxygen while submerged at depth, arterial gas embolism, and drowning. Nonfatal but serious diving accidents occur in approximately 750 cases per year.

NEAR-DROWNING

Pathogenesis

The most common sites of drownings in toddlers and preschool children by far are swimming pools. In adults, drowning also commonly occurs in ponds, lakes, and rivers used for recreational activities. Less frequent sites in adults include bathtubs, hot tubs, and other sites. In contrast, drowning in infants most often occurs in the bathtub. In these instances, child neglect or abuse should be considered.

Table 1 lists some common factors predisposing to near-drowning. Common denominators include loss of consciousness, neuromuscular weakness, poor judgment, lapses in safety, and unexpected events.

Category	Mechanisms	Examples
Intoxication	Impaired consciousness	Alcohol
	Impaired judgment	Illegal drugs
	Impaired coordination	Multiple drugs
Trauma	Closed head injury	Aquatic sports
	Spinal cord injury	Pool dives
		Auto accidents
Maladaptive response	Hypocapnic hypoxemia	Shallow water blackout
	Cardiac arrest	Sudden immersion syndrome
Medical conditions	Arrhythmias, syncope	Cardiac disease
	Seizures	Epilepsy
	Hypoglycemia	Diabetes mellitus
Hypothermia	Motor impairment	Prolonged immersion
	Arrhythmias	Frigid waters
	Loss of consciousness	
Diving accidents	Hypoxemia	Oxygen depletion
	Delirium	Nitrogen narcosis
	Seizures	Oxygen toxicity
	Neuromuscular impairment	Arterial gas embolism
	Carbon monoxide poisoning	Surface air contamination
Miscellaneous	Lack of supervision	Child drowning
	Exhaustion	Unexpected immersion
	Lack of flotation device	
	Wounds	Animal bite
	Entrapment	Bottom vegetation

TABLE 1. *Pathogenesis of near-drowning: Some common factors*

Intoxication contributes significantly to drowning in adults and adolescents. One-third to one-half of drownings in these age groups involve alcohol consumption. In addition to impairing judgment, coordination, and level of consciousness, alcohol predisposes to loss of body heat and development of hypothermia. Illegal and prescribed drugs also play a role in adult and adolescent drownings. Screening for intoxicants is appropriate in most cases of near-drowning.

Patients with closed head injury or cervical fracture typically make no attempt to surface after entry into a body of water because of unconsciousness or loss of motor function. Aquatic sports such as surfing, waterskiing, and pool diving produce hundreds of these injuries annually. Physicians should keep a low threshold for cervical immobilization and obtaining radiographic studies to exclude these injuries.

Maladaptive responses may be regarded as pathologic consequences of physiological processes or reflexes. Two maladaptive responses contribute to near-drowning episodes: shallow-water blackout and sudden immersion syndrome.

Shallow-Water Blackout

A swimmer who hyperventilates before a breath-hold swim delays the ventilatory response to rising carbon dioxide. Vigorous muscular activity while swimming underwater then depletes alveolar oxygen. This can cause hypoxemia sufficient to produce loss of consciousness, such as a P_aO_2 of 30 mmHg for 20 sec. Aspiration of water can then follow because of cessation of voluntary breath holding. Shallow-water blackout thus consists of the sequence of hyperventilation, breath holding, exercise, and loss of consciousness.

Sudden Immersion Syndrome

This phenomenon consists of a vagally mediated asystolic cardiac arrest caused by sudden immersion in very cold water. Ventricular fibrillation may supervene. Sudden immersion syndrome disrupts the circulation and thus consists of a maladaptive response. This differs from the diving reflex, which consists of bradycardia and peripheral vasoconstriction causing hypertension, reduced cardiac output, and central redistribution of the circulation.

The medical conditions listed in Table 1 have a high prevalence in the general population. Epileptic seizures contributed to drownings in 6% to 8% of cases in some series. Sudden cardiac death from ventricular fibrillation or tachycardia and syncope from valvular or muscular subaortic stenosis can present in the water as well as on land. Hypoglycemia most often occurs in diabetic patients using oral or injectable medications.

A variety of other factors predispose to near-drowning. Lack of supervision and lapses in safety cause most of the drownings and near-drownings in infants and preschool children. Lack of flotation devices, animal bites, and entrapments represent unexpected circumstances associated with near-drowning. Detailed analysis of these and many other factors exceeds the scope of this chapter.

Pathophysiology

Three mechanisms produce most of the pathologic changes associated with near-drowning: anoxia, aspiration, and hypothermia.

Anoxia

Hypoxemia constitutes the most critical pathophysiological event in near-drowning. The degree and duration of hypoxemia determine the extent of anoxic brain damage, which in turn directly affects outcome and prognosis. Other injuries can also cause death, but patients usually recover with medical support.

Many drownings begin with a period of panic associated with attempted breath holding. The victim struggles to reach the surface and may swallow large amounts of water. Oxygen becomes depleted, and carbon dioxide accumulates. The breath hold eventually ends with inspiratory efforts and aspiration of varying amounts of water. When hypoxemia reaches a critical level, the victim loses consciousness. Cardiac arrest eventually ensues. Anoxic brain injury results from profound hypoxemia and circulatory arrest.

Witnesses of near-drowning incidents may not report the pattern of struggling described above. Common explanations for the motionless drowning victim include hypothermia, shallow-water blackout, sudden immersion syndrome, closed head injury, and other causes of unconsciousness, impaired ventilatory drive, and neuromuscular weakness.

Hypoxemia remains the gravest concern even in near-drowning without struggling. Although hypoxemia develops more gradually in the absence of vigorous muscular activity, the factors inhibiting the struggle carry additional morbidity of their own.

Aspiration

Drowning occurs without significant aspiration in 10% of cases. “Dry” drowning and near-drowning events have been attributed to laryngospasm resulting from tracheal irritation by minimal aspirated fluid. Apnea or simultaneous cardiopulmonary arrest can also produce relatively dry lungs.

Aspiration of considerable fluid occurs in the vast majority of near-drowning cases. Entry of fluid into the lungs depends on the action of the respiratory muscles and stops with cessation of respirations. Table 2 presents a listing of common respiratory complications of near-drowning.

Pulmonary mechanics	Complication	Onset
Restriction[a]	Aspiration	Early
	Abdominal distention	Early
	ARDS	Delayed
	Pneumothorax	Either
Obstruction[b]	Foreign body	Early
	Bronchospasm	Early
	Laryngospasm	Early
Normal	Hypoventilation	Early
	Pneumonia	Delayed

[a] Decreased static compliance with increased airways resistance; increased peak inspiratory pressure with normal plateau pressure.
[b] Normal static compliance; increased airways resistance; increased peak inspiratory pressure with normal plateau pressure.

TABLE 2. *Respiratory complications of near-drowning*

Aspiration of water grossly contaminated with particulates may obstruct large airways, smaller bronchi, or respiratory bronchioles. Clinicians should consider sand or gravel aspiration in all cases of near-drowning in shallow waters. The Heimlich maneuver, however, should be reserved for cases with inability to ventilate at the rescue scene. Clinicians should note any history of application of the Heimlich maneuver, as this may indicate the possibility of additional particulates and may warrant observation for complications of abdominal thrusts.

Nationwide, near-drowning in fresh water occurs much more frequently than in sea water. The manifestations of hypertonic and hypotonic fluid aspiration differ in several respects. With both types of water, pulmonary edema occurs and adds to the ventilation–perfusion abnormality. Near-drowning in brackish, polluted, or waste water and industrial solutions represent less common problems. In general, aspiration of fresh, salt, brackish, or chlorinated waters has no significant effect on outcome.

Fresh water disappears relatively rapidly from the lower respiratory tract, a characteristic of hypotonic fluids. Investigators recovered little fresh water from the lower respiratory tract of experimental animals even with suctioning within 3 to 5 min after instillation in the trachea. Because of clearance of hypotonic fluid by the circulation, the space-occupying effects of fresh water near-drowning do not persist after rescue and restoration of ventilation.

Aspiration of fresh water alters surface tension in the alveoli by inactivating preexisting lung surfactant. Both chlorinated and nontreated fresh water have this property. Fresh water also may inhibit surfactant production by type II pneumocytes for a period of time. Lack of surfactant renders affected alveoli susceptible to atelectasis of varying degrees. This alters the distribution of ventilation and ventilation–perfusion ratios.

Osmotic pressure from seawater aspiration brings additional fluid from the plasma into the lungs. Seawater aspiration produces fluid-filled alveoli that persist much longer than freshwater aspiration (Fig. 1 and Fig. 2). Perfusion of fluid-filled lung units causes pulmonary venous admixture.

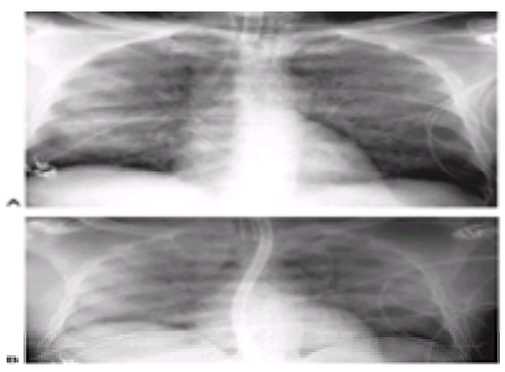

FIG. 1. Salt-water near-drowning. **(a)** Portable anteroposterior chest radiograph within 1 hr after presentation. Chest film shows extensive confluent perihilar density in the right and left lungs. Note sparing of subpleural areas at the periphery and at both bases. **(b)** Twelve hours later. Note progression of lung infiltrates throughout both lungs, air bronchograms, and reduced lung volumes despite gastric tube decompression.

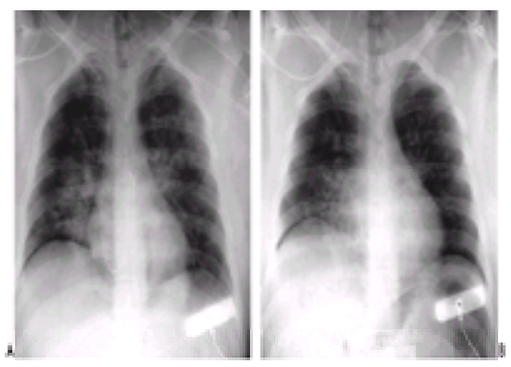

FIG. 2. Freshwater near-drowning. **(a)** Portable anteroposterior chest radiograph within hours of presentation. Note less extensive infiltrates than in Fig. 1a in the right and left midlung zones as well as reduced lung volumes. **(b)** Ten hours later. Note improvement of infiltrates with some residual RLL density and further loss of lung volumes.

Clearance of seawater from the lungs takes longer than fresh water. The space-occupying effects of seawater aspiration thus pose greater problems for rescue ventilation. Aspiration of hypertonic fluid does not inactivate pulmonary surfactant to the same extent as hypotonic fluids. Injury to type II pneumocytes, however, can occur.

Aspiration of both contaminated water and gastric contents creates additional risks. These include the risk of pneumonia and chemical injury to the pulmonary epithelium.

Hypothermia

Hypothermia can be fatal on its own without immersion or aspiration. Lowered body temperature can complicate or precipitate near-drowning in virtually any outdoor setting.

Water conducts heat 32 times faster than air because of its greater heat capacity and mass density. Depending on water temperature, immersion can rapidly lower body temperature. Unprotected persons will experience a rapid decline in body temperature in water below 72°F (22°C).

Normal clothing provides little protection from immersion hypothermia following replacement of air with water between layers of clothing and between fibers of fabric. Obesity does convey protection from hypothermia because of insulation by adipose tissue. Obesity also conveys greater buoyancy during immersion.

Hypothermia causes drowning and near-drowning by degrading functional state. Table 3 displays signs and symptoms of falling core temperature. Neuromuscular impairment develops as core temperature falls from 93° to 90°F (34° to 32°C). Loss of consciousness occurs around 84°F (29°C) unless this occurs earlier from other causes. In adults, ventricular fibrillation occurs at core temperatures around 79° to 80°F (26° to 27°C). In the absence of anoxia, survival can occur at lower temperatures.

Core temperature		Signs and symptoms	Rewarming[a]
°F	°C		
95	35	Confusion, irrationality	PER
93	34	Sensory and motor impairment	PER
90	32	Hallucinations, dysrhythmias, gross motor impairment	PER
88	31	Loss of shivering, disoriented	ACR + AER
86	30	Muscle rigidity, anesthesia	ACR + AER
84	29	Loss of consciousness	ACR + AER
81	27	Ventricular fibrillation, asystole	ACR + AER or ECR

[a]Suggested rewarming for hypothermia with a perfusing rhythm and pulse. Abbreviations: PER, passive external rewarming, e.g., blankets; ACR, active core rewarming, e.g., gastric or peritoneal lavage, heated, humidified oxygen; AER, active external rewarming (thorax only initially), e.g., heating blankets or lamps; use only with ACR if at all because of the risk of paradoxic drop in temperature; ECR, extracorporeal rewarming, considered for other pulseless hypothermia (T < 32°C).

TABLE 3. *Hypothermia and near-drowning: Effects of a falling core temperature*

Profound hypothermia can occasionally impart a protective effect on victims immersed in extremely cold water. This appears most likely in waters below 38°F (3°C) and practically never above 50°F (10°C). Such cases usually involve children over age 3 years with profound core hypothermia. The sequence of hypothermia preceding submersion by some period may be critical in order for cerebral protection to precede the anoxic insult.

Reports have attested to survival in patients immersed in frigid waters for more than 30 min and, in at least one published case with an initial rectal temperature of 72°F (22°C), 66 min.

Table 3 shows rewarming strategies for patients with a perfusing rhythm and pulse. Active core rewarming should be instituted in patients presenting with a temperature below 90°F (32°C). In patients without a pulse, CPR should be continued until rewarming has been accomplished. Extracorporeal rewarming (ECR) constitutes an efficient means for active core rewarming in pulseless severe hypothermia. Correction of hypoxemia should precede attempts at rewarming. In patients with mild hypothermia (*T* > 90°F, 32°C) passive external rewarming will usually suffice.

In most cases a lowered body temperature carries a poor prognosis. Most immersions involve water temperatures warmer than 3° to 10°C and lack the sequence of presumed hypothermia preceding asphyxia. Rather, the immersion occurs simultaneously with asphyxia. Irreversible brain damage occurs before protective cooling can take place. Moreover, adults do not cool as rapidly as small children because of greater body mass and insulation. At all ages, the combination of near-drowning and hypothermia usually causes death in the vast majority of cases.

Manifestations of Near-Drowning

Pulmonary Complication

Death rarely results from pulmonary complications, and judicious management should lead to recovery. Table 2 lists common respiratory complications in near-drowning victims.

The first concern is to ensure an adequate airway. Aspiration of a foreign body should receive a high index of suspicion especially in patients requiring clearance of pharyngeal particulates at the rescue scene. Inspection of the lower airways by fiberoptic bronchoscopy may be required to exclude foreign bodies.

In the ventilated patient, a high peak-to-plateau pressure difference may indicate residual particulate matter obstructing the lower airways or bronchospasm. In the spontaneously breathing patient, inspiratory stridor or expiratory wheezing should suggest these possibilities.

Large volumes of swallowed water can accompany near drowning. The swallowed fluid will usually be regurgitated and aspirated along with gastric contents. Large volumes of swallowed water can also restrict ventilation before and after rescue through gastric distention. After securing the airway, clinicians should decompress the stomach routinely.

Both hypertonic and hypotonic aerosol inhalation can produce bronchospasm. Direct contact of the airways with seawater or fresh water similarly can cause increased airways resistance. A trial of aerosol bronchodilator inhalation with monitoring of lung mechanics before and after treatment can confirm and relieve this complication.

Aspiration represents the next concern and requires treatment to reverse hypoxemia. The propensity for rapid changes in either direction necessitates frequent monitoring of gas exchange. Near-drowning cases typically manifest severe reduction of P_aO_2/F_IO_2 ratio; however, this index has little bearing on the eventual outcome in near-drowning and should not be used for prognosis. A P_aO_2/F_IO_2 ratio below 300 justifies consideration of positive pressure in the form of CPAP or PEEP. Chest x-rays usually reveal one of four patterns: (1) bilateral perihilar density, (2) diffuse alveolar infiltrates, (3) multifocal densities, or (4) no significant infiltrate. Seawater near-drowning will generally cause greater infiltration than freshwater aspiration at the outset (Fig. 1 and Fig. 2). Up to 20% of near-drowning cases may have clear chest films initially. Worsening of infiltrates may occur in the first 48 hr, especially with seawater near-drowning.

Initial management of aspiration depends on the degree of hypoxemia and the extent of infiltrates. Because of the systemic hypoxic injury, an oxyhemoglobin saturation of 95% or greater represents a reasonable initial target in the first few hours. Overall improvement would justify acceptance of a lower saturation around 90% thereafter.

Diffuse bilateral infiltrates and severe hypoxemia warrant the application of PEEP up to 10 to 12 cm H_2O in the intubated patient. Cerebral edema may limit the application of positive pressure. An intermediate goal consists of reduction of F_IO_2 to 0.5 or lower to prevent hyperoxic injury. Further increments of PEEP justify heB Amodynamic monitoring. Mask CPAP represents an option for the alert, spontaneously breathing patient with diffuse infiltrates.

Hypoxemia in the absence of infiltrates warrants consideration of bronchospasm or atelectasis. As noted above, freshwater drowning predisposes to atelectasis. If bronchodilators fail to improve oxygenation, cautious application of PEEP or mask CPAP can be entertained in patients with hypoxemia with mild or no infiltrates.

Precautions with application of positive airway pressure include concern for hemodynamics. In patients with unilateral or focal infiltrates, clinicians should remain alert for paradoxical worsening of hypoxemia on application of positive pressure.

The potential for lung injury and the acute respiratory distress syndrome (ARDS) exists in all cases and occurs in about 40% of near-drownings. Both seawater and freshwater near-drowning can cause injury to bronchopulmonary lining cells. Gastric aspiration, chemical constituents, and biological materials in aspirated waters or endogenous toxins from systemic injury may contribute to secondary lung injury in specific cases. Multiple organ failure from systemic injury may accompany ARDS.

Patients with near-drowning who develop ARDS usually do so within 48 hr of hospitalization. Patients with seawater near-drowning may present with an ARDS picture from the outset, which may worsen over several days. The ARDS associated with near-drowning usually responds to medical management and generally does not determine outcome. Improvement of infiltrates usually begins by the fifth or sixth day.

Corticosteroid therapy has no role in the initial management of lung injury from near-drowning. Surfactant replacement therapy also has no proven role. Diuretics can hasten resolution of pulmonary edema in hemodynamically stable patients. Delayed resolution of infiltrates in near-drowning patients with ARDS warrants consideration of pulmonary infection or fibroproliferation. Detailed consideration of the treatment of ARDS can be found in Chapter 47.

Barotrauma may complicate near-drowning. Causes include diving accidents, intubation complications such as tracheal injury or right mainstem bronchus intubation and volume injury from mechanical ventilation of lungs with low compliance.

Pneumonia can occur for several reasons. These include contaminated waters, aspiration of mouth anaerobes or pharyngeal flora, and nosocomial infection via the endotracheal tube. Nonspecific fever and leukocytosis should be anticipated early in near-drowning, but persistent or new-onset fever, leukocytosis, and infiltrates should raise concern for complicating infection.

Prophylactic antibiotics have no proven benefit in most near-drownings; however, cultures of respiratory secretions should be obtained early as a baseline and repeated based on clinical course. Leukocytes in the respiratory secretions without isolation of bacteria may indicate anaerobic infection or nonspecific lung injury. Quantitative cultures of protected specimens may be required to confirm anaerobic infection.

Indications for bronchoscopy in near-drowning include suspicion of foreign body aspiration in the upper airway, lobar collapse, and need for protected or directed specimens to exclude anaerobic or other infections.

Neurologic Complications

Neurologic outcome outweighs all other considerations in near-drowning. Anoxic encephalopathy in near-drowning can result in brain death, persistent vegetative state,

spastic quadriplegia, aphasia, cortical blindness, and recurrent seizures in addition to other deficits.

Many studies have evaluated prognostic variables in near-drowning unassociated with frigid waters. A duration of submersion longer than 25 min and a duration of rescue CPR longer than 25 min by reliable history carry a poor prognosis. Irreversible brain injury can certainly occur within a shorter interval. Initial pupillary response does not reliably predict outcome. Ongoing need for inotropic agents indicates a poor prognosis. Patients with any level of eye opening, verbal responsiveness, and purposeful movement in response to stimuli (Glasgow Coma Scale ³ 7) in the emergency room usually have a full neurologic recovery. Coma persisting after emergency room management indicates an increased risk for poor outcome, but many exceptions occur. Thus, coma has limited prognostic value.

Initial cerebral protection studies of barbiturate-induced coma and controlled hypothermia in near-drowning suggested an improved outcome; however, subsequent studies did not confirm these results. These techniques cannot be recommended at the present time. Likewise, corticosteroids have no proven benefit.

The use of intracranial pressure (ICP) monitors in near-drowning cases also has declined in recent years. An ICP greater than 20 mmHg carries a poor prognosis. Lowering the elevated ICP below 20 mmHg and maintaining cerebral perfusion pressure ³50 mmHg does not improve poor neurologic outcome but may increase survival. A normal ICP initially does not assure favorable neurologic outcome. The ICP often rises by 48 to 72 hrs, reflecting edema from anoxic injury. Monitoring ICP deserves consideration in selected cases, but in most patients empirical therapy can be implemented without ICP monitoring.

Commonly accepted management of hypoxic cerebral injury consists of hyperventilation to a P_aCO_2 of 25 mm Hg to 30 mmHg, 30° elevation of the head (after exclusion of cervical injury), fluid restriction, and mannitol infusion of 0.25 to 0.5 mg/kg ideal body weight if blood pressure allows. Individual cases may require sedation, paralysis, or anticonvulsants.

Computed tomography of the head can be useful to exclude cranial trauma and to confirm cerebral edema (Fig. 3). Cranial trauma alters the clinical picture and may justify additional interventions. Diffuse cerebral edema implies global hypoxic injury (Fig. 3).

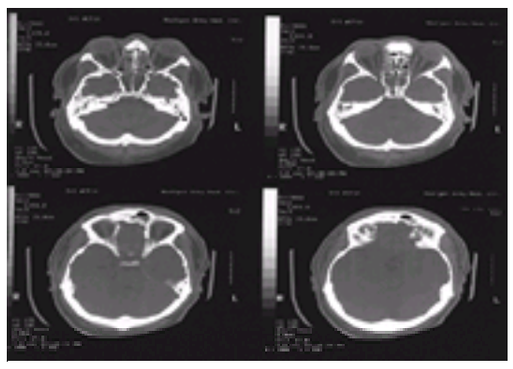

FIG. 3. Noncontrast cranial computed tomography of the patient with freshwater drowning. Note obliteration of the subarachnoid space and ventricles consistent with diffuse cerbral edema. Note also frontal and ethmoid sinus fluid density and air–fluid levels.

Computed tomography often reveals sinus opacification in near-drowning. Figure 3 reveals pansinus opacification in a case of salt-water near-drowning. Bland sinus fluid can become a source of fever later in the hospital course, particularly in the patient with nasally placed gastric tubes.

Acid–Base Disorders

Analysis of arterial blood samples generally does not occur before field resuscitation and transport to the emergency room. Severe acidemia would be expected before resuscitation because of the combination of respiratory and metabolic acidosis.

Initial arterial blood gas values obtained in the emergency room usually reflect therapeutic ventilatory support with metabolic acidosis and some degree of ventilatory compensation. Acid–base disturbances may include metabolic acidosis with incomplete respiratory compensation, combined metabolic and respiratory acidosis, or simple mild metabolic acidosis. Of note, acidosis has no particular prognostic value in near-drowning, even with pH well below 7.0.

Acid–base disorders may worsen after establishment of effective circulation. Reperfusion of ischemic tissue mobilizes lactic acid and increases carbon dioxide production. Subsequent arterial blood gases may reveal both worsening metabolic acidosis and higher P_aCO_2. Increased mechanical ventilation can compensate and should be attempted if high ventilator pressure can be avoided. Severe near-drowning injuries justify arterial catheters to monitor acid–base status and oxygenation.

Physicians may consider careful base augmentation therapy in the appropriate setting of adverse hemodynamics, maximum ventilatory support, and pH below 7.20. Unless acidosis persists, stable hemodynamics will gradually correct the disorder.

Mild cases of near-drowning may present with normal acid–base status or respiratory alkalosis. The degree of metabolic alkalosis depends on the degree of hypoxemia, anxiety, and other ventilatory stimuli.

Electrolyte Disturbances

Electrolyte disturbances occur commonly in near-drowning and may require medical management, particularly following salt-water near-drowning. In rare situations brackish waters like the Dead Sea can contribute to cardiac or systemic toxicity. Brackish waters can contain toxic amounts of divalent cations such as calcium and magnesium as well as sodium or potassium and cause specific toxicity.

Salt water consists of hypertonic concentrations of electrolytes: sodium 509 mEq/L, chloride 561 mEq/L, and potassium 11 mEq/L. Depending on the amount of salt water swallowed or aspirated, elevations of serum electrolytes can occur, resulting in hypernatremia, hyperchloremia, and hyperkalemia. Correction of hypernatremia should proceed gradually with frequent monitoring. Care should be take to avoid hyperglycemia, which may aggravate neuronal injury.

Freshwater near-drowning may lower serum sodium and chloride. These abnormalities seldom present a major clinical problem. Hypotonia in freshwater near-drowning usually responds to diuresis with normal saline replacement. Abnormalities of divalent cations may also accompany near-drowning.

Hemodynamic Complications

Near-drowning victims without hypothermia usually have normal or increased intravascular volumes and cardiac filling pressures initially. This results from swallowing and aspirating fluid. Empirical fluid administration should be avoided without hemodynamic monitoring for fear of worsening cerebral and pulmonary edema.

Later, fluid extravasation into the interstitial spaces may ensue because of systemic injury, an ominous development. Management of the patient in this situation becomes difficult because of multiple organ failure. Patients with hypothermia may present with volume contraction from diuresis.

Cardiac function can suffer from hypoxic injury initially but usually recovers with general support. Persistent need for inotropic agents has a poor prognosis. Cardiac enzymes can confirm myocardial injury. Virtually any arrhythmia can occur during resuscitation. Later, sinus tachycardia and other supraventricular arrhythmias prevail. Hypothermia can also produce characteristic ECG changes with prolongation of PR and QRS intervals, J-point elevation (Osborne waves), and cardiac dysrhythmias.

Systemic Complications

Near-drowning can produce abnormalities in other organ systems. Manifestations include renal insufficiency, coagulopathy, and hematologic abnormalities. Secondary pathophysiological processes contributing to these manifestations include disseminated intravascular coagulation, hemolysis, rhabdomyolysis, and systemic

inflammation.

Oxygen-carrying capacity remains largely intact in near-drowning. Near-normal values for red blood cell concentrations have been reported in several series. Freshwater hemolysis and salt water hemodilution do occur but have minor clinical effects on red cell mass in most cases.

Disseminated intravascular coagulation (DIC) may complicate freshwater near-drowning but not salt-water near-drowning. Bleeding diatheses, rather than thrombosis, result from DIC in most cases and may require fresh frozen plasma and platelet transfusion. Prolonged prothrombin and partial thromboplastin times and reduced platelet counts may signal the presence of DIC. Clinicians should routinely measure these values. D-dimer and fibrin split products will confirm DIC.

Near-drowning can cause acute renal failure from acute tubular necrosis. Mechanisms of injury may include hypoxemia, hemoglobinuria following hemolysis, myoglobinuria from rhabdomyolysis, or other endogenous toxin. Pigmenturia may be suspected from dark urine or, in less obvious cases, by a positive test for hemoglobin on dipstick without visible red blood cells on urinalysis. Red cell morphology or serum haptoglobin can suggest intravascular hemolysis. Urinary myoglobin and serum creatine phosphokinase (CPK) levels can confirm rhabdomyolysis with myoglobinuria. Alkalinizing the urine may merit consideration unless contraindications exist. Mild hypothermia can also affect renal tubular function and promote diuresis through nephrogenic diabetes insipidus.

Prognosis

Over 80% of patients hospitalized for near-drowning recover fully and return home. Approximately 10% of cases suffer permanent neurologic injury, and 10% die after admission. Occasional patients succumb from other complications despite neurologic recovery. No single variable can give 100% accuracy in prognosis. Coma in the first few hours cannot be relied on for individual prognosis but does indicate higher risk. Hypoxemia, acidosis, and electrolyte disturbances early in the course have no firm prognostic value. Prolonged submersion, prolonged CPR, and continuing need for inotropic support do indicate a poor prognosis.

Pulmonary injuries in near-drowning usually resolve with medical management, and neurologic injury dominates the picture for outcome. Pulmonary function testing after recovery generally reveals mild abnormalities mostly involving small airway function or bronchial airway hyperresponsiveness.

Summary

Near-drowning presents a spectrum from minimal aspiration to acute respiratory distress syndrome. Active management of pulmonary complications succeeds in most cases. Cerebral injury from anoxia is the most critical pathologic process and determines overall prognosis. Systemic organ injuries can occur, but these usually improve with medical support.

DIVING ACCIDENTS

Introduction

The term diving encompasses several techniques to safely submerge below the water surface (Table 4). These techniques include breath holding, SCUBA, surface-supplied, and saturation diving. Surface-supplied diving requires a high-pressure compressed-air conduit to a diving suit or mask. Saturation divers remain submerged for days to weeks and can enter and leave a submerged habitat.

Dive technique	Self-contained	Gas	Maximum working depth (fsw)[a]
Breath hold	Y	Air	100
SCUBA[b]			
Open system	Y	Air	130
Semiclosed	Y	32–60% O_2, N_2	150
Closed	Y	100% O_2	25
Surface-Supplied[c]			
Free flow	N	Air	200
Demand	N	16% O_2, He	300
Saturation[d]	N	O_2, He, N_2	1500

[a] Usual maximum working depth; fsw, feet of sea water.
[b] SCUBA, self-contained underwater breathing apparatus.
[c] Air supply tethered from the surface to the diver.
[d] Divers live under pressure in a deep diving chamber for days to weeks and work undersea.

TABLE 4. *Dive techniques and apparatus in common use*

In the last 20 years recreational diving has increased significantly in the United States, where diving enthusiasts number an estimated 3 to 5 million people. This rapid growth produces a steady influx of inexperienced divers. Diving accidents can occur even with adherence to accepted practices by both experienced and inexperienced divers.

Diving accidents result from environmental hazards, exposure to compressed gases, and changes of ambient pressures and volumes associated with both descent and ascent. Table 5 shows the pressure equivalents at common working depths. Because changes in pressure and volume affect the upper and lower respiratory tract, pulmonary physicians should be aware of the clinical syndromes that manifest as diving injuries. This section reviews breath-hold diving, gas-breathing disorders, descent injuries, ascent injuries, and fitness for diving.

Depth (fsw)[a]	PSIG[b]	PSIA[c]	ATA[d]	mm Hg	P_{N_2} (mm Hg)	P_{O_2} (mm Hg)
Sea level	0.0	14.7	1	760	600	160
33	14.7	29.4	2	1520	1200	320
66	29.4	44.1	3	2280	1800	480
99	44.1	58.8	4	3040	2400	640

[a] fsw, feet of sea water.
[b] PSIG, pounds per square inch gauge pressure.
[c] PSIA, pounds per square inch absolute pressure.
[d] ATA, absolute atmospheric pressure.

TABLE 5. *Pressure equivalents of various depths*

Breath-Hold Diving

Millions of people perform breath-hold dives for recreation in relatively shallow water for periods of less than 2 min. Some professional divers, such as the women divers of Japan and the pearl divers of the Tuamotu Archipelago, can dive to depths of 100 feet of seawater (fsw).

The most common medical problems associated with breath-hold diving consist of the upper respiratory tract descent injuries addressed below. Breath-hold divers often manifest the diving reflex and, occasionally, deep-water blackout, a maladaptive response.

The diving reflex accompanies breath-hold dives and immersion of the face in ice water. This reflex consists of apnea, peripheral vasoconstriction, and bradycardia, which raise systemic blood pressure and reduce cardiac output and O_2 consumption. The diving reflex may protect against hypothermia and permit increased bottom

time. Expression of the diving reflex varies considerably in humans. A variety of cardiac rhythms may accompany the diving reflex with no known significance.

Deep-water blackout results from the fall in P_aO_2 on ascent from a breath-hold dive. This maladaptive response has a similarity to shallow-water blackout (pg. 903) with the added dimension of ascent hypoxemia at the end of the dive. Dalton's law explains the pathophysiology of this phenomenon. According to Dalton's law, the partial pressure of a gas A (P_A) depends on barometric pressure and the fraction of gas A by volume: $P_A = P_B \times (\%A)$, where P_B equals barometric pressure and (%A) equals percentage of gas A by volume in the mixture.

At the beginning of the breath-hold dive, the partial pressures of oxygen, nitrogen, and carbon dioxide all increase as the barometric pressure increases with descent (Table 5). During breath-hold diving, alveolar oxygen tension tends to increase because of descent and to decrease as a result of oxygen consumption. At bottom, the P_aO_2 progressively falls because of oxygen consumption, but for a while the product of $P_B \times F_IO_2$ remains high enough to remain on bottom and suppress hypoxic drive to end the breath hold.

Breath-hold divers may hyperventilate before diving in order to lower initial P_aCO_2 and increase breath-hold time. This succeeds but also permits the P_aO_2 to decrease even lower before the urge to end breath hold. Ambient barometric pressure progressively falls as the diver ascends, and alveolar partial pressure of oxygen decreases proportionately. This can result in hypoxemic loss of consciousness and drowning. Most authorities recommend avoidance of hyperventilation before breath-hold swimming or diving.

Breath-hold divers do not normally experience pressure–volume injuries associated with ascent. Lung volumes decrease during descent in accordance with Boyle's law and can only reexpand to their original size.

Breathing Gas Disorders

Forms of diving other than breath holding utilize various combinations of inert gases and oxygen (Table 4). Some breathing gas disorders tend to occur during bottom time but can occasionally occur at other times. These include hypoxia, carbon monoxide poisoning, and carbon dioxide intoxication. Table 6 presents a differential diagnosis of loss of consciousness in divers. Some of these disorders are considered with descent or ascent injuries.

Cause	Usual time of occurrence after surfacing[a]	Phase of dive[a]	Comments
Breath-hold blackout	Before	Ascent	Without compressed air
Hypoxia	Before	Any	Equipment failure
Hypercapnia	Before	Bottom	Equipment failure
Oxygen toxicity (seizure)	Before	Bottom	
Carbon monoxide poisoning	<2 min	Ascent	Increased partial pressure of O_2 delays onset
Nitrogen narcosis	Before	Descent	May be sudden
Arterial gas embolism	<10 min	Ascent	>10 min unlikely
Decompression sickness	<6 hours	Ascent	LOC uncommon

[a]Exceptions may occur.

TABLE 6. *Differential diagnosis of loss of consciousness (LOC) in divers*

The most common cause of diving hypoxia consists of disconnection or depletion of the breathing gas supply. Another uncommon cause consists of a gas mixture with insufficient oxygen. Loss of consciousness because of lack of oxygen is the most common diving accident that results in death. Careful examination of the diving apparatus may reveal the cause of hypoxic loss of consciousness.

Carbon monoxide poisoning may result from contamination of a surface-supplied diver's air by exhaust from the air compressor or other engine entering the air intake system. Divers are usually protected during descent and at bottom by increased partial pressure of oxygen at depth. The symptoms of carbon monoxide poisoning therefore typically occur during ascent or at the surface. Divers may develop headache, nausea and vomiting, or more severe sequelae such as confusion, syncope, seizures, and loss of consciousness. Severe carbon monoxide poisoning should be treated with 100% oxygen initially, followed by recompression with hyperbaric oxygen. The diver's breathing gas should be tested for contamination.

Carbon dioxide intoxication results either from exposure to gases containing high concentrations or from retention as a result of inadequate ventilation by impaired equipment or respiratory function. With increasing levels of carbon dioxide, dyspnea and anxiety progress to impaired mental function and then loss of consciousness.

Merely surfacing will reverse mild to moderate hypoxemia and hypercapnia. In many cases a complete and reliable history may not be available. Divers with symptoms from any of these disorders at the surface should receive attention to airway, breathing, and circulation as well as 100% oxygen and consideration of recompression.

Injuries Associated with Descent

The remainder of the medical problems involving the respiratory tract can be divided into those that occur during descent or ascent. This division facilitates understanding the pathophysiology and clinical diagnosis of these entities.

Nitrogen Narcosis

Nitrogen narcosis occurs during descent to depths below 100 to 150 fsw with air breathing and becomes worse with increased depth. As mentioned earlier, according to Dalton's law, the partial pressures of all the breathed gases are increased. As the partial pressures of nitrogen and other inert gases increase, they penetrate the lipid layers of nerve cells and interfere with electrochemical transfer of signals at the synapses.

Narcosis or “rapture of the deep” may cause paresthesias, light-headedness, euphoria, overconfidence, and inability to reason. Mentation slows, resulting in memory and psychomotor impairment and even loss of consciousness (Table 6). Rapid recovery follows ascent to lesser depth. Experienced divers can develop tolerance, permitting air dives to 200 fsw.

High-Pressure Neurologic Syndrome

To overcome inert gas narcosis, divers use various mixtures of compressed gases. The most common mixture is 80% helium/20% oxygen (heliox). Helium has less lipid solubility and does not cause narcosis. With heliox, at depths greater than 500 fsw, divers can experience a different disorder with symptoms of extremity or body tremor, dizziness, nausea, vomiting, and seizure. The etiology is thought to be central nervous system hyperexcitation. The rate of descent correlates with the observation of this syndrome, and decreased rates of compression can negate the symptoms. Also, the addition of a small amount of nitrogen overcomes the features of high-pressure neurologic syndrome. Thus, trimix, the combination of helium, oxygen, and nitrogen, is used at extreme depths greater than 1000 fsw. Unfortunately some nitrogen narcosis can still occur.

Oxygen Toxicity

Recreational divers breathing compressed air seldom develop oxygen toxicity; however, some closed-circuit breathing systems use 100% O_2. The maximum depth of 100% O_2 systems is approximately 25 fsw. Divers who use mixed gases and saturation divers may become exposed to toxic levels of oxygen. Oxygen toxicity can also complicate recompression therapy. Studies of oxygen toxicities in animals and humans at increased atmospheric pressures have shown both pulmonary and central nervous system toxicities.

Pulmonary oxygen toxicity presumably results from the generation of oxygen free radicals. The resultant pulmonary pathology reveals diffuse alveolar damage and subsequent fibroproliferative changes. Divers with pulmonary oxygen toxicity may complain of substernal irritation or burning pain, cough, and dyspnea. The

appearance of symptoms is variable between individuals. Treatment consists of removal from hyperoxia and supportive care.

Divers may experience several signs and symptoms of central nervous system toxicity, which include constriction of vision, tinnitus, vertigo, facial twitching, tingling, syncope, and seizures. Seizures from oxygen toxicity are not dangerous by themselves, although in a diving environment they can precipitate a serious emergency. Oxygen toxicity should be avoided by proper attention to gas mixtures and pressure. Oxygen toxicity may be difficult to differentiate from other serious injuries. If more serious injury such as arterial gas embolism cannot be ruled out, the diver should be treated with recompression.

Upper Respiratory Tract Barotrauma

Injuries to the air-containing spaces of the auditory apparatus and paranasal sinuses are the most common conditions experienced by divers. Normally pressures in all the gas-containing spaces can be equalized to ambient pressure without resultant net change in volume. Failure to equalize pressure causes tissue injury.

Changes in pressure distort air-containing tissues until damage ensues. Boyle's law states that at constant temperature, the volume of a fixed mass of gas is inversely proportional to the pressure of the gas: $PV = K$, where P is absolute pressure, V is volume, and K is a constant. For example, if the pressure of gas is doubled, its volume is subsequently decreased by half.

Upper respiratory tract barotrauma includes external ear squeeze resulting from a tight-fitting wet suit hood, cerumen, otitis externa, or earplugs. Damage may include external ear canal hemorrhages and rupture of the tympanic membrane. Middle-ear squeeze occurs by failure of the eustachian tube to equalize pressure. The tympanic membrane may develop hemorrhage and rupture. Inner ear barotrauma can injure the round or oval window, causing perilymph fistula formation with hearing loss, tinnitus, and vertigo.

Paranasal sinus squeeze most frequently involves the frontal and maxillary sinuses as a result of obstruction of the ostia from mucus plugs, mucosal thickening, or infection. The mucosa hemorrhages, causing pain and epistaxis. Alternobaric vertigo can result from unilateral pressure differences between the middle and inner ear. This typically occurs during ascent but has been described on descent. Some divers may also experience unilateral facial paralysis from compression of air on the facial nerve as it courses near the middle ear.

Upper respiratory tract injuries usually respond to treatment with decongestants, antihistamines, and antibiotics for infection if present. Patients should refrain from diving until healing is complete. Bedrest, antiemetics, and occasionally surgery may be warranted for some of these complications.

Injuries Associated with Ascent

Pulmonary Pressure–Volume Injuries's

Boyle's law describes the pressure–volume effects of ascent and descent on air in the lungs. On ascent, the decreased pressure results in expanding volumes in the lungs. Overdistention of air spaces results in tissue injury. Normally divers continue to exhale throughout ascent, and this adequately vents excess alveolar volume. Mechanisms of pulmonary pressure/volume injury include any cause of breath holding during ascent or impedance to expiratory airflow. These causes include panic breath holding; buddy-breathing breath holding; laryngospasm, bronchospasm, or mucus plugging of the airways; pulmonary blebs and bullae; mucus impaction; coughing or forceful exhalation at low lung volume; uncontrolled ascent; and regulator malfunction.

Once the alveolus ruptures, gas escapes into the interstitial and perivascular spaces (Fig. 4). The air may be contained in the interstitium or dissect into the mediastinum, pericardium, subcutaneous tissue, retroperitoneum, or pleural space. With continued ascent, the volume of escaped gas can increase in size, causing further symptoms and signs. During ascent or within minutes of surface arrival, divers will complain of cough, chest pain, dyspnea, difficulty swallowing, hoarse voice, or hemoptysis. Table 7 presents a differential diagnosis of chest pain in the diver.

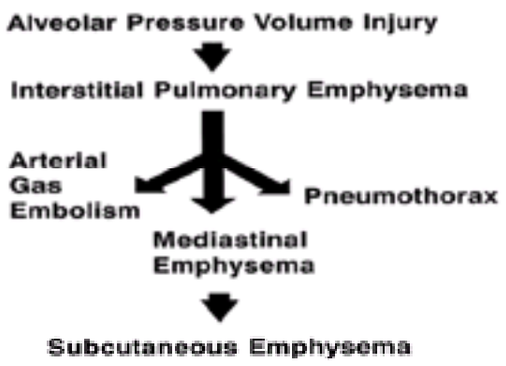

FIG. 4. Sequence of pressure–volume injury in the lung. Alveolar disruption leads to alveolar air entering the interstitial compartment of the lung. Further dissection of air proceeds along the path of least resistance. Entry of air into pulmonary veins leads to arterial gas embolism. Entry of air into the bronchovascular bundle produces mediastinal and subcutaneous emphysema. Exit of air from the interstitial space into the pleural space causes pneumothorax.

Cause	Phase of dive[a]	Comments
Pulmonary DCS[b]	Ascent	Usually accompanies other stigmata of DCS
Spinal cord DCS	Ascent	Back pain radiating to chest
Pulmonary O_2 toxicity	Bottom	Gradual onset; associated cough and dyspnea
Pneumomediastinum	Ascent	Subcutaneous crepitance
Pneumothorax	Ascent	May cause circulatory collapse
Myocardial ischemia	Any	Coronary artery disease
	Ascent	Arterial gas embolism
Hyperventilation syndrome	Any	Anxiety

[a]Exceptions may occur.
[b]DCS, decompression sickness.

TABLE 7. *Differential diagnosis of chest pain in divers*

Physical findings depend on the form of injury but may include subcutaneous crepitance, shifted trachea, distended neck veins, and absent breath sounds. Large symptomatic pneumothorax or tension pneumothorax should be treated with chest tube placement. Recompression will also decrease the size of the pneumothorax. A chest tube can be placed before decompression. If a patient with a chest tube needs recompression, the chest tube should be clamped during recompression and placed on suction during decompression.

Arterial Gas Embolization

Arterial gas embolization (AGE) constitutes the most serious form of pulmonary pressure–volume trauma. Air that escapes into the interstitium and perivascular space can also enter the pulmonary capillaries and travel to the left heart. The circulation then distributes the air systemically, most notably to the coronary and cerebral arteries. The air emboli obstruct flow, increase capillary permeability, and cause edema of surrounding tissues, disseminated intravascular coagulation, and hemoconcentration. Systemic hypertension results in increased cerebral blood flow and intracranial pressure. The latter also increases by vasogenic edema. Injury may be limited to the brain, although cardiac function usually decreases, and arrhythmias or cardiac arrest may occur.

Arterial gas embolization presents within 10 min of surfacing in over 90% of cases. Patients may present with loss of consciousness or cardiac arrest. More commonly, patients present with a wide variety of neurologic events including obtundation, seizures, vertigo, visual disturbances, headache, and sensory and motor changes.

Other features of AGE include marbling of the skin, retinal vessel emboli, and pallor of the tongue.

Treatment of AGE includes attention to the airway, breathing, and circulation. The patients should receive 100% O_2 and emergent recompression therapy. Patients with severe neurologic findings or inability to protect the airway should be intubated and hyperventilated to decrease intracranial pressure. The endotracheal tube cuff should be inflated with saline, a noncompressible material, rather than air to prevent air leak during recompression treatment.

Intravenous access should be obtained, but fluids should be administered sparingly to avoid increased intracranial pressure unless the patient has signs of obvious clinical volume depletion. Medications can include vasopressors to support hypotension and benzodiazepines for sedation and to control seizures. Patients should assume the supine position, and transport should be arranged by ground if possible or by low-flying or pressurized aircraft. The use of steroids remains controversial.

Decompression Sickness

Decompression sickness (DCS) consists of a multisystem disorder that results from nitrogen bubble formation when ambient pressure decreases after surfacing. It can occur in divers well within no-decompression guidelines or who have carefully followed decompression tables.

This phenomenon occurs as a result of Henry's law: the amount of gas that dissolves in a liquid at constant temperature is directly proportional to the partial pressure of that gas. During descent, while the diver is breathing compressed air, the alveolar partial pressures of nitrogen, oxygen, and carbon dioxide increase. The increased partial pressure of nitrogen dissolves more nitrogen in body tissues.

The depth and amount of time spent on a dive and solubility of nitrogen determine the maximum amount of gas that can be dissolved in tissues. Perfusion and tissue bulk also determine the amount of nitrogen being dissolved. Nitrogen dissolves rapidly in muscle but less so in bone and fat. The same rules apply when nitrogen leaves tissues on ascent. As a diver ascends, the ambient partial pressure of nitrogen also decreases. If ascent occurs too rapidly, nitrogen will form bubbles in body tissues.

Decompression sickness can usually be avoided by adhering to “no decompression” diving tables: a specified maximum bottom time for each depth. Repetitive dives within 12 hr require shorter bottom times because of residual nitrogen accumulation. Recreational divers should limit diving time to prevent DCS without need for decompression stops. Decompression sickness can occur in divers well within no-decompression limits or in those who have carefully followed decompression tables.

Deeper air divers and those using other mixed inert gases must ascend to a predetermined safe depth and wait to allow gases to exit tissues without bubble formation. Several decompression stops may be needed.

The bubbles can occupy interstitial, lymphatic, or intravascular spaces. They cause mechanical obstruction and compression as well as stimulating endothelial damage and hematologic abnormalities. Decompression sickness has historically been categorized into type I (joints pain and pruritus, only) and type II (other organs including CNS, lung, and heart) to distinguish mild from severe forms.

The symptoms of decompression sickness can occur immediately or most commonly 10 min to 6 hr after decompression. Symptoms appear within 24 hr after surfacing in 95% of cases. The classic presentation includes the “pain only” form, which affects the upper extremities more than the lower. The pain ranges from minimal to severe, and it is usually aggravated with movement and relieved with direct pressure. The pain may last hours and often subsides spontaneously.

The skin may be affected by marbling, rashes, and pruritus. The areas affected may be large or localized. Pruritus can be relieved with pressure. Marbling may be a sign of systemic involvement and should be treated with recompression. The lymphatics can become obstructed, resulting in edema and pain. Recompression will typically relieve pain.

The central nervous system may be affected in various forms. Bubbles frequently migrate to the white matter of the spinal cord and cause hemorrhages and degeneration. Divers may complain of back pain, although most commonly they note distal lower extremity paresthesias that spread proximally. Motor weakness may develop, and the gait may become unsteady. Bladder function may become impaired, and paraplegia soon follows. The brain can be affected less frequently with various manifestations such as vertigo, seizure, loss of consciousness, visual disturbances, and hemiplegia. Cranial nerves and the inner ear can also be affected, producing deafness, tinnitus, and vertigo.

Bubbles can form in tissues and embolize to the pulmonary circulation of the lung and give rise to increased pulmonary artery pressures, pulmonary edema, and hypoxemia. These patients complain of substernal chest pain, dyspnea, and cough.

Early recognition of DCS usually ensures survival and complete resolution of symptoms. Patients can be permanently disabled if not treated appropriately. Some patients have been successfully treated days after the onset of symptoms. Because the signs and symptoms can be subtle and confused with other less serious injuries, health care providers should err on the side of recompression treatment.

Treatment of DCS is similar to that for arterial gas embolism and includes prompt recompression and 100% O_2. Additionally, DCS victims are typically hemoconcentrated and intravascularly volume depleted secondary to third-space movement of fluids through permeable capillaries. They often have volume contraction and should be vigorously fluid resuscitated with normal saline, although pulmonary edema should be avoided. Use of dextran is no longer recommended because of the risk of fluid overload, renal failure, and anaphylaxis. Antiplatelet drugs and anticoagulants have no proven benefits for postinjury treatment. The Divers Alert Network [phone (919) 684-8111] can give advice for medical emergencies involving divers.

Air Travel After Diving

Recreational divers will frequently travel to exotic areas to dive, and many travel by air after diving. Some divers develop symptoms of decompression sickness during the air travel. Most commercial aircraft are pressurized to 5000 to 8000 feet, and this results in decreased ambient pressure. Subsequently, nitrogen may come out of solution causing decompression sickness. One study found asymptomatic intracardiac air bubbles in subjects flying at simulated altitudes of 9000 m at 12 and 24 hr after no-decompression dives. No adequate studies have established firm guidelines for air travel after diving, but most experts advise waiting 12 hr after no-decompression dives and 24 hr after decompression stop dives or multiple dives.

Medical Evaluation for Diving Fitness

All divers should obtain a physical examination before starting SCUBA diving and annually thereafter. The evaluation should focus on the use of medications as well as the upper and lower respiratory tracts, cardiovascular system, and central nervous system. Medical clearance to return to diving should be obtained following virtually any acute illness. Table 8 lists absolute and relative contraindications for fitness to dive. Some relative contraindications can be treated and relieved. Some absolute contraindications can be evaluated on a case-by-case basis.

Absolute contraindications	Relative contraindications
Pregnancy	Monomeric tympanic membrane
Active middle ear infection	Cholesteatoma
Poststapedectomy	Ear atresia/stenosis
Meniere's disease	Chronic otitis externa
Tracheostomy	Sinus obstruction
Osteomyelitis	Migraine headaches
Dental caries	Prior thoracic surgery
Poorly controlled asthma	Mild asthma
Exercise-induced asthma	History of pneumothorax
Cold air bronchospasm	Hypertension
COPD	Herniated nucleus pulposa
Active pulmonary infections and diseases	Medications
Cavitary lung diseases	Unilateral sensorineural hearing loss
Seizure disorders	
Coronary artery disease	
Prior arterial gas embolism	
Decompression sickness	
Insulin-dependent diabetes mellitus	
Sickle cell trait or disease	
Esophageal diverticulae	
Active ruptured tympanic membrane	

TABLE 8. *Fitness for diving: Recommended restrictions for common medical conditions*

The pulmonary evaluation should identify preexisting and occult pulmonary diseases that may lead to overinflation and decompensation during diving. Mass screening of divers with chest x-ray and pulmonary function testing seems unwarranted; however, any history of smoking, cough, dyspnea, asthma, pneumothorax, pneumonia, or other pulmonary disease warrants further investigation before clearance.

If history or physical examination suggest pulmonary abnormalities, clinicians should obtain pulmonary function tests, provocative tests for asthma, and chest x-ray. These still may not identify all patients at risk for injury. Physicians should avoid “clearing” divers to dive in shallow water only. The greatest change in volumes occurs in the first 33 feet of a dive.

Conclusion

Diving accidents represent medical complications with interesting manifestations and pathophysiology. These result mostly from the toxic effects of breathing gases and the physical properties of gas volumes under compression or decompression. A careful history can narrow the differential diagnosis considerably. Clinicians should consider recompression therapy for divers with loss of consciousness.

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CHAPTER

47 Acute Respiratory Failure

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INTRODUCTION

The respiratory system's primary purpose is to provide fresh gas from the environment to the alveolus, where the capillary blood can exchange oxygen for carbon dioxide across a thin gas-permeable membrane. Provision of oxygen is fundamental to sustaining aerobic metabolism, while carbon dioxide elimination, acting through the bicarbonate buffer system, helps maintain pH homeostasis.

Respiratory failure may be thought of as a problem in one or more of the steps necessary to sustain oxygen availability for mitochondrial energy production. Dysfunction of the respiratory system may occur in ventilation (the movement of gases between the environment and the lungs), in intrapulmonary gas exchange (the process in which mixed venous blood releases CO_2 and becomes oxygenated), in gas transport (the delivery of adequate quantities of oxygenated blood to the metabolizing tissue), or in tissue gas exchange (the extraction or utilization of O_2 and release of CO_2 by the peripheral tissues). The latter two steps in this process may fail independently of the performance of the lung or ventilatory pump.

This discussion examines one primary manifestation of acute respiratory insufficiency—oxygenation failure. The aim is to describe an approach to management that flows from an understanding of the underlying pathophysiology. Ventilatory failure, the second major manifestation of acute respiratory insufficiency, is discussed in Chapter 43 and Chapter 50.

OXYGENATION FAILURE

Definitions

Tissue O_2 delivery, also known as O_2 transport (DO_2), depends not only on the partial pressure of arterial oxygen (P_aO_2) but also on nonpulmonary factors—cardiac output (Q_T), hemoglobin (Hgb) concentration, and the ability of Hgb to take up and release O_2: $DO_2 = Q_T \times C_aO_2$, and $C_aO_2 = 1.36$ (Hgb) $S_aO_2 + 0.003$ (P_aO_2). Cardiogenic shock, anemia, and carbon monoxide poisoning provide clinical examples of O_2 transport failure. Laboratory abnormalities characteristic of such conditions are lactic acidosis and reduced O_2 content of mixed venous blood (even in the face of adequate arterial oxygen tension).

Failure of O_2 uptake refers to the inability of tissue to extract and utilize O_2 for aerobic metabolism. The clearest clinical examples of a derangement in this terminal phase of the oxygen transport chain are cyanide poisoning, in which cellular cytochromes (key enzymes in the electron transport process) are inhibited, and septic shock. During sepsis there is failure of an often generous cardiac output to distribute appropriately and/or an inability of the tissues themselves to make use of the O_2 available. Unlike transport insufficiency, failure of tissue uptake is distinguished by normal or high values for mixed venous oxygen tension, saturation, and content. Thus, some indices that are helpful in other forms of oxygenation failure, i.e., cardiac output, arterial O_2 tension, and mixed venous O_2 saturation (S_vO_2), may not reflect impaired tissue O_2 uptake; lactic acidosis may be the sole laboratory indicator. Therapy directed at failure of the O_2 transport and uptake mechanisms is discussed in detail elsewhere. The present discussion focuses on the problems that bear on the performance of the lung in oxygenating the arterial blood.

MECHANISMS OF ARTERIAL HYPOXEMIA

Six mechanisms may contribute to arterial oxygen desaturation (Table 1):

Low inspired F_IO_2
Hypoventilation
Impaired diffusion
V/Q mismatching
Shunt
Desaturated mixed venous blood[a]

[a] In the presence of other mechanisms for hypoxemia.

TABLE 1. *Mechanisms ofarterial hypoxemia*

1. Inhalation of a hypoxic gas mixture or severe reduction of barometric pressure.
2. Hypoventilation.
3. Impaired alveolar diffusion of oxygen.
4. Ventilation/perfusion *(V/Q)* mismatching.
5. Shunting of systemic venous blood to the systemic arterial circuit.6. Abnormal desaturation of systemic venous blood.

Low Inspired Oxygen Fraction

A decrease in the partial pressure of inhaled oxygen occurs in toxic fume inhalation, in fires that consume O_2 in combustion, and at high altitude because of reduced barometric pressure.

Hypoventilation

Hypoventilation causes the partial pressure of alveolar oxygen (P_AO_2) to fall when alveolar oxygen is not replenished quickly enough in the face of its ongoing removal by the blood. Although the arterial partial pressure of oxygen (P_aO_2) may fall much faster than P_aCO_2 rises during the initial phase of hypoventilation or apnea, the steady-state concentration of P_AO_2 is predicted by the alveolar gas equation:

$$P_AO_2 = P_IO_2 - P_aCO_2/R$$

In this equation, P_IO_2 is the partial pressure of inspired oxygen at the tracheal level (corrected for water vapor pressure at body temperature), and R is the respiratory exchange ratio, i.e., the ratio of CO_2 production to oxygen consumption at steady state. This value usually approximates 0.8. since normally the rate of oxygen consumed by the tissues exceeds that at which CO_2 is produced. Transiently, however, R can fall to very low values as oxygen is taken up faster than CO_2 is delivered to the alveolus. Such a mechanism explains posthyperventilation hypoxemia and hypoxemia that accompanies hemodialysis across membranes that remove CO_2.

Impaired Diffusion

Impaired oxygen diffusion prevents complete equilibration of alveolar gas with pulmonary capillary blood. Although this mechanism has uncertain clinical importance, many factors that adversely influence diffusion are encountered clinically: increased distance between alveolus and erythrocyte, decreased O_2 gradient for diffusion, and shortened transit time of the red cell through the capillary (high cardiac output with limited capillary reserve).

Ventilation/Perfusion Mismatching

Ventilation/perfusion *(V/Q)* mismatching is the most frequent contributor to clinically important O_2 desaturation. Lung units that are poorly ventilated in relation to perfusion cause desaturation; high-*V/Q* units contribute to physiological deadspace but not to hypoxemia. The relationship of O_2 content (C_aO_2) to P_aO_2, like that of P_aO_2 and hemoglobin saturation, is curvilinear. At normal barometric pressure, little additional O_2 can be loaded onto blood with already saturated Hgb, no matter how high the O_2 tension in the overventilated alveolus may rise. Because samples of blood exiting from different lung units mix gas contents (not partial pressures), overventilating some units in an attempt to compensate for others that are underventilated does not maintain P_aO_2 at a normal level. Hence, when equal volumes of blood from well-ventilated and poorly ventilated units mix, the blended sample will have an O_2 content halfway between them but a P_aO_2 disproportionately weighted toward that of the lower-*V/Q* unit. Even though total V_E and Q may be absolutely normal, regional *V/Q* mismatching will cause P_aO_2 to fall.

Supplemental O_2 will reverse hypoxemia when *V/Q* mismatching, hypoventilation, or diffusion impairment is the cause. (The P_AO_2 of even poorly ventilated units climbs high enough to achieve full saturation.) After a sufficient period of time has been spent breathing 100% O_2, only perfused units that are totally unventilated (shunt units) contribute to hypoxemia. However, when hypoxemia is caused by alveolar units with very low *V/Q* ratios, relatively concentrated O_2 mixtures must be given before a substantial change in the P_aO_2 is observed.

Shunting

The term *shunt* refers to the percentage of the total systemic venous blood flow that bypasses the gas-exchanging membrane and transfers venous blood unaltered to the systemic arterial system. Changes in F_IO_2—either upward or downward—have very little influence on P_aO_2 when the true shunt fraction, as measured on pure oxygen, exceeds 30% (Fig. 1). In contrast, venous admixture of similar magnitude is variably responsive to the extent that low-*V/Q* units account for the hypoxemia. Shunting can be intracardiac, as in cyanotic right-to-left congenital heart disease, opening of a patent foramen ovale because of right ventricular overload, or result from passage of blood through abnormal vascular channels within the lung, e.g., pulmonary arteriovenous communications. However, by far the most common cause of shunting is pulmonary disease characterized by totally unventilated lung units that cannot respond to oxygen therapy. After an extended exposure to an F_IO_2 of 1.0, all alveoli that remain open are filled with pure oxygen. Hence, the percentage of shunt can be calculated from the formula:

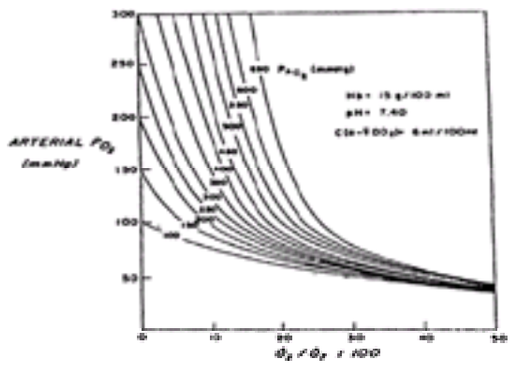


FIG. 1. Relationship of arterial oxygen tension (P_aO_2) to true shunt fraction (Q_S/Q_T) for a range of alveolar oxygen tensions (P_AO_2) that are achieved by varying fractions of inspired oxygen (F_IO_2) from room air to pure oxygen. Variations of F_IO_2 exert negligible effects on P_AO_2 when true shunt exceeds 30%. (Reprinted with permission from Pontoppidan et al. Acute respiratory failure in the adult. *N Engl J Med* 1972;287:743–752.)

$$Q_S/Q_T = [(C_cO_2 - C_aO_2)/(C_cO_2 - C_vO_2)] \times 100$$

In this equation, *C* denotes content, and the lower case subscripts *c, a,* and *v* denote end-capillary, arterial, and mixed venous blood, respectively. In making such calculations, end-capillary and calculated alveolar oxygen tensions are assumed equivalent. For a patient breathing pure O_2, shunt fractions <25% can be estimated rapidly by dividing the alveolar-to-arterial O_2 tension difference (»670 – P_aO_2) by 20, assuming also that the P_aCO_2 and C_vO_2 are normal. Note that some absorption atelectasis may occur in very low-*V/Q* areas when pure oxygen is breathed, adding to the measured shunt. In the clinical setting, however, the magnitude of this artifact is usually small.

At inspired oxygen fractions less than 1.0, true shunt cannot be estimated reliably by an analysis of oxygen contents, but venous admixture or physiological shunt can. (Note: many authors refer to a venous admixture from any cause as “shunt.”) Any degree of arterial O_2 desaturation can be considered as if it all originated from true shunt units. To calculate venous admixture, C_cO_2 in the shunt formula is estimated from the ideal alveolar PO_2 at that particular fraction of inspired oxygen (F_IO_2).

Many indices have been devised in an attempt to characterize the efficacy of oxygen exchange across the spectrum of F_IO_2. Although no index is completely successful, the P_aO_2/P_AO_2 ratio and the alveolar-to-arterial oxygen tension difference $D(A\text{-}a)O_2$ are often utilized. Both, however, are affected by changes in S_vO_2, even when the lung tissue itself retains normal ability to transfer oxygen to the blood. Another imprecise but commonly used indicator of gas exchange is the P_aO_2/F_IO_2 ratio (the “*P/F*” ratio). In healthy adults, this ratio normally exceeds 400, whatever the F_IO_2 may be. Hypoventilation and changes in the inspired O_2 concentration minimally alter these ratios in the absence of F_IO_2-related absorption atelectasis or cardiovascular adjustments. Whatever index is employed, it should be emphasized that the end-expiratory lung volume and mean alveolar pressures can exert a profound influence. For this reason, many centers utilize an oxygenation index that incorporates

the mean airway pressure when assessing the efficiency of transpulmonary O_2 transfer under conditions of controlled mechanical ventilation.

Abnormal Desaturation of Systemic Venous Blood

The admixture of abnormally desaturated venous blood is an important mechanism acting to lower P_aO_2 in patients with impaired pulmonary gas exchange and reduced cardiac output. C_vO_2, the product of Hgb concentration and S_vO_2, is influenced by cardiac output (Q), arterial oxygen saturation (S_aO_2), and oxygen consumption (VO_2):

$$S_vO_2 \approx S_aO_2 - [VO_2/(\text{Hgb} \times Q)]$$

It is clear from this equation that S_vO_2 is directly influenced by any imbalance between VO_2 and oxygen delivery. Thus, anemia uncompensated by an increase in cardiac output or a cardiac output too low for metabolic needs can cause both S_vO_2 and P_aO_2 to fall when the venous admixture percentage is abnormal.

Fluctuations in S_vO_2 exert a more profound influence on P_aO_2 when the shunt is fixed, as in *regional* lung diseases (e.g., atelectasis), than when the shunt varies with changing cardiac output, as it tends to do in diffuse lung injury (ARDS) (Fig. 2). Even when S_vO_2 is abnormally low, P_aO_2 will remain unaffected if all mixed venous blood gains access to well-oxygenated, well-ventilated alveoli. A marked decline in S_vO_2 without arterial hypoxemia occurs routinely during heavy exercise in healthy subjects. Thus, abnormal *V/Q* matching or shunt is necessary for venous desaturation to be a contributing mechanism in hypoxemia.

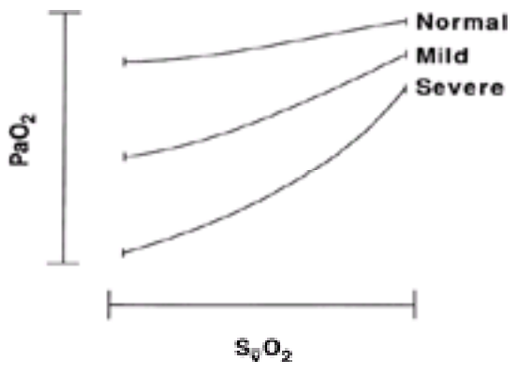
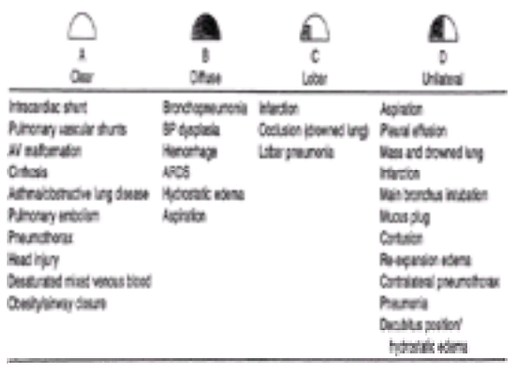


FIG. 2. Influence of mixed venous oxygen saturation (S_vO_2) on P_aO_2 in patients with mild and severe lung disease. Variations in S_vO_2 related to an oxygen consumption/delivery imbalance have minimal effects on P_aO_2 in normal subjects but may profoundly affect P_aO_2 in patients with extensive lung disease. (Reprinted with permission from Marini JJ, Wheeler AP. *Critical Care: The Essentials,* 2nd ed. Baltimore: Williams & Wilkins, 1997.)

COMMON CAUSES OF HYPOXEMIA

Oxygenation crises are conveniently categorized by their radiographic appearances, which give important clues to the appropriate management approach. Lung collapse (atelectasis), diffuse or patchy parenchymal infiltration, hydrostatic edema, localized or unilateral infiltration, and a clear chest x-ray (CXR) are common patterns (Fig. 3).



Clear	Diffuse	Lobar	Unilateral
Intracardiac shunt	Bronchopneumonia	Infarction	Aspiration
Pulmonary vascular shunts	BP dysplasia	Occlusion (drowned lung)	Pleural effusion
AV malformation	Hemorrhage	Lobar pneumonia	Mass and drowned lung
Cirrhosis	ARDS		Infarction
Asthma/obstructive lung disease	Hydrostatic edema		Main bronchus intubation
Pulmonary embolism	Aspiration		Mucus plug
Pneumothorax			Contusion
Head injury			Re-expansion edema
Desaturated mixed venous blood			Contralateral pneumothorax
Obesity/airway closure			Pneumonia
			Decubitus position/ hydrostatic edema

FIG. 3. Classification of oxygenation failure by radiographic pattern. (Reprinted with permission from Marini JJ, Wheeler AP. *Critical care: the essentials,* 2nd ed. Baltimore: Williams & Wilkins, 1997.)

Atelectasis

Variants of Atelectasis

There are several morphologic types and mechanisms of atelectasis. Regional microatelectasis spontaneously develops in a healthy lung during shallow breathing when it is not periodically stretched beyond its usual tidal range. Plate-like atelectasis may be an exaggeration of this phenomenon caused by regional hypodistention (i.e., pleural effusion or impaired diaphragmatic excursion). Both micro- and plate-like atelectasis occur most commonly in dependent regions. Lobar collapse usually results from gas absorption in an airway plugged by retained secretions, a misplaced endotracheal tube, or a central mass. External bronchial compression and regional hypoventilation are important in some patients. Micro- and plate-like atelectasis occur routinely in patients at prolonged uninterrupted bed rest and in postoperative patients who have undergone upper abdominal incisions.

Potential consequences of acute atelectasis are worsened gas exchange, pneumonitis, and increased work of breathing. The P_aO_2 drops precipitously to its nadir within minutes to hours of a sudden bronchial occlusion, but it then improves steadily over hours to days as hypoxic vasoconstriction and mechanical factors increase pulmonary vascular resistance through the local area. Whether an individual patient manifests hypoxemia depends heavily on the vigor of the hypoxic vasoconstrictive response, the abruptness of collapse, and the tissue volume involved. If small areas of atelectasis develop slowly, hypoxemia may never surface as a clinical problem.

Diffuse microatelectasis may be radiographically silent but detectable on physical examination by dependent (posterior or basilar) end-inspiratory rales that improve after several sustained deep breaths (“sighs”) or coughs. Plate atelectasis yields similar physical findings plus tubular breath sounds and egophony over the involved area. Lobar atelectasis gives a dull percussion note and diminished breath sounds if the bronchus is occluded by secretions but tubular breath sounds and egophony if the central airway is patent. (The latter findings correlate well with the presence of air bronchograms on CXR.) Plate atelectasis most frequently develops at the lung base above a pleural effusion or above a raised, splinted, or immobile hemidiaphragm. Lobar atelectasis most commonly occurs in patients with copious airway secretions and limited power to expel them. Acute upper lobe collapse is less common and tends to resolve quickly because of comparatively good gravitational drainage. Collapse of the left lower lobe is more frequent than collapse of the right lower lobe, perhaps because of its retrocardiac position and its smaller-caliber, sharply angulated bronchus. Lobar atelectasis may be complete or partial, but in either case it is radiographically recognized by opacification, displaced fissures, compensatory hyperinflation of surrounding tissue, and obliterated air–soft tissue boundaries. Small amounts of pleural fluid are a natural concomitant of lobar collapse and do not necessarily signify an additional pathologic process.

Management of Atelectasis

Prophylaxis

Effective prevention of atelectasis in high-risk patients counteracts shallow breathing and improves secretion . Obesity, chronic bronchitis, secretion retention, neuromuscular weakness, pain, and advanced age are predisposing factors. Atelectasis is to be expected whenever the patient is prevented from taking a deep breath by pain, splinting, or weakness. Upper abdominal, thoracic, and lower abdominal incisions are associated with the highest incidence of postoperative atelectasis (in that order). Preoperatively, the airways should be maximally dilated and free of infection. Postoperatively, patients should be encouraged to breathe deeply, to sit upright, and to cough vigorously. Pain should be relieved, but alertness preserved. Frequent turning and early mobilization are among the most important prophylactic maneuvers. Continuous positive airway pressure (CPAP) may be helpful, especially in intubated patients. Respiratory therapy (RT) techniques such as airway suctioning, incentive spirometry, and chest physiotherapy are prophylactically (as well as therapeutically) effective in well-selected patients.

Treatment

Whenever possible, mobilization is the best treatment. Periodic deep breathing effectively reverses plate and microatelectasis. Sustained deep breaths are particularly effective. Whether a higher lung volume is achieved by positive airway pressure or by negative pleural pressure is immaterial, assuming that a similar extent and distribution of distention occurs in both cases. Although rational, the place of positive end-expiratory pressure in treatment of *established* collapse has not been clarified. Relief of chest wall pain helps to reduce splinting and enables more effective coughing. Intercostal nerve blocks with anesthetic agents such as bupivacaine may be effective for 8 to 12 hrs. Intrapleural instillation of lidocaine or bupivicaine (via catheter) can occasionally be effective, but pleural anesthesia may induce temporary ipsilateral diaphragmatic paralysis. Epidural narcotics may also be effective in certain settings. Retained secretions must be dislodged from the central airways. In the unintubated patient, effective bronchial hygiene is inconsistently accomplished with blind tracheal suctioning alone. Pharyngeal airways certainly help, but they are not well tolerated in awake patients and are not intended for extended care. Vigorous respiratory therapy initiated soon after the onset of lobar collapse can reverse most cases of atelectasis secondary to airway plugging within 24 to 48 hrs. As a general rule, fiberoptic bronchoscopy should be reserved for patients with symptomatic lobar collapse who lack central air bronchograms and who cannot undergo (or fail to respond to or tolerate) 48 hrs of vigorous respiratory therapy (external chest physiotherapy, internal percussive ventilation at pulmonary resonant frequency, etc.). Even whole-lung collapse usually merits at least one respiratory therapy treatment before bronchoscopy is performed. After reexpansion, a prophylactic respiratory therapy program should be initiated to prevent recurrence. Adjunctive measures (e.g., bronchodilators, hydration, and frequent turning) should not be ignored.

Diffuse Pulmonary Infiltration

When fluid or cellular infiltrates cause alveolar flooding or collapse, severe refractory hypoxemia may result. Fluid confined to the interstitial spaces may cause hypoxemia as a result of peribronchial edema, *V/Q* mismatching, and microatelectasis; however, interstitial fluid itself does not interfere with oxygen exchange. Very few processes are confined exclusively to the air spaces or to the interstitium. Radiographic signs of alveolar filling include segmental distribution, coalescence, fluffy margins, air bronchograms, rosette patterns, and silhouetting of normal structures. A diffuse infiltrate is said to be largely interstitial if these signs are largely absent and the infiltrate parallels the vascular distribution. Any diffuse interstitial process will appear more radiodense at the bases than at the apices, in part because there is more tissue to penetrate and because vascular engorgement tends to be greater there. Alveoli are also less distended at the bases, so the ratio of aerated volume to total tissue volume declines.

The major categories of acute disease that produce diffuse pulmonary infiltration and hypoxemia are pneumonitis (infection and aspiration), cardiogenic pulmonary edema, intravascular volume overload, and the acute respiratory distress syndrome (ARDS). From a radiographic viewpoint, these processes may be difficult to distinguish; however, a few characteristic features are helpful.

Hydrostatic Edema

Perihilar infiltrates (sparing the costophrenic angles), a prominent vascular pattern, and a widened vascular pedicle suggest volume overload or incipient cardiogenic edema (Fig. 4). A gravitational distribution of edema is highly consistent with well-established left ventricular failure (or long-standing severe volume overload), especially when accompanied by cardiomegaly and a widened vascular pedicle. Patchy peripheral infiltrates that lack a gravitational predilection and show reluctance to change with position suggest ARDS. Interestingly, septal (Kerley) lines and distinct peribronchial cuffing are very seldom seen in classical ARDS. On the other hand, prominent air bronchograms are quite unusual with hydrostatic etiologies but occur commonly in permeability edema (ARDS) and pneumonia.

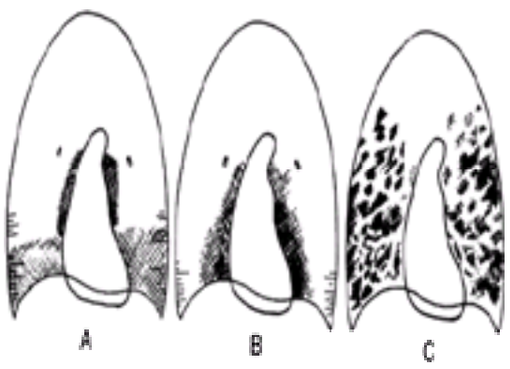


FIG. 4. Radiographic patterns in patients with impaired oxygenation as a result of congestive heart failure **(left),** vascular congestion caused by volume overload **(middle)**, and acute respiratory distress syndrome **(right)**. Kerley lines, widened vascular pedicle, costophrenic angle sparing, blurred hilar structures, and paucity of air bronchograms help distinguish congestive heart failure from ARDS. (Reprinted with permission from Milne et al. *Am J Roentgenol* 1985;144:879–894.)

Variants of Hydrostatic Edema

Hydrostatic edema (high-pressure edema, HPE) may occur in multiple settings that have different implications for prognosis and treatment. The most familiar form of HPE accompanies left ventricular failure. In this setting, signs of systemic hypoperfusion and inadequate cardiac output often accompany oxygenation failure. However, HPE can develop even with a normally well-compensated ventricle during transient heart dysfunction (ischemia, hypertensive crisis, arrhythmias). When the myocardium fails to relax fully during diastole (“diastolic dysfunction”), superimposed loading or temporary disturbances of left heart contractility (e.g., ischemia), mitral valve functioning, or heart rate or rhythm may cause rapid, transient alveolar flooding known as “flash pulmonary edema.” In this setting, extensive radiographic infiltrates may both develop and resolve with impressive speed.

Acute Lung Injury and Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) was originally called *adult* respiratory distress syndrome. In current parlance, acute lung injury is the general term that refers to all degrees of radiographically apparent, diffuse hypoxemic lung injury. The ARDS is the most severe form of acute lung injury. Acute respiratory distress syndrome is an imprecise term, often applied to any acute diffuse parenchymal infiltration associated with severe hypoxemia and not attributable to HPE. However, the ARDS designation is most useful when restricted to acute noncardiogenic pulmonary edema with certain characteristic features:

1. Delay between the precipitating event and the onset of dyspnea.
2. Impaired respiratory system compliance.
3. Markedly reduced aerated lung volume.
4. Refractory hypoxemia.
5. Delayed resolution.

The pathogenesis of permeability edema is almost certain to vary with the inciting event. Despite its many diverse causes, sepsis, aspiration, and multiple trauma account for the vast majority of cases. The core pathophysiology of ARDS is sufficiently similar to warrant a common treatment approach. A prominent feature of all forms of ARDS is injury to the alveolar–capillary membrane from either the gas side (e.g., smoke inhalation, aspiration of gastric acid) or the blood side (e.g., sepsis, fat embolism). Increased membrane permeability allows seepage of protein-rich fluid into the interstitial and alveolar spaces. Such fluids inhibit surfactant, contributing to widespread atelectasis. Although wedge pressure usually remains normal, increased pulmonary vascular resistance and some degree of pulmonary hypertension are almost invariable in the latter stages of severe disease. Extreme pulmonary hypertension is a very poor prognostic sign. Diffuse pulmonary infiltration with a normal wedge pressure can be seen in other problems, such as flash pulmonary edema and partially treated heart failure. Apart from any difference in capillary pressure,

permeability edema differs from hydrostatic edema in that it resists clearance by diuretic therapy and initiates a cellular inflammatory response that may require weeks to recede and even longer to heal.

Rapidly Resolving Noncardiogenic Edema

A few disorders that fall loosely under the heading of ARDS are worth noting because of their fundamentally different pathophysiology and clinical course. In certain settings, transient disruption in the barrier function of the pulmonary capillary can occur without overt endothelial damage. Neurogenic and heroin-induced pulmonary edema, for example, are two problems in which a transiently elevated pulmonary venous pressure is believed to open epithelial tight junctions, forcing extravasation of proteinaceous fluid. However, resealing and resolution of edema occur promptly without widespread endothelial damage or protracted inflammation. A similar process may be seen in settings such as severe metabolic acidosis and cardiopulmonary resuscitation. From the alveolar side, certain inhalational injuries (e.g., limited chlorine gas or ammonia exposure) can produce a dramatic initial picture, only to clear rapidly over a brief period.

Hypoxemia with a Clear Chest X-Ray

It is not uncommon for patients to present with life-threatening hypoxemia without major radiographic evidence of infiltration. In such cases, occult shunting and severe *V/Q* mismatching are the most likely mechanisms (Table 1). Intracardiac or intrapulmonary shunts, asthma and other forms of airway obstruction, low lung volume superimposed on a high closing capacity (i.e., bronchitis in a supine obese patient), pulmonary embolism, and occult microvascular communications (such as occur in patients with cirrhosis) are potential explanations. Hypoxemia is amplified by profound desaturation of mixed venous blood, by reversal of hypoxic vasoconstriction with therapeutic vasoactive agents (i.e., nitroprusside, calcium channel blockers, and dopamine), and by the severe *V/Q* imbalance consequent to acute head injury. (Acute oxygenation crises following head trauma has been termed “nonedematous respiratory distress syndrome,” NERDS).

Unilateral Lung Disease

Unilateral infiltration or marked asymmetry of radiographic density suggests a confined set of etiologic possibilities, most of which occur in highly characteristic clinical settings (Fig. 3). Marked asymmetry of radiographic involvement should prompt an especially careful search for an unaddressed and readily reversible cause of hypoxemia. In some cases, especially pneumonitis or airway plugging, precautions (i.e., positioning, careful airway suctioning) should also be taken against generalization of the process.

Techniques to Improve Tissue Oxygenation

Basic Therapeutic Principles

Although atelectasis, fluid overload, and infection (Table 2) often yield to specific measures, the treatment of diffuse lung injury remains largely supportive. The primary therapeutic aims are to maintain oxygen delivery, to relieve an excessive breathing workload, and to establish electrolyte balance while preventing further damage from oxygen toxicity, barotrauma, infection, and other iatrogenic complications. To these ends, the clinician should bear in mind a few fundamental principles.

Increase F_{IO_2}
Increase mean lung volume and alveolar pressure
PEEP/Auto-PEEP
Extend inspiratory time fraction
Decubitus, upright, or prone positioning
Bronchodilation
Improve O_2 delivery/consumption ratio
Reduce O_2 requirements
Work of breathing
Fever
Agitation
Increase cardiac output
Increase hemoglobin
Remove pulmonary vasodilators (e.g., nitroprusside)
Consider adjunctive support
Vibration
Nitric oxide or inhaled prostacyclin

TABLE 2. *Techniques to improve tissue oxygenation*

Minimize the Risk/Benefit Ratio

Positive airway pressure, oxygen, and vasoactive drugs are potentially injurious. Therefore, there should be frequent reassessment of the need for current levels of positive end-expiratory pressure (PEEP), F_IO_2, and use and intensity of ventilator support. An oxygen saturation of 85% may be acceptable if the patient has adequate oxygen-carrying capacity and circulatory reserve without signs of oxygen privation (e.g., lactic acidosis cardiac ischemia, arrythmia, and cerebral dysfunction). On the other hand, a reduced O_2 saturation may stimulate ventilatory drive and increase dyspnea in a patient with ventilatory insufficiency. Allowing P_aCO_2 to climb slowly (buffering pH, if necessary, with $NaHCO_3$) may minimize the ventilatory requirement and reduce the risk of barotrauma. Mean intrathoracic pressure can be reduced by allowing the patient to provide as much ventilatory power as possible, compatible with ventilatory capability and comfort.

Prevent Therapeutic Accidents

Patients should be kept under direct observation at all times by well-trained personnel prepared to intervene appropriately, 24 hrs per day. Paralyzed patients must be watched with special care, as ventilation is totally machine-dependent. Furthermore, the hands must be restrained in semiconscious, agitated, confused, or disoriented patients who receive mechanical ventilation; abrupt ventilator disconnections and extubations can produce lethal bradyarrhythmias, hypoxemia, asphyxia, or aspiration. Special caution is warranted in orally intubated patients, who tend to self-extubate readily. In the setting of pulmonary edema, the interruption of PEEP for even brief periods (suctioning, tubing changes) may cause profound, slowly reversing desaturation as lung volume falls and the airways rapidly flood with edema fluid. The stomach should be decompressed in most recently intubated patients who demonstrate air swallowing or ileus. In mechanically ventilated patients, the clinician must stay alert to the possibility of tension pneumothorax, especially in patients with radiographic evidence of pneumomediastinum or subcutaneous emphysema. Because of the very high incidence of tissue rupture, prophylactic chest tubes may be indicated for patients who form tension cysts that evolve on serial films.

Optimize Extrapulmonary Management

Intravascular volume must be carefully regulated. Although excessive administration of fluids must clearly be avoided to minimize lung water and improve oxygen exchange, severe fluid restriction may compromise perfusion of gut and kidney. Appropriate levels of nutritional support and prophylaxis for deep venous thrombosis, skin breakdown, and gastric stress ulceration should be considered for all mechanically ventilated or immobile patients.

The routine early use of corticosteroids is not justified; adverse changes in immunity, mental status, metabolism, and protein wastage tend to outweigh any potential therapeutic benefit in the first week of the course. Acute respiratory distress syndrome caused by known vasculitis, fat embolism, or allergic reactions may be exceptions to this rule. Corticosteroids may also be life saving in certain steroid-responsive diseases that mimic ARDS (i.e., bronchiolitis obliterans with organizing pneumonia, pulmonary hemorrhage syndromes, *Pneumocystis carinii* pneumonia). Moreover, under such life-threatening circumstances, adrenal insufficiency occurs with certain frequency; if the presentation is compatible, this problem should be pursued diagnostically and stress doses of hydocortisone given. Corticosteroids may also help resolution in the fibroproliferative stage of this illness, but there is no firm consensus on this point. Ibuprofen appears to hold promise in blocking some of the systemic manifestations of inflammation, but the indications and risks of this drug for this specific setting need better definition.

Improving Tissue Oxygen Delivery

In the setting of acute lung injury, attention focuses on maintaining an adequate oxygen delivery/consumption ratio while reversing the underlying lung pathology. Oxygen delivery is the product of cardiac output and the O_2 content of each milliliter of arterial blood. [Oxygen content (ml/dl) equals 1.36 times the product of hemoglobin concentration (g/dl) and percentage saturation/100, plus 0.003 times the P_aO_2.] The O_2 carrying capacity can be improved by increasing hemoglobin (Hgb) concentration and optimizing its dissociation characteristics. Both factors may be important. Increasing Hgb tends to increase mixed venous oxygen saturation as it

reduces the need for any rise in cardiac output compensatory to anemia. Both of these actions (lower cardiac output and higher mixed venous O_2 saturation) tend to reduce venous admixture. Hemoglobin performance is improved by reversing alkalemia to facilitate O_2 offloading. As Hgb concentration rises, blood viscosity increases, retarding passage of erythrocytes through capillary networks. Thus, actual O_2 delivery can be impaired as hematocrit (Hct) rises over 50%. Although the optimal Hct in patients with an oxygenation crisis is unknown, it makes sense to restore Hct to 35% to 40%. More extensive supplementation increases the risks of transfusion without proven benefit.

A very high percentage of the oxygen contained in blood is bound to Hgb; the proportion solubilized in plasma is very small (3%) at ambient pressure. However, in severe anemia, the Hgb-bound fraction is disproportionately small, so that total O_2-carrying capacity is significantly boosted when 100% O_2 is used, and breathing pure oxygen helps dissociate carbon monoxide from Hgb. After carbon monoxide exposure, high partial pressures of O_2 (particularly those delivered under hyperbaric conditions) can deliver life-sustaining quantities of dissolved O_2.

Because extravascular water accumulates readily in the setting of permeability edema, fluids should be used judiciously to keep the wedge pressure as low as feasible consistent with adequate oxygen delivery. Liberal use of inotropes and other vasoactive drugs can occasionally be helpful, especially in certain postoperative or posttrauma settings. Driving the cardiac output to supraphysiological levels, however, appears not to improve the mortality rate of medical patients with ARDS.

Oxygen Therapy

Increasing the F_IO_2 improves P_aO_2 in all instances in which shunt is not responsible for desaturation. The goal is to increase the saturation of Hgb to 85% to 90% or more without risking O_2 toxicity. Oxygen toxicity is both concentration- and time-dependent. As a general rule, very high inspired fractions of oxygen can safely be used for brief periods as efforts are made to reverse the underlying process. Sustained elevations in $F_IO_2 > 0.6$ result in inflammatory changes and eventual fibrosis in experimental models; therefore, it seems logical that efforts be made to keep $F_IO_2 < 0.65$ during the support phase of acute lung injury.

Positive End-Expiratory Pressure, Positioning, and Other Techniques for Raising Lung Volume

Positive end-expiratory pressure (PEEP) and other techniques (e.g., inverse-ratio ventilation) for increasing mean alveolar pressure are often successful in maintaining lung volume recruitment. Virtually all patients benefit from low levels of PEEP (3 to 5 cm H_2O), which help to compensate for the loss of volume that accompanies the supine posture and translaryngeal intubation. There is no evidence, however, that low to moderate levels of PEEP help in prophylaxis against the onset of ARDS. Although PEEP may be highly effective in the relaxed subject, its volume-recruiting effects can be negated by patient effort. Vigorous expiratory muscle action forces the chest to a lung volume lower than the equilibrium position. When this happens, silencing the expiratory muscles by sedation (and/or paralysis, if needed) can prove very helpful. When infiltration is predominately unilateral, PEEP may be ineffective or hazardous, as PEEP causes already-functional lung units to overdistend. In this setting, repositioning the patient (i.e., to a lateral decubitus posture) or the combination of selective intubation and independent lung ventilation may allow individual tailoring of the pattern of lung inflation, F_IO_2, and PEEP, thereby improving oxygenation and reducing the risk of barotrauma.

The potential benefits of position changes are often overlooked. Alert patients should remain upright, if possible, and recumbent patients should be turned every few hours. (This is especially important during coma or paralysis.) Intermittent shifts from the supine to the prone position often help dramatically in reversing hypoxemia in the early stage of ARDS. Alternating lateral decubitus positions puts different regions of the lung on maximal stretch and improves the secretion drainage of the upper lung. Indeed, the incidence of pulmonary infections may be reduced by such mechanisms. Several types of motorized beds perform this function continuously, although the patient is generally rotated through less extreme angles. When one lung is differentially affected, oxygenation occasionally improves dramatically with the good lung in the dependent position, but this is not reliably observed. Care should be taken to ensure that secretions from the infiltrated lung are not aspirated into the airway of the dependent viable lung during this process.

Recruiting Maneuvers

It must be remembered that PEEP itself does not recruit atelectatic lung units but only keeps recruited units from recollapsing. Maintaining patency of inflamed airways and alveoli may be instrumental in allowing healing to occur. To accomplish maximal recruitment, sufficient pressure must be applied to exceed the airway opening pressure, and sufficient total PEEP must be utilized to exceed the closing pressure. It stands to reason, therefore, that periodic application of sustained high recruiting pressure (e.g., 35 to 45 cm H_2O CPAP applied for at least 10 to 15 sec) may be needed to achieve and sustain optimal arterial oxygenation when small tidal volumes are used in patients with acute oxygenation failure, as they often are in ARDS.

Secretion Management and Bronchodilation

Although ARDS is often regarded as a problem of parenchymal injury, airway edema, bronchospasm, and secretion retention often contribute to hypoxemia. Retained secretions pose an overlooked problem that increases endotracheal tube resistance, infection risk, the hazard of barotrauma, and maldistribution of ventilation. In some patients with diffuse lung injury, profound bradycardia develops during ventilator disconnections, discouraging airway suctioning. Although hypoxemia occasionally contributes, this bradycardia is usually reflex in nature and responds to prophylactic (parenteral) atropine or reapplication of positive airway pressure. Circuits that do not interrupt PEEP during suctioning may offer some advantage.

Reducing Oxygen Requirements

Reducing the tissue demand for O_2 can be as effective as improving oxygen delivery. Fever, agitation, overfeeding, vigorous respiratory activity, shivering, sepsis, and a host of other commonly observed clinical conditions can markedly increase V_{O_2}. Fever reduction may have therapeutic value, but shivering must be prevented in the cooling process. Sedation and the use of antipyretics rather than cooling blankets make good therapeutic sense. (Although phenothiazines may prevent shivering, their use may inhibit the cutaneous vasodilation necessary for rapid heat loss.)

Paralysis is a valuable adjunct to reduce oxygen consumption and improve P_aO_2 in patients who remain agitated or fight the ventilator despite more conservative measures. Although paralysis is helpful in the first hours of machine support, protracted paralysis must be avoided for several reasons. Paralysis places the entire responsibility for achieving adequate oxygenation and ventilation with the medical team. Furthermore, the patient is defenseless in the event of an unobserved ventilator disconnection. Paralysis also silences the coughing mechanism and creates a monotonous breathing pattern that encourages secretion retention in dependent regions. Finally, protracted and unmonitored paralysis may cause weakness or devastating neuromyopathy.

Mechanical Ventilation of Acute Lung Injury and ARDS

Conventional Approach to Ventilatory Support

The basic principles of managing acute lung injury (ALI) are well accepted. The primary objective is to accomplish effective gas exchange at the least inspired oxygen fraction (F_IO_2) and pressure cost. On the basis of recent experimental and clinical information, an objective of crucial importance is to establish and maintain patency of all potentially recruitable lung units. The relative hazards of oxygen therapy, high-pressure ventilatory patterns, and abnormal target values for arterial blood gases, pH, and cardiac output are vigorously debated (Table 3).

Conventional	"Lung protective"
Large tidal volume	Small tidal volume
Minimum PEEP	"Sufficient" PEEP
Normalize P_aCO_2	Permissive hypercapnia
Unrestrained P_{pl}	Pressure limitation

TABLE 3. *Approaches to ARDS ventilation*

Most traditional ventilatory strategies used in intensive care evolved directly from anesthetic and surgical postoperative practice. When the lungs are uninjured, and their capacity to expand remains normal (as is common in the perioperative period), large tidal volumes (V_T) of 10 to 15 mL/kg generate only modest end-inspiratory transalveolar pressure. In fact, large tidal volumes prevent the microatelectasis that accompanies monotonous shallow breathing and are needed by many spontaneously breathing patients to satisfy high ventilatory demands (i.e., metabolic acidosis). Postoperatively, the mandatory respiratory rate is usually adjusted to "normalize" pH and/or P_aCO_2, and sufficient positive end-expiratory pressure (PEEP) is used to achieve acceptable O_2 delivery at what is assumed to be a nontoxic F_IO_2. (An $F_IO_2 < 0.65$ is commonly targeted.) Typically, airway pressures are monitored but not rigidly constrained.

With few modifications, this high-tidal-volume, normoxic, normocapnic ventilation paradigm developed as the standard approach to supporting most critically ill patients as well. Consequently, tidal volumes that exceed 800 ml and end-tidal (plateau) alveolar pressures > 50 cm H_2O are still common in many intensive care units during the ventilation of ARDS. How best to select "optimal" PEEP remains controversial, but many practitioners advocate using the *least* PEEP consistent with accomplishing acceptable arterial oxygenation. Others rely on computations of systemic oxygen delivery or best tidal compliance to make their selections of PEEP and V_T. Unfortunately, the machine settings that achieve all important clinical objectives do not invariably coincide. A relatively small but growing number of practitioners are now shifting first priority from optimizing gas exchange, oxygen delivery, or respiratory system compliance to a strategy that minimizes the potentially injurious effects of mechanical ventilation.

Ventilator-Induced Lung Damage

Implications of Evolving Histology

Histologic findings evolve continuously (but heterogeneously) over the course of acute lung injury (Table 4). It is reasonable to assume that all lung regions sustain the initial insult more or less simultaneously and that, in the most severe cases, proliferation, organization, remodeling, and fibrosis sequentially follow an initial phase of edema and atelectasis. Although parenchymal damage is widespread, the nature, severity, pace of evolution, and perhaps even stage of injury vary from site to site within the damaged lung. Early in the course of ARDS, gravitationally dependent areas are extensively consolidated and atelectatic, whereas nondependent regions tend to aerate better. Regional blood flows and vascular pressures also vary (Fig. 5). Changes of body position alter lung (or chest wall) mechanics, influence the radiographic findings, and affect gas exchange. Although counterexamples occasionally occur, perhaps 60% to 70% of patients respond to prone positioning by improving P_aO_2 significantly during this early phase of ARDS. The efficacy of PEEP in improving oxygen exchange relates directly to the reversal of atelectasis and the redistribution of lung water. It is not surprising, therefore, that PEEP's effectiveness in improving oxygen exchange tends to decline as time passes.

	Early phase (0–3 days)	Late phase (>7 days)
Structural collagen	Strong	Degraded
Atelectasis	Prevalent	Less prevalent
Edema	Prevalent	Less prevalent
Mechanics	Heterogeneous	Less heterogeneous
Ventilator lung injury	Edema and hemorrhage	Pneumothorax Cystic barotrauma

TABLE 4. *Characteristics of early- and late-phase ARDS*

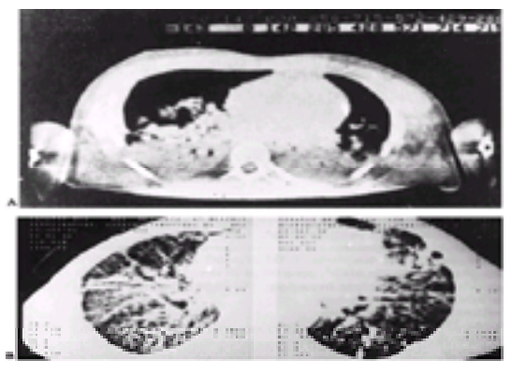


FIG. 5. Computed tomography (CT) appearance of the chest in early **(A)** and late **(B)** phases of ARDS. Although on chest radiographs the lungs appear to be diffusely and uniformly affected in the early stage, the CT image demonstrates a preponderance of atelectasis in the dependent (dorsal) regions. Later, infiltrates are more widely distributed, and cystic spaces often form. In this stage, atelectasis is less prevalent, and infiltrates are more evenly distributed in the transverse plane, as seen in this CT image.**(A)** Reprinted with permission from Gattinoni L, et al. Body position changes redistribute lung computer tomography density in patients with acute respiratory failure. *Anesthesiology* 1991;74:15–23. **(B)** Reprinted with permission from Meduri G. Late adult respiratory distress syndrome. *New Horizons* 1993;1:563–577.]

The collagen framework of the normal lung remains relatively intact during the first days of injury but later weakens as inflammation gradually degrades structural protein and nonuniformly remodels the lung's architecture. Therefore, the same pressures that were withstood acceptably well initially may cause alveolar disruption after the disease is well established. This may explain the tendency for radiographically detectable barotrauma to occur late in the course of the disease—often well after gas-exchange abnormalities have noticeably improved and ventilatory pressures have declined.

Dangers of Excessive and Insufficient Lung Volumes

After acute injury, only a fraction of the injured lung is accessible to gas; in severe cases, no more than one-third of all alveoli remain patent. Because well-ventilated lung units may retain nearly normal elastance and fragility, the apparent "stiffness" of the lung in the early phase of ALI is explained better by fewer functioning alveoli than by a generalized increase in recoil tension. Increased tissue recoil contributes more significantly later on, when cellular infiltration is intense, edema has been reabsorbed or organized, atelectasis is less extensive, and fibrosis is under way. Because the lung's reduced functional compartment must accommodate the entire tidal volume, large (conventional) tidal volumes may cause overdistention, local hyperventilation, and inhibition or depletion of surfactant. Moreover, during rapid inflation to high transalveolar pressures, intense shearing forces may develop at the junctions of structures that are mobile (aerated lung units) with those that are immobile (collapsed or consolidated alveoli, distal conducting airways).

Tidal pressures within the alveolus must neither rise too high at any time during the disease course nor fall too low during the first 3 to 5 days of treatment. Experimental damage resulting from overdistension of the alveolar-capillary membrane has been convincingly documented. The absolute value of peak inflation pressure is not the stretching pressure or the true causative variable of barotrauma; rather, peak transalveolar pressure (roughly approximated by the difference between alveolar and pleural pressures) is the relevant variable. The plateau pressure is perhaps the best clinical correlate of peak alveolar (but not necessarily transalveolar) pressure. The severity of stretch injury appears greatest when maximum transalveolar pressures exceed 25 to 30 cm H_2O and insufficient PEEP cannot keep dependent lung units fully recruited. Failure to maintain a certain minimum alveolar volume in the early phase of ALI may induce or accentuate lung damage.

Unsupported by PEEP, certain collapsible alveoli may wink open and closed with every tidal cycle, generating shearing stresses within junctional tissues and tending to deplete surfactant. Increases in cycling frequency and duration of exposure to adverse ventilatory patterns accentuate any tendency for damage. The magnitude of blood flow in these stressed areas may also play an important role.

Bronchiolar dilation, cystic changes, and/or microabscesses can be demonstrated in the large majority of patients with ALI ventilated for lengthy periods with peak airway pressures considered modest by traditional clinical standards. Such airway damage not only impairs gas exchange but also predisposes to secretion retention and pulmonary infection.

Importance of Cycling Frequency

At levels of minute ventilation and tidal volume that are traditionally accepted, the ventilator may cycle in excess of 30,000 times per day (20 breaths/min × 60 min/hr × 24 hr/day). Even if the tidal pressure profile is only slightly damaging, the cumulative effect can be severe. It is very important to reduce V_E requirements and cycling frequency whenever high cycling pressures are in use.

P_{flex} *and the Choice of* ***PEEP***

A lower inflection (P_{flex}) region on the static pressure–volume curve of the passive respiratory system suggests the existence of a population of alveoli at risk for excessive tidal stresses (Fig. 6). Not all patients exhibit a lower P_{flex} region, but those who do are likely to experience extensive end-expiratory atelectasis at lower levels of PEEP. Indeed, arterial oxygenation often improves markedly as the end-expiratory pressure range just below P_{flex} is exceeded. Many investigators currently believe that tidal excursions into the lower inflexion range must be avoided. Either provision of sufficient PEEP or the progression of disease over time obliterates the "P_{flex} point" as well as narrows the hysteresis of the static pressure–volume curve. In contrast, in late-stage ARDS, high PEEP levels may simply add to the risk of lung rupture, or, when peak pressure is capped (out of a concern for barotrauma), increasing PEEP may reduce the safe operating tidal volume.

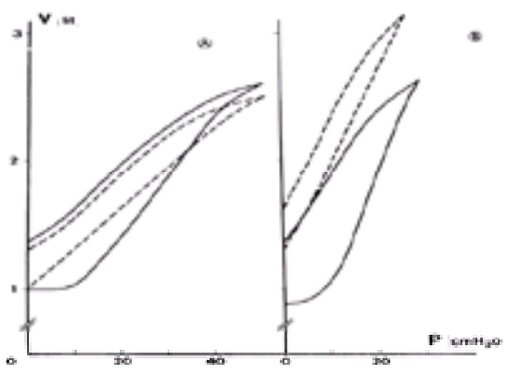


FIG. 6. Pressure–volume curves of the respiratory system from two patients in the earlier and late stages of ARDS. In the earlier stage of ARDS *(solid lines),* distinct lower inflection and upper deflection limbs are prominent. Later *(dashed lines),* the inflection and deflection zones are less well demarcated, and hysteresis is reduced. (Reprinted with permission from Matamis et al. Total respiratory pressure–volume curves in the adult respiratory distress syndrome. *Chest* 1984;86:58–66.)

As a composite of the behaviors of all alveoli within the heterogeneous lung, the contours of the static pressure–volume curve obscure very important regional differences. Alveoli in dependent regions are most susceptible to collapse, and those in nondependent regions are vulnerable to overdistention. This variability of opening pressures helps account for the *zones* (rather than *points*) of lower and upper inflection.

Implications of Pressure Limitation for Tidal Volume

The tidal volumes that correspond to the restricted range of safe ventilating pressures are generally »4 to 8 mL/kg of lean weight, or 300 to 600 mL for a 75-kg patient. However, because values for lung and chest wall compliance vary through wide ranges in different patients, unique values for tidal volume that are consistent with desirable pressure limits cannot be prespecified. Therefore, when a flow-controlled volume-cycled mode of ventilation is used, V_T should be adjusted with guidance by plateau pressure and the response of oxygen exchange to increments of tidal volume. The need to constrain tidal volume suggests the potential value of high frequency ventilation.

Modes of Mechanical Ventilation in ARDS

Something of a mystique has grown up around the topic of mode selection in ARDS. Although many would disagree, we believe that many choices are equivalent, so long as the practitioner assures adequate O_2 delivery at a safe F_IO_2, follows the same guidelines for lung protection, and remains alert to the potential shortcomings and complications of the mode in use. As a general rule, spontaneous ventilation should be encouraged except when oxygenation is marginal, heart function is seriously compromised, or ventilatory efforts are labored. It has been argued that newer techniques such as pressure control, pressure-regulated volume control, inverse-ratio ventilation, and airway pressure release ventilation confer advantages over more traditional approaches, but none has yet been shown in a fair comparison to be consistently superior to its alternatives. The important difference in managing patients with ARDS is that the choices of maximum allowed tidal pressure and chosen level of PEEP may be crucial to safe ventilatory support.

Alternative Ventilatory Strategies

Permissive Hypercapnia

Carbon dioxide retention may be an inevitable consequence of a "lung protective" strategy that tightly restricts applied pressure and maintains a certain minimum (end-expiratory) lung volume. Maintaining normocapnia may not be appropriate if the cost is impaired lung healing and a heightened risk of extending tissue damage. "Permissive hypercapnia," a strategy that allows alveolar ventilation and peak ventilatory pressures to fall and P_aCO_2 to rise, may reduce barotrauma and enhance survival in status asthmaticus and ALI, as several nonrandomized or retrospective studies without concurrent controls have suggested. The basis for any survival advantage there might be has not yet been determined. However, the lung acutely damaged by stretch injury is susceptible to pneumonia and may be a source of inflammatory mediators transferred to the systemic circulation. Disruption of the lung's architecture may also promote bacteremia.

Physiologic Effects of Hypercapnia. The physiologic effects of CO_2 retention are determined by the severity of hypercapnia and the rate of its buildup (Table 5). Except in the most severe cases or those complicated by extraordinary CO_2 production, the CO_2 retention that results from the pressure-targeted ventilation itself is generally modest (P_aCO_2 < 70 mmHg). Chronic hypercapnia of this magnitude appears to have few notable side effects apart from the reduction in ventilatory drive attendant to compensatory metabolic alkalosis. Although gradual elevations of P_aCO_2 (<5 mmHg increase per hour) are often tolerated remarkably well, the rapid development of respiratory acidosis can evoke impressive sympathetic discharge. Allowing hypercapnia may not be advisable for all patients with ALI, i.e., patients with coexisting head injury, recent cerebral vascular accident, or significant cardiovascular dysfunction (Table 6). Acute elevations in P_aCO_2 increase sympathetic activity, raise cardiac output, heighten pulmonary vascular resistance, alter bronchomotor tone, impair skeletal muscle function, dilate cerebral vessels, and impair central nervous system function. Carbon dioxide retention may be poorly tolerated by patients with autonomic insufficiency, b-blockade, or other conditions interfering with sympathetic tone and compensatory mechanisms.

System	Effect[a]
Respiratory	Reduced alveolar P_{O_2}
	Rightward shift of oxygen/hemoglobin curve
	Impaired diaphragm function
	Pulmonary vasoconstriction
	Worsened V/Q mismatching
Renal	Enhanced bicarbonate reabsorption
CNS	Cerebral vasodilation
	Increased intracranial pressure
	Depressed consciousness
	Biochemical changes
Cardiovascular	Reduced cardiac contractility[b]
	Stimulation of sympathoadrenal axis
	Lower systemic vascular resistance

[a] Most effects wane with time as cellular and extracellular pH readjust.
[b] Only if not offset by adrenergic reflex compensation.

TABLE 5. *Consequences of hypercapnia*

Intracranial hypertension
Head trauma
Hemorrhage
Severe systemic hypertension
Space-occupying lesions
Cardiovascular instability
Cor pulmonale
β-Blockade
Severe uncorrected metabolic acidosis or hypoxemia

TABLE 6. *Contraindications to permissive hypercapnia*

Especially over the short term, arterial pH may not closely reflect the pH of the intracellular environment. The magnitude of any intracellular acidosis resulting from permissive hypercapnia, however, is almost certain to be less than the profound intracellular pH changes produced by ischemia. Because CO_2 affects cardiac output and influences vascular and bronchomotor tone, it is uncertain if hypercapnia disturbs ventilation/perfusion matching or modulates the extent of lung injury and edema during the course of mechanical ventilatory support. Implementation of permissive hypercapnia often requires deep sedation and/or paralysis, a requirement that may be associated with serious side effects: impaired secretion clearance, fluid retention, and residual muscle weakness. Moreover, permissive hypercapnia may not be advisable (or even possible to implement safely) in the setting of coexisting metabolic acidosis or uncorrected hypoxemia.

Adjuncts to the Ventilatory Management of ARDS

In recent years, there has been renewed interest in devising ways in which to accomplish effective arterial oxygenation without inflicting further damage on the injured lung. Some of these innovations modify the fundamental nature of ventilatory support (high-frequency ventilation), but others provide gas exchange external to the lungs (extracorporeal or intravenacaval gas exchange), alter body position (prone positioning), or administer therapeutic agents designed to improve ventilation/perfusion matching (nitric oxide, aerosolized prostacyclin). One technique modifies the nature of the gas-carrying medium itself (partial liquid ventilation). Each of these adjuncts should be considered as a promising technique that is currently just beyond the perimeter of routine clinical practice.

High-Frequency Ventilation

When conducted at an appropriate lung volume and frequency, HFV seems well aligned with current principles of lung protection and has a clear rationale. To this point, however, its superiority has neither been shown nor disproven.

Extrapulmonary Gas Exchange

Partial substitution for the lung's gas-exchanging function reduces the requirement for ventilating pressure. Methods for assisting in the process of exchanging respiratory gases include extracorporeal membrane oxygenation (ECMO), extracoporeal CO_2 removal ($ECCO_2R$), and intravenacaval gas exchange (IVOX). All are costly, highly technical methods best undertaken by an experienced and dedicated team. Each has a good rationale, and laboratory experience and various clinical reports have been encouraging; yet, for adult patients none has been confirmed by well-controlled trials to add consistently to routine measures. Although initial experience with these techniques has been frustrating, they continue to hold promise for well-selected patients.

Prone Positioning

Frequent changes of body posture are integral to normal activity, but positional variation is forgone for lengthy periods in the bedridden, critically ill patient. By tradition, the patient is cared for in the supine position, which allows more direct eye contact with the caregivers, family, and visitors as well as better access to the vascular system and vital structures, thereby facilitating nursing care. Cardiopulmonary resuscitation must be conducted in the supine position. Despite these undeniable advantages, there is good reason to question our current practice of utilizing only the supine orientation. A growing interest in therapeutic positioning has been stimulated by the observation that the prone position improves oxygen exchange in 50% to 70% of patients treated in the early phase of ARDS, allowing the physician to reduce both $F_{I}O_2$ and PEEP. Recruitment of dorsal lung units with a more even distribution of pleural pressure and improved ventilation/perfusion matching seems best to explain this benefit. Airways serving the expansive dorsal regions are generally better drained in this position as well. Based on theoretical considerations and limited personal experience, prone positioning is less likely to benefit patients with large continuous pleural air leaks, especially if pneumothorax is radiographically evident and bilateral. Once the lung is surrounded by gas, the normal pleural gradient of pressure is erased or substantially altered, making the effect of prone positioning unpredictable. Under such circumstances, prone positioning should only be attempted with caution—if at all.

Practical Points in Prone Positioning

Although hemodynamic parameters tend to remain unchanged, hypotension, desaturation, and arrhythmias may occur during the process of turning from the supine to the prone position (Table 7). These transient problems do not generally persist and can be minimized by using sedation, prior airway suctioning, and 100% oxygen during the maneuver. Continuous arterial pressure monitoring, electrocardiography, and pulse oximetry are strongly advised. Deep sedation and occasionally paralysis will be required to secure patient compliance. Attention must also be given to preserving the position and patency of intravascular lines and endotracheal tubes during the turning process. Use of a soft (air-cushioned) bed is all but mandatory for comfort. Pillows must be used to support the hips, pelvis, shoulders, and head. Patients with tracheostomies present a particular challenge. The compliance of the respiratory system generally changes little in shifting to the prone position. This is variable, however; tidal volume should be monitored (and adjusted if necessary) during pressure-controlled ventilation, which is influenced by any position-related changes in chest wall compliance. Furthermore, for the same plateau pressure, peak pressures may change if flow-controlled volume-cycled ventilation is used. For similar reasons, a given level of PEEP may be more or less effective in one position than in another. Although the optimal frequency of supine–prone interconversions is not clear, in current practice, most experienced centers “flip” patients once or twice daily. Supine repositioning allows certain nursing procedures (washing, line dressing changes, etc.) to be delivered and helps resolve facial edema. It seems reasonable to assign the relative duration of each position in proportion to the gas-exchange response. (For example, equal times would be assigned if only a minor important gas-exchange difference is observed between positions.) Prone repositioning should be reevaluated often in the first 3 to 5 days of illness, after which time it tends to lose its oxygen-exchange effectiveness.

Soft bed
Secure endotracheal tube and all lines before transition
Sedate and preoxygenate before turning
Monitor carefully during transitions
Support shoulders and hips
Adjust PEEP and tidal volume after positioning
Protect eyes, facial areas
Exercise special caution if bronchopleural fistula present
Alternate prone and supine positions one to three times daily

TABLE 7. *Practical points for prone positioning in ARDS*

Partial Liquid Ventilation

Perfluorochemicals (PFCs) proposed for clinical purposes are environmentally innocuous liquids at room temperature that dissolve extraordinary volumes of oxygen and carbon dioxide, allowing effective gas exchange to take place. Biologically inert and immiscible in both aqueous and lipid media, they cause no known tissue reaction—even during extended use. Perfluorooctyl bromide (Perflubron), a PFC currently undergoing clinical trials, has a desirably low vapor pressure (it clears itself by evaporating slowly), a high spreading coefficient (it distributes homogeneously), and a low surface tension. Although its viscosity is similar to water, perflubron has nearly twice the density; airway secretions and alveolar exudates float on it, allowing such debris to migrate centrally for airway suctioning. Infections may occur less commonly in a lung filled with inert, nonnutritive liquid hostile to bacterial growth, but this is unproven. Its radiodensity may interfere with conventional imaging (Fig. 7). Perflubron has the potential to keep surfactant-deficient alveoli open by two distinct mechanisms: (1) reduction of interfacial surface tension and (2) physical distention by noncompressible fluid ("liquid PEEP"). The former property may be especially important in the infant respiratory distress syndrome, whereas alveolar splinting may assume primacy in ARDS.

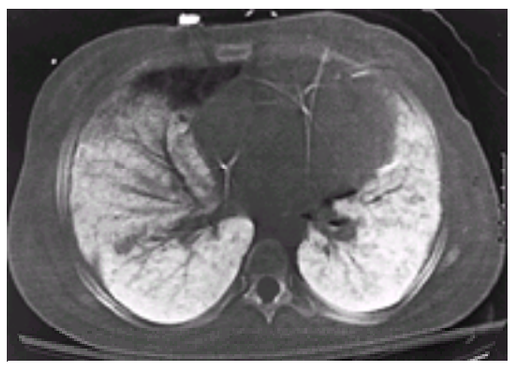


FIG. 7. Computed tomographic scan of a patient with ARDS receiving partial liquid ventilation with Perflubron. (Reprinted with permission from Marini JJ. Evolving concepts in the ventilatory management of acute respiratory distress syndrome. *Clin Chest Med* 1996;17:555–575.)

Sustained *partial* liquid ventilation (PLV) preserves the key benefits of liquid breathing while allowing gas ventilation to proceed with standard mechanical ventilators and connecting circuitry. Initial clinical experience has been promising. In stark contrast to total liquid ventilation, PLV is rather simply implemented. The liquid preferentially distends the dependent alveoli most in need of expansion during the initial phase of ARDS, providing the vertically graded PEEP-like effect required by the underlying pathoanatomy. Simultaneously, blood flow diverts toward nondependent regions, which receive a disproportionate share of the gaseous tidal volume. Reduced venous admixture, therefore, has at least two explanations—effective oxygen exchange directly across alveolar units reopened by liquid, and redirection of pulmonary arterial blood toward the better ventilated nondependent regions. The exciting potential of perfluorocarbons in ARDS has yet to be confirmed.

Tracheal Gas Insufflation

An alternative to allowing extreme or rapidly developing hypercapnia or to using extrapulmonary techniques for gas exchange in ARDS is to enhance the efficiency of CO_2 elimination at low V_T and cycling pressures by the tracheal insufflation of fresh gas (TGI). This minimally invasive approach reduces the effective series (anatomic) dead space by bypassing the airway proximal to the carina during inspiration, by washing out the PCO_2 of this same region during expiration, or both (Fig. 8). During TGI-aided ventilation, fresh gas delivery occurs either throughout the respiratory cycle (continuous catheter flow) or only during a segment of it (phasic catheter flow). In either mode, the crucial variable appears to be the volume of fresh gas injected per breath during expiration. During expiration, low to moderate continuous flows of fresh gas introduced near the carina dilute the proximal anatomic dead space (dead space flushing). At high catheter flow rates, turbulence generated at the catheter tip can also enhance gas mixing in regions beyond its orifice, thereby contributing to CO_2 elimination. Expiratory insufflation appears to be the safest and most effective modality of implementing TGI, avoiding problems with overpressuring the airway, allowing manipulation of the inspiratory time fraction without influencing inspired tidal volume, and minimizing the volumes of fresh gas that must be injected to achieve a given level of CO_2 elimination.

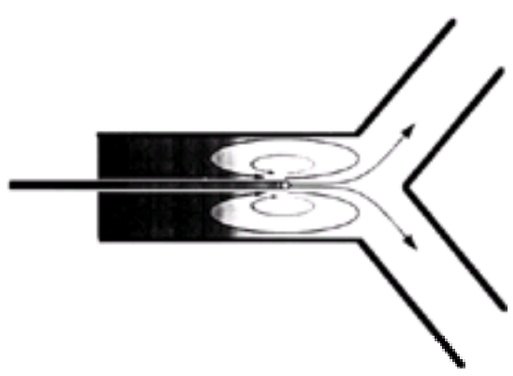


FIG. 8. Tracheal gas insufflation (TGI). CO_2-laden gas that fills the central airways at end-expiration is recycled to the alveolus with the subsequent inspiration. Expiratory flushing of CO_2 from the central airway by fresh gas helps improve CO_2 elimination and reduces dead space. The effectiveness of TGI is reduced when a high alveolar dead space lowers the end-expiratory tracheal CO_2.

Because much lower concentrations of CO_2 are delivered to the central airway, TGI loses its effectiveness when there is a large amount of alveolar (as opposed to anatomic and apparatus) deadspace. Acute respiratory distress syndrome, emphysema, and pneumonia are typical examples of such diseases. Conversely, permissive hypercapnia boosts the CO_2 concentration, improving the utility of TGI.

Used improperly, TGI has the clear potential to cause mucosal damage, secretion retention, and interference with catheter suctioning. These effects should be mitigated by adequate humidification, using selective expiratory TGI, and the injection of fresh gas via channels imbedded within the walls of the endotracheal tube itself. Injection of catheter gas retrograde to the exhalation stream tends to increase expiratory resistance and generate auto-PEEP; continuous gas injection allows the TGI injector to act as a constant-flow generator during inspiration, when the machine's valves are closed, risking overdistention. Auto-PEEP and barotrauma are

distinct possibilities when high gas flow rates are used—whatever the injection mode (selective expiratory or continuous). The experience of workers using transtracheal ventilation in outpatients with COPD as well as other results with TGI in critically ill patients indicates that once perfected, it may eventually prove helpful in a variety of acute and chronic settings. Because of its potential to moderate the rate and extent of CO_2 retention, TGI appears particularly well suited to serve as an adjunct to a pressure-targeted, lung-protective ventilatory support for ARDS.

Inhaled Nitric Oxide and Prostacyclin

Nitric oxide (NO) is a key biological mediator of smooth muscle relaxation. When inhaled, NO has the therapeutic potential to dilate the pulmonary vasculature in well-ventilated regions, tending to reduce pulmonary hypertension and improve the matching of ventilation and perfusion in an unevenly damaged lung. Inhaled nitric oxide is active only locally, as it is quenched immediately on exposure to hemoglobin. Because inhaled NO cannot influence the vasculature of collapsed lung units that it cannot access, the effectiveness of NO often depends on the provision of sufficient PEEP to fully recruit the lung and maintain alveolar patency. Extremely low concentrations of NO achieve nearly full effect; biological activity is often detectable at concentrations as low as 2 parts per million, and beneficial effects on gas exchange are fully saturated at 5 to 20 ppm in most patients. Somewhat higher concentrations of NO may be needed to maximize its pulmonary vasodilating effects. Nitric oxide's physiological effects in ARDS are highly variable—sometimes dramatic, but often quite modest. Although the onset and offset of NO's effects are extremely rapid, gradual accommodation to its beneficial vasodilatory effects can result in rebound vasoconstriction when it is abruptly terminated. High concentrations of NO and minute quantities of its associated oxides (NO_2^{1-} and NO_3^{2-}) are histotoxic and must be avoided. Although it is extremely appealing physiologically, the eventual place of NO in the management of ARDS has not yet been settled. At present, it appears most likely to benefit those cases whose hypoxemia is refractory to other measures or those in whom hypoxic vasoconstriction accentuates symptomatic pulmonary hypertension.

Vasodilating aerosols (inhaled prostacyclin and lysosome-encapsulated prostaglandin F_2) operate by the same principle of selectively increasing perfusion to well-ventilated regions. Each may also inhibit inflammation and reduce pulmonary artery pressure. Although their physiological effects can be dramatic, their routine clinical benefit has yet to be demonstrated.

A Pressure-Targeted Approach to Ventilating ALI and ARDS

Although definitive clinical data are needed to confirm the wisdom of adopting a “pressure-targeted” approach, a rational strategy for ventilating patients with ALI can be formulated grounded on a firm theoretical and experimental basis (Table 8). Such a strategy recognizes that several mechanically distinct alveolar populations coexist within the acutely injured lung, that a poorly chosen ventilatory pattern can be damaging, and that the underlying pathophysiology changes over time. This approach gives higher priority to controlling maximal and minimal transalveolar pressures than to achieving normocapnia. Establishing and maintaining full alveolar recruitment while avoiding lung overdistention is the primary guiding principle.

Tailor ventilatory strategy to the phase of the disease (generous PEEP in early stage; withdraw PEEP later)
Minimize oxygen demands
Minimize pulmonary vascular pressures
Control alveolar pressure, not P_aCO_2
Maintain total end-expiratory P_{aw}[a] (PEEP + auto-PEEP) several centimeters of water above P_{aw}[a]. In general, this will be more than 7 cm H_2O but less than 20 cm H_2O
Avoid large V_t and use least P_{aw} required to meet *unequivocal* therapeutic goals
Hold transalveolar pressure <35 cm H_2O
Consider making necessary increases in mean P_{aw} by changing T_I/T_{tot}
Consider specialized adjunctive measures to improve gas exchange and O_2 delivery[b]

[a] Abbreviations: P_{aw}, alveolar pressure; P_{flex}, lower inflection point of the static pressure–volume relationship of the respiratory system.

[b] In addition to such standard measurements as skillful management of pulmonary vascular pressure, repositioning, use of cardiotonic agents, specialized adjunctive measures might include (where available) such experimental methods as ECCO$_2$R, inhaled Nitric Oxide or prostacyclin, partial liquid ventilation, and intravenous (IVOX) or intratracheal catheter-assisted gas exchange (TGI).

TABLE 8. *A lung protective strategy for ventilating ARDS*

Once oxygen and ventilatory demands have been minimized and fluid balance and cardiac function have been optimized, the essential strategic elements are as follows:

First, sufficient end-expiratory transalveolar pressure must be used to avert tissue damage resulting from surfactant depletion or stresses associated with persistent collapse or repeated opening and closure of collapsible units during the tidal breathing cycle. The total PEEP applied (the sum of PEEP and auto-PEEP) should be sufficient to obliterate any lower inflection “point” of the pressure–volume curve of the respiratory system, which, at tidal volumes of 7 to 8 mL/kg, generally occurs at a pressure of 10 to 15 cm H_2O in the early phase of ARDS. (For a patient with a stiff chest wall, the PEEP required may be considerably higher.) In truth, there is an inflection *range* rather than a single inflection point, as dependent alveoli in the lower regions of the lung require a greater end-expiratory alveolar pressure to maintain patency than those above them. Improved arterial oxygenation tends to parallel effective recruitment, and CO_2 retention is a consequence of alveolar overdistention. Although actual construction of the pressure–volume curve (by any of a variety of static or dynamic methods) is theoretically appealing, in some patients it is inadvisable to eliminate spontaneous breathing efforts. One simple way to select PEEP (with or without spontaneous efforts) is first to choose the operating tidal volume (4 to 7 ml/kg), initially setting PEEP at 8 to 10 cm H_2O. The PEEP is then increased in small (2 cm H_2O) steps, looking for (1) an increase in peak static (plateau) pressure that substantially exceeds the previous PEEP increment (by 2 cm H_2O), signaling overdistention, and (2) markedly improved oxygenation that corresponds to obliteration of the P_{flex} point. (Under certain circumstances, a reasonable alternative to the empirical PEEP step approach is gradually to extend the inspiratory time fraction to create auto-PEEP.) Failure of oxygenation to improve significantly after two successive PEEP steps and a recruitment maneuver (see below) strongly suggests that nearly full recruitment had been achieved with that tidal volume at a lower PEEP value. The PEEP should be lowered accordingly.

Second, because alveolar subpopulations with nearly normal elastic properties may coexist alongside flooded or infiltrated ones, the clinician must avoid applying transalveolar pressures greater than normal lung tissue is able to sustain at its maximum capacity (30 to 35 cm H_2O). This pressure generally corresponds to end-inspiratory static airway pressures (“plateau” pressures) of 35 to 50 cm H_2O, depending on the stiffness of the chest wall. Pressures in this range are generally sufficient to reopen closed airways. Whatever the appropriate maximal pressure setting might be for an individual patient, it seems wise to avoid the upper inflection range of the static pressure–volume curve whenever possible. Incursion into this zone is signaled by deterioration of tidal compliance and, in a passively inflated patient, by convexity of the inspiratory airway pressure curve to the horizontal (time) axis during constant-flow ventilation.

Relatively small tidal volumes often result from imposing these upper and the lower bounds on ventilatory pressure. Therefore, periodic recruiting breaths (e.g., pressures of 35 to 45 cm H_2O sustained for 5 to 15 sec every 10 min) may be needed in some patients to maintain adequate lung volume and avoid hypoxemia. One interesting approach to making selections of PEEP and tidal volume when using pressure-controlled ventilation is to fix maximal airway pressure at »30 to 35 cm H_2O and begin with PEEP of 8 cm H_2O. (Somewhat higher maximum and minimum pressures are more appropriate for a patient with an inflexible chest wall.) Positive end-expiratory pressure is then increased gradually while maximal airway pressure remains constant (allowing V_T to fall) until the point at which calculated tidal compliance begins to decline—one definition of the optimum PEEP value.

Third, under conditions of passive inflation (no spontaneous efforts), the practitioner should adjust mean airway opening pressure ($\bar{P}_{aw}$) to achieve acceptable pulmonary O_2 exchange by extending the duty cycle (T_I/T_T) or by raising PEEP. Cardiac output is supported as necessary to offset any detrimental effects of rising $\bar{P}_{aw}$. Extending the duty cycle improves the distribution of ventilation and may help to recruit or hold open otherwise collapsible lung units. Raising PEEP (and preserving a well-tolerated T_I/T_T) may be the preferred option, however, when the patient retains control of the breathing rhythm.

Fourth, when not contraindicated, hypercapnia should be accepted from the onset of therapy (buffered, when necessary, by judiciously infused sodium bicarbonate or other buffer) in preference to violating the guidelines of controlling alveolar pressure. Pharmacologic buffering may also be needed to allow hypercapnia when deep sedation and/or paralysis is not used. The strategy of permissive hypercapnia may be difficult to implement in the presence of metabolic acidosis, when other measures (i.e., dialysis) may be needed adjunctively.

Fifth, consider the prone position from the outset of management. Prone positioning generally offers its greatest oxygenation benefit early in the course of illness. When both available and necessary, consider the use of such adjunctive measures as nitric oxide, tracheal gas insufflation, or partial liquid ventilation.

Sixth, after the first 3 to 5 days of treatment, begin to reduce PEEP and the frequency of prone positioning as oxygenation allows, seeking to reduce maximum alveolar pressure and prevent alveolar rupture.

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CHAPTER

48 Mechanical Ventilatory Support

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INTRODUCTION

Mechanical ventilation serves two basic functions: ventilatory support and oxygenation support. Ventilatory support is designed to provide, either totally or partially, gas transport between the environment and the alveoli. Usually this is done by using positive airway pressure in a manner that mimics the normal tidal volume and breathing frequency pattern. In contrast, oxygenation support is designed to optimize ventilation–perfusion *(VQ)* matching in order to effect alveolar–capillary gas transport. The most common technique to accomplish this goal is the application of positive end-expiratory pressure (PEEP), but manipulations of the ventilatory pattern and other strategies can also be employed.

Ventilatory failure is defined as failure of the respiratory system to move gas adequately between alveoli and the environment. Ventilatory failure results in abnormalities in both P_aO_2 and P_aCO_2. However, it is usually defined and quantified by an abnormal P_aCO_2 (and resulting acidemia) because CO_2 transport is predominantly determined by ventilation and is much less affected by *VQ* matching and diffusion than is O_2. Ventilatory failure is usually defined as an elevation in P_aCO_2 that results in an arterial pH of 7.25 or less. This corresponds to a P_aCO_2 of 55 torr in patients with normal baseline values for P_aCO_2. In patients with chronic CO_2 elevations, however, ventilatory failure would be defined by higher values for P_aCO_2. Ventilatory failure can result from several factors with different manifestations and potential causes (Table 1).

Pathophysiology	Clinical criteria	Potential causes
Decreased respiratory drive	P_aCO_2 (>55 torr) Bradypnea–apnea	Neurologic dysfunction, drugs
Ventilatory muscle fatigue resulting from working on stiff or obstructed lungs	P_aCO_2 (>55 torr) Tachypnea (>35 torr) Muscle weakness (<25 cm H_2O negative inspiratory force) ↓CL ↑RAW	Obstructive lung disease Restrictive lung disease
Ventilatory muscle fatigue resulting from large deadspace ventilation requirements	P_aCO_2 (>55 torr) Tachypnea (>35 torr) ↑MDINT (>30 l/l)	Pulmonary vascular disease

TABLE 1. *Ventilatory failure*

Oxygenation failure is characterized by impairment of the alveolar-to-arterial transport of oxygen (A-aDO_2). This occurs physiologically because of disease-imposed *VQ* mismatch, shunts, and (occasionally) diffusion block. Oxygenation failure is usually defined as an arterial PO_2 that is less than 55 to 60 torr (hemoglobin saturation less than 86%). Oxygenation failure can also be defined by inadequate oxygen delivery (DO_2) to tissues (e.g., DO_2 less than 300 to 400 ml/min per m^2).

CONVENTIONAL MECHANICAL VENTILATOR DESIGN PRINCIPLES

Conventional mechanical ventilation uses positive-pressure breaths to provide ventilatory support. Gas transport is thus by bulk flow. Devices to deliver these positive-pressure breaths have a number of important features (Fig. 1).

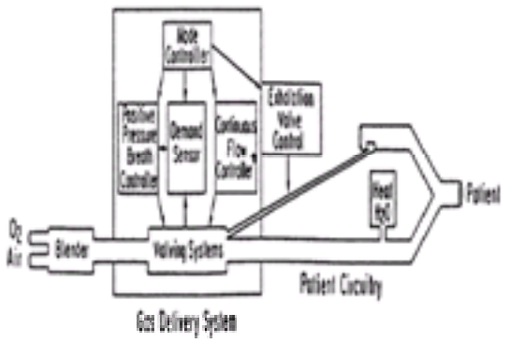

FIG. 1. Ventilator design principles. Modern mechanical ventilatory support systems take blended fresh gas and regulate its flow through complex valving systems (that may include pistons or bellows). The positive-pressure breath controller sets the characteristics for machine-delivered breaths. Circuit demand (effort) sensor provides input for interactive breaths. A continuous-flow circuit for unassisted breathing exists on some systems. The mode controller sets the desired combination of controlled, interactive, and unassisted breaths. The exhalation valve control interacts with the valving system and the mode control to determine expiratory pressure. The patient circuitry delivers these gases to the patient. Heat and moisture are added to the gases delivered. (From MacIntyre NR. Mechanical ventilation. *ACCP Pulm Clin Update* 1985;1:21, with permission.)

Gas Delivery Systems

The important components of the gas delivery system are as described in the following paragraphs.

Positive-Pressure Breath Controller

Most modern adult ventilators utilize piston/bellows systems or controllers of high-pressure sources to drive gas flow. Tidal breaths are generated by this gas flow and can either be controlled entirely by the ventilator or be interactive with patient efforts. Generally, pneumatic, electronic, or microprocessor systems provide for various breath types to be available. These can be classified by what initiates the breath (trigger variable), what controls gas delivery during the breath (limit variable), and what terminates the breath (cycle variable). Trigger variables are generally either patient effort (see patient-circuit sensors, below) or a set machine timer. Limit variables are either a set flow or a set inspiratory pressure. Cycle variables are generally a set volume, a set inspiratory time, or a minimal flow. On current mechanical ventilators, five basic positive-pressure breaths can be delivered, and they can be described by these three variables (Fig. 2).

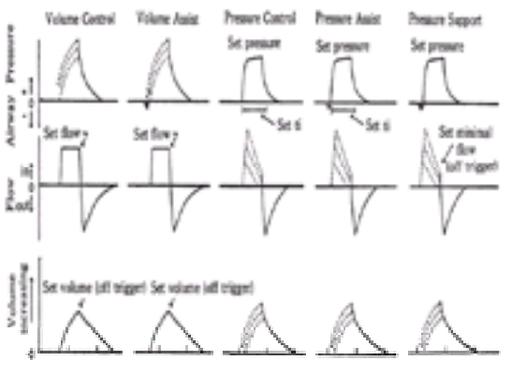

FIG. 2. The five basic breaths. These breaths are categorized by the trigger variable (patient effort or machine timer), the limit variable (flow or pressure), and the cycle variable (volume, flow, or time).

The current generation of mechanical ventilators provides wide versatility. Breathing frequencies to 150 breaths/min, tidal volumes to 2500 mL, peak inspiratory pressures to 150 cm H_2O, flow rates to 180 L/min, inspiratory:expiratory (I:E) timing ratios ranging from 1:5 to 4:1, and a variety of inspiratory flow profiles (i.e., accelerating, decelerating, square, or sine wave) are commonly available. These delivery systems should be equipped with pressure relief valves to avoid dangerously high airway pressures.

Mode Controller

The desired combination of ventilator and spontaneous breaths is termed the mode of mechanical ventilatory support. The mode controller is an electronic, pneumatic, or microprocessor-based system that is designed to provide the proper combination of breaths according to set algorithms and feedback data (conditional variables) (Table 2). Newer designs can incorporate advanced monitoring and feedback functions into these controllers to allow for continuous adjustments in mode algorithms as patient conditions change.

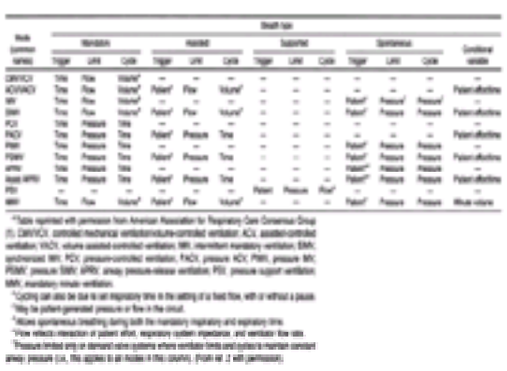

TABLE 2. *Classification of commonly used modes of ventilation*[a]

Effort (Demand) Sensors

Current ventilators allow for a number of patient ventilator interactions. Examples of these interactions include patient-triggered breaths (ventilator initiates flow in response to patient demand) and pressure-limited breaths (ventilator adjusts flow in response to patient demand). Patient effort sensors are needed to allow the ventilator to properly deliver these interactive breaths. These sensors are usually either pressure or flow transducers in the ventilatory circuitry.

Effort sensors are characterized by their sensitivity and responsiveness. Sensitivity refers to how much of a circuit pressure or flow change must be generated to initiate a ventilator response. Responsiveness refers to the delay in providing this response. Both properties are critical in providing a proper response to patient efforts. The work imposed on a patient as a consequence of insensitivity/unresponsiveness of interactive systems is termed “dyssynchrony” (see “Complications,” below).

Subsystems of Mechanical Ventilators

In addition to the gas delivery system, several additional components exist on modern mechanical ventilators.

Gas Blenders

These mix air and O_2 to produce a delivered F_IO_2 from 0.21 to 1.0.

Humidifiers

With the upper airway bypassed by tracheal intubation, sufficient heat and moisture must be added to the inspired gas mixtures to avert mucosal desiccation. Used effectively, humidifiers can adjust blended gas mixtures to near body conditions. Although most systems warm the gas to increase water vapor content, particulate nebulizers have also been employed. Simple and inexpensive heat and moisture exchange humidifiers (HME, “artificial noses”) reutilize moisture trapped from expired gas. These disposable units usually supply adequate heat and moisture (i.e., greater than 28° to 30°C and greater than 25 mg H_2O/L of ventilation) for many patients, particularly those requiring mechanical ventilation for only short periods of time.

Expiratory Pressure Generator

Positive airway pressure can be sustained throughout expiration (PEEP) to help maintain alveolar patency and improve *VQ* matching (see “Physiologic Effects,” below). The PEEP is usually applied by regulating pressure in the expiratory valve of the ventilator system, but a continuous flow of source gas during the expiratory phase can provide a similar effect. Note that some expiratory valves, even when fully open, have measurable resistance, which may result in some inadvertent applied PEEP.

Gas Delivery Circuit

This usually consists of flexible tubing that often has pressure or flow sensors and exhalation valves included. It is important to remember that this tubing has measurable compliance (4 mL/cm H_2O is a representative figure), and significant amounts of delivered gas may serve only to distend this circuitry rather than enter the patient's lungs when high airway pressures are encountered.

PHYSIOLOGICAL EFFECTS OF POSITIVE-PRESSURE VENTILATION

A positive-pressure breath has a number of important effects in the lung–thorax system (Fig. 3).

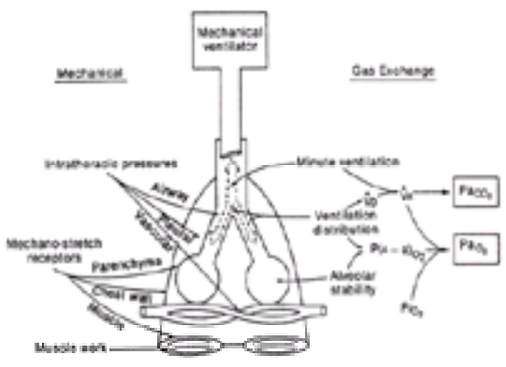

FIG. 3. Physiological effects of mechanical ventilation. Gas exchange is influenced by the delivered minute ventilation, the distribution of that ventilation with respect to perfusion, the alveolar stability, and the F_IO_2. Mechanical effects result from the developed intrathoracic pressures, the ventilatory pattern interactions with thoracic mechanoreceptors, and the ventilatory pattern interactions with the inspiratory muscle efforts. (From MacIntyre NR. Mechanical ventilation. *ACCP Pulm Clin Update* 1985; 1:21, with permission.)

Relationship of V_A, P_aCO_2, and VCO_2

Conventional mechanical ventilation provides fresh gas by periodically inflating the lungs with positive pressure. Such “bulk flow” or “convective transport” results in alveolar or “effective” ventilation (V_A) that is often defined by the ability of the lungs to remove CO_2. This relationship of V_A to P_aCO_2 and CO_2 production is expressed by $V_A = VCO_2/P_aCO_2 \times k$. Alveolar ventilation is also quantified mechanically by the expression: alveolar ventilation (V_A) = breathing frequency (f) × [tidal volume (V_T) - wasted or dead space volume (V_D)]. For given values of VCO_2 and V_D, changes in P_aCO_2 can be predicted by changes in delivered f or V_T using these relationships (Fig. 4). Note, however, that VCO_2 and V_D may change depending on both the underlying disease and the mechanical ventilatory support parameters utilized. For example, VCO_2 can change because the patient's work of breathing and comfort significantly affect the overall metabolic requirement, and V_D can change as a consequence of airway pressures producing regional decreases in blood flow.

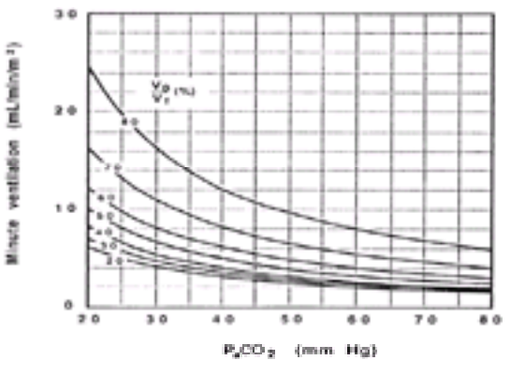

FIG. 4. Relationship of minute ventilation *(vertical axis)* to alveolar ventilation *(P_aCO_2,horizontal axis)*. Isopleths represent different dead space conditions. In this example, CO_2 production is 112 ml/min per m^2, P_B is 760 torr, and temperature is 37°C. (From Chatburn R, Lough M. *Handbook of Respiratory Care.* Chicago: Yearbook, 1990, with permission.)

Delivered V_A and the V_T, f Relationship

The overall amount of ventilation supplied by the ventilator is the product of the tidal volume and the frequency (minute ventilation = $V_T \times f$). Normal values are (5 to 7 mL/kg) × (12 to 20 breaths/min). Minute ventilation requirements in sick patients, however, are often higher than this because of increased metabolic needs (i.e., VO_2 and VCO_2) and increased V_D. Supplying adequate ventilatory support thus often requires increases in V_T, f, or both. In increasing minute ventilation, increases in V_T (rather than f) offer the advantage of a lower V_D/V_T ratio (given a constant V_D) and thus a lower total $f \times V_T$ requirement. On the other hand, increases in V_T will increase maximal alveolar distention and the risk for lung injury (see “Complications,” below). Regardless of whether V_T or f is used to increase V_A, airway resistance to flow and the need to exhale place practical limits on the amount of minute ventilation that can actually be given to patients.

The Inspiratory Flow Pattern

The inspiratory flow pattern (i.e., flow magnitude and flow patterns during either flow-limited or pressure-limited breaths) affects both the distribution of delivered gases and the synchrony of ventilatory support with patient effort during assisted or supported breaths.

Distribution

The distribution of gas from a positive-pressure breath is a complex interaction of delivered flow and regional compliance and resistance that is beyond the scope of this discussion. However, a few general clinical points can be made about inspiratory flow and ventilation distribution: (1) The longer the inspiratory time, the more even is gas distribution among alveoli with different mechanical properties. (2) On the other hand, the longer the inspiratory time, the shorter is the expiratory time, and thus, the greater is the potential for air trapping. (3) The flow pattern (square versus sine versus decelerating versus accelerating) has not been shown to have marked effects on overall ventilation effectiveness, although the patterns with more rapid initial flows may augment gas mixing in the lung and thereby improve gas exchange. In practice, ventilation distribution goals are generally met when the inspiratory:expiratory ratio is in the physiological 1:2 range and flow is delivered as either a decelerating or square wave. Lengthening the inspiratory time beyond this physiological range is discussed below under ventilation strategies.

Synchrony

Synchrony refers to the matching of ventilator-delivered flow to patient-demanded flow during assisted or supported breaths. Flow below that demanded by the patient can result in significant imposed work on the patient and further worsening of P_aO_2 and P_aCO_2 ("flow dyssynchrony"; see "Complications," below).

Inspiratory and expiratory time relationships affect the lung's ability to return to the FRC determined by the set PEEP and the respiratory system's recoil pressure. In general, as compliance increases, resistance increases, and expiratory time shortens, the potential for an "intrinsic" PEEP and air trapping to develop increases. This is discussed in more detail under "Complications," below.

Total Versus Partial Ventilatory Support

Positive-pressure breaths can be used to supply either all or part of the V_A. In supplying all of the V_A, these breaths perform all of the work of breathing and thereby rest the ventilatory muscles. This is termed *total* mechanical ventilatory support. Total support is guaranteed when modes of ventilation are used that provide only controlled breaths in sedated/paralyzed patients. Near-total support is also delivered by using modes that provide mixtures of assisted and controlled breaths if the assisted breaths are properly synchronized to patient demand. Near-total support can also be delivered by using modes providing pressure-supported breaths if the level of machine support is adequate for the work of each breath.

On the other hand, if positive-pressure breaths are used to supply only *part* of the V_A and thus only *part* of the work of breathing (with the patient supplying the remainder), this is termed *partial* ventilatory support. Partial support is generally provided in one of two ways: (1) using modes that allow intermittent spontaneous breaths among assisted/controlled breaths; or (2) using assisted or supported pressure-limited breaths that provide a level of support for each breath that is less than that required for total support.

Total support is usually used in the initial phases of severe respiratory failure, when muscles are fatigued, and when the ventilatory drive is either absent or unreliable. Partial support is usually used during the weaning process. Partial support is also used in patients requiring substantial ventilatory support (i.e., are not ready for active weaning) but who have a reliable ventilatory drive and relatively stable mechanics. In this setting, partial ventilatory support results in (1) less airway pressure being delivered by the ventilator (and thus perhaps a lower lung injury risk; see below) and (2) some level of patient muscle activity (which may forestall muscle atrophy).

Alveolar PO_2 (P_AO_2)

There are essentially two ways to increase the alveolar P_AO_2: (1) increase the P_IO_2 through increases in the F_IO_2 (or, less commonly, through increases in barometric pressure, P_B), and (2) increase the V_A. The relationship among these factors is expressed in the simplified alveolar air equation:

$$P_AO_2 \propto P_IO_2 - P_aCO_2/R \quad \textbf{(1)}$$

which can be rearranged to:

$$P_AO_2 \propto P_IO_2 - VCO_2/V_A/R \quad \textbf{(2)}$$

Note from these relationships that P_IO_2 has a linear relationship with P_AO_2, whereas the effect of an increase in V_A on P_AO_2 is curvilinear (Fig. 5).

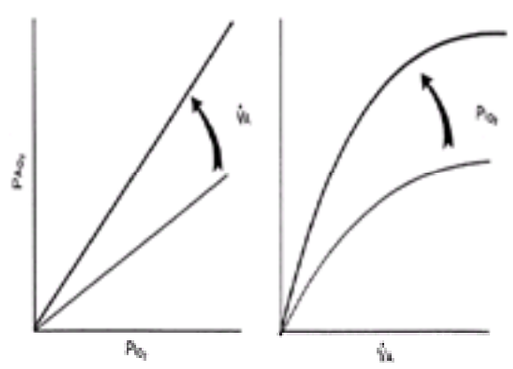

FIG. 5. Relationship of alveolar PO_2 (P_AO_2) to inspired PO_2 (P_IO_2 a P_B and F_IO_2) and to alveolar ventilation (V_A). Note that the relationship of P_AO_2 to P_IO_2 is linear and that V_A affects the slope. On the other hand, the relationship of P_AO_2 to V_A is a curvilinear one that asymptotically approaches the P_IO_2. (From MacIntyre NR. In Dantzker D, MacIntyre N, Bakow E, eds. *Comprehensive Respiratory Care.* Philadelphia: WB Saunders, 1995, with permission.)

The effect of an increase in P_AO_2 on ultimate arterial O_2 content depends on the other factors in O_2 transport affecting the A-aDO_2, especially ventilation–perfusion mismatch and shunt. Thus, predicting the effects of a change in F_IO_2 on P_aO_2 is an approximation at best.

Baseline/Expiratory Pressure

A commonly used technique to improve *VQ* matching is to recruit and stabilize unventilated alveoli with the application of an elevated baseline or expiratory pressure (Fig. 6). Properly applied, expiratory pressure maintains alveolar patency and improves compliance, possibly through improved surfactant function (Fig. 7, curve A to B). Excessive expiratory pressure, however, may serve only to overdistend already recruited alveoli (Fig. 7, curve B to C). In adults with diffuse lung injury, alveoli that are potentially recruitable appear to require between 5 and 20 cm H_2O expiratory pressure. Levels above this, although possibly recruiting some additional alveoli, are probably counterproductive because of overdistention of the already patent alveoli (see "Ventilator Strategies," below).

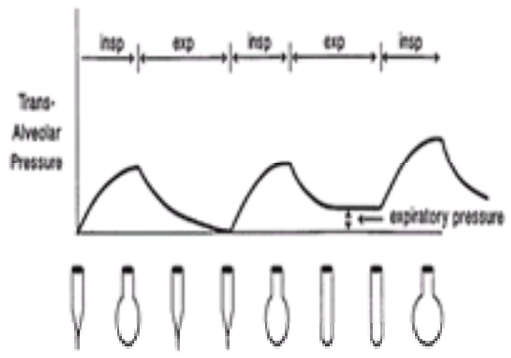

FIG. 6. Behavior of unventilated but recruitable alveoli when expiratory pressure is applied. Note that alveolar patency and the functional residual capacity are restored with appropriate PEEP (recruitment). (From MacIntyre NR. In Dantzker D, MacIntyre N, Bakow E, eds. *Comprehensive Respiratory Care.* Philadelphia: WB Saunders, 1995, with permission.)

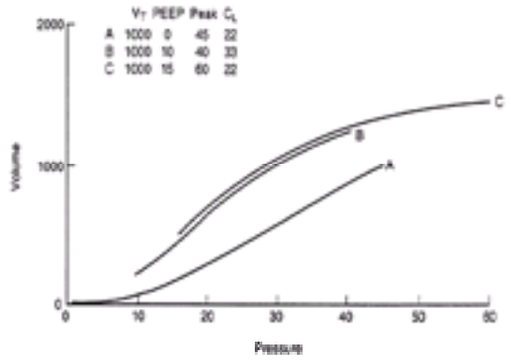

FIG. 7. Mechanical changes in alveoli when ventilated with increasing levels of end-expiratory pressure (PEEP). *Curve A* represents alveoli that remain unventilated until 7 cm H_2O pressure is applied (opening pressure). Subsequent delivery of a 1000-ml tidal volume (V_T) produces a peak pressure of 45 cm H_2O and a calculated compliance (C_L) of 22 mL/cm H_2O. Maintaining alveolar patency during expiration with 10 cm H_2O PEEP improves C_L *(curve B)* Levels of PEEP above this opening pressure, however, may serve only to overdistend the alveoli, thereby worsening C_L *(curve C)* (From MacIntyre NR. In Dantzker D, MacIntyre N, Bakow E, eds. *Comprehensive Respiratory Care.* Philadelphia: WB Saunders, 1995, with permission.)

When used in a spontaneously breathing patient, expiratory pressure can be applied either only during exhalation (EPAP) or else as part of a constant positive airway pressure (CPAP). The CPAP approach minimizes the inspiratory pressure drop (and thus muscle work) that must occur to provide a V_T. Thus, EPAP is rarely used. When it is used in mechanically ventilated patients, the elevated baseline pressure is referred to as positive end-expiratory pressure (PEEP).

COMPLICATIONS OF POSITIVE-PRESSURE VENTILATION

There are a number of hazards associated with positive-pressure mechanical ventilatory support that can result in significant morbidity and mortality if not appropriately recognized and minimized by clinicians.

Hazards Associated with the Endotracheal Tube

There are several potential hazards associated with the “artificial airway.” First, endotracheal tube dislodgement can occur in as many as 5% to 10% of all patients. If monitored and alarmed properly, this usually poses no serious threat to the patient. However, an unrecognized ventilator disconnect can be fatal. Endotracheal tubes also bypass the normal gas-conditioning process of the upper airway. Thus, the mechanical ventilatory support system must supply appropriate heat and humidity as described above. Inadequate heat and humidity can result in tracheal mucosal injury as well as plugging of the endotracheal tube and airways with dried secretions. Another hazard of the endotracheal tube is the fact that it imposes a significant resistive load on spontaneous breaths. This obviously becomes worse with narrow tubes and high patient demand. This form of imposed muscle load has been reported to increase the normal baseline work of breathing severalfold under certain conditions. This imposed work always should be considered in assessing a patient who is difficult to wean from the mechanical ventilator.

Mechanical Malfunctions

The modern generation of mechanical ventilators is remarkably reliable. Nevertheless, any mechanical system can fail. The most common mechanical failure is the exhaled flow transducer (up to 2% failure rate per year). This is not surprising because it is the one part of the machine that is exposed to patient secretions and nebulized solutions. Modern microprocessor systems usually have a variety of self-checks and alarms available. Alarms themselves rarely fail. Of more concern is the fact that alarms are often turned off. This may be a consequence of the fact that too many alarms are set too tightly and thus create so many false alarms that the normal reaction is to shut the alarm down. Clinician awareness of what alarms are important and what alarms may serve only to annoy is critical.

Patient–Ventilator Dyssynchrony

A mechanical ventilator must interact with patient efforts during assisted, supported, and spontaneous breaths. This interaction exists during all three phases of the breath: trigger, limit, and cycle. Inappropriate effort sensors (poor sensitivity or responsiveness) can impose significant loads on patients during triggering. Equally important is that during breath delivery to a patient with an active ventilatory drive, the machine limit and cycling settings can also impose significant loads if not properly “synchronized” to the patient's muscular efforts. This appears to be particularly true when fixed, flow-limited, volume-cycled breaths are used, especially in patients with very active ventilatory drive. Improving synchrony with these types of breaths can sometimes be achieved by adjusting the flow pattern, increasing the assisted breath rate, or else by sedating the patient. Perhaps a better approach to improving synchrony is to utilize the variable flows that exist with a pressure-limited breath (Fig. 8). This capability has recently been enhanced by the addition of a pressure rise time adjustor on newer systems. A consideration of patient–ventilator dyssynchrony ought to be made in all cases of patient agitation and/or weaning difficulty.

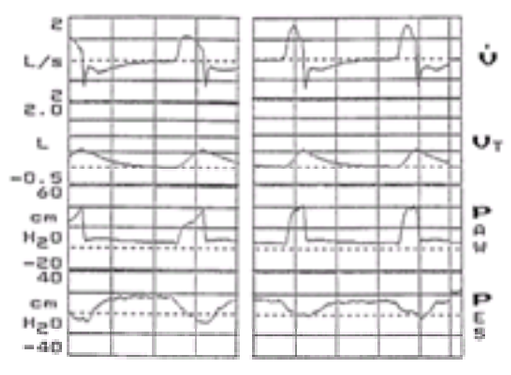

FIG. 8. Flow (V), volume (V_T), airway pressure (P_{aw}), and esophageal pressure (P_{es}) in a patient receiving flow-limited, volume-cycled breaths **(left panel)** and pressure-limited, flow-cycled breaths **(right panel).** Patient-imposed load from flow dyssynchrony is reflected by the area under the baseline of the P_{es} tracing during inspiration. In this example, the variable flows of the pressure-limited breath synchronize with patient effort better than the fixed flows of the volume-cycled breath.

Thus, imposed load is less.

Air Trapping or Intrinsic PEEP ($PEEP_i$)

An inadequate expiratory time can result in air trapping and the development of so-called intrinsic or auto-PEEP. This can have profound effects on delivered ventilation and intrathoracic pressures (Fig. 9). Although intrinsic PEEP is sometimes recommended as a goal in strategies designed to lengthen inspiratory time (see "Ventilator Strategies," below), usually this phenomenon is undesirable because it is difficult to monitor and can cause unrecognized pressure-related hazards. One of the best ways to monitor the development of inadequate expiratory time is to follow a flow graphic. When expiratory time is inadequate, the expiratory flow signal does not return to the zero baseline (Fig. 9, middle panels). In the absence of a flow graphic, one should suspect inadequate expiratory time in the setting of patients with high ventilatory demands, especially those patients with airway dysfunction. Clinically, the development of intrinsic PEEP is manifested by applied high peak airway pressures (if using volume-cycled ventilation), loss of tidal volume (if using a pressure-limited mode), patient discomfort, or cardiac compromise. Ventilator adjustments to reduce intrinsic PEEP from inadequate expiratory time include a slower frequency (longer expiratory time) or a shorter inspiratory time from either faster flows or lower tidal volumes.

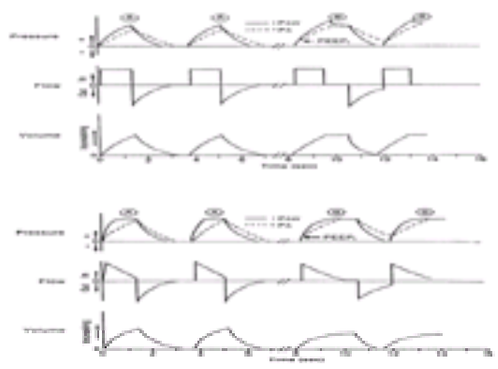

FIG. 9. Intrinsic positive end-expiratory pressure ($PEEP_i$) developing from shortened expiratory times during volume-targeted ventilation **(upper panel)** and pressure-targeted ventilation **(lower panel). Top:** airway pressure *(solid line)* and alveolar pressure *(dotted line)* are plotted. **Center:** flow is plotted. **Bottom:** volume is plotted. Volume-targeted breaths are delivered either without **(A)** or with **(B)** inspiratory holds that affect expiratory time. In the **A** curves, expiratory time allows complete lung emptying such that expiratory flow is zero before the next inspiration. There is no air trapping, and $PEEP_i$ is zero. In the **B** curves, expiratory time does not allow complete lung emptying, such that expiratory flow is greater than zero before the next inspiration. Now there is air trapping, and $PEEP_i$ is greater than zero. Note that $PEEP_i$ in volume-targeted ventilation raises peak pressure but keeps delivered volume constant. In contrast, $PEEP_i$ in pressure-targeted ventilation reduces delivered volume because airway pressure is limited. (From MacIntyre NR. In Fulkerson W, MacIntyre NR, eds. *Complications of Mechanical Ventilation. Problems in Respiratory Care.* Philadelphia: JB Lippincott, 1991, with permission.)

Air trapping can also develop as a consequence of dynamic airway collapse, even in the presence of a reasonable expiratory time. In addition to the above-mentioned effects of intrinsic PEEP, this type of air trapping is often associated with a difficulty in triggering assisted or supported breaths. Under these circumstances, a small amount of applied PEEP (less than the intrinsic PEEP) will reduce this imposed load (Fig. 10).

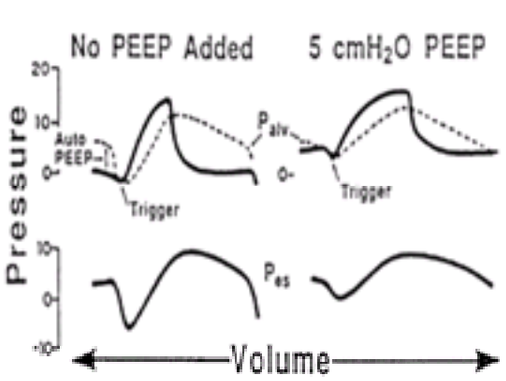

FIG. 10. Impact of auto-PEEP (intrinsic PEEP) on trigger sensitivity and inspiratory effort. To trigger a machine cycle, alveolar pressure (P_{alv}) must fall by the amount of auto-PEEP plus the set trigger sensitivity. The large dip in esophageal pressure (P_{es}) reflects this effort. The addition of PEEP downstream from dynamically compressed airways reduces the P_{alv}–P_{aw} gradient and attenuates the breathing workload without a significant increase in end-inspiratory P_{alv}. (From Marini JJ. In Cherniak NS, ed. *Chronic Obstructive Pulmonary Disease.* Philadelphia: WB Saunders, 1990, with permission.)

Oxygen Toxicity

Raising the P_AO_2 can cause alveolar capillary injury through the toxic effects of oxygen radicals. Depending on the baseline lung pathology, the presence of certain drugs (e.g., bleomycin) and perhaps mechanical forces from positive-pressure breaths, even mild increases in P_AO_2 have been associated with oxygen toxicity. Generally, most clinicians accept the concept that an F_IO_2 below 0.4 can be tolerated for prolonged periods, whereas F_IO_2 values exceeding 0.6 are associated with increased risk. In addition, an F_IO_2 approaching 1.0 can result in absorption atelectasis and worsening of ventilation perfusion (*VQ*) mismatch and shunt.

Stretch Injury (Volutrauma/Barotrauma)

Stretch injury refers to lung damage caused by alveolar overdistention. Alveolar overdistention tends to occur in the less injured lung regions that become overinflated by a high intrathoracic pressure. Although damage appears to be caused primarily by the magnitude of the physical stretching, confounding factors include the duration of stretch and the frequency of stretch. Use of PEEP also plays an important role in stretch injury in two ways. First, in injured alveoli subjected to repeated opening and closing from positive-pressure breaths, a certain minimal PEEP to recruit and prevent collapse may *reduce* stretch injury (Fig. 7, curve A to B). On the other hand, PEEP in already patent alveoli may serve only to increase the end-inspiratory stretch and thus *potentiate* stretch injury (Fig. 7, curve C). Optimal PEEP is conceptually a balance between these two effects (see "Ventilator Strategies," below).

End-inspiratory alveolar stretch is usually assessed by the "plateau" pressure. This is the airway pressure at end-inspiration under no-flow conditions. Provided that chest wall and/or abdominal compliances are not low, this pressure is a reasonable guide to the level of alveolar stretch that is occurring during positive-pressure ventilation. Normal end-inspiratory transalveolar pressures at total lung capacity are 30 to 40 cm H_2O.

The manifestations of stretch injury are of two types. The most obvious type is alveolar rupture, which results in mediastinal emphysema, subcutaneous emphysema, and pneumothorax. The risk is high when alveolar (plateau) pressures exceed 60 cm H_2O. A less appreciated form of stretch injury, however, is tissue injury without rupture. This form of tissue injury can mimic many features of the adult respiratory distress syndrome and may worsen the underlying lung disease. This injury may be potentiated by concurrent oxygen injury and appears to occur in relatively normal alveoli that are overdistended with end-inspiratory pressures above the normal maximum of 30 to 40 cm H_2O.

Infections

Pulmonary infections are also a common complication of mechanical ventilatory support (estimates range from 15% to 40% of all ventilated patients). The reasons for this are several: (1) the endotracheal tube impairs the lung's physical defense against invading organisms and impairs cough and mucus clearance; (2) cough is often decreased by disease and sedation; and (3) atelectasis occurs frequently in patients on mechanical ventilators. A common source of infecting organisms is the GI tract. Prophylactic antibiotics, gut sterilization, and maintaining acidity in the stomach have been advanced as ways to protect against infectious complications, but the results of these interventions have not been shown to improve outcome. Contaminated circuits and humidifiers are also a potential source of infecting organisms. One of the best ways to prevent nosocomial infections, however, is the simple step of hand washing when working with the patient's ventilator circuitry.

Cardiovascular Effects

Increased intrathoracic pressure can affect cardiovascular function. These increased pressures can be the result of ventilation pressures (i.e., tidal breaths and inspiratory time), applied expiratory pressure, and alveolar expiratory pressure resulting from air trapping (“intrinsic” PEEP). Although many mechanisms for consequent cardiac depression have been proposed, it appears the most important is the fact that elevated intrathoracic pressure impedes venous return and thus cardiac filling. Indeed, it has been known for years that to compensate for a reduction in cardiac output with high ventilatory pressures, one should increase the intravascular volume. The airway pressure measurement that seems to correlate best with cardiovascular filling difficulties is the mean airway pressure.

One of the more interesting approaches to manipulation of airway pressure to affect cardiac function is the use of a ventilator breath synchronized to cardiac systole. If the positive airway pressure is timed to occur during systole, and the airway pressure is released during diastole, cardiac output can sometimes be increased such that the ventilator, rather than being a hindrance to cardiac function, can actually function as a partial ventricular assist device. Note that although this approach is still experimental, it does offer an interesting and important lesson in the physiology of heart–lung interactions.

VENTILATOR STRATEGIES TO PROVIDE TOTAL VENTILATORY SUPPORT

Current approaches to total ventilatory support generally attempt to duplicate the normal bulk flow ventilatory pattern and use tidal volumes of 7 to 12 mL/kg, machine breath rates of 10 to 30 breaths/min, and inspiratory to expiratory ratios of 1:4 to 1:2. These positive-pressure breaths are generally delivered as either flow-limited, volume-cycled breaths or pressure-limited, time-cycled breaths. Positive-pressure ventilatory support is usually used in conjunction with elevations in baseline (end-expiratory) pressure (PEEP) and supplemental O_2.

These settings generally provide safe and effective total ventilatory support in most patients in respiratory failure. There are, however, patients in whom these conventional approaches either do not provide adequate blood gas values or else do so with excessive intrathoracic pressures (e.g., plateau pressure exceeding 30 to 40 cm H_2O). Under these circumstances, strategies that balance potential tradeoffs between lung protection and gas exchange must be considered.

Balancing Alveolar Recruitment with Alveolar Overdistention Using PEEP

On the one hand, as noted above, PEEP is used to recruit unventilated alveoli (Fig. 7, curves A to B). Recruited alveoli generally provide better gas exchange and thus a lower F_IO_2 requirement. Moreover, recruited alveoli may be less prone to injury related to the stress of repeated opening and closing. On the other hand, providing high levels of PEEP in an attempt to “normalize” P_aO_2 may be counterproductive if it results in alveolar overdistention in already patent alveoli (Fig. 7, curve C). Several clinical studies in patients with diffuse lung injury have used static pressure–volume plots to show that a reasonable balance between recruitment potential and overdistention risk is generally achieved with PEEP levels of only 5 to 20 cm H_2O. Because this balanced PEEP approach may not provide the maximal P_aO_2, tradeoffs occur. Specifically, a higher F_IO_2 may be required, or a lower S_aO_2 may need to be tolerated (“permissive hypoxemia”). The effects of a lower S_aO_2 (e.g., in the 85% to 89% range) can sometimes be ameliorated by lowering oxygen consumption (e.g., sedation, pain control, fever control) or by increasing other components of oxygen delivery (e.g., hemoglobin concentration, cardiac output).

Balancing Alveolar Ventilation with Alveolar Overdistention Using the V_T

As noted above, the two determinants of end-inspiratory alveolar distention are the baseline distention (see PEEP discussion above) and the tidal distention. Historically, delivered tidal volumes were often recommended to be as high as 15 to 20 mL/kg. This, however, was a reflection of practice in anesthesia before the development of PEEP, when large tidal volumes were required to overcome atelectasis. Lowering tidal volumes to 6 to 8 mL/kg will clearly reduce alveolar pressures and alveolar distention if more conventional V_T settings result in unacceptable plateau pressures (e.g., >30 to 40 cm H_2O). Under these circumstances, alveolar ventilation can be maintained up to a point by increasing the respiratory frequency. Ultimately, however, rapid rates cannot compensate for the loss of tidal volume, and alveolar ventilation will fall, arterial PCO_2 will rise, and arterial pH will fall, creating a respiratory acidosis. This tradeoff is often referred to as “permissive hypercapnia,” and pHs with this strategy have been reported to fall below 7.0. The effects of normoxic hypercapnia under those circumstances are only beginning to be understood. In general, however, humans seem to tolerate an arterial pH of 7.15 and PCO_2 of 80 torr quite well. The rate at which the P_aCO_2 is allowed to rise should probably be slow (e.g., 10 torr/hr) to permit intracellular pH to adjust.

Caution should be used in permitting respiratory acidosis in patients with intracranial mass effects, recent myocardial infarcts, pulmonary hypertension, and possibly gastrointestinal bleeding. Respiratory acidosis may also contribute to dyspnea and agitation in critically ill patients and thus may require heavy sedation or paralysis. In animal models with acute lung injury, pulmonary shunt was higher when ventilation was achieved with smaller tidal volumes. Thus, smaller tidal volumes may require an increased level of PEEP and/or F_IO_2 to maintain acceptable levels of arterial oxygenation.

A low-tidal-volume strategy has resulted in lower mortality when compared to historical controls matched for physiological scores. More compelling is a recent preliminary report of a controlled trial using static pressure–volume plots to determine the lower (recruitment) and upper (overdistention) “inflection” points (Fig. 11). This strategy places baseline pressures (PEEP) above the lower inflection point and limits V_T to pressures below the upper inflection point. Patients ventilated with this approach appear to have less lung stretch injury and improved outcome.

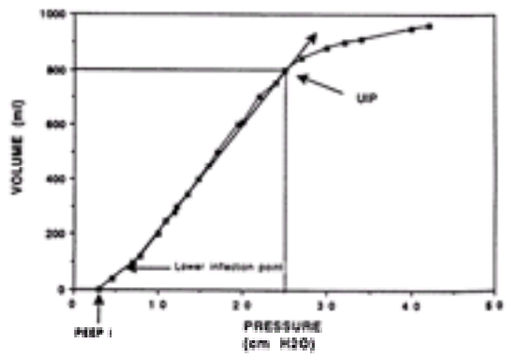

FIG. 11. Static pressure–volume curve of the respiratory system obtained in a patient with diffuse lung injury. Intrinsic PEEP ($PEEP_i$), present during the course of mechanical ventilation, represents the starting point of the curve. Inflection points were defined as lower (LIP) and upper (UIP) points on this sigmoid curve, where data consistently separated from the middle linear part of the curve. (From Rouple E, Dambrosio M, Serviool G, Mentec H, El Altrous S, Beydon L, Brun-Buisson C, Lemaire F, Brochard L. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;152:121–128, with permission.)

Long-Inspiratory-Time Strategies as an Alternative to PEEP/F_IO_2

The conventional inspiratory-to-expiratory (I:E) ratio is generally 1:2 to 1:4. This range of I:E ratios tends to synchronize with the patient's spontaneous ventilatory drive

and permits adequate expiratory time for the lung to return to functional residual capacity (FRC) using the recoil pressure of the respiratory system.

Lengthening the inspiratory time to I:E ratios approaching 1:1 or even exceeding it (so-called inverse-ratio ventilation) can be accomplished in either volume-cycled or pressure-limited modes by either providing a very slow inspiratory flow pattern or by holding the alveoli fully inflated for a period of time (inspiratory “pause”). Prolonging inspiration has several physiological effects. First, the alveolus is held at its inspiratory volume for a longer period of time. Theoretically, this should allow more mixing time between alveolus and conducting airway and more exposure of capillary blood to fresh gas. The few clinical studies that have studied only this longer gas mixing and alveolar “dwell time” phenomenon have tended to show improvement in ventilation–perfusion (*VQ*) matching and modest increases in P_aO_2.

A second effect of longer inspiratory times is the potential for incomplete lung emptying. Under these conditions, the lung cannot return to its normal FRC, and “intrinsic” PEEP develops (Fig. 9). Much like applied PEEP, intrinsic PEEP, by increasing FRC, can affect gas exchange by improving *VQ* matching. Indeed, many of the studies on long inspiratory time and inverse-ratio ventilation showing improvement in gas exchange have probably had this occur as a consequence of intrinsic PEEP.

It is important to separate these two effects of longer inspiratory times from a mechanical perspective. Specifically, a longer inspiratory time *without* air trapping is designed to provide *VQ* improvement without affecting tidal volume, baseline alveolar pressure, or maximal alveolar pressure. Conversely, a longer inspiratory time *with* air trapping may also improve *VQ* matching, but, because it functions like applied PEEP, it will necessarily raise baseline alveolar pressure. This will reduce tidal volume in a pressure-limited mode and raise maximal alveolar pressures in a volume-cycled mode (Fig. 9). It is also important to note that once one exceeds the normal I:E ratio, the need for sedation and even paralysis starts to increase.

Investigational Strategies

There are a number of total-support strategies in the adult that may find clinical utility in the future. These include high-frequency ventilation (frequencies exceeding 150 breaths/min and tidal volumes approaching dead space), nitric oxide inhalation, surfactant replacement therapy, and liquid ventilation (using an oxygen-soluble fluorocarbon to function as “liquid” PEEP). All of these are in various stages of development, and we must await definitive outcome data before widespread clinical application can be recommended.

VENTILATOR STRATEGIES TO PROVIDE PARTIAL VENTILATORY SUPPORT

Partial ventilatory support, as defined above, is designed to provide only part of the work of breathing. Generally this form of support is given to patients as they recover from lung injury and recover the ability to do some of the work of breathing. Reducing partial support is often termed *weaning*

The argument is sometimes made that weaning is an unnecessary process. This argument states that total support should be given to patients until they can breathe entirely on their own. At this point, the ventilator is then discontinued. This approach is certainly appropriate for rapidly resolving processes such as anesthesia recovery. However, it is probably inappropriate in patients with much slower recovery process for two reasons: (1) partial support (as opposed to total support) requires less positive pressure in the thorax and thus a lower risk of stretch injury or hemodynamic compromise; (2) partial support (as opposed to total support) demands some patient activity, which will help prevent muscle atrophy and may even contribute to a muscle-conditioning process. These two effects would seem desirable in a patient requiring prolonged support.

There are at least three established ways of providing partial support during the weaning process. The oldest technique is *intermittent spontaneous breathing* alternating with periods of total support (“T-piece” weaning). Weaning progresses by having the patient take longer and longer periods of spontaneous breathing. In between these periods, the ventilator takes over all of the work of breathing and allows the patient to rest. A second technique is *intermittent mandatory ventilation* (IMV). With IMV, patients take spontaneous breaths interspersed among mandatory ventilator breaths. Weaning progresses by providing decreasing numbers of ventilator breaths such that patients take increasing numbers of spontaneous breaths. A variation on this approach is synchronized IMV (SIMV), which utilizes volume-assisted breaths along with backup volume-control breaths. Another variation is the addition of 5 to 10 cm H_2O of pressure support to the spontaneous breaths of IMV to reduce (or eliminate) the imposed work of breathing through narrow endotracheal tubes. The third technique is stand-alone *pressure-limited ventilation* With this technique, partial support is provided with every breath by using a pressure-limited, patient-triggered breath. Usually this is provided by the pressure-support breath, although a pressure-assist breath (patient-triggered, pressure-limited, time-cycled breath; Table 2) can also provide a similar level of partial support while guaranteeing a certain inspiratory time. Weaning progresses from a high level of inspiratory pressure (enough to provide virtually all the work of each breath, usually associated with tidal volumes of 7 to 10 mL/kg) to lower levels of pressure where the patient contributes substantial work to each breath.

“T-piece” breathing trials and IMV offer the advantage of a certain mandatory minute ventilation being provided by the ventilator. In contrast, stand-alone pressure-limited breaths cannot guarantee a minimum minute ventilation but do offer the theoretical advantage of being a more comfortable and physiological way to have the muscles work because a pressure “boost” is provided with each ventilatory effort (Fig. 8). Clinical studies comparing outcomes of these different approaches have given conflicting results (Fig. 12). In general, however, it appears that aggressive weaning approaches (e.g., T-piece) are appropriate in rapidly resolving lung injury, whereas more comfortable approaches (e.g., pressure support) are more appropriate in a more slowly resolving lung injury. The use of short spontaneous breathing trials each morning may be useful to distinguish these different types of patients recovering from lung injury.

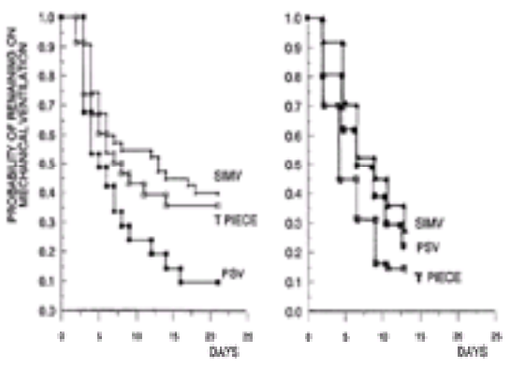

FIG. 12. Results of two large randomized weaning trials. On the *vertical axis* is probability of remaining on the ventilator. On the *horizontal axis* is number of days after randomization to one of three weaning protocols: spontaneous breathing trials (T-piece), synchronized intermittent mandatory ventilation (SIMV), and stand-alone pressure support (PSV). **Left panel** represents data from Brochard L, Rauss A, Benito S, Conti G, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994;150:896–903. **Right panel** represents data from Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med*1995;332:345–350.

Regardless of which technique is used, proper monitoring of the weaning process is crucial for proper aggressiveness and safety in advancing the weaning process. Because the goal is to return ventilatory work to the patient as quickly as tolerable, indicators of patient load tolerance should be the best parameters to monitor during weaning (Table 3). The respiratory rate is a particularly useful sign in this regard. Specifically, tachypnea is one of the earliest signs of respiratory muscle overload and fatigue and is an excellent guide to setting the appropriate level of partial support. Arterial blood gases are also useful to monitor during the weaning process, but it should be noted the changes in PCO_2 and PO_2 may not occur until long after respiratory muscle fatigue has begun to develop. Arterial blood gases thus should not be the exclusive guide to weaning. Other indirect indications of a patient tolerating the weaning process include stable hemodynamics, subjective comfort, and a regular breathing pattern.

Respiratory rate
Arterial blood gases
Work (normal <5–10 joules/min)
Pressure–time product (nonfatiguing if less than 15% of maximal diaphragmatic pressure)
Patient assessment for comfort, tachycardia, blood pressure stability

TABLE 3. *Monitoring patient tolerance of partial support*

When the weaning process has progressed to a fairly low level of partial support (e.g., spontaneous breathing trials lasting 30 to 60 min, IMV rates less than 4 breaths/min, pressure support levels less than 10 cm H_2O), the patient's ability to tolerate prolonged spontaneous breathing without any support needs to be assessed (Table 4). Again, the respiratory pattern may be the best predictor of success, and a frequency to tidal volume ratio less than 105 has been found to be among the best of these. Extubation criteria also need to take into account the patient's ability to protect the airway and to provide an adequate cough for secretion clearance.

Negative inspiratory force stronger than 25 cm H_2O
Vital capacity >10 ml/kg
Minute ventilation <10 liters/min
Frequency/tidal volume <105/liter
"CROP" index [(compliance X negative inspiratory force X P_aO_2/P_AO_2)/respiratory rate] >13 ml/breath per min

TABLE 4. *Extubation criteria*

In addition to treating the underlying disease and setting the proper level of partial support, there are a number of other aspects that must be considered for total management of the patient requiring prolonged support. First, the ventilator mode should be a comfortable one for the patient. Specifically, required triggering efforts should be small, and ventilator flows should be in accordance with patient demand. Pressure-limited breaths with adjustable "rise times" seem beneficial in this regard. In addition, an experimental interactive breath that uses a flow "gain" setting based on lung impedances (proportional-assist ventilation) may be even better. Second, airway management must be meticulous with proper suctioning techniques, aspiration precautions, humidification, and circuit hygiene. Third, nutritional considerations are important, particularly in the patient who may have undergone a serious stress such as surgery or complicating sepsis. Fourth, cardiovascular management must include proper fluid balance and an appropriate cardiac output. During the weaning process, the ventilatory muscles are being asked to take over an increasing workload, and proper oxygen delivery is critical. Finally, patience is needed on the part of the clinicians. Remember, weaning can progress no faster than respiratory system healing. The ventilator management goal is thus not to "cure" the lung but rather to provide an adequate level of support and to not hinder the recovery process with iatrogenic complications.

NONINVASIVE TECHNIQUES FOR VENTILATORY SUPPORT

There are two fundamental approaches to providing ventilatory support without the use of an artificial airway: (1) techniques designed to expand the thorax by negative pressure and (2) techniques designed to inflate the chest with positive pressure applied through a mask. Because these approaches are often awkward to use and are usually incapable of high levels of ventilatory support, they are generally used as either intermittent partial support (e.g., nocturnal ventilation) or as a short-term technique to "buy time" in an acute situation.

Negative-Pressure Approaches

These approaches range from iron lungs to chest wraps to rocking beds. Although they all can provide some degree of lung inflation, they are generally very cumbersome, incapable of any synchrony with patient efforts, and provide no airway protection. Because of this, application is generally limited to patients with neuromuscular dysfunction in whom some nocturnal assistance and muscle "rest" results in improved ventilatory function during the day. See chapter 50.

Positive-Pressure Mask Approaches

Ventilatory support or continuous positive airway pressure (CPAP) can be provided by positive pressure applied through mask systems. Full-face mask ventilation using either pressure-limited or flow-limited breaths can be done through tight-fitting masks. Such systems can respond to patient effort to provide either assisted or supported breaths. However, leaks are common, and gastric overdistention can result in vomiting and aspiration. These systems would appear to be a reasonable strategy for short-term support in acute respiratory failure if monitored properly. Indeed, several studies have suggested that short-term face-mask ventilation may prevent the need for endotracheal intubation in patients with rapidly reversible respiratory failure (e.g., asthma). The role of this technique in long-term support without close monitoring (e.g., home care) is less clear because of concerns over leaks, undetected circuit occlusions, and gastric distention.

Positive airway pressure can also be provided by nasal mask. The inevitable mouth leak can be compensated for by continuous gas flows. This approach to providing CPAP has been very effective in managing obstructive sleep apnea and probably has a role in noninvasively restoring FRC and improving *VQ* mismatch in mild to moderate pulmonary edema. It may also have a role in overcoming some intrinsic PEEP caused by dynamic airway collapse in patients with airway dysfunction (Fig. 10). The role of nasal-mask positive-pressure breaths in providing ventilatory support (generally using pressure-limited breaths) is less clear. Reports exist suggesting short-term nasal-mask ventilation can be useful in preventing endotracheal intubation in reversible respiratory failure. However, mask function, leak tolerance, and patient synchrony with these systems are variable, and thus, they usually require close monitoring to be effective for short-term support in dyspneic patients. An advantage to a nasal mask is that, because the mouth is open, there is less concern about vomiting and aspiration and the danger of undetected circuit occlusion. Long-term usage is thus a potential application of such systems (e.g., nocturnal support), and, indeed, treatment of some obstructive sleep apnea patients appears enhanced when positive pressure during inspiration is added to the elevation in baseline pressure. However, the long-term role of such systems in patient with intrinsic lung disease and dyspnea is unknown.

CONCLUSION

Mechanical ventilation utilizes positive pressure to support ventilation (through tidal breath delivery) and oxygenation (through ventilation distribution effects and alveolar recruitment in expiration). Potential hazards include "stretch" injury, cardiac compromise, endotracheal tube dysfunction, oxygen toxicity, patient discomfort, and infections. Ventilatory support can either be total or partial. During total ventilatory support, the ventilator supplies all the work of respiration. Under these conditions, tradeoffs between gas-exchange goals and the risks associated with high intrathoracic pressures must sometimes be made. During partial ventilatory support, the ventilator supplies only a portion of the work of respiration, with the patient supplying the remainder. Reduction in partial support is termed weaning. Under these conditions, the need to aggressively reduce support must be balanced against the potential to fatigue the patient. It must always be remembered that mechanical ventilation provides *support*, not *therapy*, for respiratory failure. As such, it cannot be expected to cure lung disease. Rather, it can only be expected to support life with minimal complications while more definitive therapies are given time to work.

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CHAPTER

49 Weaning from Ventilatory Support

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INTRODUCTION

The term weaning is open to misunderstanding. In the strict sense, it means a slow, gradual decrease in the amount of ventilator support. More commonly, it is used to refer to all methods of discontinuing mechanical ventilation, although this usage of the term is incorrect in the strict literal sense. In most instances of mechanical ventilation, weaning is quite straightforward, and patients can resume spontaneous breathing with little or no difficulty. About 20% to 30% of patients fail initial attempts at discontinuing mechanical ventilation, and these difficult-to-wean patients account for a disproportionate amount of health care resources. Overall, about 40% of the time that a patient receives mechanical ventilation is spent trying to wean the patient from the ventilator, and in patients with certain disease states, such as chronic obstructive pulmonary disease, the weaning process accounts for about 60% of ventilator time.

PATHOPHYSIOLOGICAL DETERMINANTS OF WEANING OUTCOME

A patient's ability to tolerate discontinuation of ventilator support is determined by the adequacy of pulmonary gas exchange, the performance of the respiratory muscle pump, and psychological factors.

Adequacy of Pulmonary Gas Exchange

During failed attempts at weaning from mechanical ventilation, hypoxemia may result from hypoventilation, impaired gas exchange, or decreased oxygen content of venous blood. By and large, severe hypoxemia is a relatively uncommon mechanism of weaning failure, because weaning is not attempted in patients who appear prone to problems in oxygenation.

Respiratory Muscle Performance

Failure of the respiratory muscle pump is the most common cause of failure to wean from mechanical ventilation. This may result from decreased neuromuscular capacity, increased respiratory muscle pump load, or a combination of both factors (Table 1).

Decreased respiratory neuromuscular capacity
Decreased respiratory center output
Phrenic nerve dysfunction
Neuromuscular disorders
Decreased respiratory muscle strength and/or endurance
Hyperinflation
Malnutrition
Decreased oxygen supply
Respiratory acidosis
Mineral and electrolyte abnormalities
Renal failure
Endocrinopathy
Drug-induced abnormalities
Disuse muscle atrophy
Respiratory muscle fatigue
Increased respiratory muscle pump load
Increased ventilatory requirements
Increased CO_2 production
Increased deadspace ventilation
Inappropriately increased respiratory drive
Increased work of breathing

TABLE 1. *Causes of respiratory muscle pump failure*

Decreased Respiratory Neuromuscular Capacity

Respiratory Center Output

Patients who fail a weaning trial commonly develop respiratory acidosis, raising the possibility that respiratory center drive may be decreased. However, indices of respiratory drive, such as airway occlusion pressure at 0.1 sec ($P_{0.1}$) or mean inspiratory flow (tidal volume divided by inspiratory time interval; V_T/T_I), are usually above the normal range in such patients. Furthermore, an increase in V_T/T_I has been observed in patients who developed severe alveolar hypoventilation (Fig. 1).

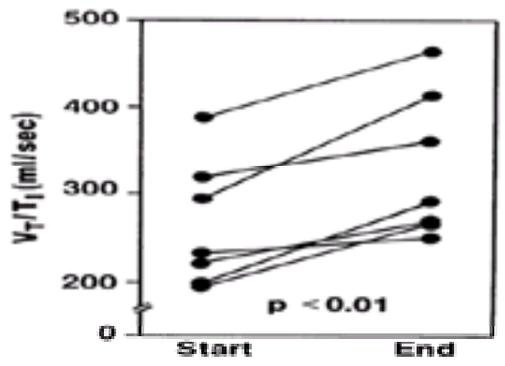

FIG. 1. Measurements of mean inspiratory flow (V_T/T_I) at the beginning and end of a trial of spontaneous breathing in patients who required the reinstitution of mechanical ventilation. (From Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. *Am Rev Respir Dis* 1986;134:111, with permission.)

Phrenic nerve dysfunction results in raised left hemidiaphragm, and electrophysiological studies reveal evidence of phrenic nerve injury in about 10% of these patients. Factors that appear to be important in causing phrenic nerve injury include inadvertent sectioning, stretching or compression of the nerve, or compromise of blood flow to the vaso vasorum of the nerve. However, attention has mainly focused on another mechanism: hypothermic injury caused by the use of topical cardioplegia, which involves filling the pericardium with crushed ice or chilled saline. The precise nature of the phrenic nerve injury is unknown, although the clinical course is most compatible with axonal degeneration. A small number of patients develop bilateral diaphragmatic paralysis resulting in prolonged ventilator dependency.

Respiratory Muscle Function

Respiratory muscle function may be impaired by a variety of conditions commonly observed in critically ill patients (Table 1). Of the clinical conditions that cause a decrease in respiratory muscle strength and/or endurance, *hyperinflation* is one of the most important. Worsening of lung mechanics leads to prolongation of the respiratory time constant (i.e., resistance × compliance) and is commonly associated with an increase in respiratory rate. As a result, expiratory time becomes insufficient for lung emptying, and dynamic hyperinflation occurs. Hyperinflation has a number of adverse effects (Fig. 2): respiratory muscles operate at an unfavorable position of their length–tension curve; flattening of the diaphragm increases the radius of curvature, and, thus, according to Laplace's law, tension within the muscle is less effectively translated into transdiaphragmatic pressure; chest wall efficiency is impaired as a result of the medial orientation of the diaphragmatic fibers, the decrease in the zone of apposition, and the horizontal (rather than oblique) orientation of the fibers; and the inwardly directed elastic recoil of the chest wall poses an added elastic load.

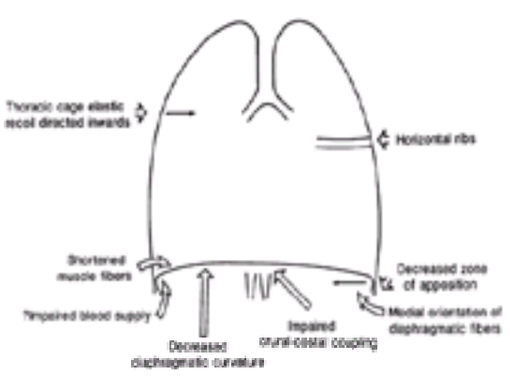

FIG. 2. The detrimental effects of hyperinflation on respiratory muscle function (see text for explanation). (From Tobin MJ. Respiratory muscles in disease. *Clin Chest Med* 1988;9:263–286.)

Malnutrition is common in critically ill patients and has a number of adverse effects on respiratory function: a decrease in the ventilatory response to hypoxia, a decrease in muscle mass and thickness, and a reduction in respiratory muscle strength and endurance. The O_2 supply to a muscle is decreased if cardiac output falls, the O_2 content of arterial blood decreases, or O_2 extraction is impaired. In a study of patients who failed a trial of weaning from mechanical ventilation, increases in pulmonary artery wedge pressure and left ventricular end-diastolic volume were observed (Fig. 3); these changes were attributed to augmentation of venous return (because of low pleural pressure during spontaneous breathing and central translocation of blood volume secondary to peripheral venoconstriction) and increased left ventricular afterload (because of markedly negative pleural pressure swings and increased catecholamine release). In a study employing thallium-201 (^{201}Tl) myocardial scintigraphy, resumption of spontaneous breathing was found to result in isotope redistribution in the myocardium and/or transient left ventricular dilation. Both of these changes were interpreted as being ischemic in origin and were thought to result from increased left ventricular preload and afterload. A number of studies have shown that moderate hypoxemia exacerbates respiratory muscle endurance and fatigability, whereas hyperoxia enhances respiratory muscle endurance.

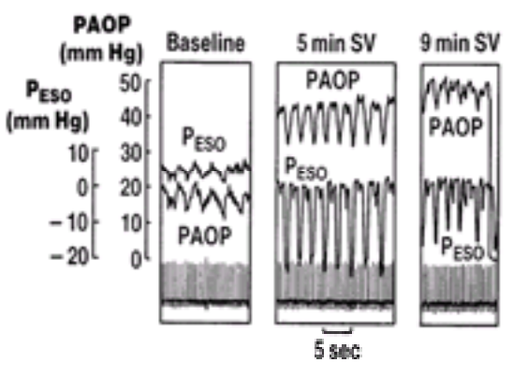

FIG. 3. Measurements of esophageal pressure (P_{eso}) and transmural pulmonary artery occlusion pressure (PAOP) in a patient who failed a weaning trial. Measurements were obtained during mechanical ventilation (baseline) and after 5 and 9 min of spontaneous ventilation (SV). Note that markedly negative swings in P_{eso} and the increase in PAOP during spontaneous ventilation. (Reproduced with permission from Lemaire F, Teboul JL, Cinotti L, et al. Acute left ventricle dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology* 1988;69:171–179.)

Acute respiratory acidosis has been shown to cause a decrease in the contractility and endurance time of the diaphragm in healthy subjects. A number of metabolic abnormalities commonly observed in critically ill patients, such as abnormalities of phosphate, potassium, calcium, or magnesium, may adversely affect respiratory muscle function. Endocrine disturbances such as hyperthyroidism or hypothyroidism may impair respiratory muscle function. Probably more relevant to the weaning situation is the use of corticosteroid therapy. Several reports have drawn attention to the development of myopathic changes (including respiratory muscle involvement) in patients receiving corticosteroid therapy. A number of pharmacologic agents may cause respiratory muscle weakness. Recently, there have been a number of disturbing reports describing prolonged respiratory muscle weakness after discontinuation of neuromuscular blocking agents such as pancuronium and vecuronium.

Respiratory muscle atrophy may develop during a period of prolonged mechanical ventilation. In baboons, controlled mechanical ventilation for 11 days caused decreased performance of the respiratory muscles. Studies of limb immobilization have shown that disuse of skeletal muscle produces a marked decline in muscle

mass. This occurs rapidly, and the greatest reduction in muscle size is observed in the early stages of immobilization.

The question of whether respiratory muscle fatigue occurs during the weaning process is of major importance. Patients who fail a weaning trial commonly display severe abnormalities in respiratory mechanics, and their respiratory muscles perform in an inefficient manner, which places them at considerable risk of developing respiratory muscle fatigue. Resting the respiratory muscles with mechanical ventilation is the major method of reversing fatigue, but if rest is excessive, muscle atrophy can occur. Consequently, the optimal timing and pace of weaning are problematic in these patients. The first study to provide evidence that respiratory muscle fatigue may be a common cause of weaning failure was that by Cohen et al. They studied 12 patients exhibiting difficulty during weaning and found that seven patients developed a power-spectral shift on surface recordings of the diaphragmatic electromyogram (EMG), which was considered indicative of diaphragmatic fatigue. Six of the seven patients displaying EMG changes also exhibited paradoxic motion of the abdomen (inward displacement during inspiration), which was accompanied by tachypnea and “respiratory alternans” (phasic alternation in the contribution of the rib cage and abdomen to tidal volume) in four patients. None of these signs was observed in the patients who did not develop EMG changes. The investigators considered that these changes in breathing pattern permit a diagnosis of respiratory muscle fatigue to be made with reasonable certainty. However, certain factors need to be considered before this interpretation can be accepted. All of the patients, including those without EMG changes and an abnormal breathing pattern, were returned to mechanical ventilation within 40 min, thus limiting the clinical significance of these findings. Also, a shift in the power spectrum of the EMG has not been shown to bear a relationship to the form of fatigue that is physiologically important, i.e., low-frequency fatigue; it is affected by factors other than fatigue, and its physiological basis remains unknown. In addition, no attempt was made to separate the effect of work of breathing from fatigue in these patients.

In a subsequent study, patients who failed a weaning trial were found to display an immediate onset of rapid shallow breathing and abnormal rib cage–abdominal motion on discontinuation of ventilator support, with no further progression during the period of the weaning trial (Fig. 4 and Fig. 5). Conceptually, it is difficult to reconcile this pattern of immediate alteration in the breathing pattern without subsequent progression with the development of respiratory muscle fatigue. In a study conducted in healthy subjects breathing against resistive loads and using an experimental design that permitted the separation of the effect of loading from fatigue, fatigue was shown to be neither necessary nor sufficient to induce asynchrony, paradox, or increased variability in rib cage–abdominal motion (Fig. 6). In contrast, respiratory loading was sufficient to induce abnormal motion.

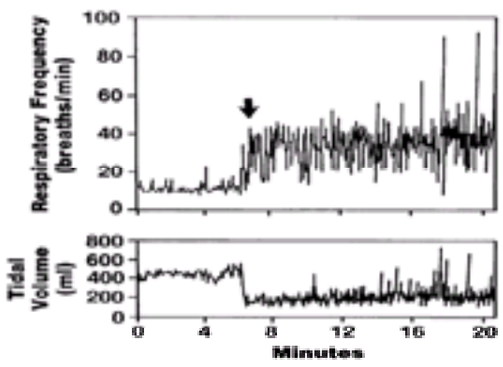

FIG. 4. A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The *arrow* indicates the point of resuming spontaneous breathing following discontinuation of ventilator support. Rapid, shallow breathing developed almost immediately, suggesting the prompt establishment of a new steady state. Although it has been considered that rapid, shallow breathing may reflect the presence of respiratory muscle fatigue, its almost instantaneous development without subsequent progression is difficult to reconcile with the development of respiratory muscle fatigue. (From Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. *Am Rev Respir Dis* 1986;134:1111, with permission.)

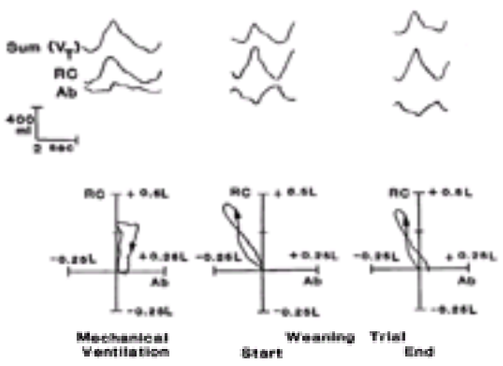

FIG. 5. Analog tracing of the sum (V_T), ribcage (RC), and abdominal (Ab) signals during mechanical ventilation and at the beginning and end of a weaning trial in a patient with an unsuccessful weaning outcome. The terminal portion of the preceding breath and the initiation of the subsequent breath are also shown. For clarity, the baselines of the individual analog signals have been arbitrarily adjusted to provide visual separation of the signals. The respective Konno–Mead plots of the RC–Ab relationship are displayed below each of the breaths. During mechanical ventilation, there is some Ab paradox, which increases immediately on discontinuation of the ventilator. There is no progression in the extent of abnormal RC–Ab motion from the beginning to the end of the weaning trial 24 min later. (From Tobin MJ, Guenther SM, Perez W, et al. Konno–Mead analysis of rib cage–abdominal motion during successful and unsuccessful trials of weaning from mechanical ventilation. *Am Rev Respir Dis* 1987;135:1320, with permission.)

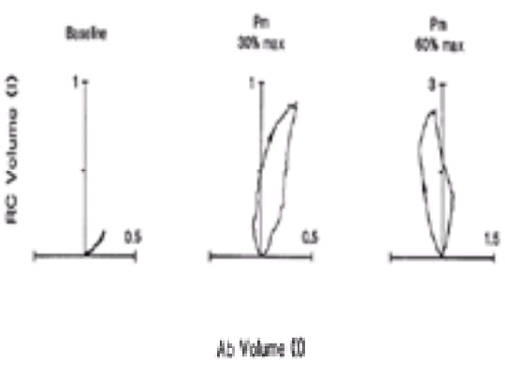

FIG. 6. Konno–Mead plots of rib cage (RC)–abdominal (Ab) motion in a subject during resting breathing and while breathing against a resistive inspiratory load of sufficient magnitude to require the generation of 30% and 60% of maximum mouth pressure (P_{mmax}). At 30% of P_{mmax}, a loop forms, indicating RC-Ab asynchrony, and some Ab paradox is also evident. At 60% of P_{mmax}, the degree of Ab paradox increases further, as indicated by the leftward shift in the plot. The presence of abnormal RC-Ab motion at 30% of P_{mmax} is of significance, since this level of pressure can be sustained indefinitely without the development of respiratory muscle fatigue. (From Tobin MJ, Perez SM, Guenther SM, et al. Does the rib-cage abdominal paradox signify respiratory fatigue? *J Appl Physiol* 1987;63:851.)

Increased Respiratory Muscle Pump Load

An increase in the load on the respiratory muscle pump may result from increased ventilatory requirements or increased work of breathing (Table 1).

Increased Ventilatory Requirements

Factors causing an increase in ventilatory requirements include increased CO_2 production, increased deadspace ventilation, and an inappropriately elevated respiratory

drive. Although an increase in CO_2 production predisposes to the development of CO_2 retention, it is never the sole cause of hypercapnia. An increase in CO_2 production may occur as a complication of excessive use of carbohydrate calories during nutritional support. In normal subjects, an increase in alveolar ventilation prevents the development of hypercapnia. This is not possible in patients with respiratory compromise, and several patients have been reported to develop hypercapnia when given excessive nutritional support at the time of being weaned from mechanical ventilation.

Dead Space Ventilation

Physiological dead space is usually related to tidal volume and expressed as V_D/V_T; in healthy subjects the V_D/V_T ratio is between 0.33 and 0.45. Dead space is increased in a number of disease states associated with regions of lung possessing high $\dot{V}_A/\dot{Q}$ ratios, and this requires an increase in minute ventilation if hypercapnia is to be prevented. If CO_2 production is high, an increase in V_D/V_T to 0.6 or above is generally considered to predict an unsuccessful weaning outcome because the associated increase in minute ventilation necessary for satisfactory gas exchange causes marked encroachment on ventilatory reserve.

Increased Respiratory Drive

An inadequate level of respiratory drive causes hypoventilation and respiratory acidosis, but an inappropriately heightened drive places unnecessary stress on the respiratory muscle pump and predisposes to fatigue.

Work of Breathing

Patients requiring ventilator support may have an increase in airway resistance or a decrease in pulmonary compliance, and, thus, the level of respiratory work could be a major determinant of their ability to resume and sustain spontaneous ventilation. Measurements of work of breathing in patients being weaned from mechanical ventilation have been obtained by a number of investigators, and although work was greater in weaning failure patients, the threshold values separating weaning success from weaning failure patients differed among the various studies. Furthermore, these threshold values were determined on a *post-hoc* basis, and the value of work measurements as a predictor of weaning outcome has not been examined in a prospective fashion. Respiratory workload can also be assessed by measuring the O_2 cost of breathing. This is usually taken as the difference in total body O_2 consumption between spontaneous breathing and that when a patient is relaxed and receiving mechanical ventilation. In resting healthy subjects, the O_2 cost of breathing is <5% of the total body O_2 consumption, but it can exceed 50% in patients being weaned from mechanical ventilation. Such a marked increase in the O_2 cost of breathing decreases the availability of O_2 for delivery to other vulnerable tissue beds and may precipitate myocardial ischemia or other problems.

Psychological Factors

Psychological factors may seriously interfere with the weaning process in some patients. Dependence on mechanical ventilation can be associated with feelings of insecurity, anxiety, fear, agony, and panic. Many patients develop a fear that they will remain dependent on mechanical ventilation and that discontinuation of ventilator support will result in sudden death. Apart from a few isolated reports, however, there is little information on the extent to which psychological disturbances contribute to ventilator dependency.

PREDICTING WEANING OUTCOME

One of the major challenges in mechanical ventilation is deciding when is the best time to wean a patient from the ventilator. If a physician is too conservative and postpones weaning onset, the patient is placed at an increased risk of life-threatening ventilator-induced complications. If weaning is commenced prematurely, the patient may suffer severe cardiopulmonary and/or psychological decompensation, which sets the patient back in his or her clinical course. The first prerequisite for initiation of weaning is that the disease process that precipitated the need for mechanical ventilation has resolved sufficiently so that the patient has a reasonable chance of being able to sustain spontaneous ventilation. Although careful clinical assessment is necessary in deciding when to wean a patient, this alone is not sufficient, and recent studies have shown that experienced clinicians frequently err in their predictions. Accordingly, functional tests are helpful in determining a patient's readiness for weaning (Table 2).

Gas exchange
$P_aO_2 \geq 60$ torr with $F_IO_2 \leq 0.35$
Alveolar–arterial P_{O_2} gradient <350 torr
P_aO_2/F_IO_2 ratio >200
Ventilatory pump
Vital capacity >10–15 ml/kg body weight
Maximum negative inspiratory pressure less than −30 cm H_2O
Minute ventilation <10 liters/min
Maximum voluntary ventilation more than twice resting minute ventilation

TABLE 2. *Variables used to predict weaning success*

Pulmonary Gas Exchange

Discontinuation of ventilator support is generally not contemplated in a patient with persistent hypoxemia, e.g., arterial oxygen tension (P_aO_2) <55 mmHg with an inspired oxygen concentration (F_IO_2) ³0.40. A number of indices derived from arterial blood gas (ABG) measurements have been proposed as predictors of weaning outcome (Table 2), although these criteria are not based on prospective investigation. In a retrospective study, an arterial to inspired O_2 ratio (P_aO_2/F_IO_2 ratio) of 238 (equivalent to a P_aO_2 of 50 torr with an F_IO_2 of 0.21) had a positive predictive value (the probability that a patient will be successfully weaned when the test predicts success) of 90%. However, its negative predictive value (the probability that a patient will fail a weaning trial when the test predicts failure) was only 10%. In another study, an arterial/alveolar O_2 tension (P_aO_2/P_AO_2) of 0.35, which was the value that provided best separation between weaning success and weaning failure in an initial "training data set," was found to have a positive predictive value of only 0.59 and a negative predictive value of only 0.53.

Maximal Inspiratory Pressure

Maximal inspiratory pressure (P_{Imax}) is one of the standard measurements used to predict weaning outcome, based on its excellent performance in a classic study by Sahn and Lakshminarayan. They studied 100 patients and found that all patients who generated P_{Imax} values of -30 cm H_2O were successfully extubated, whereas all those with a P_{Imax} less negative than -20 cm H_2O were unable to sustain spontaneous ventilation. However, in a subsequent prospective study, Tahvanainen et al. found that a P_{Imax} value of -30 cm H_2O was falsely negative in 100% of patients (predicted failure but actually succeeded) and falsely positive in 26% (predicted success but actual failure). Other investigators have also found that P_{Imax} has limited power in predicting weaning outcome, which may reflect the difficulty of making the measurement in uncooperative patients. A modified technique has been developed in an attempt to make the measurements more reliable. A one-way valve is attached to the airway to ensure that inspiratory efforts are made at a low lung volume, and the period of occlusion is maintained for 20 sec. In a study that employed this technique, a P_{Imax} value of -30 cm H_2O continued to be a poor predictor of weaning outcome: positive predictive value of 0.58 and negative predictive value of 0.55. Thus, standardizing the method of measurement did not improve its usefulness as a predictor of weaning outcome.

Vital Capacity

A vital capacity of 10 mL/kg or more has been suggested to predict a successful weaning outcome. However, in a study of weaning outcome, a vital capacity of 15 mL/kg was falsely positive in 15% and falsely negative in 63% of patients.

Minute Ventilation and Maximum Voluntary Ventilation

A minute ventilation of less than 10 L/min is considered to predict a successful weaning outcome. However, in a subsequent study, this criterion was very inaccurate: positive and negative predictive values were only 0.50 and 0.40, respectively. In the study of Sahn and Lakshiminaryan, the combination of a minute ventilation of less than 10 liters/min and the ability to double this value during a MVV maneuver was able to predict 100% of the weaning successes and 71% of the failures. However, Tahvanainen et al. found that the MVV criterion was falsely positive in 14% of patients and falsely negative in 76%.

Airway Occlusion Pressure

Airway occlusion pressure is measured as the pressure at 0.1 sec after commencing an inspiratory effort against an occluded airway and is commonly termed $P_{0.1}$. In a study of patients with COPD, when $P_{0.1}$ values were >6 cm H_2O, all of the patients failed the weaning trial, whereas all patients who were successfully weaned had $P_{0.1}$ values <6 cm H_2O. In another study, measurements during a hypercapnic challenge (inhaling 3% CO_2) were similar in weaning success and weaning failure patients, 7.0 ± 1.0 and 6.6 ± 1.6 cm H_2O, respectively. However, hypercapnic augmentation of $P_{0.1}$, expressed as the ratio of the CO_2-stimulated $P_{0.1}$ to the baseline $P_{0.1}$, was greater in the patients who were successfully weaned, 2.04 ± 0.25, than in the failure group, 1.17 ± 0.03.

Rapid Shallow Breathing

Patients who fail a weaning trial commonly develop an immediate increase in respiratory frequency and decrease in tidal volume on discontinuation of ventilator support (Fig. 4). Yang and Tobin measured tidal volume and respiratory frequency with a simple bedside spirometer attached to the patient's endotracheal tube while the patient spontaneously breathed room air for 1 min. Measurements of frequency (f) and tidal volume (V_T) were combined into an index of rapid shallow breathing—the f/V_T ratio. In an initial "training data set" obtained in 36 patients, they found that an f/V_T value of 105 breaths/min per liter best differentiated patients who were successfully weaned from those in whom weaning failed. The predictive power of this value was then assessed in 64 patients who constituted the "prospective-validation data set" (Fig. 7). The positive and negative predictive values were 0.78 and 0.95, respectively, which were the highest values noted for any of the predictive indices in the study. In a recent study, Lee et al. reported that eight of nine patients who failed a weaning trial had f/V_T < 105 breaths/min per liter. In the original report, f/V_T was measured with a hand-held spirometer over 1 min of spontaneous breathing after the patient was disconnected from the ventilator circuit, whereas Lee et al. made the measurements during pressure support (level not stated), which is known to decrease f and increase V_T; it is hardly surprising that the f/V_T threshold value developed during unassisted breathing will not apply during pressure support. As a predictive index, the f/V_T ratio has a number of attractive features: it is easy to measure, it is independent of the patient's effort and cooperation, it appears to be quite accurate in predicting the ability to sustain ventilation, and, fortuitously, it has a "rounded off" threshold value (100) that is easy to remember.

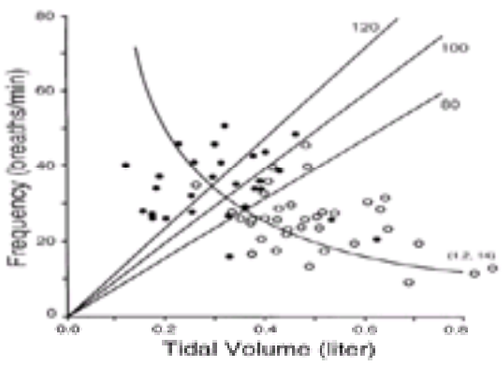

FIG. 7. Isopleths for the ratio of frequency to tidal volume (f/V_T), representing different degrees of rapid shallow breathing. Patients who fell to the left of the 100 breaths/min per liter isopleth had a 95% likelihood of failing a weaning trial, whereas patients who fell to the right of this isopleth had an 80% likelihood of a successful weaning outcome. The hyperbola represents a minute ventilation of 10 liters/min, a criterion commonly used to predict weaning outcome; it is apparent that this criterion was of little value in discriminating between weaning success *(open circles)* and weaning failure patients *(solid circles).* Values for one patient (V_T 1.2 liters, f 14 breaths/min) lay outside the graph. (Reproduced with permission from Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991;324:1445–1450.)

Integrative Indices

Weaning failure is commonly multifactorial in origin, and, thus it is not very surprising that an index that assesses a single function is unreliable. Accordingly, an index that integrates a number of physiological functions should have greater predictive accuracy. Such an index is the CROP index, which incorporates a measure of pulmonary gas exchange and an assessment of the demands placed on the respiratory system and the capacity of the respiratory muscles to handle them. The rationale for this index is the following:

$$\text{fraction of inspiratory effort reserve/breath} = P_{br}/P_{Imax} \quad \textbf{(1)}$$

where P_{br} is the pressure required for the generation of each breath, and P_{Imax} is the maximal inspiratory pressure. Measurement of P_{br} during spontaneous breathing poses logistic problems (e.g., insertion of an esophageal balloon catheter). However, for a given tidal volume during mechanical ventilation, pressure is inversely proportional to the "dynamic compliance" of the respiratory system (C_{dyn}); thus, equation 1 can be expressed as follows:

$$\text{fraction of inspiratory effort reserve/breath} \propto (1/C_{dyn})/P_{Imax} \quad \textbf{(2)}$$

Likewise, an index of the rate of energy expenditure per minute can be obtained by multiplying equation 2 by the respiratory rate:

$$\text{rate of energy expenditure/minute} \propto rate/[C_{dyn} \times P_{Imax}] \quad \textbf{(3)}$$

For convenience, the elements in equation 3 can be inverted so that a high value indicates that respiratory demands are well matched by respiratory muscle strength. A measure of gas exchange, the P_aO_2/P_AO_2, is also incorporated because some patients fail a weaning trial as a result of impaired oxygenation rather than ventilatory pump failure. The final form of the equation is

$$\text{integrative index} = C_{dyn} \times P_{Imax} \times (P_aO_2/P_AO_2)/rate \quad \textbf{(4)}$$

(4)and is labeled the CROP index, an acronym for compliance, rate, oxygenation, and pressure. When this index is prospectively evaluated, positive and negative predictive values are 0.71 and 0.70, respectively.

Another integrative index was recently developed by Jabour et al. This consists of a measure of ventilatory endurance (pressure–time index, PTI) and an estimate of the efficiency of gas exchange, $\dot{V}_{E40}$, which is the minute ventilation needed to bring P_aCO_2 to 40 torr:

$$\text{weaning index} = \text{PTI} \times (V_{E40}/V_{Tsb})$$

where V_{Tsb} is the tidal volume during spontaneous breathing. This index had a positive predictive value of 0.96 and a negative predictive value of 0.95 on *post-hoc* analysis, but the investigators did not examine its accuracy prospectively.

WEANING TECHNIQUES

Clinical Approach to Weaning

Attention must be directed to several factors before mechanical ventilation is discontinued, especially in patients with limited cardiorespiratory reserve or unusually high workloads. An organized plan of action and a team approach are particularly helpful in the difficult-to-wean patient. Adequate control of pain, fever, arrhythmias, and infection is necessary. Correction of fluid and electrolyte imbalance is imperative. Metabolic alkalosis, which decreased the ventilatory drive, can usually be corrected by chloride and potassium replacements. Although adequate sleep is necessary, medications that cause excessive sedation or impairment of respiratory muscle function can be harmful. The patient should receive adequate nutrition and be psychologically prepared for the weaning process. Promoting verbal communication helps in relieving a patient's fear. A tracheostomy can be advantageous in a patient requiring prolonged mechanical ventilation because it promotes comfort, enhances a patient's ability to swallow, and improves oral hygiene. In patients with airways obstruction, suctioning of the airways and administration of bronchodilators may facilitate weaning by reducing airway resistance and, thus, the work of breathing. Bronchodilators can be delivered effectively and conveniently to mechanically ventilated patients with a metered-dose inhaler and spacer in the inspiratory limb of the ventilator circuit. During a weaning trial, the ideal posture for a patient depends on the underlying pathophysiology. Although most patients do better while sitting, some find greater relief from dyspnea in the supine position. A variety of measures have been suggested to help with difficult-to-wean patients, such as biofeedback and endurance training of the respiratory muscles, but their application has been limited to a select group of patients, and further studies are needed to document their efficacy in a broader range of patients.

Trials of Spontaneous Breathing

To assess a patient's ability to sustain spontaneous ventilation, he or she can be disconnected from the ventilator and receive supplemental O_2 through a T-tube system. During such a trial, the patient's clinical status should be closely monitored. The traditional approach has been to employ relatively brief trials of spontaneous breathing (approximately 5 min) interposed with resumption of mechanical ventilation and gradually to increase their duration according to a patient's performance. Another approach is to go directly from a high level of ventilator assistance to a spontaneous breathing trial, and if the patient does not develop signs of intolerance, extubation is performed without any further weaning. In a study of over 500 patients, Esteban et al. reported that two-thirds of the patients could be extubated after an initial trial of spontaneous breathing. If a patient develops respiratory muscle fatigue during such a trial, the duration of mechanical ventilation required to rest the respiratory muscles has not been defined. Laghi et al. recently demonstrated that diaphragmatic contractility remains significantly depressed for at least 24 hrs following the induction of fatigue. Similar studies have not been undertaken in patients who fail a weaning trial, and it is conceivable that the rate of recovery may be even further delayed.

Intermittent Mandatory Ventilation

Intermittent mandatory ventilation (IMV) is the most popular weaning technique in North America. This is a unique mode of ventilation in that it allows the patient to breathe spontaneously between periodic positive-pressure breaths delivered at a preset volume and rate from the ventilator. When the patient is considered ready for weaning, the mandatory rate from the ventilator is reduced in steps of 1 to 3 breaths/min, and an arterial blood gas is obtained after about 30 min. Intermittent mandatory ventilation was introduced with claims of superiority over other management strategies. About 10 years after the introduction of IMV, it was shown that the demand valve, which was incorporated in the ventilator circuit to achieve synchronized IMV, resulted in a twofold or greater increase in the work of breathing by the patient. This problem has now been largely overcome with newer valves. Another and probably more fundamental problem is that patients have difficulty in adapting to the intermittent nature of ventilator assistance during IMV (Fig. 8). It had been assumed that the degree of respiratory muscle rest with IMV was proportional to the number of mandatory breaths delivered by the machine. Recent studies show that a patient's respiratory centers are unable to adapt to this type of intermittent unloading. Indeed, at IMV rates of 14 breaths/min or less, inspiratory efforts of the patient are increased to a level likely to cause respiratory muscle fatigue, and this occurs not only for the intervening spontaneous breaths but also with ventilator-assisted breaths. As a result, use of IMV may actually contribute to the development of respiratory muscle fatigue or prevent its recovery. The originators of IMV recommended that the number of breaths from the ventilator should be titrated in accordance with the results of arterial blood gases. This can result in a false sense of security because two to three positive-pressure breaths per minute can achieve acceptable blood gas values, but these values provides no information regarding the patient's work of breathing, which may be excessive.

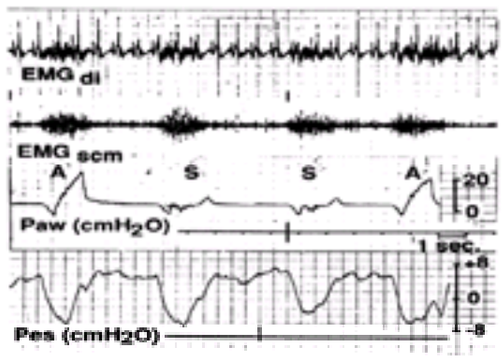

FIG. 8. Electromyograms of the diaphragm (EMGdi) and of the sternocleidomastoid muscles (EMGscm) in a representative patient receiving synchronized intermittent mandatory ventilation, showing similar intensity and duration of electrical activity in successive assisted (A) and spontaneous (S) cycles. P_{aw}, airway pressure; P_{es}, esophageal pressure. (Reproduced with permission from Imsand C, Feihl F, Perret MD, Fitting JW. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. *Anesthesiology* 1994;80:13–22.)

Pressure Support

With pressure support, the ventilator augments spontaneous breathing with a fixed amount of positive pressure. When pressure support is used for weaning, the level of pressure is reduced gradually in decrements of 3 to 6 cm H_2O, titrated on the basis of respiratory frequency. Several investigators have shown that pressure support can be used to counteract the work of breathing imposed by endotracheal tube and ventilator circuit. This has led to the notion that if a patient can sustain spontaneous ventilation at this “compensatory level” of pressure support, he or she will tolerate extubation. The problem with this strategy is that a compensatory level of pressure support varies between 3 and 14 cm H_2O, and there is no reliable method for accurately determining the required level in an individual patient. The algorithm used to cycle from inspiration to expiration during pressure support is based on a decrease in inspiratory flow to a preset level, such as 25% of peak inspiratory flow. Patients with airway obstruction have a long time constant, and more time will be required for flow to fall to this threshold; consequently, mechanical inflation may persist into neural expiration. To counteract such neural–mechanical asynchrony, patients may activate their expiratory muscles at a time when the ventilator is inflating the thorax, causing the patient to “fight the ventilator” (Fig. 9).

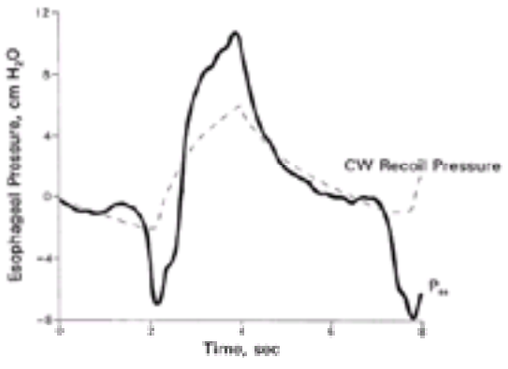

FIG. 9. Tracings of esophageal pressure (P_{es}, *continuous line*) and estimated recoil pressure of the chest wall (P_{escw}, *interrupted line*) in a patient receiving pressure-support ventilation of 20 cm H_2O. Pressure tracings have been superimposed so that P_{escw} is equal to P_{es} at the onset of the rapid fall in P_{es} during late expiration. Times at which P_{es} tracing are higher than P_{escw} represent lower-bound expiratory effort. Note the presence of expiratory muscle activation during late inspiration. (Reproduced with permission from Jubran A, Van de Graff WB, Tobin MJ. Variability of patient–ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:129–136.)

Relative Efficacy of Weaning Techniques

Recently, two rigorously controlled studies have prospectively compared the efficacy of three different weaning techniques: IMV, pressure support, and trials of spontaneous breathing. Brochard et al. found that weaning time was significantly shorter with pressure support [5.7 ± 3.7 (SD) days] than with IMV (9.9 ± 8.2 days) or trials of spontaneous breathing (8.5 ± 8.3 days). In contrast, using a similar experimental design, Esteban et al. found that a once-daily trial of spontaneous breathing led to extubation about three times more quickly than did IMV and about twice as quickly as pressure support (Fig. 10). There was no difference in the rate of successful weaning between a once-daily trial of spontaneous breathing and intermittent trials of spontaneous breathing (attempted at least twice a day), nor between IMV and pressure support. The reason for the different outcomes in the two studies is probably related to the constrained manner in which IMV and trials of spontaneous breathing were employed in the study of Brochard et al. During application of IMV, patients had to tolerate a ventilator rate of under four breaths per minute for at least 24 hrs before extubation; this constitutes a significant ventilatory challenge. In contrast, Esteban et al. extubated patients when they tolerated a ventilator rate of five breaths per minute for 2 hr. For the trials of spontaneous breathing in the study of Brochard et al., physicians could request up to three separate trials over a 24-hr period, each lasting 2 hr, before deciding to extubate a patient, whereas in the study of Esteban et al., patients in the once-daily trials of spontaneous breathing were extubated when this was tolerated for 2 hr. The findings in these two studies are complementary; both demonstrate that the pace of weaning depends on the manner in which the technique is applied. When IMV and trials of spontaneous breathing are employed in a constrained manner, weaning is delayed compared with pressure support. When a spontaneous breathing trial is employed once a day, weaning is expedited.

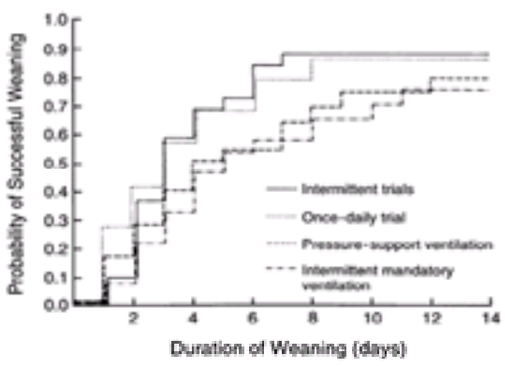

FIG. 10. Kaplan–Meier curves of the probability of successful weaning with intermittent mandatory ventilation, pressure-support ventilation, intermittent trials of spontaneous breathing, and a once-daily trial of spontaneous breathing. After adjustment for baseline characteristics in a Cox proportional-hazards model, the rate of successful weaning with a once-daily trial of spontaneous breathing was 2.83 times higher than that with intermittent mandatory ventilation ($p < 0.006$) and 2.05 times higher than that with pressure-support ventilation ($p < 0.04$). (Reproduced with permission from Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995;332:345–350.)

EXTUBATION

Patients who can sustain spontaneous ventilation without distress may have difficulty following extubation as a result of upper airway obstruction, inability to protect the upper airway, or inability to clear secretions. In contrast to the many parameters that have been introduced to predict the outcome of a weaning trial, indices that reliably predict the likelihood of complications following extubation have not been developed. Instead, evaluation consists of clinical assessment of factors such as the level of consciousness, the quantity of secretions, and the patient's ability to cough.

SUMMARY

In summary, up to 30% of patients of patients receiving mechanical ventilation pose considerable difficulty in being weaned. These patients present enormous clinical, economic, and ethical problems. The major determinants of weaning outcome are respiratory muscle function with the adequacy of pulmonary gas exchange and psychological problems playing subsidiary roles. Many of the physiological indices that have been used to predict weaning outcome are frequently inaccurate, and of those available, the ratio of frequency to tidal volume appears to be the most reliable. A number of techniques can be used for weaning, and of these a once-daily trial of spontaneous breathing appears to be the most expeditious.

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CHAPTER

50 Chronic Respiratory Failure and Noninvasive Ventilation

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INTRODUCTION

Chronic respiratory failure refers to the sustained inability to maintain normal gas exchange. Usually, the term indicates ventilatory failure and is diagnosed when blood gases show a chronic respiratory acidosis in the absence of symptoms to suggest an acute deterioration. The term chronic respiratory insufficiency is sometimes used interchangeably, denoting compromised respiratory function but not necessarily abnormal gas exchange. Chronic respiratory failure arises from dysfunction of any component or combination of components of the respiratory system. Therapy is contingent on delineation of the dysfunctional component(s). Before ventilatory support is contemplated, reversible contributing factors should be sought. In the past, if treating these was unsuccessful, invasive ventilation via a tracheostomy was often deemed necessary. In recent years, however, with the increasing use of nasal ventilation, noninvasive ventilation has become the preferred means of ventilatory support. This chapter considers the various mechanisms that lead to chronic respiratory failure, presenting manifestations and diagnostic and therapeutic approaches. The various modes of noninvasive ventilation are then discussed, including mechanisms of action, applications, selection of appropriate patients, and possible complications, with a focus on noninvasive positive-pressure ventilation (NPPV).

PATHOPHYSIOLOGY OF CHRONIC RESPIRATORY FAILURE

Normal function of the respiratory system depends on the integrity of each of its components. Chronic respiratory insufficiency arises from compromise of any one component or combination of components (Table 1). Respiratory failure occurs when the compromised system is unable to meet the demand for ventilatory work, either because of limitations in the ability to supply ventilatory work or because of excessive demands for ventilatory work, or both. Thus, any pathologic process that interferes with transmission of the signal to breathe, from the respiratory center, through central and peripheral neurons, to the myoneural junction, or the ability of the respiratory muscles to respond to the signal, may reduce ventilatory function enough to cause respiratory failure. CO_2 retention is likely when maximal inspiratory force (P_{Imax}) is less than 30% of predicted. In addition, processes that increase the work of breathing, such as airway obstruction, pulmonary fibrosis, or chest wall deformity, shift the supply–demand balance toward respiratory failure, particularly if respiratory muscle function is compromised. For chest wall deformity, the onset of respiratory failure correlates with an angle of scoliosis exceeding 120°.

TABLE 1. *Causes of chronic respiratory failure*[a]

If the factors contributing to respiratory failure are overwhelming or occur precipitously, acute respiratory failure ensues. If the dysfunction occurs gradually, however, the respiratory system may compensate by permitting the accumulation of carbon dioxide (CO_2). In essence, chronic respiratory failure represents a compromise in which the efficiency of carbon dioxide excretion is improved; i.e., more carbon dioxide can be excreted with each breath; at the expense of an increase in both alveolar and arterial PCO_2 and a decrease in arterial PO_2. The tendency to make this compromise is partly determined by the sensitivity of the ventilatory control center for carbon dioxide. Evidence for this derives from studies of patients with chronic obstructive pulmonary disease (COPD) who are chronic CO_2 retainers. Close relatives of these patients have less ventilatory sensitivity to CO_2 and to hypoxia than relatives of patients with equally severe COPD who are not CO_2 retainers. Thus, even though patients with severe COPD and CO_2 retention usually have elevated respiratory drive compared to normals, a relatively low inherited respiratory center sensitivity to CO_2 compared to normocapnic COPD patients may contribute to CO_2 retention.

Other factors thought to contribute to chronic respiratory failure include respiratory muscle weakness or fatigue. Defined as a reduction in muscle contractility during exhausting work, respiratory muscle fatigue contributes to acute respiratory failure and occurs during exercise in patients with severe COPD. However, the contribution of respiratory muscle fatigue to chronic respiratory failure, if any, has not been clearly defined. Recently, the concept of central fatigue has been advanced as a mechanism contributing to the development of chronic CO_2 retention. The concept proposes that the respiratory center fatigues before actual respiratory muscle fatigue occurs, permitting the gradual accumulation of CO_2. In this way, the overloaded respiratory system avoids or at least postpones the onset of muscle fatigue that would likely presage an acute deterioration.

Other attributes of patients who develop respiratory failure include the development of a rapid shallow breathing pattern. Patients with severe COPD and CO_2 retention breathe more rapidly and may have more ventilation–perfusion mismatching and higher dead space ratios than those without CO_2 retention. In addition, during sleep, respiratory drive is blunted, and muscle tone of upper airway structures is reduced. These effects are magnified in patients with respiratory insufficiency leading to sleep-disordered breathing and contributing to CO_2 retention. Thus, although patients with chronic respiratory failure have identifiable primary functional disturbances, they also undergo secondary central adaptations, leading to alterations in breathing pattern and to breathing disturbances during sleep, providing opportunities for

therapeutic interventions.

OCCURRENCE OF VARIOUS ETIOLOGIES FOR CHRONIC RESPIRATORY FAILURE

The most common cause of chronic respiratory failure at most centers in the United States is COPD. To gain insight into rates of occurrence of the various etiologies of chronic respiratory failure, Strumpf et al. recorded the diagnoses of patients seen at an outpatient chest clinic in a teaching hospital during a 6-month period. As shown in Table 2, these authors confirmed that COPD was responsible for chronic CO_2 retention in the majority of cases. The next most common single cause was the obstructive sleep apnea (OSA) syndrome, which should be considered in any patient with unexplained chronic hypoventilation. Sleep apnea also commonly contributes to chronic hypoventilation in patients with severe COPD or kyphoscoliosis. Restrictive chest wall disease was also a common cause of chronic hypoventilation in this series, but restrictive lung disease was a relatively unusual cause. Chronic respiratory failure in patients with interstitial lung disease is relatively uncommon. The CO_2 retention in these patients is usually transient, occurring late in the course as a preterminal event.

Etiology	Number	Percentage of total
COPD	46	58
Sleep apnea	6	8
Chest wall deformity		
Thoracoplasty	4	5
Kyphoscoliosis	4	5
Muscular dystrophy	4	5
Interstitial lung disease	3	4
Lung resection for cancer	2	3
CHF	1	1
Multifactorial	9	11
Total	79	100

[a] Data were collected from all patients seen in the outpatient chest clinic at Rhode Island Hospital, a 719-bed general hospital, between January 1, 1989 and July 15, 1989 with P_aCO_2 > 45 mm Hg. Patients experiencing an acute exacerbation were excluded. The multifactorial category includes patients with two or more of the above etiologies as well as one patient with COPD and laryngeal carcinoma with recurrent aspiration. From Strumpf et al., *Chest* 1990; 98:474–480, with permission.

TABLE 2. *The etiology of chronic hypoventilation in an outpatient chest clinic*[a]

The second largest overall category responsible for chronic CO_2 retention in the Strumpf series was multifactorial, underscoring the fact that a variety of factors often contribute to chronic hypoventilation. As noted above, chronic respiratory failure should not be seen as the consequence of a single abnormality in the respiratory system but rather as the interplay of different factors at a number of levels. Chronic CO_2 retention may develop in a patient with severe COPD whose respiratory center is insensitive to CO_2 and who has an increased number of apneic episodes during sleep. Another patient with equally severe COPD who has a high sensitivity to CO_2 and normal sleep may not retain CO_2. Multiple factors may also contribute to chronic respiratory failure in patients with the obesity–hypoventilation syndrome. These patients have an increased mechanical load related to their adiposity, may have a relatively low central sensitivity to CO_2, and often have other contributing factors such as congestive heart failure; OSA as a contributing factor should be excluded. The possible multifactorial etiology of chronic respiratory failure should always be considered in the evaluation of patients in order to maximize therapeutic results.

CLINICAL MANIFESTATIONS OF CHRONIC RESPIRATORY FAILURE

Patients with chronic respiratory failure as a result of severe lung disease usually have prominent respiratory symptoms, prompting a pulmonary evaluation that reveals the hallmark arterial blood gas result showing compensated hypercarbia. However, patients with chronic respiratory failure secondary to neuromuscular disease, central ventilatory defects, or mixed disturbances commonly have few or no respiratory complaints. Their earliest symptoms are related to nocturnal exaggeration of CO_2 retention that disrupts normal sleep patterns and causes nightmares, enuresis, and morning headaches. During the day, fatigue, hypersomnolence, and mood disorders are common, often leading to the misdiagnosis of depression. The physician must be alert to the insidious manner in which chronic hypoventilation may present in these patients so that blood gases are obtained and the condition is not missed.

Although signs of chronic respiratory failure are nonspecific, the physical examination is nevertheless very important for detecting predisposing illnesses. Severe obstructive or restrictive lung diseases should be detectable on physical examination. Morbid obesity, retrognathia, tonsillar hypertrophy, and macroglossia point to the obstructive sleep apnea syndrome. An examination of the thoracic cage for scoliosis and a neurologic examination seeking muscle weakness suggestive of a neuromuscular syndrome or cerebrovascular disease are important components of the evaluation. A bedside evaluation of respiratory muscle function should seek evidence of accessory muscle use by inspection or palpation, or bilateral diaphragmatic paralysis. This is best achieved by having the patient lie supine and observing paradoxic motion of the abdomen during inspiration.

LABORATORY EVALUATION OF CHRONIC RESPIRATORY FAILURE

All patients with symptoms and signs suggestive of chronic hypoventilation should undergo a workup as outlined in Table 3 beginning with blood gases measured via arterial puncture. Noninvasive methods such as pulse oximetry or end-tidal CO_2 monitoring are not sufficiently sensitive to exclude the diagnosis but may be helpful for following trends. The evaluation should include a complete blood count to exclude polycythemia, thyroid function tests, and serum chemistry studies.

Routine
1. History and physical examination
2. Arterial blood gas
3. Laboratory studies
Complete blood count
Serum electrolytes
Thyroid function tests
Mg, PO_4
4. Pulmonary function tests
Spirometry
Lung volumes
Bronchodilator responses
Maximal inspiratory and expiratory pressure
Supine vital capacity
For selected patients
5. Nocturnal polysomnography
6. Transdiaphragmatic pressure measurements

[a] From Strumpf et al., *Chest* 1990; 98:474–480, with permission.

TABLE 3. *Diagnostic studies for patients with chronic respiratory failure*

Pulmonary function testing including spirometry, measurement of lung volumes, and determination of maximal inspiratory and expiratory pressures should also be routine. These measurements detect patients with severe obstructive or restrictive lung diseases as well as those with muscle weakness. If bilateral diaphragmatic paralysis is suspected, vital capacity should be measured in the supine and upright positions. In the presence of paralyzed diaphragms, supine vital capacity falls by 50% compared to the upright. Pulmonary functions may also help in identifying those patients with an additional contributing factor to their chronic hypoventilation besides lung disease alone. If the FEV_1 exceeds 1L in a patient with chronic respiratory failure, lung disease is probably not the sole cause, and other contributing factors should be sought.

Because of the frequency of sleep-disordered breathing in patients with chronic respiratory failure, polysomnography occupies a central role in the evaluation of such patients. Ideally, polysomnography should consist of an overnight sleep study with monitoring of the electroencephalogram, electromyogram, electrooculogram, airflow at the mouth and nose, chest wall motion, and oximetry. Noninvasive monitoring of carbon dioxide levels by end-tidal or transcutaneous techniques has not proven reliable, so if accurate measurements of PCO_2 are desired, arterial blood gas sampling via an indwelling catheter will be necessary. Afternoon nap studies and overnight monitoring of oximetry alone are useful if they yield positive results, but a negative study should not be used to exclude sleep apnea. Polysomnography is indicated for any patient with chronic respiratory failure and symptoms to suggest OSA, such as snoring or excessive daytime sleepiness, an FEV_1 exceeding 1 L, even in the

absence of suggestive symptoms, and anyone being considered for ventilatory assistance using a negative-pressure device.

In addition to the evaluation described above, some other studies may occasionally be useful. Measurement of transdiaphragmatic pressures using gastric and esophageal balloons is useful to confirm the diagnosis of bilateral diaphragmatic paralysis. Assessment of CO_2 or hypoxic ventilatory responsiveness is primarily a research technique. It is of little value clinically because studies are almost invariably abnormal because of pulmonary function abnormalities or blunting of respiratory drive secondary to chronic CO_2 retention.

THERAPY OF CHRONIC RESPIRATORY FAILURE

Reversal of Contributing Factors

The first priority in the therapy of patients with chronic respiratory failure is to treat reversible factors that have been identified in the course of evaluation. Reversal of airway obstruction using bronchodilators or steroids, treatment of congestive heart failure with diuretics, and correction of metabolic alkalosis may be the only interventions necessary to normalize ventilation. Hypothyroidism, hypophosphatemia, and hypomagnesmia are less often encountered, but correction may ameliorate hypoventilation. Drugs such as benzodiazepines or narcotics are uncommon causes of chronic CO_2 retention in otherwise normal individuals but may be contributory in patients with compromised pulmonary function or depressed respiratory drive, and discontinuation may be salutary.

Pharmacologic Management

Progestational agents stimulate ventilation during pregnancy and can be used to enhance ventilatory drive in normal nonpregnant subjects. They may reduce hypercarbia in patients with central hypoventilation or the obesity hypoventilation syndrome. Medroxyprogesterone doses of up to 50 mg orally three times daily are usually well tolerated, but adverse side effects may include acne, ageusia, and sexual dysfunction. Unfortunately, results with progestational agents in the therapy of uncomplicated OSA have been disappointing.

A number of other pharmacologic agents have been used to enhance respiratory drive in patients with chronic respiratory failure, but efficacy is limited, and none are widely used for this indication. Aminophylline is an acute respiratory stimulant and, when given intravenously to COPD patients with chronic CO_2 retention, may acutely reduce hypercarbia. However, long-term studies on effects of theophylline in patients with COPD and chronic hypercarbia have not shown consistent reversal of chronic respiratory failure. Almitrine bismesylate, a peripheral chemoreceptor agonist, has been used to enhance oxygenation in patients with COPD during both sleep and wakefulness. However, the drug's effect appears to be related more to an improvement in *V/Q* relationships rather than increased respiratory drive, and the role of almitrine in the treatment of chronic respiratory failure remains questionable. Doxapram hydrochloride is another agent shown to acutely stimulate ventilation in patients with exacerbations of COPD. Unfortunately, adverse side effects including muscle spasm, agitation, and seizures occur frequently, the drug is available only in the intravenous form, and use is not recommended for more than two consecutive hours. Thus, it has no role in the therapy of chronic respiratory failure.

Continuous Positive Airway Pressure

For patients with symptomatic OSA, nasal continuous positive airway pressure (CPAP) has become the therapy of choice and can be effective in reversing chronic respiratory failure of OSA. Its mechanism of action is to splint the upper airway open, preventing collapse and permitting unimpeded spontaneous ventilation. Although it does not provide ventilatory assistance, CPAP can reduce the work of breathing by raising FRC and allowing breathing to occupy a more favorable portion of the respiratory system compliance curve or by counterbalancing intrinsic PEEP in patients with severe COPD. Accordingly, CPAP has been used to treat respiratory failure in patients who stand to benefit by these mechanisms, such as those with acute deteriorations of COPD or congestive heart failure. Nasal CPAP may also be beneficial when used nocturnally in patients with other primary causes for their respiratory failure but in whom sleep-disordered breathing appears to be contributory. Many practitioners will initiate CPAP in such patients if the respiratory failure is mild and then proceed to nasal ventilation (see below) if the response to CPAP is inadequate.

Noninvasive Ventilation

Noninvasive ventilation, referring to mechanical ventilatory assistance administered without an invasive artificial airway, has become the therapy of choice in patients with many forms of chronic respiratory failure. Although noninvasive ventilators have been available for the past 150 years and were the mainstay of mechanical ventilatory assistance for the polio epidemics that occurred during the first half of the 20th century, invasive positive-pressure ventilators became the preferred means of acute mechanical ventilatory support in the 1960s. Noninvasive ventilators, mainly of the negative-pressure type, continued to be used for chronic respiratory failure until the early 1960s, but invasive positive-pressure ventilation became more widely used for this indication as well because of perceived effectiveness and reliability. In recent years, however, noninvasive positive-pressure ventilation (NPPV) has seen a resurgence, related to the development of nasal ventilation. This mode of administration has the potential of providing mechanical ventilatory assistance to selected individuals with greater convenience, comfort, safety, and less cost than invasive ventilation. The following describes the various techniques and equipment available for noninvasive ventilation, considers evidence for efficacy and appropriate indications in patients with chronic respiratory failure, and provides general guidelines for application, monitoring, and avoidance of complications.

Why Noninvasive Instead of Invasive Ventilation?

Invasive mechanical ventilation has certainly proven to be effective and reliable, but placement of an endotracheal airway carries attendant risks of complications. These complications have been described in detail by Pingleton and may be categorized in three ways. These include traumatic complications, such as vocal cord paralysis or tracheal laceration, complications related to the violation of the airway defense system, and discomfort-related complications, including pain and interference with communication and swallowing. These complications apply to acute translaryngeal intubations as well as to chronic tracheostomies. Furthermore, airway invasion interferes with normal airway clearance mechanisms such as cough and serves as a continual irritant, increasing mucus production and necessitating intermittent suctioning. The special skills required to care for patients with artificial airways increase personnel needs, adding to the total cost of care. By avoiding these complications, noninvasive ventilation has the potential of enhancing patient satisfaction and reducing the cost of care. However, it must be emphasized that the techniques are not interchangeable and that candidates for noninvasive ventilation must be selected carefully using established guidelines, which are discussed in detail later.

Techniques and Equipment for Noninvasive Ventilation

Various noninvasive techniques are available to assist ventilation. Although NPPV has become the preferred technique in the United States today, other techniques, such as negative-pressure or abdominal-displacement ventilation, may occasionally be useful. These other techniques are still popular in some centers around the world and may be effective when positive-pressure techniques are poorly tolerated or fail to adequately assist ventilation. Accordingly, although the emphasis of the following is on positive-pressure techniques, mechanisms of action and principles of application for the various forms of noninvasive ventilation are also discussed.

Noninvasive Positive-Pressure Ventilation

Noninvasive PPV requires a positive-pressure ventilator connected via tubing to an interface that applies positive air pressure to the nose or mouth. The interfaces and ventilators commonly used for NPPV are described below.

Interfaces

Nasal Masks

Nasal masks are the most commonly used interfaces for chronic respiratory failure because they are convenient and permit normal speech and swallowing. In addition, many different nasal masks are available commercially, largely because of the demand for such devices in the treatment of obstructive sleep apnea. Numerous manufacturers offer various modifications of three basic types of nasal mask. The standard nasal CPAP mask is a triangular clear plastic device that fits over the nose and utilizes a soft cuff to form an air seal (Fig. 1). Nasal pillows consist of soft rubber or silicone cones that are inserted directly into the nostrils (Fig. 2). Third, custom masks are molded to fit a variety of facial shapes.

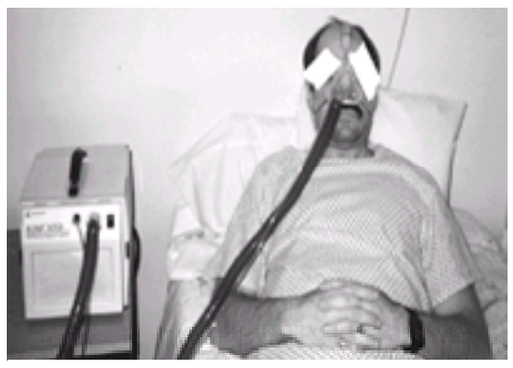

FIG. 1. Standard nasal CPAP mask connected to a “bilevel” type of portable pressure-limited ventilator (BiPAP S/T, Respironics, Inc., Murrysville, PA).

FIG. 2. Nasal “pillows.” Note that the nasal bridge is uncovered.

Manufacturers of standard nasal CPAP masks include Respironics, Inc. (Murrysville, PA), Healthdyne, Inc. (Marietta, GA), Devilbiss, Inc. (Sunrise Medical, Inc., West Blake Village, CA), and Rescare, Inc. (San Diego, CA). These masks exert pressure over the bridge of the nose in order to achieve an adequate air seal, often causing redness and skin irritation and occasionally leading to ulceration. Modifications are available that minimize these complications, such as use of forehead spacers (Respironics, Inc.), or the addition of a thin plastic flap (Comfort Flaps, Respironics or Sullivan bubble mask, Rescare, Inc.) that permits air sealing with less mask pressure on the nose. Straps that hold the masks in place are also important for patient comfort. Double-strap systems that use Velcro tighteners are most popular, and various elastic caps have also been well received by patients.

Nasal pillows (Adam Circuit, Nellcor Puritan-Bennett, Inc., Lenexa, KA) or seals (Healthdyne) have been useful in patients with nasal bridge irritation or ulceration because they exert no pressure over the bridge of the nose. Occasional patients will alternate between different types of masks as a way of minimizing discomfort. Other patients prefer custom-fitted masks that use rapidly drying plastics (Sefam, Inc., available through Respironics) or heat-molded materials. However, most patients adapt successfully to one commercially available nasal mask interface or another, so custom fitting is usually unnecessary.

Oronasal Masks

These cover both the nose and mouth and, in the author's experience, are rarely tolerated for chronic home use. Oronasal masks have the capability of preventing air leaking through the mouth, but they interfere with speech and eating more than nasal masks, limiting patient acceptability. Currently available oronasal masks include those provided by Vital Signs, Inc. (Totowa, NJ) and Respironics (Spectrum) (Fig. 3). The latter comes with a quick-release strap and an antiasphyxia valve to prevent rebreathing in the event of ventilator failure. Further improvements, such as more comfortable cuffs and improved air-sealing capabilities, will be necessary to increase acceptability in the chronic setting.

FIG. 3. Oronasal face mask designed for use with noninvasive ventilation (Spectrum, Respironics, Inc., Murrysville, PA). The tubing is connected to the mask via an “antiasphyxia” valve, and a quick-release strap rests on the tubing below the mask.

Oral Interfaces

These may be preferable for use in patients requiring around-the-clock ventilatory assistance. Commercially available oral interfaces use a mouthpiece inserted into a lip seal (Nellcor Puritan-Bennett) strapped tautly around the head to minimize air leaking. In the author's experience, this device is poorly tolerated because of interference with speech and swallowing. Mouthpieces that are custom fitted by an orthodontist may not require a strap for adequate sealing and can be easily expectorated if necessary, even by patients with severe neuromuscular disease. Bach et al. have reported success using these devices in a large number of patients with neuromuscular disease, some with little or no measurable vital capacity. During the daytime, these patients receive ventilatory assistance via a mouthpiece held by a gooseneck attached to their wheelchairs.

Ventilators for NPPV

Volume-limited or pressure-limited portable positive-pressure ventilators have been used to deliver NPPV. The choice among ventilators depends largely on practitioner preference and patient needs. For example, sophisticated alarm systems are unnecessary for patients requiring only nocturnal ventilatory assistance and, in fact, may be counterproductive because they may needlessly interrupt sleep. For chronic use in the home, simplicity and portability are important features.

Volume-Limited Ventilators

Portable volume-limited ventilators commonly used to administer NPPV to patients with chronic respiratory failure include the PLV 100 and 102 (Respironics), the LP-10 (Aequitron, Inc., Minneapolis, MN), the Companion 2801 (Nellcor Puritan-Bennett, Inc., Carlsbad, CA), and many others used worldwide. The ventilators are usually set in the assist/control mode to allow for spontaneous patient triggering, and back-up rate is usually set at slightly below the spontaneous patient breathing rate. The only important difference relative to invasive ventilation is that tidal volume is usually set higher (10 to 15 mL/kg) to compensate for air leaking. Currently available volume-limited ventilators have more alarm and pressure-generating capabilities than most portable pressure-limited ventilators and may be better suited for patients in need of continuous ventilation or those with severe chest wall deformity or obesity who need high inflation pressures.

Pressure-Limited Ventilators

Simple pressure-limited ventilators to deliver IPPB have been available for many years (Bird 7, Bird, Inc.; PR2, Nellcor Puritan-Bennett, Inc.) but are rarely used to provide ventilatory support. Portable ventilators that deliver the newer pressure-support ventilation (PSV) mode have seen increasing use in recent years. This mode delivers a preset inspiratory positive airway pressure (IPAP) that can be combined with positive end-expiratory pressure (PEEP or EPAP). The difference between the IPAP and EPAP is the level of inspiratory assistance or pressure support. These ventilators have sensitive inspiratory triggering and expiratory cycling mechanisms, permitting excellent patient–ventilator synchrony, reducing diaphragmatic work, and improving patient comfort.

Portable devices that deliver PSV (BiPAP, Respironics; 321, Puritan-Bennett; Sullivan VPAP, Rescare; Quantum, Healthdyne; and others available outside of the United States such as the SEFAM and Onyx, Pierre Medical, FR) are used for both acute and chronic applications. These devices, sometimes referred to as “bilevel” devices, are lighter (5 to 10 kg) and more compact (< 1 ft^3) than critical-care ventilators, offering greater portability at lower expense. Some, such as the BiPAP, offer not only a spontaneously triggered (or S) mode but also a time cycled (or T) mode for patients with apnea or who fare better resting on a rate-controlled mode. However, these devices have limited IPAP capabilities (up to 20 to 35 cm H_2O, depending on the ventilator) and lack sophisticated alarm or battery back-up systems. Therefore, they are not recommmended for patients requiring high inflation pressures, dependent on continuous mechanical ventilation, or receiving invasive ventilation unless appropriately modified.

The bilevel devices, by virtue of their light weight and convenience, have proven ideal for home use in patients with chronic respiratory failure who require only nocturnal ventilatory assistance. In addition, unlike volume-limited ventilators, they are able to adjust inspiratory airflow to compensate for air leaks, thereby potentially providing better support of gas exchange during leaking. However, in addition to limited alarm capabilities, other concerns have been raised about bilevel ventilators. Because they use a single tube with a passive exhalation valve, rebreathing may occur if the patient exhales nasally. Ferguson et al. have found substantial rebreathing that may interfere with the ability of the BiPAP to augment alveolar ventilation, particularly during use of the whisper-swivel valve (Respironics, Inc.) at low EPAP settings. A recently developed plateau valve (Respironics, Inc.) eliminates the rebreathing, and use of EPAP pressures of 4 cm H_2O or greater reduces it.

Negative-Pressure Ventilation

Negative-pressure ventilators (NPVs) are used much less often now than at times in the past, but a knowledge of their characteristics and applications is still useful because they may be effective in patients who fail to adapt to NPPV. The NPVs include the very efficient and reliable tank ventilators (like the iron lung) and the smaller, more portable wrap (or jacket) and cuirass (or shell) ventilators. The wrap (Numowrap, Respironics, Inc.) consists of an impermeable nylon jacket suspended by a rigid chest piece that fits over the chest and abdomen. The cuirass is a rigid plastic or metal dome fitted over the chest and abdomen. Both must be connected to negative-pressure generators such as the Maxi-Vent (Nellcor Puritan-Bennett), Emerson NPV (J.H. Emerson, Inc., Cambridge, MA), or NEV 100 (Lifecare).

Negative-pressure ventilators expand the lungs by intermittently applying a subatmospheric pressure to the chest wall and abdomen, and expiration occurs passively by elastic recoil of the lung and chest wall. The efficiency of negative-pressure ventilation (tidal volume generated for a given negative pressure) is determined by the compliance of the chest wall and abdomen and by the surface area over which the negative pressure is applied. Thus, the tank is the most efficient and the cuirass the least efficient of the ventilators. Problems with air leaking may reduce efficiency of the wrap and chest shell ventilators and, to a lesser extent, the iron lung, which has to seal only around the neck.

The tank ventilator is reliable and relatively comfortable, but it is bulky (3 m long) and heavy (300 kg). It is also intolerable to claustrophobic patients and interferes with nursing care, although it does have portholes on the sides. A more portable fiberglass tank ventilator is available (Portalung, Nellcor Puritan-Bennett), but it still weighs approximately 50 kg. The chest shell and wrap are lightweight, but the negative-pressure generators used with them weigh 12 to 25 kg. Also, the tank and wrap ventilators restrict patients to the supine position, often inducing musculoskeletal back and shoulder pain. The chest shell may be used in the sitting position, but it can cause discomfort and pressure sores at points of skin contact, particularly if the fit is suboptimal. Patients with chest wall deformities are poor candidates for NPVs, although they can be managed with custom-fit cuirasses.

Most of these limitations of negative-pressure ventilation can be overcome with fitting adjustments or nonsteroidal antiinflammatory drugs. However, the tendency for negative-pressure ventilators to exacerbate or even induce OSA can limit use. Obstructive sleep apneas associated with severe oxygen desaturations are common in patients with neuromuscular disease using negative-pressure ventilators and may necessitate a switch to NPPV. The lack of preinspiratory contraction of pharyngeal muscles that prevents collapse of upper airway structures during a normal patient-initiated breath appears to be responsible for the apneas. Traditional negative-pressure ventilators lack patient-triggered modes, making the upper airway susceptible to collapse before ventilator-triggered breaths. It remains to be seen whether newer patient-triggered negative-pressure ventilators, such as the NEV-100 or Emerson NPV, will alleviate this problem.

Abdominal Displacement Ventilators

The rocking bed and pneumobelt both rely on displacement of the abdominal viscera to assist diaphragm motion and, hence, ventilation. The rocking bed consists of a mattress on a motorized platform that rocks in an arc of approximately 40°. The patient lies supine on the mattress with the head and knees raised slightly to prevent sliding. When the head rocks down, the abdominal viscera and diaphragm slide toward the head, assisting exhalation. As the head rocks up, the viscera and diaphragm slide toward the feet, assisting inhalation. The rocking rate is between 12 and 24 time/min, adjusted to optimize patient comfort and minute volume, as measured with a hand-held spirometer or magnetometer. The chief advantages of the rocking bed are ease of operation, lack of encumbrances, and patient comfort, although bulkiness, noisiness, and lack of portability and efficacy limit its appeal.

The pneumobelt consists of a corset wrapped around the patient s midsection, holding an inflatable rubber bladder firmly against the anterior abdomen. Intermittent inflation of the rubber bladder by a positive-pressure ventilator compresses the abdomen, forcing the diaphragm upward and actively assisting exhalation. With bladder deflation, gravity returns the diaphragm to its original position, assisting inhalation. Tidal volume is increased by raising bladder inflation pressure, usually between 35 and 50 cm H_2O. Desired minute volume can then be attained by adjusting ventilator rate, usually between 12 and 22/min. The pneumobelt is highly portable, can be mounted on a wheelchair to facilitate mobility, is easily hidden under clothing, and leaves the hands and face unencumbered, facilitating desk work. Because it requires gravity to pull the diaphragm down during bladder deflation, it is ineffective unless patients sit at angles of at least 30°. Hence, nocturnal use is limited to patients who can learn to sleep while sitting.

Because their main action is to assist diaphragm motion, both the rocking bed and the pneumobelt are well suited for patients with bilateral diaphragmatic paralysis. However, they are both relatively ineffective ventilators and are of limited use in patients with acute respiratory deterioration. Furthermore, efficacy of both depends on abdominal and chest wall compliance, so that patients with severe kyphoscoliosis, excessive thinness, or obesity may not be adequately ventilated.

Other Types of Ventilatory Assistance

Diaphragm pacing and glossopharyngeal breathing are ventilatory methods used in selected patients to enhance independence. Diaphragm pacing as currently applied was developed by Glenn and co-workers during the 1960s. It consists of a radiofrequency transmitter and antenna that signal a surgically implanted internal receiver and electrode to stimulate the phrenic nerve. Use of diaphragm pacing is limited to patients who have an intact diaphragm and phrenic nerve. Candidates include those with central hypoventilatory syndromes or quadriplegia from high spinal cord lesions. However, recent advances in noninvasive positive-pressure ventilation have virtually eliminated the need for diaphragm pacing in patients with central hypoventilation.

Diaphragm pacing has a number of limitations including high cost, the potential to fail abruptly despite a lack of built-in alarms, and the tendency to produce upper airway obstruction by the same mechanism as negative-pressure ventilators, necessitating tracheostomy placement in up to 90% of users. In addition, there are no controlled studies that demonstrate long-term efficacy. Nevertheless, diaphragm pacers are very easy to use once installed, highly portable, and patients are freed from positive-pressure ventilators. Thus, some patients with high cord lesions may still prefer diaphragm pacing over other types of ventilatory assistance. Its chief application at the present time is in children who have difficulty adapting to noninvasive forms of ventilation.

Glossopharyngeal or frog breathing utilizes intermittent motions of the tongue and pharyngeal muscles to force air into the trachea. When gulping, the patient lowers and then raises the tongue against the palate in piston-like fashion, injecting air into the trachea. With practice, each 0.5 sec gulp injects roughly 50 to 150 mL of air. The patient closes the glottis between gulps to prevent escape of air and rapidly repeats the gulping until a tidal volume of approximately 500 or 600 mL is achieved. The air is then exhaled, and the maneuver is repeated eight to ten times/min so that a normal minute volume can be achieved. The technique can be used to provide freedom from mechanical ventilation for periods of up to several hours, even in patients with severely weakened lower respiratory muscles. It can also be used to augment individual breaths in patients with low tidal volumes or to achieve inhaled volumes of 2 to 2½ L to assist in coughing. However, use is limited to patients who have intact upper airway musculature, more or less normal lungs and chest walls, and are capable of learning the technique. Good candidates include those with high spinal cord injuries, postpolio syndrome, and appropriate patients with other neuromuscular diseases.

EVIDENCE FOR EFFICACY OF NONINVASIVE VENTILATION IN THE TREATMENT OF CHRONIC RESPIRATORY FAILURE

"Body" Ventilators

Tank-type negative-pressure ventilators served as the main means of ventilatory support during the polio epidemics. Negative-pressure ventilation has also been used to provide intermittent ventilatory assistance to patients with symptomatic chronic respiratory failure secondary to slowly progressive neuromuscular diseases, chest wall deformities, or central hypoventilation. Uncontrolled studies during the early 1980s on patients with these diagnoses showed consistent improvements in gas exchange and symptoms of hypoventilation after several months of nocturnal ventilatory assistance using negative-pressure ventilation. Long-term follow-up of these patients, including those with Duchenne muscular dystrophy and postpolio syndrome, show that although the underlying illnesses steadily progress, survival rates are favorable.

The most controversial application of negative pressure ventilation has been its use in resting respiratory muscles in patients with severe stable COPD. Theorizing that these muscles are chronically fatigued and will benefit from intermittent rest, Braun and Marino showed that intermittent daytime sessions using the wrap ventilator improved daytime gas exchange and inspiratory and expiratory muscle strength in patients with severe COPD. However, this study was uncontrolled so that a beneficial effect of some other aspect of a rehabilitation program could not be excluded. Later, other controlled studies showed similar benefits, but they were very short-term (3–7d). Longer-term controlled studies have failed to demonstrate favorable effects of intermittent negative pressure ventilation in patients with severe COPD. Shapiro et al, in the largest study, randomized 184 patients to receive 3 mos of wrap or sham ventilation for 4-5 h daily, but found no improvements in gas exchange, muscle function or exercise capacity. In addition, like Zibrak et al in an earlier study, they found that patients tolerated the ventilators poorly, using them for less time daily than recommended, and having trouble sleeping during use.

The rocking bed and pneumobelt have also been reported to be effective in supporting ventilation in patients with neuromuscular disease, particularly those with weakened or paralyzed diaphragms. These patients are severely dyspneic in the supine position, frequently complain of restless sleep, and use of the rocking bed facilitates sleep and prevents nocturnal hypoventilation. Abd et al described use of the rocking bed in 10 patients who developed bilateral diaphragm paralysis following open heart surgery and were supported nocturnally until diaphragm function returned between 4 and 27 months later. The rocking bed may also be effective in other neuromuscular diseases with diaphragm involvement and a relatively normal body habitus.

Introduced as a daytime aid that frees the hands and face in patients with severe respiratory muscle weakness who use other ventilatory aids at night, the pneumobelt can be used as the sole means of respiratory support in occasional patients who can sleep in a sitting position. Like the rocking bed, it is been particularly useful in patients with diaphragm weakness or paralysis, and in recent years, it has been used as a daytime aid in patients with high cervical cord lesions.

Positive-Pressure Ventilation

Restrictive Thoracic Diseases

Since the first anecdotal series were published in 1987, numerous uncontrolled studies have shown efficacy of nasal NPPV in various neuromuscular and chest wall diseases. These studies consistently show improvements in gas exchange and symptoms after a few weeks of nocturnal nasal ventilation. They also demonstrate reversal of chronic hypoventilation in patients with severe kyphoscoliosis and obstructive sleep apnea who failed to improve with nasal CPAP alone. Although nasal NPPV appears to be better tolerated than mouthpiece NPPV, Bach et al. have reported that mouthpiece NPPV may be used for long-term ventilatory support in patients with severe neuromuscular diseases who have virtually no measurable vital capacity. However, no studies have compared nasal and mouthpiece NPPV directly.

Because no prospective, randomized studies on the use of NPPV in patients with restrictive thoracic diseases have been done, some might question whether efficacy has been proven. However, Hill et al. and others have shown that temporary withdrawal of NPPV from stable long-term users with restrictive thoracic diseases leads to a deterioration of nocturnal gas exchange, daytime symptoms, and sleep quality, offering strong evidence that NPPV is effective in reversing nocturnal hypoventilation and improving symptoms in patients with chronic respiratory failure from restrictive thoracic diseases.

Although the efficacy of NPPV appears to be well established, the optimal time for initiation is unclear. Some investigators have hypothesized that early initiation, before the onset of symptoms or daytime hypoventilation, may slow the progression of respiratory dysfunction in patients with neuromuscular diseases. In patients with Duchenne muscular dystrophy, Raphael et al. tested this hypothesis by randomizing patients to receive nasal NPPV or standard therapy. Contrary to their hypothesis, NPPV-treated patients had no slowing of disease progression. In addition, unexpectedly, the trial had to be stopped because of excess mortality in the NPPV group. Shortcomings of the study such as failure to document compliance with the device and an excess of patients with severe cardiac dysfunction in the NPPV group raise doubts about the significance of the mortality findings, but the study suggests that early initiation may not be beneficial. The present author recommends awaiting the onset of symptoms and daytime hypercarbia before initiation of NPPV, partly because patients are often reluctant to use NPPV unless motivated by the desire for symptom relief.

A recent French follow-up study by Leger et al. on several hundred patients treated with nasal NPPV found 5-year survival rates approximating 80% for postpolio and kyphoscoliosis patients. These survival rates compared favorably with those observed for similar patients treated with invasive mechanical ventilation reported earlier by Robert et al. (see Fig. 4). On the other hand, the likelihood of patients with Duchenne muscular dystrophy continuing NPPV (and surviving) was substantially lower than for the postpolio patients. This raises questions about the ability of NPPV to prolong survival in all groups of patients with restrictive thoracic disease, particularly when the mortality findings of Raphael et al. are considered. Larger randomized trials on patients with Duchenne muscular dystrophy, comparing noninvasive ventilation with earlier invasive ventilation, may be warranted.

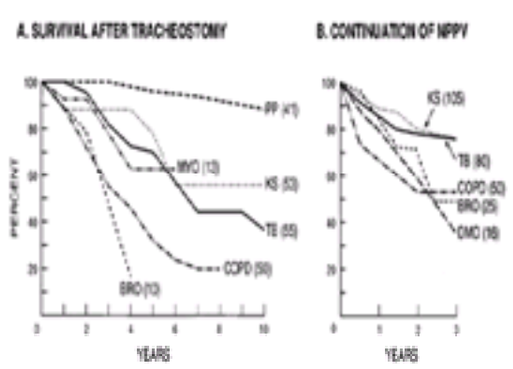

FIG. 4. (A) Survival over time of patients with chronic respiratory failure of various etiologies after placement of a tracheostomy. **(B)** The likelihood of continuing noninvasive positive-pressure ventilation (NPPV) over time in similar patients with chronic respiratory failure. BRO, bronchiectasis; COPD, chronic obstructive pulmonary disease; DMD, Duchenne muscular dystrophy; KS, kyphoscoliosis; MYO, myopathies; PP, postpolio syndrome; TB, old tuberculosis. Numbers in parentheses are number of patients with each diagnosis. (From Robert D, Gerard M, Leger P, et al. La ventilation méchanique a domicile définitive par trachéostomie de l'insuffisant respiratoir chronique. *Rev Fr Mal Respir* 1983;11:923–936 and Leger P, Bedicam JM, Cornette A, et al. Nasal intermittent positive pressure. Long-term follow-up in patients with severe chronic respiratory insufficiency. *Chest* 1994;105:100–105, with permission.)

Chronic Obstructive Pulmonary Disease

Studies on the use of NPPV in patients with severe obstructive lung diseases have yielded conflicting results. In a 3-month crossover trial on 19 patients with severe COPD, seven of whom completed the trial, Strumpf et al. found improvement only in tests of neuropsychological function but not nocturnal or daytime gas exchange, sleep quality, pulmonary functions, exercise tolerance, or symptoms. In contrast, Meecham-Jones et al. performed a study of nearly identical design on 18 patients with severe COPD, 14 of whom completed the trial, and found that NPPV use improved nocturnal and daytime gas exchange, total sleep time, and symptoms.

The substantial differences in baseline characteristics of entered patients may offer an explanation for the conflicting results. Patients entering the Meecham-Jones study had greater hypercarbia (P_aCO_2 57 mmHg versus 47 mmHg) and more nocturnal oxygen desaturations despite having less severe airway obstruction (FEV_1 0.81 liter versus 0.54 L) than patients in the Strumpf study. This suggests that the studies were examining different subsets of patients with COPD and that those with more

daytime CO_2 retention and nocturnal oxygen desaturations may be the group most likely to benefit from NPPV. Further support for this possibility is provided by anecdotal series of cystic fibrosis patients with severe CO_2 retention who have been successfully supported using NPPV while awaiting lung transplantation. Additional studies will be necessary to determine whether different ventilator modes or settings can improve the efficacy of NPPV in COPD patients and whether NPPV enhances quality of life or prolongs survival relative to oxygen therapy alone in appropriate subgroups.

Other Forms of Chronic Respiratory Failure

Noninvasive PPV improves daytime gas exchange and symptoms in patients with OSA who fail to improve after use of nasal CPAP alone. In addition, patients with central hypoventilation syndromes have been successfully supported using NPPV. Interest in NPPV has been increasing among pediatric practitioners, who report successful application in patients with bronchopulmonary dysplasia. Noninvasive PPV may also be used to speed extubation of patients who become chronically ventilator dependent after bouts of acute respiratory failure.

SELECTION GUIDELINES FOR PATIENTS TO RECEIVE NONINVASIVE VENTILATION

Based on the many uncontrolled trials, a number of characteristics can be identified that permit selection of appropriate candidates for noninvasive ventilation (Table 4). In general, there should be at least mild to moderate daytime CO_2 retention (usually an indication of more severe nocturnal CO_2 retention). Symptoms attributable to hypoventilation and associated poor sleep quality such as morning headache, daytime hypersomnolence, and energy loss should also be present. Patients with symptomatic nocturnal hypoventilation but no daytime CO_2 retention may also benefit. Unless motivated by the desire for symptom relief, patients have difficulty complying with noninvasive ventilation.

I. Chronic stable or slowly progressive respiratory failure
1. Significant CO_2 retention (P_aCO_2 > 50 mm/Hg)
2. Mild CO_2 retention with symptoms
a. Morning headache
b. Daytime hypersomnolence
3. Nocturnal hypoventilation or oxygen desaturation[b]
II. Inappropriate candidates excluded
1. Upper airway function adequate
2. No excessive airway secretions
3. Reversible underlying disorders (hypothyroidism, congestive heart failure, etc.) adequately treated
III. Appropriate condition
1. Slowly progressive neuromuscular disorder
2. Chest wall deformity
3. Obstructive sleep apnea unresponsive to CPAP
4. Control hypoventilation
5. Obstructive lung disease with:[b]
a. Significant CO_2 retention
b. Nocturnal desaturations

[a] From Hill, *Noninvasive Mechanical Ventilation in Pulmonary and Critical Care Medicine*, update 4. Chicago: Mosby Year Book, in press.
[b] Tentative indication.

TABLE 4. *Guideline for selection of patients with chronic respiratory failure for noninvasive ventilation*[a]

Patients should also have adequate airway defenses. Those with swallowing impairment or excessive secretions, particularly if combined with a weakened cough mechanism, are at risk for aspiration or mucus plugging. If such patients desire aggressive support, they are usually more safely managed with invasive ventilation.

The patient's diagnosis is also an important consideration. Those with stable or slowly progressive neuromuscular diseases or chest wall deformities are the best candidates, assuming that airway protection mechanisms are intact. Others, such as those with central hypoventilation or obstructive sleep apnea who have failed a trial of nasal CPAP, are also acceptable candidates. On the other hand, patients with rapidly progressive neuromuscular processes like Guillain-Barré syndrome, particularly if there is upper airway involvement, are poor candidates. Among patients with chronic airway obstruction, those with daytime CO_2 retention and nocturnal oxygen desaturations may warrant a trial of noninvasive ventilation, as may those with end-stage cystic fibrosis who are deteriorating while awaiting lung transplantation.

Mechanism of Action

Both invasive and noninvasive PPV work by intermittently raising airway and thereby transpulmonary pressure, inflating the lungs, and assisting alveolar ventilation. However, noninvasive ventilation differs in that it provides no direct access to the airway, rendering patient cooperation mandatory. If the patient closes his mouth or glottis or actively resists, ventilator air merely follows the path of least resistance and leaks out around the mask or through the mouth. In cooperative, awake patients, coordination with the ventilator can usually be achieved fairly quickly. During sleep, however, patients must learn to direct air into their lungs and relax their breathing muscles in order to receive optimal benefit. The process by which this nocturnal adaptation takes place is not fully understood, but patency of the glottis appears to be an important determinant of delivered tidal volume. Other poorly understood aspects of nasal NPPV include the role of nasal resistance in determining efficacy and mechanisms for controlling air leaking through the mouth. The latter is seen to a greater or lesser extent in virtually all patients using nasal NPPV, appears to contribute to sleep arousals, but only occasionally is severe enough to negate ventilatory benefits.

The mechanism responsible for sustained improvement of gas exchange and symptoms in patients with chronic respiratory failure receiving assisted ventilation for as little as 4 to 6 hrs nightly has also eluded delineation. Three main theories have been proposed to explain the sustained improvements. One postulates that noninvasive ventilation rests chronically fatigued respiratory muscles in patients with chronic respiratory failure, thereby improving daytime ventilatory muscle function. Supporting this theory are studies demonstrating that respiratory muscles do indeed rest during noninvasive ventilation and that indices of respiratory muscle strength and endurance may improve in patients with chronic respiratory failure after varying periods of noninvasive ventilatory assistance. However, chronic respiratory muscle fatigue has never been adequately defined or convincingly demonstrated, and a number of studies have failed to demonstrate improvement in respiratory muscle function despite amelioration of gas-exchange abnormalities and symptoms after periods of intermittent ventilatory assistance.

A second theory postulates that noninvasive ventilation improves respiratory system compliance by reversing microatelectasis of the lung, thereby diminishing daytime work of breathing. This theory derives from studies showing improvements in FVC without changes in indices of respiratory muscle strength after periods of positive-pressure ventilation. Once again, however, data are conflicting, with a number of studies showing no changes in vital capacity after periods of noninvasive ventilation.

A third theory proposes that noninvasive ventilation lowers the respiratory center set point for CO_2 by ameliorating nocturnal hypoventilation. In this context, the respiratory center is thought to adjust its output so that the work of respiratory muscles will not exceed the level that would precipitate muscle fatigue, a process sometimes referred to as “central” fatigue. Particularly at night, when upper respiratory muscle tone and activity of nondiaphragmatic inspiratory muscles diminish, progressive nocturnal hypoventilation may develop, permitting an upward resetting of the respiratory center and worsening daytime hypoventilation. Nocturnal ventilatory assistance ameliorates the hypoventilation and allows resetting of the respiratory center, thereby reducing daytime hypercarbia. Evidence for this theory derives from a study showing that when ventilatory assistance was discontinued for a night in patients with chronic respiratory failure who had been stabilized using noninvasive ventilation, the degree of nocturnal hypoventilation was less severe than before initiation, suggesting resetting of respiratory center sensitivity for CO_2. In a more recent study, worsening of nocturnal hypoventilation, oxygen desaturation, and daytime symptoms occurred without loss of respiratory muscle strength or vital capacity when nocturnal NPPV was discontinued for a week in patients whose chronic respiratory failure had previously been reversed by nocturnal NPPV. The worsening nocturnal hypoventilation and symptoms were promptly alleviated by resumption of NPPV. These studies suggest that prevention of nocturnal hypoventilation with resetting of respiratory center sensitivity for CO_2 may be an important mechanism for the efficacy of NPPV. However, the three theories are not mutually exclusive, and all could conceivably contribute to varying degrees depending on the patient.

Practical Considerations

Initiation

The process of initiating noninvasive ventilation is largely a trial-and-error process that must be modified for each individual patient. Unlike patients with acute respiratory failure, who have an urgent need for ventilatory assistance, most patients with chronic respiratory failure can begin noninvasive ventilation gradually, in a relaxed fashion, so that chances for success are optimized. After identification of an appropriate patient, a ventilator or combination of ventilators must be selected for the initial trial. Nasal NPPV should be considered the mode of first choice for most patients with chronic respiratory failure because of its greater convenience and portability compared to body ventilators and its ability to eliminate obstructive sleep apneas. On the other hand, body ventilators may be advantageous in patients who

have excessive air leaking through the mouth during NPPV or in the occasional patient who is unable to tolerate masks because of discomfort or claustrophobic reactions. In other situations, a combination of ventilators may work best, such as in a patient with a high spinal cord lesion who uses NPPV at night and a pneumobelt during the daytime.

The author advises performing the initial trial during the daytime in a relaxed setting, often on an outpatient basis. To establish continuity, the home respiratory therapist who will follow the patient is asked to assemble the necessary equipment and meet the patient in the physician's office or hospital room. Experienced practitioners then optimize fit and adjust initial settings, explaining each step to minimize patient anxiety. For fitting of nasal masks, the smallest standard mask that adequately covers the nose usually works best. Straps are tightened with the least tension necessary to avoid excessive air leakage. Some air leakage is acceptable because the strap tension necessary to eliminate leaking entirely often induces pressure sores, and the ventilator can be adjusted to compensate for leaks. With body ventilators, fitting may also be necessary. The tightness of the neck seal and body positioning are important with tank and wrap ventilators, and for the cuirass and pneumobelt ventilators, the proper size must be selected.

When the patient is fitted comfortably with the device, ventilation can be started. The author advises low initial pressures to facilitate patient acceptance, with gradual increases later as tolerated by the patient. Typical initial settings on pressure-limited ventilators are 8 to 12 cm H_2O for IPAP and 2 to 4 cm H_2O for EPAP (pressure support of 4 to 10 cm H_2O and PEEP of 2 to 4 cm H_2O). For volume ventilation, initial tidal volumes range from 10 to 15 mL/kg. The ventilator is usually set in the S/T or A/C mode to allow patient triggering. Ventilator back-up rate is set at spontaneous breathing rate if the aim is to entrain the patient's breathing and minimize respiratory muscle work, or slightly lower to encourage spontaneous breathing. If necessary, supplemental oxygen can be connected to ports in the mask or tubing, with liter flow titrated to maintain the desired oxygen saturation. Patient comfort should be a higher priority initially than improvement in gas exchange or tidal volume, which can be attained later as pressures are increased during the adaptation phase.

Initiation of body ventilation follows a similar approach, with initial adjustment of presures to optimize patient acceptance and later adjustments to achieve gas exchange goals. Measurement of assisted tidal volume is easier than with NPPV and should aim for increases of perhaps 30% to 50% over spontaneous. With both NPPV and body ventilators, end-tidal PCO_2 and oximetry monitoring or an arterial blood gas measurement obtained after the first hour or two of use may help in assessing the need for further adjustments. Typical pressure ranges and rates used for the various ventilators are listed in Table 5.

	Settings			Costs (US$/month)	
Ventilator	Rate (Breaths/min)	Pressure (cm H_2O)	Efficiency	Primary device	Pressure generator
Negative pressure					
Iron lung	12–24	−10 to −35	+++	378[b]	
Porta lung	12–24	−10 to −35	+++	562	380
Wrap	14–28	−15 to −45	++	159	380
Shell	14–28	−15 to −45	+	64	380
Pneumobelt	12–24	+15 to +50	++	50	310
Rocking bed	12–24	40°	+	250[b]	—
Positive pressure	12–24	+10 to +30	+++	453[c]	—

[a] From Hill, Respir Care 1994;39:532, with permission.
[b] Not including $500 delivery charge.
[c] Allowable Medicare charge for standard portable volume ventilator (DME code E0 450).

TABLE 5. *Typical settings, relative efficacy, and rental costs of body and positive-pressure ventilators*[a]

Adaptation and Monitoring

After the initial trial, the patient is encouraged to begin nocturnal use, but gradually, sometimes for only an hour or two at the start, and to extend the hours of use as tolerated. Comparing the process to that of mastering a musical instrument may be helpful. During this period, frequent visits from an experienced home respiratory therapist help to assure proper use of the device and allow adjustments in mask sizes and types, straps, and pressure settings that are often necessary. Some patients successfully sleep through the night within days of initiation, but others require several months. A trial should not be considered unsuccessful unless numerous adjustments have been tried over a period of at least several weeks. Perhaps 20% to 25% of patients are unable to tolerate NPPV, usually because of mask intolerance. In these patients, trials with alternative noninvasive ventilators such as negative-pressure or abdominal ventilators may still be successful, as long as the patient has no more than mild obstructive sleep apnea.

Patients should be seen every few weeks by a physician during the initial adaptation period. Once adaptation has been successful, physician visits may be scheduled much less often, as infrequently as twice or thrice yearly. At the time of office follow-up, symptoms and physical signs should be assessed for evidence of nocturnal hypoventilation or cor pulmonale. Spirography is indicated, particularly in patients with progressive neuromuscular syndromes, to assess loss of pulmonary function. Daytime arterial blood gases or pulse oximetry and end-tidal PCO_2 should be obtained at the time of physician visits or when symptoms worsen. Although there is no consensus on the ideal target level for daytime P_aCO_2 in patients receiving noninvasive ventilation, values ranging from the 40s to mid-50s mmHg are usually associated with good control of symptoms.

Nocturnal monitoring is also useful after adaptation to noninvasive ventilation to assure adequacy of oxygenation and ventilation. Nocturnal oximetry at home may help in screening but will not identify specific problems should desaturations occur. Thus, home monitoring of chest wall motion, mask pressure, and airflow in addition to oximetry, such as is possible with portable multichannel recorders (Edentrace II, Edentec, Eden Prairie, MN; Night Watch, Healthdyne), is useful to detect evidence of persistent apneas or excessive air leaking. Electroencephalographic recording may help to determine whether episodes of air leak though the mouth or sleep-disordered breathing during ventilator use are associated with desaturations, sleep arousals, and poor sleep quality. Monitoring of nocturnal PCO_2 is desirable, but neither transcutaneous nor end-tidal monitoring systems have proven reliable enough to be of much value in characterizing problems. The need for repeated nocturnal monitoring after succesful adaptation to noninvasive ventilation has not been evaluated. One approach is to initially establish adequacy of overnight gas exchange using a portable multichannel monitor in the home and then to repeat studies as dictated by changes in symptoms or daytime gas exchange. More sophisticated polysomnographic monitoring can be used when the portable monitor is insufficient to characterize problems.

Commonly Encountered Problems and Possible Solutions

Noninvasive ventilation is safe and well tolerated in most properly selected patients. With NPPV, the most commonly encountered problems occur during the adaptation phase and are interface-related (Table 6). Patients often complain of mask discomfort that can be alleviated by minimizing strap tension or trying different mask sizes or types. Excessive air pressure leading to sinus or ear pain is another common complaint and can be alleviated by lowering pressure temporarily and then gradually raising it again as tolerance improves. Patients may also complain of dryness or congestion of the nose or mouth. For dryness, nasal saline or efforts to reduce air leaking may help. Flow-by humidifiers may also be helpful, particularly in dry climates, but mask pressure should be verified when these are added to pressure-limited ventilators. For nasal congestion, inhaled steroids or decongestants or oral antihistamine–decongestant combinations may be used. Other commonly encountered problems include erythema, pain, or ulceration on the bridge of the nose related to nasal mask pressure. This can be ameliorated by minimizing strap tension, using artificial skin, or switching to alternative masks such as nasal “pillows.” Gastric insufflation is common but is usually not severe, probably because inflation pressures are low compared to those used with invasive ventilation.

Problem	Approximate rate of occurrence (%)	Possible remedy
Minor		
Interface-related		
Nasal dryness	40–60	Inhaled steroids, saline
Nasal congestion	40–60	Nasal saline or humidification
Skin reddening	25–40	Loosen straps, topical lotions
Mask intolerance	15–30	Different masks
Nasal ulceration	5–10	Loosen straps, artificial skin
Air-pressure-related		
Sinus, ear pain	5–30	Reduced pressure temporarily
Eye irritation	5–10	Reposition mask, straps
Gastric insufflation	5–10	Simethicone
Air leaking		
Around mask	50–100	Reposition mask, try different types
Through mouth	50–100	Chin straps
Through nose (with mouthpiece)	—	Nasal plugets
Major		
Aspiration	0–5	Careful patient selection, nasogastric tubes as indicated
Failure to improve ventilation	10–20	Increase pressure, V_T, or rate; reduce air leaks
Deterioration after prior stabilization	5–10	Alternative noninvasive ventilators, invasive ventilation

[a] Adapted from Hill, Noninvasive Mechanical Ventilation in *Pulmonary and Critical Care Medicine*, update 4, Chicago: Medby Year Book, 1997.

TABLE 6. *Problems encountered during noninvasive ventilation and possible remedies*[a]

Air leaking through the mouth (with nasal masks), through the nose (with mouthpieces), or around the mask (with all interfaces) is inevitable during NPPV. Pressure-limited devices compensate for air leaks by maintaining inspiratory airflow during leaking; tidal volumes on volume-limited ventilators may be increased by the practitioner to compensate. To reduce air leaking through the mouth, patients are coached to keep the mouth shut or use chin straps or oronasal masks. Air leaking occurs during the majority of sleep in many patients, but, fortunately, gas exchange is usually well maintained. Leaks may still contribute to arousals and poor sleep quality, however, and ventilatory assistance may occasionally be compromised. In this case, options include trials of alternative interfaces or ventilators or, if these fail, tracheostomy. Major complications of noninvasive ventilation, such as aspiration or pneumothorac, are unusual if patient selection guidelines are observed.

Failure of daytime gas exchange to improve is often related to the patient's inability to tolerate the device and use it for enough nocturnal hours. However, if the patient is using the device for most of the night, failure to improve may be related to inadequate inspiratory pressures or tidal volumes, ventilator rate, or excessive air leaking through the mouth. Further adjustments in settings and follow-up monitoring are indicated. When daytime gas exchange deteriorates after prior stabilization, the patient's underlying neuromuscular or respiratory disorder may have progressed and often responds to increases in inspiratory pressure, tidal volume, or ventilator rate. If gas exchange fails to respond to repeated adjustments, or the patient fails to tolerate NPPV, trials with alternative noninvasive ventilators may be successful. In patients who are intolerant of the devices or have persisting symptomatic hypoventilation despite prolonged trials of various noninvasive ventilators, tracheostomy placement may be necessary if the patient desires aggressive ventilatory support.

CONCLUSION

Chronic respiratory failure is most often caused by mechanical problems of the respiratory system, in particular, COPD. Patients also have secondary disturbances that may contribute to their CO_2 retention. These include insensitivity of the respiratory center to CO_2, hypothyroidism, and sleep-disordered breathing. It is important to seek these secondary contributing factors in formulating an effective therapy. The first therapeutic intervention should be to reverse these contributing factors, either by treating airway obstruction or by using a central stimulant. Nasal CPAP should be used as a next step if upper airway collapse is documented and CO_2 retention is mild. If this approach fails, nasal ventilation is the preferred alternative. Nasal NPPV enhances convenience, portability, and patient comfort, offering the advantages of simplified care, reduced complications, and lowered costs relative to invasive ventilation. Recent evidence strongly supports nasal NPPV as the ventilatory mode of first choice in patients with respiratory failure secondary to slowly progressive neuromuscular diseases, chest wall deformities, and central hypoventilatory disorders, but the use of noninvasive ventilation in patients with severe COPD remains controversial.

Initiation of noninvasive ventilation for chronic respiratory failure requires identification of an appropriate patient and selection of a ventilator. Patient intolerance for the device may limit reductions in P_aCO_2 or increases in minute volume initially, but these can be adjusted later, during the adaptation process. A minority of patients are unable to adapt despite prolonged efforts, and for these, alternative noninvasive ventilators, such as negative-pressure devices, pneumobelts, or rocking beds, may be successfully used as long as obstructive sleep apnea has been excluded. If these also fail to improve symptoms or gas exchange abnormalities, there is loss of the ability to adequately protect the upper airway, or a need for continuous ventilatory support, invasive ventilation may be necessary.

Complications of noninvasive ventilation are minimal if patients are selected according to established guidelines and are appropriately monitored. Most complications of NPPV are interface related, such as discomfort caused by air or mask pressure. Because NPPV is an open-circuit system, air leaks may compromise efficacy and interfere with sleep quality. Complications of other forms of noninvasive ventilation are also usually minor, such as musculoskeletal shoulder and back discomfort, but exacerbation of obstructive sleep apnea may occur. Follow-up nocturnal monitoring should be done with NPPV or alternative ventilators to assure adequacy of nocturnal gas exchange.

The role of noninvasive ventilation in respiratory care continues to evolve. Some indications are well established, such as use for patients with chronic respiratory failure from neuromuscular disease, but other indications, such as use for patients with severe COPD, await further study. Studies aimed at establishing the optimal applications for noninvasive ventilation and technologic advances in ventilators and interfaces should lead to wider use as indications are expanded and better defined.

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CHAPTER

51 Pulmonary Rehabilitation and Outcome Measurement

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INTRODUCTION

The major goal of treatment of any chronic and irreversible disorder is to allay symptoms and minimize the impact of the illness by enhancing the individual's performance of desired activities. Pulmonary rehabilitation is an effective therapeutic intervention that can be employed to achieve these goals. Of the numerous respiratory conditions, patients with chronic obstructive pulmonary disease (COPD) frequently have the most chronic, debilitating symptoms, which are not completely eliminated or controlled by medications and other traditional medical treatments. Because of the severity of the dyspnea associated with increasing activity in patients with COPD, this disease frequently impairs the patient's ability to engage and participate constructively in daily activities. Comprehensive pulmonary rehabilitation has also been employed successfully in patients with cystic fibrosis and respiratory insufficiency associated with severe neuromuscular disorders. In addition, the approaches and comprehensive efforts, including disease-management programs, used with asthma to decrease utilization of health care resources, assure continued adherence with treatment programs and health-enhancing behaviors, and enhance collaborative self-management employ many of the principles of pulmonary rehabilitation.

This chapter defines pulmonary rehabilitation, describes the key components of a comprehensive pulmonary rehabilitation program, discusses the techniques and physiological basis for therapies employed during rehabilitation, and reviews the outcomes that can be achieved as a result of this therapy. Because COPD is the most common chronic respiratory disease, and because patients with COPD are the most common recipients of pulmonary rehabilitation, this chapter focuses on pulmonary rehabilitation as employed in these patients. However, all of the principles of pulmonary rehabilitation and many of the specific therapeutic modalities and approaches may also be applied to patients with other respiratory disorders.

DEFINITION AND CONCEPT OF PULMONARY REHABILITATION

Historically, rehabilitation has been the term applied to the therapeutic techniques used for patients with limitations as a result of physical impairments such as loss of function of an extremity through injury or birth defect or loss of function secondary to neurologic or muscular conditions such as polio. The principles of rehabilitation are based on the broad goal of restoring individuals to the fullest medical, mental, emotional, social, and vocational potential possible. This goal may also be applied to patients with chronic disorders of any organ system that impair ability to participate in functional activities. Pulmonary rehabilitation is the term used when the recipients of rehabilitation efforts are patients with disorders of the respiratory system and was originally defined by a committee of the American College of Chest Physicians (ACCP) and later revised by a National Institutes of Health (NIH) Workshop. A careful evaluation of the published definitions of pulmonary rehabilitation provides important insights into this form of therapy.

The ACCP Definition

The original definition of pulmonary rehabilitation was conceived in an era when there was little information about the efficacy of this form of therapy and limited information supporting the physiological basis for the therapeutic modalities employed. Pulmonary rehabilitation was defined as:

> an art of medical practice wherein an individually tailored, multidisciplinary program is formulated which through accurate diagnosis, therapy, emotional support, and education, stabilizes or reverses both the physio- and psychopathology of pulmonary diseases and attempts to return the patient to the highest possible functional capacity allowed by his pulmonary handicap and overall life situation.

There are several important implications of this definition.

Individually Tailored

The first implication of the definition of pulmonary rehabilitation is that, as in the practice of other types of rehabilitation, the efforts of the program are based on the individual needs of each patient. Not only is a carefully performed and complete assessment of the patient by the an experienced health care professional necessary to determine the medical needs, but the individual patient must also provide input to determine his or her individual needs and goals. Because rehabilitation requires the active participation of the recipient, patients must be involved in setting the goals of their efforts.

Multidisciplinary

Second, rehabilitation is not usually considered to be a single therapy but rather is a coordinated program of a number of therapies, most often applied by health care professionals with a variety of backgrounds and with different areas of expertise. Indeed, results and outcomes have most commonly been assessed in response to comprehensive multimodality pulmonary rehabilitation programs. As noted in the rest of this chapter, the various multifaceted components of pulmonary rehabilitation are not usually within the expertise of a single member of the health care team and often require personnel with knowledge and experience in exercise training, psychosocial evaluation and counseling, use of the unique respiratory medications and breathing exercises used in patients with lung disease, education of adults with chronic lung disease, energy conservation and management techniques, nutritional issues, and medical issues of patients with respiratory disorders.

Improvement in Function

Although individual goals may vary from one patient to another, the objective of pulmonary rehabilitation is to improve the ability of the patient to function to the maximal extent possible given the limitations imposed by the underlying respiratory disorder. Although it may not be possible to reverse the pathologic effects of the disease, the physiological and psychological responses to the disease may be amenable to treatment. For example, although pulmonary rehabilitation does not improve oxygenation, limitations in activity by hypoxemia-induced dyspnea may be partially reversed with supplemental oxygen therapy used during periods of increased daily activities such as grocery shopping and thereby improve overall patient function. The measurement of patient function as an outcome of pulmonary rehabilitation is thus important to determine the effectiveness of this therapy.

The NIH Definition

Although the earlier definition of pulmonary rehabilitation noted the importance of the art of medical practice, the National Institutes of Health later reviewed the scientific basis for pulmonary rehabilitation. The NIH Workshop convened to assess research needs in pulmonary rehabilitation formulated another definition of pulmonary rehabilitation:

> a multidimensional continuum of services directed to persons with pulmonary disease and their families, usually by an interdisciplinary team of specialists, with a goal of achieving and maintaining the individual's maximum level of independence and functioning in the community.

Rather than providing a completely new definition, the NIH Workshop expanded on the earlier effort and attempted to integrate the concept of pulmonary rehabilitation into the evolving health care environment in several ways. First, the Workshop recognized the evolution of health care delivery, which has increasingly focused on providing care at multiple sites ranging from the acute care hospital to the home and to patients at all life stages—a concept referred to as the continuum of health care delivery. Second, pulmonary rehabilitation is now seen not as a time-limited therapy employed within a defined period to achieve a particular end result but rather as requiring an ongoing program of organized and integrated services provided to the patient to maintain function over the long term. Although this is a laudable goal that will likely improve long-term outcomes, the current practice of pulmonary rehabilitation does not usually fulfill this definition but is still traditionally implemented as a defined program over a limited period of time. Third, the NIH definition takes a broader view of pulmonary rehabilitation by recognizing the importance of family members and viewing the patient as functioning and participating within the larger community outside of the boundaries of the home. Last, this newer concept of rehabilitation recognizes that, although usually implemented by a multidisciplinary team, some of the individual elements of pulmonary rehabilitation may more commonly be applied in a limited fashion to patients not enrolled in a comprehensive rehabilitation program. For example, prescription of medications always requires education of the patient in proper medication use. Although education is one of the components of pulmonary rehabilitation, patients should be educated about their medications even when they are not enrolled in a rehabilitation program. In recognition of the NIH definition, this chapter describes pulmonary rehabilitation as a long-term continuum of a set of comprehensive services provided in an organized manner.

KEY COMPONENTS OF COMPREHENSIVE PULMONARY REHABILITATION

It is generally accepted that there are several key elements of a state-of-the-art comprehensive pulmonary rehabilitation program (Table 1). These components may be categorized into five areas: (1) medical evaluation and management, (2) initial assessment and goal setting, (3) therapeutic modalities of exercise training, psychosocial counseling, nutritional counseling, daily living training and energy management, and education, (4) evaluation of outcomes, and (5) a maintenance program. Each component is discussed individually.

Medical evaluation and management
Initial assessment and goal setting
Therapeutic modalities
Smoking cessation
Exercise training
Psychosocial counseling
Breathing retraining
Daily activity performance and energy management
Nutritional counseling
Outcome evaluation
Maintenance program

TABLE 1. *Components of a comprehensive pulmonary rehabilitation program*

MEDICAL EVALUATION AND MANAGEMENT

The physician (whether a general practitioner, internist, or pulmonary specialist) who provides primary and ongoing care of the patient with respiratory disease plays an integral role in pulmonary rehabilitation. The physician not only refers the patient for rehabilitation but also helps to assure the patient's participation by explaining the rationale and benefits of rehabilitation, integrating rehabilitation into the patient's continuing medical care, and monitoring the patient's ongoing adherence with the components of rehabilitation.

An appropriate diagnosis and optimal medical treatment of the patient with respiratory disease are prerequisites for initiation of pulmonary rehabilitation. The goal of evaluation and management by the physician is to minimize the medical impact of the disease on the patient and thereby maximize the patient's ability to benefit from the pulmonary rehabilitation program. The results of the medical evaluation should be available and communicated to the rehabilitation team. Because patients referred for pulmonary rehabilitation usually have at least moderately severe airflow limitation and significant functional limitations as a result of their illness, it is appropriate for a physician with specialized training in pulmonary medicine to play a major role in confirming the diagnosis and reviewing the medical plan.

As outlined in Table 2, medical evaluation and management have multiple components. One of the most important elements of the evaluation is the diagnosis of conditions of other organ systems that might potentially limit the patient's ability to participate in and obtain maximal benefit from rehabilitation. For example, COPD patients referred for rehabilitation are usually older and may have concomitant osteoarthritis of the knees, which may impair their ability to perform walking exercise. Establishing and communicating the diagnosis will allow the rehabilitation team to choose exercise programs that minimize stress on the knees. Providing appropriate medications to reduce inflammation and pain will not only ensure that the patient is comfortable but also maximize participation in the exercise program. The physician should also consider the diagnosis of osteoporosis, particularly in older postmenopausal women and individuals with a history of corticosteroid administration. Because patients are older, commonly have a history of cigarette use, and because the cardiovascular system will be stressed during exercise training, cardiac disease should be excluded. A maximal exercise test may not only be used to screen for ischemic cardiac disease but is also useful to evaluate the presence of oxygen desaturation with exercise and to determine the appropriate dose of oxygen to prevent desaturation.

Evaluation
Respiratory diagnosis
Severity of respiratory disease
Other conditions potentially interfering with pulmonary rehabilitation
Arthritis
Osteoporosis
Cardiac disorders
Oxygenation at rest and during activity
Management
Reduce airflow limitation
Minimize pulmonary secretions
Eliminate/reduce medication adverse effects
Promote collaborative self-management
Provide plan to address changes in symptoms
Reduce impact of other conditions on participation in rehabilitation program
Provide plan for maintaining continuity of medical care

TABLE 2. *Medical evaluation and management component of pulmonary rehabilitation*

The medical treatment plan should include prescriptions and specific instructions on the dose, frequency, and route of administration of all medications, particularly those required to reduce airflow limitation. Some patients with COPD have notable difficulty clearing secretions, leading to dyspnea and increased work of breathing. Although the rehabilitation team can provide assistance in secretion management, the physician should prescribe antibiotics when necessary to control infection. Finally, the physician must provide a referral and an order for pulmonary rehabilitation. Because the team providing comprehensive pulmonary rehabilitation will be skilled and experienced in patient assessment in order to individualize the program for each patient, determine the goals and duration of therapy, and apply each component of rehabilitation, in most cases the physician's order may be very general.

Selection of Patients for Rehabilitation

Based on the definitions, goals, and outcomes of pulmonary rehabilitation, a comprehensive rehabilitation program is recommended for patients with disorders of the respiratory system who, despite optimal medical management, have functional limitations preventing them for participating fully in daily activities or vocational activities. As noted in Table 3, patients with a variety of respiratory conditions may be candidates for pulmonary rehabilitation. Because of the varied nature of the underlying disorders of patients suitable for rehabilitation and the imprecise relationship between pulmonary function and functional capacity, there are no specific physiological indices to assist in selecting patients for pulmonary rehabilitation. Unfortunately, tools assessing functional capacity and quality of life are not useful in this task. The patient and the physician providing ongoing care, often in conjunction with the physician specialist in pulmonary medicine, are in the best position to evaluate the need for pulmonary rehabilitation. It is important to note that third-party payers typically require documentation not only of functional limitations but also of a treatment plan incorporating short- and long-term goals before providing reimbursement for rehabilitation.

Obstructive lung disease
Chronic obstructive pulmonary disease
Asthma
Cystic fibrosis
Bronchiectasis
Restrictive lung disease
Interstitial lung diseases
Tuberculosis and other mycobacterial diseases
Restrictive respiratory system disorders
Neuromuscular
Postpolio
Muscular dystrophy
Guillain-Barré syndrome
Chest wall
Kyphoscoliosis
Thoracoplasty
Other
Pre and post lung surgery lung volume reduction
Lung transplant
Lung cancer
Ventilatory dependency
Sleep apnea

TABLE 3. *Respiratory disorders suitable for pulmonary rehabilitation*

Although pulmonary rehabilitation should not be delayed until the patient has a very severe degree of physiological impairment, some general guidelines for patient selection based on the severity of the respiratory impairment may be outlined. In general, patients requiring chronic ambulatory oxygen therapy and patients with frequent emergency room visits or hospitalizations are candidates for pulmonary rehabilitation.

Oxygen Therapy

Assessment of the patient's oxygenation and need for oxygen therapy should be performed either before rehabilitation or during the initial assessment for pulmonary rehabilitation. In order to determine the need for supplemental oxygen administration during activity, it is recommended that oxygen saturation (S_aO_2) be assessed with pulse oximetry during activity in all patients participating in pulmonary rehabilitation. Although any type of activity performed by the patient on a regular basis may be used for this evaluation, many centers assess pulse oximetry while the patient is walking at his or her normal pace for a defined period of time such as 6 min. The medical aspects of oxygen therapy are covered in more detail elsewhere in this text.

One of the goals of pulmonary rehabilitation is to enhance health-promoting behaviors, and this goal should be applied to the use of oxygen therapy. Whenever oxygen therapy is prescribed, the patient should receive sufficient education to assure safe and effective use of this important therapeutic modality. Education should include not only the benefits and safe use of oxygen therapy but also details of the specific prescription for oxygen for the individual patient including the flow rate to be used at rest, with activity, and during sleep. Such education is routinely provided during pulmonary rehabilitation and should include efforts to enhance use of oxygen as prescribed by the physician. Barriers to use, such as patient fears about the safety of oxygen and the visibility and unsightly nature of the nasal canula, should be addressed. Patients should be instructed on how to use the specific oxygen system supplied for them including how to turn the oxygen on and off, how to fill the portable system or obtain additional portable oxygen supplies, and the name and phone number of the vendor supplying the oxygen.

Providing chronic outpatient supplemental oxygen therapy to patients with respiratory disorders may impair patient mobility and thus quality of life. Despite the benefits of improved exercise capacity and lessened dyspnea with the use of ambulatory oxygen, the size, weight, and limited duration of the portable oxygen supply usually appear to the patient to present a barrier to achieving the benefits of greater and more comfortable capacity for activity. Pulmonary rehabilitation can assist in reducing this barrier to the use of oxygen. For example, patients often feel that oxygen use during activity does not lessen dyspnea. During rehabilitation, it may be helpful to assist the patient to objectively assess the benefits of oxygen; one method is having the patient walk with and then without oxygen while a health care professional measures the distance walked and the patient quantifies the degree of shortness of breath. In this manner, patients can determine for themselves whether oxygen is beneficial.

During pulmonary rehabilitation, patients should be informed of the different types of portable supply systems available to allow the choice of a system that best meets their needs. One method of overcoming the difficulties with the size and weight of the portable oxygen system is to employ oxygen conservation devices, i.e., oxygen reservoirs, inspiratory demand delivery devices, and transtracheal oxygen. The lightest portable oxygen systems utilize demand delivery oxygen conservers and include cylinders of compressed gas with a device that delivers oxygen only during inspiration and small liquid systems that incorporate a similar conserver.

The physician can initiate discussions with the patient about the types of available oxygen systems and refer the patient to the pulmonary rehabilitation team for incorporation of oxygen therapy into the patient's daily routine. The physician also serves an important role in writing the prescription for the type of oxygen system that best meets patient needs and helps to ensure not only patient adherence with the oxygen prescription but also enhanced mobility and quality of life.

INITIAL ASSESSMENT

Probably the most important element of pulmonary rehabilitation is the performance of an initial assessment that culminates in the development of goals to guide the rehabilitation process and coordinate the actions of all team members. This element deserves special mention because it is not universally considered a separate component of pulmonary rehabilitation.

The goal of the assessment is to (1) determine the individual needs of the patient, (2) develop short-term goals for the patient to achieve during the initial rehabilitation program, (3) provide a baseline in order to assess changes that result from rehabilitation, and (4) develop long-term goals that may be incorporated into the continuing management of the patient. This assessment is separate and distinct from the physician's medical evaluation and management and may be performed by a single pulmonary rehabilitation team member such as the program coordinator; alternatively, portions of the assessment may be performed by multiple team members. The importance of this process lies in the communication and interactions between practitioners and patients with development of mutual trust and respect and the subsequent incorporation of the health professional's assessments with the patient's needs and desires. From this mutual process flows a therapeutic plan and a set of patient-centered goals. The initial goals must be mutually agreed on by the patient and the rehabilitation team. In addition, short-term goals should also be readily achievable within a limited period of time in order to enhance patient motivation and thus help assure adherence with continued rehabilitation efforts. Longer-term goals should also be developed and revised as the patient progresses through rehabilitation.

One of the major goals of pulmonary rehabilitation is to improve the individual's level of function. This process should begin with a careful assessment of all the activities the patient does every day and what perceived and observed difficulties are encountered in accomplishing these tasks. Activities that are important to the patient include not simply the basic activities of daily living (ADL) such as bathing, toileting, and dressing but also vocational, social, and recreational pursuits both in the home and in the community. Physical and occupational therapy team members may be very useful in assessing these aspects and in developing goals based on the patient's functional ability. Functional assessments may include a history and exam along with use of appropriate questionnaires and observation of the performance of functional tasks. Functional goals are important guides for the interventions provided by all pulmonary rehabilitation team members, and most third-party payers require that therapy be based on written functional goals with defined short- and long-term outcomes including the time frame expected for patients to achieve those goals.

SMOKING CESSATION

Although many physicians have an aversion to refer patients who continue to smoke for pulmonary rehabilitation, there is no reason to withhold pulmonary rehabilitation from such patients. Rather, smoking cessation should be considered as a part of comprehensive pulmonary rehabilitation, and smoking cessation may be the primary goal for some patients enrolled in pulmonary rehabilitation. When conducted during a comprehensive rehabilitation program, other positive health-enhancing behaviors such as exercise may be substituted for smoking. Additional support and encouragement during the smoking cessation effort can be provided by all rehabilitation team members as well as by other patients.

The physician has a key role in promoting, encouraging, and implementing a smoking cessation program. The approach and consequences of smoking cessation are discussed in the chapter on COPD (Chapter 43).

As an aid to routinely determining patient smoking habits, it has been suggested that office staff record the patient's smoking status at every office visit in a manner similar to routine reporting of other significant vital signs such as heart rate, blood pressure, respiratory rate, and temperature. When recorded in this manner, smoking becomes the “fifth vital sign,” and this record can serve as a reminder to the physician and office staff to discuss smoking cessation during the visit. Further smoking cessation assistance should include recommendations on the use of nicotine replacement therapy such as nicotine gums or patches; such recommendations should include information about the appropriate method of administration including dose and frequency of use. This is particularly important with the use of nicotine gum, which should be chewed whenever patients note a craving for a cigarette and then for only a very brief period until tingling of the mouth is noticed; this should be subsequently followed by “parking” the gum between the inside of the cheek and teeth. Because the use of nicotine replacement alone can not assure smoking cessation, a program of counseling should accompany all smoking cessation efforts. Written self-help materials are available from many sources including the National Institutes of Health, American Lung Association, American Cancer Society, and American Heart Association. Patients may be referred to group programs conducted by local hospitals or nonprofit health organizations to assist in providing social supports for the patient. Family members should also be encouraged to assist the patient in smoking cessation. A follow-up visit with the physician should be scheduled to assess the patient's progress and provide ongoing encouragement and support for long-term smoking cessation. The physician should recognize that relapse is common and that many patients require multiple cessation efforts to achieve long-term abstinence from smoking.

EXERCISE TRAINING

The most important aspect of pulmonary rehabilitation is exercise training, and the most important training method is endurance training of the lower extremities. However, in order to understand the effects of training, a brief overview of the effects of chronic airflow limitation (CAL) on exercise capacity is necessary.

Exercise Capacity in COPD

Whereas in normal individuals exercise is limited by the cardiovascular system, in patients with severe CAL exercise is usually limited by the respiratory system. This limitation may be caused by one or more of several factors including abnormal lung mechanics, impaired oxygenation, respiratory muscle dysfunction, and impaired cardiac function.

It is also likely that exercise limitation in COPD is related at least in part to deconditioning, which may be related to inactivity resulting from the fear of dyspnea and associated anxiety. It is generally acknowledged that patients terminate activities performed in the course of their daily lives because of the uncomfortable and fear-provoking symptom of dyspnea. According to the model of COPD shown in Fig. 1, patients with COPD consciously and unconsciously learn to recognize not only that activity leads to dyspnea but also that avoidance of activity will prevent dyspnea. Thus, patients become inactive, which leads to deconditioning and decreased cardiovascular and peripheral muscle strength and endurance. This sequence has also been termed the downward spiral of disease leading to disability, inactivity, and resultant deconditioning. Moreover, anxiety can lead to dyspnea even without an increase in physical activity. In addition, the anticipatory anxiety associated with the thought of increasing activity, even in the absence of the actual stimulus of the activity, can cause shortness of breath.

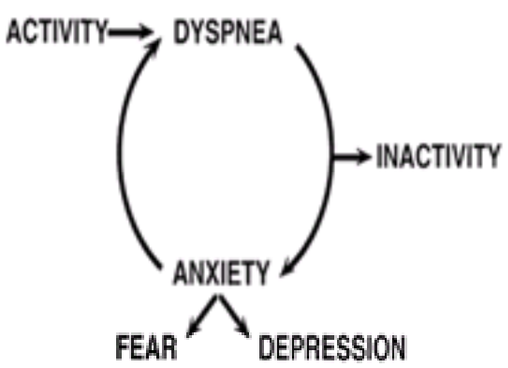

FIG. 1. The vicious circle of dyspnea. Because increased activity leads to dyspnea in patients with COPD, patients learn to prevent dyspnea by reducing their level of activity. Dyspnea not only is provoked by anxiety but also dyspnea causes anxiety. (Modified with permission from Make B. COPD: Management and rehabilitation. *Am Fam Physician* 1991;43:1315–1324.)

Training

Pulmonary rehabilitation does not improve lung mechanics, and the mechanical limitations to exercise noted above should not be expected to improve following exercise training. However, there are multiple potential mechanisms to explain the beneficial effects of exercise training in patients with respiratory disease including increased efficiency in activity performance, enhanced motivation, desensitization to the sensation of dyspnea, improved cardiovascular function, improved muscle function, and increased aerobic capacity. Although one or more of these mechanisms may occur in a given individual, published evidence indicates that patients with severe COPD can obtain a physiological benefit from exercise training. It has been demonstrated, for example, that improved aerobic capacity can be achieved in these patients. After training, reduced levels of lactate are seen at a given level of exercise; the reduced lactate production is associated with a reduced minute ventilation, which in turn is associated with a reduced level of dyspnea (Fig. 2). It has also been demonstrated that high-intensity exercise is more effective than low-intensity training. Although the most effective exercise prescription has not been precisely determined, pulmonary rehabilitation programs uniformly incorporate lower extremity aerobic endurance exercise. Following the principles of exercise training for healthy individuals, the mode, intensity, duration, and frequency of exercise

training should be precisely prescribed for the individual patient and based on the baseline exercise capacity of the individual.

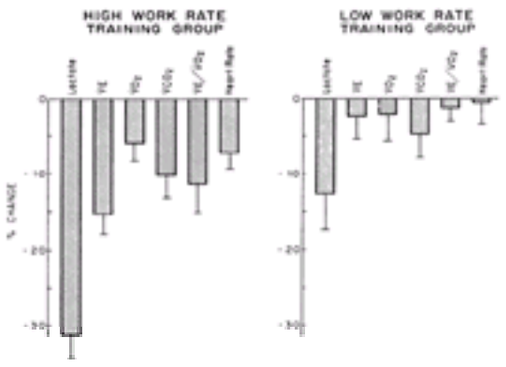

FIG. 2. Changes in physiological responses to exercise produced by two training strategies in patients with COPD (FEV_1 56% predicted). The *left panel* shows results in 11 patients trained at a high work rate (60% of the difference between the anaerobic threshold work rate and maximal work rate) for 45 min a day five times a week for 8 weeks. The *right panel* shows results in eight patients who trained at a lower work rate (90% of the anaerobic threshold work rate). Reductions in lactate and minute ventilation (VE) were greater with high-work than with low-work training. (Reproduced by permission from Casaburi R, Patessio A, Ioli F, Silvio Z, Conner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in pa-tients with obstructive lung disease. *Am Rev Respir Dis* 1991;143:9–18.)

Mode of Exercise Training

Lower extremity aerobic exercise training is the cornerstone of exercise training during pulmonary rehabilitation. In healthy individuals, the effects of exercise training are specific to the muscles that are trained. This concept of the specificity of training implies that leg exercises will improve the performance of leg muscles and arm exercise will improve performance of the arms. Because most daily activities require walking and use of the legs, leg exercise is beneficial in improving a patient's functional performance during activities of daily living. Nevertheless, lower extremity exercise performed by using a stationary bicycle also improves exercise capacity and may be used in training programs. There is less information available concerning the efficacy of other training modalities such as swimming.

Exercise Intensity

Although there are few guidelines for the optimal intensity of training, it is generally felt that there is a minimum intensity that is required to achieve benefits. Lactate production, heart rate, and oxygen uptake have been proposed as indicators of the appropriate level of training. Although in healthy individuals it has been suggested that patients need to exercise above 60% of their predicted maximal heart rate, this may not be appropriate in patients with lung disease whose heart rate is limited by their lung disease. Nevertheless, patients who can achieve this level of heart rate during training are likely to achieve benefits from exercise. Alternatively, it has also been suggested that patients should exercise above their anaerobic threshold; however, such an exercise prescription requires a more formal exercise test before training to determine the anaerobic threshold. Last, some investigators recommend training at a predefined level of maximum exercise capacity and have utilized intensities of between 50% and 80% of the patient's maximal exercise capacity. Whichever intensity is chosen, the patient's level of dyspnea must be considered. Some training programs simply employ continuous walking as long as tolerated and limited by the patient's sensation of dyspnea. Nevertheless, with continued encouragement and training, most patients with COPD should be able to reach the higher intensities of exercise required to achieve benefits.

Training Session Duration

Although there is limited information to recommend a precise duration, the exercise sessions should probably be 30 to 45 min in length. Longer sessions may predispose to injury, and, based on information in healthy individuals, sessions of less than 20 min will likely be ineffective. The training duration should be based on the goals to be achieved. If weight loss is the major goal, longer periods (45 to 60 min in duration) of activity are likely to be more beneficial than shorter periods. It is generally accepted that aerobic activity should be preceded by a short warm-up period and that stretching exercises should follow the training.

Most programs incorporate a single exercise session each day. Although the efficacy of more frequent daily sessions has not been studied, some patients cannot tolerate continuous exercise. Patients with severe interstitial lung disease may have severe exercise-induced hypoxemia that is not correctable with supplemental oxygen therapy. In such individuals, interval training (brief periods of exercise initially for as little as 1 min followed by rest periods of equal or longer time periods) may be necessary not only to prevent desaturation but also to limit severe dyspnea.

Training Frequency

Although benefits may accrue from as little as twice-weekly training sessions, it is generally agreed that training should take place three to five times each week to obtain maximal benefits. This recommended frequency is applicable both to initial training and also to maintenance exercise regimens. Daily training is impractical in most cases and probably accrues little additional benefit. Although many rehabilitation programs offer formal supervised training twice each week, patients should be expected to exercise on their own as well.

Training Program Duration

The optimal duration of the initial training is unknown. In healthy individuals using a constant intensity exercise program, maximal physiological benefits are achieved in about 3 to 4 weeks. Thus, an initial exercise program could be conducted in as little as 3 weeks. Nevertheless, most rehabilitation programs offer structured training sessions for 6 to 12 weeks in an attempt to achieve maximal benefit from the initial program.

After the initial training component, a maintenance exercise program is necessary to retain the benefits of the initial training. Patients may need to restart their exercise program at a lower level following exacerbations of their underlying lung disease or intercurrent illness that reduce their activity level. Although lifelong exercise is recommended, there are few studies outlining methods of assuring continued patient adherence with exercise. Because it is likely that most patients do not continue to exercise following the initial training, education about continued exercise and behavioral approaches to assured continued patient adherence should be incorporated into the rehabilitation program.

Upper Extremity Training

Although many daily functional tasks require the use of the arms, until recently little emphasis has been placed on training of the upper extremities during pulmonary rehabilitation. In healthy individuals, arm work results in a higher metabolic demand than leg work. Thus, for a given workload, upper extremity activity is associated with a higher oxygen uptake, minute ventilation, heart rate, blood pressure, and lactate production than leg exercise. In addition, as individuals age, they tend to lose muscle mass and strength in the arms, which are used to a lesser extent in daily activities than the legs. These factors suggest that upper extremity training may be beneficial in patients with COPD.

In patients with COPD, arm exercise is terminated at a lower oxygen consumption than leg exercise. During arm exercise, patients with severe airflow limitation may develop irregular and dyssynchronous movements of the thorax and abdomen and even abdominal paradox accompanied by severe dyspnea. It has been suggested that upper extremity exercise places a dual burden on the muscles of the shoulder girdle, requiring them to participate simultaneously in arm activity and ventilatory activity. As a result, demand is placed on the diaphragm to increase its contribution to ventilation, leading to an increase in shortness of breath.

The simple act of raising the arms without support increases the ventilatory and metabolic demands of patients with COPD. Furthermore, it has been shown that following pulmonary rehabilitation including unsupported arm exercise, there is a reduction in work required for simple arm elevation.

Based on the available evidence, it appears prudent to include upper extremity exercise during pulmonary rehabilitation, and it has been suggested that both supported and unsupported training may be beneficial. Unsupported exercises usually require the patient to lift a dowel to the level of the shoulders, inhaling during dowel raises and exhaling as the dowel is lowered, and pacing that activity with a comfortable respiratory rate. Because dyspnea occurs rapidly during such exercise, interval training has been recommended, initially with a very brief periods of 1 min of exercise followed by 2 min of rest. The exercise intervals may be increased as tolerated,

weights may be added to the dowel, and the session duration may be increased to a total of 20 to 30 min. Supported arm training, such as with an arm rest, may also be employed.

Strength Training

In order for patients to participate in an aerobic training program, they must have sufficient strength to perform the exercise. In patients who have muscle weakness from age, disuse, deconditioning, or from the effects of medications such as oral corticosteroids, strength training may be necessary before embarking on an intensive aerobic conditioning program. An evaluation by a trained physical therapist employing a manual muscle test can be helpful in identifying muscle groups that are weak and may benefit from strength training. Alternatively, isokinetic muscle testing equipment may provide similar objective information about muscle strength.

Even in patients who demonstrate relatively normal strength, strength training is routinely employed by most pulmonary rehabilitation programs in order to preserve and enhance strength and as an adjunct to aerobic conditioning. Strength training is usually recommended for 3 to 5 days each week in addition to lower and upper extremity training. Training may employ use of free weights or even weight-training equipment when such is readily available to the patient.

Ventilatory Muscle Training

Patients with severe COPD commonly have reduced inspiratory muscle strength as measured by maximum inspiratory pressure at the mouth. There are likely several mechanisms for this effect including reduced diaphragm curvature associated with hyperinflation and associated reduced force-generating capacity, alterations in the orientation of other respiratory muscles associated with hyperinflation, and possible diaphragm weakness associated with increased demands imparted by increased work of breathing. Further speculation suggests that diaphragm weakness or fatigue may impair ventilation and increase dyspnea in COPD. It is therefore attractive to hypothesize that specific training of the inspiratory muscles may improve not only ventilatory muscle strength but also endurance and ventilatory capacity and reduce dyspnea.

If ventilatory muscle training is used, it should follow the principles of intensity, frequency, mode, and duration suggested for other forms of muscle training. In particular, training load should be carefully monitored. Training devices with a linear resistance pattern should be used that permit the specified work load to be maintained over a wide range of inspiratory flow rates. With alinear resistors, patients may alter their breathing pattern to minimize inspiratory resistance and thus not achieve the desired training load. An initial training resistance that assures a mouth pressure of ³30% of maximal inspiratory pressure (P_{Imax}) should be used.

PSYCHOSOCIAL COUNSELING

Psychological Issues in COPD

Patients with chronic lung disease frequently exhibit emotional and psychological concerns related to their illness. Anxiety is a common complaint, particularly in patients with more severe degrees of COPD. As noted in Fig. 1, anxiety may in part be caused by the disabling symptom of dyspnea and may be severe enough to be considered panic and to limit patient activities. The consequence of expressions of patient emotional response is often increasing shortness of breath. To avoid this fear-provoking symptom, patients may repress their emotions, a situation described as placing these patients in an “emotional strait-jacket.”

Depressive symptoms are frequently present in patients with COPD and may in part be caused by reduced functional capacity and resultant impairment in vocational pursuits, recreational interests, and activities of daily living. These changes in life style have been documented to impair quality of life and consequently diminish the patient's role within the family and community. Patients may express feelings of worthlessness and despair because of their inability to provide financial or emotional support to family members. Depression is the most common emotional consequence of COPD and is more common in this illness than in patients with other chronic medical disorders.

Sexual functioning may also be altered in patients with COPD and may be more impaired in patients with more severe lung disease. Dyspnea may limit intercourse, lead to impotence, alter relationships with spouses or significant others, and lead to reduced sexual self-image. Physicians should recognize that impotence and reduced sexual activity seen in these patients may not be associated with advancing age but may rather be caused by the impact of the lung disease. Educational programs and counseling to address sexual issues are routinely included in most pulmonary rehabilitation programs.

Neuropsychological deficits may also be seen in patients with COPD. Decreased fine motor speed and coordination, impaired perceptual motor skills, and difficulty with abstracting have been documented. However, memory is usually spared. More severe neuropsychological dysfunction is seen in patients with more severe degrees of hypoxemia.

Psychosocial Interventions

Exercise Training

Based on the theory depicted in Fig. 1, depressive symptoms and anxiety may improve with pulmonary rehabilitation as exercise capacity is improved. The importance of the emotional support and encouragement provided by health professionals during exercise training should not be underestimated. Exercising under the supervision and direct observation of a physical therapist, respiratory therapist, or nurse experienced in the management of patients with respiratory disease and in whom the patient has confidence is an important factor in allaying anxiety and fear and reducing panic associated with activity.

Antidepressant Medications

If significant clinical depression is confirmed, consideration should be given to therapy with antidepressant medications. Careful consideration should be given to the side effects of antidepressants in patients with COPD, who tend to be older, may have excessive respiratory secretions, and have a tendency to prostatic hypertrophy. Some antidepressants produce sedation, and others are associated with activation, and these drugs should be tailored to the needs of individual patients. In patients with hypercapnia, drugs that act centrally and reduce respiratory drive should be avoided. Agents with cholinergic properties are not appropriate for patients with prostatic hypertrophy. Anxiolytic agents may be effective in selected patients with severe agitation and anxiety that is unresponsive to counseling, relaxation, and the other components of pulmonary rehabilitation.

Psychosocial Support

Psychosocial clinicians including licensed clinical social workers, clinical psychologists, and psychiatrists may be helpful in structuring the psychosocial component of the rehabilitation program and providing psychosocial evaluation and support services. Psychosocial support techniques include group and individual counseling, stress management, relaxation, and use of support groups. Group sessions with the patient and family that incorporate counseling and peer group support are used in many rehabilitation programs. Groups of patients with the same disease may be useful to allow patients to see that their expressed feelings are also shared by others; the group may provide insights into methods of coping that have proved effective. The anxiety noted by patients with lung disease may be lessened by giving patients stress management and relaxation techniques to allow them to gain control over their symptoms.

BREATHING RETRAINING

Breathing retraining includes pursed-lip breathing, diaphragmatic breathing, and paced breathing. The goal of these controlled-breathing techniques is to reduce dyspnea, and they have the additional benefit of improving respiratory physiological parameters. Controlled breathing may be practiced during exercise and with daily activities to lessen dyspnea or whenever patients experience increased shortness of breath. These methods may improve oxygenation, slow the respiratory rate, increase tidal volume, decrease air trapping, and reduce work of breathing.

Pursed-Lip Breathing

This is the most commonly used technique and is often learned and adopted by patients without instruction from health care professionals. Patients breath in slowly through the nose and then exhale slowly over 4 to 6 sec or longer through lightly pursed lips. Pursed-lip breathing (PLB) may be used with diaphragmatic breathing during inspiration. One explanation for the physiological benefits of PLB is that airway pressure is increased during exhalation, thereby preventing airway collapse in patients with reduced elastic recoil resulting in decreased hyperinflation and improved oxygenation. However, PLB has also been shown to improve oxygenation in patients with interstitial lung disease who have increased elastic recoil. In some studies, work of breathing has been shown to increase with the use of PLB, an effect

that might be exaggerated if the lips are pursed too tightly, resulting in a significantly higher expiratory resistance.

Diaphragmatic Breathing

With this technique, patients are encouraged to use their diaphragm by attempting to push the abdomen outward during inspiration. The technique was originally described for use while the patient is supine with the hands placed on the abdomen to facilitate the patient's ability to assess outward abdominal motion. The physiological and clinical benefits of diaphragmatic breathing have been less well studied, and patients often report greater relief of dyspnea using PLB.

Controlled Breathing

During periods of greatly increased effort, most healthy individuals have a tendency to hold their breath. During activity, patients with lung disease often develop breathing patterns that are irregular and not coordinated with their activity. Controlled or paced breathing is the use of a regular breathing pattern and coordination of regular breathing with activity. For example, during arm activities, inhalation might be coordinated with raising of the arms and exhalation with lowering of the arms. During stair climbing, exhalation might be coordinated with raising the body up to the next higher stair. Controlled breathing during exercise training may also increase exercise endurance and delay the onset of shortness of breath.

DAILY ACTIVITY PERFORMANCE AND ENERGY MANAGEMENT

Based on the initial patient assessment, appropriate treatment goals for improving performance of daily activities may include (1) reducing shortness of breath with basic ADL, (2) applying regular coordinated breathing patterns, (3) increasing functional endurance, (4) using energy and time management methods, (5) using adaptive equipment, (6) obtaining assistance from others including family members, and (7) enhancing performance at work. These potential treatment goals are in addition to the goals of reducing stress and providing relaxation, which will also decrease the energy required during the day.

In patients with limited functional capacity, energy management techniques can allow greater achievement of desired tasks. Energy management includes employing energy conservation techniques, improving work efficiency, using proper body mechanics, incorporating time management, pacing, and careful planning. These techniques are not tools that need to be practiced routinely by healthy individuals, and so they are not usually self-evident to patients. However, incorporation of these principles into daily life can enhance functional performance. For example, it may be impossible for a patient to run up a flight of stairs to a restaurant after walking from a parked car. The stairs to the restaurant may be more easily attainable by leaving the home with sufficient time to avoid rushing (planning), leaving the patient off at the door to the building (planning and energy conservation), resting before climbing the stairs (energy management), walking up the stairs more slowly (pacing), resting on the stairs when needed (energy management), and using a regular breathing pattern incorporating pursed-lip breathing.

An important part of one's daily life is recreation and leisure pursuits. Evaluation of leisure function includes assessment of barriers limiting participation in such activities. Such barriers potentially relate to financial issues such as limited income, physical concerns secondary to the patient's dyspnea, and emotional factors such as the fear of dyspnea associated with increased activity. Addressing these barriers and discussion of the methods of successfully participating in leisure activities may enhance patient quality of life.

EDUCATION

The traditional goal of education has been to increase cognitive knowledge, i.e., to inform patients about their disease. Such education requires teaching an understanding of the lungs and how they work, the nature of the lung disease and its signs and symptoms, and the names, actions, and side effects of medications. However, a more appropriate and effective role of education for individuals with chronic illness is to effect a positive behavioral change. For example, the goal of education about inhaled medications is to assure patient use of the medications to achieve the desired benefits, i.e., reduction of dyspnea and increases in daily activities. Patient knowledge about the mechanism of action of the inhaled bronchodilator is likely to be less important in achieving this goal than information about the benefits to be achieved by the individual patient. In addition, important dosing information including time and frequency of medication administration and technique of administration for the individual may help assure adherence with use of the medication.

Based on the health belief model, patients and families should be queried about their perceptions of the seriousness of their disease, susceptibility to further illness and complications, threat of their disorder, benefits of treatment, and barriers to therapy. An understanding of the health beliefs of the patient and family will assist the educational efforts of the rehabilitation team to change the health beliefs so the treatment plan will be more readily accepted and result in improved adherence with the prescribed therapies.

An initial educational evaluation is useful in all patients enrolled in pulmonary rehabilitation. Because learning styles differ, it is useful to determine if the patient will learn best by using verbal or visual methods and to provide the educational material in a manner that is most appropriate for the patient's learning style. The patient's educational level, native language, and reading level are also important to assess, along with any difficulty in vision and hearing. Written information should be provided to all patients, particularly when memory problems are evident.

Education may be conducted both formally and informally throughout comprehensive pulmonary rehabilitation and should be guided by learning objectives based on the needs of the individual patient. Education begins before patient enrollment in rehabilitation by explanations of the purpose, goals, expected results, and nature of the rehabilitation program. Formal education may be provided through group classes, one-on-one teaching with a health care professional, or using written or audiovisual materials. Informal education should occur with every member of the pulmonary rehabilitation team such as when a physician prescribes a new medication, a respiratory therapist performs a pulmonary function test, a physical therapist performs chest physiotherapy, an occupational therapist evaluates activities of daily living, and a social worker implements a relaxation program. Patient learning should be assessed both formally and informally to determine whether the learning objectives have been met.

NUTRITIONAL COUNSELING

It is reasonable to assume that in order for patients to participate in pulmonary rehabilitation that incorporates exercise training program adequate nutritional intake must be assured, weight excess should be treated, and weight loss should be avoided. Even though there is limited scientific information on the best approaches to nutritional counseling in patients with respiratory disease, recommendations for counseling patients about the common problems of weight loss and dyspnea during meals are outlined in Table 4.

Problem	Recommendations
Anorexia, weight loss	Eat high-calorie foods first Have favorite foods available Try more frequent small meals and snacks throughout the day Add butter, mayonnaise, sauces, and gravies to add calories Limit liquids in meals; sip liquids an hour after meals Cold foods can give less of a sense of fullness than hot foods Instruct patients to push themselves
Dyspnea	Rest before meals Use bronchodilators before meals Use secretion clearance strategies if indicated Eat more slowly Use pursed-lip breathing between bites Use tripod position for meals Have readily prepared meals available Evaluate for oxygen desaturation during meals

[a] Modified from Rogers RM, Donahoe M. Nutrition in pulmonary rehabilitation. In: Fishman AP, ed. Pulmonary Rehabilitation. New York: Marcel Dekker, 1996:555.

TABLE 4. *Symptoms and counseling strategies for nutritional therapy in chronic obstructive pulmonary disease*[a]

A nutritional evaluation should be performed on all patients involved in pulmonary rehabilitation. A dietary history including what the patient actually consumes and a history of any weight loss or weight gain are important to elicit. The patient may be asked to recall his or her diet for the last 24 hrs or maintain a diary of foods eaten to determine the amount and types of food consumed. From the patient's height and body weight, tables can be used to identify ideal body weight. However, it is also important to determine lean body mass (LBM) and fat mass to develop an optimal nutritional program for each individual patient. A relatively simple way to assess lean body mass involves measurement of skinfold thickness and skeletal circumference at established sites. One of the goals of nutritional counseling should be to ensure

optimal lean body mass, which includes muscle mass, and minimize excessive fat mass.

In part because of reduced activity levels associated with severe respiratory disease and decreased caloric needs associated with advancing age, patients with COPD may be overweight and have excess fat mass. Individuals who are overweight, particularly those who are obese (>120% of ideal body weight), may be expected to have more limited exercise capacity for weight-bearing activity than normal-weight patients. Thus, weight loss in this group of patients is theoretically desirable to reduce the metabolic and thus the ventilatory demands of daily activities. Weight loss should be associated with decreased dyspnea and improved exercise capacity and is an important adjunct to the other elements of pulmonary rehabilitation.

Patients with severe COPD may be underweight (<90% of ideal body weight). Weight loss has several potential implications for the patient with respiratory disease and may be associated with decreased diaphragm and respiratory muscle function, decreased hypoxic and hypercapnic ventilatory responses, and decreased respiratory clearance and defense mechanisms. It has also been demonstrated that weight loss in patients with COPD is associated with increased mortality. Whether the weight loss in some undefined manner directly causes early mortality or whether weight loss is simply a marker for more severe lung disease has not been determined. Although some carefully controlled investigations that allow patients access to adequate caloric intake have been associated with weight gain, improved mortality has not been documented. Nevertheless, adequate caloric intake can be expected to be helpful in improving muscle strength and endurance in underweight patients.

MAINTENANCE PROGRAM

It is understandably difficult for older individuals who have developed life-long habits of not exercising as well as acting independently without advice from others to incorporate changes into their daily lives. Based on the techniques learned during the initial phase of pulmonary rehabilitation, patients with chronic lung disease are nonetheless expected to permanently change their life style by incorporating regular exercise training and adhere to advice from health care professionals.

Although the degree of patient adherence and nonadherence to continued exercise and pulmonary rehabilitation is unknown, it is likely that adherence is less than optimal. In studies of patients with chronic illness, non-adherence rates vary greatly and are frequently greater than 50%.

There is little available literature to guide clinicians and suggest the best methods of assuring long-term adherence with the key elements of pulmonary rehabilitation. However, it is prudent to incorporate as many techniques as possible to assist the patient to adhere to a long-term maintenance program. It is the responsibility of every pulmonary rehabilitation program not only to provide long-term goals for the patient but also to assist the patient in developing daily routines that incorporate methods of achieving those goals. In addition, barriers to long-term maintenance, such as the site and costs of regular ongoing exercise training, should be addressed and resolved in a cooperative manner by the patient and the rehabilitation team. Collaborative self-management has been the term applied to a long-term cooperative effort by the patient and physician to emphasize the importance of the patient's central role in making decisions and choices regarding disease management and the physician's role as educator and facilitator. The role of education in allowing patients to become active participants in their care and responsible for their own health can not be overemphasized.

POTENTIAL OUTCOMES OF PULMONARY REHABILITATION

Many of the 13 potential outcomes listed in Table 5 may be affected by multidimensional pulmonary rehabilitation programs. Determination of the results, or outcomes, of pulmonary rehabilitation is important for three major reasons. First, a clear and concise description of the expected outcomes of pulmonary rehabilitation can be used to convey the benefits of pulmonary rehabilitation to patients who are considering participation in rehabilitation, physicians who refer patients for rehabilitation, and medical benefits providers paying for such services. Information about outcomes that have been documented by other programs may be gleaned from studies published in the medical literature and provide a basis for the medical necessity for rehabilitation services. Second, assessment of outcomes of programs within the local community must be used to evaluate the results in individual patients to assure that desired results are actually achieved. Third, outcomes assessment should be used to guide the development and ongoing evaluation of comprehensive programs. Each pulmonary rehabilitation program should assess outcomes and should decide which outcomes are important to measure.

"Medical" factors
Mortality
Morbidity
Respiratory symptoms
Physiological indices
"Nonmedical" factors
Functional capacity
Neuropsychological function
Health-related behaviors
Health-related quality of life
Physical health
Mental/emotional health
Social health
Role function
Perception of general well-being
Ability to work
Caregiver burden
Use of assistive technology
Patient satisfaction
Costs
Direct costs of medical care
Indirect costs

[a] Modified with permission from Make B, Glenn K. Outcomes of pulmonary rehabilitation. In: Baum JH, ed. *Pulmonary Rehabilitation: The Obstructive and Paralytic Conditions*. 1985.

TABLE 5. *Potential outcomes of pulmonary rehabilitation*[a]

Medical issues are addressed by the first four outcomes listed in Table 5. Traditionally, *mortality,* or survival, is the most important outcome of medical care. However, patients with chronic disease frequently indicate that quality of life is much more important than the quantity of life. Medical *morbidity* in patients with respiratory disease includes complications of the primary respiratory process. In patients with COPD pulmonary hypertension with subsequent cor pulmonale (right-sided heart failure from chronic hypoxemia), acute exacerbations of COPD, and respiratory tract infections increase the morbidity of the illness. In addition, morbidity also includes hospitalizations for acute exacerbations and the need for emergency or urgent medical care related to the respiratory disorder, although these may also be considered as costs.

Respiratory symptoms are prominent complaints in patients with respiratory disorders. The primary symptom of respiratory disease is shortness of breath (dyspnea), which may be disabling for patients with severe airflow limitation. Secondary symptoms related to the effects of respiratory disease, such as headaches related to hypoxemia and fatigue, should also be considered.

Physiological indices in individuals with respiratory disorders may be measured by simple spirometry and include the forced vital capacity (FVC) and forced expired volume in 1 sec (FEV_1). However, in patients with COPD, these physiological indices as well as measures of oxygenation are not expected to change because the underlying respiratory disorder is not altered by pulmonary rehabilitation. On the other hand, improved adherence to medications may improve airflow limitation in patients with reversible disorders such as asthma. One of the more important physiological indices is direct assessment of exercise capacity, which may be most objectively evaluated with a cardiopulmonary exercise tolerance test performed in a controlled laboratory setting. Workload, oxygen consumption, heart rate, and minute ventilation are relatively easy to measure with commercially available equipment while the patient exercises on a treadmill or bicycle ergometer using steady-state or incremental exercise protocols.

The remainder of the potential outcomes of pulmonary rehabilitation listed in Table 5 address “nonmedical issues,” which are not considered as important as the “medical” factors. The nonmedical issues are frequently identified as goals of patients and thus incorporated into rehabilitation programs. Functional capacity refers to the ability to perform tasks required during the course of an individual's daily life. Because walking is an important daily activity, functional capacity may be measured in patients with pulmonary disease as the distance walked in 6 or 12 min. This walk test is an outgrowth of the 12-min run developed to evaluate the fitness of army recruits. Although the run has been shown to correlate with maximum exercise capacity, the walk test is more appropriately considered as a functional evaluation tool in patients with respiratory disease. Because encouragement by the tester can increase the distance walked, the walk test should be performed according to a rigid protocol defining the number of walks and methodology to be used by the tester.

Patients with COPD are often hypoxemic and demonstrate associated reductions in neuropsychological function, which may also be affected by advancing age. Patient adherence to health-related behaviors should be stressed during pulmonary rehabilitation. Cigarette smoking is the major cause of chronic obstructive pulmonary disease, and smoking cessation efforts are often incorporated into pulmonary rehabilitation programs. Adherence to medication, oxygen, and exercise prescriptions are other behavioral outcomes that foster continued health and thus should be assessed following pulmonary rehabilitation.

Physical function, mental/emotional function, social function, role function, and perception of well-being are often considered together as “health-related quality of life.” Although a perception by the patient of his or her own condition, quality of life can nevertheless be objectively measured. *Physical health* is the ability to perform

everyday activities including self-care and mobility. *Mental/emotional health* incorporates patients' feelings such as anxiety, nervousness, and depression; control over behaviors, feelings, and thoughts; and cognitive functions such as memory, orientation, and alertness. *Social health* incorporates interactions with other individuals in the community. *Role function* refers to the performance of activities such as employment, school, and housework. A global perception of *general well-being* can also be evaluated.

The *ability to work* may be important for younger individuals but may not be as critical for elderly, retired patients. The ability of children to attend school and participate in the full range of school activities should be considered. Lost time from work or school because of illness may also be an important outcome. *Caregiver burden* refers to the effects of the patient's illness on family, friends, and others who may assist with the patient's care. This includes financial issues such as time lost from work for family members as well as psychological stressors on family caring for chronically ill patients. Patients with limited function may benefit from the use of assistive technology such as wheelchairs and vans for people with neuromuscular disorders, which may be lessened by rehabilitation. As health care expenditures are being more tightly controlled, costs are increasingly of concern. Direct costs of medical care include not only the cost of rehabilitation but also of hospitalizations, emergency medical care, and prescription medications. Indirect costs include lost wages for patients and families and the psychosocial impact of illness on both patients and their families.

TOOLS TO ASSESS QUALITY-OF-LIFE OUTCOMES

Because enhancement in quality of life is one of the major goals of pulmonary rehabilitation, and because assessment of quality of life is a relatively new field, this section reviews the use of questionnaires to assess health-related quality of life.

Criteria for Quality-of-Life Questionnaires

Before a measurement tool is selected, the intent of the measurement must be defined in order to ensure that the measurement instrument can adequately assess the desired outcome. Measurement tools can be classified into three types (discriminative, predictive, and evaluative), based on the purpose for which they are used. The measurement of outcomes that result from pulmonary rehabilitation requires use of evaluative tools, which are designed to detect a difference over time in a group, such as before and after pulmonary rehabilitation in patients with COPD. An established evaluative measurement tool must meet three fundamental psychometric criteria: reliability, validity, and sensitivity.

The reliability of a measurement tool refers to its accuracy and its lack of change over time. Using a scale as an example of a reliable measurement tool for weight, repeated measurements of the same object with the same scale should yield the same results. To assess the reliability of a questionnaire, the tool may be administered twice to a group of people who are thought to be stable and then the results of the two tests are compared, a process known as test–retest reproducibility. Interobserver reliability assesses differences related to results obtained by different observers administering the same instrument to the same subject and is important when questionnaires cannot be completed without a trained administrator.

Demonstration of the validity of a quality-of-life instrument is a process of accumulating sufficient evidence to document that the tool actually measures the desired attribute. Because there is no universally agreed-on “gold standard” measure of quality of life, the validity of quality-of-life measurement instruments is difficult to assess. Development of quality-of-life questionnaires is usually based on expert knowledge and experience of the disease, and the tool is derived from such evidence combined with theories and postulations. However, both the instrument and its underlying theories must be assessed for accuracy.

Pulmonary rehabilitation programs are interested in changes that occur in response to the program intervention and thus must assure that they utilize tools that are able to measure change. When evaluative tools are readministered after rehabilitation, such tools should have the ability to reflect a clinically relevant difference, referred to as sensitivity or responsiveness.

General Quality-of-Life Tools

Quality-of-life instruments are structured as either general or disease-specific tools. General health or generic tools are intended to comprehensively profile the areas believed to be impacted by any disease or treatment and include physical and emotional function and general well-being. These instruments can be used across cultures, genders, populations, and diseases. General health profiles have the advantage of measuring the global impact of a disease or a medical intervention. Three general quality-of-life tools have been used in patients with COPD.

SF-36 Health Survey

This instrument (SF-36) contains 36 written questions that can be answered independently by the patient in 5 to 10 min. Eight subscale scores are generated: physical functioning, social functioning, role-physical, role-emotional, bodily pain, general health, vitality, and mental health. Each subscale score ranges from 0 to 100, with 100 representing the most desirable score. Two summary scores (physical and mental) have also been described.

Quality of Well-Being Scale

This (QWB) is a somewhat complex tool requiring administration by a trained interviewer, and a response-coding procedure must be applied before the questionnaire can be scored. The interviewer must keep an elaborate record of the subject's verbal and bodily responses. The QWB contains 50 items and can be administered in about 10 to 15 min. Components include mobility, physical activity, social activity, and symptoms, and the results are weighted by general population preferences. The measured general health status can be reported as a continuum between optimal functioning (represented as a score of 1) and death (represented by a score of 0). Subjects can be classified into one of 43 states of functioning ranging between 1 and 0; the weight of each state is derived from community surveys to reflect social preference. The QWB can be used to profile a single day or a span of several days, with the interviewer probing health, symptoms, and performance. In addition, the effects of a treatment can be expressed as well-years.

Sickness Impact Profile

This tool (SIP) is designed to assess the impact of illness on behaviors and activities. This questionnaire contains 136 questions, which are grouped into 12 subscales and further summarized into two broad scores and an overall summary score. The general scale of physical activity includes subscales of ambulation, mobility, and body care and movement. The psychosocial score includes subscales of social interaction, communication, alertness, and emotional behavior. The remaining subscales include sleep and rest, eating, work, home management, and recreation and pastimes. Although this questionnaire is long, it has been widely used and can be completed independently by the patient.

Respiratory Disease-Specific Quality-of-Life Tools

Although general health surveys can provide useful information, there is the potential for limited sensitivity in patients with severe disease and with specific symptom complexes such as COPD. One dimension of health where this issue is likely to arise is physical activities. For example, a physical functioning scale with questions that include running, lawn mowing, or other strenuous activities lack the sensitivity to differentiate among individuals with extremely limited abilities who are recipients of pulmonary rehabilitation. Moreover, a scale can inhibit detection of differences if it contains a significant proportion of items to which most COPD patients would typically respond in a similar manner, either with or without therapeutic interventions. Some disease-specific tools allow patients to identify individual areas or activities that they feel are most impacted and allow these patient-selected areas to be reassessed over time. This process allows individuals to determine the impact of disease on their own lives. Although this individualization increases the sensitivity to detect change for an individual, comparisons across disease groups or populations are difficult.

Chronic Respiratory Disease Questionnaire

The most widely used tool to evaluate patients with respiratory disease is the CRDQ, which was designed to measure the impact of chronic airflow limitation on quality of life. Because different individuals with chronic lung disease often identify different physical tasks that have been affected by their lung disease, this questionnaire allows each patient to choose activities in which their performance has been most altered. The interviewer asks each subject to identify five activities most impacted by dyspnea, and these same activities are queried on each subsequent questionnaire administration, at which time it is suggested that patients be informed about their response to the prior questionnaire. Responses are recorded using a seven-point Likert scale ranging from 1, indicating extreme disability, to 7, indicating no disability. This questionnaire includes 15 items measuring dyspnea and fatigue (physical functioning scale), anxiety and depression (emotional functioning scale), and the sense of control over respiratory disease (mastery scale). After the initial interviewer administration, the patient may complete the questionnaire independently.

St. George's Respiratory Questionnaire

This self-administered questionnaire incorporates 76 items for use in patients with respiratory disease including COPD and asthma. The questions are weighted as to their importance, and a computerized scoring system is required to obtain a total score and three component scores: respiratory symptoms, performance of activities, and impact of the illness. Normal ranges have been determined, and the instrument appears sensitive to change. This instrument is unique in that clinically significant changes in the scores have been determined.

OUTCOMES OF PULMONARY REHABILITATION

Improvements in many of the important outcome domains have been demonstrated following pulmonary rehabilitation in patients with chronic obstructive pulmonary disease (Table 6). Although it is not always clear which component of pulmonary rehabilitation is most responsible for a specific outcome, most of the results noted below have been demonstrated in response to comprehensive multidisciplinary programs. The reader is referred to several evidence-based reviews of pulmonary rehabilitation included in the References, which provide documentation of the outcomes of pulmonary rehabilitation.

Component/symptom	Outcome	Grade*	Recommendation
Survival	Survival may be improved	C	
Health care utilization	Reduced number and days of hospitalizations	B	
Dyspnea	Reduced dyspnea	A	Dyspnea outcomes should be routinely measured
Quality of life	Improved quality of life	B	
Lower extremity exercise training	Improved exercise tolerance without appreciable adverse outcome	A	Exercise training of muscles of ambulation is recommended
Upper extremity exercise training	Improved arm function with strength and endurance	B	Arm exercise is recommended
Ventilatory muscle training	Improved dyspnea and exercise tolerance in some studies	B	Not an essential component of pulmonary rehabilitation, may be considered in selected patients with decreased respiratory muscle strength and dyspnea who remain symptomatic despite optimal therapy
Psychosocial and education	Decreased affective distress Cognitive and behavioral intervention enhance exercise adherence	C	Recommended based on expert opinion

*Grade, grade of evidence supporting recommendation: A, evidence provided by controlled trials with statistically significant consistent results; B, evidence provided by observational studies or controlled trials with less consistent results; C, supporting expert opinion because of results or lack of controlled trials.

TABLE 6. *Summary of demonstrated outcomes of pulmonary rehabilitation*

Survival

Mortality is most closely related to the degree of airflow limitation as measured by the FEV_1 but is also related to age and possibly exercise tolerance and perceived physical disability. Because pulmonary rehabilitation does not change the underlying pulmonary disease and FEV_1 in patients with COPD, it might be anticipated that survival would be unchanged following rehabilitation in patients with very severe airflow limitation. On the other hand, in selected groups of patients with COPD who have decreased exercise capacity and increasingly frequent exacerbations with resulting deconditioning, pulmonary rehabilitation may decrease the frequency of exacerbations, lessen physical disability, and improve exercise tolerance and thus might improve survival.

Oxygen therapy in patients with COPD and severe hypoxemia has been clearly shown to improve survival. However, conclusive evidence that comprehensive pulmonary rehabilitation decreases mortality is lacking. Using historical control groups and observational studies, several publications have suggested that pulmonary rehabilitation may improve 5-year survival by 13% to 28%, and randomized studies have demonstrated a trend to improved survival. Nevertheless, further controlled randomized studies are required to more completely address the effects of rehabilitation on survival. The investigations evaluating survival have frequently not incorporated a concurrent control population that did not receive pulmonary rehabilitation. In addition, the available studies include patients with differing severity of underlying pulmonary disease as measured by the FEV_1 and report divergent survival rates, making comparisons between studies difficult.

Morbidity

Several studies have demonstrated a reduction in hospital days in COPD patients following pulmonary rehabilitation including programs based in the home, utilizing the services of a nurse and other ancillary health care personnel when necessary, and in other outpatient settings. It is most likely that decreased hospitalizations might occur in those patients with frequent hospital admissions and moderately severe pulmonary disease who were enrolled in a home care program. In the current health environment, with its focus on cost reductions and reduction in hospitalizations, the role of pulmonary rehabilitation in reducing morbidity and the utilization of expensive health care resources in the hospital and emergency room is of critical importance.

Because of a reduction in hospital days, pulmonary rehabilitation can decrease the costs of medical care in patients with COPD. The cost savings associated with reduced hospitalizations following pulmonary rehabilitation is in the range of $2,000 per patient per year. The cost-effectiveness of rehabilitation in patients with COPD has also been evaluated by using the Quality of Well-Being scale to measure years of quality life (well-years) as an outcome measure. The cost per additional year of well-being was $24,256, considered cost-effective by current standards when compared to other therapeutic modalities for other diseases.

Respiratory Symptoms

The major respiratory symptom of interest to patients with COPD is breathlessness. Randomized controlled clinical trials have shown that dyspnea decreases as a result of pulmonary rehabilitation, both when measured by the specific questionnaires assessing breathlessness and when measured by disease-specific quality-of-life questionnaires such as the CRDQ (Fig. 3). Reduction in dyspnea as measured during formal exercise tests has also been documented following rehabilitation. Improved breathlessness has been noted with rehabilitation when applied in different sites including the home outpatient setting and the inpatient setting. The major rehabilitation component leading to reduced breathlessness is lower extremity exercise training. Breathing retraining including pursed lips and diaphragm breathing are also known to decrease dyspnea. Because of the importance of this cardinal symptom and the frequency with which reduction in dyspnea is a stated goal of the patient, dyspnea is an important symptom to monitor and assess in response to pulmonary rehabilitation. The respiratory disease-specific questionnaires (such as the CRDQ and St. George's Respiratory Questionnaire) incorporate measures of dyspnea. Specific dyspnea questionnaires are also available (such as the Baseline and Transitional Dyspnea Indices), and other tools are designed to assess dyspnea during exercise (such as the Borg Dyspnea Scale and Visual Analog Scale).

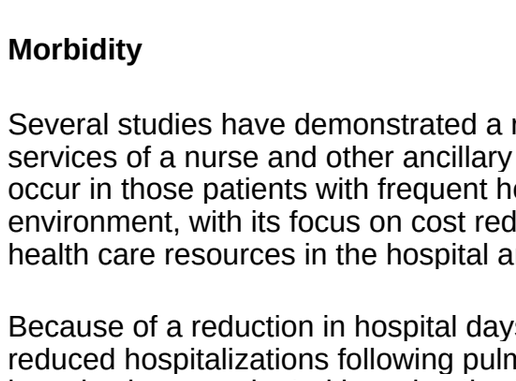

FIG. 3. Treadmill endurance is improved at 2, 6, and 12 months in patients with COPD randomized to receive comprehensive pulmonary rehabilitation compared to patients receiving education only. (Reproduced by permission from Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiological and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;122:823–832.)

Functional Capacity

Pulmonary rehabilitation improves objectively assessed functional capacity as well as patient-perceived functional status. Some studies have classified patients by their functional ability and demonstrate improved functional classification following rehabilitation. The 6- or 12-min walk test can also be used to assess functional capacity; walk distance improves about 20% to 25% following rehabilitation in patients with COPD.

Exercise Capacity

It has been repeatedly demonstrated that pulmonary rehabilitation including aerobic exercise training of the lower extremities improves exercise tolerance (Fig. 4). Exercise capacity can be measured objectively in the laboratory on a bicycle or treadmill with an incremental maximal test or a steady-state endurance test. During steady-state exercise, declines in oxygen consumption, heart rate, respiratory rate, and minute ventilation and an increase in exercise duration are noted following rehabilitation. Improvement in peak exercise capacity (peak work and oxygen consumption) has also been demonstrated.

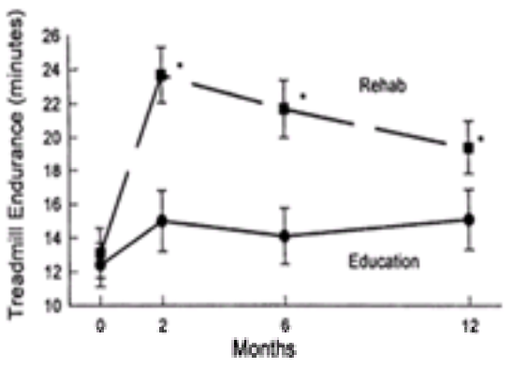

FIG. 4. Self-reported shortness of breath with activities of daily living is improved at 2, 6, and 12 months in patients with COPD randomized to receive comprehensive pulmonary rehabilitation compared to patients receiving education only. (Reproduced by permission from Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiological and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;122:823–832.)

Strength Training

Other forms of exercise, including strength training, have also been employed, but to a lesser extent. Strength training of the upper and lower extremities has been shown to improve dyspnea, mastery, and bicycle exercise endurance time in COPD.

Upper Extremity Training

Training of the upper extremities in COPD is specific for arm function and reduces the increased metabolic demand and ventilation associated with arm elevation and arm work. Upper extremity training does not appear to improve performance in other tests not related to the training such as lower extremity walking or treadmill exercise. In addition, although upper extremity training increases endurance for arm exercise, there is no documented improvement with arm exercise as the sole intervention in activities of daily living. A reduction in perceived dyspnea during upper extremity performance has also been noted. Current recommendations indicate that supported and unsupported upper extremity training should be incorporated into comprehensive pulmonary rehabilitation programs.

Ventilatory Muscle Training

The only modes of respiratory muscle training that increase strength and endurance of the ventilatory muscles are those that achieve an adequate training load, thus emphasizing the importance of the linear resistance characteristics of the training device. With adequate training loads, it appears that endurance and function of the inspiratory muscles are improved when resistance training is performed with controlled flow breathing patterns. However, published studies indicate inconsistent results in other outcomes of inspiratory muscle training. For example, exercise capacity and quality of life are not uniformly improved following inspiratory muscle training in patients with COPD, in part because of the lack of an adequate training stimulus. Ventilatory muscle training may be considered as an adjunctive form of therapy to improve exercise and quality of life in selected patients if an adequate training load can be assured.

Quality of Life

Based on published studies, comprehensive pulmonary rehabilitation should be considered as a therapeutic intervention that improves quality of life (QoL) in patients with chronic obstructive pulmonary disease. Although most studies that have evaluated quality of life have demonstrated improvements following comprehensive pulmonary rehabilitation, not all studies have used standard quality-of-life tools nor controlled randomized study designs. Nevertheless, recent randomized controlled studies employing respiratory disease-specific quality-of-life instruments have documented improved quality of life. However, some studies using general-health quality-of-life measures have not shown improvement in QoL, emphasizing the importance of choosing QoL instruments that are sensitive to change. Improved QoL has been noted for rehabilitation conducted in an outpatient setting, inpatient setting, and in the home.

The precise components of comprehensive rehabilitation that are most responsible for improvement in quality of life are unclear. However, it appears that comprehensive programs that include exercise training may be necessary to achieve improved QoL. Education alone has not been shown to result in significant quality-of-life benefits.

Ability to Work

It is unclear whether pulmonary rehabilitation can assist patients in returning to gainful employment. It is important to emphasize that this is not generally a goal of pulmonary rehabilitation, particularly in patients with more advanced COPD who are generally older and retired because of a combination of age and respiratory symptoms. Pulmonary rehabilitation is generally considered more effective in maintaining employment in younger patients with less advanced disease and thus should be started earlier in the course of COPD. Some investigators have noted a poor compliance with vocational rehabilitation, and others have suggested that vocational rehabilitation success was related to intelligence test scores. Patients with higher IQ levels might have decreased energy requirements in their jobs because of decreased physical demands of employment, thus allowing better vocational outcomes.

Other Outcomes

Little information is available concerning caregiver burden and use of assistive technology outcomes in COPD. Improved self-care ability and decreased need for nursing home care have been reported.

Prediction of Beneficial Outcomes

Although it is tempting to evaluate which patients are most likely to benefit from pulmonary rehabilitation, previous investigations have not consistently been able to identify such individuals. Age and sex do not appear to be predictors of outcome. The ability of baseline functional capacity and airflow limitation to predict outcome are questionable. It has been suggested that patients with less airflow limitation (i.e., a higher FEV_1) are more likely to show improvement with rehabilitation, and thus, rehabilitation should be started earlier in the course of COPD to achieve greater cumulative benefits. However, some studies have demonstrated a greater degree of improvement in walk distance (as measured by percentage increase in walk distance) in patients with the lowest baseline walk distance. Whether these benefits in more functionally limited patients represents the effect of deconditioning or the degree of airflow limitation before rehabilitation was not evaluated.

In the absence of the ability to identify patients most likely to benefit from rehabilitation, and because pulmonary rehabilitation improves dyspnea, exercise capacity, quality of life, and hospitalizations, it is reasonable to enroll patients with dyspnea, reduced exercise capacity, impaired quality of life, and frequent hospitalizations in comprehensive pulmonary rehabilitation.

CONCLUSION

Comprehensive pulmonary rehabilitation programs can improve physiological measures of exercise capacity, functional capacity and health-related quality of life. The variety, diversity, and number of potential outcomes of pulmonary rehabilitation suggest that not all outcomes will be of equal importance for all patients with chronic obstructive pulmonary disease. Based on the nature and needs of the populations and individuals being served, pulmonary rehabilitation programs should determine which outcomes should be the focus for their rehabilitative efforts. Periodic assessment of the outcomes achieved by rehabilitation can be used to modify the rehabilitation program with the goals of improving outcomes and thus enhancing patient care.

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CHAPTER

52 Lung Transplantation

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INTRODUCTION

Lung and heart-lung transplantation have become viable options for end-stage pulmonary parenchymal and vascular diseases over the last decade. Lung transplantation has lagged behind other solid-organ transplantation primarily because of surgical difficulties and inadequacy of immunosuppressive agents. Many of the immediate and short-term postoperative complications have been solved, with many centers reporting 1-year actuarial survival in excess of 70%. This chapter covers important aspects of lung transplantation and includes lessons from the early years as well as current and future challenges facing the transplant community.

HISTORICAL BACKGROUND

The first human lung transplant was reported in 1963 by Hardy in a patient with advanced bronchogenic carcinoma. The recipient died with renal failure 18 days after transplantation. At autopsy there was no evidence of rejection. This case demonstrated the feasibility of the operation and the capability of the allograft to function. After Hardy's experience, approximately 40 lung or lobar transplantations were performed during the next two decades. The longest survivor during this period was a 23-year-old Belgian man with acute silicosis who survived 10 months after one lung was transplanted but spent almost 9 months in the hospital. Bronchial dehiscence and pulmonary sepsis were major causes of mortality in these early cases because of the use of high-dose (1 to 2 mg/kg) corticosteroids. The introduction of cyclosporine A in the early 1980s as an immunosuppressive agent allowed for a reduction in the corticosteroid dose after transplantation. This, together with improvement in surgical technique (by using omental wraps), reduced the incidence of airway complications and resulted in improved early survival after transplantation.

PATIENT SELECTION

One of the most important aspects of lung transplantation is the selection of appropriate patients for the procedure. Basic criteria have been developed enabling the selection of optimal candidates to ensure the best possible chance for survival (Table 1). The criteria cited continue to evolve as experience in this field continues to accrue.

End-stage lung disease (life expectancy <12 to 24 months)
Age <65 for SLT, <55 for BLT[a]
No other significant systemic disease[b]
Medical compliance
Psychological stability, no substance abuse
Ambulatory with oxygen (if required)
No history of malignancy[c]
Adequate social support
Adequate nutrition
Systemic steroids <15 mg prednisone/day

[a] Patients older than 60 must be in exceptional condition.
[b] Patients should not have renal or significant hepatic dysfunction.
[c] If there is a prior malignancy, it must be remote and cured.

TABLE 1. *Selection criteria for transplantation*

Age

Most centers accept patients up to 60 to 65 years of age as candidates for single lung transplantation (SLT). The upper age limit for heart–lung (HLT) and bilateral lung

transplantation (BLT) is 50 to 55 years of age, although these limits are somewhat arbitrary. In general, older patients are more likely to have complicating medical conditions and postoperative complications.

Single Organ Failure

The ideal candidate would have end-stage lung disease as the only medical condition. End-stage liver or renal disease is considered an absolute contraindication to lung transplantation, as these organs are subject to the toxicity of the immunosuppressive agents. Even a mildly elevated creatinine is a concern. More recently, patients with systemic hypertension and diabetes mellitus have been successfully transplanted. These patients should be well controlled with medical management and without any evidence of end-organ damage.

Cancer

A recent history of primary or metastatic pulmonary neoplasm is considered an absolute contraindication to transplantation. This is mainly because of the poor prognosis associated with such malignancies and because of the potential for such malignancies to recur with the use of heavy immunosuppression after transplantation. Patients with a remote history (in excess of 5 years) of extrapulmonary malignancy have successfully undergone lung transplantation.

Corticosteroid Therapy

Most transplant centers accept recipients on low doses of corticosteroids (prednisone 10 to 20 mg/day), as such doses have no significant deleterious effect on short-term survival. However, potential candidates on chronic steroid therapy should be carefully screened for osteoporosis. Evidence of osteoporosis is considered a relative contraindication to transplantation, and most centers exclude patients with severe osteoporosis. The adverse impact of complications associated with osteoporosis on the quality of life after transplantation should not be underestimated.

Functional Status

Most centers require that their recipients be ambulatory and able to undergo rehabilitation in a comprehensive program both preoperatively and postoperatively. Pulmonary rehabilitation programs increase endurance levels as measured by the 6-min walk test. This improvement in endurance may translate to more rapid extubation after transplantation, especially in cases of severe reperfusion injury requiring prolonged mechanical ventilation. However, there are inadequate objective data addressing the results of preoperative rehabilitation on the immediate outcome after transplantation. Successful transplantation of ventilator-dependent patients has been performed by many centers, but this should be performed by experienced teams and in patients who are relatively well nourished and ambulatory.

Chronic Infection

Patients with chronic respiratory tract infections should be carefully screened. High rates of reinfection (after transplantation) with poor survival have been reported when the upper airways of the recipient are colonized with highly resistant bacteria. A common clinical scenario is colonization of a cystic fibrosis patient with highly resistant pseudomonas aeruginosa. Many centers will not list patients if they have resistant pseudomonas, especially if synergy studies do not reveal any potentially useful antibiotic combination. The colonization of recipient airways with *Aspergillus* species is generally not considered a contraindication to transplantation. However, patients with aspergillomas are probably not ideal candidates because of the potential for recurrence after transplantation. Prophylaxis with inhaled amphotericin B or oral itraconazole may have a role in these settings. Uncontrolled extrapulmonary infection is an absolute contraindication to transplantation.

Psychosocial Factors

Active psychosis or drug abuse is a contraindication to transplantation because it would interfere with the recipient's ability to adhere to strict and complicated medication regimens after transplantation. Most programs require strict smoking cessation for 6 to 12 months before consideration for transplantation. Good social support is essential.

Nutritional Factors

Most centers avoid transplanting severely cachectic or obese individuals because of their relatively poor potential for physical rehabilitation after transplantation. Malnourished cystic fibrosis patients may be able to achieve weight gain with percutaneous feeding tubes. However, it is not clear if such a response will result in a significant survival advantage after transplantation.

Previous Chest Surgery

Previous lung biopsy, resection, or violation of the pleural space by pleurodesis is not considered an absolute contraindication to transplantation. These may place the recipients at a slightly increased risk of perioperative bleeding, but this risk is generally not prohibitive. Parietal pleurectomy precludes transplantation on the operated side.

INDICATIONS

The most common indication for SLT is chronic obstructive pulmonary disease (COPD), and cystic fibrosis is the leading indication for BLT (Table 2). Approximately 1500 patients were listed for lung transplantation by 90 centers in the United States in 1994. The median waiting time was 553 days. This compares with 125 patients listed in 1988 with a median waiting time of 386 days (United Network for Organ Sharing, *personal communication*). The waiting time for HLT is usually longer because heart transplant centers compete for organs. Approximately 500 SLT, 300 BLT, and 100 HLT were performed worldwide in 1994.

Chronic obstructive pulmonary disease
Idiopathic pulmonary fibrosis
Cystic fibrosis[a]
Diffuse bronchiectasis
Sarcoidosis
Eosinophilic granuloma
Extrinsic allergic alveolitis
Drug-induced lung disease
Primary pulmonary hypertension[b]
Secondary pulmonary hypertension[b]
Lymphangiomyomatosis

[a] Cystic fibrosis and bronchiectasis ("septic lung disease") require bilateral transplantation to avoid contamination of a new lung by severe infection.
[b] Bilateral sequential transplantation is preferred by many centers for pulmonary hypertension.

TABLE 2. *Examples of end-stage lung disease treated with lung transplantation*

Single lung transplantation is generally applied for emphysema and pulmonary fibrosis. It is also applied, with good results by some centers, for pulmonary vascular disease. A single lung allograft with normal vasculature can accommodate the entire cardiac output without a rise in pulmonary artery (PA) pressure. Most enlarged right ventricles will recover significant function after SLT, mirroring the phenomenon of right ventricular recovery after pulmonary thromboendarterectomy.

The only absolute indication for BLT is bilateral pulmonary sepsis. The presence of severe infection in the remaining native lung precludes SLT. Some centers also perform BLT for severe bilateral bullous emphysema. Bilateral lung transplant is also performed routinely for patients with pulmonary hypertension at many institutions. Either BLT or SLT (with repair of cardiac anomalies) can be applied in patients with Eisenmenger's syndrome unless left ventricular dysfunction is present or the congenital anomaly is not amenable to repair.

Heart-lung transplantation is indicated in a subset of patients with Eisenmenger's syndrome. These patients usually have a surgically irreparable congenital anomaly or

severe left ventricular dysfunction. The HLT allows the transplantation of patients with combined cardiac and pulmonary diseases (Table 3).

Pulmonary vascular or parenchymal disease with associated left ventricular dysfunction[#]
Pulmonary hypertension with irreparable congenital cardiac defect

[#]Even extreme right ventricular dysfunction appears to recover isolated lung transplantation in the vast majority of cases.

TABLE 3. *Indications for heart–lung transplantation*

PATIENT EVALUATION

General Concerns

Lung transplantation is appropriate in patients with irreversible, progressive end-stage pulmonary disease and an estimated life expectancy of 12 to 24 months despite the use of appropriate medical therapy. Certain parameters have been used to predict survival in end-stage lung disease. Such predictors are not necessarily reliable in estimating survival in an individual patient, and clinical judgment is necessary to determine when transplantation is appropriate. In general, patients should be considered for transplantation when they are oxygen dependent, have failed medical therapy, and demonstrate progressive deterioration in their functional status. Because patients are listed according to size and blood type, patients with common blood types such as O may merit earlier listing; many similar patients may precede them on the list.

A typical transplant evaluation appears in Table 4. The general evaluation for potential lung transplant recipients includes a detailed laboratory, radiographic, and consultative evaluation. Computerized tomographic (CT) scanning of the chest is routinely performed to evaluate for evidence of bronchiectasis, extent of bullous disease, and for mediastinal and pleural abnormalities. Measurement of serum creatinine (some centers include creatinine clearance), liver enzyme studies, and serologic tests to determine previous exposure to opportunistic microbes (HIV, CMV, HSV) are routinely performed. Echocardiography is included to detect cardiac anomalies and ventricular dysfunction. Cardiac catheterization is performed in patients over 40 years of age and in those with significant risk factors for coronary artery disease. Nutritional, psychosocial, and physical therapy assessments are also routinely performed.

Testing
Detailed history and physical exam
Chest x-ray, ECG
Pulmonary function with ABG
Differential ventilation–perfusion scan
Radionuclide ventriculography
Two-dimensional echocardiogram
24-hr Holter monitor
Chest CT scan
Bronchoscopy (if indicated)
Right/left heart catheterization (as indicated)
Laboratory testing: Serologies (hepatitis, HIV, EBV, and CMV), ABO blood group, HLA typing, panel reactive antibodies
Consults
Physical therapy
a. 6-min walk test
b. Musculoskeletal assessment
c. Rest/exercise oxygen saturation
Social work
Psychology[#]
Nutrition
Anesthesiology
Pulmonary

[#]Psychiatry evaluation if indicated.

TABLE 4. *Transplant evaluation*

Chronic Obstructive Pulmonary Disease

Postbronchodilator forced expiratory volume in 1 sec (FEV_1) and mean pulmonary artery pressure (PAP) are among the most important parameters used to assess prognosis in patients with COPD who are less than 65 years of age. Patients with a postbronchodilator FEV_1 < 30% of predicted or a mean PAP > 25 mmHg have an estimated 2-year survival of 50% to 60%. However, this survival may be variable; as stated by Burrows in his 1979 report, “The variability in survival should cause clinicians to be cautious when discussing longevity with their patients.” Usually patients who are transplanted have an FEV_1 less than 20% of predicted.

Pulmonary Fibrosis

Patients with idiopathic pulmonary fibrosis (IPF) generally have a median survival of 5 years from the time of diagnosis. However, their rate of progression may be variable. These patients tend to have the highest mortality while awaiting transplantation. Patients with lung volumes < 50% of predicted and diffusing capacity values < 40% are unlikely to survive more than 2 years. These patients should be referred for lung transplantation evaluation as soon as medical therapy fails, particularly when the oxygen requirement begins to increase.

Cystic Fibrosis

The mean survival of patients with cystic fibrosis is approximately 30 years of age. The FEV_1 is probably the most reliable parameter in predicting 2-year survival. Patients with FEV_1 < 30% of predicted have an average 2-year survival of 50%. Other ominous features in patients with cystic fibrosis are hypercapnia and increasing hospitalizations in the previous 1 to 2 years. Once on the transplant list, they should be encouraged to remain ambulatory and to emphasize nutrition. Patients with panresistant *Pseudomonas aeruginosa* or *Burkholderia cepacia* tend to have a poor outcome after transplantation because of the increased mortality associated with the recurrence of these organisms.

Pulmonary Hypertension

Patients with pulmonary vascular disease include those with primary pulmonary hypertension (PPH), those with congenital heart disease and associated secondary pulmonary hypertension, and certain patients with severe parenchymal lung disease such as COPD, sarcoidosis, and IPF. This feature needs to be considered when patients are listed and transplanted. Patients with PPH have a mean survival of 2.7 years from the time of diagnosis. Right atrial pressure, cardiac index, and mean PAP have been used to predict survival in this population. Patients with right atrial pressures > 16 mmHg, cardiac index < 2 L/min per m^2, and mean PA pressures > 80 mmHg have an estimated 2-year survival of 30%. Patients with such indices should be promptly referred for transplantation because of their poor prognosis without transplantation. Patients with right atrial pressure < 12 mmHg, cardiac index > 2 L/min per m^2, and mean PAP < 60 mmHg have an estimated 2-year survival of approximately 70%, comparable to the 2-year actuarial survival after lung transplantation. These patients should be followed closely and referred for transplantation at the earliest signs of progressive right ventricular failure. Calcium channel blocker therapy is generally utilized early. Prostacyclin therapy is now much more commonly used for PPH and has been shown to improve exercise tolerance and survival. Patients on prostacyclin therapy may be observed very carefully, with listing and transplantation occurring when survival is deemed limited. Unlike PPH, there are no clear predictors of survival in secondary pulmonary hypertension. In this subgroup, the level of debility may be the most important factor when considering referral.

SURGICAL TECHNIQUE AND INTRAOPERATIVE CONSIDERATIONS

The surgical technique for SLT and BLT has evolved substantially, as have intraoperative and postoperative management. The patient undergoing lung transplantation requires rigorous intraoperative hemodynamic monitoring because of the substantial alterations in ventilation, perfusion, ventricular filling pressures, and pulmonary function that take place during the operation. Monitoring via a pulmonary artery catheter and peripheral arterial line together with pulse oximetry and end-tidal CO_2 monitoring facilitate management. Transesophageal echocardiography permits continuous assessment of right ventricular function which is useful in determining the need for cardiopulmonary bypass. A double-lumen endotracheal tube is generally in place during transplantation and removed prior to transfer to the surgical intensive care unit.

Single Lung Transplantation

The Toronto group was the first to perform SLT in humans with successful short-term results. This procedure was accomplished through a standard lateral thoracotomy incision and did not require cardiopulmonary bypass. An end-to-end bronchial anastomosis was wrapped with omentum tunneled up through the diaphragm. The pulmonary artery was directly reanastomosed, and a cuff of the donor's left atrium (containing the pulmonary veins) was connected to the recipient's left atrium. Veith demonstrated in dogs that a telescoping bronchial anastomotic connection was associated with a lower incidence of bronchial dehiscence. This procedure is accomplished by pulling either the donor or recipient bronchus inside the other and suturing them together. Since first being performed by the San Antonio group, it has been widely adopted. With this technique, omentopexy became unnecessary for bronchial healing. The SLT procedure is performed via a posterolateral thoracotomy and is considered acceptable for all pulmonary disease requiring transplantation except cystic fibrosis and other septic lung disease. Many centers also prefer bilateral lung transplantation for pulmonary hypertension.

Bilateral Lung Transplantation

Double lung tranplantation was developed for patients with chronic pulmonary sepsis or emphysema associated with severe bilateral bullous disease. The procedure was perfected in dogs via median sternotomy. The donor lungs were transected at the level of the distal trachea and were removed en bloc with the main pulmonary artery and a large left atrial cuff. Because of the high incidence of tracheal anastomotic complications as well as bleeding complications and poor exposure to the posterior mediastinum, bilateral sequential SLT was performed by the Washington University group. The incision was changed from median sternotomy to anterior thoracosternotomy (the “clam shell” incision). The lungs were thus implanted as two single lungs with separate vascular and bronchial anastomoses. This procedure generally eliminates the need for cardiopulmonary bypass.

Heart–Lung Transplantation

The technique of HLT was first described by the Stanford group. The airway anastomosis is at the distal level of the trachea, and the vascular anastomoses are at the right atrium and aorta. Some transplant centers wrap the distal trachea with omentum. The domino procedure allows the heart of the intended heart–lung recipient to be removed and used as a donor heart, which may improve the donor heart supply.

Living-Related Lobar Transplantation

This technique has been applied primarily in children because of the small donor pool. Donation of a lobe from a living relative has been proposed as a life-saving procedure, with minimal risk to an otherwise healthy donor. Despite the potential immunologic advantage of a related donor, the complication rate has not been shown to be significantly less than with unrelated donors. Bilateral lower lobe living-related implantation has been performed predominantly in CF patients by Starnes and colleagues at the University of Southern California. Potential cases are carefully reviewed with ethical considerations a prime concern.

DONOR SELECTION

In the setting of brain death, the lung is particularly susceptible to injury from hemodynamic instability, noncardiogenic pulmonary edema, or aspiration. Thus, procurement of acceptable lungs for transplantation is more difficult than for other solid organs. At the present time, cold ischemic times of up to 6 hr appear to be well tolerated. Ideal donor characteristics include an insignificant smoking history, ABO compatibility, a PO_2 > 300 mmHg on 100% inspired oxygen and 5 mmHg of positive end-expiratory pressure (PEEP), a clear chest radiograph, and absence of purulent secretions at bronchoscopy. Size matching is estimated from the chest radiograph using vertical (apex to diaphragm at midclavicular line) and horizontal (level of dome of diaphragm) measurements. Oversizing is better tolerated in SLT than in BLT. The increased demand for donor lungs together with increased experience has led to the use of donor lungs previously judged unsuitable. Minimal pulmonary infiltrates, borderline oxygenation, or secretions that can be easily cleared by bronchoscopy may not contraindicate donation. Such cases need to be individualized.

POSTOPERATIVE CONSIDERATIONS

The postoperative course in the lung transplant patient is often determined by the operative procedure, the need for cardiopulmonary bypass, and the underlying pulmonary disease. Patients without pulmonary hypertension undergoing SLT tend to require minimal hemodynamic and ventilatory support, which can often minimize the intensive care unit length of stay and allow discharge from the hospital within 7 to 10 days. A number of events may complicate the postoperative course. Routine postoperative care as well as issues specific to the lung transplant patient are important to address.

After transfer from the operating room to the surgical intensive care unit, the lung transplant recipient is managed by a multidisciplinary team including the transplant surgeons, the critical care nursing staff, the transplant coordinators, the transplant pulmonologist, physical and respiratory therapists, and nutritionists. Infectious disease specialists are often involved. Routine early postoperative care includes careful monitoring of vital signs, accurate documentation of intake and output, daily chest radiographs, and laboratory analysis including cyclosporine or tacrolimus levels. The serum creatinine must be monitored particularly closely because attempts at keeping the patient relatively intravascularly volume depleted together with the use of nephrotoxic immunosuppressive agents and antibiotics may have adverse effects on renal function. Patients always have a pulmonary artery catheter and arterial line in place on arrival from the operating room. A postoperative perfusion scan is performed to detect pulmonary artery anastomotic abnormalities and thrombosis. Venous thromboembolism and gastrointestinal prophylaxis as well as adequate pain management are crucial. Placement of an epidural catheter for analgesia is frequently beneficial and facilitates early postoperative ambulation and physical therapy. Nutrition should be addressed early, particularly in patients with cystic fibrosis. Enteral tube feeding should be initiated early if a patient is unable to be fed orally within a few days. If postoperative ileus prevents this, then total parenteral nutrition should be administered.

Hemodynamic Management

Optimal hemodynamic management is essential after lung or heart–lung transplantation. Because the lymphatic drainage of the lung has been interrupted during transplantation, and because of capillary damage from ischemia and preservation injury of the transplanted lung(s), there is susceptibility to pulmonary edema formation. Early rejection or infection may also contribute. The reimplantation response may result in severe noncardiogenic pulmonary edema and requires aggressive diuresis, cautious use of PEEP, and, in the SLT patient, positioning the affected lung up. Independent lung ventilation has been used when pulmonary edema is severe and the lungs have markedly differing compliances.

Patients with pulmonary hypertension undergoing SLT present particular difficulties, and cardiopulmonary bypass is usually required. These individuals often develop reperfusion edema from the tremendous diversion of blood flow to the new lung. This may result in extreme hemodynamic instability. Discontinuing chronic continuous prostacyclin therapy may result in an acute increase in right ventricular afterload. Weaning of this medication is often delayed until the patient is more stable in the intensive care unit. The early postoperative course is generally notable for labile pulmonary arterial and systemic pressures requiring vasopressor and inotropic agents, and paralysis is often required in addition to heavy sedation. Prostaglandin E may also contribute to hemodynamic stability. Thus, patients are kept relatively intravascularly volume depleted, and diuretic and vasoactive medications are used liberally, but with careful monitoring. Extreme volume depletion is avoided to protect renal function and to minimize bronchial anastomotic ischemia. When BLT is performed in patients with pulmonary hypertension, hemodynamic management is less difficult.

Mechanical Ventilation

Management of the ventilator after transplantation depends on the underlying disease, the operative procedure, and the stability of the patient. In COPD patients undergoing SLT, minimal or no PEEP and lower tidal volumes are utilized to minimize overdistention of the more compliant native lung. The latter phenomenon can result in lung herniation with mediastinal shift. Occasionally, replacing the double-lumen tube to permit separate lung ventilation or even volume reduction surgery on the native lung may be helpful. In SLT recipients with underlying pulmonary fibrosis, low tidal volumes and flow rates may help to avoid barotrauma in the stiff native lung.

Bronchoscopy

Examination of the airways is performed in the operating room and again before extubation to evaluate the anastomoses. In patients requiring prolonged mechanical ventilation after transplantation, frequent bronchoscopy may be required for clearance of secretions and to obtain microbiological specimens. Impairment of the cough reflex may suggest the need for bronchoscopy as often as daily in some patients during the intensive care unit stay. Aggressive physical therapy is crucial after transplantation. Incentive spirometry, chest physical therapy, frequent turning, and early ambulation are emphasized.

Infection Prophylaxis

Protocols for infection prophylaxis are routinely utilized for bacterial, CMV, *Pneumocystis,* and *Toxoplasma* infections. Certain patients may benefit from fungal prophylaxis as well. Patients with cystic fibrosis undergo periodic preoperative sputum culture analysis to allow appropriate postoperative antibiotic administration. Synergy studies are often useful in determining appropriate antibiotic combinations. Because CMV is such a frequent pathogen after transplantation, most programs utilize prolonged prophylaxis, particularly in CMV-seronegative recipients receiving CMV-positive lung grafts. Such prophylaxis will delay but not necessarily prevent the development of CMV infection.

IMMUNOSUPPRESSION

Cyclosporine A has served as the cornerstone for immunosuppression after lung transplantation. An oral dose may be administered 4 hr before surgery, followed by a postoperative intravenous infusion at 3 to 4 mg/hr and adjustment to 250 to 300 ng/ml using the high-pressure liquid chromatography assay. When adequate blood levels are achieved and the gastrointestinal tract is functional, oral cyclosporine is initiated every 12 hr. A number of agents can affect cyclosporine levels and need to be considered. This drug is metabolized by cytochrome P_{450} IIIA, and inhibitors of this enzyme such as fluconazole and itraconazole may significantly increase cyclosporine levels. Diltiazem may be useful in treating posttransplant hypertension as well as lowering the required dose of cyclosporine. Erythromycin also increases cyclosporine levels. Adverse effects of this immunosuppressive agent include nephrotoxicity, hypertension, hypertrichosis, gastrointestinal disturbances, neurotoxicity, gingival hypertrophy, hyperglycemia, and hyperkalemia. Tacrolimus is being used increasingly instead of cyclosporine after lung transplantation. Less data is available for lung allografts than in liver or kidney transplantation. This immunosuppressive agent bears no chemical resemblance to cyclosporine but exhibits similar activity. It is also metabolized by cytochrome P_{450} IIIA, and, as with cyclosporine, certain drug interactions can be expected. Nonsteroidal antiinflammatory drugs should be avoided in patients on either agent in view of nephrotoxicity. The principal adverse effects include nephrotoxicity, neurotoxicity (including headache, insomnia, and tremor), gastrointestinal disturbances, hyperglycemia, hyperkalemia, and hair loss. Anaphylaxis has been reported with this drug as well as with cyclosporine.

Azathioprine is initiated preoperatively at a dose of 2 mg/kg and is adjusted downward for a white blood cell count of 5000 or less. We administer methylprednisolone as 500 mg intravenously before reperfusion of the transplanted lung followed by 125 mg every 12 hr for 48 hrs. It is then given as 20 mg/day until oral prednisone can be taken. The latter is tapered to 10 mg/day over the first 6 months. Mycophenolate, a morpholinoethylester of mycophenolic acid, has been used to replace azathioprine. More data in the setting of lung transplantation will more clearly define the role of this drug. Induction immunosuppression with T-cell-lytic therapy such as OKT-3, ATGAM, or RATG is utilized by some groups. Although there may be the potential benefit of a reduced incidence of graft rejection, these agents increase the incidence of infections and lymphoproliferative disorders.

POSTOPERATIVE COMPLICATIONS

Acute Rejection and Graft Dysfunction

Rejection may be manifested by such nonspecific findings as low-grade fever, worsening oxygenation, reduction in the FEV_1, and by the presence of pulmonary infiltrates. Reduced air flow may be the only manifestation. Early after transplantation, infection is excluded and treatment is instituted with intravenous methylprednisolone (bolus of approximately 500 mg daily for 3 days). A clinical response suggests a correct diagnosis, but continued observation for infection is prudent. Possible rejection after the first few weeks is determined by more objective parameters (see “Long-Term Follow-Up”).

Early graft dysfunction appears to be related to ischemia/reperfusion injury and presents as abnormal gas exchange in the absence of infection or rejection. This is addressed with supportive therapy and exclusion of the latter complications.

Infectious Complications

Infections remain the most frequent complication after lung transplantation. The incidence of bacterial pneumonia is highest within the first 4 weeks, and many centers practice routine bacterial prophylaxis for the first 5 to 7 days after transplantation. The organisms frequently involved include *Staphylococcus aureus* and gram-negative bacilli. *Pseudomonas* infections commonly occur after BLT for cystic fibrosis. In SLT recipients, pneumonias generally arise in the transplanted lung. Bronchoscopy is frequently used in the setting of pneumonia after transplantation unless clearly adequate sputum samples are obtained.

Fungal infections account for substantial morbidity and mortality after lung transplantation. *Candida* and *Aspergillus* species account for the majority of these infections, but nearly all other common and many unusual pathogens have been described. The respiratory tract, gastrointestinal tract, intravascular catheters, and donor organ may all serve as potential sources of infection. Treatment should be aggressive, particularly early after transplantation. Fluconazole, itraconazole, and amphotericin B (inhaled and intravenous) are often utilized, and continued efforts are necessary to determine appropriate prophylactic and therapeutic protocols.

Cytomegalovirus infections occur commonly in the posttransplant setting and may range from asymptomatic presence on immunostained surveillance biopsies or bronchoalveolar lavage specimens or cultures to severe pneumonitis resulting in death. Less severe infections are far more common. A common scenario includes malaise, myalgias, low-grade fever, and leukopenia. Infections with CMV generally do not appear before 30 days and are further delayed with appropriate prophylaxis. More frequent and severe CMV disease occurs in CMV-negative recipients receiving CMV-positive lungs. Ganciclovir is administered at 5 mg/kg twice daily (adjusted for renal function), and outcome is generally good. Intravenous immunoglobulin for CMV has been recommended in high-risk patients by some centers. Other viral infections such as adenovirus and respiratory syncytial virus may occur and may be severe.

Airway complications are relatively common after lung transplantation. Early success in lung transplantation was marred by frequent anastomotic complications, generally related to ischemia. Immediately postoperatively, the donor bronchus is relatively ischemic and relies on retrograde flow from the pulmonary artery. Collateral flow from the bronchial circulation develops over the first several weeks. Significant ischemia can lead to bronchial necrosis with airway collapse and/or stricture formation. Bronchomalacia or stenosis may require stent placement. Silicone and metal stents have been used with success, with an increasing trend toward the use of expanding metal stents. Balloon dilation may be utilized before stent placement. In the absence of bronchomalacia, dilation alone may be sufficient. Fungal infections frequently involve the anastomotic site and are aggressively treated with systemic antifungal agents. Nebulized amphotericin B has been used as adjuvant therapy in this setting to provide direct administration to the airway.

Gastrointestinal complications occur frequently after lung transplantation. An extremely frequent syndrome consists of nausea and bloating with gastroparesis occurring over the first month after surgery. The necessary polypharmacy in transplant patients (particularly cyclosporine and tacrolimus) may contribute significantly, and the syndrome is clearly not caused solely by vagotomy. Treatment with metoclopramide, cisapride, or domperidone may help but often does not lead to complete resolution. Feeding tubes are often temporarily required. Patients with cystic fibrosis may develop distal intestinal obstruction syndrome leading to constipation and abdominal distention. Gastrointestinal bleeding of various causes and diverticulitis may occur after lung transplantation. Diarrhea may develop from infection (commonly with *Clostridium difficile*) or as a result of tube feeding or antibiotics.

Other complications occurring after transplantation include cardiac arrhythmias, venous thromboembolism, steroid-induced osteoporosis, mild anemia, hyperlipidemia, and hyperglycemia. Hypertension is an extremely common result of cyclosporine use and should be treated aggressively. Recurrence of native lung disease has been reported in sarcoidosis, lymphangiomyomatosis, and diffuse panbronchiolitis. Recurrence of other underlying pulmonary disease has not been described.

LONG-TERM FOLLOW-UP AND LATE COMPLICATIONS

Before discharge, extensive postoperative teaching takes place, and at discharge patients are immediately enrolled in pulmonary rehabilitation for 1 month and are followed closely. They are encouraged to continue a regular exercise program. Daily incentive spirometry is recommended by many programs as well as daily diagnostic microspirometry. A persistent decrease in the FEV_1 by more than 10% over several days, although not specific, should arouse suspicion for acute rejection. Standard pulmonary function testing is performed frequently, and a decrease in the forced expiratory flow over the midportion of the vital capacity maneuver ($FEF_{25–75}$) may be even more sensitive than the FEV_1 for acute rejection, although less specific. After the first month, acute rejection is less likely to be radiographically apparent

than it is earlier in the course. Transbronchial biopsies together with bronchoalveolar lavage are performed routinely at Duke University Medical Center at 1, 3, 6, and 9 months after transplantation. Thereafter, patients without previous rejection or CMV infection do not appear to benefit. It remains to be definitively proven whether or not even the early surveillance bronchoscopies are advantageous over close clinical follow-up. When rejection is diagnosed, episodes of grade 2 (mild) or higher are treated with bolus steroid therapy, which is often followed by a tapering oral regimen over 10 to 14 days. Continued frequent monitoring of cyclosporine or acrolimus levels is crucial. Serum CMV antigen samples may be sent for analysis at periodic intervals, but the specificity and sensitivity remain to be determined.

Obliterative Bronchiolitis

The major impediment to long-term survival after lung transplantation is obliterative bronchiolitis (OB). The OB syndrome is defined clinically by graft deterioration characterized by progressive obstructive airways dysfunction for which there is no other proven cause. Entities to be excluded include bronchial stenosis or other airway complications, infection, reversible airway reactivity, congestive heart failure, and other pleural or pulmonary parenchymal disease. The condition initially appeared to be confined to HLT patients but clearly occurs in SLT and BLT patients. It may occur in as many as 50% of patients with a mortality of between 29% and 50%.

The pathogenesis of OB is unknown, but the data available suggest that it is an immunologically mediated process directed against the airway epithelial cells and is presumably a manifestation of chronic rejection. Patients with an unexplained FEV_1 decline of 20% or more compared with previous baseline studies are considered to have OB. The $FEF_{25–75}$ may be a more sensitive marker for OB but is a less specific parameter. Chest CT scanning with expiratory views to evaluate for air trapping may be useful, but the precise sensitivity and specificity remain to be defined. Bronchiectasis may also be detected by chest CT suggesting OB. Because the yield of transbronchial biopsy is generally low for OB, and because open lung or thoracoscopic biopsy procedures are invasive, pulmonary function testing together with exclusion of other diagnoses remains the accepted diagnostic approach. This disorder has been reported as early as the second month after transplantation but generally appears between 6 months and 2 years after the procedure. The clinical course may be rapidly progressive or insidious. Some patients may deteriorate rapidly with a subsequent stabilization of lung function. Therapy for this disorder has proven frustrating, with augmentation of immunosuppression and retransplantation the primary modalities. Augmentation of steroid therapy or changing from cyclosporine to tacrolimus and/or from azathioprine to mycophenolate are generally considered, but prospective, randomized trials remain to be completed.

A recent multicenter study of retransplantation for OB has documented a 1-year survival of approximately 43% and 2-year survival of 35% in 72 patients in whom a second transplant has been performed.

Posttransplant Lymphoproliferative Disease

This entity develops in fewer than 10% of recipients and often presents as low-grade fever with fatigue and weight loss with radiographic changes involving the transplanted lung. The syndrome results from proliferation of Epstein-Barr-infected donor B lymphocytes. It develops more commonly in the setting of intense immunosuppression, with Epstein-Barr virus donor seropositivity and in seronegative recipients. Patients may respond transiently to a reduction in immunosuppression, but allograft rejection may then increase in incidence. Conventional chemotherapy has been utilized. The incidence of other malignancies is probably increased, as has been shown in other solid-organ transplants. The skin should be regularly inspected.

OUTCOME AND SURVIVAL

Exercise tolerance is generally markedly improved after SLT, BLT, and HLT. Objective measurements, such as the 6-min walk test, are slightly better after BLT than after SLT. Pulmonary function testing reveals marked improvement, with BLT recipients improving more than SLT patients and attaining essentially normal spirometric values. The arterial oxygenation generally returns to normal or near normal after transplantation. Maximum oxygen consumption increases substantially after the procedure but remains below normal in most cases. Pulmonary artery pressure decreases dramatically, and right ventricular function improves substantially, after transplantation for pulmonary hypertension.

The average 1-year actuarial survival after SLT is approximately 70%, with a 4-year actuarial survival of 42%. This statistic includes all lung transplants performed worldwide. However, many centers are reporting a 1-year actuarial survival in excess of 80%. The average 1-year actuarial survival after BLT is 67%, with the 4-year survival being 47%. HLT has a 1-year actuarial survival of 56% and a 10-year survival of 20%. Obliterative bronchiolitis is a major determinant of long-term survival.

THE FUTURE

Lung transplantation offers an option for patients with end-stage lung disease meeting certain rigid criteria. It should be performed at centers with considerable expertise. The major factor preventing lung transplantation is the limited supply of adequate donors. Extensive efforts are being made to research preservation methods to allow more prolonged donor ischemic times. New immunosuppressive medications are on the horizon, as are new methods to diagnose and treat common infections such as CMV.

Lung volume reduction surgery is an alternative in carefully selected patients with COPD and severe hyperinflation particularly older patients in whom lung transplantation is not an option. The donor cell chimerism occurring naturally after lung transplantation has been suggested to reduce the incidence of obliterative bronchiolitis. In view of this, donor bone marrow cell infusions have been administered during lung transplantation with demonstration of donor cell chimerism in the peripheral blood of the majority of recipients. Such efforts may lead to better understanding of graft acceptance. Xenotransplantation offers another alternative, with perhaps pig-to-human transplantation being the most realistic option. There is some evidence that the lung xenograft may be less susceptible to hyperacute rejection (a significant barrier to xenotransplantation) than the heart or kidney.

It is our hope that future efforts will lead to more efficient use of donor organs, improved graft acceptance with lower toxicity, and a reduction in infectious complications. Lung transplantation remains an exciting and evolving realm of medicine.

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CHAPTER

53 Rheumatologic Diseases

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INTRODUCTION

The rheumatologic diseases encompass a variety of connective tissue disorders, collagenoses, autoimmune diseases, and vasculitic syndromes. Respiratory complications in vasculitic syndromes are discussed in Chapter 54. The majority of rheumatologic diseases have no known etiologic factors even though the inflammatory processes in most of these diseases are immunologically mediated and manifested by the presence of various autoantibodies, rheumatoid factor, immune complexes, elevated erythrocyte sedimentation rate, and certain clinical characteristics. Genetic predisposition, environmental factors, and exposure to chemicals may play significant roles in the etiology of many of these diseases. As a general rule, the histologic changes are nonspecific in the majority of rheumatologic diseases. Clinical features are as diverse as are the organ systems involved by these disorders. In disorders such as systemic lupus erythematosus, multiple criteria are necessary to establish the diagnosis. Although secondary vasculitis is present in the pathologic specimens obtained from patients with these disorders, they are not usually considered primary vasculitides. At times, however, it becomes difficult to separate the vasculitides from rheumatologic diseases.

In each of the rheumatologic disorders discussed below, it is common for one major organ system to be affected to a greater extent than others. Not infrequently, pulmonary manifestations are the major complications. Indeed, it is common to see the pulmonary manifestation as the presenting symptom or sign of many rheumatologic diseases. Herein are described the pulmonary manifestations in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma or systemic sclerosis (SSc), polymyositis-dermatomyositis (PM-DM), mixed connective tissue disease (MCTD), Sjögren's syndrome, and relapsing polychondritis (RPC). For detailed definitions, criteria for classification, and nonpulmonary manifestations of various rheumatologic diseases, the reader is referred to a standard textbook of rheumatology or the *Primer on Rheumatic Diseases* published by the Arthritis Foundation.

SYSTEMIC LUPUS ERYTHEMATOSUS

Lupus is a disorder of unknown etiology characterized by immunologically mediated inflammation that affects multiple organs, including the skin, musculoskeletal, renal, and central nervous systems, and by the presence of multiple autoantibodies in the serum. Clinical criteria necessary to establish the diagnosis of SLE have been published by the American Rheumatologic Association. Almost any organ system can be affected by the disease. Pleuropulmonary complications occur in 50% to 60% of patients with SLE, a higher percentage than in any other rheumatologic disease. Intrathoracic complications described in SLE are listed in Table 1. Histopathologic abnormalities in pleuropulmonary tissues are nonspecific. Many of the pathologic lesions are not caused by SLE itself but by secondary factors such as secondary vasculitis, congestive cardiac failure, infection, aspiration, and drug-induced pulmonary complications.

Pleurisy with or without pleural effusion
Lupus pneumonitis
Shrinking lung syndrome (atelectasizing pneumonitis)
Interstitial pneumonitis and fibrosis
Lymphocytic interstitial pneumonitis
Pulmonary alveolar hemorrhage
Diaphragmatic dysfunction
Respiratory infections
Pulmonary edema
Obstructive lung disease
Bronchiolitis obliterans with organizing pneumonia (BOOP)
Pulmonary vasculitis including capillaritis
Pulmonary thromboembolism
Pulmonary venoocclusive disease
Pulmonary hypertension
Acute reversible hypoxemia
Upper airway disease (epiglottitis, subglottic stenosis, laryngeal edema, vocal cord paralysis, and cricoarytenoid arthritis)

TABLE 1. *Pulmonary complications in systemic lupus erythematosus*

Pleural Involvement

Pleurisy is the most common and often the presenting manifestation of SLE. Pleural abnormalities have been found in 50% to 83% of autopsies in patients with SLE. However, a prospective study of 34 patients with SLE who underwent high-resolution chest CT concluded that pleural abnormalities are less common than previously suggested. Pleural effusions are more frequent in older patients and in patients with drug-induced SLE. Histopathologic changes in the pleura are nonspecific and include infiltration by lymphocytes, mononuclear cells, and plasma cells along with various degrees of fibrosis. Pleuritic pain caused by pleurisy may be the first symptom in up to 50% of patients. Patients, particularly young women, who present with pleurisy or pleural effusion should be evaluated for SLE. An important differential diagnosis in such patients is pulmonary embolism because patients with SLE have a higher incidence of pulmonary thromboembolism (see below). Pleuritic pain may be unilateral or bilateral and is usually located at the costophrenic margins. Pleural effusions are small to moderate, bilateral in 50% of patients, occasionally associated with small pericardial effusion, and frequently accompanied by dyspnea, cough, and fever (Fig. 1). Large pleural effusions are rare. Other reasons for the development of pleural effusions in a patient with SLE include pulmonary embolism and infarction, lupus-induced nephrotic syndrome, or pleuropulmonary infection.

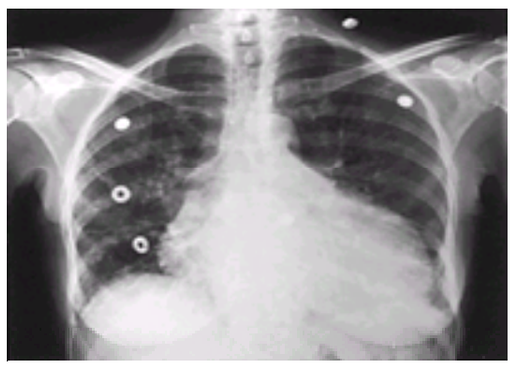

FIG. 1. Chest roentgenogram demonstrates a large pericardial effusion, blunting of the left costophrenic angle, and patchy pulmonary infiltrates in a patient with systemic lupus erythematosus.

Thoracentesis is not indicated in all SLE-induced pleural effusions unless the cause of effusion is in doubt. The pleural fluid is clear or serosanguineous. Grossly bloody effusions are uncommon. The fluid is usually an exudate with a mild to moderate increase in leukocytes. The total and differential leukocyte counts in SLE-associated pleural effusion are nonspecific. The glucose level is usually normal (greater than 60 mg/dl). Decreased levels of total hemolytic complement as well as of C3 and C4 components of the complement and increased immune complexes in the pleural fluid are useful diagnostic tests of SLE-induced pleurisy. Decreased levels and, occasionally, undetectable levels of complement components, observed in nearly 80% of lupus effusions, have been used to corroborate the diagnosis of lupus pleuritis, although similar findings can be found in pleural effusion caused by rheumatoid arthritis and other disorders. The presence of antinuclear antibody in the pleural fluid is nondiagnostic. Likewise, the diagnostic role of immune complexes in SLE-induced pleural effusion is unclear. Lupus erythematosus cells (LE cells) have been found in zero to more than 85% of lupus effusions. The presence of LE cells in pleural effusion is characteristic of SLE-induced effusion and has not been described in other conditions except in pleural effusion caused by drug-induced SLE. Pleural biopsy is rarely required because histologic findings are nonspecific.

Acute Lupus Pneumonitis

Acute lupus pneumonitis has been described in several publications. The syndrome, however, is distinctly uncommon and is usually accompanied by other manifestations of SLE. In two large series of 150 and 207 patients, the incidence of acute lupus pneumonia was 9.3% and 1.4%, respectively. The immediate postpartum period is reported to increase the risk for the development of acute lupus pneumonitis. The pathophysiology of acute lupus pneumonitis involves deposition of immune complexes in blood vessels and alveolar walls with or without associated vasculitis. Acute lupus pneumonitis mimics acute lung infection. Clinical features of acute lupus pneumonitis include acute onset of dyspnea, high fever, and cough with occasional hemoptysis. Physical findings are minimal unless hypoxia leads to cyanosis. Mild to moderate leukocytosis, an elevated erythrocyte sedimentation rate, and significant hypoxemia are noted. Chest roentgenogram may reveal unilateral or bilateral localized, diffuse, or patchy lung infiltrates, predominantly in the lower-lung zones, with small pleural effusions (Fig. 2). Morphologic features of lupus pneumonitis consist of nonspecific changes such as interstitial pneumonia, edema, and arteriolar thrombi. Vasculitis of major vessels is distinctly uncommon. Lung tissue culture for pathogenic organisms is negative. Because respiratory infections and other nonspecific pulmonary parenchymal abnormalities are common in these patients, a diagnostic bronchoalveolar lavage is recommended to exclude an infectious process. The diagnosis of lupus pneumonitis is one of exclusion. The chronic form of lupus pneumonitis produces patchy interstitial processes leading to dyspnea on exertion and nonproductive cough. Lung biopsy is seldom necessary.

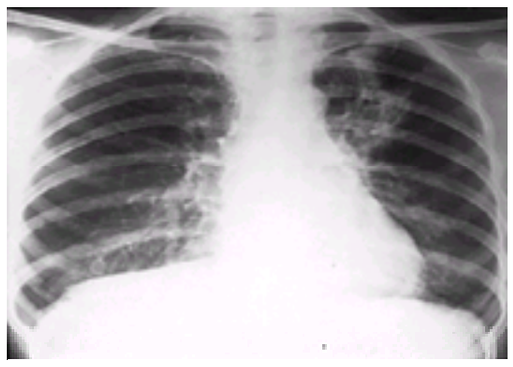

FIG. 2. Lupus pneumonitis involving left upper-lobe segment. This entity is very rare.

Pulmonary Hemorrhage

Pulmonary hemorrhage is a serious and frequently fatal complication of SLE. Pulmonary hemorrhage was observed in 1.6% of 750 patients with SLE and was the primary cause of death in 14.4% of 76 autopsy cases of SLE collected over a period of 20 years. In another series of 57 patients with SLE, pulmonary hemorrhage was the cause of death in 10.5%. It is clear that acute pulmonary alveolar hemorrhage is a common cause of mortality in patients with SLE. Pulmonary hemorrhage is likely mediated by activation of the complement system and leukocytes, the latter attracted by immune complex deposits in the lungs. Disruption in the integrity of alveolocapillary basement membrane leads to hemorrhage. Presence of uremia, bleeding diathesis, oxygen toxicity, and infection increase the risk of pulmonary

hemorrhage. Pathologic features in SLE-induced lung hemorrhage are similar to those in lupus pneumonitis. Vasculitis of small vessels can be seen.

Pulmonary hemorrhage is more common in patients with active and progressive SLE. Pulmonary hemorrhage can be the presenting feature of SLE. Pulmonary hemorrhage can be subclinical or massive. Renal failure caused by SLE enhances the risk of lung hemorrhage. Significant hemoptysis is noted in 8% to 15% of patients. The onset of hemoptysis and progressive respiratory distress can be abrupt, and the clinical presentation frequently resembles that of acute lupus pneumonitis. Chest roentgenograms usually reveal bibasal, patchy, alveolar infiltrates (Fig. 3). Bronchoscopy may help visualize diffuse bleeding from segmental bronchi, and the effluent from bronchoalveolar lavage will be bloody throughout the procedure. A diagnostic bronchoalveolar lavage is likely to show a large number of hemosiderin-laden macrophages, although this finding by itself is not diagnostic. Chronic subclinical pulmonary alveolar hemorrhage occurs less commonly than the acute variety and may occur intermittently. Chronic subclinical pulmonary alveolar hemorrhage may lead to a clinical and pathologic picture of pulmonary hemosiderosis.

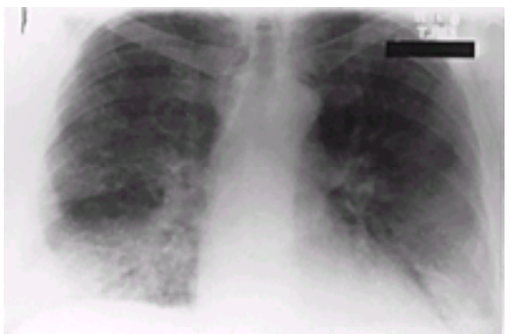

FIG. 3. Pulmonary alveolar hemorrhage in a patient with systemic lupus erythematosus and severe renal involvement. Alveolar infiltrates are basal and patchy in distribution.

Death frequently occurs within the first several days of SLE-induced pulmonary hemorrhage. Massive lung hemorrhage requires emergent treatment to prevent respiratory failure. The initial therapy may require supplemental oxygen, endotracheal intubation and ventilation, and bronchoscopy. The medical treatment consists of high-dose (1.5 to 2.0 mg/kg/day) corticosteroid therapy supplemented by a cytotoxic agent such as cyclophosphamide (2 mg/kg/day). However, this treatment protocol has been of only limited value. Plasmapheresis should be strongly considered in SLE patients with severe or life-threatening pulmonary hemorrhage.

Interstitial Pneumonitis

Extensive interstitial fibrosis, as encountered in patients with RA and SSc, is rarely observed in patients with SLE. The prevalence of a diffuse interstitial process in SLE is about 3%. Patchy and irregular areas of nonspecific interstitial pneumonitis and fibrosis develop in 15% to 45% of patients (Fig. 4). Lung biopsy specimens subjected to immunofluorescent stains for IgG may show patchy and lumpy staining of the alveolar basement membrane (Fig. 5). Clinically, patients commonly pre sent with insidious onset of chronic nonproductive cough, dyspnea on exertion, and recurrent pleuritic pain. Less commonly, the diffuse process may develop after a bout of acute lupus pneumonitis. Clinical features of diffuse interstitial processes are similar to those in RA and SSc. In a study of 18 patients with SLE-induced diffuse lung disease, the mean age was 45.7 years, and the mean duration of the disease was 10.3 years; respiratory symptoms were present for a mean of 6 years. Restrictive types of pulmonary dysfunction along with diminished diffusing capacity for carbon monoxide are noted. The clinical course is similar to that of diffuse lung disease associated with RA or SSc.

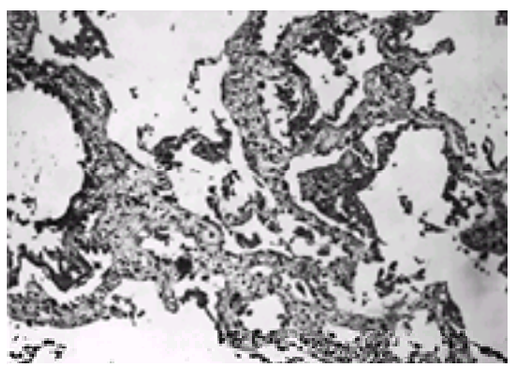

FIG. 4. Lung changes in systemic lupus erythematosus showing edema and thickening of alveolar septa, fibrinous exudate, and hyaline membrane formation in the alveoli.

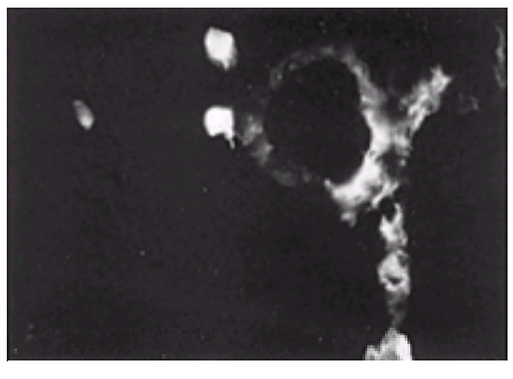

FIG. 5. Immunofluorescence of lung specimen for IgG in systemic lupus erythematosus shows patchy staining of alveolar wall as well as a few intraalveolar cells.

Plate-like or discoid atelectatic areas are more common and usually occur in the lower two-thirds of lung fields (Fig. 6). Infectious processes, particularly in patients who are on immunosuppressive therapy, are the most common cause of lung infiltrates. Sepsis and renal disease are more frequent causes of mortality than are pulmonary complications.

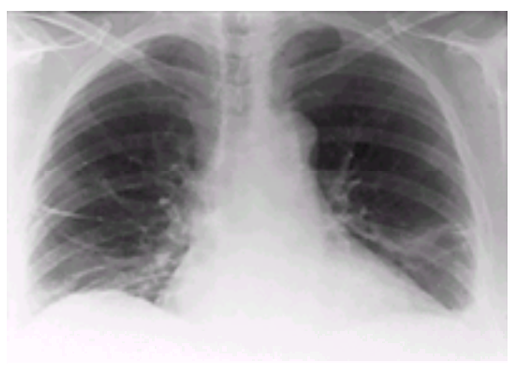

FIG. 6. Discoid or plate-like atelectasis, also called atelectatic pneumonitis, is perhaps the most common chest roentgenographic finding in patients with chronic systemic lu pus erythematosus. Diffuse interstitial process is distinctly uncommon.

Pulmonary Thromboembolism

Thrombophlebitis occurs in up to 10% of patients with SLE. The factors that predispose patients with SLE to thrombophlebitis and pulmonary embolism include chronic low-grade disseminated intravascular coagulation, small-vessel angiitis, prolonged bed rest, and increased thromboplastin generation.

An important factor responsible for the thromboembolic complications in SLE is the antiphospholipid antibody syndrome.

Antiphospholipid Antibody Syndrome

Also known as lupus anticoagulant syndrome, anti-cardiolipin antibody syndrome, the antiphospholipid antibody syndrome is characterized by the presence of antiphospholipid antibodies in serum. The term antiphospholipid antibody refers to a spectrum of autoantibodies, including lupus anticoagulant antibodies and anticardiolipin antibodies, that bind to negatively charged phospholipids. The antiphospholipid antibody syndrome is responsible for the majority of thromboembolic phenomena involving extremities and pulmonary vasculature. In addition to the presence of these antibodies, laboratory abnormalities include a prolonged activated partial thromboplastin time in association with otherwise normal clotting and platelet counts and a false-positive VDRL test. Secondary pulmonary hypertension caused by recurrent pulmonary thromboembolism is a serious consequence of this syndrome. Therapy for these complications consists of inferior vena caval filter insertion and life-long anticoagulant therapy. Adult respiratory distress syndrome caused by extensive small vessel thrombosis of multiple organs including the lungs has been described.

Pulmonary Hypertension

Pulmonary hypertension has been described in up to 15% of patients with systemic lupus erythematosus. It is not usually clinically significant. The pathology of pulmonary hypertension in systemic lupus erythematosus is not well understood. Vasculitis of pulmonary vasculature is rarely seen. As discussed above, the role of recurrent pulmonary thromboembolism and antiphospholipid antibody syndrome should be considered among the major etiologies of pulmonary hypertension. Other potential mechanisms include chronic hypoxic state from interstitial fibrosis and chronic alveolar hemorrhage syndrome. Clinically, pulmonary hypertension in systemic lupus erythematosus is analogous to primary (idiopathic) pulmonary hypertension. Raynaud's phenomenon is common. The secondary form of pulmonary hypertension caused by chronic and recurrent pulmonary emboli can be treated by pulmonary thromboembolectomy. The prognosis in those with persistent pulmonary hypertension is grave. Response to vasodilator therapy is unsatisfactory.

Diaphragmatic Dysfunction

Diaphragmatic elevation and decreased diaphragmatic function have been observed in patients with SLE. Unexplained dyspnea in some patients with SLE may be the result of this phenomenon. The term *shrinking lung syndrome* has been used to describe this. Diaphragmatic weakness may be the result of recurrent diaphragmatic pleurisy, basal atelectasis, and steroid myopathy. Maximal inspiratory expiratory pressures may be diminished. Diaphragm dysfunction does not appear to respond to corticosteroid therapy.

Other Complications

Obstructive airway disease is rare in SLE. Anecdotal reports of severe airway obstruction have been published. The airflow obstruction may be attributable to bronchiolitis, a known complication of SLE. Several cases of upper airway involvement from laryngeal inflammation have been observed. Epiglottitis, subglottic stenosis, laryngeal edema or ulceration, inflammatory mass lesions or nodules, vocal cord paralysis, and cricoarytenoid arthritis have been reported.

Acute reversible hypoxemia is a syndrome reported in a small group of acutely ill patients with SLE. This phenomenon is postulated to be the result of aggregation of circulating leukocytes within the pulmonary vasculature because of complement-mediated phenomena. Corticosteroid therapy leads to decreased levels of complement components and reversal of leukocyte aggregation and hypoxemia. Other thoracic complications reported in patients with SLE include bronchiolitis obliterans with organizing pneumonitis (BOOP), bilateral hilar adenopathy, lymphocytic interstitial pneumonitis, and pulmonary amyloidosis.

A prospective study of 34 patients with SLE who underwent high-resolution CT of the chest showed abnormalities in 24 patients (70%), although pulmonary function abnormalities were present in only 14 patients (41%), and the plain chest roentgenograph was abnormal in only eight (24%). The most common HRCT findings included interstitial lung disease, bronchiectasis, mediastinal or axillary lymphadenopathy, and pleuropericardial abnormalities.

Lung biopsies from patients with SLE may demonstrate areas of vasculitis. However, vasculitis is not characteristic of all lupus-induced pleuropulmonary processes. Nevertheless, vasculitic lesions of large pulmonary vessels as well as capillaritis have been observed in up to 50% of patients.

Drug-Induced SLE and the Lung

Drug-induced SLE is an important clinical syndrome because of the large number of drugs known to cause SLE (see Chapter 22). Pleuropulmonary complications are common in drug-induced SLE. Pleural disease is more common with certain drugs such as procainamide and hydralazine. The pleural fluid shows biochemical characteristics similar to the classic form of SLE. Withdrawal of the drug usually results in resolution of symptoms and signs within days or weeks.

Treatment and Prognosis

Pleural effusion responds favorably to systemic corticosteroid therapy, with an occasional large effusion being refractory. Lupus pneumonitis and alveolar hemorrhage syndrome may respond to high-dose corticosteroid therapy. Cytotoxic agents have been used in patients refractory to corticosteroid therapy. Sepsis and progressive renal dysfunction are the most frequent causes of mortality in patients with SLE, but acute pulmonary alveolar hemorrhage is also important. In patients with lupus pneumonitis, dramatic response can be expected following systemic corticosteroid therapy, although a review of 12 cases of lupus pneumonitis noted a mortality of approximately 50%.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic systemic inflammatory process characterized by nonsuppurative arthritis involving the diarthrodial joints, with frequent involvement of tendons, ligaments, fascia, muscle, and bone. The American Rheumatism Association has established the diagnostic criteria for RA. Extraskeletal organ systems are frequently involved in RA. Indeed, the nonarthritic symptoms may be the presenting features of RA. The pulmonary system is among the most commonly affected organs. Pleuropulmonary manifestations are encountered in 2% to 45% of patients, depending on whether chest roentgenographs or diffusing capacity for carbon monoxide is used to assess the prevalence of lung involvement. The involvement of the lungs is peculiar in that although RA occurs more frequently in women, respiratory complications are more common in middle-aged men with RA. Furthermore, pleuropulmonary complications may precede the onset of arthritic symptoms. Many of the intrathoracic manifestations have the potential to cause critical illness and respiratory distress (Table 2).

Pleurisy and pleural effusion
Interstitial pneumonitis and fibrosis
Lymphocytic interstitial pneumonitis
Obstructive airway disease
Bronchiolitis obliterans with organizing pneumonia (BOOP)
Necrobiotic nodules (rheumatoid nodules)
Rheumatoid pneumoconiosis (Caplan's syndrome)
Cricoarytenoid arthritis
Laryngeal rheumatoid nodules
Pulmonary hypertension
Bronchiectasis
Pulmonary vasculitis

TABLE 2. *Pulmonary complications in rheumatoid arthritis*

Pleural Involvement

Pleural involvement is the most common intrathoracic manifestation of RA (Fig. 7). In a study of 309 patients with RA, chest roentgenographic evidence of pleural involvement was observed in 24% of men and 16% of women. Autopsy studies have demonstrated pleural involvement in nearly 50%. In contrast to the common occurrence of painful pleurisy encountered in patients with SLE, one-third of patients with rheumatoid pleurisy are asymptomatic. Patients with active (seropositive) RA are more likely to develop pleurisy with effusion than those with inactive disease. Pleural effusion may precede the onset of arthritic symptoms by months. The effusions are usually unilateral, small, persistent, or recurrent. Occasionally, effusions become chronic and persist for months to years. Other pulmonary complications (Table 2) may occur along with pleural involvement. One-third of rheumatoid pleural effusions are associated with other lung processes.

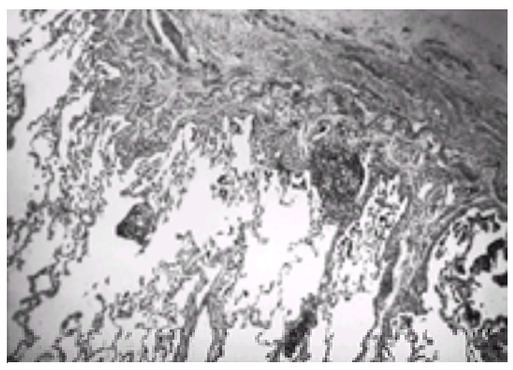

FIG. 7. Pleuropulmonary interphase (upper right) in rheumatoid arthritis. Virtually all patients with rheumatoid arthritis show evidence of pleural thickening at autopsy.

Pleural fluid in RA is typically an exudate, usually yellow and occasionally bloody. Chronic effusions may appear opalescent green because of high cholesterol content (pseudochylothorax). The glucose content in the fluid is very low (<30 mg/dl) in more than 80% of patients; the very low level of glucose is the result of selective blockage of glucose transport into the pleural space as well as from increased utilization of glucose by the inflamed and metabolically active pleural mesothelial cells. Pleural fluid hypoglycemia is not diagnostic of RA-induced pleurisy because pleural fluid glucose levels are also diminished in effusions secondary to empyema, malignant mesothelioma, and tuberculosis. In some patients, the low pH of pleural fluid is the result of localized acidosis caused by blockage to the efflux of end products of glucose metabolism (lactate and CO_2) in the pleural space. Total complement levels in pleural fluid are low in 40% of patients. The presence of rheumatoid factor and the so-called RA cell (monocytes containing cytoplasmic inclusions representing phagocytized IgM in immune-complex form) are not specific in the diagnosis of rheumatoid pleural effusion. High cholesterol levels, including some of the highest ever recorded, are common in chronic pleural effusions associated with RA. High pleural fluid:serum neuron-specific enolase (NSE), found in small-cell lung cancer, has been found consistently in pleural effusions from patients with RA. Pleural fluid concentrations of NSE correlate inversely with pleural fluid glucose concentrations and the pH of the pleural fluid. High levels of soluble interleukin 2 receptor associated with local T-cell-mediated reaction have been found in pleural fluid of patients with RA.

Rheumatoid Lung

Rheumatoid lung is defined as diffuse interstitial pneumonitis or fibrosis associated with RA (Fig. 8 and Fig. 9), and it is perhaps the most serious pulmonary complication of RA. A diffuse pulmonary process is observed in up to 5% of chest roentgenograms in patients with RA. Restrictive pulmonary dysfunction can be demonstrated in more than one-third of patients with rheumatoid lung disease. Clinically, physiologically, and morphologically, the respiratory involvement in RA is identical to that in idiopathic pulmonary fibrosis. It appears that smoking and the presence of secondary Sjögren's syndrome might be important in predisposing the patient with RA to the development of lung disease. Cough and dyspnea are common symptoms, and clubbing has been observed in up to 70%. Chest roentgenograms generally demonstrate a bibasilar interstitial process or micronodules. Honeycombing occurs in late stages of the disease. High-resolution computed tomographic scan of lungs is superior to plain chest roentgenography in the detection of rheumatoid lung disease. In one study of 91 patients with RA, HRCT detected subclinical interstitial lung disease in approximately 50% of patients. High-resolution CT of chest in early stages of the disease may show the ground-glass infiltrates, and as the disease progresses, interstitial processes and honeycombing appear. Fewer than 6% of patients with RA have been shown to develop a bilateral upper-lobe process similar to the pulmonary abnormalities in ankylosing spondylitis. Physiologically, restrictive dysfunction is noted. The earliest physiological abnormality is diminished D_LCO. Exercise-induced hypoxia is common in patients with advanced disease.

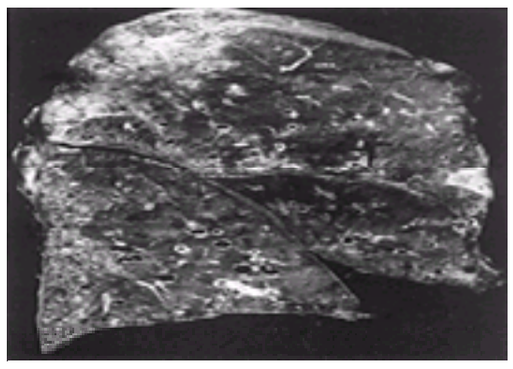

FIG. 8. Gross photograph of chronic interstitial pneumonia in rheumatoid arthritis. Zones of honeycombing can be seen in the posterior subpleural regions. Some contraction and thickening of the lung also is noted along with pleural thickening.

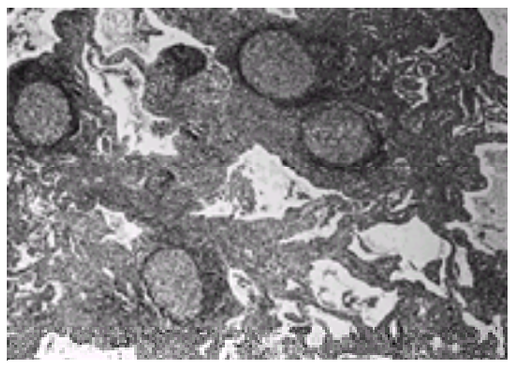

FIG. 9. Chronic fibrosing interstitial pneumonia with associated lymphoid hyperplasia and germinal centers in rheumatoid arthritis. Alveolar architecture is somewhat preserved.

Diagnostic bronchoalveolar lavage has demonstrated abnormalities similar to those in idiopathic pulmonary fibrosis, namely increased neutrophils as well as lymphocytes. Even though it has been suggested that increased lymphocytosis of bronchoalveolar lavage fluid is associated with a good pulmonary prognosis, the supporting data for this assertion are scanty. One study of 40 patients with RA and active pulmonary process described five histologic patterns of pulmonary disease: rheumatoid nodules, nonspecific interstitial pneumonitis, bronchiolitis obliterans with patchy organizing pneumonia, lymphoid hyperplasia, and cellular interstitial infiltrates (Fig. 9 and Fig. 10), In the majority of patients with rheumatoid lung, the morphologic features are nonspecific, without clinical correlates, because the observed abnormalities are dependent on the stage of the disease. Therefore, bronchoscopy, bronchoalveolar lavage, and lung biopsy are rarely indicated. However, diagnostic bronchoalveolar lavage and lung biopsy may be indicated in complicated situations, particularly in patients with immunocompromised status as a result of therapy.

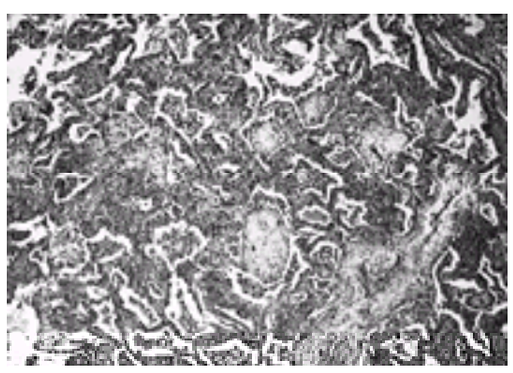

FIG. 10. Bronchiolitis obliterans with patchy organizing pneumonia in rheumatoid arthritis. Several pale rounded polyps of edematous granulation tissue are seen within the air space, between which mildly thickened alveolar septa with a mild chronic inflammatory infiltrate can be seen.

Systemic corticosteroid therapy in early stages may reverse the lung process. It is important to recognize that several drugs used to treat RA can by themselves cause pulmonary disease. These include methotrexate, gold, and penicillamine.

Necrobiotic Rheumatoid Nodules

Necrobiotic rheumatoid pulmonary nodules are different from the nodules observed in Caplan's syndrome. Necrobiotic nodules occur within the lung parenchyma and are histologically similar to subcutaneous rheumatoid nodules. They are more common in men than in women and in those with seropositive RA. Necrobiotic nodules are known to precede the arthritic symptoms. The pulmonary nodules produce minimal symptoms and often are discovered incidentally. They measure from a few millimeters to several centimeters in diameter and are usually bilateral (Fig. 11), occur near pleural surfaces, cavitate in two-thirds, and may rupture into the pleural space to produce pneumothorax or empyema. Aspergilloma is a complication of rheumatoid nodules. The necrobiotic nodules usually wax and wane with activity of the RA, although they may resolve spontaneously despite continuously active RA.

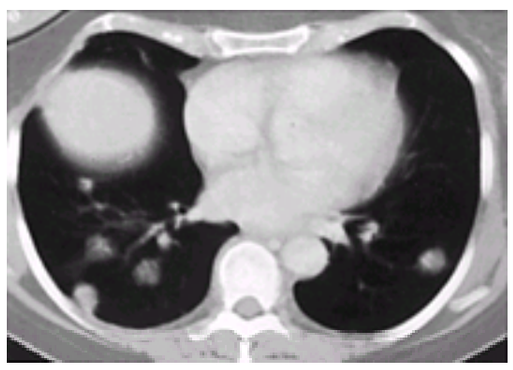

FIG. 11. Multiple bilateral rheumatoid nodules in the lower lung zones. Cavitation is not seen clearly in this computed tomographic image, even though one-third of the nodules cavitate.

Rheumatoid Pneumoconiosis (Caplan's Syndrome)

Caplan's syndrome denotes the presence of rheumatoid nodules in association with pneumoconiosis. Originally described in coal workers with RA, Caplan's syndrome now encompasses persons with silicosis, asbestosis, aluminosis, and the like. The syndrome is uncommon in North America, and most reports have been from Europe. Pulmonary parenchymal nodules in Caplan's syndrome measure 1 to 5 cm in diameter, evolve rapidly, undergo cavitation, appear in crops, and are frequently associated with other lung lesions. Histologically, features are identical to those of rheumatoid nodules except for the presence as well of pneumoconiotic material in the center. Occasionally, the nodules remain quiescent and heal by fibrosis.

Obstructive Airways Disease

Obstructive airways disease occurs in nearly one-third of patients (nonsmokers) with RA. In one study of patients with active rheumatoid lung disease, 23% were found to have obstructive dysfunction secondary to rheumatoid bronchiolitis; others had follicular bronchiolitis and bronchitis. In a study of 100 patients with unselected RA, both airflow obstruction and bronchial reactivity measured by methacholine inhalation challenge were significantly increased relative to controls. The combination of RA and smoking is associated with a much higher prevalence of obstructive lung disease than is either of these factors alone. Mucociliary clearance may be diminished in some patients with RA. Genetic predisposition to obstructive lung disease appears to be a contributing factor. Congenital deficiency of a_1-antitrypsin causes panlobular emphysema and obstructive airway disease. Patients with RA and airway disease have been found to exhibit a 50% incidence of non-PiM (that is, PiMZ and PiMS) phenotypes for a_1-antitrypsin. Penicillamine and gold salts are used to treat RA, and because these drugs are known to cause bronchiolitis obliterans, this complication should be considered in patients with RA who present with obstructive airway symptoms. High-resolution computed chest tomography may show pulmonary parenchymal ground-glass-type alveolar infiltrates (Fig. 12). Progressive rheumatoid airway disease with rapid progression may lead to respiratory distress. Although

unusual, anecdotal reports of life-threatening obstructive airway disease associated with RA have been published.

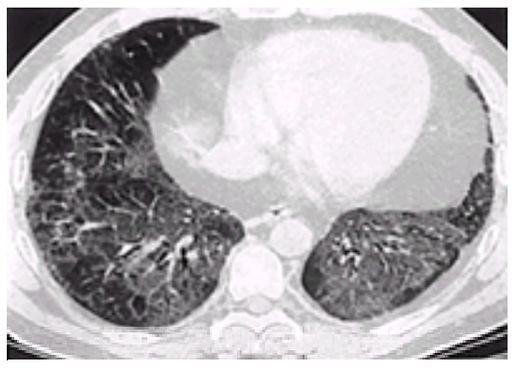

FIG. 12. High-resolution computed tomographic image of basal regions of lungs in bronchiolitis obliterans associated with rheumatoid arthritis. Diffuse but patchy "ground-glass"-type infiltrates are well seen.

Upper Airway Disease

Cricoarytenoid arthritis caused by RA is clinically recognized in 25% to 35% of cases, although it is present in a significant number of autopsies. Clinically, manifestations consist of chronic persistent sore throat and hoarseness. Both inspiratory and expiratory difficulty may result from a fixed obstruction at the laryngeal level. Laryngoscopy reveals edema and erythema of the vocal apparatus, abnormal motion of vocal cords, and dysfunction of the arytenoids. Rheumatoid nodules occur in the laryngeal region and produce hoarseness, cough, and dyspnea. It is important for specialists in critical care and anesthesia to recognize that laryngeal nodules may remain asymptomatic and pose problems at the time of tracheal intubation.

Bronchiectasis

Bronchiectasis is a late complication of RA. In many published cases, bronchiectasis has been documented in patients with advanced and severe RA. Rheumatoid bronchiolitis appears to predispose to this complication. Patients with rheumatoid bronchiolitis have been shown to have a significantly higher incidence of positive bacterial cultures in their sputum specimens. Bronchiectasis occurs with greater frequency in patients with Felty's syndrome; rheumatoid arthritis associated with hypersplenism and pancytopenia.

Other Complications

Pulmonary hypertension is an uncommon complication of RA. Pulmonary vasculitis, also an uncommon complication, may play a role in the development of pulmonary hypertension. Vasculitis may also cause alveolar hemorrhage, another rare complication of RA. Goodpasture's syndrome has also been reported in association with RA.

Rheumatoid arthritis involving cervical spines may lead to instability of the cervical spinal column. This can preclude extension of the neck for purposes of laryngoscopic tracheal intubation. The tracheal intubation in such patients should be accomplished with a flexible bronchoscope.

Treatment and Prognosis

Nonsteroidal antiinflammatory agents, if successful in controlling RA, may subdue many of the acute respiratory manifestations. Specific complications such as large pleural effusion and obstructive airway disease may require individualized therapy. Systemic corticosteroid therapy in the earlier stages of rheumatoid interstitial lung disease may reverse the acute inflammatory process and slow or stop progression to irreversible fibrotic lung disease. As the lung disease becomes chronic, the ability to reverse it with corticosteroid and other pharmacologic agents diminishes. A poor prognosis results when the interstitial process is advanced. In one large series, such patients had a median survival of 3.5 years and a 5-year survival rate of 39%. Poor prognosis follows rheumatoid bronchiolitis. It is important to recognize that certain cytotoxic agents used in the treatment of rheumatoid arthritis can produce pulmonary toxicity. The agents with known pulmonary toxicity include gold, methotrexate, and penicillamine. Methotrexate, however, has no significant effect on pulmonary function in the majority of patients with RA. Also, there is no evidence that patients with preexisting pulmonary disease are at increased risk for further deterioration in lung function following methotrexate therapy. It should be noted, however, that fatal pulmonary fibrosis following short courses of low-dose methotrexate therapy for RA has been reported.

SYSTEMIC SCLEROSIS OR SCLERODERMA

Systemic sclerosis (SSc) is a systemic connective tissue disease of unknown etiology characterized by a fibrosis of the skin and visceral organs, vasculitis, and presence of relatively specific antinuclear antibodies. The major pathologic attributes of SSc include vascular changes, immune dysfunction, and increased collagen synthesis. It has been suggested that the neutrophil participates in the pathogenesis of lung disease through the release of elastase and that alveolar macrophage, through the release of interleukin-8, recruits neutrophils into the alveoli. Spontaneous and stimulated interleukin-6 secretion by blood monocytes is also increased. Pulmonary involvement is common in patients with SSc. The majority of patients are minimally symptomatic during life, but postmortem examinations have shown abnormal lung histology in up to 80%. Risk factors for developing severe restrictive lung disease include black race, male sex, early onset of SSc, and primary cardiac involvement secondary to SSc. Antihistone antibodies (AHA) in the serum are suspected to indicate more severe lung disease. Several of the pulmonary complications in SSc are listed in Table 3.

Pulmonary interstitial fibrosis
Organizing pneumonitis
Pulmonary hypertension
Aspiration pneumonia
Bronchiolitis obliterans
Chest wall restriction
Bronchiectasis (traction bronchiectasis)
Pleural effusion and fibrosis
Calcification of lung and soft tissues of chest cage (especially in patients with CREST syndrome)
Resorption of ribs
Alveolar hemorrhage
Spontaneous pneumothorax
Pulmonary hemosiderosis-like syndrome
Diaphragmatic dysfunction
Telangiectasia of the airways leading to hemoptysis
Cancer of lung (scar cancer?)

TABLE 3. *Pulmonary complications in scleroderma*

Pulmonary Fibrosis

Progressive interstitial pulmonary fibrosis is the most common pulmonary complication of SSc and develops in up to two-thirds of patients. The frequency of roentgenographic interstitial fibrosis is increased in patients with serum anti-Scl-70 antibody and decreased in those with anticentromere antibody. Histologic features are analogous to those of idiopathic pulmonary fibrosis. Alveolar inflammation has been recognized as a primary event in the pulmonary manifestation of SSc. In early stages, alveolar edema with lymphocytic and monocytic infiltrates occurs. Later, severe fibrosis with honeycombing and cyst formation is noted (Fig. 13). The incidence of pneumothorax in late stage is a complication. Although only one-third of patients have abnormal chest roentgenographs, more than 50% complain of dyspnea on exertion and exhibit diminished D_LCO. Subclinical alveolitis diagnosed by bronchoalveolar lavage occurs in asymptomatic patients. Studies have shown that increased pulmonary vascular leakage and neutrophilic alveolitis are perhaps the earliest features of interstitial lung disease in SSc and that these changes are associated with enhanced type II collagen synthesis. Bronchoalveolar lavage and pulmonary functions in patients with SSc-induced lung disease have shown both neutrophilic and

lymphocytic alveolitis; bronchoalveolar lavage that shows active alveolitis is associated with more severe impairment of lung function than is bronchoalveolar lavage that shows inactive alveolitis. Neutrophilic alveolitis is generally associated with extensive fibrotic lung disease, whereas eosinophilic alveolitis is often seen in less advanced disease, particularly when computed tomographic appearances suggest lung inflammation. Pulmonary in volvement is more severe in patients with the CREST (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, and telangiectasia) variant of SSc.

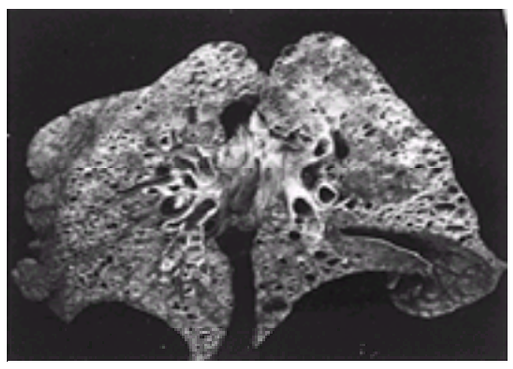

FIG. 13. Gross appearance of lungs in a patient with severe scleroderma. Lungs show extensive honeycombing.

Chest roentgenograph in SSc-induced lung disease shows changes similar to those in idiopathic pulmonary fibrosis. Thoracic (mediastinal) lymphadenopathy is prevalent in patients with SSc and lung disease regardless of clinical subtype or interstitial pattern, and the lymphadenopathy increases as a function of the profusion of the lung infiltrates rather than the morphology of lung disease. Pulmonary function tests in patients with SSc most commonly reveal restrictive dysfunction with diminished D_LCO, the latter being the earliest to occur. The D_LCO is also an important predictor of mortality. Pulmonary dysfunction appears to be related to involvement of the right side of the heart but not to involvement of other extrapulmonary systems. Patients with SSc and Raynaud's phenomenon tend to have lower D_LCO than those with SSc alone.

Pulmonary Hypertension

Pulmonary hypertension is a serious complication that occurs in up to 60% of patients with SSc. This complication is the result of medial hypertrophy of the pulmonary arteries (Fig. 14) and is a major cause of morbidity and mortality. Pulmonary hypertension occurs with greater frequency in patients with the CREST variant of SSc. Chronic hypoxia induced by pulmonary fibrosis also may contribute to the development of pulmonary hypertension. Progressive decrease in D_LCO is an early sign of pulmonary hypertension. The results of treatment, using vas odilators, have been discouraging. The incidence of renovascular pathology is high among patients with pulmonary vascular involvement.

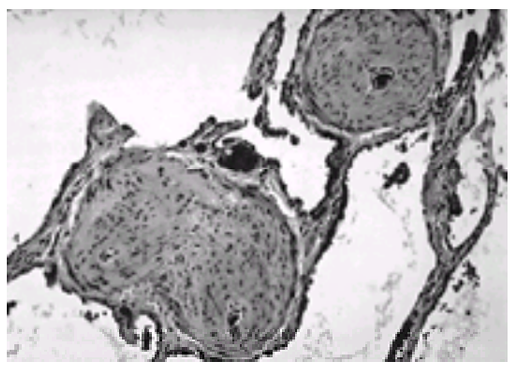

FIG. 14. Pulmonary hypertension in scleroderma, with marked thickening of the muscular wall of small pulmonary arteries.

Aspiration Pneumonia

Esophageal involvement in the form of motor dysfunction occurs in more than 90% of patients with SSc. Acid reflux caused by esophageal dysfunction may lead to aspiration pneumonia. Although chronic aspiration has been considered to play a role in the etiology of pulmonary fibrosis, one study of 39 patients with SSc reported that changes in total lung capacity and forced vital capacity do not appear to be related to abnormal gastroesophageal acid reflux.

Other Complications

Diffuse pulmonary calcification, (especially in patients with CREST syndrome), resorption of ribs, alveolar hemorrhage, a syndrome resembling pulmonary hemosiderosis, diaphragmatic dysfunction, hemoptysis caused by telangiectasia of the airways, and rare instances of pleural thickening have been described.

Chronic SSc is associated with an increased risk of lung cancer. Some have reported that the risk for developing bronchoalveolar carcinoma is increased, but other histologic types of lung carcinoma have also been described. Among 248 patients with SSc who were followed up, cancers developed in 18 patients (7.3%) during 2001 patient-years at risk. The most frequent types were cancers of the lung (seven patients) and breast (five patients). Lung cancer was associated with the presence of pulmonary fibrosis. It is not clear whether such cancers represent the so-called scar cancers.

Treatment and Prognosis

Systemic corticosteroid therapy has had no effect on prognosis in patients with SSc. However, some studies have indicated that active alveolitis, as determined by the results of bronchoalveolar lavage, may respond favorably to immunosuppressive agents. In one study of patients with scleroderma lung disease and an FVC less than 70% predicted, the group treated with cyclophosphamide showed significantly more improvement in FVC over time than did the patients treated with other drugs. D-Penicillamine has been used to prevent progression of pulmonary complications. Fibrosing alveolitis associated with SSc is reported to have a better prognosis than idiopathic fibrosing alveolitis. When patients with SSc develop hypoxemia, supplemental oxygen therapy may relieve dyspnea. Single lung transplantation has been performed in selected cases.

POLYMYOSITIS-DERMATOMYOSITIS

Polymyositis and dermatomyositis are idiopathic myopathies characterized by inflammation of skeletal muscles with resultant weakness of proximal muscles and a characteristic skin rash (heliotrope hue). The autoimmune type of PM-DM (types I, II, and V) discussed here is different from the paraneoplastic type of PM-DM associated in up to 10% of cases with carcinoma of lung and other organs. Underlying malignancy, however, must be excluded before the diagnosis of autoimmune PM-DM is considered. The disease is more common in women. The diagnosis is based on clinical features, elevation of creatine phosphokinase and aldolase, electromyographic studies, and muscle biopsy. The clinical hallmark of PM-DM is proximal limb and neck weakness, sometimes associated with muscle pain. Lung involvement has been described in up to 5% of patients. In one-third of patients, respiratory manifestations may precede musculocutaneous signs and symptoms. A relationship between the severity and progression of the myositis and the severity of respiratory disease is lacking.

Interstitial Pneumonitis and Fibrosis

Interstitial pneumonitis and fibrosis is the most common pulmonary complication and occurs in 5% to 10% of patients. Pulmonary disease precedes the dermatologic or myopathic manifestations by 1 to 24 months in nearly one-third of patients. Respiratory features include dyspnea, cough, and hypoxemia. Symptoms related to

gastroesophageal reflux may be the initial manifestation in some. The process starts in the lung bases and may extend upward. It may present as acute pneumonitis with alveolar or mixed alveolar–interstitial infiltrates. Hypersensitivity to autoantibodies is considered responsible for the lung disease. The anti-Jo-1 antibody in the serum is associated with lung disease; over 50% of patients with anti-Jo-1 antibody exhibit interstitial pulmonary disease. There are reports of patients with anti-Jo-1 syndrome presenting as cryptogenic organizing pneumonia and developing adult respiratory distress syndrome. Pulmonary capillaritis with diffuse alveolar hemorrhage has been described as the primary manifestation of PM-DM. Anti-EJ antibodies have been demonstrated in the sera of some patients with inflammatory myopathy, rash typical of DM, arthritis, Raynaud's phenomenon, and interstitial lung disease. Morphologically, the lung exhibits nonspecific fibrosis and bronchiolitis obliterans with organizing pneumonitis (BOOP) and desquamation of alveolar lining cells (Fig. 15). Pulmonary dysfunction is present in over 50% of patients and consists of decreased lung volumes, $D_L CO$, and arterial oxygenation. Results of bronchoalveolar lavage do not provide diagnostic characteristics.

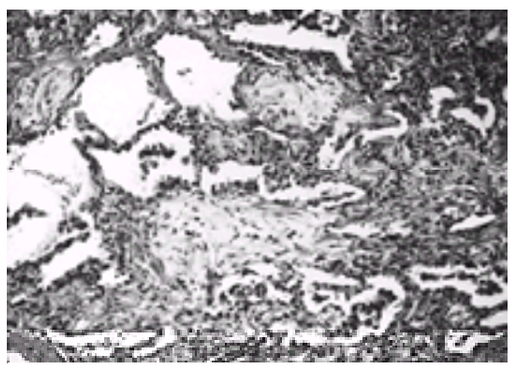

FIG. 15. Bronchiolitis obliterans with patchy organizing pneumonia in polymyositis-dermatomyositis. Two rounded edematous masses of intraalveolar fibrous connective tissue can be seen in the center of the figure.

Hypoventilation

Hypoventilation and respiratory failure are caused by weakness of the respiratory muscles because of the myopathy. Progressive hypercapnia is a poor prognostic sign. Muscle weakness may severely compromise the respiratory bellows mechanism, thereby worsening the basal atelectasis. An ineffective cough increases the risk of bacterial pneumonia.

Aspiration Pneumonitis

Esophageal involvement is common in patients with PM-DM. Uncoordinated peristalsis, esophageal reflux, odynophagia, and delayed gastric emptying are noted. Bulbar involvement and deranged deglutition often lead to recurrent aspiration and pneumonia. Poor cough as a result of respiratory muscle weakness contributes to the development and progression of aspiration pneumonia. Aspiration pneumonia is often the cause of death.

Treatment and Prognosis

Corticosteroids, azathioprine, methotrexate, total body irradiation, and thymectomy have been tried, with varying rates of success. The pulmonary involvement in PM-DM is usually progressive, and long-term response to corticosteroid therapy is poor even though the initial response may be good. Patients receiving high-dose therapy (prednisolone, 1 to 2 mg/kg per day) have shown less morbidity.

MIXED CONNECTIVE TISSUE DISEASE

The terms *overlap syndrome, undifferentiated connective tissue disease, sclerodermatomyositis, RUPUS* (RA and SLE), and *lupoderma* (SLE and SSc) have been used to describe patients who exhibit clinical features of more than one rheumatologic disease. The term *mixed connective tissue disease* (MCTD) refers to patients with clinical features of SLE, SSc, and PM-DM and high titers of a specific circulating antibody to an extractable nuclear ribonucleoprotein antigen (ENA). The presence of high titers of antibody to ENA and the absence of antibodies to Sm antigen are believed to be specific for MCTD. The prevalence of MCTD is more common than PM-DM and less common than SLE. The majority of patients are women, and the average age at diagnosis is 37 years. Renal disease occurs in 10% to 20%, and some patients may require aggressive or prolonged therapy. Pleuropulmonary involvement occurs in 20% to 80% of patients. Many of these manifestations, both clinical and pathophysiological, are similar to those observed in SLE, SSc, and PM-DM.

Interstitial Fibrosis

Interstitial lung disease in patients with MCTD exhibits morphologic features similar to those of idiopathic pulmonary fibrosis. Alveolar septal infiltration by lymphocytes, plasma cells, and type III collagen has been demonstrated. The degree of fibrosis tends to be severe if the predominant clinical feature is that of SSc. Abnormal pulmonary function tests and chest roentgenograms have been noted in 69% of patients without respiratory symptoms. In a multicenter study of 100 patients with MCTD, impaired $D_L CO$ and restrictive lung volumes were noted in 67% and 50%, respectively.

Chest roentgenographic findings are akin to idiopathic pulmonary fibrosis if the clinical profile is predominantly scleroderma-like. Mixed infiltrates can be seen in those with primarily PM-DM-like features. In a study of 81 patients, respiratory symptoms included dyspnea (16%), chest pain and tightness (7%), and cough (5%). Chest roentgenograms revealed abnormalities in 21%, the most common being an interstitial process in both lower lung fields. Pulmonary function testing demonstrated a restrictive type of defect in 69%. $D_L CO$ is the most sensitive single parameter in evaluating pulmonary dysfunction in MCTD.

Pleural Effusion

Pleurisy is a common manifestation of MCTD. Nearly 40% of patients in a prospective study were noted to have pleuritic pain. Pleural fluid shows the same characteristics as that in SLE. The effusions are usually small and resolve spontaneously.

Pulmonary Hypertension

Progressive pulmonary hypertension is the most severe pulmonary complication of MCTD and may be accompanied by severe vasculitic lesions. In an evaluation of 34 patients, significant pulmonary hypertension was noted in 67% of the 15 patients studied. Examination of lung biopsy tissue has revealed muscular hypertrophy of small pulmonary arteries. Plexogenic angiopathy and chronic intimal thickening of medium-size pulmonary arteries have been observed. Fatal pulmonary hypertension has been reported.

Aspiration Pneumonitis

Abnormal esophagograms and esophageal manometry are common in MCTD. Hypotonicity and dilation of the esophagus, similar to that in SSc, are responsible for the reflux and aspiration pneumonia.

Other Complications

Circulating lupus anticoagulant, recurrent thromboemboli complicated by pulmonary embolism and pulmonary hypertension, pulmonary hemorrhage, cavitated pulmonary nodules, and mediastinal lymphadenopathy have been described in patients with MCTD.

If the characteristics of PM-DM are prominent in a patient with MCTD, significant proximal muscle weakness and diaphragmatic weakness may cause hypoventilatory respiratory failure.

Treatment and Prognosis

Corticosteroids are the mainstay of therapy. In a prospective study of 34 patients with MCTD, a favorable response to corticosteroids was noted in two-thirds of the patients, though patients with predominantly SSc-like disease respond poorly. Pleurisy responds well to corticosteroid therapy, whereas pulmonary hypertension does not. In a retrospective study of 81 patients, a 5-year follow-up observed six deaths from carcinoma of the esophagus, aspiration pneumonia, pulmonary hypertension, cardiorespiratory arrest, and myocardial infarction.

SJÖGREN'S SYNDROME

Sjögren's syndrome is a chronic, slowly progressive inflammatory autoimmune exocrinopathy of unknown etiology and characterized by keratoconjunctivitis sicca and xerostomia as a result of diminished lacrimal and salivary gland secretion. Recent studies suggest that the systemic manifestations of Sjögren's syndrome are probably caused by the attraction of lymphocytes by different epithelial tissues. Because of the primary role played by epithelium, the term “autoimmune epitheliitis” has been proposed in lieu of Sjögren's syndrome.

When it is not associated with other connective tissue diseases, the term *primary* Sjögren's syndrome is used. *Secondary* Sjögren's syndrome occurs in association with RA, SLE, SSc, myositis, biliary cirrhosis, cryoglobulinemia, vasculitis, and thyroiditis. Approximately half the patients with secondary Sjögren's syndrome have RA. Sjögren's syndrome is a lymphoproliferative disorder; the incidence of lymphoma in patients with chronic Sjögren's syndrome is increased 44-fold. Lymphocytic infiltration of the exocrine glands, reticuloendothelial system, kidneys, muscles, and other organs is present in one-fourth of the patients. When lymphoid tumors occur that have not met the histologic criteria for malignancy, the term pseudolymphoma has been used, although many pseudolymphomas represent low-grade lymphomas.

Pulmonary complications occur in 1.5% to 75% of patients with both primary and secondary Sjögren's syndrome. Significant abnormalities in pulmonary function occur in about 24% of patients, and the most common cause of dyspnea is interstitial fibrosis, with a prevalence rate of about 8%. In a study of 343 patients with the syndrome, 9% were found to have respiratory involvement. The pulmonary manifestations described in the literature are listed in Table 4.

Nonspecific interstitial pneumonitis
Lymphocytic interstitial pneumonitis
Desiccation of the upper respiratory tract (xerotrachea)
Recurrent tracheobronchitis
Lymphocytic bronchitis
Lymphoma
Bronchiectasis
Obstructive disease of large and small airways
Bronchiolitis obliterans and organizing pneumonia (BOOP)
Localized lung infiltrates, nodules
Discoid atelectasis
Asthma
Pleurisy, pleural effusion
Pulmonary hypertension
Amyloidosis (secondary)
Vasculitis
Diaphragmatic myopathy

TABLE 4. *Pulmonary complications in Sjögren's syndrome*

Airway Disease

Xerotrachea refers to drying of upper airways. It is more common in those with the primary extraglandular form. However, there is no convincing evidence of diminished mucosal secretions or ciliary dysfunction. Nonproductive cough despite normal chest roentgenogram and pulmonary function tests is noted in 17% of patients.

Pulmonary function tests have shown obstructive phenomena in 2.5% to 35% of patients with both primary and secondary forms of Sjögren's syndrome. Patients with both RA and Sjögren's syndrome are more likely to demonstrate obstructive airway disease. Pulmonary functional, roentgenologic, and histopathologic studies have shown that the lesion starts peribronchially. Lymphocytic bronchitis is partly responsible for the obstructive disease, even though mononuclear cell infiltrates can be seen around small airways. Invasion of bronchial mucosa by lymphocytes may represent low-grade lymphoma.

Diffuse Interstitial Process

Diffuse interstitial pulmonary process develops in 15% to 38% of patients with Sjögren's syndrome. Bronchoalveolar lavage may yield increased percentages of lymphocytes and neutrophils, suggesting a subclinical alveolitis. The physiological dysfunction is usually mild. Clinically, lymphocytic interstitial pneumonitis should be differentiated from nonlymphocytic interstitial pneumonitis (see below). A study of 20 patients with Sjögren's syndrome observed pulmonary symptoms in 18, and nine exhibited restrictive lung dysfunction and interstitial involvement. Bronchoalveolar lavage showed higher cell counts with increases of lymphocytes and/or polymorphonuclear cells. Lung biopsy in 12 patients showed follicular bronchiolitis, lymphoid interstitial pneumonia, and lung fibrosis with honeycombing.

Lymphocytic Interstitial Pneumonitis

Lymphocytic interstitial pneumonitis is characterized by parenchymal lung infiltrates consisting of small lymphocytes, plasma cells, and transformed lymphocytes (Fig. 16). Chest roentgenograms show a diffuse interstitial process that is predominantly basal in distribution. Among 343 patients with Sjögren's syndrome, eight (2.3%) developed lymphoproliferative pathology in the lungs; three had lymphocytic interstitial pneumonitis, two had pseudolymphoma, and three were found to have lymphoma. Lymphocytic interstitial pneumonitis should be considered a precursor to the development of lymphoma. Bronchoalveolar lavage may aid in the in vestigation of the clonality of lymphocytes which may allow early and specific diagnosis of lymphomatous proliferation.

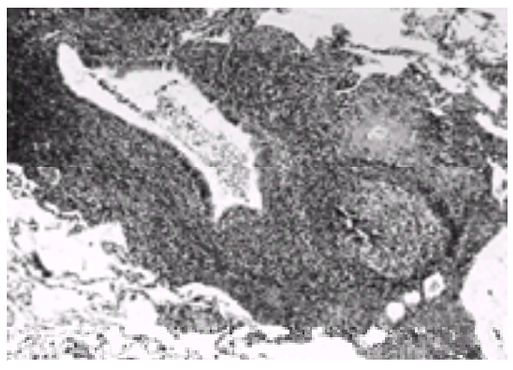

FIG. 16. Chronic bronchiolitis in Sjögren's syndrome with marked chronic inflammation in the wall of the bronchiole associated with lymphoid hyperplasia with germinal centers (*right*).

Pseudolymphoma

Localized lymphoid infiltrates form pseudolymphomas that are clinically and histologically difficult to distinguish from lymphoma. These lesions represent the mid-portion of the spectrum from benign lymphocytic process to malignant lymphoma. Most pseudolymphomas are probably indolent, well-differentiated lymphocytic and lymphoplasmacytic lymphomas, and the majority demonstrate a benign clinical course, whereas only a few are aggressive. Immunohistochemical techniques have shown that most pseudolymphomas of lung are lymphomas. Some pseudolymphomas and even low-grade lymphomas regress spontaneously or with systemic corticosteroids, but others may develop into more malignant lymphomas. Pseudolymphomas are believed to develop in patients with secondary Sjögren's syndrome

alone. Pseudolymphomas exhibit highly heterogeneous infiltrates consisting of large and small lymphocytes, plasma cells, and reticulum cells.

Pseudolymphomas are generally detected on chest roentgenograms in asymptomatic patients and may appear as rounded mass lesions or nodular lesions. The lesions may be well defined and usually solitary and measure from 1.5 to 6 cm.

Pulmonary Lymphoma

A National Institutes of Health study of 136 women with Sjögren's syndrome, followed for an average period of 8 years, observed development of non-Hodgkin's lymphoma in seven and Waldenström's macroglobulinemia in three patients. The occurrence of lymphoma was 44 times the incidence expected in the general population. Patients with a history of parotid enlargement, splenomegaly, and lymphadenopathy were particularly at risk. Another study of 36 men with Sjögren's syndrome observed lymphoproliferation in 17% and concluded that men are at the same risk as women for the development of lymphoma. The majority of malignant lymphomas reported in patients with this syndrome have been monoclonal B-cell neoplasms.

Pulmonary involvement by lymphoma is more likely to occur in those with systemic lymphoma complicating Sjögren's syndrome. A study of 50 patients with Sjögren's syndrome and associated lymphoma revealed pulmonary involvement in ten patients; the mean age of the ten patients was 59.7 years, and eight were women; the mean duration of the syndrome was 7.2 years, and the mean interval between the onset of the syndrome and lymphoma was 5.4 years. Of the ten patients, four died from 8 to 48 months after lymphoma was diagnosed. Lung biopsies revealed a spectrum of low-grade to high-grade lymphomas.

An initial diagnosis of benign lymphocytic interstitial pneumonitis may, on further pathologic analysis, reveal low-grade lymphomas. Thus, many of the published cases of lymphocytic interstitial pneumonitis may represent malignant lymphoma. It has been proposed that all cases of lymphocytic interstitial pneumonitis are actually low-grade lymphomas. Although it is difficult to differentiate lymphocytic interstitial pneumonitis from malignant lymphoma when the chest roentgenogram reveals an interstitial process, the presence of multiple nodular lesions suggests lymphoma. Hilar lymphadenopathy or masses should also suggest a high likelihood of lymphoma. Patients with low-grade lymphomas fare significantly better than those with high-grade lymphomas. Patients with pulmonary lymphomas are believed to have a better prognosis.

Treatment and Prognosis

Azathioprine-based treatment has been shown to reverse pulmonary abnormalities of Sjögren's syndrome and favorably change the outcome. The treatment of the lymphomas in Sjögren's syndrome depends on the histologic grade of the tumor; low-grade lymphoma may not require chemotherapy. Because of the potential of these tumors to assume the status of high-grade malignancy, close surveillance is indicated. Because most patients with Sjögren's syndrome do not have disabling pulmonary symptoms, only symptomatic therapy is indicated.

RELAPSING POLYCHONDRITIS

Relapsing polychondritis (RPC) is a rare and often episodic form of inflammatory disease of unknown etiology characterized by destructive lesions involving cartilaginous structures of nose, ears, larynx, tracheobronchial tree, cardiac valves, and joints. Clinical manifestations include iritis, episcleritis, hearing deficit, cataract, aortic valvular insufficiency, anemia, elevated erythrocyte sedimentation rate, and abnormal liver functions. The majority of patients are between ages of 40 and 60 years, with equal distribution between the sexes. The disease primarily affects Caucasians.

Relapsing polychondritis, as an idiopathic disorder, is a diagnosis of exclusion. In approximately one-third of published cases, RPC has been associated with Wegener's granulomatosis, RA, SLE, Sjögren's syndrome, ankylosing spondylitis, Reiter's syndrome, Behçet's disease, hypothyroidism, Graves' disease, chronic ulcerative colitis, cryptogenic cirrhosis, cryoglobulinemia, and hydralazine therapy. In many patients, these diseases precede the onset of polychondritis by months to years. Biopsy of affected cartilage is nondiagnostic; only nonspecific cartilaginous destruction is noted. There are no specific serologic or other tests to aid in the diagnosis. If three of the following six criteria are present in the proper clinical setting, then RPC can be suspected: auricular chondritis; nonerosive inflammatory polyarthritis; nasal chondritis; ocular inflammation (conjunctivitis, keratitis, scleritis, episcleritis, uveitis); laryngeal, tracheal, or bronchial chondritis; and cochlear or vestibular damage.

Pulmonary Disease

Recurrent inflammation of the nasal cartilage leads to structural damage and saddle-nose deformity. More than 50% of patients develop respiratory complications. Involvement of the laryngotracheal region portends poor prognosis. Airway pathology includes thickening of mucosa, loss of elasticity, and development of stenotic segments. When multiple cartilaginous segments become affected, expiratory collapse of the airway occurs (Fig. 17). The resultant weak cough, combined with recurrent infections because of the inability to clear mucus, may cause bronchiectasis. Flow–volume curves in patients with significant respiratory symptoms demonstrate the plateau patterns of maximal inspiratory or expiratory flows. Tracheal tomography and cine-computed tomography may provide further insight into the abnormal anatomy of the major airways. Bronchoscopy in more useful in assessing the dynamic function of the airways.

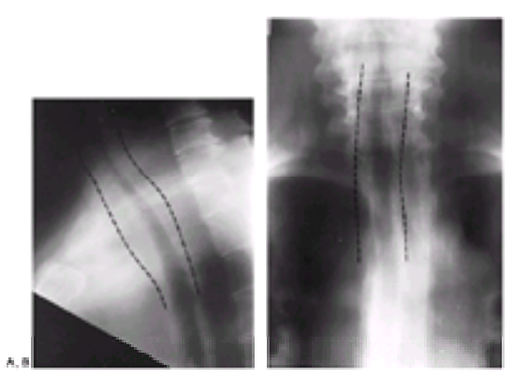

FIG. 17. Tomogram showing severely narrowed trachea as determined by the size of the air tracheogram in relapsing polychondritis. Anteroposterior view **(A)** and lateral view **(B)** delineate the normal dimensions of the trachea.

Treatment and Prognosis

Nonsteroidal antiinflammatory agents or corticosteroid (prednisolone, 30 to 60 mg/dl) often effectively suppresses acute manifestations. Refractory and recurrent disease has been treated with cyclophosphamide, 6-mercaptopurine, azathioprine, cyclosporine A, and dapsone. Major airway stenosis may require insertion of tracheobronchial prosthesis or resection if the strictures are localized. Tracheostomy may aggravate the expiratory collapse. Nasal continuous positive airway pressure or similar physiological stenting may help some patients.

Respiratory failure is the cause of death in up to 50% of patients. Among 112 patients in one report, the median survival period was 11 years from the time of diagnosis. Seven of 41 deaths were attributed primarily to pneumonia or laryngotracheal chondritis, and the 5- and 10-year probabilities of survival were 74% and 55%, respectively.

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CHAPTER

54 Vasculitis Syndromes

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INTRODUCTION

The primary vasculitis syndromes are a heterogeneous group of disorders of unknown or imprecisely determined etiology characterized by inflammation and necrosis of blood vessels. Depending on the type of vasculitis, the pathologic process may predominantly affect either the arteries or veins or both. Capillaritis is the term used to describe the pathologic process that primarily affects the capillaries. In some cases, capillaritis may be the sole pulmonary vascular manifestation of a systemic disorder. Occurrence of systemic necrotizing vasculitis in association with human parvovirus B19 and hepatitis B and C virus infections has prompted the speculation that certain vasculitic syndromes are infectious in etiology. Secondary vasculitides occur in association with collagenoses, malignancies, immunologic disorders, absence or deficiency of certain chemical mediators in the body, and mycoses, especially from *Aspergillus* and *Mucor* species. Occupational exposure has been suggested as an etiologic factor in Wegener's granulomatosis.

There is no clinically satisfactory classification of vasculitides. In the mid-1980s, the American College of Rheumatology (ACR) used preestablished criteria to determine the incidence of different vasculitis syndromes in 48 centers in the United States and Canada over a 5-year period. Among a total of 1020 patients encountered, only 807 patients met the established criteria for the diagnosis of several types of primary vasculitides. The majority of the remainder had vasculitis secondary to rheumatologic diseases. Indeed, many of the vasculitides are considered as part of the spectrum of collagenoses or rheumatologic diseases. As in the case of rheumatologic diseases, pulmonary complications are common in most of the primary vasculitides.

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is a systemic vasculitis of arteries and veins and characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract, glomerulonephritis, and variable degrees of small-vessel vasculitis. Wegener's granulomatosis is more likely a necrotizing granulomatous disorder than a true vasculitis. The Wegener's triad consists of necrotizing granulomas of the upper or lower respiratory tract or both, generalized focal necrotizing vasculitis of arteries and veins in lungs (Fig. 1) and other organs, and focal necrotizing glomerulitis. Although renal involvement with focal segmental glomerulonephritis remains a hallmark, the term *limited* Wegener's granulomatosis is used to describe Wegener's granulomatosis involving the respiratory system without glomerulonephritis. It should be noted, however, that many patients with the limited form of Wegener's granulomatosis develop renal involvement in the course of their disease, and renal biopsy shows typical morphology. Histologic features include discrete or confluent granulomatosis and necrotizing granuloma with vasculitis (Fig. 2). Fibrinoid necrosis, microabscesses, focal vasculitis, thrombosis, and fibrous obliteration of vascular lumen may be seen (Fig. 3 and Fig. 4). A report has described 16 cases of Wegener's granulomatosis in which bronchiolitis obliterans-organizing pneumonia (BOOP)-like fibrosis was the main histologic finding. Other atypical histologic variants have been recognized, including bronchocentric inflammation, a marked eosinophil infiltrate, alveolar hemorrhage, and capillaritis or interstitial fibrosis.

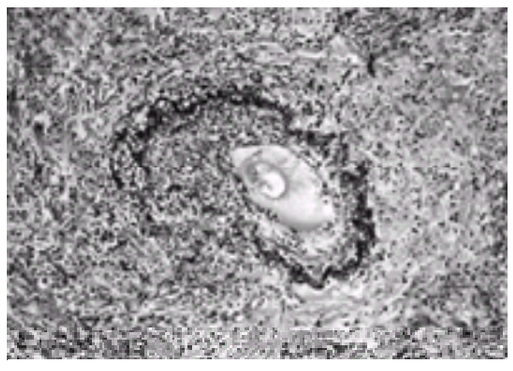

FIG. 1. Wegener's granulomatosis with vasculitis involving a medium-size vein. Inflammatory infiltrate is eccentric and segmental and is associated with destruction of the vascular elastica.

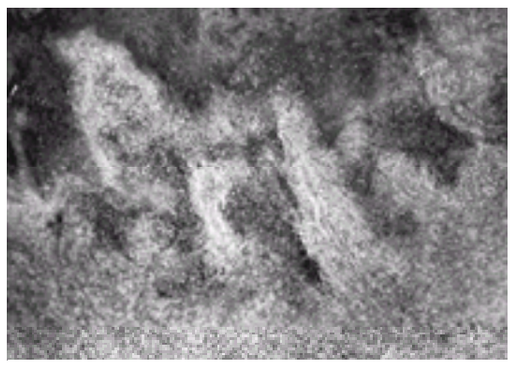

FIG. 2. Geographically dark irregular zones of necrosis in Wegener's granulomatosis are seen in a lung specimen.

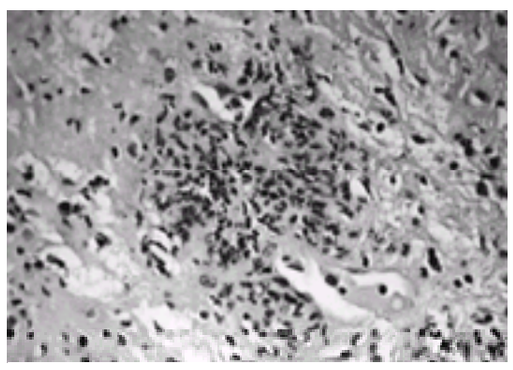

FIG. 3. An early microscopic granuloma in Wegener's granulomatosis manifests as a cluster of cells, often centered on a capillary, with central neutrophilia and surrounding histiocytes. Such a lesion ultimately would enlarge to form the characteristic geographic necrotic Wegener granulomas.

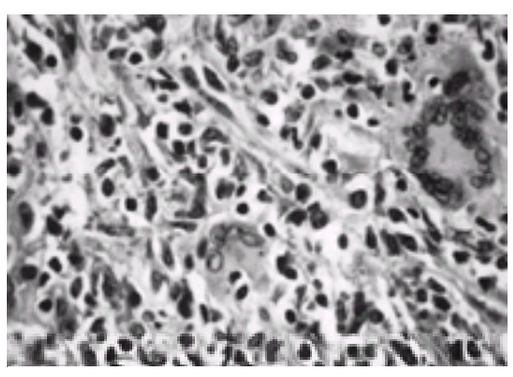

FIG. 4. Background inflammatory infiltrate in Wegener's granulomatosis includes mixed chronic inflammatory cells, usually with numerous plasma cells and occasional eosinophils as well as scattered giant cells. Sarcoid-like granulomas and nonnecrotizing granulomas are lacking.

The etiology of Wegener's granulomatosis is unknown. Occupational exposure has been suggested as an etiologic factor. When 16 cases with Wegener's granulomatosis with renal involvement were compared to 32 age- and sex-matched controls, a sevenfold risk for development of Wegener's granulomatosis was observed in those with history of inhalation of silica-containing compounds and grain dust. A Scandinavian study reported that heterozygotes for the PiZ variant of the a_1-antitrypsin gene have a sixfold risk of developing Wegener's granulomatosis relative to the general population.

The prevalence of Wegener's granulomatosis in the United States is approximately 3.0 per 100,000 persons. The annual incidence of Wegener's granulomatosis in the adult population in the United Kingdom is 8.5 per million. Between 1979 and 1988, 1784 death certificates in the United States listed Wegener's granulomatosis as a cause of death, and an estimated 10,771 hospitalizations included Wegener's granulomatosis among the discharge diagnoses. Some reports have noted a tendency for disease exacerbations during winter, but others have questioned the seasonality.

Among the 807 patients with various vasculitides studied by the ARC, 10.5% had Wegener's granulomatosis. The mean age at onset of symptoms of the disease was 45.2 years, the male-to-female ratio was 2:1, and 91% were Caucasians. Initial symptoms in Wegener's granulomatosis are nonspecific and may include fever, malaise, weight loss, arthralgias, and myalgias. The incidence of involvement of other organs is as follows: skin, 40% to 50%; eyes, 43%; arthralgias, 58%; arthritis, 28%; and neurologic involvement, 25%. The cardiovascular system also may be involved. Patients above the age of 60 years show a relatively low incidence of upper respiratory tract complaints but a high incidence (4.5-fold) of neurologic involvement.

Laboratory tests in patients with Wegener's granulomatosis may reveal mild to moderate normochromic normocytic anemia, mild leukocytosis, mild thrombocytosis, positive rheumatoid factor, and elevations of immunoglobulins IgG and IgA and circulating immune complexes. Highly elevated erythrocyte sedimentation rate (often exceeding 100 mm/hr) is one of the consistent findings. Peripheral blood eosinophilia is not a feature of Wegener's granulomatosis. All of these abnormalities are nonspecific except that they indicate a systemic inflammatory disease. Urinalysis is an important test because hematuria, proteinuria, and red cell casts are observed in 80% of patients.

The antineutrophil cytoplasmic antibodies (ANCA) are used to corroborate the diagnosis of Wegener's granulomatosis and other vasculitis syndromes. The ANCAs are perhaps involved in the pathogenesis of ANCA-associated diseases, and their presence in the blood is considered diagnostic of certain vasculitides. Two main patterns of ANCA are cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA). Almost all c-ANCA are directed to proteinase 3 (Pr3), whereas myeloperoxidase (mpo) is the major target antigen of p-ANCA. The presence of c-ANCA and p-ANCA-mpo is strongly associated with systemic vasculitis, often involving the lungs. Indeed, a study of 220 patients who tested positive for ANCA estimated that the relative frequency of pulmonary involvement was 56% in patients who tested positive for c-ANCA and 33% in patients who tested positive for p-ANCA-mpo. Patients with ANCAs other than c-ANCA (Pr3) and p-ANCA-mpo usually have nonvasculitic diseases or secondary vasculitides such as rheumatoid arthritis, ulcerative colitis, Crohn's disease, autoimmune chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis, celiac disease, dermatitis herpetiformis, and aspergillosis with oxalosis.

Cytoplasmic ANCA is highly specific and sensitive for Wegener's granulomatosis. It should be noted, however, that a positive c-ANCA without evidence of disease does not establish the diagnosis. Cytoplasmic ANCA is present in more than 90% of patients with systemic Wegener's granulomatosis, whereas in those with limited Wegener's granulomatosis, the positive rate is in the range of 67% to 86%. The overall sensitivity and specificity are 81% and 98%, respectively, for the diagnosis of Wegener's granulomatosis. However, one prospective study reported that the overall sensitivity of c-ANCA is only 28%, with an overall false-negative rate of 72%. The titers and sensitivity of c-ANCA correlate with activity of the disease, whereas the specificity of the test depends on the type of controls chosen for analysis. In active disease, the sensitivity and specificity are 91% and 98%, respectively, whereas in the inactive disease, the sensitivity and specificity are 63% and 99.5%, respectively. Thus, serial titers of c-ANCA can be used to monitor the disease and to plan long-term therapy. The following points regarding the relationship between Wegener's granulomatosis and c-ANCA are worth reiterating: (1) some patients with active disease show negative c-ANCA; (2) some patients show persistently positive c-ANCA results despite inactive disease or disease in remission; (3) c-ANCA titers may increase without evidence of increase in disease activity; indeed, fewer than 65% of patients show a concurrent change in c-ANCA titers with improvement or worsening of disease; and (4) c-ANCA is present in other diseases such as hepatitis C virus infection, some cases of microscopic polyangiitis, ulcerative colitis, and as a manifestation of sulfasalazine toxicity. A publication indicated that 44% of patients with hepatitis C virus infection tested positive for c-ANCA. The soluble serum thrombomodulin (sTM), a marker of endothelial cell injury, is reported to be a promising marker of disease activity and progression in active forms of limited and generalized Wegener's granulomatosis. The antiendothelial cell antibodies (AECA) also are reported to

correlate with disease activity. Further studies are needed to evaluate the clinical usefulness of these tests.

Acute Airways Disease

Symptoms referable to the head and neck are noted initially by more than 85% of patients with Wegener's granulomatosis. Rhinorrhea, purulent or bloody nasal discharge, nasal mucosal drying and crust formation, epistaxis, and otitis media are common. Deep facial pain from paranasal sinus involvement, nasal septal perforation, and ulceration of the vomer are important signs of Wegener's granulomatosis. The incidence of bacterial infection is increased in Wegener's granulomatosis as the result of a disruption in the mucosal barrier and failure to clear secretions. Superinfection, particularly from *Staphylococcus aureus,* is common. Other clinical signs include aphthous lesions of the nasal and oral mucosa and inflammation and destruction of the nasal cartilages leading to the saddle-nose deformity, which is usually a subacute or, more often, a chronic complication. Ulcerated lesions of the larynx and trachea are present in 30% of untreated cases. Hemoptysis in such cases may arise from mucosal ulcerations in the tracheobronchial tree, and bronchoscopic examination usually reveals extremely friable mucosa that bleeds profusely on instrumentation.

Pulmonary Parenchymal Disease

Although only one-third of patients with Wegener's granulomatosis manifest symptoms of lower respiratory tract involvement, the lower respiratory tract is involved in nearly all patients. The term *limited* Wegener's granulomatosis has been applied to isolated involvement of the lower respiratory tract in the absence of renal disease. When lungs are affected, symptoms include hemoptysis, dyspnea, cough, and chest pain. Hemoptysis, the most common symptom, was noted in 98% of patients studied by the ARC. Overall, pulmonary involvement was seen in 94%, paranasal disease in 91%, and nasal and pharyngeal involvement in 64% of patients.

Chest pain, which also is common, may be caused by pleural effusion, which is described in 5% to 55% of cases of Wegener's granulomatosis. The clinical presentation can vary from subacute nonspecific respiratory illness to rapidly progressive respiratory failure. Pulmonary symptoms are almost always associated with chest roentgenographic abnormalities. The ACR study noted abnormal chest roentgenograms in 65% of patients. An analysis of 80 patients reported from three separate studies observed the following chest roentgenographic abnormalities: unilateral, 55%; bilateral, 45%; infiltrates, 63%; nodules, 31%; infiltrates with cavitation, 8%; and nodules with cavitation, 10%. The nodules usually are rounded, range from a few millimeters to several centimeters in diameter, and commonly are bilateral (Fig. 5). One-third contain cavities, which are irregular in outline, thick-walled, and possess a shaggy inner lining (Fig. 6). Solitary nodules occur in 30% to 40% of patients with Wegener's granulomatosis. Unusual manifestations of the disease include diffuse pulmonary infiltrates (Fig. 7), lymphadenopathy, pneumonic infiltrates, lobar consolidation, and pleural effusions. Pure interstitial infiltrates are uncommon. Diffuse alveolar infiltrates may indicate alveolar hemorrhage.

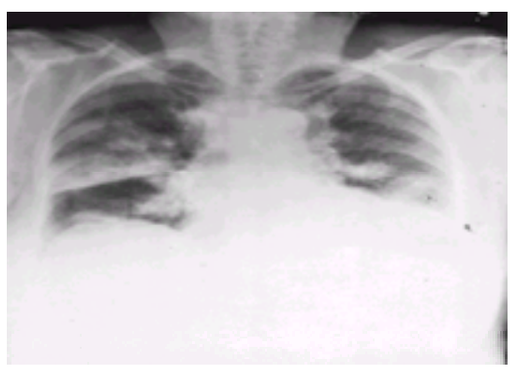

FIG. 5. Bilateral multiple nodular as well as mass-like lesions in Wegener's granulomatosis.

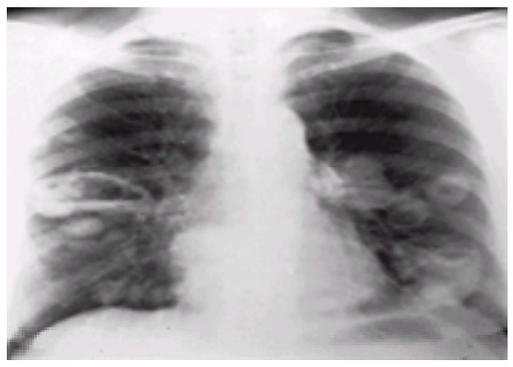

FIG. 6. Bilateral multiple cavitated nodules of various sizes in Wegener's granulomatosis.

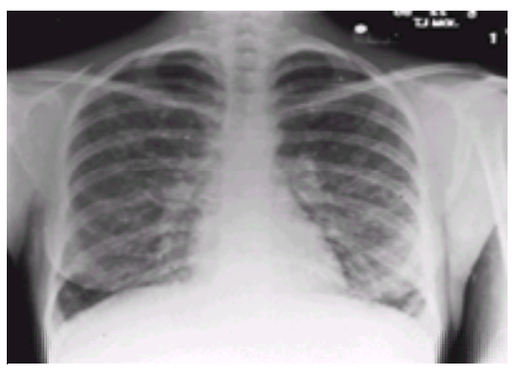

FIG. 7. Diffuse micronodular infiltrates in Wegener's granulomatosis.

Before the diagnosis of Wegener's granulomatosis can be firmly established, vasculitis secondary to infectious processes and collagenoses must be excluded. Mycobacteria, fungi, and helminths can cause systemic illness, pulmonary infiltrates, and histologic evidence of granulomatous vasculitis. The ACR classification criteria for Wegener's granulomatosis included four features: nasal inflammation, abnormal chest roentgenogram, abnormal urinary sediment, and granulomatous inflammation on biopsy. However, in the absence of biopsy, hemoptysis was used as a surrogate criterion based on the high incidence (98%) of hemoptysis. Currently, the diagnosis should be based on clinical features, the presence of c-ANCA (Pr3), exclusion of other causes of vasculitis, and biopsy if the diagnosis remains doubtful.

A study of the histologic features in 87 open-lung biopsies from 67 patients (72% of whom had classic Wegener's granulomatosis with renal involvement and 28% of whom had limited disease) yielded the following findings: interstitial fibrosis in 26%; alveolar hemorrhage in 49%; tissue eosinophilia in 100%; organizing intraluminal fibrosis in 70%; endogenous lipoid pneumonia in 59%; lymphoid aggregates in 37%; and a variety of bronchial or bronchiolar lesions including acute and chronic bronchiolitis in 51% and 64%, respectively, follicular bronchiolitis in 28%, and bronchiolitis obliterans in 31%. As noted above, bronchiolitis obliterans-organizing pneumonitis (BOOP) can be the predominant feature.

Alveolar Hemorrhage

Wegener's granulomatosis is an important cause of alveolar hemorrhage syndromes (see Chapter 57). Massive pulmonary alveolar hemorrhage is uncommon. However, it can be the presenting and life-threatening feature of Wegener's granulomatosis. Diffuse pulmonary hemorrhage from necrotizing capillaritis is seen in 5% to

45% of biopsy or necropsy cases. However, diffuse pulmonary hemorrhage is the dominant pathologic finding in fewer than 10% of all specimens. Diffuse alveolar hemorrhage has been noted in 49% of 87 open-lung biopsies from 67 patients. The alveolar hemorrhage occurs more frequently in patients with rapidly progressive glomerulonephritis and renal failure. Upper airway disease is uncommon in these patients. Patients who develop diffuse alveolar hemorrhage exhibit a more fulminant course with an acute mortality of 65%. In patients with active Wegener's granulomatosis who test positive for c-ANCA, renal disease may follow an aggressive course. In the presence of renal dysfunction and urinary sediment abnormalities, differentiating Wegener's granulomatosis from Goodpasture's syndrome (antiglomerular antibody disease) becomes difficult. Biopsy and special immunofluorescent studies may be necessary to establish the diagnosis.

Tracheobronchial Stenosis

Stenosis of major airways is a common complication of Wegener's granulomatosis. Subglottic stenosis is seen in 5% to 8% of treated patients, whereas benign-appearing stenoses of the tracheobronchial tree are more likely in chronic cases and in patients whose disease is stable. In a report on 189 patients studied by the NIH, 43 developed subglottic stenosis; this complication was diagnosed in the absence of other features of active disease in the airways, although the airway problems began while the patients were receiving systemic immunosuppressive therapy for disease activity involving other sites. Tracheostomy was required in ten of 18 patients who were treated with systemic immunosuppressive therapy. In another study of 51 patients with Wegener's granulomatosis, 30 (59%) had endobronchial abnormalities. They were caused by subglottic stenosis in five (17%), ulcerating tracheobronchitis with or without inflammatory pseudotumors in 18 (60%), tracheal or bronchial stenosis without inflammation in four (13%), and hemorrhage without identifiable source in two (4%) patients.

The symptoms tend to be insidious in onset. Pulmonary function tests, particularly inspiratory and expiratory flow–volume loops, may aid in assessing the impairment of the upper airway as well as in the follow-up of these patients. Bronchoscopy is invaluable in the assessment and treatment of airway lesions.

Treatment and Prognosis

Corticosteroids administered in combination with cyclophosphamide result in complete remission in more than 90% of patients. The usual dosage of these is up to 2 mg/kg/day of each orally. In milder cases, corticosteroids alone may be sufficient, although some believe this is inadequate. A report on high-dose prednisone and monthly intravenous cyclophosphamide therapy in 14 consecutive patients with active Wegener's granulomatosis noted long-term remission in 42% of patients. Some patients require prolonged treatment with smaller doses of corticosteroids or cyclophosphamide or both. A prospective study of 43 patients showed that only 42% of the patients showed complete or partial remission that lasted at least 6 months after cessation of pulse cyclophosphamide therapy and that pulse cyclophosphamide therapy is effective in patients with moderate disease activity and low titers of c-ANCA but of little benefit in patients with severe disease. Therefore, pulse cyclophosphamide should not be used as first-line therapy in patients with severe and rapidly progressing disease with high titers of c-ANCA. Refractory disease has been successfully treated in several cases using high-dose intravenous immunoglobulin. As observed earlier, limited Wegener's granulomatosis may not be a distinct entity because most patients with obvious respiratory involvement also have clinically undetectable renal lesions. Although the original description of the limited disease reported that these patients have an excellent prognosis, it is important to treat them aggressively.

Immunosuppression resulting from corticosteroid and cyclophosphamide therapy predisposes these patients to opportunistic infections. The overall incidence of *Pneumocystis carinii* pneumonia in these patients is approximately 6%. Cyclophosphamide predisposes to urologic complications, the most serious being transitional-cell carcinoma of bladder, which develops in 5% of patients. Those at risk are patients whose total cumulative cyclophosphamide exceeds 100 g and whose cumulative duration of therapy exceeds 2.7 years. Microscopic nonglomerular hematuria also is a significant risk factor for the development of bladder cancer. The estimated incidence of bladder cancer after the first exposure to cyclophosphamide is 5% at 10 years and 16% at 15 years.

Relapse of pulmonary Wegener's granulomatosis usually is associated with viral or bacterial infections. Respiratory infection, particularly from *Staphylococcus aureus,* is more common. Nasal carriage rate for this bacteria is higher in patients with Wegener's granulomatosis. If infections are not promptly treated or remain untreated, Wegener's granulomatosis may recur within 1 year. A prospective study has shown that a combination of trimethoprim, 160 mg/day, and sulfamethoxazole, 800 mg/day, is effective as a prophylactic drug to prevent relapse of Wegener's granulomatosis; 82% of treated patients remained in remission at 24 months compared with 60% in the placebo group. Furthermore, the treated patients had fewer respiratory infections. There were no differences in the titers of c-ANCA at any time. The prophylactic drug therapy had to be stopped in 20% of patients because of side effects. A prospective study in 72 patients reported that trimethoprim/sulfamethoxazole induced long-term remission in more than 50% of patients in the initial phase of disease; however, neither trimethoprim/sulfamethoxazole alone nor trimethoprim/sulfamethoxazole plus low-dose prednisone sustained remission in generalized disease. It appears that pregnancy may be a significant contributing factor to the relapse of Wegener's granulomatosis.

Stenosis of large airways may require various types of therapy. In the NIH study on 189 patients with Wegener's granulomatosis, 43 developed subglottic stenosis. Of the 20 patients who were treated with intratracheal dilation and glucocorticoid injection therapy, none required tracheostomy, and six with previous tracheostomies were decannulated. In a study of 51 patients with airway problems, bronchoscopic interventions included dilation by rigid bronchoscope, YAG-laser treatment, and placement of silastic airway stents; only the stents provided persistent airway patency.

Nd:YAG-laser therapy followed by stent dilation or bronchoscopic balloon dilation has been used to treat tracheal stenosis. The CO_2 laser can be used treat subglottic stenosis. Surgical resection and anastomosis of tracheal stenoses has been performed.

The American College of Rheumatology follow-up of 77 patients (over a 4.5-year period) with Wegener's granulomatosis noted 28 deaths; the standardized mortality ratios for women was 4.7, and that for men was 6.8. In a study that compared patients above the age of 60 years to those under this age, the older patients had a markedly higher mortality rate (54% versus 19%; $p < 0.01$); almost all deaths were caused by overwhelming infections.

MICROSCOPIC POLYANGIITIS

Microscopic polyangiitis or arteritis is a pauci-immune small-vessel systemic vasculitis associated with focal and segmental necrotizing glomerulonephritis without clinical or histologic evidence of granulomatosis, malignancy, or other small-vessel vasculitides. Microscopic polyangiitis is distinct from the classic polyarteritis nodosa, which typically affects medium-sized arteries. Pulmonary capillaritis is the most common lesion in microscopic polyangiitis but is absent in classic polyarteritis nodosa. Clinically, renal involvement is the major feature of microscopic polyangiitis and is characterized by rapidly progressive glomerulonephritis. Most of the patients have renal impairment at admission, and renal function deteriorates rapidly without therapy. Microscopic polyangiitis has been noted in approximately 50% of patients with necrotizing (pauci-immune) glomerulonephritis in combination with systemic small-vessel vasculitis but without granulomatous inflammation. Almost all patients are negative for hepatitis B virus surface antigen. Men are more frequently affected than women, and the median age of onset is 50 years. Most patients experience systemic symptoms. Lung involvement is common; pulmonary hemorrhage is observed in 12% to 29% and is an important contributory factor to morbidity and mortality. Microaneurysms, commonly present in polyarteritis nodosa, are rarely seen on visceral angiograms. Microscopic polyangiitis is part of a spectrum of systemic vasculitides. Differentiation between polyarteritis nodosa and microscopic polyangiitis should be based on clinical manifestations (especially lung and kidney involvement), biological signs (ANCA, infection by hepatitis B or C viruses), and angiographic data. Even though the absence of granulomatous reaction is one of the criteria for the diagnosis, an occasional patient develops changes typical of Wegener's granulomatosis. Like Wegener's granulomatosis, microscopic polyangiitis is considered a pauci-immune necrotizing vasculitis because the affected tissue specimens demonstrate normal immunofluorescence and show no evidence of circulating immune complexes.

The ANCAs are detected in 75% of patients with microscopic polyangiitis, and the majority of the ANCAs are of p-ANCA-mpo type. The p-ANCA-mpo is considered to play a role in the pathogenesis of microscopic polyangiitis. In a prospective study of 43 patients presenting with pulmonary hemorrhage, 33 underwent lung biopsies, and all 33 had pauci-immune capillaritis as the main morphologic substrate. Renal involvement (pauciimmune crescentic glomerulonephritis) was common. Of the 43 patients, 13 exhibited c-ANCA (Pr3) and 30 had p-ANCA-mpo. The p-ANCA-mpo was principally found in those patients with pulmonary capillaritis and microscopic polyangiitis. The c-ANCA (Pr3) was mainly detected in patients with alveolar capillaritis and a well-established diagnosis of Wegener's granulomatosis. The myeloperoxidase (mpo) specificity is usually not detected in diseases in which c-ANCA (Pr3) is positive unless the patient subsequently develops Wegener's granulomatosis. One-third of the patients with antiglomerular basement membrane disease (Goodpasture's syndrome) also test positive for p-ANCA-mpo. Patients with Goodpasture's syndrome who test positive for p-ANCA-mpo are more prone to develop fulminant pulmonary hemorrhage. Many patients with pulmonary capillaritis, described below, also may test positive for p-ANCA-mpo.

PULMONARY CAPILLARITIS

Pulmonary capillaritis is strictly a histologic diagnosis and denotes capillary inflammation as the sole or predominant pathologic feature. Classic histologic features include interstitial erythrocytes and/or hemosiderin, fibrinoid necrosis of capillary walls, intraalveolar septal capillary occlusion by fibrin thrombi, neutrophils, and nuclear dust in the interstitium and the adjacent alveoli, and fibrin clots attached to intraalveolar septa. Light microscopy shows extensive intraalveolar hemorrhage. Pulmonary capillaritis is not a single distinct entity, even though it may be the only pulmonary vascular feature of a systemic vasculitis. The major presenting manifestation of pulmonary capillaritis is diffuse alveolar hemorrhage. Not all patients with diffuse alveolar hemorrhage have pulmonary capillaritis. Pulmonary capillaritis has been identified in antiphospholipid antibody syndrome, Behçet's disease, Goodpasture's syndrome, microscopic polyangiitis, systemic lupus erythematosus, Wegener's

granulomatosis, IgA nephropathy, Henoch–Schönlein purpura, unclassified pulmonary–renal syndromes, and phenytoin toxicity. In a study on the histologic features of 25 open-lung biopsies and two autopsy cases from 13 patients with c-ANCA (Pr3) and 14 patients with p-ANCA-mpo, capillaritis was the most common vascular lesion, noted in 63%, and was found with similar frequency in patients with c-ANCA and p-ANCA-mpo. Pulmonary capillaritis is present in up to 40% of patients with Wegener's granulomatosis. It is seldom the only abnormality in Wegener's granulomatosis.

CHURG–STRAUSS SYNDROME

Churg–Strauss syndrome, also known as allergic granulomatosis and angiitis, is separate from hypersensitivity vasculitis and polyarteritis nodosa. Significant confusion exists in the definition of this syndrome. The original report described 13 cases of severe asthma with a strikingly uniform clinical picture including fever, hypereosinophilia, and vascular abnormality in various organ systems. The records of 11 patients who died were located through autopsy files, and in all 11 the original histologic diagnosis was polyarteritis nodosa. In 1981, the syndrome was redefined to include eosinophilic pneumonitis, eosinophilic nonnecrotizing angiitis, bronchocentric granulomatosis, allergic granuloma, and necrotizing angiitis. Nevertheless, Churg-Strauss syndrome is characterized by some as an overlap syndrome that includes hypereosinophilic disease (Löffler's syndrome), systemic vasculitides (polyarteritis nodosa and hypersensitivity vasculitis), and Wegener's granulomatosis. In many patients, the clinical and pathologic features overlap those of other systemic vasculitides. The confusion is further exacerbated by the associations, made in the published literature, among Churg-Strauss syndrome and bacterial endocarditis, chronic active hepatitis, leukemia, lymphoma, myeloma, rheumatoid arthritis, systemic lupus erythematosus, and ulcerative colitis.

Churg-Strauss syndrome is an uncommon disease. In the ACR study of 807 patients with various vasculitides, Churg-Strauss syndrome constituted only 2.5% of cases. At a large tertiary medical center, only 30 cases were identified between 1950 and 1974.

The two diagnostically essential lesions of Churg-Strauss syndrome are granulomatous or nongranulomatous angiitis and extravascular necrotizing granulomas, usually with eosinophilic infiltrates. The angiitis is disseminated and involves pulmonary and systemic arteries and veins (Fig. 8). Unlike Wegener's granulomatosis, extrapulmonary lesions are found more commonly in the gastrointestinal tract, spleen, and heart than in the kidney. Thus, renal failure is rarely seen in Churg-Strauss syndrome. Other characteristic features include pulmonary and systemic vasculitis, extravascular granulomas, and eosinophilia occurring almost exclusively in patients with asthma or a history of allergy. The limited Churg-Strauss syndrome occurs in isolated organs or tissues and in some patients with collagenoses or autoimmune disorders. The Churg-Strauss granulomas of cutaneous and subcutaneous tissues lack diagnostic specificity because approximately 50% of these lesions occur in systemic diseases other than Churg-Strauss syndrome. Hypereosinophilia in peripheral blood and elevation of serum IgE are common.

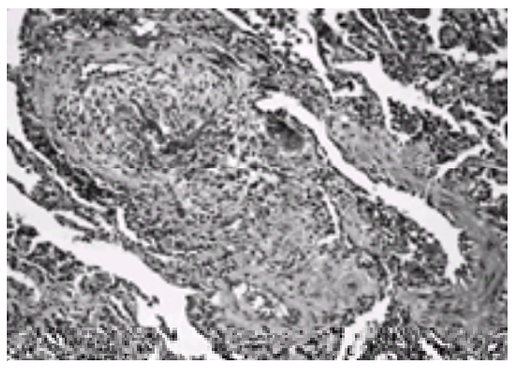

FIG. 8. Churg–Strauss syndrome involving the lung shows mixed inflammatory infiltrates including occasional giant cells *(upper center)* as well as a necrotic granuloma with central eosinophilic debris involving a vessel wall *(upper left).*

Upper Airways Disease

The 20 patients studied by the ACR had a mean age of 50 years at the onset of Churg-Strauss syndrome. Nasal symptoms such as allergic rhinitis, nasal polyps, nasal mucosal crusting, and septal perforation are present in more than 70% of patients. Nasal polyps are the major clinical finding. All 20 patients in the ACR study had chronic paranasal sinus pain or tenderness, 18 had seasonal allergy, and 14 had opacification of paranasal sinuses. In contrast to Wegener's granulomatosis, major airway involvement is seldom seen in Churg-Strauss syndrome.

Pulmonary Disease

The major pulmonary symptom in Churg-Strauss syndrome is related to underlying asthma, which is believed to be present in all patients, although the syndrome has been described in the absence of asthma in a 38-year-old man. In the ACR report on 20 patients, 19 had asthma, and all had transitory pulmonary infiltrates on the chest roentgenogram, peripheral blood eosinophilia, and mononeuritis or polyneuritis multiplex. The 15 patients, among 30 patients reported in one series, who died from Churg-Strauss syndrome had asthma for a mean interval of only 3 years before the onset of vasculitis; the mean duration of asthma among the remaining 15 survivors was 13 years. A phasic pattern of Churg-Strauss syndrome has been described, beginning with allergic rhinitis, evolving into asthma, followed by peripheral blood eosinophilia and eosinophilic tissue infiltrates, and ultimately developing to vasculitis.

In one study of 154 patients, 84 of whom were male, the mean age was 28 years at the onset of allergic rhinitis, 35 years at the onset of asthma, and 38 years when vasculitis was diagnosed. The mean peak eosinophil count was 12.9×10^9/L. Anemia was present in 83%, granulomas in 40%, tissue eosinophilia in approximately 50%, and vasculitis in more than 70%. The patients surviving longer than 1 year had a mean of 6.6 years interval between the onset of asthma and vasculitis. Whereas those who died within 1 year of onset of vasculitis had a mean interval of 4.2 years. Respiratory failure was the cause of death in 2%; 8% died from status asthmaticus. The main causes of mortality were heart failure (48%), renal failure (18%), cerebral hemorrhage (16%), and gastrointestinal hemorrhage (8%). Massive pulmonary alveolar hemorrhage, although rare, has been described in Churg-Strauss syndrome. Bronchoalveolar lavage in untreated patients has shown a high percentage of eosinophils, even though no significant correlation could be established between these results and clinical data, of pulmonary function abnormalities.

Chest roentgenographic abnormalities are present in more than 60% of patients. The findings may include patchy and occasionally diffuse alveolar–interstitial infiltrates in the perihilar area with a propensity to occur in the upper two-thirds of the lung fields (Fig. 9). Areas of cavitation rarely occur. Nodular changes seen in Wegener's granulomatosis are uncommon in Churg-Strauss syndrome, though pleural effusion can occur.

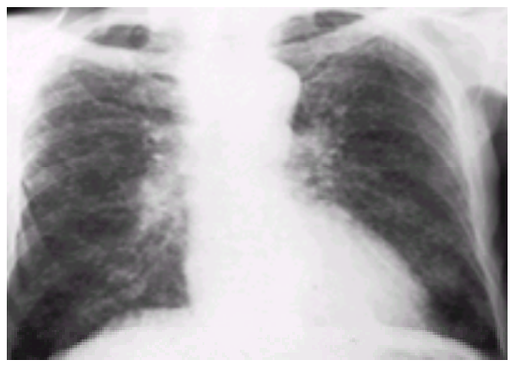

FIG. 9. Diffuse fine nodular infiltrates in Churg–Strauss syndrome. Note the relative sparing of lower lung zones and the hyperinflation from asthma.

Treatment and Prognosis

None of the 20 patients described in the ACR report died from Churg-Strauss syndrome. Dramatic response is usual following high-dose systemic corticosteroid

therapy, which should be instituted as soon as the diagnosis is made. In refractory cases, therapy using high doses of intravenous immunoglobulin has been shown to be successful.

GIANT-CELL ARTERITIS

Giant-cell arteritis, also known as *temporal arteritis, cranial arteritis,* and *granulomatous arteritis,* was the most common form of vasculitis, observed in 26.5% of 807 patients with various types of vasculitides studied by the ACR. Giant-cell arteritis is a vasculitis of unknown etiology, and, although morphologic findings are variable, the characteristic findings consist of lymphocytic infiltration with fragmentation of the internal elastic lamina, granulomatous inflammation, histiocytes, and multinucleate giant cells. The classic pathologic features of giant-cell arteritis are seen in approximately 60% of temporal artery biopsies. Although giant-cell arteritis has been described in association with polymyalgia rheumatica, the relationship between these two entities remains uncertain. Giant-cell arteritis usually affects middle-aged or older persons. There has been an increase in the annual incidence of giant-cell arteritis, with rates of 24.1 cases per 100,000 persons per year reported in the mid-1980s.

The onset of arteritis and blindness may be sudden, but usually the clinical illness has a gradual onset, with the development of nonspecific systemic symptoms such as low-grade fever, malaise, and weight loss. Headache, variable but often severe, is the most common symptom in giant-cell arteritis. The generalized symptoms may be followed by more specific symptoms such as jaw claudication and sudden loss of vision. Amaurosis fugax is observed in 20% and visual loss in 10% of cases. There are no specific laboratory tests available to diagnose giant-cell arteritis, though a moderate elevation of erythrocyte sedimentation rate is common. Overlapping features of giant-cell arteritis and Wegener's granulomatosis occur in some patients.

Pulmonary Involvement

Pulmonary complications of giant-cell arteritis were first recognized in 1984, when a report described 16 patients with giant-cell arteritis and observed that 9% of them had prominent respiratory tract symptoms. The presenting symptoms originated from the respiratory tract in 4%, and the respiratory symptoms, which included cough, sore throat, and hoarseness, were the initial findings in ten patients and resolved quickly when corticosteroids were given. A population-based study of 94 patients with giant-cell arteritis noted respiratory symptoms in 30%. With the progressive increase in the population of the elderly, giant-cell arteritis is an important diagnosis in any older patient with a new cough or throat pain without obvious cause.

Isolated small airways disease has been detected in 46% of patients with giant-cell arteritis, but the abnormalities have not been significantly different from those of the controls; chest roentgenograms in those with abnormal pulmonary function tests have been normal. However, pulmonary nodules, interstitial infiltrates, and occlusion and aneurysms of the pulmonary artery have been described. Multinodular pulmonary lesions and a diffuse interstitial pattern have resolved following corticosteroid therapy. Publications have included individual case reports of giant-cell arteritis in association with asthma, eosinophilic interstitial infiltrates, small lung nodules, pulmonary vascular disease, and focal necrosis as well as granulomatous inflammation of large and medium pulmonary arteries, as well as giant-cell arteritis limited to large pulmonary arteries. Pleural effusion has been described in a patient as the presenting manifestation of giant-cell arteritis.

Treatment and Prognosis

Virtually all patients respond favorably to systemic corticosteroids. Uniform resolution of pulmonary complications are reported following corticosteroid therapy among the patients in the literature just cited.

BEHÇET'S DISEASE

Behçet's disease is a chronic, relapsing multisystemic inflammatory disorder characterized by aphthous stomatitis along with two or more of the following: aphthous genital ulcerations, uveitis, cutaneous nodules or pustules, synovitis, or meningoencephalitis. Major and minor diagnostic criteria have been established. The prevalence rates in Japan (1:16,000) are approximately equivalent to those in the United States (1:20,000). However, the disease runs a more severe course in the Japanese and in patients from the eastern Mediterranean. HLA-B5 and its subtype B51 are three to six times more common, and the presence of B51 antigen indicates a severe course.

Histologic examination of mucocutaneous lesions is nonspecific. When present, the vasculitic lesions may exhibit varying degrees of severity with lymphocytic and plasma cell infiltration and deposition of IgM and C3 in the dermal vessels. Any large or small artery, vein, or organ may be involved in an unpredictable combination. Occlusion of major vessels and aneurysms occurs in 10% to 37% of patients. Thrombosis of superficial and deep veins of both upper and lower extremities and superior and inferior vena cavae develops in 7% to 37% of patients. Renal involvement is uncommon.

Pulmonary Involvement

The most serious respiratory complication is the occurrence of massive hemoptysis. An earlier review of the literature noted pulmonary involvement in only 13 patients, four of whom developed massive hemoptysis. Another report noted a definite clinical pattern of hemoptysis, fever, chest pain, and dyspnea in all 28 patients. Lung involvement was characteristically associated with active disease at other sites, and patients often had hemoptysis. Thrombophlebitis and hemoptysis were more common in men. Serious hemoptysis was common, initially responsive to corticosteroid therapy, showed a propensity to recur, and was the cause of death in 39%; and all deaths from hemoptysis occurred within 6 years of the onset of disease.

Another report on 49 patients with respiratory involvement noted that recurrent dyspnea, cough, chest pain, and hemoptysis were the primary clinical signs, particularly in young men, and appeared 3.6 years after the initial presentation of Behçet's disease. Fever, elevated erythrocyte sedimentation rate, and anemia were common, and chest roentgenograms demonstrated pulmonary infiltrates, pleural effusions, and prominent pulmonary arteries (Fig. 10). Aneurysms of the pulmonary artery were detected in 7 of 13 patients who underwent angiography.

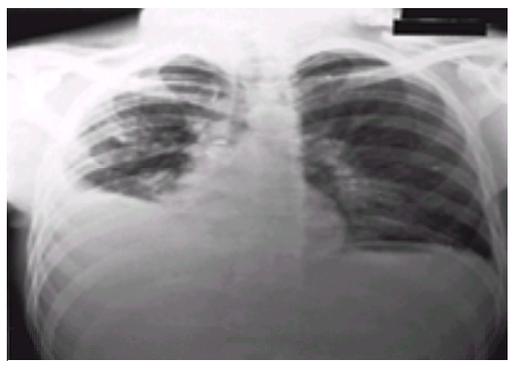

FIG. 10. Behçet's disease showing loss of lung volume on the right as a result of right lower lobectomy to treat a bronchoarterial fistula that caused massive hemoptysis. Small infiltrates seen in both lungs were caused by minor intraalveolar bleeding.

A report on Behçet's disease in 111 patients from Saudi Arabia revealed a male-to-female ratio of 3.4:1, a mean age of 29 years, oral ulcer in all patients, genital ulcer in 87%, ocular involvement in 65%, pleuropulmonary manifestations in 16%, deep venous thrombosis in 25%, and arterial thrombosis and aneurysm in 18%. Another publication on 12 patients with Behçet's disease reported that the chief complaint was hemoptysis of varying degree in 11 of the 12 patients. Chest roentgenographic abnormalities included unilateral hilar enlargements, elevated diaphragm, horizontally or obliquely oriented linear opacities, diffuse ill-defined infiltrates in the upper and lower zones, wedge-shaped peripheral opacities, and bilateral pleural effusions. Computed tomography of the thorax in nine patients with Behçet's disease and pulmonary involvement showed aneurysms, narrowing, and cutoffs of the main, lobar, segmental, or peripheral branches of the pulmonary artery and irregular configuration of other pulmonary vessels. Pulmonary angiography revealed amputation of branches of the pulmonary artery and aneurysmal dilations.

Pathologic analysis of lung tissue has shown vasculitis of pulmonary vessels of various sizes, thrombosis, pulmonary embolism, destruction of the elastic laminae, aneurysms, aphthous lesions of the tracheobronchial tree, and arterial–bronchial fistulae. Other abnormalities described include mucoid degeneration and intimal thickening of larger elastic pulmonary arteries, with medial hyperplasia, intimal fibroplasia, and angiomatoid lesions in muscular pulmonary arteries. Recurrent pneumonia and bronchial obstruction from mucosal involvement have also been reported. Immunopathologic studies indicate that pulmonary vasculitis is a result of

circulating immune complexes.

Aneurysms of the pulmonary artery communicating with the bronchial tree (bronchovascular anastomosis) should be considered in patients with Behçet's disease and hemoptysis. Because of the high incidence of deep vein thrombosis of the extremities and the vena cavae, pulmonary embolism commonly occurs in these patients. Ventilation-perfusion scans are misleading, and anticoagulant therapy for presumed pulmonary embolism can be catastrophic. Thrombolytic therapy, however, has been used with success. Even though pulmonary angiography is diagnostic, it has been stated that the chest roentgenograph is the best diagnostic method for evaluating thoracic involvement in Behçet's disease. Because aneurysms develop at the arterial puncture sites and veins become quickly thrombosed after injection of contrast material, angiography and venography should be avoided whenever possible. Computed tomography and magnetic resonance imaging are less invasive and safer in the detection of pulmonary artery aneurysms.

Chest roentgenograms may show patchy interstitial infiltrates, rounded opacities, and lobar consolidations. Cavitation and pleural involvement are uncommon. Proximal perihilar densities or opacities usually represent the lobular or segmental pulmonary artery aneurysms. Tuberculosis has been reported in patients with Behçet's disease.

Treatment and Prognosis

Corticosteroids are palliative. However, sudden deaths in corticosteroid-treated patients have indicated that corticosteroid alone may be inadequate. Drugs such as colchicine, chlorambucil, methotrexate, and azathioprine may be needed for chronic therapy. Anticoagulant therapy should be avoided in the presence of pulmonary arteritis and fistula, even though successful use of a thrombolytic drug has been reported in patients with thrombotic complications. The prognosis is poor in those who develop significant hemoptysis or diffuse pulmonary infiltrates. A review of 49 patients with respiratory involvement from Behçet's disease recorded 16 deaths, 15 from fatal pulmonary hemorrhage; 80% died within 2 years after the onset of lung disease.

TAKAYASU'S ARTERITIS

Takayasu's arteritis, also described as *pulseless disease, aortic arch syndrome,* or *reversed coarctation,* is a chronic inflammatory disease of unknown etiology that primarily affects the aorta and its major branches (including the proximal coronary arteries and renal arteries) and the elastic pulmonary arteries. Among the 807 patients with various vasculitides studied by the ACR, 7.8% met the criteria for Takayasu's arteritis.

The disease primarily occurs in young adults of Asian descent, although it has been described in the population in the West. The female-to-male ratio is 8.5:1, and 80% of patients are between 11 and 30 years of age. Pulseless disease and aortic arch syndrome are classic manifestations, but claudication and renovascular hypertension may be the more disabling complications of the disease. Initial or acute clinical features of Takayasu's arteritis include fever, malaise, weight loss, arthralgias, and night sweats lasting for 4 to 6 weeks. Chronic disease is the result of ischemia of affected organs.

Pulmonary Involvement

Although clinically not apparent, involvement of the pulmonary artery is common. Up to 50% of all patients with Takayasu's arteritis develop lesions generally localized to medium and large pulmonary arteries. One report described three patients with disease involving the aorta and its major branches, and all exhibited a unique small pulmonary arteriopathy characterized by the deficiency of the outer media, with capillary ingrowth and thickened, fibrosed intima; other histologic features included granulomatous arteritis, transmural inflammation, patchy destruction of the medial musculoelastic lamellae, and lymphoplasmacytic infiltrates confined to the media with a variable number of giant cells. Such abnormalities lead to pulmonary arterial occlusion and stenoses, which are found in the majority of cases.

A retrospective study of 180 perfusion lung scans of 120 patients with Takayasu's arteritis showed abnormalities in 76% of the patients. Initial anomalies developed in the upper lobes, whereas the middle and lower lobes were affected at later stages of the disease. There was a poor correlation between these abnormalities and results of spirometric and arterial blood gas analysis. In another study, intravenous digital subtraction angiography in 42 patients with Takayasu's arteritis showed involvement of the pulmonary artery in 14% of patients, even though the respiratory problem was not suspected clinically in any patient and the chest roentgenograms were abnormal in only two. A comparison study of 59 patients with Takayasu's arteritis showed that although chest roentgenograms were abnormal in 68%, pulmonary angiography revealed arterial occlusions in 86%. Because the disorder affects women in childbearing age, it may be recognized the first time during pregnancy. Massive hemoptysis that occurred in a pregnant woman and led to the diagnosis of Takayasu's arteritis has been described.

There are case reports of diffuse unilateral involvement of the right pulmonary artery associated with fistulas between the right coronary artery and the right pulmonary artery or between the right bronchial artery and the right pulmonary artery, with pulmonary hypertension as the presenting manifestation, and interstitial pulmonary fibrosis.

Treatment and Prognosis

Corticosteroid therapy has resulted in symptomatic remission within days to weeks. Patients with significant vascular disease may require surgical treatment. Death is usually the result of vascular complications such as rupture of an aneurysm, myocardial infarction, congestive cardiac failure, or cerebrovascular accident. Pulmonary involvement signifies a poor prognosis.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura, also known as *anaphylactoid purpura* or *allergic purpura,* is a syndrome characterized by acute purpura, arthritis, colicky abdominal pain, and nephritis. Although Henoch-Schönlein purpura is much more common in children, an adult form of the disease exists. Among the 807 cases of various vasculitides studied by the ARC, Henoch-Schönlein purpura accounted for 10.5% of cases. The mean age of the patients was 17.4 years, and nearly two-thirds were younger than 16 years old. The male-to-female ratio was approximately 1.

Pathologic features include acute arteriolitis and venulitis in the superficial dermis and the bowel. Proliferative and necrotizing glomerulonephritis usually is mild. A similar type of renal lesion is seen in patients with infective endocarditis, Wegener's granulomatosis, systemic lupus erythematosus, Goodpasture's syndrome, and polyarteritis nodosa. Immunofluorescence microscopy exhibits large deposits of IgA in the skin and kidney, but the presence of this immunoglobulin as a diagnostic indicator is questionable. Adults with Henoch-Schönlein purpura exhibit elevations in serum IgA- and IgG-containing complexes.

Palpable purpura, usually distributed over the buttocks and lower extremities, and fever are generally the first signs of Henoch-Schönlein purpura. The purpura may precede, accompany, or follow arthralgias and abdominal colic. The triad of purpura, arthritis, and abdominal pain is present in approximately 80% of patients. Joint involvement is typically monoarticular and transient, involves large joints, and causes pain out of proportion to objective evidence of synovitis. Peritonitis and melena are common.

Pulmonary Involvement

Lung involvement is rare in Henoch-Schönlein purpura. Indeed, among the 85 cases of Henoch-Schönlein purpura studied by the ARC, not a single respiratory complication was described. However, several pulmonary complications occur including perihilar patchy opacities, reticulonodular changes, and pulmonary alveolar hemorrhage. Pulmonary hemorrhage in Henoch-Schönlein purpura carries a high mortality if it is not aggressively treated. A publication on four patients with Henoch-Schönlein purpura and pulmonary hemorrhage reported that three patients survived the episode, whereas three of the four cases reported earlier in the literature did not. Several adult cases of pulmonary hemorrhage with pulmonary capillaritis have been described.

Lung function tests in 29 children with HenochSchönlein purpura at the initial phase of the disease revealed a decrease in lung diffusing capacity for carbon monoxide in 28 patients. Lung volumes and blood gas values were normal. Slight roentgenologic signs of interstitial lung involvement were observed in 18 of 26 patients. The diminished lung diffusing capacity for carbon monoxide is probably related to alteration of the alveolar capillary membrane by circulating immune complexes.

Treatment and Prognosis

High-dose corticosteroid therapy (0.5 to 1.0 mg/kg per day) results in full recovery. However, relapse of purpura, abdominal pain, and arthritis may occur for 3 to 6 weeks before the disease resolves completely.

URTICARIAL VASCULITIS

Urticarial vasculitis is a systemic disorder characterized by urticarial wheals or papules similar to those in the usual urticaria, with itching and arthralgias, in 60% of cases, arthritis in 28%, abdominal pain in 25%, and glomerulonephritis in 5%. Angioedema, fever, uveitis, episcleritis, and seizures also may occur. Urticarial vasculitis with or without hypocomplementemia occurs in systemic lupus erythematosus. The erythrocyte sedimentation rate is elevated in 66% of patients, and hypocomplementemia is seen in 38%. The hypocomplementemic form of urticarial vasculitis has been associated with pulmonary complications.

Vasculitis of the pulmonary vasculature is not characteristic of this disease. However, obstructive pulmonary disease occurs in many of these patients. Airways disease results from a combination of smoking and an immunologic process that has yet not been identified. Up to 62% of patients with hypocomplementemic urticarial vasculitis develop chronic obstructive pulmonary disease, with tobacco smoking contributing to rapid progression of the disease. A publication reported that among 17 patients with hypocomplementemic vasculitis, 11 had dyspnea, and all dyspneic patients had moderate to severe airflow obstruction, which progressed in all 11 and subsequently improved in only one. Six of the 11 patients died of respiratory failure, one underwent lung transplantation, and three of the remaining four had moderately severe to life-threatening respiratory insufficiency. Treatment did not appear to alter the progression of obstructive lung disease. In contrast, renal insufficiency in two patients improved with treatment. Another report on 16 patients with hypocomplementemic urticarial vasculitis reported severe obstructive airways disease in eight of ten smokers studied, one of whom died of lung disease. Severe obstructive pulmonary disease developed in three patients at a young age after smoking cigarettes for a relatively low number of pack-years. A review of 72 cases of biopsy-proved urticarial vasculitis revealed that 32% had hypocomplementemia and 21% had obstructive lung disease. Case reports of bilateral pleural effusion and pulmonary capillaritis characterized by repeated episodes of diffuse alveolar hemorrhage as well as progressive irreversible airway dysfunction have been published.

LEUKOCYTOCLASTIC VASCULITIS

Leukocytoclastic vasculitis is characterized by necrotizing vasculitis and fibrinoid necrosis of the vessel walls, with leukocytoclasis of the inflammatory cells in the wall of the vessel. Leukocytoclastic vasculitis may occur in association with inflammatory, autoimmune, and malignant disease. It commonly presents as palpable purpura.

Several respiratory complications have been described. Patchy pneumonitis secondary to biopsy-proved leukocytoclastic vasculitis of the pulmonary veins, manifested by hemoptysis and pleuritic chest pains, has been described in a patient who also exhibited obstructive airways disease.

MIXED CRYOGLOBULINEMIA

Mixed cryoglobulinemia is manifested by recurrent purpura, arthralgias, systemic involvement, and, frequently, elevated cryoglobulin and rheumatoid factor. Biopsy of vascular structures reveals findings similar to those in leukocytoclastic vasculitis. The most serious complication is glomerulonephritis caused by deposition of immune complexes. Lung function tests in 19 patients (17 of whom were female, with a mean age of 49.6 years) showed diminished diffusing capacity of lung for carbon monoxide and maximal expiratory flow at 50% of forced vital capacity, total lung capacity, and functional residual capacity. Respiratory complications described include bronchiectasis, pulmonary fibrosis, pulmonary insufficiency, and Sjögren's syndrome-like illness with lung involvement. Severe pulmonary hemorrhage also has been described in cryoglobulinemia.

Bronchoalveolar lavage and pulmonary function tests in 16 nonsmoking women with mixed cryoglobulinemia associated with hepatitis C virus, free of clinical pulmonary symptoms, and with normal chest roentgenograms showed a subclinical T-lymphocytic alveolitis without evidence of deterioration in lung function. No correlations between bronchoalveolar lavage results and pulmonary function tests were found; a 5-year follow-up of five patients did not demonstrate deterioration in lung function. Several reports have been published on the occurrence of diffuse pulmonary vasculitis with alveolar hemorrhage and bronchiolitis obliterans-organizing pneumonia in association with essential mixed cryoglobulinemia.

POLYARTERITIS NODOSA

Polyarteritis nodosa is characterized by a necrotizing arteritis of small and medium muscular arteries, affecting multiple organ systems. The ACR study of 807 patients with various vasculitic syndromes recorded polyarteritis in 14.6%. Differentiating polyarteritis nodosa from Churg-Strauss syndrome can be difficult. This confusion is accentuated by the fact that many reports include Churg-Strauss syndrome, classic polyarteritis nodosa, and other vasculitic syndromes under the umbrella of polyarteritis nodosa group of systemic vasculitides.

It is important to recognize that polyarteritis nodosa rarely involves the lungs. In the ACR study of 118 patients with polyarteritis nodosa, pulmonary complications were not observed in a single patient. The literature cites vasculitis in the bronchial and pulmonary vessels, but many of the patients exhibited granulomatous lesions with eosinophilic infiltrates, features more in accordance with the diagnosis of Churg–Strauss syndrome. A study published in 1993 on pathologic analysis of pulmonary diseases in ten autopsy cases of polyarteritis nodosa noted arteritis affecting bronchial arteries in seven patients and diffuse alveolar damage involving all lobes bilaterally in five patients. The diffuse alveolar damage was acute in two patients and organizing in three. Five patients died of respiratory failure resulting from diffuse alveolar damage. Anecdotal cases of pulmonary arterial involvement have been described.

EOSINOPHILIA-MYALGIA SYNDROME

The eosinophilia-myalgia syndrome is a multisystem inflammatory disease with characteristic features of myalgia and eosinophilia. This syndrome occurred in epidemic proportions in the United States during 1989, affecting more than 1500 persons and causing approximately 30 deaths. Cases of the eosinophilia-myalgia syndrome have been reported from Canada, Europe, and other countries.

Epidemiologic studies have demonstrated that the eosinophilia-myalgia syndrome is the result of ingestion of L-tryptophan, used by lay people as a remedy for insomnia, depression, premenstrual syndrome, and other health disorders. Several contaminants—3(phenylamino)alanine, 1,1'-ethylidenebis(tryptophan), and 3-anilino-L-alanine—involved in the manufacturing of L-tryptophan have been implicated as the causative agents of both the eosinophilia-myalgia syndrome and the Spanish toxic oil syndrome.

The clinical manifestations resemble those of the Spanish toxic oil syndrome, caused by ingestion of adulterated rapeseed oil. Symptoms and signs include myalgias, fatigue, muscle weakness, arthralgias, edema of the extremities, skin rash, oral and vaginal ulcers, scleroderma-like changes, fasciitis, ascending neuropathy, and profound eosinophilia.

Respiratory complications were observed in approximately 60% of patients with the eosinophilia-myalgia syndrome. Pulmonary manifestations included parenchymal lung infiltrates associated with severe respiratory distress and progressive hypoxemia, pleural effusion, diffuse bilateral reticulonodular infiltrates, and pulmonary hypertension. In a study of five cases of pathologically proved eosinophilia-myalgia syndrome, all patients were women ranging in age from 34 to 65 years, and all presented with pulmonary symptoms that began after 1 to 9 months of L-tryptophan therapy. Four patients exhibited peripheral eosinophilia and bilateral interstitial infiltrates (one had a normal chest roentgenogram). Lung specimens revealed vasculitis and perivasculitis associated with eosinophilia and mild interstitial pneumonitis. Clinical or morphologic evidence of pulmonary hypertension was noted in three, and one patient had follicular bronchiolitis. Whereas four patients responded promptly to discontinuation of Ltryptophan ingestion and systemic corticosteroids, one patient showed only minimal symptomatic improvement.

Other histologic changes described in the lungs of patients with the eosinophilia-myalgia syndrome have included alveolar exudate made up of eosinophils and histiocytes, changes characteristic of hypersensitivity pneumonitis, interstitial and perivascular infiltrates, and fibrointimal hyperplasia of small pulmonary vessels (Fig. 11).

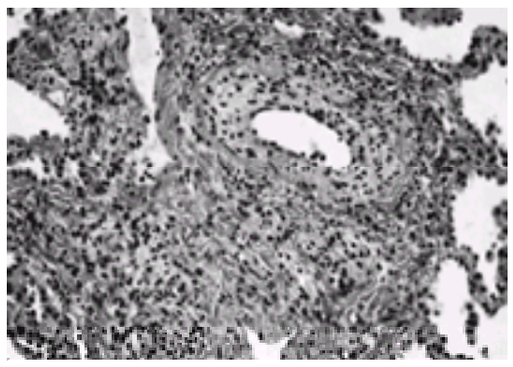

FIG. 11. Pulmonary involvement in L-tryptophan-induced eosinophilia-myalgia syndrome. A mixed inflammatory infiltrate involves a septal vein. There is marked intimal proliferation and infiltration by cells that include relatively numerous eosinophils.

SECONDARY VASCULITIS

Many of the rheumatologic diseases, discussed in Chapter 53, may exhibit secondary vasculitic processes in the organs involved. Infectious processes, particularly secondary to *Aspergillus* and *Mucor* species, invade vascular structures and produce secondary vasculitis. The role of hepatitis C virus in the causation of vasculitis is now well recognized. Certain drugs and chemicals also can induce vasculitis. Other uncommon secondary vasculitic entities include benign lymphocytic angiitis and granulomatosis, bronchocentric granulomatosis, and necrotizing sarcoid angiitis. Whether these are distinct entities or represent uncommon phases of the vasculitides discussed in this chapter is unclear.

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CHAPTER

55 Immunodeficiency Diseases

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INTRODUCTION

Immunodeficiency diseases are encountered in different forms, often in association with other diseases. Disorders of immunodeficiency, whether total or partial, can be congenital or acquired. These disease states are the consequences of impaired function in one or more components of the immune system, including both B and T lymphocytes, phagocytes, and the complement system. Immunodeficiency can develop as a sequel of malignancy, long-term corticosteroid therapy, cytotoxic chemotherapy, malnutrition, or alteration of the helper-suppressor T-lymphocyte ratio as seen in the acquired immunodeficiency syndrome (AIDS). Because the clinical features of immunodeficiency states are not highly specific and vary from one entity to another, definitive diagnosis is often delayed. Normally, these immunodeficiency syndromes are recognized when a subject develops a predisposition to unusual or recurrent infections. The majority of these infections occur in the respiratory system and are the most common cause of morbidity and mortality.

In this chapter, immunodeficiency syndromes and etiologic and diagnostic evaluation of the immunocompromised patients including recipients of bone marrow and heart organ transplantations are discussed. Pulmonary complications of human immunodeficiency virus infection (HIV) are discussed in Chapter 26.

IMMUNODEFICIENCY SYNDROMES

X-Linked Agammaglobulinemia

Also known as Bruton's infantile agammaglobulinemia, X-linked agammaglobulinemia is a disease characterized by a disorder of B-lymphocyte maturation. As a result, the synthesis and secretion of immunoglobulins and antibodies are deficient or absent, leading to recurrent infections. T-lymphocyte function remains intact, and indeed, the number of T cells is usually increased. A diagnosis of X-linked agammaglobulinemia is considered if serum levels of IgG, IgA, and IgM are significantly below the 95% confidence limits for appropriate age- and sex-matched controls. The total immunoglobulin level in patients with X-linked agammaglobulinemia usually is less than 100 mg/dl.

Clinically, recurrent sinopulmonary infections, otitis, meningitis, and skin lesions (eczema) are encountered in infants between 4 and 6 months of age. Allergic rhinitis and asthma occur at a higher rate than in the normal population. Undue susceptibility to bacterial infections is seen, usually after the first year of life. An important clue to the diagnosis is a unique susceptibility to infection with encapsulated pyogenic organisms, including *Streptococcus pneumoniae, Streptococcus pyogenes, Hemophilus influenzae, Pseudomonas aeruginosa,* and staphylococci. This phenomenon probably reflects a requirement for specific opsonization of these bacteria before efficient phagocytic cell ingestion is possible. Recurrent purulent sinusitis, bronchitis, and pneumonia, if untreated, may develop into progressive bronchiectasis and secondary respiratory failure. Adults with the disease are specially prone to *Mycoplasma* infection of the respiratory tract. *Pneumocystis carinii* pneumonia, although rare in agammaglobulinemia, has been described in congenital agammaglobulinemia. There is no evidence of increased susceptibility to viral infections of the respiratory system, but these patients are prone to viral infections of the central nervous system. Restrictive lung disease and lymphocytic interstitial pneumonitis are the other long-term pulmonary complications.

In a multicenter study involving 96 patients (53 familial and 43 nonfamilial) with X-linked agammaglobulinemia, pulmonary infections were observed in 65%: pneumonitis in 56%, bronchitis in 9%, and bronchiolitis in 5%. Bacterial cultures of sputum were available for 33 patients with chronic or recurrent pneumonia; bacterial species isolated included *H. influenzae* in 82%, *S. aureus* in 27%, and *S. pneumoniae* in 21%. Chronic pulmonary disease was the most frequent long-term complication, occurring in 46% of all patients. The prevalence of lung disease was age-related, present in 13% of those younger than 10 years and 76% of those older than 20.

High-dose intravenous immunoglobulin therapy has been shown to prevent recurrent infections. A clinical evaluation of 10 patients with X-linked agammaglobulinemia followed for a mean of 12.5 years reported that most patients treated with intramuscular gamma globulin and long-term oral antibiotics had very few pneumonias.

Common Variable Immunodeficiency

Common variable immunodeficiency, also known as acquired agammaglobulinemia, is among the most frequently encountered primary immunodeficiency disorders. Genetic basis exists for this disorder because it more commonly occurs in first-degree relatives of patients with selective IgA deficiency. A primary defect in B-cell maturation is the problem. Most patients with this disorder have normal number of immunoglobulin-bearing B cells in their blood and lymphoid tissue but lack mature plasma cells. Depressed T-cell function has been noted. Serum levels of IgG are absent or low, and IgA and IgM are variably diminished; thus, antibody production is diminished. There is, however, a tendency to autoantibody formation. The role of immunologic defense mechanisms in the development of acute or recurrent or chronic sinusitis is obviously important, but the incidence of such immune problems is unknown. Common variable immunodeficiency has been known to be associated with thymoma, hemolytic anemia, gastric atrophy, achlorhydria, follicular lymphoid hyperplasia, celiac disease-like syndrome, and several other disorders.

Common variable immunodeficiency occurs in both sexes and usually presents in the second or third decade, although its onset may occur at any age. Pulmonary disease occurs more commonly and is more severe than in patients with X-linked agammaglobulinemia. Sinopulmonary infections begin in the second or third decade. Chronic complications include bronchitis, cystic bronchiectasis, patchy pulmonary fibrosis, and interstitial pneumonitis. Infections caused by encapsulated bacteria are more common. Bronchiectasis and obstructive airway disease occur in up to 40% of patients. Roentgenographic features may include atelectasis, bronchiectasis (Fig. 1), and homogeneous and heterogeneous segmental opacities. Patients with late-onset agammaglobulinemia and recurrent pulmonary infections have occasionally presented with pulmonary hypertrophic osteoarthropathy. In a review of patients who developed pneumonia or empyema as a result of infection with *Moraxella catarrhalis,* nearly one-third were found to have immunoglobulin abnormalities. Bronchiolitis obliterans with organizing pneumonitis (BOOP) and allergic

bronchopulmonary aspergillosis also are described in common-variable immunodeficiency.

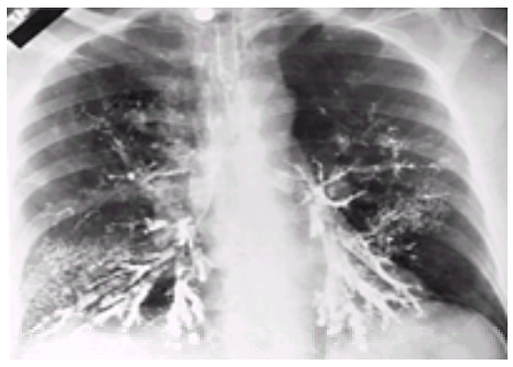

FIG. 1. Bronchography demonstrating bronchiectasis of both lower lobes in a patient with acquired agamma-globulinemia.

A clinical evaluation of 12 patients with common-variable immunodeficiency followed for a mean of 10.5 years revealed that most patients treated with intramuscular g-globulin and long-term oral antibiotics had very few pneumonias.

Selective Immunoglobulin Deficiencies

Selective deficiencies of one or more, but not all, immunoglobulin subclasses are characterized as dysgamma-globulinemias. Patients with these disorders usually demonstrate normal total serum IgG concentrations. Thus, it is important to measure levels of IgG subclasses in patients suspected of having selective immunoglobulin deficiencies. It is also important to recognize that the majority of patients with selective deficiencies of IgG subclasses are asymptomatic, and routine administration of intravenous immunoglobulin therapy is not justified unless they are known to have clinical features of the disorder.

Immunoglobulin A deficiency (less than 10 mg/dl), whether isolated or in combination with deficiency of another Ig subclass, is the most commonly occurring immunoglobulin deficiency. The estimated incidence of selective IgA deficiency ranges from one in 333 to one in 1000, with most occurring sporadically, although some persons inherit it as an autosomal dominant or a recessive trait. Deficiency of IgA, combined with deficiencies of IgG_2 and IgG_4, increases the risk of recurrent respiratory infections. Bronchitis and bronchiectasis are associated with greater numbers of cells that produce IgA in the bronchi because cells that contain IgA_1 predominate in the major bronchi and the number of cells containing IgA_2 is higher in the bronchi than in nonmucosal lymphoid tissues. A study that evaluated 29 patients with IgA deficiency and recurrent upper and lower respiratory infections observed decreased levels of IgG_2 and IgG_3 in 21% of patients; low levels of IgG_2 and IgG_3 were also significantly related to abnormal lung functions. These studies suggest that there may be a causal relationship between low levels of IgG subclasses and deterioration in lung function, implying that patients with combined IgA and IgG subclass deficiencies may benefit from immunoglobulin prophylaxis. As is the case in common-variable immunodeficiency, selective IgA deficiency frequently exists with rheumatologic and collagen disorders including rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, ankylosing spondylitis, thyroiditis, diabetes mellitus, hepatitis, drug toxicity, and a significant number of other disorders.

Respiratory complications usually are mild and include atopic asthma, repeated respiratory infections, bronchiectasis, sinusitis, and otitis media. Pulmonary hemosiderosis has been described in some patients. A prospective study of 43 children reported that the probability of developing asthma was much higher in those without any measurable IgA and elevated IgE. Variable deficiencies of IgG and IgA in children have been associated with lymphoid interstitial pneumonitis. The factors responsible for the B-lymphocyte dysfunction and lymphoid infiltrations in the pulmonary parenchyma are unknown.

Recurrent bacterial infections of the lungs and upper respiratory tract are common in these patients. Selective IgG subclass (IgG_1, IgG_2, IgG_3, and IgG_4) deficiencies predispose patients to recurrent infections of the ears, upper respiratory tract, and lungs. Encapsulated bacteria such as *S. pneumoniae* and *H. influenzae* are responsible. Deficiencies of IgG, especially subclasses IgG_2 and IgG_4 (often in combination with IgA) or IgG_4 alone, correlate well with upper respiratory tract infections and chronic bronchial inflammation that contribute to bronchiectasis. Asthma has been noted in some patients with this disorder. Deficiency of IgG_3 and poor response to pneumococcal antigen 7 were demonstrated in more than 50% of 61 pediatric patients with refractory sinusitis. Isolated IgG_4 deficiency appears to be associated with impaired respiratory tract defenses and may occur in the absence of an easily definable antibody deficiency state. Acquired hypogammaglobulinemia rarely is associated with obstructive lung disease, and the pathogenesis of lung disease may be related to an associated increase in elastase load and a reduction in protease inhibitor function.

Functional deficiency of IgG may come to light in patients who present with recurrent pulmonary infections, but such patients may have normal serum levels of IgG. Furthermore, combined deficiencies of IgG_2 subclass and IgG- and IgM-specific antibodies may be associated with normal serum immunoglobulin concentrations. For instance, IgG_2 contains an important group of antibodies against common bacteria such as *S. pneumoniae* and *H. influenzae,* and patients with this isolated deficiency may develop recurrent sinopulmonary infections despite normal serum levels of total IgG. Patients with community-acquired pneumonia of bacterial or unknown cause generally demonstrate decreased concentrations of serum IgG_2 subclass at the time of admission, after recovery, and 9 months later. In patients with recurrent lung infections and bronchiectasis who show normal serum concentrations of immunoglobulins, it is important to determine both IgG subclasses and antibody production because immunoglobulin replacement has been shown to be beneficial in these patients. Other functional deficiencies of IgG result from an absence of IgG antibody response to polysaccharide antigens and antibody deficiency because of IgG degradation, such as that found in cystic fibrosis. Immunoglobulin G subclass deficiencies, particularly IgG_1, appear to be related to long-term, low-dose corticosteroid therapy in patients with obstructive lung disease. After immunization with pneumococcal vaccine, the increases in serum concentrations of IgG subclass and antipneumococcal antibodies in patients do not differ from those in control subjects.

Familial deficiency of serum IgE, presumably an autosomal dominant trait with variable penetrance, associated with sinopulmonary infections has been described. Examination of sera from 23 family members, of whom 14 were symptomatic, revealed very low levels (less than 5 IU/ml) of serum IgE in 12 of the symptomatic group.

Selective IgM deficiency (less than 10 mg/dl) is a rare disorder. Respiratory complications described have included otitis, bronchiectasis, and lung infections caused by streptococci, mycobacteria, and other organisms. There is no specific therapy other than appropriate antimicrobial treatment of bacterial infections.

Hyperimmunoglobulinemia E

Hyperimmunoglobulinemia E, also known as Job's syndrome or Buckley's syndrome, is a rare disorder characterized by phagocyte dysfunction, high serum IgE (often above 4000 IU/ml) and IgD levels, poor antibody- and cell-mediated responses to new antigens, blood and sputum eosinophilia, and normal concentrations of IgG, IgA, and IgM. Both sexes are affected; an autosomal dominant form of inheritance has been suggested. More than 100 cases of this disorder have been described, mostly in young children. Severe and recurrent staphylococcal abscesses involving skin, lungs, and joints begin in infancy.

Clinically, the syndrome may include eczematoid dermatitis, dysmorphic syndrome with retarded growth, coarse facies, prognathism, osteogenesis imperfecta, and axial osteoporosis. Respiratory complications include sinusitis, pneumonia, and bronchiectasis caused by *S. aureus, S. pneumoniae,* gram-negative bacilli, *Candida albicans,* and *Aspergillus* species, pneumatoceles, and chronic dermatitis. Asthma has been reported in approximately 10% of patients. The frequency of pneumatoceles is remarkably high, and surgical therapy often is necessary (Fig. 2). The primary chest roentgenologic abnormalities include recurrent lung infiltrative process and pneumatoceles. Pneumothorax may occur occasionally.

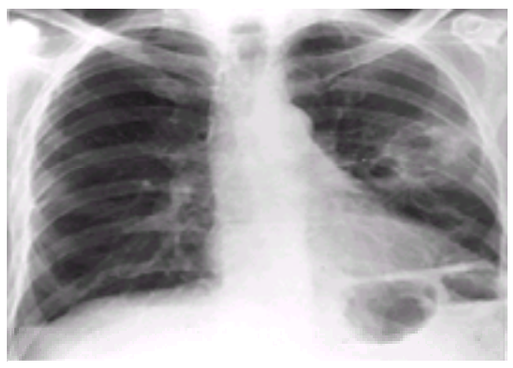

FIG. 2. Hyperimmunoglobulinemia E syndrome (Job's syndrome) with left lung abscess caused by *Staphylococcus aureus.* Beginning stages of pneumatoceles, a common complication in this syndrome, can be seen.

Hyperimmunoglobulinemia M

Hyperimmunoglobulinemia M with hypogammaglobulinemia is an uncommon syndrome that has been described as both an X-linked and an autosomal recessive disease. Patients with this disorder become symptomatic during the first or second year of life. Occasional sporadic cases occur in later life. The tests of cellular immunity are normal, but abnormalities in immunoglobulin production are believed to be the result of dysfunctional regulation of B cells by defective T cells. Patients with this syndrome usually exhibit elevated levels of IgM and IgD but very low levels of IgA and IgG. Patients demonstrate a propensity to pyogenic infections, including otitis media, sinusitis, and pneumonia. Because these patients do not have the ability to make IgG antibodies, the therapy includes monthly immunoglobulin administration.

Thymic Aplasia

Congenital thymic aplasia or DiGeorge's syndrome, is characterized by thymic aplasia or hypoplasia due to dysmorphogenesis in the third and fourth pharyngeal pouches during embryogenesis. Other abnormalities that result from this include failure of the development of parathyroid glands, neonatal hypocalcemia and tetany, and cardiac defects, including tetralogy of Fallot, right-sided aortic arch, and truncus arteriosus. Immunologic defect is the result of T-lymphopenia. Lymphocyte counts are normal, but all lymphocytes are B cells. Serum immunoglobulin concentrations usually are normal, but IgG and IgA antibody responses frequently are impaired.

Pulmonary complications described include both viral and bacterial infections and interstitial pneumonitis. Other pulmonary abnormalities reported include hypoplastic lungs with abnormal anatomic location and hypoplastic pulmonary artery.

Wiskott–Aldrich Syndrome

The Wiskott–Aldrich syndrome is a rare X-linked immunologic disorder characterized by the clinical triad of eczema, profound thrombocytopenia with purpura, and recurrent infections. Deficiency of IgM, elevated levels of IgA and IgG, and very high levels of IgE are seen frequently.

Respiratory complication in the form of otitis media followed by pneumonia is common. In younger patients, bacterial infections are more commonly caused by encapsulated organisms. Patients are also susceptible to herpes simplex, cytomegalovirus, *P. carinii,* and varicella infections. Gram-positive and gram-negative bacterial infections are common. Pulmonary vasculitis with features typical of lymphomatoid granulomatosis has been described. Survival beyond the teenage years is uncommon. Nearly 12% of patients develop fatal malignant neoplasms, and more than 80% of these lesions are leukemias and lymphoreticular tumors. However, infections and bleeding are the major causes of mortality.

Idiopathic $CD4^+$ T-Lymphocytopenia

A report on four patients with opportunistic infections and without major risk factors for HIV infection described the phenomenon of idiopathic $CD4^+$ T-lymphocytopenia. All four patients had severe, persistent $CD4^+$ T-lymphocytopenia (range, 12 to 293 cells/mm^3); the $CD4^+$ cell count progressively declined in only one. All four patients had significantly reduced numbers of circulating $CD8^+$ T cells, natural killer cells, or B cells (or all three). All presented with severe opportunistic infections including *Pneumocystis carinii* pneumonia, cryptococcal meningitis (two patients, one with concurrent pulmonary tuberculosis), and histoplasmosis-induced brain abscess. During up to 68 months of observation, none of the four patients had evidence of infection with HIV.

Ataxia-Telangiectasia

Transmitted as an autosomal recessive disease, hereditary ataxia-telangiectasia is characterized by progressive cerebellar ataxia followed by choreoathetoid movements and, several years later, development of ocular and cutaneous telangiectasia. Dysfunctional helper T cells may account for the underlying diminished activity of B cells. Lack of both serum and secretory fractions of IgA is noted in more than 80% of patients, and serum IgA is absent in approximately 50%. Deficiency of IgG_2 is common. Isolated deficiency of IgG_4 with normal levels of total IgG and other subclasses occurs.

Chronic sinopulmonary infections caused by bacteria occur in 80% of patients. These may lead to severe bronchiectasis. This complication has been observed in children as well as in adults. Repeated infections of the sinuses and lungs from viral agents and bacteria are common (Fig. 3). Chest roentgenograms have demonstrated a prominent, symmetric thicket-like pattern in the lungs. One study of 160 patients with ataxia-telangiectasia reported recurrent sinopulmonary infections in 66% of patients and low or absent serum IgA in 51%.

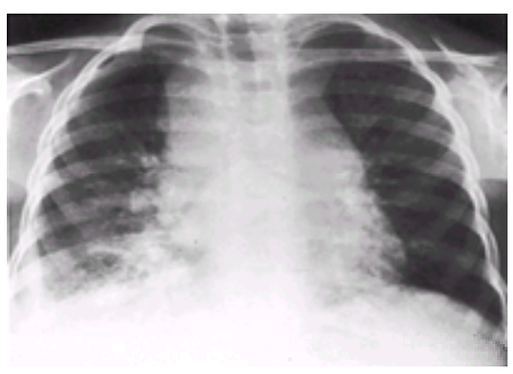

FIG. 3. Bilateral lower-lobe infiltrates in a child with ataxia-telangiectasis. This patient has recurrent pulmonary infections caused by *Hemophilus influenzae.*

Patients with ataxia-telangiectasia have a marked propensity to develop lymphoma and acute lymphocytic leukemia, and more than 10% succumb to malignancy.

Nezelof's Syndrome

Nezelof's syndrome denotes thymic dysplasia with normal immunoglobulins. It is an inherited disorder characterized by lymphopenia, diminished lymphoid tissue, abnormal architecture of thymus, and normal or elevated immunoglobulin levels. Flawed function of interleukin-2 has been observed in several patients. Deficiency of T-cell function is the main abnormality in these patients, although Nezelof's syndrome sometimes is discussed in conjunction with the severe combined immunodeficiency syndrome. Although this is normally a disease of children, several adult cases have been described. Recurrent respiratory infections secondary to

bronchiectasis and sinusitis are common. Fatal bronchiolitis caused by cytomegalovirus has been described in a child.

Hyposplenism

Decreased or absent splenic function occurs in congenital aplasia, splenectomy, hyposplenism secondary to hemolytic states, malignancy involving the spleen, and chronic sickle-cell disease. Phagocytosis of encapsulated bacteria is dependent on normal splenic function. Hyposplenism results in loss of protection against encapsulated organisms such as *S. pneumoniae* and *H. influenzae.* Pneumococcal vaccine and prompt treatment of infections are important.

PULMONARY DISEASE IN THE IMMUNOCOMPROMISED PATIENT

The term immunocompromised patient or compromised host generally describes a patient whose defense mechanisms are impaired, thereby rendering the patient more susceptible to infections. However, the pulmonary abnormalities in these patients do not always represent an infectious process. The etiologic possibilities for the abnormal chest roentgenogram in the immunocompromised patient are varied because the lungs are involved in most of the complications in such a patient. If the pulmonary involvement is diffuse, the mortality approaches 50%.

Most immunocompromised patients with diffuse pulmonary infiltrates exhibit typical clinical features: fever, nonproductive cough, dyspnea, abnormal chest roentgenograms, anemia, normal or low leukocyte count, decreased platelet count, and hypoxemia of varying degree. Many of these features also are dependent on the underlying primary disease. The chest roentgenogram is rarely helpful in making a definitive diagnosis. Faced with a rapidly deteriorating immunocompromised patient with progressive chest roentgenographic abnormalities, the clinician is forced quickly to consider a myriad of diagnoses. Simplifying the possibilities by grouping the differential diagnoses in such a patient is extremely helpful in planning the appropriate diagnostic procedures and administration of optimal therapy (Table 1). In almost all immunocompromised patients, the first indicator of respiratory complication is an abnormal chest roentgenograph. The abnormal chest roentgenogram in the immunocompromised patient may indicate one or more of the following diagnoses: (1) extension of the basic disease process, (2) opportunistic infection, (3) drug-induced lung disease, (4) alveolar hemorrhage, (5) nonspecific interstitial pneumonitis, (6) lymphocytic interstitial pneumonitis, (7) B-cell neoplasia and other cancers associated with chronic immunosuppression, (8) a new pulmonary problem unrelated to the preceding diagnoses, or (9) a combination of two or more of the preceding diagnoses. Among these, the first four complications can produce acute or life-threatening respiratory distress, whereas the others can be subclinical and cause subacute or slowly progressive chronic illness.

Extension of basic disease process into the lungs
Opportunistic lung infections
Drug-induced lung disease
Alveolar hemorrhage
Obstructive airways disease
Nonspecific interstitial pneumonitis
Lymphocytic interstitial pneumonitis
Pulmonary "immune" neoplasia
Pulmonary problem unrelated to immunodeficiency
Combination of two or more of the above

TABLE 1. *Differential diagnosis of pulmonary disease in the immunocompromised patient*

Up to one-third of immunocompromised patients have two or more of the complications listed above. The most common types of impaired defense mechanisms are reductions in the number of granulocytes, B lymphocytes, and T lymphocytes. Nearly one-fourth of the pulmonary complications in these patients are noninfectious. The increasing use of chemotherapeutic agents, with consequently more frequent remissions and relapses of the basic disease process and more frequent cytotoxic pulmonary reactions to the chemotherapy, has made it increasingly difficult to pinpoint the cause of a pulmonary abnormality in a compromised host. Because some of the respiratory problems are associated with a rapid downhill clinical course, it is imperative that diagnostic consideration of an abnormal pulmonary process include the following steps: (1) recognition of the patient as an immunocompromised host, (2) definition of the derangement of the host defense mechanism, (3) categorization of chest roentgenographic and computed tomographic abnormalities, (4) assessment of the degree of urgency with regard to various diagnostic procedures, and (5) determination and performance of the most productive diagnostic procedure. This step-by-step approach is most likely to help in designing the optimal therapy in this group of patients.

Recognition that the patient is at added risk of infection is the first important step toward diagnosis of the pulmonary process. The various immunodeficiency syndromes that may be seen in immunocompromised patients were discussed earlier. The patients who are organ transplant recipients, discussed below, should be included in this category of immunocompromised patients. Additionally, local mechanical factors that predispose these patients to special problems include diseases of the airways, defects in mucociliary clearance, deficiency of secretory IgA, absence of surfactant from acute lung injury, and preexisting pulmonary structural damage such as bullous lesions, bronchiectasis, ancient cavities, and a fibrotic process. The etiologic factors of pulmonary abnormalities in compromised hosts are outlined in Table 2 and Table 3. Each of the broad categories of diagnostic possibilities listed in Table 1 is briefly described below.

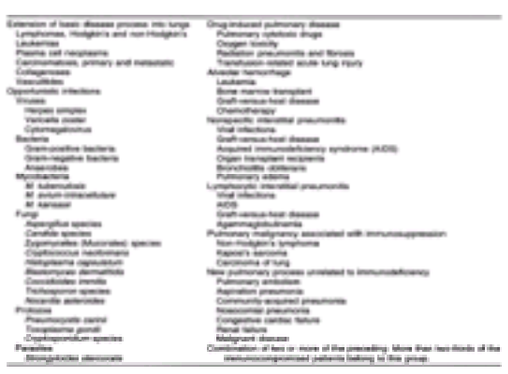

TABLE 2. *Etiologic classification of pulmonary complications in the immunocompromised patient*

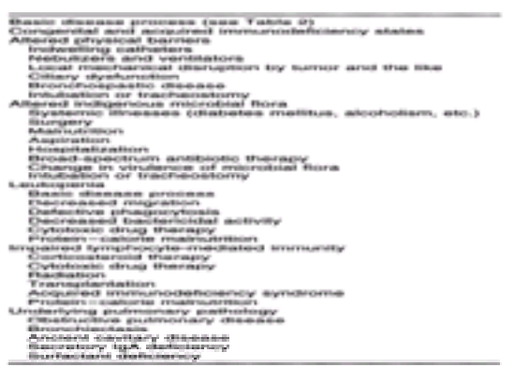

TABLE 3. *Factors predisposing the host to opportunistic pulmonary infection*

Differential Diagnosis

Pulmonary Extension of Basic Disease Process

The basic disease processes listed in Table 2 are often associated with various degrees of suppression of immune defense mechanisms. In the present context, patients with such disorders may be considered as compromised hosts. When presented with pulmonary problems in such a patient, the clinician must ascertain whether the pulmonary manifestations represent extension of the basic disease into the lungs or other complications. Intrathoracic spread of primary pulmonary and extrapulmonary malignancies together constitutes the most common cause of pulmonary extension of the basic disease process. Lymphangitic metastases from pulmonary and nonpulmonary malignancies should be included in the differential diagnosis of lung infiltrates in this group.

Hematologic malignancies, especially leukemias and lymphomas, also can produce chest roentgenographic abnormalities (Fig. 4). Leukemias as a group exhibit mediastinal and hilar lymphadenopathy in 50% of cases at autopsy and pulmonary involvement in 25%. Occasionally, patients may present with acute respiratory distress from extensive leukemic infiltrates in the lungs. Hodgkin's lymphoma produces roentgenographically detectable mediastinal lymphadenopathy in 50% of patients and pulmonary parenchymal lesions in 30%. Non-Hodgkin's lymphoma exhibits mediastinal lymphadenopathy in 35% of cases. Primary pulmonary lymphoma may present as an alveolar infiltrate or as a homogeneous mass. In such cases, elaborate diagnostic investigations may be necessary to rule out an extrapulmonary focus of the lymphoma. Lung involvement is more common in untreated lymphoproliferative diseases than in myeloproliferative diseases. Opportunistic infections are the most common cause of morbidity and mortality in these patients. However, opportunistic infections of lungs are very uncommon in patients with hematologic malignancies who have no history of chemotherapy, radiation therapy, bone marrow transplantation, or malnutrition.

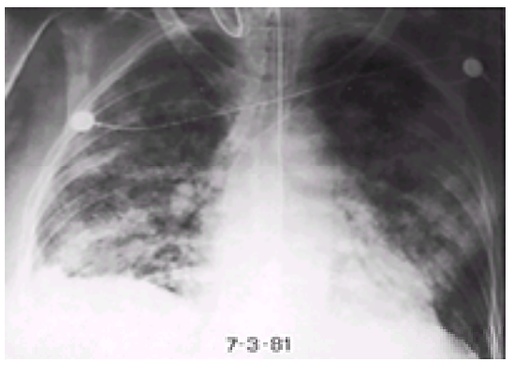

FIG. 4. Pulmonary extension of non-Hodgkin's lymphoma refractory to chemotherapy. Diffuse alveolar infiltrates are seen in both lungs.

Collagenoses and vasculitides are often associated with pulmonary manifestations. Untreated rheumatologic entities such as rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis or scleroderma, polymyositis-dermatomyositis, Sjögren's syndrome, mixed connective tissue disease, Wegener's granulomatosis, temporal arteritis, and Churg–Strauss vasculitis are well-known causes of pulmonary complications. Pulmonary manifestations of these disorders are discussed at length in Chapter 53 and Chapter 54. As in the case of malignancies, pulmonary opportunistic infections are uncommon in these patients unless they have received prolonged immunosuppressive therapy for their disease. Because the majority of patients with symptomatic rheumatologic and vasculitic disorders are treated with immunosuppressive therapy, they become prime targets for opportunistic infections, drug-induced lung disease, and other pulmonary complications.

Opportunistic Pulmonary Infections

Overwhelming pneumonias remain an important cause of morbidity and mortality. Many of these infections progress rapidly and are fatal. An immunocompromised patient is prone to develop pulmonary infections caused by viruses, bacteria, mycobacteria, fungi, protozoa, and parasites. In the setting of immunocompromised status, the clinical manifestations of viral pneumonitis are variable. Fever may be impressive or absent. Cough and dyspnea are present in most patients, as are varying degrees of hypoxemia and chest roentgenographic abnormalities. Cytomegalovirus and herpes zoster virus infections are seen in patients with a wide variety of underlying problems. Hematologic malignancies, corticosteroid therapy, and broad-spectrum antibiotics may predispose patients to primary varicella pneumonia. Pulmonary cytomegalovirus infection not detected by conventional histologic examination may be present in patients with diffuse alveolar damage associated with bone marrow transplantation.

Because most immunocompromised patients are hospitalized, hospital-acquired pneumonitis is a major threat to their lives; infections caused by gram-positive, gram-negative, and anaerobic bacteria are common. Oropharyngeal colonization by gram-negative organisms is increased in patients with chronic alcoholism, chronic obstructive pulmonary disease, diabetes mellitus, congestive cardiac failure, immunologic diseases, bronchiectasis, azotemia, intubation, tracheostomy, and malnutrition, and in those on chronic antimicrobial therapy and corticosteroid therapy. Carrier rates for aerobic gram-negative rods in pharyngeal secretions have been found to be higher for alcoholics and diabetics. Patients with malignant disease are frequently at risk of developing a wide variety of infections as a result of their immune-suppressed state. *Moraxella catarrhalis,* a gram-negative bacterium, has emerged as an opportunistic organism. Nearly one-third of the cases of pneumonia and empyema caused by *M. catarrhalis* have occurred in patients with various immunologic abnormalities.

Fungal infections, particularly aspergillosis and candidiasis, are common in leukemic patients, in debilitated individuals, and in those receiving long-term antimicrobial therapy. Immunocompromised patients, especially those with severe and sustained granulocytopenia, have a high propensity to develop potentially fatal *Aspergillus* and *Candida* infections. *Candida* epiglottitis has been described in these patients either as a localized lesion or as a source of *Candida* bronchopneumonia. Infection with *C. neoformans* may be seen in patients receiving corticosteroid therapy for sarcoidosis and in patients with chronic pulmonary disease. *Aspergillus* exists commonly as a saprophyte. Invasive and disseminated aspergillosis, however, is almost always seen in patients with malignancy or severe immunosuppression. Granulocytopenic patients with leukemic are particularly susceptible. *Nocardia asteroides* becomes an opportunistic invader in patients with chronic diseases, especially those receiving corticosteroid therapy and patients with preexisting lung diseases such as bronchiectasis.

Pneumocystis carinii is a relatively common pulmonary pathogen in immunocompromised patients, especially those receiving corticosteroids and other immunosuppressive agents, and in those with underlying diseases, including hematologic malignancies, solid tumors, organ transplants, and collagen-vascular diseases. The most common disease associated with *P. carinii* infection is AIDS. Coexisting pulmonary infection is a major negative prognostic factor in patients with *P. carinii* pneumonia.

Drug-Induced Lung Disease

Many drugs, including thoracic radiation, employed for the purposes of immunosuppression and therapy of immunologic and neoplastic diseases, render the lungs vulnerable to various types of damage mediated by different pathogenic mechanisms. Although some chemotherapeutic agents have cumulative dosage thresholds, others produce idiosyncratic reactions in the lungs. As discussed above, immunosuppression caused by the chemotherapeutic drugs renders patients susceptible to opportunistic lung infections. Diagnosis of a pulmonary process becomes a formidable challenge when the patient is receiving such treatment. In addition to excluding the possibilities of extension into the lungs of the basic disease and the presence of an opportunistic infection, one has to rule out a drug-induced pulmonary response. The drug-induced lung diseases are discussed at length in Chapter 22. Only brief discussions on lung disease caused by commonly used chemotherapeutic agents and corticosteroids are included below.

Bleomycin is a commonly used chemotherapeutic agent and a well-known cause of chronic interstitial pneumonitis-fibrosis. The drug has a propensity to concentrate in lung tissue and initiate oxidant-mediated injury to both alveolar and capillary cells. Pulmonary toxicity occurs in up to 40% of patients. The risk factors for the development of interstitial pneumonitis-fibrosis include age over 70, total dose in excess of 400 units, concurrent or simultaneous administration of oxygen, radiation, and granulocyte colony-stimulating factor, and renal insufficiency. Delayed occurrence of bleomycin lung can be seen months or years later, when bleomycin therapy is followed later by the administration of oxygen, radiation, or other chemotherapy drugs. Chest roentgenographs resemble those in idiopathic pulmonary fibrosis. Hypersensitivity lung disease and acute chest pain syndrome can be independent of cumulative dose. Hypersensitivity lung disease is associated with skin rash, eosinophilia, and reticulonodular infiltrates. The acute chest pain syndrome is associated with intravenous infusion and may be accompanied by pleuropericarditis.

Busulfan (Myleran), a chemotherapeutic agent used in the treatment of leukemia, causes clinical pulmonary toxicity in up to 5% of patients and subclinical lung damage in nearly half. Although pulmonary toxicity is more likely to occur if the total dose exceeds 500 mg, it is not always dose-dependent. Use of other chemotherapeutic agents and radiation increases the risk of lung toxicity. Slowly progressive interstitial pneumonitis-fibrosis associated with cough, dyspnea, and fever may appear

weeks, months, or years later (Fig. 5).

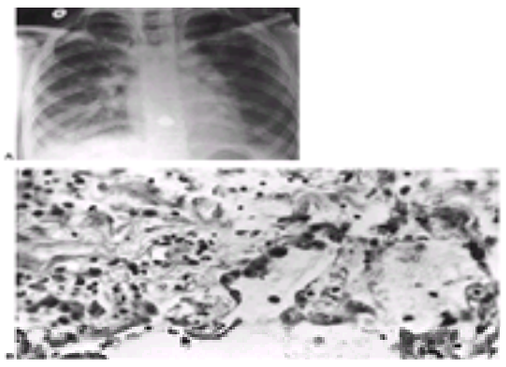

FIG. 5. Cytotoxic pulmonary damage secondary to busulfan in the immunocomprised patient. **(A)** Chest roentgenogram shows diffuse alveolar-interstitial infiltrates. **(B)** Lung biopsy demonstrates inflammatory changes, fibrosis, and hypertrophy of alveolar lining cells following busulfan therapy.

Cyclophosphamide causes dyspnea, nonproductive cough, and fever associated with interstitial pneumonitis-fibrosis or reticulonodular process within 2 weeks of therapy. The incidence of lung toxicity from cyclophosphamide alone is about 1% but increases when other drugs are used.

Mitomycin is associated with lung toxicity in up to 12% of patients. The threshold for lung toxicity is about 30 mg/m^2 of body surface area. Pulmonary toxicity is greatly enhanced when mitomycin is administered with bleomycin, cisplatin, and vincristine. Acute dyspneic episodes and acute noncardiogenic pulmonary edema associated with bronchospasm occur in up to 4% of patients who receive mitomycin therapy along with vinca alkaloids, sometimes within hours of vinca administration. Alveolar hemorrhage and noncardiogenic pulmonary edema may complicate mitomycin-induced hemolytic-uremic syndrome. Interstitial pneumonitis-fibrosis usually occurs 2 to 4 months after therapy and responds to corticosteroid therapy.

Methotrexate produces pulmonary toxicity in up to 8% of patients who receive high doses of the drug. The risk of pulmonary disease is directly related to the frequency with which the drug is administered. Chronic low-dose therapy used in rheumatologic diseases also is capable of causing lung damage. Respiratory manifestations include acute pleuritic chest pain with pleural effusion, noncardiac pulmonary edema following intrathecal administration of the drug, hypersensitivity lung disease that occurs several days after therapy, and subacute to chronic pneumonitis-fibrosis with subacute onset of dyspnea, cough, fever, and myalgias. Eosinophilia is common. Lung biopsy may show small interstitial granulomas; the bizarre type II pneumocytes seen in lung diseases induced by other chemotherapeutic agents are conspicuously absent.

Chemotherapeutic agents, other than those above, with known pulmonary toxicity include azathioprine (chronic interstitial process), carmustine (chronic interstitial process), chlorambucil (interstitial process), cytosine arabinoside (noncardiac pulmonary edema), ifosamide (chronic interstitial process), interleukin-2 (chronic interstitial process), melphalan (subclinical interstitial process), and 6-mercaptopurine (chronic interstitial process). Radiation-induced pneumonitis can confuse the issue, particularly in a patient with an intrathoracic neoplasm or a breast cancer for which radiation is administered, with exposure of adjacent lung to radiation.

Corticosteroid therapy is a well-known risk factor for the development of opportunistic infections. Corticosteroid-induced panlymphopenia predisposes patients to opportunistic infections. As little as 2.5 mg prednisone given every 6 hr has the ability to depress the helper–suppressor T-cell ratio. Corticosteroid-induced lymphopenia is maximal 4 to 6 hr after a single administration of the drug but disappears within 24 hr. The decrease in the helper–suppressor T-cell ratio results from a disproportionate decrease in the number of helper-inducer T cells. B lymphocytes are less affected than the T cells. Long-term administration (prednisone equivalent of more than 15 mg/day for 6 months or longer) is likely to produce prolonged lymphopenia and thus to expose the patient to the risk of opportunistic infections. Most opportunistic infections usually occur in patients on very high doses (more than 40 mg/day).

Protein-calorie malnutrition adversely affects more or less all immunocompetent cells. It results in the impaired function of phagocytes and decreases both the quantity and quality of lymphocytes. Protein-calorie malnutrition is generally considered the most frequent cause of immunodepression.

Alveolar Hemorrhage

Pulmonary alveolar hemorrhage is an important cause of respiratory symptoms and respiratory distress syndrome in immunocompromised patients. This complication accounts for 11% to 64% of pneumonic infiltrates in this group of patients. However, alveolar hemorrhage is rarely the sole cause of pulmonary infiltrates, with fewer than 5% exhibiting pulmonary hemorrhage as the only respiratory manifestation. Even when it is clinically considered an isolated phenomenon in immunocompromised patients, it is important to consider and exclude occult invasive aspergillosis infection. Indeed, close to 50% of patients with severe pulmonary hemorrhage may have documented aspergillosis. A significant association exists between thrombocytopenia and *Aspergillus* infection and pulmonary hemorrhage. Alveolar hemorrhage is also associated with other complications such as mucormycosis, pulmonary venoocclusive disease, graft-versus-host disease, mitomycin therapy, or other processes. Alveolar hemorrhage is seen more frequently in recipients of heart transplant. In one study, 75% of bronchoalveolar lavage samples deemed positive for alveolar hemorrhage were in heart transplant recipients. In another study, alveolar hemorrhage was detected in 21% of 141 consecutive recipients of autologous bone marrow transplant. Alveolar hemorrhage is significantly associated with thrombocytopenia (platelet count less than 50,000/mm^3), other coagulopathies, renal failure (serum creatinine ^{3}2.5 mg/dl), history of heavy smoking (>10 pack-years), leukopenia, thoracic radiation, and chemotherapy.

The difficulty in establishing the diagnosis of alveolar hemorrhage can be ascribed to the following factors: highly nonspecific clinical and roentgenographic features, absence of hemoptysis in most patients, and lack of specificity of imaging procedures including chest roentgenography, high-resolution computed tomography, and radionuclide scans. Carbon monoxide diffusing capacity, when tested serially, has been reported to increase with alveolar bleeding as a result of increased uptake of carbon monoxide by the red blood cells in the alveoli. The necessity to obtain this test serially in a sick patient renders it impractical. Furthermore, its reliability in the diagnosis of alveolar hemorrhage has not been established. Although thoracoscopy and open-lung biopsy can document the diagnosis, they are high-risk procedures in these patients. Bronchoalveolar lavage has been used to diagnose alveolar hemorrhage in immunocompromised patients. The mere presence of hemosiderin-laden macrophages in the bronchoalveolar lavage effluent without quantification is not diagnostic. Therefore, estimation of the number of hemosiderin-laden macrophages is used to diagnose this complication. In a study of 240 bronchoalveolar lavage samples in 194 immunocompromised hosts, the presence of at least 20% siderophages was considered to be diagnostic of alveolar hemorrhage. By this definition, alveolar hemorrhage was present in 87 (36%) of the samples; 20% to 65% siderophages was related to moderate hemorrhage (Golde score between 20 and 100), and a percentage greater than 67% was related to severe hemorrhage (Golde score >100). Even when a diagnosis of alveolar hemorrhage is established, it is essential to exclude coexistence of basic disease process and infections in the lungs.

Obstructive Airways Disease

Progressive airways disease leading to life-threatening respiratory distress is one of the most serious pulmonary complications encountered in immunocompromised patients. Obstructive airways disease occurring as a result of the immunocompromised status is almost exclusively limited to organ transplant recipients. Patients with graft-versus-host disease are at risk of developing this complication. Bronchiolitis obliterans that occurs in patients with rheumatoid arthritis and other collagen diseases is not considered here. It is, however, important to recognize that in a patient with rheumatoid arthritis or other collagenoses who is being treated with specific nonsteroidal antiinflammatory agents such as penicillamine or gold preparations who develops features of obstructive airway disease, the drugs themselves may be responsible for the airways disease.

Obstructive airways disease can occur in the form of bronchospastic disease, lymphocytic bronchitis, or bronchiolitis obliterans. Lymphocyte-mediated pathologic process is most likely responsible for these complications. The clinical features of the various types of obstructive airways diseases are reviewed below under the discussion on pulmonary complications in organ transplant recipients.

Nonspecific Interstitial Pneumonitis

Nonspecific pathologic changes are common in the lung tissue of immunocompromised patients with a diffuse pulmonary process (Fig. 6). The nonspecificity of biopsy-based diagnosis is helpful in excluding other causes of interstitial process. For example, in a study of 70 immune-suppressed patients with diffuse lung disease who underwent open-lung biopsy, even though the procedure provided diagnostic accuracy in 97%, 45% of the diagnoses were nonspecific (fibrosis); there was no significant difference in mortality between those with a specific diagnosis and those without, nor between those whose biopsy diagnosis caused an alteration of their

therapy and those for whom it did not. In contrast, another study noted a recovery rate of only 25% in those without a specific diagnosis following lung biopsy, whereas in patients in whom a treatable problem had been diagnosed, the overall recovery rate was 70%.

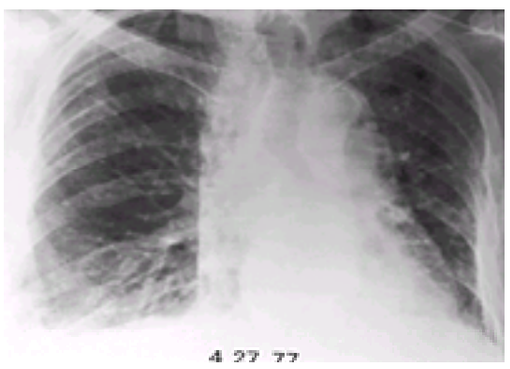

FIG. 6. Nonspecific interstitial pneumonitis in an immunocomprised patient who developed dyspnea and cough after thoracic radiation and multiple courses of chemotherapy for Hodgkin's lymphoma. Open-lung biopsy revealed nonspecific inflammation and fibrosis.

High-dose whole-body irradiation is commonly included in conditioning regimens for bone marrow transplantation for treatment of patients with hematologic malignancies. Interstitial pneumonitis is a major complication after bone marrow transplantation, and nearly one-fourth of all bone marrow transplant patients die from this complication. In approximately half these patients, an infectious agent, particularly cytomegalovirus, is involved. Additional factors such as remission-induction chemotherapy, cyclophosphamide, methotrexate, cyclosporine, and graft-versus-host disease combine to cause interstitial lung disease in these patients. Lymphocytic interstitial pneumonitis associated with bone marrow transplantation is considered in Chapter 56.

Lymphocytic Interstitial Pneumonitis

The differential diagnosis of lymphocytic interstitial pneumonitis is discussed in Chapter 56. In the immunocompromised patient, the etiology for lymphocytic interstitial pneumonitis includes viral infections, AIDS discussed earlier (also see Chapter 56), graft-versus-host disease, and agammaglobulinemia. Because many of the diseases associated with lymphocytic interstitial pneumonitis involve lymphoma, immunocompromised patients with lymphocytic interstitial pneumonitis should be closely observed for the possibility of lymphoproliferative disease.

Pulmonary "Immune" Neoplasia

Non-Hodgkin's lymphomas occur with increasing frequency in immunocompromised patients as a result of iatrogenic immunosuppressive therapy. Such lymphomas are more common in organ transplant recipients than in other immunocompromised patients. Lymphomas may be oligoclonal or polyclonal in origin (Fig. 7) and may be related to the use of cyclosporine. In contrast, non-Hodgkin's lymphomas seen in AIDS are Burkitt-like lymphomas, B-cell lymphomas, or B-cell immunoblastic sarcomas, with or without plasmacytoid features. They tend frequently to be extranodal.

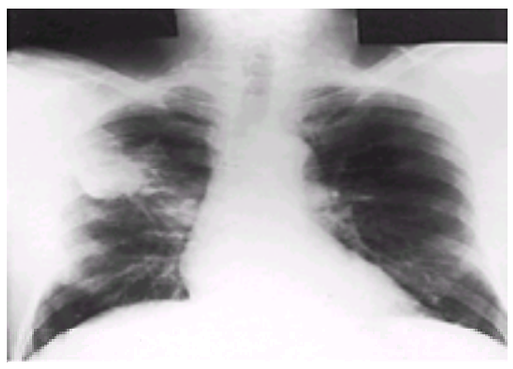

FIG. 7. B-cell lymphoma developing in right upper lobe in a patient on chronic immunosuppressive therapy following renal transplantation.

As a result of successful treatment with radiation, chemotherapy, or both, patients with lymphoma are living longer. Long-term follow-up of these patients has shown an increased incidence of lung carcinoma. Patients treated for Hodgkin's and non-Hodgkin's lymphoma accrue a relative risk two to three times that of the normal population for developing newer malignancies. Previous radiation therapy also may increase the risk of developing pulmonary nonlymphomatous malignancies.

Small-cell carcinoma is the predominant histologic type of lung cancer in both smoking and nonsmoking irradiated patients. However, patients with Hodgkin's lymphoma who receive supradiaphragmatic irradiation or combined-modality therapy may be at higher risk for developing non-small-cell carcinoma of the lung. In a study of such patients, the risk ratio for the development of lung cancer among Hodgkin's lymphoma patients was 5.6 times that expected in the general population. The median age at diagnosis of Hodgkin's lymphoma and lung carcinoma was 39 and 45 years, respectively. The interval between the diagnosis of Hodgkin's lymphoma and metachronous lung cancer averaged 7 years but appeared to vary inversely with age, thus emphasizing the need for close long-term observation.

Pulmonary Problems Unrelated to Immunodeficiency

The immunocompromised patient is more susceptible to the medical processes that affect nonimmunocompromised subjects. An abnormal chest roentgenogram in an immunocompromised patient may represent cardiac or noncardiac pulmonary edema, pulmonary embolism, community-acquired pulmonary infections, aspiration pneumonitis, or the delayed effects of thoracic irradiation. More than one-third of immunocompromised patients will demonstrate a combination of two or more of these complications.

Pulmonary Complication in Organ Transplant Recipients

The lungs more frequently manifest complications following organ transplantation than other organs. Respiratory complications are often the initial or presenting feature in these patients. Pulmonary complications in organ transplant recipients can be related to infection, transfusion of blood products, immunosuppressive drugs, graft-versus-host disease, alveolar hemorrhage, or obliterative bronchiolitis. Pulmonary infections are the most common cause of death in patients with organ transplants. Some complications are more commonly encountered with certain types of organ transplants, whereas others are nonspecific and occur in most organ recipients, irrespective of the organ transplanted. Pulmonary infection by *P. aeruginosa* should be considered in all patients hospitalized for more than 48 hrs. The crude mortality secondary to bacterial pneumonia in solid-organ transplantation exceeds 40%. Gram-negative bacilli, *S. aureus,* and *Legionella* predominate in the first 3 months after transplantation and are associated with mortality rates in excess of 60%. Bacterial pneumonias after 3 months are caused by *S. pneumoniae* and *H. influenzae* and are associated with lower mortality.

The following is a brief discussion of the common pulmonary complications among recipients of bone marrow and heart transplantations. Lung transplantation and related complications are discussed in Chapter 52. Respiratory complications in kidney and liver transplant recipients are discussed in Chapter 57 and Chapter 58, respectively.

BONE MARROW TRANSPLANTATION

Pulmonary complications occur in 40% to 60% of patients with bone marrow transplants and are often serious and life-threatening. One of the contributing factors is the presence of suboptimal pulmonary functions before bone marrow transplantation as a result of multiple episodes of infections, cytotoxic chemotherapy, and total-body

irradiation. The pulmonary complications seen in bone marrow transplantation can be broadly classified as early and late (Table 4). Pneumonia complicates approximately half of all bone marrow transplantations. In approximately one-third of the cases, no specific cause is identified, and the term *idiopathic pneumonia syndrome* has been used to describe this.

Clinical and roentgenographic features	Differential diagnosis
Early*	
Pulmonary edema	Fluid overload Myocardial injury Acute hemorrhagic edema (cyclosporine toxicity) Transfusion reactions Septicemia
Adult respiratory distress syndrome	Pulmonary edema
Bronchopneumonia	Idiopathic Bacterial Fungal (aspergillosis, candidiasis) Viral (cytomegalovirus)
Interstitial pneumonitis	Idiopathic Infectious (*Pneumocystis carinii*, cytomegalovirus) Pulmonary embolism Venoocclusive disease
Late†	
Bronchopneumonia	Bacterial Viral Fungal Protozoal (*Pneumocystis carinii*) Pulmonary embolism (fat embolism) Venoocclusive disease
Interstitial pneumonitis	Nonspecific interstitial pneumonitis Bronchiolitis obliterans Lymphocytic interstitial pneumonitis

*Occurring within 100 days of transplantation.
†Occurring 100 days or more after transplantation.

TABLE 4. *Pulmonary complications following bone marrow transplantation*

Viral infection occurs commonly in bone marrow transplant recipients. Overall, 80% of all bone marrow transplant recipients develop cytomegalovirus pneumonia, generally 30 to 150 days after transplantation. However, cytomegalovirus pneumonia is uncommon in recipients of autologous or syngeneic bone marrow transplants. Pneumonia from cytomegalovirus carries a mortality rate of approximately 90%. Risk factors for developing cytomegalovirus pneumonia include advanced age of patients, seropositivity, multiple blood transfusions, total body radiation, and presence of graft-versus-host disease. Pretransplantation pulmonary dysfunction is a strong predictor and risk factor for the posttransplantation development of cytomegalovirus pneumonia and interstitial process. Other viral infections, including herpes simplex, parainfluenza, and the respiratory syncytial viruses, are uncommon.

Bacterial infection is uncommon during the early stages after bone marrow transplantation. However, the overall incidence is 20% to 50%. During the early granulocytopenic period, gram-negative organisms predominate. Most late cases of bacterial pneumonia (occurring more than 6 months after bone marrow transplantation) are encountered in patients with graft-versus-host disease.

Fungal infections of the lung are more likely in neutropenic patients receiving broad-spectrum antibiotics. Infections caused by *Aspergillus* species are the most common and most lethal. Among 271 consecutive patients treated with bone marrow transplantation during a 9-year interval, *Aspergillus* pneumonia was noted in 36%; the crude mortality for these patients was 95%. Invasive aspergillosis may present with fever, dyspnea, cough, pleuritic chest pain, and hemoptysis. Chest roentgenologic abnormalities include diffuse or focal interstitial infiltrates, triangular peripheral infiltrates caused by infarction, and cavitated lesions. The diagnosis is established by documentation of fungal invasion of the pulmonary parenchyma, although the presence of *Aspergillus* species in respiratory secretions in the appropriate clinical setting may be highly suggestive.

Tracheobronchial aspergillosis is another serious complication in neutropenic and other immunocompromised patients, including those with AIDS and recipients of a lung or heart-lung transplant. In the latter group, the tracheobronchial anastomotic sites seem particularly affected by the process. Clinically, cough, upper airway wheezes, and progressive dyspnea are present in most patients. Respiratory failure can result from tracheobronchial obstruction. Bronchoscopy is both diagnostic and initially therapeutic in the relief of dyspnea by removal of the obstructing pseudomembrane secondary to tracheobronchial aspergillosis. Results of clinical trials in which prophylactic aerosolized amphotericin B, in doses varying from 5 mg to 100 mg, or oral itraconazole suggest that in high-risk patients these treatments are well tolerated and efficacious in preventing disseminated tracheobronchial aspergillosis. Infections by *Candida albicans* and the zygomycetes as well as other fungi are also seen.

Mycobacterial infections are uncommon after allogeneic bone marrow transplantation, although several cases of infections caused by *M. avium* complex have been described. The incidence of *P. carinii* pneumonitis is greater in patients who receive total body radiation before bone marrow transplant. The incidence, however, of *P. carinii* pneumonia in bone marrow transplant recipients is low, with only 4% of cases of interstitial pneumonitis being caused by *P. carinii.* Prophylactic administration of trimethoprim–sulfamethoxazole before bone marrow transplantation and after marrow engraftment is responsible for the low incidence.

Pulmonary edema is perhaps the earliest and most common complication of bone marrow transplantation. This phenomenon usually is seen 2 to 3 weeks postoperatively. The etiology for the pulmonary edema includes fluid overload, cardiac dysfunction caused by chemotherapy with doxorubicin hydrochloride (Adriamycin), transfusion-related acute lung injury, graft-versus-host disease, fat embolism syndrome, renal dysfunction, and, occasionally, irradiation. Congestive cardiomyopathy associated with the use of Adriamycin and daunorubicin is dose dependent (>550 mg/m^2). Pulmonary edema, both cardiogenic and noncardiogenic, is rapid in onset and occurs between the second and third week posttransplantation. Hemorrhagic pulmonary edema is more likely in those receiving mismatched transplants and high doses of cyclosporine. It also may result from fluid retention, hypoalbuminemia, hypotension, and incipient renal failure.

Graft-versus-host reaction that occurs after bone marrow transplant is responsible for the majority of the noninfectious pulmonary complications, which include acute noninfectious pneumonia, lymphocytic bronchitis, patchy interstitial pneumonitis, lymphocytic interstitial pneumonitis, and obstructive airway disease including bronchiolitis obliterans. Contributing factors include higher radiation dose to the lung, posttransplant pulmonary infection, particularly cytomegalovirus infection, and chemotherapy.

Lymphocytic bronchitis as a result of graft-versus-host reaction occurs in 25% of allogeneic bone marrow transplant recipients. It is manifested by lymphocytic infiltration of the bronchial mucosa, loss of cilia and goblet cells, and occasional necrosis of mucosa and submucosa. The lymphocytic bronchitis may be complicated by bronchopneumonia, frequently caused by *Pseudomonas aeruginosa.* Lymphocytic interstitial pneumonitis is a late complication of bone marrow transplantation, but the relationship between lymphocytic interstitial pneumonitis and graft-versus-host disease is uncertain. Several large studies have shown that clinical chronic graft-versus-host disease is present in all bone marrow transplant recipients before or concurrent with the onset of posttransplant obstructive lung disease.

Unexplained pleural effusions occur in recipients of allogeneic bone marrow transplants but not autologous transplants. The effusions are more common in patients with acute and/or chronic graft-versus-host disease. Acute graft-versus-host disease has been implicated in endothelial cell injury. This mechanism may be responsible for the high occurrence rate of alveolar hemorrhage in bone marrow transplant recipients with graft-versus-host disease. In one series, 59% of the patients with significant acute graft-versus-host disease died of acute respiratory failure as a result of recent pulmonary hemorrhage as opposed to 25% of those without acute graft-versus-host disease.

Nonspecific interstitial pneumonitis is a serious threat after bone marrow transplantation (Fig. 8). It occurs in 35% to 50% of recipients of allogeneic transplants and in approximately 20% of syngeneic or autologous bone marrow transplants. In approximately 50% of these patients, an infectious agent, particularly cytomegalovirus, is involved. Progressive dyspnea, cough, end-inspiratory crackles, interstitial infiltrates on chest roentgenogram, and hypoxemia occurring 40 to 75 days after grafting should strongly suggest interstitial pneumonitis. Factors contributing to the development of this complication include the following: older patients for whom there is a long interval between primary diagnosis of leukemia and bone marrow transplantation and who are then treated with cyclosporin and develop graft-versus-host disease; HLA disparity; graft-versus-host disease; and combined chemotherapy and radiation therapy prior to transplantation. The probability of developing interstitial pneumonitis from radiation during the first year is approximately 31%. High-dose radiation therapy results in significantly reduced diffusing capacity for carbon monoxide for the first 3 months, followed by some improvement over a 2- to 3-year period.

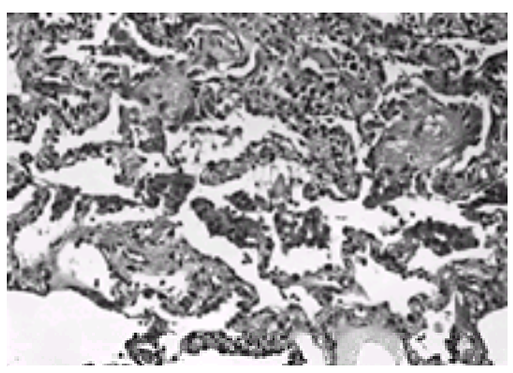

FIG. 8. Idiopathic interstitial pneumonitis in a bone marrow transplant recipient has the pattern of diffuse alveolar damage. Mild thickening and inflammatory infiltrate of alveolar septa lined by type II pneumocytes as well as edema fluid, exudate, and macrophages are present in the alveoli.

Lymphocytic alveolitis is a late occurrence and usually is seen in those with chronic graft-versus-host disease. The interstitial process is indistinguishable from nonlymphocytic interstitial pneumonitis and occurs after a median period of over 200 days after allogeneic bone marrow transplantation. Bronchoalveolar lavage shows lymphocytosis, with an overall expansion of $CD8^+$ subsets.

Obstructive lung disease as a result of bronchiolitis obliterans occurs in up to 15% of all bone marrow transplant recipients (Fig. 9). Bronchiolitis obliterans usually occurs within 5 months of bone marrow transplantation, although it can occur 9 months to 2 years after transplantation. Even though bronchiolitis obliterans more commonly occurs after allogeneic bone marrow transplantation, it has been reported following autologous bone marrow transplantation. Different pathologic mechanisms contribute to the pathogenesis of obstructive lung disease in these patients. Bronchiolitis obliterans occurs more commonly in patients with graft-versus-host disease, cytomegalovirus, and other viral and nonviral infections, radiation, and recurrent gastroesophageal reflux. Respiratory failure requiring assisted mechanical ventilation in 23% of patients has been reported. Clinically, the patient develops dyspnea, cough, hyperinflation of the thoracic cage on chest roentgenogram, and reduced elastic recoil pressure. The clinical course is variable and the mortality high, although some patients respond to corticosteroids and azathioprine.

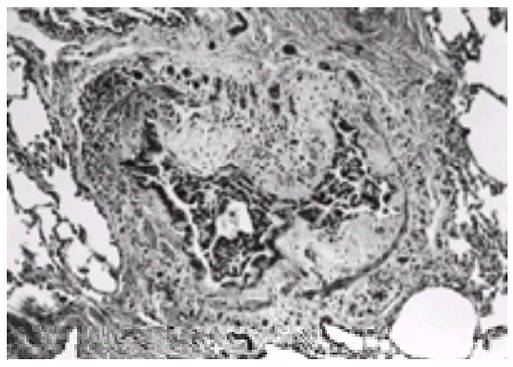

FIG. 9. Bronchiolitis obliterans-associated progressive airflow obstruction following bone marrow transplantation. Note fibrous thickening of the submucosa and distortion of the muscularis with resultant compromise in the bronchiolar lumen.

Pulmonary venoocclusive disease has been observed in patients receiving chemotherapy and after bone marrow transplantation. Other etiologic factors for pulmonary venoocclusive disease include radiation, multiple high-dose chemotherapies, and acute graft-versus-host disease. Endothelial damage from radiation therapy and cytotoxic chemotherapy also may predispose to thrombosis of pulmonary veins. Significant association has been found between bacterial pneumonia and venoocclusive disease and chronic graft-versus-host disease. Clinical features consist of progressive dyspnea and signs of right-sided congestive cardiac failure. High-dose corticosteroids have been used with mixed results. Pulmonary embolism is uncommon in bone marrow transplant recipients.

HEART TRANSPLANTATION

Many of the complications observed in bone marrow transplant recipients also occur in recipients of heart transplant. Among the solid organs transplant recipients, the incidence of bacterial pneumonia is highest in recipients of heart-lung (22%) and intermediate in recipients of heart transplants (5%). A publication on 200 episodes of infections occurring in 73 heart-lung transplant recipients reported that cytomegalovirus was the most common viral agent, accounting for 15% of infections and usually occurring in the second month after transplantation; *P. carinii* occurred 4 to 6 months after transplantation, and *Nocardia* later than 12 months after transplantation.

A multiinstitutional study of 814 consecutive patients from 24 institutions undergoing primary heart transplantation between 1990 and 1991 with mean follow-up of 8.2 months noted that the lung was the most common organ infected; the mortality rate was 23%. Bacterial and viral infections were most common, 47% and 41%, respectively, with fungi and protozoa accounting for 12%. Overall mortality per infection was 13%, but mortality with fungal infections was 36%. The single most frequently isolated infectious organism was cytomegalovirus, accounting for 26% of all infections.

Bronchiolitis obliterans is one of the most important complications of heart-lung transplantation, occurring in 10 to 50% of patients who leave the hospital with normal cardiopulmonary function. The obliterative bronchiolitis is a manifestation of lymphocyte-mediated chronic rejection. In a study of 32 recipients of single, double, or heart-lung transplantation who were followed-up for at least 3 months posttransplant, 50% of patients developed bronchiolitis obliterans, which was associated with a 56% mortality. Cytomegalovirus infection occurred with greater frequency in patients with bronchiolitis obliterans and, in most cases, preceded or occurred concomitantly with the diagnosis of acute rejection or bronchiolitis obliterans. Although bronchiolitis obliterans may appear as early as 2 months and as late as 4 years posttransplantation, it usually occurs between 8 to 12 months. One study assessed the risk factors for the development of obliterative bronchiolitis in a large group of heart-lung transplant recipients and concluded that acute rejection is the most significant risk factor.

Even though the ventilatory response to exercise is significantly improved after heart transplantation, the gradual deterioration in pulmonary function tests indicates the possibility of bronchiolitis obliterans. Spirometry is a sensitive indicator of early pathologic changes caused by bronchiolitis. The earliest physiological abnormality is the reduction in forced expiratory flow during the middle half of exhalation ($FEF_{25–75}$). Periodic pulmonary function testing is indicated to detect the occurrence and to monitor the obstructive airway disease. High-resolution computed tomography may show the typical mosaic pattern with signs of air trapping in the peripheral lung zones. Aggressive immunosuppressive therapy in the initial stages may retard the rate of progression.

When bronchiolitis obliterans is suspected, the diagnosis should be confirmed by lung biopsy if possible. Bronchoalveolar lavage can diagnose opportunistic infections in these patients, but it is not diagnostic for bronchiolitis obliterans. Obliterative bronchiolitis responds, if detected early, responds to augmented immunosuppressive therapy. Therefore, many centers routinely perform surveillance bronchoscopic lung biopsy. Azathioprine and cyclosporin are currently the main drugs used to treat acute rejection and bronchiolitis obliterans.

Pulmonary edema is common in the immediate postoperative period after heart transplantation. Atelectasis can be expected in 65% to 90% of patients undergoing heart transplantation, and although nearly 50% of patients develop bilateral atelectasis, the vast majority exhibit atelectasis of the left lower lobe. Left hemidiaphragmatic dysfunction from paresis or paralysis is the result of hypothermic cardioplegia and can last from weeks to months.

Pleural effusions also occur in up to 78% of patients who undergo heart transplantation. The etiologies are multifactorial. Most effusions are small, bilateral, and often associated with atelectasis. Collection of fluid or blood in the mediastinum may be seen in heart transplant recipients.

Mediastinitis, usually caused by bacteria, is a serious complication of cardiac surgery and should be considered in any patient who presents with fever, leukocytosis, inflammation, or instability of the sternal wound after cardiac transplantation. Other complications reported following heart transplantation include trapping and incarceration of the right lower lobe in the left hemithorax.

The incidence of developing malignancy after heart transplantation is approximately 7%, the majority being lymphomas.

DIAGNOSTIC APPROACH TO PULMONARY PROBLEMS IN THE COMPROMISED HOST

As discussed earlier, when one is confronted with a compromised host with an abnormal chest roentgenogram, one must consider various etiologic factors (see Table 2 and Table 3). A detailed history and complete physical examination will provide important clues to diagnosis. Routine laboratory procedures such as blood counts, cultures of blood and urine, and other analyses, when used appropriately, will provide additional help. The choice of diagnostic approach depends on the expertise available in one's own institution, the sensitivity of the procedure for the diagnosis of likely processes in the differential diagnoses, the severity of the patient's illness,

and the rapidity with which the illness is progressing.

IMAGING PROCEDURES

Chest roentgenograms are essential for characterizing the abnormalities and for narrowing the spectrum of possible diagnoses. However, it should be stressed that the typical roentgenographic features produced by isolated disease entities may not manifest their classic form in the case of a compromised host because of the effect of various factors on the lung, including opportunistic infections, cytotoxic changes, and radiation pneumonitis. Furthermore, because most of these patients are very sick and debilitated, obtaining roentgenographs of optimal quality may be difficult. Lateral decubitus films may help in confirming the presence of free pleural effusions. A study of chest radiographs in 149 consecutive acute pulmonary complications (25 in HIV-infected and 125 in non-HIV-infected patients) in immunocompromised patients observed that the most common complication in patients with AIDS was *P. carinii* pneumonia, and in the non-AIDS patients, the most common complications included invasive aspergillosis, drug reaction, and *P. carinii* pneumonia. The radiologists made the correct first-choice diagnosis in 90% of patients with AIDS and 34% of patients with non-AIDS patients. In non-AIDS patients with invasive pulmonary aspergillosis, drug reaction, and *P. carinii* pneumonia, the correct first-choice diagnosis was made in 38%, 26%, and 43% of readings, respectively.

Computed tomography of the chest with high-resolution imaging (HRCT) is invaluable in the diagnosis of pulmonary processes in immunocompromised patients. Several studies have documented the usefulness of HRCT in the detection of bronchiectasis in patients with immunodeficiency syndromes. The diagnosis of bronchiolitis obliterans with organizing pneumonia (BOOP) may be suggested by the HRCT images. The CT imaging is helpful in providing the bronchoscopist and the surgeon with a road map to the most abnormal anatomic area to plan procedures such as bronchoscopy or open-lung biopsy.

Assessing the degree of clinical urgency is of great importance in these patients, for in the absence of a specific diagnosis and proper therapy, many follow a rapid downhill course. The selection and prompt application of an appropriate investigative procedure help to reach proper decisions and provide optimal therapy. When routine blood tests, cultures from extrapulmonary sources, and biopsies fail to yield a specific answer, the course of diagnostic procedures is shown in Fig. 10.

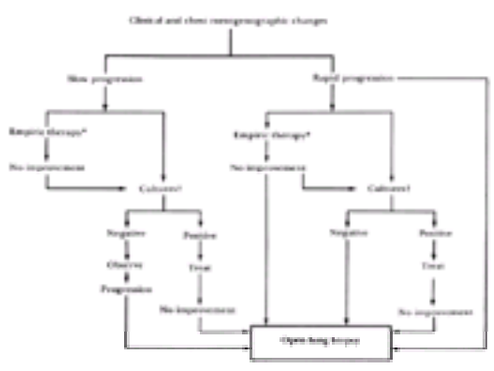

FIG. 10. Diagnostic approach to the immunocompromised patient with an abnormal chest roentgenogram. *Empiric therapy should be individualized and may include antiviral, antibacterial, and antifungal drugs and trimethoprim-sulfamethoxazole against *Pneumocystis carinii.* It may also include systemic corticosteroids, discontinuation of cytotoxic drugs, and therapy for pulmonary edema. +Cultures should be individualized depending on the clinical situation and chest roentgenographic abnormalities, but may include blood and other easily obtainable body fluids and secretions and bone marrow, as well as bronchoalveolar lavage and transbronchial lung biopsy.

When the battery of routine tests fail to provide clues to the etiology of the pulmonary process, direct examination of specimens from the respiratory tract is indicated. This can be accomplished by one or more the following: (1) study of easily obtainable secretions and fluid (sputum, gastric washings, and pleural fluid), (2) percutaneous (transthoracic) needle aspiration and needle biopsy of pleura and lung, (3) diagnostic bronchoalveolar lavage, (4) bronchoscopic brushing and aspirations or bronchoscopic lung biopsy, and (5) thoracoscopic or thoracotomy biopsy of pleura and lung. To reiterate, the degree of diagnostic urgency and the appropriateness of a given procedure should be weighed against the potential effect of delay on the subsequent outcome. The procedures just listed have varying yields and complication rates. The following is a brief summary of these aspects.

RESPIRATORY SECRETIONS AND FLUIDS

Sputum cultures usually are of limited value in diagnosing bacterial infections in the immune-suppressed host. However, induced sputum is valuable in the detection of *P. carinii.* Overwhelming growth of saprophytic fungi in the oropharyngeal regions of these patients is a hindrance in isolating true pathogenic bacteria and fungi. Sputum examination is also valuable in diagnosing mycobacterial infections and bronchogenic carcinoma. Gastric washings are helpful in the diagnosis of tuberculosis and certain fungal infections. Pleural fluid culture is very useful in diagnosing bacterial infections and malignancies. Minor pneumothoraces occur in fewer than 5% of thoracenteses and in fewer than 10% of pleural biopsies. Transtracheal and transthoracic needle aspirations are rarely indicated in patients with diffuse lung disease. Peripherally localized nodular lesions and lung masses are better approached by CT-guided transthoracic needle aspirations.

BRONCHOSCOPY

Flexible bronchoscopy has become the procedure of choice for diagnosing opportunistic pulmonary infections in patients with AIDS and in other immunocompromised patients. It is probably the safest of the invasive pulmonary diagnostic procedures. With supplemental oxygenation and appropriate preparation, the procedure can be performed in patients with severe hypoxemia. Furthermore, bronchoscopy and bronchoalveolar lavage can be performed in patients with severe thrombocytopenia, other coagulation disorders, and renal failure; the risk of hemorrhage is minimal. Major complications occur in less than 1% of patients. Both diagnostic bronchoalveolar lavage and bronchoscopic lung biopsy should be considered if diffuse lung infiltrates are present. Bronchoalveolar lavage alone, however, is adequate in the diagnosis of infections caused by *P. carinii,* bacteria, viruses, and mycobacteria. Lung biopsy is necessary to document tissue invasion by the fungi. Bronchoscopic lung biopsy, when used with bronchoalveolar lavage, increases the diagnostic yield in patients with *P. carinii* pneumonia, mycobacteriosis, and lymphangitic carcinomatosis. An overall diagnostic yield from bronchoalveolar lavage and bronchoscopic lung biopsy in the diagnosis of *P. carinii* in immunocompromised hosts is 82% and 92%, respectively. One study in patients with AIDS reported that an additional 8% of *P. carinii* pneumonia diagnoses, which were missed by bronchoalveolar lavage, were made by bronchoscopic lung biopsy. The study also documented that bronchoscopic lung biopsy is much more important to diagnose infections other than those caused by *P. carinii.* A staged approach is an option: for patients in whom *P. carinii* pneumonia is a major diagnostic consideration but whose sputa are negative for *P. carinii,* only a diagnostic bronchoalveolar lavage is performed initially; bronchoscopic lung biopsy is added to the initial bronchoalveolar lavage if other diagnostic possibilities are considered likely; and if the initial bronchoalveolar lavage is nondiagnostic despite strong clinical suspicion of *P. carinii,* a bronchoscopic lung biopsy is performed. Bilateral bronchoalveolar lavage has been shown to increase the diagnostic yield significantly in patients with opportunistic pulmonary infections. Cytomegalovirus can frequently be diagnosed from examination and culture of the diagnostic bronchoalveolar lavage fluid. Recovery of *M. avium* complex is highest with culture of both washings and lavage. Bronchoalveolar lavage in patients with leukemia and pulmonary infiltrates is not helpful in diagnosing invasive aspergillosis, unless a lung biopsy also is performed.

Extension of basic disease process into the lungs may require lung biopsy, although bronchoalveolar lavage provides a high diagnostic yield (over 75%) in patients with lymphangitic pulmonary metastasis. Bronchoscopic lung biopsy is routinely employed by many in the follow-up of patients who undergo lung or heart-lung transplantation because obliterative bronchiolitis, a common complication in this group of patients, responds to treatment with augmented immunosuppression when it is detected early by surveillance bronchoscopic lung biopsy.

LUNG BIOPSY

Thoracoscopy, which allows biopsy of pleura or lung under direct vision, is an excellent way to obtain material for culture as well as for histologic analysis. Open-lung biopsy is a more invasive pulmonary diagnostic procedure. This procedure yields the diagnosis in up to 95% of patients. With increasing use of bronchoalveolar lavage and thoracoscopy, the number of open-lung biopsies has decreased.

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Weiss SM, Hert RC, Gianola FJ, Clark JG, Crawford SW. Complications of fiberoptic bronchoscopy in thrombocytopenic patients. *Chest* 1993;104:1025–1028. *In this study of 47 bone marrow transplant recipients with thrombocytopenia, bronchoscopy was performed nasally in 37, orally in five, and via endotracheal tube in 16. Complications occurred in seven of 58 (12%) thrombocytopenic patients (epistaxis and/or hemoptysis, four; bradycardia, two; bronchospasm, one), of which all but one were minor and self-limiting. One life-threatening complication of severe epistaxis occurred during a transoral FOB in a patient with prior epistaxis.*

Witte RJ, Gurney JW, Robbins RA, Linder J, Rennard SI, Arneson M, Vaughan WP, Reed EC, Dicke KA. Diffuse pulmonary alveolar hemorrhage after bone marrow transplantation: radiographic findings in 39 patients. *Am J Roentgenol* 1991;157:461–464. *Among 39 bone marrow transplant recipients with a diagnosis of diffuse alveolar hemorrhage, the initial radiographic abnormalities developed an average of 11 days after bone marrow transplantation, and the radiographic abnormalities preceded the clinical diagnosis by an average of 3 days. The initial radiographic pattern was interstitial in 27 and alveolar in ten. The mortality rate in patients with diffuse alveolar hemorrhage was 77%.*

Yousem SA. The histological spectrum of pulmonary graft-versus-host disease in bone marrow transplant recipients. *Hum Pathol* 1995;26:668–675. *The histologic changes in 17 lung specimens in bone marrow transplant recipients included diffuse alveolar damage, lymphocytic bronchitis/bronchiolitis with interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia, and cicatricial bronchiolitis obliterans. Pulmonary disease correlated with the presence of graft-versus-host disease at extrathoracic sites. Patients with active lymphocytic bronchitis/bronchiolitis, cicatricial bronchiolitis obliterans, and diffuse alveolar damage had particularly poor outcomes.*

CHAPTER

56 Hematologic Diseases

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INTRODUCTION

The erythropoietic system plays a major role in tissue oxygenation because the erythrocytes are the primary carriers of oxygen in the form of oxyhemoglobin. Therefore, anemia, polycythemia, abnormal hemoglobins, and significant changes in blood volume frequently produce alterations in various respiratory functions. Additionally, myeloproliferative, lymphoproliferative, and plasmacytic disorders and other hematologic malignancies frequently affect the pulmonary system. Pulmonary complications are the most common cause of mortality in patients with hematologic malignancies. Respiratory manifestations in these disorders may be caused by pulmonary extension of the basic disease process, cytotoxic drug-induced pulmonary pathology, opportunistic infections, or a combination of these factors. This chapter discusses the various thoracic manifestations in hematologic diseases. Pulmonary complications in bone marrow transplantation are discussed in Chapter 55.

HEMOGLOBINOPATHIES

A *hemoglobinopathy* is an abnormality of hemoglobin synthesis manifested by the production of globin with a structural abnormality. More than 90% of these abnormalities are the result of single amino acid replacements. The clinically significant hemoglobinopathies, as far as the pulmonary system is concerned, include sickle syndromes, hemoglobinopathies with high oxygen affinity (familial erythrocytosis), hemoglobinopathies with low oxygen affinity (familial cyanosis), M hemoglobinopathies (familial cyanosis), and methemoglobinemia and sulfhemoglobinemia. Although cyanosis as a result of these disorders is rare in clinical practice, the possibility of abnormal hemoglobin should be considered in the differential diagnosis of a cyanotic patient (Table 1).

Inadequate oxygenation of hemoglobin (common)
Pulmonary diseases
Cardiac and noncardiac right-to-left shunt
Vascular collapse (shock)
Low-oxygen-affinity hemoglobin variant
Methemoglobinemia (uncommon)
Hereditary (congenital)
Cytochrome b_5 reductase deficiency
M hemoglobinopathies
Acquired (toxic)
Nitrites and nitrates: amyl nitrite, nitroglycerine, nitroprusside, silver nitrate, sodium nitrite
Other drugs: acetanilid, benzocaine, lidocaine, phenazopyridine, phenacetin, procaine, sulfonamides
Industrial and environmental toxins: aniline dyes, chlorate, etc.
Sulfhemoglobinemia (uncommon)
Congenital (?)
Acquired: acetaminophen, acetanilide, arylamines, phenacetin, sulfur, toxins, etc.
Pseudocyanosis
Argyria
Hemochromatosis
Chloroma

TABLE 1. *Differential diagnosis of cyanosis*

Hemoglobinopathies with High Oxygen Affinity

More than 120 human hemoglobin variants are known to exhibit increased oxygen affinity. By definition, these hemoglobins demonstrate a shift to the left of the whole-blood oxygen dissociation curve. The hemoglobinopathies with high oxygen affinity result from amino acid substitution at sites crucial to hemoglobin function. These disorders are manifested in the heterozygous state and follow an autosomal codominant pattern of inheritance. A partial list of abnormal hemoglobins with increased affinity for oxygen include Chesapeake, J-Capetown, Malmo, Yakima, Kempsey, Ypsilanti, Hiroshe, Brigham, Rainier, Bethesda, Hiroshima, Little Rock, Olympia, Tarrant, Sureness, Helsinki, Creteil, Hotel Dieu, Radcliffe, Alberta, British Columbia, Heathrow, San Diego, Syracuse, York, and Cowtown.

Many of these hemoglobinopathies are manifested by secondary erythrocytosis. Most patients are asymptomatic, and the diagnosis is considered when unexplained erythrocytosis is detected. Patients with hemoglobin variants with a marked increase in oxygen affinity may demonstrate cyanosis. Because of the defective hemoglobin function, the arterial blood is partially unsaturated despite normal oxygen tension, which results in elevated levels of deoxyhemoglobin in the blood—hence

the cyanosis. However, the cyanosis is a cosmetic problem and warrants no specific therapy. Several individuals with high-affinity variants have had persistent leukocytosis, and an occasional subject has exhibited splenomegaly. Pulmonary fibrosis has been described in several members of a family with hemoglobin Malmo, but the occurrence seems coincidental.

Hemoglobinopathies with Low Oxygen Affinity

More than a dozen variants of hemoglobinopathies with low oxygen affinity have been described. A partial list includes Kansas, Beth Israel, St. Mande, Titusville, Connecticut, Bologna, Rothschild, Mobile, Hope, J-Cairo, Raleigh, Vancouver, Presbyterian, and Yoshizuka. Many affected family members exhibit slightly diminished hemoglobin levels. The shift to the right of the oxyhemoglobin dissociation curve reduces the erythropoietin-mediated stimulus to erythropoiesis. In hemoglobin Kansas, cyanosis in heterozygotes results from increased deoxyhemoglobin. The patients with hemoglobin Kansas demonstrate a marked decrease in whole-blood oxygen affinity. Despite the diminished oxygen content of the arterial blood, the shift to the right of the oxyhemoglobin dissociation curve allows adequate oxygen release. The subjects with hemoglobin Kansas may develop limited tolerance to strenuous muscular exercise, which depends on a greatly increased oxygen unloading.

In addition to hemoglobin Kansas, cyanosis can be seen in hemoglobin variants Beth Israel and St. Mande. Both have amino acid substitutions at the same site as hemoglobin Kansas (i.e., a substitution of threonine for asparagine at 102). Familial pulmonary hypertension has been described in association with abnormal hemoglobin with low oxygen affinity.

M Hemoglobinopathies

The main group of hemoglobins that produce cyanosis are known as *M hemoglobinopathies.* Hemoglobins M-Boston, M-Iwate, M-Saskatoon, M-Hyde Park, and M-Milwaukee exhibit abnormal absorbance spectra owing to the oxidation of the heme iron in the affected subunit. These hemoglobinopathies behave as autosomal codominant mutations. In the heterozygous state, they produce methemoglobinemia, which results in chronic cyanosis. The Bohr effect is markedly decreased to absent in the a-chain variants but normal to only slightly decreased in variants of the b chain. Thus, hemoglobins Iwate and Boston, both associated with a-chain alterations, show decreased oxygen affinity and decreased Bohr effect; hemoglobins Hyde Park and Saskatoon, which exemplify b-chain mutations, have essentially normal oxygen affinity and Bohr effect.

The predominant characteristic of hemoglobin M disorders is the presence of cyanosis from early childhood. Subjects with a-chain variants (M-Boston and M-Iwate) are cyanotic at birth, whereas those with b-chain variants (M-Saskatoon, M-Hyde Park, M-Milwaukee) do not exhibit cyanosis until approximately 5 to 6 months of age, when fetal hemoglobin is replaced by adult hemoglobin. Hemoglobin Freiburg, resulting from a b-chain mutation, is associated with mild cyanosis, whereas hemoglobin Seattle is not associated with cyanosis but does show decreased oxygen affinity. Despite the cyanosis in these hemoglobinopathies, there is no evidence of cardiac disease or clubbing. Exertional dyspnea is not a feature.

Methemoglobinemia and Sulfhemoglobinemia

Methemoglobinemia results when more than 1% of hemoglobin is oxidized to ferric form. When hemoglobin is oxidized to methemoglobin, the heme iron becomes Fe^{3+} and is incapable of binding oxygen. Methemoglobin content of normal red cells is less than 1%. When methemoglobin level exceeds 1.5 g/dl (10% of total hemoglobin), cyanosis becomes clinically obvious. Both hereditary (congenital) and acquired forms of methemoglobinemia exist. *Congenital methemoglobinemia* results from either hereditary deficiency of the enzyme cytochrome b_5 reductase (methemoglobin reductase) or the presence of one of the M hemoglobins. The major clinical feature is presence of cyanosis without cardiopulmonary problems.

Acquired methemoglobinemia, also known as *toxic methemoglobinemia,* results when drugs or toxins oxidize hemoglobin directly in the circulation or facilitate its oxidation by molecular oxygen (see Table 1). Toxic methemoglobinemia may be acute or chronic. In the latter, chronic administration of the offending agent leads to an increased steady-state concentration of methemoglobin that results in asymptomatic cyanosis. Blood gas analysis usually reveals normal arterial oxygen tension with disproportionately low arterial oxygen saturation and increased levels of methemoglobin. Acute methemoglobinemia, especially when the level of methemoglobin exceeds half the total hemoglobin, may present a serious medical emergency. When the methemoglobin level exceeds 35%, headaches, weakness, and dyspnea develop. The severity of methemoglobinemia depends on the dose of the causative agent as well as on the susceptibility of the exposed individual. Levels in excess of 80% are incompatible with life. Severe toxic methemoglobinemia should be treated with intravenous methylene blue (2 mg/kg).

Sulfhemoglobinemia refers to the presence, in peripheral blood, of hemoglobin derivatives that are poorly characterized chemically. Occasionally, subjects exposed to oxidant compounds will develop cyanosis that cannot be explained by simple hemoglobin oxidation. Because of its high absorbance in the red region of the visible spectrum, sulfhemoglobinemia causes more cyanosis than an equivalent percentage of methemoglobinemia. Congenital and acquired forms of sulfhemoglobinemia have been described. A number of pharmacologic and other agents (see Table 1) also produce sulfhemoglobinemia and cyanosis.

Sickle Cell Anemia

Sickle cell disease is caused primarily by hemoglobin SS, SC, or Sb thalassemia. Sickle cell anemia is a chronic, hereditary hemolytic disease resulting from clinical expression of homozygosity for hemoglobin S. The affected persons predominantly belong to the black race who have inherited the mutant gene from both parents. Pulmonary complications are common in patients with sickle cell anemia (SS hemoglobin) but less so in patients with SC hemoglobin. Pulmonary complications are important causes of morbidity and mortality.

Pneumococcal pneumonia is a major cause of morbidity and mortality in children with sickle cell disease. Pneumonia, especially in children and probably in all age groups, is the most common lung disease encountered in sickle cell anemia, where its incidence is 20 times greater than in the normal population. The major factors that predispose these patients to infections include abnormal complement activity, poor splenic function, and a lack of type-specific pneumococcal antibody. Local factors such as previous or concomitant pulmonary damage by vasoocclusion probably play a role. In children with sickle cell disease, the incidence of pneumonia increases significantly after the age of 8 months. The pneumonia in children usually is caused by *Streptococcus pneumoniae,* whereas in adults, *Staphylococcus aureus* or *Haemophilus* species predominate. The majority of suspected pneumonias in adults are caused by pulmonary embolism, and the differentiation of infectious pneumonia from acute chest syndrome or pulmonary embolism is difficult. One study of 166 patients with sickle cell anemia reported that 45% were hospitalized because of acute bacterial pneumonia, and half of this group had positive bacterial cultures. However, in another study of 18 patients with acute chest syndrome, respiratory secretion was obtained via bronchoscopy, and the study concluded that bacterial pneumonia was uncommon in this group of patients. Multilobar involvement is not uncommon, with the upper and middle lobes being involved more often than the others. Administration of pneumococcal vaccine is mandatory in patients with sickle cell anemia.

Fungal infections are uncommon in patients with sickle cell anemia, but occasional cases of cryptococcal infection have been described. Although a higher incidence of tuberculosis has been reported by some, others have not been able to substantiate this.

The *acute chest syndrome* (also called sickle chest syndrome, chest crisis, pulmonary sickle crisis, and pulmonary infarction) is seen in up to 35% of patients hospitalized with sickle cell disease; it is associated with significant morbidity and is the leading cause of death in patients with sickle cell disease. It is a common manifestation of sickling-induced vasoocclusive crises. The syndrome is characterized by fever, chest pain, and pulmonary infiltrates. Sudden onset of pleuritic chest pains, cough without hemoptysis, fever, and leukocytosis are common. Hypoxemia ($P_aO_2 < 50$ mmHg) is present in up to 40% of patients. Dense bilateral lower-lung consolidations are common. A retrospective analysis of 100 hospitalized pediatric cases of sickle cell anemia revealed lower-lobe pulmonary infiltrates in 86% and upper- and middle-lobe infiltrates in 25% and 22%, respectively; pleural effusions were observed in 38%. Sickle cell crisis may be precipitated by asthmatic attacks.

Bone marrow fat embolism of pulmonary vasculature is a common complication in patients with sickle cell disease and is responsible for many cases of severe acute chest syndrome. To diagnose fat embolism, one study evaluated the presence of fatty macrophages recovered by bronchoalveolar lavage in 20 consecutive patients with acute chest syndrome; a cutoff of >5% of alveolar macrophages containing fat droplets was determined (from a control group) for the diagnosis of fat embolism. In 12 episodes of acute chest syndrome, bronchoalveolar lavage yielded >5% of fatty macrophages (median 47%; range 10% to 100%), and in 11 cases, fat embolism was associated with proven or probable bone marrow infarction. Overall, the diagnostic yield of bronchoalveolar lavage for fat embolism was 60%.

Secretory phospholipase A_2 as an important mediator of acute lung injury of the fat embolism syndrome has been used for the diagnosis; phospholipase A_2 activity appears to correlate with acute chest syndrome.

Pulmonary complications are common in patients with sickle cell disease who are hospitalized with acute chest syndrome. Incentive spirometry has been shown to prevent the pulmonary complications associated with the acute chest syndrome. A prospective, randomized trial in 29 patients (8 to 21 years of age) with sickle cell diseases who had 38 episodes of acute chest or back pain above the diaphragm and were hospitalized showed that the incidence of thoracic bone infarction was 40% (15 of 38 hospitalizations). Pulmonary complications in the form of atelectasis or infiltrates developed during only one of 19 hospitalizations of patients assigned to the

spirometry group, as compared with eight of 19 hospitalizations of patients in the nonspirometry group.

Pulmonary pathologic features include pulmonary vascular occlusion, capillary stasis, thrombus formation, infarction, alveolar wall necrosis, and emboli of necrotic bone marrow. These complications are more common in women, particularly during late pregnancy or shortly after delivery. Patients with hemoglobin SC disease may be at risk of *in situ* thrombosis of pulmonary vessels. The roentgenographic appearance of these lesions is no different from that produced by thromboemboli. A postmortem study of 36 older patients with sickle cell disease identified thromboemboli in most. However, pulmonary infarction is a much less frequent complication among younger patients. Anticoagulant therapy does not help. Although circulatory stasis may develop *in situ,* vascular occlusion by marrow embolus is probably a more common cause of pulmonary infarction and has been discovered at autopsy in 13% of patients with sickle cell disease. In patients with sickle cell anemia, pulmonary hemosiderosis may result from repeated blood transfusions.

Pulmonary edema is another complication of sickle cell crisis. Vigorous hypotonic fluid replacement and parenteral analgesic therapy, commonly used in patients in sickle cell crisis, may contribute to its development. Autopsy findings in patients who died from pulmonary edema are consistent with a diffuse pulmonary vasoocclusive disease.

Decreased diffusing capacity of lung for carbon monoxide has been demonstrated in sickle cell anemia and has been attributed to a loss of membrane area as a result of obstruction of pulmonary vessels. Other physiological studies have shown a decreased vital capacity, normal maximal breathing capacity, arterial oxygen desaturation, and a widened alveolar–arterial oxygen tension difference in most patients with the disease. Both venoarterial shunting and abnormal ventilation–perfusion relationships play major roles in this. The arterial oxygen desaturation predisposes to *in vivo* sickling and its consequences. The heterozygous state of sickle cell trait (hemoglobin AS) may lead to abnormal pulmonary function, as a result of sickling, at high altitudes. The sickling phenomenon can result in pulmonary thromboembolism and can further aggravate sickling, with deterioration in hypoxia. Short exposures to hypoxia at high altitudes do not acutely or cumulatively alter diffusing capacity or spirometric values in healthy persons with sickle cell trait.

Sickle cell disease and sarcoidosis are two disorders commonly affecting black people. Studies have shown the prevalence rates of hemoglobinopathies in sarcoid patients to be 18% to 20%.

b-Thalassemia Major

Thalassemia major is characterized by an unbalanced synthesis of globin chain, resulting in ineffective hematopoiesis and severe anemia. Severe hemolytic anemia and ineffective erythropoiesis from infancy are the main characteristics of this disorder. The ability of these patients to increase their oxygen-carrying capacity with physical stress is limited. Patients succumb at a young age to congestive cardiac failure. Patients with thalassemia major who are chronically transfused exhibit a high cardiac output during exercise, regardless of hemoglobin concentration, and the mechanism for this phenomenon is unknown. Cardiopulmonary evaluation of 35 patients with homozygous b-thalassemia observed hypoxemia in 85%, reduced lung volumes and flow rates in 51% and 63%, respectively, and diminished diffusing capacity for carbon monoxide in 50%. Pulmonary hypertension was present in 75%, and right ventricular dysfunction was more prevalent than left ventricular dysfunction. The possible causes for these complications include left ventricular failure, iron deposits in the pulmonary vessels, and a hypercoagulable state with thrombotic obstruction of the pulmonary arteries. Transfusion-induced decreases in forced vital capacity and P_aO_2 in the absence of pulmonary edema have been observed, but the mechanism is unclear.

HEMORRHAGIC DISEASES

Pulmonary complications such as pulmonary embolism and alveolar hemorrhage can result from an underlying disorder of coagulation. Both hypercoagulable and hypocoagulable states may be associated with these complications. The presence of a hemorrhagic disorder predisposes to pulmonary bleeding, and the risk of bleeding is increased if the patient has a preexisting pulmonary lesion such as a tumor, bulla (Fig. 1), cyst, cavity, or bronchiectasis.

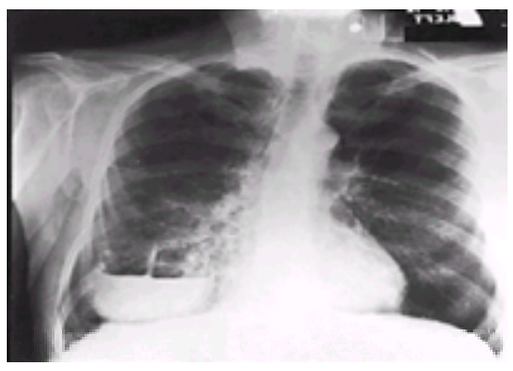

FIG. 1. Hemorrhage into a bullous lesion in the right lower lobe in a patient with excessive bleeding tendency secondary to coumarin therapy.

Hemophilia

Classic hemophilia is the result of functional deficiency of antihemophilic factor (factor VIII) because of an X-linked recessive gene. The most serious complication is the occurrence of the acquired immunodeficiency syndrome (AIDS) in those who were administered factor VIII contaminated by the human immunodeficiency virus. This risk has significantly diminished as a result of stringent improvements in blood banking. Pulmonary manifestations are unusual in hemophilia but have included spontaneous pneumothorax, hemomediastinum, tracheal obstruction by a hematoma, and pleural hematomas. In a review of chest roentgenograms, abnormalities were recorded in 26 of 33 adult hemophiliacs; scarring, fibrosis, and pleural thickening were seen in 12 cases, and abnormalities of pulmonary vessels were seen in the remaining 14, of which four had evidence of hyperinflation. Several cases of primary pulmonary hypertension have been described in patients receiving factor VIII infusion.

Disseminated Intravascular Coagulation

Pulmonary hemorrhage occurs in patients with disseminated intravascular coagulation and other coagulopathies. The incidence of pulmonary hemorrhage is estimated to be approximately 14% in disseminated intravascular coagulation. Often, it is subclinical with very little or no hemoptysis and patchy nondescript lung infiltrates. Massive bleeding is uncommon. The pulmonary hemorrhage syndrome has features in common with the adult respiratory distress syndrome, such as hyaline membrane formation and pulmonary hypoperfusion. Thrombocytopenia has been shown to lead to the development of pulmonary hematoma, hemothorax, and fatal pulmonary hemorrhage.

Pulmonary infarction has been described in several patients with disseminated intravascular coagulation. Thromboembolism and hemorrhage are the main pathologic findings in the lungs of patients dying with disseminated intravascular coagulation. A postmortem comparative study of 87 patients whose illnesses were complicated by disseminated intravascular coagulation and 64 control patients observed thromboembolism in 51 cases (59%), infarction in six, hemorrhage in 14, microscopic fibrin thrombosis in 43 (49%), and microthromboembolism in 45 (52%) patients with disseminated intravascular coagulation. The frequency of pulmonary infarction increased in proportion to the frequency of thromboembolism. In the control group, macroscopic thromboembolism was identified in 20 cases (31%).

MYELOPROLIFERATIVE DISORDERS

Leukemia

Pulmonary involvement in leukemia occurs more often than is usually suspected. The reported mortality rate associated with pulmonary complications in leukemia is approximately 60% to 65%. The respiratory complications depend on the type of leukemia, the nature and course of treatment, and the presence or absence of significant neutropenia. Many of the complications, particularly infections, are secondary to the immunocompromised status of leukemic patients, which is caused either by the leukemic state itself or by treatment.

Infectious pneumonia is a frequent and often fatal complication and is responsible for up to 75% of deaths in patients with acute leukemia. In a series of 68 leukemic

patients with pulmonary infiltrates, 82% of focal and 35% of diffuse infiltrates were caused by infectious causes. Gram-negative organisms are the most common cause of pneumonia. Fungal pneumonia occurs in up to 30% of patients. In acute leukemia, *Pneumocystis carinii* pneumonia occurs less often in adults than in children. In a review of 53 cases of *P. carinii* pneumonia, including four in children, leukemia was the underlying hematologic disorder in 28%. In another study, 52 episodes of pneumonia were recorded among 68 leukemic patients; most pneumonias were caused by gram-negative bacilli, with a 25% incidence of fungal pneumonia. The overall mortality was 65%. In childhood leukemia, viruses are more important as respiratory pathogens and are major causes of morbidity.

Granulocytopenia, hypogammaglobulinemia, and lymphocytic bronchitis in graft-versus-host disease may follow bone marrow transplantation and predispose these patients to infectious complications (see Chapter 55). Granulocytopenia in leukemic patients poses a significant risk of invasive aspergillosis and acute respiratory distress syndrome because invasive pulmonary aspergillosis is a life-threatening complication. The risk for the development of invasive aspergillosis is directly proportional to the duration of granulocytopenia. The rapidity of bone marrow recovery markedly influences the clinical and roentgenographic course of the disease. For patients with acute leukemia, granulocytopenia persisting longer than 3 weeks is the major risk factor for developing this life-threatening infection. In an observation of such patients, granulocyte recovery, with counts exceeding 500/mm^3, was followed by cavitary pulmonary aspergillosis in 73%. Nearly one-third of the patients with malignancies who receive empiric antibiotic therapy during episodes of granulocytopenia develop pulmonary fungal infections. Massive hemoptysis may occur in some patients. Prognosis has been uniformly poor, with mortality rates exceeding 70% in some series. A study reported that early diagnosis of aspergillosis in leukemic patients on chemotherapy can be established by computed tomography, which will reveal a characteristic progression from multiple fluffy masses to cavitation or air crescent formation.

Zygomycosis (mucormycosis) of lung is another serious fungal infection in severely neutropenic patients. It also can occur, however, in nonneutropenic patients and in patients long after hospital discharge following bone marrow transplantation. In a 17-year consecutive series of patients with bone marrow transplant, 0.9% (13 patients) of 1500 patients developed mucormycosis; ten allogeneic and three autologous transplant recipients. Seven patients were neutropenic. Six infections occurred within 90 days of transplant, and six occurred at or within several days of autopsy. Sites of infection were lung and brain in four, sinonasal region in three, lung in two, disseminated in two, and lung and kidney in one patient. Death from mucormycosis occurred in ten (77%) of 13 patients.

Hypogammaglobulinemia, related to inherent abnormalities of B-lymphocyte function and T-cell imbalances, is present in approximately 50% of patients with chronic lymphocytic leukemia. Infections, particularly with encapsulated microorganisms, are a frequent cause of morbidity and mortality.

Hairy-cell leukemia is an unusual hematologic malignancy and may exhibit splenomegaly, pancytopenia, and circulating mononuclear cells with prominent cytoplasmic projections. Infections are secondary to granulocytopenia and defects in cell-mediated immunity. Bacterial, fungal, and mycobacterial infections occur frequently. Disseminated infections caused by *Mycobacterium kansasii* and *M. avium* complex occur in patients with hairy-cell leukemia.

Autopsy studies have revealed that noninfectious intrathoracic involvement by leukemia is a common late development. Mediastinal and hilar adenopathy is seen in 50% of cases, and pulmonary parenchyma is involved in approximately 25%. Acute myelogenous leukemias produce pulmonary parenchymal leukemic infiltrates more commonly than the chronic varieties, but among the chronic group, lymphocytic leukemia is more likely than the granulocytic type to invade pulmonary parenchyma (Fig. 2 and Fig. 3). The usual roentgenographic abnormality within pulmonary parenchyma is a diffuse bilateral reticulonodular infiltration resembling that of lymphangitic metastasis (Fig. 4). This is not uncommon in the terminal stages of leukemia. However, several cases of acute leukemia presenting with diffuse pulmonary infiltrates and respiratory failure have been described. As noted above, in patients who are granulocytopenic, presence of diffuse lung infiltrates should warn of the possibility of invasive aspergillosis (Fig. 5). Rapidly progressive pulmonary infiltrates have been noted as a major clinical problem in chronic myelogenous leukemia. The leukemic infiltrates may be parenchymal (focal or diffuse), pleural, peribronchial, or endobronchial. In the Richter's transformation, chronic lymphocytic leukemia may convert from a low-grade histologic picture to high-grade non-Hodgkin's lymphoma and produce hilar or mediastinal lymphadenopathy. Pleural effusion, usually unilateral, is seen in up to 25% of cases.

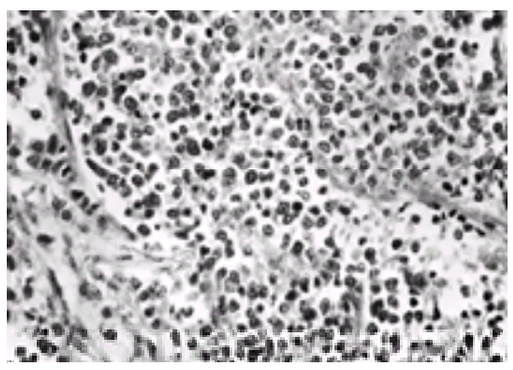

FIG. 2. Pulmonary infiltration by acute granulocytic leukemia.

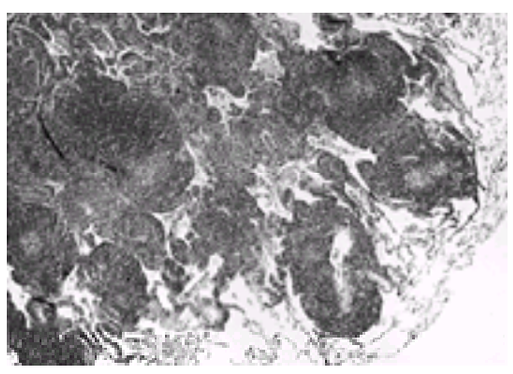

FIG. 3. Pulmonary involvement by chronic lymphocytic leukemia. A dense infiltrate of small lymphocytes can be seen around vessels and in alveolar septa.

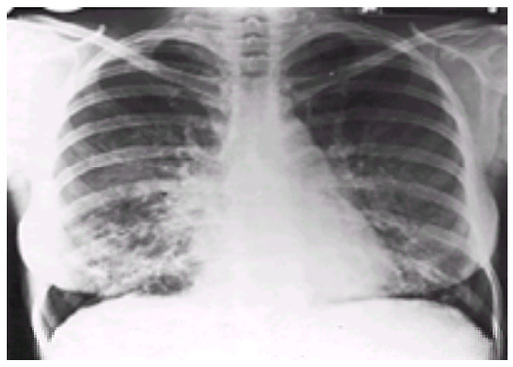

FIG. 4. Leukemic infiltrates in the lower lobes of both lungs in a patient with acute monomyelocytic leukemia.

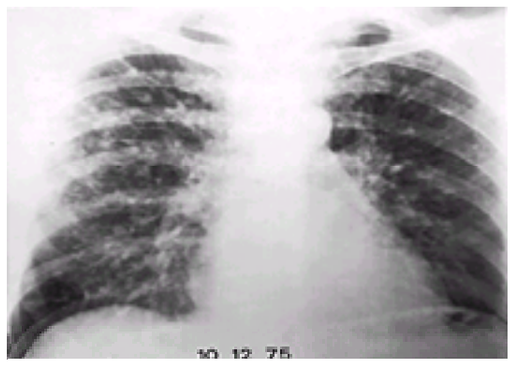

FIG. 5. Diffuse nodular-reticular infiltrates in a severely granulocytopenic patient on chemotherapy for acute monomyeloctic leukemia.

Pulmonary alveolar hemorrhage is found often at autopsy in leukemic patients. In a necropsy study of 50 patients with acute leukemia, pulmonary hemorrhage and leukemic pulmonary infiltrates were recorded in 54% and 64%, respectively. Pulmonary hemorrhage usually is associated with thrombocytopenia and may be extensive. Another predisposing cause is invasive pulmonary aspergillosis. The majority of patients with pulmonary alveolar hemorrhage do not exhibit hemoptysis.

Hyperleukocytosis denotes peripheral white blood cell count in excess of 50,000/mm^3. This condition has the potential to cause pulmonary leukostasis, which is a serious, frequently fatal, complication. Pulmonary leukostasis usually occurs in patients with acute granulocytic leukemias. A clinicopathologic study of 16 leukemic patients with circulating leukocytes counts of less than 50,000/mm^3 and pulmonary leukostasis concluded that hyperleukocytosis *per se* cannot be the cause of pulmonary leukostasis but that other factors, such as the presence of circulating blasts and the affinity of neoplastic cells for the pulmonary endothelium, may be related to the development of acute respiratory distress. Leukemic cell lysis pneumopathy, which occurs as a result of pulmonary vascular occlusion by destroyed leukemic cells within 48 hrs of initiation of chemotherapy, may cause respiratory failure. The development of acute respiratory failure in patients with hematologic disorders is a life-threatening condition. Irrespective of the etiology of acute respiratory failure in this group of patients, the outcome is dismal, with a mortality rate of 80%.

Granulocyte colony-stimulating factor, by augmenting leukocyte production, pulmonary sequestration of white blood cells, and margination and production of toxic oxygen radicals, may exacerbate underlying subclinical bleomycin pulmonary toxicity. In a series of 12 patients with aggressive non-Hodgkin's lymphoma who received chemotherapy that included bleomycin in combination with recombinant human granulocyte colony-stimulating factor, three of four patients who developed a rapidly progressive pneumonic illness died; no infection was detected. The lung abnormalities were characterized by diffuse infiltrates and hypoxemia. Caution should be exercised before using granulocyte-stimulating factors in bleomycin-containing regimens.

All-*trans* retinoic acid induces complete remission in most cases of acute promyelocytic leukemia. Its use, however, is associated with potentially fatal pulmonary toxicity in approximately 25% of patients in the setting of a rapidly rising peripheral leukocyte count. A prospective multicenter study has shown the efficacy of oral corticosteroid for prophylaxis against pulmonary toxicity from retinoic acid.

In patients with leukemia, lung biopsy may suggest areas of pulmonary alveolar phospholipoproteinosis. This is secondary to the monocytopenia in leukemia. Alveolar macrophages are derived from monocytes, and the deficiency of monocytes in leukemia results in the inability of the limited number of alveolar macrophages to ingest intraalveolar phospholipids. In addition, opportunistic infections and cytotoxic drugs may affect the alveolar clearance of phospholipids and produce patchy areas of secondary pulmonary alveolar (phospholipo)proteinosis. However, this finding is clinically insignificant, and chest roentgenograms may or may not show patchy areas of alveolar infiltrates.

Pseudohypoxemia or spurious hypoxemia, also described as leukocyte larceny, denotes low oxygen tension and saturation in arterial blood in the absence of clinical evidence of tissue hypoxia. This phenomenon occurs in patients with extreme degrees of leukocytosis. During the *in vitro* transportation of an arterial blood sample from the patient to the laboratory, the large number of leukocytes in the syringe consume significant amounts of oxygen, and hence, the measurement reveals a low P_aO_2. Pseudohypoxemia is seen also in patients with severe thrombocytosis.

Polycythemia

Defined as a sustained excess of red blood cell volume, polycythemia occurs in either a primary or a secondary form. Secondary polycythemia is a compensatory mechanism seen in various chronic hypoxemic states. The pulmonary manifestations in patients with such diseases are those of the underlying disease.

Primary polycythemia, or *polycythemia rubra vera,* is a chronic disease of unknown etiology characterized by hyperplasia of all the cellular elements of the bone marrow, nucleated red blood cells being more prominently involved. Chest roentgenographic abnormalities consist of accentuated vascular markings and minor infiltrates and, occasionally, nodular lesions in the midlung zones. Thrombosis, stasis, or infarction in pulmonary veins is believed to produce discrete lesions. Other abnormal roentgenographic findings include enlargement of hilar vessels and passive pulmonary congestion. Symptoms are those of pulmonary insufficiency from pulmonary edema. Acute airway obstruction caused by spontaneous retropharyngeal bleeding and hematoma formation has been described in a patient with polycythemia rubra vera.

Normal arterial oxygen saturation (S_aO_2 > 92%) is regarded as one of the features that differentiates polycythemia vera from the secondary (hypoxemic) form, because almost all patients with primary polycythemia have normal arterial oxygen saturation. However, mild degrees of desaturation may occur with otherwise well-documented polycythemia vera in the absence of cardiopulmonary problems. The pathogenesis of this desaturation is not apparent.

Pulmonary function studies have shown that patients with polycythemia vera usually have normal vital capacity, airway resistance, and alveolar ventilation. The diffusing capacity of lung for carbon monoxide may be slightly increased. This, however, is an inconsistent finding. Pulmonary capillary blood volume and the size of the pulmonary vascular bed may be reduced in some patients, resulting in ventilation–perfusion abnormalities.

LYMPHOPROLIFERATIVE DISORDERS

Hodgkin's Disease

Intrathoracic involvement in Hodgkin's disease is common, occurring in up to 40% of patients, especially in those with advanced stage IIIB or IV disease. Pulmonary involvement may be seen in more than 50% of cases of Hodgkin's lymphoma at postmortem. Intrathoracic involvement is twice as common with Hodgkin's as with non-Hodgkin's lymphoma.

Primary pulmonary Hodgkin's disease is a distinct entity and denotes involvement of the lung without hilar adenopathy or disseminated disease. Fewer than 100 cases of pulmonary Hodgkin's disease have been reported. This form of Hodgkin's lymphoma is more common in women, typically involves upper lung fields, and may appear as a solitary mass or a multinodular process with or without cavitation.

Almost any type of chest roentgenographic abnormality can be seen in patients with thoracic manifestation of Hodgkin's disease. However, the most common abnormality is the enlargement of mediastinal lymph nodes, noted in 50% of cases. Bilateral lymph node enlargement is common, particularly if the paratracheal nodes are involved (Fig. 6). Enlargement also affects retrosternal nodes, posterior mediastinal nodes, and the diaphragmatic group of parietal lymph nodes. Intrapulmonary lymph node involvement may not be visible on the chest roentgenogram (Fig. 7).

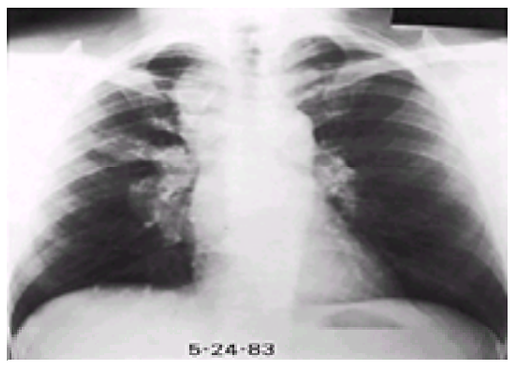

FIG. 6. Bilateral hilar and right paratracheal lymphadenopathy caused by Hodgkin's lymphoma.

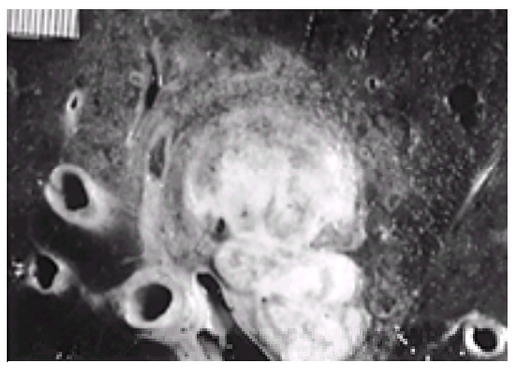

FIG. 7. Involvement of intrapulmonary peribronchial lymph node by Hodgkin's lymphoma, found at autopsy.

Pulmonary parenchymal involvement is seen in up to 30% of patients (Fig. 8, Fig. 9 and Fig. 10), especially in those with the nodular sclerosing type of Hodgkin's disease, and is usually accompanied by mediastinal lymphadenopathy. In a study of 112 patients with advanced Hodgkin's disease, more than 25% were found to have parenchymal disease without lymphadenopathy. The parenchymal features include direct invasion of lung from regional lymph nodes (characterized by linear, feathery densities), massive homogeneous infiltrates with lymphadenopathy, nodular infiltrates, and generalized dissemination resembling miliary tuberculosis. Pulmonary parenchymal involvement ordinarily results from direct extension from mediastinal nodes along the lymphatics of bronchovascular sheaths. The parenchymal masses may develop cavities, and usually these are multiple and located in lower lobes. Cavitation of pulmonary nodules secondary to Hodgkin's disease is rare and has been noted in approximately 55 cases.

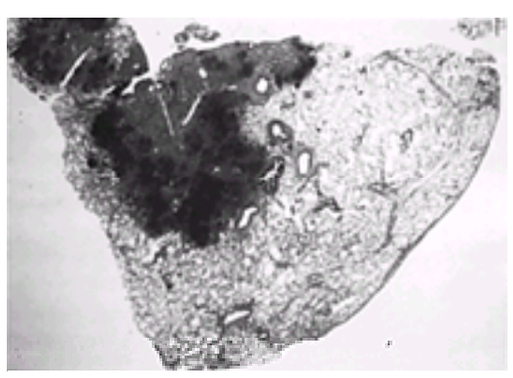

FIG. 8. Hodgkin's lymphoma presenting as a localized nodular lesion. The histologic pattern was nodular sclerosing Hodgkin's lymphoma. Some of the darker nodules of lymphoid tissue seem to be surrounded by a paler fibrous tissue indicative of a nodular sclerosing pattern.

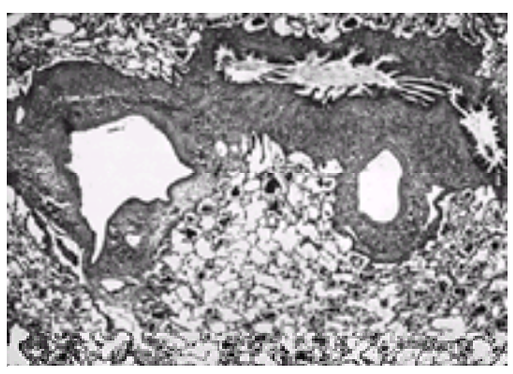

FIG. 9. Hodgkin's lymphoma in the lung as part of disseminated disease at presentation. The lung infiltrates were caused by a cellular proliferation around vessels and airway that have the cytologic features of Hodgkin's lymphoma.

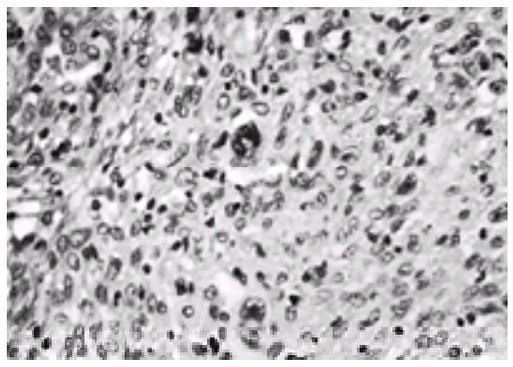

FIG. 10. Hodgkin's lymphoma replacing normal lung parenchyma. Reed-Sternberg cell is the center.

Endobronchial involvement occurs in nearly 5% of patients with Hodgkin's lymphoma. Lobar or segmental atelectasis, cough, and hemoptysis may result. Bronchial mucosal involvement from non-Hodgkin's lymphoma may become severe enough to cause airflow obstruction. Extrinsic compression of the trachea and mainstem

bronchi by large mediastinal Hodgkin's lymphoma can lead to airway obstruction and respiratory failure. Patients may experience varying degrees of dyspnea in supine posture.

Several cases of acute airway obstruction and respiratory failure during general anesthesia have been described. During general anesthesia, the extrinsic airway compression is exacerbated by diminished lung volumes secondary to reduced inspiratory muscle tone, relaxation of bronchial smooth muscle tone and the resultant compressibility of airway, diminished expiratory flow rate, and severely diminished movement of the diaphragm. Pulmonary function tests performed in 43 patients with Hodgkin's disease before mantle irradiation (total dose of 36 to 42 Gy) and at 3, 6, 9, 12, and 15 or more months thereafter have revealed only small variations in the functional indices. More than 5 years after therapy, respiratory symptoms and reduction in lung function occur in nearly one-third of otherwise healthy survivors of Hodgkin's disease. Women are at significant risk for pulmonary complications following therapy for Hodgkin's disease.

Pleural effusion occurs in 30% of patients and usually is associated with other intrathoracic lesions. The main factor responsible for the collection of pleural fluid is the obstruction to lymphatics by the enlarged hilar lymph nodes. The pleural fluid is commonly an exudate, serous, and chylous in one-third. Chylothorax is the accumulation of chyle in the pleural space because of disruption of the thoracic duct or a major lymphatic tributary. Intrathoracic malignancy is the most common cause of chylothorax, and lymphoproliferative disorders are responsible 75% of the time. In a study of 38 patients with chylous effusions, 20 effusions were caused by lymphomas. Diagnostic thoracentesis and needle biopsy of the pleura may aid in determining whether the pleural space or the pleura is involved with Hodgkin's or non-Hodgkin's lymphoma. However, the clinical correlation is extremely important in interpreting cytologic preparations. In one report, pleural biopsy was helpful in diagnosing non-Hodgkin's lymphoma in nine of ten patients. In contrast, a large series demonstrated that the finding of lymphocytic pleuritis on biopsy or lymphocytosis of pleural fluid was nondiagnostic and that clinical correlation was essential to confirm the diagnosis. Massive pleural effusions have occurred as a late complication of radiation therapy for Hodgkin's lymphoma, probably from impaired lymphatic drainage secondary to mediastinal fibrosis induced by radiation.

Spontaneous pneumothorax is an unusual complication in Hodgkin's disease. One study noted 17 episodes of pneumothorax in eight patients, seven with Hodgkin's lymphoma and one with non-Hodgkin's lymphoma. The observed incidence of pneumothorax among 1977 patients with lymphoma was tenfold higher than expected; this included a significantly higher incidence in patients younger than 30 years compared to those older than 30 years and a higher incidence in patients with Hodgkin's lymphoma than in those with non-Hodgkin's lymphoma. This study suggested a strong relationship between radiation and pneumothorax. Pneumothorax associated with lymphoma is more complex and difficult to manage. Other unusual manifestations include thoracic cage involvement and diaphragmatic paralysis.

Non-Hodgkin's Lymphomas

The most common intrathoracic manifestation of non-Hodgkin's lymphoma is mediastinal lymph node enlargement, which is seen in nearly 35% of patients. Primary pulmonary lymphoma ordinarily presents as an alveolar infiltrate or a homogeneous mass. Bronchial obstruction or endobronchial involvement occurs, but less frequently than with Hodgkin's lymphoma.

When the lung is involved by non-Hodgkin's lymphoma, the typical roentgenographic pattern is that of solitary or multiple nodules 3 mm to several centimeters in diameter, more frequently in the lower lobes. Other manifestations are similar to those in Hodgkin's disease. Endobronchial recurrence of non-Hodgkin's lymphoma can be seen in patients who are unresponsive to therapy. Diagnostic bronchoalveolar lavage provides specimens for lymphocyte subtyping and classification of lymphoma.

Pleural effusions are common in non-Hodgkin's lymphoma. Indolent lymphomas may produce chylous pleural effusions. Among 26 pleural effusions associated with non-Hodgkin's lymphomas, 20 were exudative, and five were chylous. Cytologic examinations were positive in 86% of exudative effusions, whereas 61% of pleural biopsies were positive for the disease. In a study of 19 patients with pleural effusion caused by non-Hodgkin's lymphoma, pleural tissue disclosed lymphoma in 17 patients, supporting the contention that pleural effusion in patients with non-Hodgkin's lymphoma is usually secondary to pleural lymphoma rather than to obstruction of mediastinal lymphatics. Systemic chemotherapy results in resolution of pleural effusion in approximately half the patients; the prognosis is poor in those with refractory effusions.

Patients treated for Hodgkin's and non-Hodgkin's lymphoma should be observed for the development of other hematologic and solid neoplasms because these patients accrue a relative risk two to three times that of the normal population of developing newer malignancies. Patients with Hodgkin's disease who receive supradiaphragmatic irradiation or combined-modality therapy may be at higher risk for developing non-small-cell lung cancer. In a study of such patients, the risk ratio for the development of lung cancer among Hodgkin's patients was 5.6 times that expected in the general population. The median ages at diagnosis of Hodgkin's disease and lung cancer were 39 and 45 years, respectively. The interval between the diagnoses of Hodgkin's disease and metachronous lung cancer averaged 7 years but appeared to vary inversely with age.

Primary Lymphoma of the Lung

Primary lymphomas of the lung are rare, representing fewer than 1% of all primary pulmonary malignancies. They usually are well-differentiated B-cell tumors of the IgM type, although a few cases of the IgG and IgA types have been described. Among 62 cases of primary lymphoma of lung, 58 were B-cell and two T-cell type; two other cases could not be classified. The largest group (43 cases) consisted of low-grade B-cell lymphoma of the bronchus-associated lymphoid tissue (BALT). The histologic features were similar to low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) of the stomach. The BALT hyperplasia can vary, from multifocal proliferations that arise in and remain in the airway walls (follicular hyperplasia of BALT) to those that form a solitary mass or nodule (nodular lymphoid hyperplasia of BALT or “pseudolymphoma”) to multifocal or diffuse lymphoid hyperplasia of BALT (“lymphoid interstitial pneumonitis”).

The definitive diagnosis of primary pulmonary lymphoma rests on the typical histopathologic and immunochemical staining pattern. Low-grade lymphomas show a peak occurrence in the sixth decade of life, whereas the high-grade lymphomas occur most often in the seventh decade. There is a slight male predominance. Nearly 75% of the patients with low-grade B-cell lymphoma of BALT exhibit solitary or multiple sharply defined lung nodules. The prognosis is favorable in those without systemic symptoms.

The majority of primary extranodal lymphomas (not to be confused with primary lymphoma of lung) originate in MALT, and the term maltoma has been applied to them. The maltomas seem to be associated with good prognosis. In a study of 161 cases of non-Hodgkin's lymphomas and pseudolymphomas of lung, lymphomas were noted in 32%—plasmacytoid lymphocytic and small, cleaved, follicular center-cell lymphomas in 22% and 12% of cases, respectively. The remainder were follicular center-cell lymphomas and B-immunoblastic sarcomas. Most patients were elderly and asymptomatic, and, in most cases, a solitary nodule or infiltrate was seen on the chest roentgenogram. Hilar lymphadenopathy was also observed.

Mycosis Fungoides and Sezary Syndrome

Cutaneous T-cell lymphomas encompass a spectrum of diseases, including mycosis fungoides and Sezary syndrome, characterized by the malignant proliferation of phenotypically mature T lymphocytes with a propensity to infiltrate the skin. Microscopic infiltration of the lung parenchyma occurs in 43% to 56% of these patients. Lung biopsy and sometimes the sputum cytology will show distinctive large and small mononuclear cells with an indented cerebriform and hyperchromatic nuclei. Lymphadenopathy precedes visceral involvement. Pulmonary manifestations may include diffuse basilar infiltrates, nodular densities, perihilar densities, pneumonic processes, consolidative lesions, and pleural effusion. Hemoptysis and hypoxemia are described. Rapid pulmonary dissemination can occur in Sezary syndrome.

LYMPHOMATOID GRANULOMATOSIS

Recently renamed *angiocentric T-cell lymphoma,* lymphomatoid granulomatosis is also known polymorphic reticulosis, midline malignant reticulosis, midline granuloma, and Stewart's granuloma. Even though clinically and roentgenologically lymphomatoid granulomatosis mimics Wegener's granulomatosis and is frequently discussed in the context of vasculitides, lymphomatoid granulomatosis is a lymphoproliferative disorder and not a primary vasculitis. Similarities have been noted in the histologic patterns of lymphomatoid granulomatosis and Epstein–Barr virus (EBV)-associated lymphoproliferative disease involving the lung. Epstein–Barr virus has also been identified by polymerase chain reaction in most cases of pulmonary lymphomatoid granulomatosis. It appears that some cases of lymphomatoid granulomatosis represent B-cell lymphoma associated with EBV infection, whereas others (perhaps those limited to head and neck region) are of T-cell origin and are probably unrelated to EBV infection. However, because of the similarity between lymphomatoid granulomatosis and nasal angiocentric lymphoma, the term angiocentric immunoproliferative lesion has been proposed for both entities.

A familial lymphoproliferative disorder is described in three male siblings with primary pulmonary involvement manifested as either lymphoid interstitial pneumonia or an angiodestructive lesion resembling lymphomatoid granulomatosis. Epstein–Barr virus, frequently associated with proliferative lesions in men in the X-linked lymphoproliferative syndrome, was not demonstrated in any of the pulmonary lesions. The lack of involvement by EBV in the pulmonary lesions suggests that this is perhaps a previously undescribed familial lymphoproliferative disorder.

Morphologically, lymphomatoid granulomatosis is a destructive angiocentric process characterized by prominent vascular infiltrates and necrosis of medium and small blood vessels with formation of granulomas (Fig. 11). Impairment of the immune system of unknown causes may predispose patients with lymphomatoid

granulomatosis to develop anergy and, eventually, lymphoma. Histologic features often include a spectrum of benign-appearing lymphocytic interstitial pneumonitis to overtly malignant lymphoma in the same patient. Progression to non-Hodgkin's T-cell lymphoma occurs in over 50% of patients. Lymphomatoid granulomatosis is an uncommon disease, with approximately 350 cases reported. The disease usually presents during middle age, and there is a slightly higher prevalence in men. The presenting symptoms are nonspecific and include fever, malaise, and weight loss. Lymphomatoid granulomatosis can affect any organ system, but the disease is found with greatest frequency in the central nervous system, skin, kidney, and lymphatic system. Nearly one-fourth of patients demonstrate involvement of the central nervous system. Ataxia, hemiparesis, blindness, and dizziness are the presenting symptoms. Almost half of patients with lymphomatoid granulomatosis develop skin lesions in the form of erythematous, macular, or plaque-like lesions over the extremities.

FIG. 11. Lymphomatoid granulomatosis showing angiocentric infiltration by dense lymphoid infiltrates. Cytologically, this case had features of a diffuse large-cell lymphoma.

Laboratory tests are not helpful in the diagnosis. Leukocytosis (in 30% of patients), leukopenia (in 20% of patients), mild to moderate elevation of the erythrocyte sedimentation rate, and mild elevations of IgG or IgM may be present. Urinalysis usually is normal in patients with lymphomatoid granulomatosis because the glomerulus is characteristically spared.

The diagnosis of lymphomatoid granulomatosis requires biopsy examination of the affected tissue, usually lung, skin, or head and neck lesions. Lung biopsy characteristically shows an angiocentric angiodestructive infiltration of atypical lymphocytoid and plasmacytoid cells (Fig. 11).

Pulmonary Disease

Pulmonary involvement is present in virtually all patients with lymphomatoid granulomatosis. Along with the systemic symptoms, cough and dyspnea are prominent respiratory symptoms. If head and neck areas are involved, patients may present with symptoms similar to those of Wegener's granulomatosis. Hemoptysis is more likely in those with cavitated lung lesions. Chest roentgenograms most frequently disclose nodular infiltrates. Nodular densities may cavitate and are more common in the lower lung zones. In one series, multiple nodules with poorly defined borders were observed in 88% of patients, with cavitation in 25%. Occasionally, alveolar infiltrates are noted. Pleural effusions occur in 25% of patients. One review of 173 patients collected from two separate series noted the following chest roentgenologic abnormalities: multiple bilateral nodules in 80% of patients; cavitation of nodules in 30%; air bronchograms in 35%; pleural effusion in 33%; atelectasis in 30%; pneumonitis or mass-like lesions in 30%; and pneumothorax in 5% (Fig. 12 and Fig. 13).

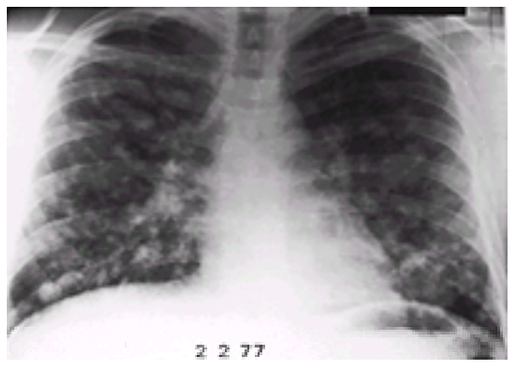

FIG. 12. Bilateral multiple nodular lesions in lymphomatoid granulomatosis.

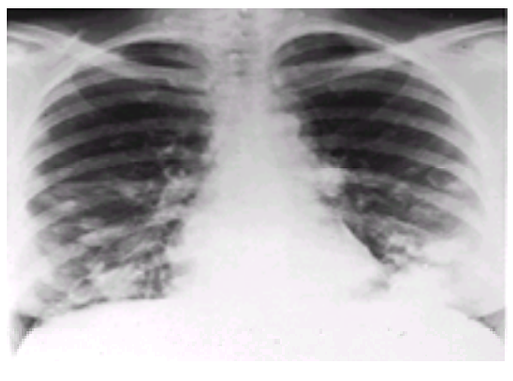

FIG. 13. Bilateral multiple nodules of varying sizes in lymphomatoid granulomatosis. Several nodules are cavitated.

Presence of hilar or mediastinal lymphadenopathy usually signifies lymphomatous transformation. Unilateral or bilateral large pulmonary masses measuring more than 10 cm in diameter often signal the presence of lymphoma.

Airway involvement is unusual but can be extensive. Pathologic findings described include bronchiolitis obliterans, bronchial ulceration, and destruction and occlusion of bronchioles by masses of inflammatory cells and fibrous tissue.

Treatment and Prognosis

There is no definitive therapy for lymphomatoid granulomatosis. In most patients, a therapeutic approach similar to that for highly malignant lymphoma must be considered. Adequate clinical staging and multiple biopsies to assess properly the degree of malignancy are necessary before multiple-drug therapy can be started. Multiple chemotherapeutic agents with a corticosteroid may be needed in patients who demonstrate highly malignant features. Preliminary reports indicate that interferon-a_{2b} is effective. Localized lesions in the head and neck area may respond to radiation. Progressive respiratory involvement, usually because of lymphoma and related complications, is the most frequent cause of death. Fever, leukopenia, cutaneous anergy, and hepatomegaly are considered poor prognostic indicators.

Pseudolymphoma

Lymphoid tumors that do not fulfill the criteria for malignant lesions have been called pseudolymphoma, although many pseudolymphomas have been reclassified as

indolent well-differentiated lymphocytic and lymphoplasmacytic lymphomas on the basis of immunologic proof of clonality. In a study of 161 cases of primary non-Hodgkin's lymphomas of the lung, pseudolymphoma was observed in 14%. Pseudolymphoma of the lung is characterized pathologically by the presence of a mixed cellular infiltrate (mostly mature lymphocytes), the presence of germinal centers, and regional lymph nodes free of lymphoma. Nonetheless, it often is difficult to distinguish pulmonary pseudolymphoma, lymphoma, and other lymphoid neoplasms and infiltrates by simple histologic examination. Pulmonary manifestations consist of well-delineated nodules, segmental parenchymal consolidation, or diffuse interstitial infiltration. Localized lesions are best treated by resection, whereas diffuse lesions may need immunosuppressive therapy.

Angioimmunoblastic Lymphadenopathy

Angioimmunoblastic lymphadenopathy mimics lymphomas. It is a disorder in which diffuse obliteration of the lymph node architecture occurs as a result of proliferation of small vessels and immunoblasts. Both an autoimmune mechanism and a T-cell defect leading to polyclonal B-cell activation may be responsible. The disease is systemic, and histopathologic features appear benign, although progression to lymphoma can occur. Angio-immunoblastic lymphadenopathy usually presents as generalized lymphadenopathy with hepatosplenomegaly and constitutional symptoms and mimics Hodgkin's disease. Differentiating features include polyclonal gammopathy, autoimmune hemolytic anemia, and a predilection for men older than 50 years. The chest roentgenographic features are similar to those of Hodgkin's disease, namely, hilar lymphadenopathy, interstitial infiltrates, and pleural effusion. Superior vena caval obstruction has been described.

Castleman's Disease

Originally reported as mediastinal lymph node hyperplasia resembling thymoma, Castleman's disease is also described by other terms, including angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, lymph node hamartoma, benign giant lymphoma, multifollicular lymph node hyperplasia. The two histologic types of Castleman's disease are the hyaline-vascular (proliferation of hyalinized blood vessels) and plasma-cell (abundance of plasma cells) types. The former accounts for 90% of cases and is usually asymptomatic, whereas the latter is associated with systemic manifestations. The disease has no predilection for age, sex, or race. It occurs in the thoracic cage in up to 70% of cases. The most common clinical manifestation is the well-defined and lobulated enlargement of anterior mediastinal lymph nodes adjacent to thymus and tracheobronchial tree. Symptoms are caused by compression of the tracheobronchial tree by enlarged lymph nodes and may include cough, dyspnea, and hemoptysis. Intrapulmonary lesions, nodules, and pleural effusion are uncommon. Computed tomography shows vascular lesions that are well rounded and lobulated. Surgical resection is curative if the disease is limited to resectable lymph nodes.

POEMS Syndrome

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, also known as Crow–Fukase syndrome, is a rare variant of plasma cell dyscrasia with multisystemic manifestations. Multiple lung tumorlets have been described. Greatly raised vascular endothelial growth factor has been observed in this syndrome. This perhaps is responsible for the acute arterial obliteration described in several patients. Pulmonary hypertension has been described in this syndrome.

Lymphocytic Interstitial Pneumonitis

Lymphocytic interstitial pneumonitis is characterized by pulmonary parenchymal infiltrates that consist predominantly of small lymphocytes and variable numbers of plasma cells and transformed lymphocytes. Many patients with lymphocytic interstitial pneumonitis have developed lymphomas. Indeed, all cases of lymphocytic interstitial pneumonitis are thought to represent low-grade lymphomas. It is not clear whether the lymphocytic infiltrative lung diseases are premalignant, initially neoplastic, or caused by a hypersensitivity reaction, with neoplasia developing subsequently. They comprise a poorly defined group that includes lymphocytic interstitial pneumonitis, immunoblastic lymphadenopathy, plasma cell interstitial pneumonitis, lymphomatoid granulomatosis, and benign lymphocytic angiitis and granulomatosis. The diseases associated with lymphocytic interstitial pneumonitis are listed in Table 2. Many of these demonstrate similar histologic features, but involvement of the central nervous system, skin, kidneys, and lymph nodes outside the thorax varies, with a course that may be slow or rapidly fatal.

Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Lymphomatoid granulomatosis
Chronic lymphocytic leukemia
Waldenstrom's macroglobulinemia
Angioimmunoblastic lymphadenopathy
Sézary syndrome
Pseudolymphoma
Sjögren's syndrome
Acquired immunodeficiency syndrome (AIDS)
Children of mothers at high risk for AIDS
Graft-versus-host disease
Congenital agammaglobulinemia
Chronic active hepatitis
Primary biliary cirrhosis
Crohn's regional enteritis
Nontropical sprue
Myasthenia gravis
Autoimmune hemolytic anemia
Systemic lupus erythematosus
Chronic thyroiditis
Idiopathic

TABLE 2. *Differential diagnosis of lymphocytic interstitial pneumonitis*

The occurrence of lymphocytic interstitial pneumonitis in patients with AIDS is well recognized. Lymphocytic interstitial pneumonitis occurs frequently in children of mothers who are at high risk for developing AIDS.

Low-grade lymphoid malignancies respond well to therapy. The treatments, however, may lead to acute, subacute, or chronic pulmonary complications. A literature analysis of 2269 patients with low-grade lymphoid malignancies who received more than 7547 cycles of fludarabine noted that 3% of patients developed opportunistic infections; among the latter group, 97% of infections occurred in patients who were pretreated with alkylating regimens or corticosteroids, and 45 (2%) of these were of respiratory origin and associated with a 56% mortality rate.

PLASMA CELL DISORDERS

Amyloidosis

Amyloidosis is a plasma cell disorder of unknown etiology, characterized pathologically by the extracellular deposition of acellular fibrils derived from the light chain of a monoclonal immunoglobulin. In primary amyloidosis, 35% to 70% of cases show roentgenographic evidence of amyloid deposition in the lung, whereas in secondary amyloidosis, pulmonary involvement is rare. A review, in 1983, of 126 reported cases of primary localized amyloidosis of the lower respiratory tract revealed the following pulmonary abnormalities: hilar or mediastinal lymphadenopathy in 5%, tracheobronchial multifocal submucosal plaques in 45%, tracheobronchial amyloid tumor-like masses in 8%, discrete nodules in the pulmonary parenchyma in 44%, and diffuse alveolar septal amyloidosis in 3%. A review in 1996 observed that 35 of 55 patients with pulmonary amyloidosis had primary systemic amyloidosis that presented roentgenologically as an interstitial or reticulonodular pattern with or without pleural effusion. The median survival after diagnosis was 16 months. Nodular pulmonary “amyloidomas” (nodular amyloid lesions) were not associated with systemic disease and were associated with a benign prognosis. Despite its localized nature, tracheobronchial amyloid deposition may be asymptomatic or may result in significant morbidity from obstructive phenomena. Pleural effusion is uncommon unless it is caused by congestive cardiac failure.

Pulmonary amyloidosis may be classified as shown in Table 3. Macroglossia associated with amyloidosis has been reported to cause airway obstruction and sleep apnea. Laryngeal and subglottic deposition of amyloid may contribute to the airway obstruction (Fig. 14). Diffuse tracheobronchial submucosal plaques result in generalized narrowing of the tracheobronchial tree and cause progressive stridor, dyspnea, cough, atelectasis, and hemoptysis. Bronchoscopic examination reveals submucosal elevation of the tracheobronchial mucosa, pale, shiny ridges, and areas of stenoses with various degrees of luminal narrowing. A deep submucosal bronchoscopic biopsy of the submucosa yields the diagnosis.

Type	Pulmonary symptoms
Macroglossia	Sleep apnea
Laryngeal and subglottic (localized, stenotic)	Stridor, dyspnea
Diffuse tracheobronchial (submucosal plaques)	Stridor, dyspnea, hemoptysis
Localized tracheobronchial (mass-like lesions)	Stridor, dyspnea, hemoptysis
Diffuse nodular (parenchymal)	Mild symptoms, bronchiectasis, cavitation in 30%
Solitary nodular (parenchymal; amyloidoma)	Rare, minimal symptoms, incidental finding
Diffuse parenchymal (septal or interstitial)	Progressive dyspnea, hemoptysis
Mediastinal and hilar lymphadenopathy[a]	Seen in 5% of all amyloidoses
Secondary[b]	Incidental (biopsy or autopsy finding, asymptomatic)
Senile	Incidental (autopsy or biopsy finding, asymptomatic)
Malignancy associated[c]	Incidental

[a] Sometimes associated with multiple myeloma.
[b] Associated with tuberculosis, syphilis, bronchiectasis, and hypergammaglobulinemia.
[c] Pulmonary malignancy, carcinoid, and amyloid associated with medullary thyroid carcinoma.

TABLE 3. *Pulmonary amyloidosis*

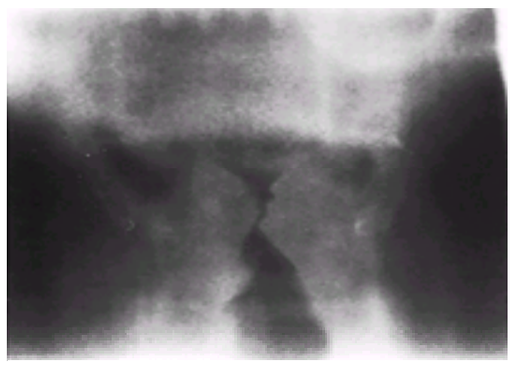

FIG. 14. Tracheal tomogram demonstrates amyloidosis involving subglottic and upper trachea.

Tracheobronchial amyloidosis is an indolent form of disease. However, hemoptysis and stridor can pose life-threatening emergencies. In contrast to the submucosal variety, localized tracheobronchial amyloidosis will exhibit, on bronchoscopy, endobronchial tumor-like amyloid masses that are usually polypoid and solitary and occur only in major bronchi. Secondary changes may include atelectasis, obstructive emphysema, obstructive pneumonitis, or bronchiectasis. Fatal hemorrhage has been described.

The lower respiratory tract often is involved in systemic primary amyloidosis, and, occasionally, disease is restricted to lungs. Chest roentgenographs may exhibit nodular changes or diffuse infiltrations. Amyloid nodules in the pulmonary parenchyma are peripheral and grow slowly, may be solitary (amyloidoma) or multiple (Fig. 15), and cavitate in one-third of patients. Calcification of the nodule can occur.

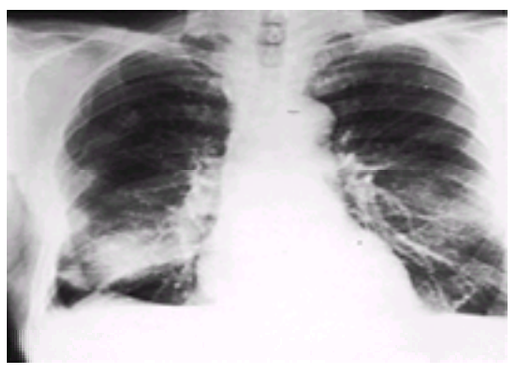

FIG. 15. Localized amyloidosis (amyloidoma) of right lower lobe treated by surgical resection.

The diffuse alveolar septal form of pulmonary parenchymal amyloidosis usually is associated with systemic amyloidosis and carries the worst prognosis of all types of pulmonary amyloidosis (Fig. 16). Progressively restrictive lung dysfunction abnormality, severely diminished diffusing capacity of lung for carbon monoxide, and significant hypoxemia are common. Lung biopsy shows diffuse deposition of amyloid in interstitium and alveolar walls (Fig. 17). Electron microscopic studies have shown that deposition of amyloid is confined to the interstitial space of alveolar septa and that capillaries are involved in the later stages. Involvement of pulmonary vasculature in amyloidosis may lead to medial dissection of pulmonary arteries and hemoptysis. Congestive cardiac failure with secondary pulmonary edema may contribute to the pulmonary distress.

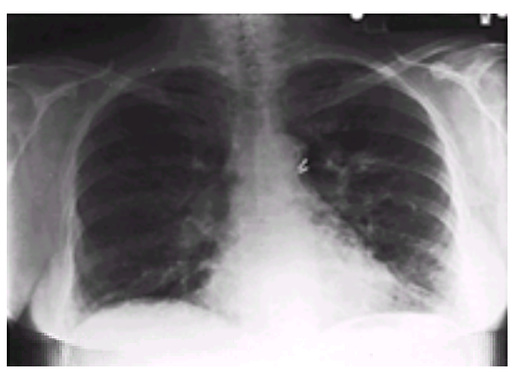

FIG. 16. Diffuse parenchymal amyloidosis showing basal interstitial infiltrates.

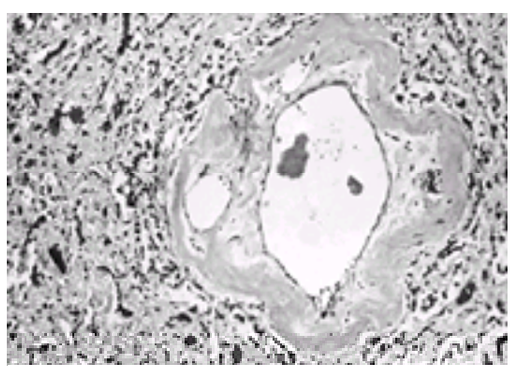

FIG. 17. Amyloid deposits surrounding pulmonary blood vessels in primary amyloidosis.

The prognosis is much better for the nodular pulmonary parenchymal type than for the tracheobronchial obstructive or diffuse interstitial forms of amyloidosis. The latter often lead to death from respiratory insufficiency. Localized tracheobronchial amyloidosis may respond to repeated bronchoscopic Nd:YAG or carbon dioxide laser photoresection, although the treatment is often unsatisfactory. Although it has been suggested that tracheobronchopathia osteoplastica is the end result of tracheal amyloidosis or other metabolic diseases, the literature fails to support this contention. Diaphragmatic myopathy from amyloidosis infiltration may result in respiratory failure. Secondary localized amyloidosis of the lower respiratory tract has been noted in tuberculosis, syphilis, hypogammaglobulinemia, malignancies (usually pulmonary), and carcinoid.

Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia is an uncommon disorder characterized by monoclonal IgM gammopathy, anemia, and lymphocytic or plasmacytic infiltration of bone marrow. Pleuropulmonary involvement is relatively common. Five of 20 patients exhibited abnormalities, asymmetric nodular lesions in four and pleural effusion in one; biopsies showed infiltration of lungs by lymphocytes and plasmacytes in four, and roentgenograms demonstrated resolution of abnormalities. Characteristically, the chest roentgenogram shows a diffuse reticulonodular pattern and, occasionally, local homogeneous consolidation (Fig. 18). Pleural effusion is present in nearly 50% of patients. Chylothorax is rare.

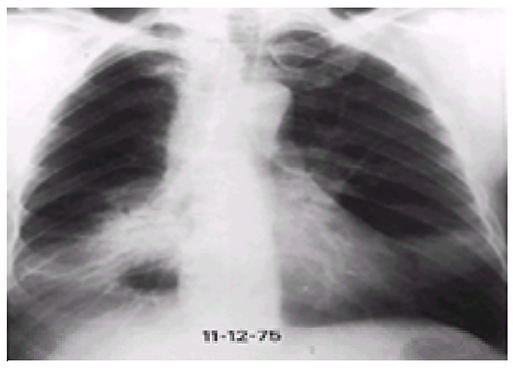

FIG. 18. Bilateral lower-lung infiltrates associated with a large right pleural effusion in Waldenstrom's macroglobulinemia.

In a 1980 literature review of pulmonary complications of Waldenström's macroglobulinemia documented by biopsy of pleura or lung (or both) in 44 patients (26 men; ages 33 to 84 years, median age 64 years), mass lesions were noted in 50%, infiltrates in 70%, and pleural effusions in 43%. Mediastinal lymphadenopathy was associated with pulmonary disease in 25%. Fifty-five percent of patients had two or more of these manifestations. Dyspnea (54%), nonproductive cough (33%), and chest pain (7%) were the main pulmonary symptoms, and 15% of patients were asymptomatic. Many had pulmonary manifestations at the time of initial disease. Respiratory involvement appeared 2 to 67 months after the diagnosis of Waldenström's macroglobulinemia in two-thirds. Bronchoalveolar lavage studies in a patient with diffuse pulmonary involvement from Waldenström's macroglobulinemia have shown abnormal plasma cells (10% to 47%), lymphocytes (60%), and myeloma protein.

Pulmonary manifestations respond to alkylating agents, corticosteroids, and radiation and do not appear to affect prognosis adversely. In one study, 19 of the 31 patients responded to chlorambucil given alone or with corticosteroids.

Multiple Myeloma

A malignant neoplasm of plasma cells, multiple myeloma is manifested primarily by widespread skeletal destruction and frequently is associated with anemia, hypercalcemia, and renal dysfunction. Pulmonary manifestations are rare. The chest roentgenographic finding of a plasmacytoma is typically that of a homogeneous mass associated with an osteolytic rib lesion, with the mass normally protruding into the thoracic cage (Fig. 19). Pulmonary parenchymal involvement by the abnormal plasma cells is unusual. Diffuse pulmonary infiltration by neoplastic plasma cells occasionally produces interstitial changes on the chest roentgenograph.

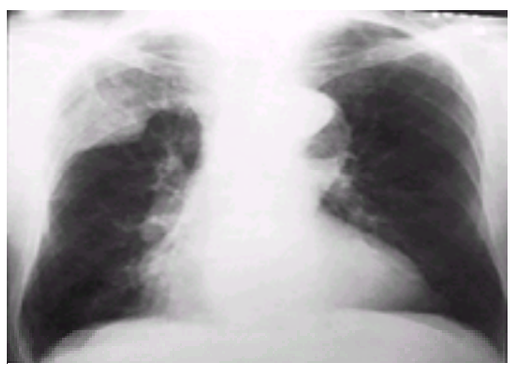

FIG. 19. Multiple myeloma involving right upper ribs with protrusion of the bony tumor into the chest cavity.

Solitary plasmacytoma of the upper respiratory tract or the pulmonary parenchyma may occur. Primary tracheal plasmacytoma, when present, appears as a solitary or multiple mass of homogeneous density. Unusual manifestations include nonosseous pleural lesions, pleural effusions, chylothorax, and pulmonary parenchymal calcification. Alveolar hemorrhage has been described as a presenting feature of myeloma. Metastatic pulmonary calcification that resolved with therapy is described in a patient with multiple myeloma.

Transfusion and the Lung

The use of blood and blood products, even under the best circumstances, carries considerable risk for the recipient. Immediate pulmonary reactions include dyspnea, bronchospasm, and pulmonary edema. It should be emphasized that pulmonary edema following blood transfusion need not be the result of overloading the circulation. In addition to the blood and blood products, patients receive crystalloid solutions and other drugs via the intravenous route. Transfusion-related acute lung injury and the postperfusion syndrome are discussed here.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a form of noncardiogenic pulmonary edema. Passive transfusion of granulocyte or lymphocyte antibodies, or both, in donor sera is the most common setting for this unusual reaction. The antibodies in the donor serum may activate granulocytes and complements. The use of therapeutic or prophylactic granulocyte transfusion has been associated with the development of cytomegalovirus pneumonia. Granulocyte transfusion in association with amphotericin B or in the setting of endotoxemia has been associated with acute respiratory failure.

The incidence of TRALI may be underestimated. One review of 36 cases over a 2-year period indicated an incidence of 0.02% per unit and 0.16% per patient transfused. The clinical features are dramatic. Acute respiratory distress within 4 hr after transfusion (in most cases, after 2 hr) is the *sine qua non* of this syndrome.

Other features include acute onset of chills, fever, tachycardia, nonproductive cough, and blood eosinophilia. Roentgenograms show patchy opacities in the perihilar and lower-lung regions (Fig. 20). Although recovery is rapid and complete in 81%, some form of respiratory support may be required in more than two-thirds of the patients. Pulmonary infiltrates and hypoxemia have persisted for 7 days in 17% of patients. Granulocyte antibodies in the serum of at least 1 unit of donor blood were demonstrated in 89% of cases, whereas lymphocytotoxic antibodies were present in 72%.

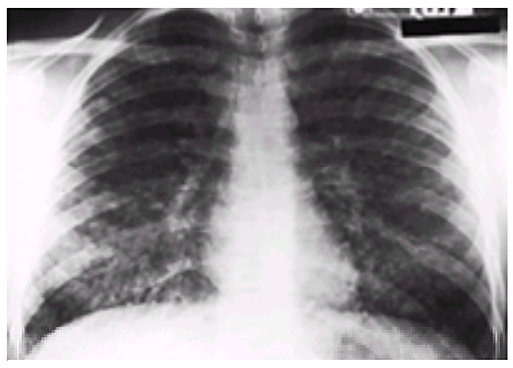

FIG. 20. Diffuse bilateral soft nodular infiltrates as a result of transfusion-related acute lung injury.

Postperfusion Syndrome

Pulmonary complications following prolonged cardiopulmonary bypass have been termed postperfusion syndrome, pump lung, perfusion lung, or postperfusion atelectasis. The etiology remains unknown, although immunologic mechanisms have been suggested. After prolonged maintenance on cardiopulmonary bypass, patients develop progressive pulmonary insufficiency, which is manifested by cyanosis, hypoxemia, increased work of breathing as a result of severely diminished compliance, and widening of the alveolar–arterial oxygen tension gradient. Chest roentgenograms reveal patchy, diffuse alveolar infiltrates that resemble pulmonary edema. Pathologic changes are similar to those seen in the respiratory distress syndrome, namely diffuse alveolar damage.

Factors that contribute to the postperfusion lung syndrome include hypoxia, interruption of blood supply to pulmonary tissues (especially to alveolar cells), loss of surfactant, interaction of homologous blood with a pump gas exchanger, and an underlying pulmonary disease process.

Prevention of the postperfusion syndrome is important because treatment is not promising. Corticosteroids given early may help, but the results are similar to those seen in the respiratory distress syndrome from other causes.

Langerhans-Cell Histiocytosis

Langerhans-cell histiocytosis is also known as pulmonary eosinophilic granuloma or primary pulmonary histiocytosis X. It is a granulomatous disease of unknown etiology characterized by abnormal proliferation of histiocytes and an unpredictable natural history, although the disease usually exhibits a slowly progressive course. Langerhans-cell histiocytosis belongs to the group of diseases collectively known as *histiocytic reticulocytosis* or *histiocytic reticuloendotheliosis;* the latter category of disorders includes Letterer–Siwe disease (acute disseminated histiocytosis X), Hand–Schuller–Christian disease (chronic disseminated histiocytosis X), and localized histiocytosis X or eosinophilic granuloma. The main discussion here is on the pulmonary form of Langerhans-cell histiocytosis.

Pathologic Features

The etiology of pulmonary Langerhans-cell histiocytosis is unknown. An immune mechanism has been suggested because of the presence of circulating immune complexes and granular IgG and complement components in alveolar walls and pulmonary capillaries. Macrophage colony-stimulating factor and platelet-derived factor may have a role in initiating and/or maintaining pathologic lesions. The most striking association, however, is between pulmonary Langerhans-cell histiocytosis and tobacco smoking; a history of tobacco smoking has been observed in more than 95% of patients with the disorder.

The effector cells, generally referred to as histiocytes, are a combination of pigment-laden alveolar macrophages and histiocytosis X cells (H-X cells), which are closely related to Langerhans cells in normal skin. A Langerhans cell is seldom seen in normal lungs. The H-X cells are judged to be reactive or activated Langerhans cells, and therefore, pulmonary Langerhans-cell histiocytosis is considered to represent a pathologic proliferation of Langerhans cells. Electron microscopy shows a common marker organelle (X-body or Birbeck granule) in the H-X cell. These pentalaminar cytoplasmic inclusion bodies are not specific for the disorder. They are present also in nearly one-fourth of patients with idiopathic pulmonary fibrosis and hypersensitivity pneumonitis but absent in inorganic pneumoconioses, pulmonary lymphangioleiomyomatosis, and sarcoidosis.

Bronchoalveolar lavage can be used to establish the diagnosis. The H-X cells are not normally present in the alveolar wall and rarely are seen in the bronchiolar wall but may constitute 2% to 20% of the effector cells in Langerhans-cell histiocytosis. Langerhans cells express surface antigen identified by the monoclonal antibody OKT6 or positive immunoperoxidase staining for S-100 protein. Even though S-100 protein staining is non-specific, OKT6-reactive cells are more specific for Langerhans-cell histiocytosis.

Gross morphologic features in the early phase of the disease show subpleural nodules that measure 2 to 10 mm or more and small, irregular cystic lesions. The nodules contain a wide variety of cells, including cells with large vesicular nuclei, cells with vacuolated cytoplasm, giant cells, histiocytes, lymphocytes, eosinophils, and polymorphonuclear leukocytes, and the degree of lymphocytic and plasma cell infiltration, extent of eosinophilia, number of foam cells, and amount of necrosis or fibrosis vary considerably from lesion to lesion (Fig. 21 and Fig. 22). The histiocytes fuse to form multinucleate giant cells, which results in the accumulation of so-called foam cells, vacuolated histiocytes with sudanophilic material in the cytoplasm. Langerhans bodies and fibrils are apparent also in cytoplasm. The H-X cells are seen in large numbers in acute and active forms of the disease, decreasing in number as the disease becomes chronic. Fibrosis eventually replaces the granulomatous process, and formation of characteristic honeycomb cysts occurs.

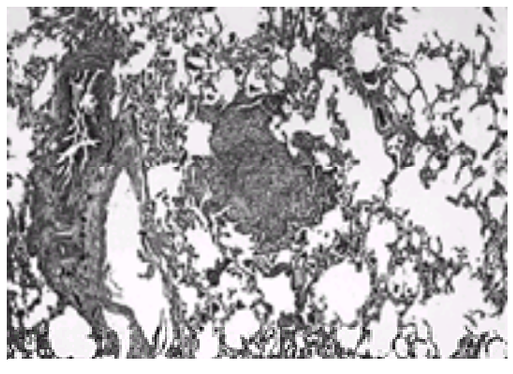

FIG. 21. The earliest lesions of pulmonary eosinophilic granuloma are central lobular proliferations of cells along small bronchioles and alveolar ducts, seen here as a small parenchymal nodule.

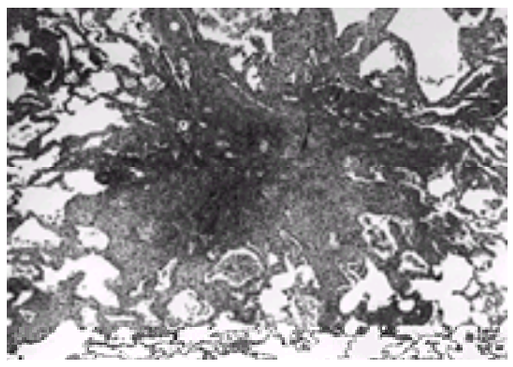

FIG. 22. In established cases of pulmonary eosinophilic granuloma, the classic lesion is a stellate nodule with central pigmentation and scarring and peripheral cellularity in which Langerhans histiocytes can be found.

Clinical Features

Pulmonary Langerhans-cell histiocytosis usually is a disease of adults and is more commonly limited to the lungs or the bones or both. The incidence of the disease is unknown. More than 1000 cases have been reported, and more than 300 of these have displayed diffuse abnormalities on chest roentgenography and an interstitial pulmonary process on pathologic examination. Most patients are 20 to 40 years old, and the male-to-female ratio is approximately equal, although most series have shown a slight male predominance. The disorder occurs most frequently in Caucasians and is rare in blacks. Familial incidence has been reported in one instance.

One-fourth to one-third of patients with pulmonary disease are asymptomatic, the disease being uncovered by a routine chest roentgenogram. One-third of patients complain of fatigue, fever, and weight loss. The most common symptom is a nonproductive cough, observed in 65% of patients. Dyspnea and chest pain are present in 40% and 25% of patients, respectively. Chest pain may be secondary to a spontaneous pneumothorax or an osteolytic rib lesion.

Commonly, pulmonary functions are only minimally abnormal even when the chest roentgenogram shows significant abnormalities. Up to 15% of patients will demonstrate normal lung functions. In contrast, in one study of the disorder in children, 13% of patients with Langerhans-cell histiocytosis had abnormal pulmonary functions even though chest roentgenograms were normal. The most common pulmonary function abnormality is a restrictive defect with decreased lung volumes, normal flow rates, and diminished diffusion capacity of lung for carbon monoxide. Significant obstructive airways disease is present in up to 20% of patients with advanced disease. These patients present with symptoms of severe airways disease. Tobacco smoking, peribronchial fibrosis with compression of airways by the cystic lesions, and obliterative bronchiolitis from infiltration of bronchial walls by cells and granulomas may contribute to airways obstruction.

Chest roentgenologic abnormalities in Langerhans-cell histiocytosis usually are diffuse, bilateral, and most pronounced in the upper two-thirds of the lung fields. Initially, a nodular pattern with lesions ranging from 1 to 12 mm in diameter is found (Fig. 23). Later on, a reticulonodular pattern and honeycomb appearance, with cysts varying from 5 to 30 mm and averaging less than 1 cm, is typical. The honeycomb pattern in upper lung zones is highly suggestive of Langerhans-cell histiocytosis. Spontaneous pneumothorax is the first indicator of this condition in up to 20% of patients (Fig. 24). The sparing of costophrenic angles, a common finding, is considered to indicate good prognosis. Pleural reaction, effusion, or thickening are uncommon, even in patients with recurrent pneumothoraces. Uncommon pulmonary symptoms include hemoptysis and wheezing. Unusual roentgenologic features include hilar prominence (in fewer than 25%), hilar vascular prominence, alveolar consolidation, solitary nodules, cavitation of nodules, and mediastinal masses with development of cavitation within the mass, mass lesions of the anterior chest wall, and tracheobronchial lesions.

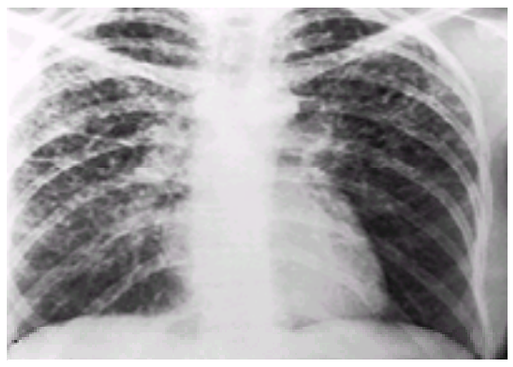

FIG. 23. Pulmonary eosinophilic granuloma with diffuse reticulonodular pattern and honeycombing. Upper-lung distribution of the infiltrates is noteworthy.

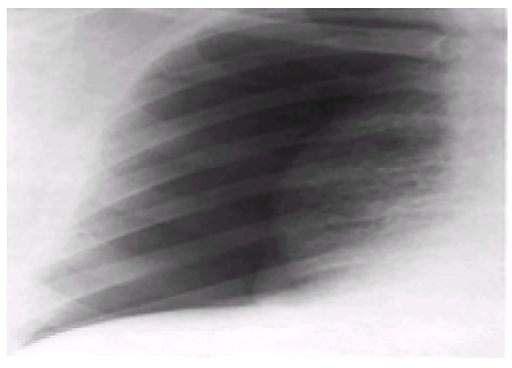

FIG. 24. Spontaneous pneumothorax in pulmonary eosinophilic granuloma. Fine honeycombing can be seen in the partially collapsed lung.

Nonpulmonary manifestations of Langerhans-cell histiocytosis include diffuse maculopapular skin nodules, solitary or multiple bony lesions, diabetes insipidus (seen in 20% of patients), head and neck lesions, otologic involvement, periodontal disease, gynecologic disease, renal disease, hepatic nodules, and hepatic cirrhosis. Two examples are reported of the disorder presenting as lymphadenopathy and confined to lymph nodes.

Diagnosis

High-resolution computed tomography (HRCT) of the chest is very useful in diagnosing pulmonary Langerhans-cell histiocytosis (Fig. 25). A study of 18 patients by HRCT revealed the following abnormalities: thin-walled cysts in 94%, nodules in 78%, cavitated nodules in 17%, thick-walled cysts in 39%, reticulation in 22%, ground-glass opacities in 22%, and irregular interfaces in 22%. The lesions were most often diffuse (89%), with a predominant distribution in the upper or middle lung zones in nine patients (50%). Comparison of HRCT and chest roentgenograms showed that small and large cysts and micronodules were better detected by HRCT. Longitudinal studies in some patients suggested that HRCT patterns progressed from nodules to cavitated nodules, thick-walled cysts to cysts, and distinct cysts to confluent cysts. Similar studies have shown that many small nodules are distributed in the centers of secondary lobules around small airways and that HRCT findings correlate better with the diffusing capacity than do the chest roentgenologic findings.

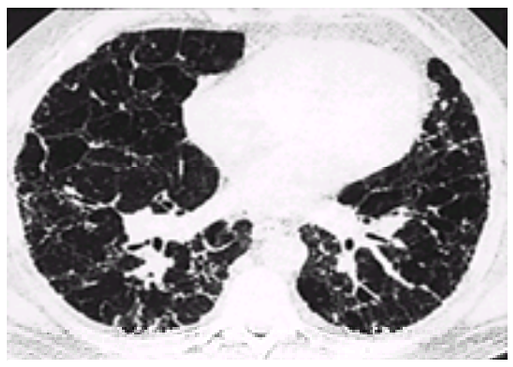

FIG. 25. High resolution computed tomogram of lung in advanced stages of pulmonary eosinophilic granuloma shows extensive cystic changes.

The diagnosis of Langerhans-cell histiocytosis is made on the basis of typical clinical features, chest roentgenologic findings, HRCT of the thorax, bronchoalveolar lavage, and bronchoscopic lung biopsy. Not every patient requires each of these diagnostic procedures. In the proper clinical setting, diagnosis can be made on the basis of clinical features and HRCT of chest. For instance, a young man who presents with a spontaneous pneumothorax and in whom the chest roentgenogram reveals diffuse honeycombing or a reticulonodular process is assumed to have pulmonary Langerhans-cell histiocytosis unless proved otherwise. The pulmonary examination is usually normal unless obstructive lung disease is present. Clubbing may occur in patients with advanced disease and chronic hypoxia. Lymphadenopathy and hepatosplenomegaly are conspicuously absent in patients with isolated pulmonary disease. Routine hematologic and serologic data are generally normal, and sedimentation rate is either normal or only minimally elevated. Peripheral eosinophilia is not a feature of Langerhans-cell histiocytosis (eosinophilic granuloma).

Bronchoalveolar lavage shows the Langerhans cells (Fig. 26). The cells obtained from bronchoalveolar lavage should be analyzed to detect surface antigens using OKT6 monoclonal antibodies, antibodies to S-100 protein, or antibodies to the HLA-DR protein. As noted above, the presence of OKT6 monoclonal antibody is more specific for the diagnosis. Electron microscopy of lung biopsy or lavage effluent reveals cytoplasmic Langerhans-cell inclusion bodies (Birbeck granules or X bodies).

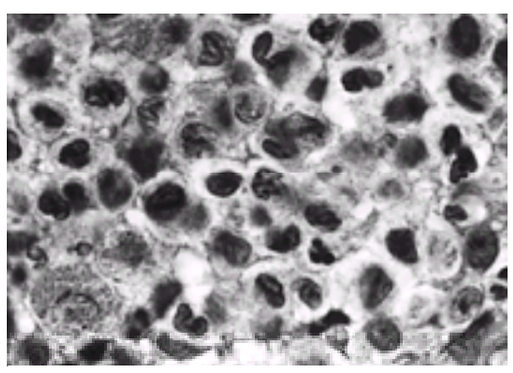

FIG. 26. Langerhans cells of pulmonary eosinophilic granuloma have delicate folded and indented nuclei and are distinct from pulmonary alveolar macrophages. An eosinophil with cytoplasmic granules is seen at lower left.

Letterer–Siwe Disease

Letterer–Siwe disease is almost always limited to infants and children. The disease becomes manifest before the age of 2 years and is characterized by extensive systemic dissemination and a fulminating, fatal course. However, Letterer–Siwe disease has been reported in 26 adult patients, with involvement of the lungs in half of them. If the symptoms appear after the age of 2 years, the 10-year survival rate is 85%, and in those who develop symptoms earlier, 10-year survival is 40%.

Hand–Schuller–Christian Disease

Patients with Hand–Schuller–Christian disease may manifest one or all of the classic three signs: exophthalmos, diabetes insipidus, and osteolytic lesions of the skull. The characteristic triad, however, is observed in only 10% of children with multifocal Langerhans-cell histiocytosis. Hand–Schuller–Christian disease usually becomes apparent during later childhood or adolescence and progresses slowly, so that most patients reach adulthood. It has been suggested that the Hand–Schuller–Christian triad is nonspecific and that the term *multifocal eosinophilic granuloma* be used to describe the abnormalities in various organs.

Treatment and Prognosis

Pulmonary Langerhans-cell histiocytosis in adults demonstrates a fluctuating course and frequent tendency toward spontaneous resolution. Asymptomatic patients and those with stable chest roentgenologic abnormalities may be observed without specific therapy. Smoking cessation should be stressed. Progressive disease may require prolonged high-dose corticosteroid therapy (prednisone, 0.75 to 1.0 mg/kg per day for 6 to 12 months). In refractory cases, a therapeutic trial of vinca alkaloids (vinblastine or vincristine) has been tried. In children, therapy using vinca alkaloids with or without corticosteroid has proved to be equally efficacious. Expanding or symptomatic bone lesions are treated with steroids, excision and curettage, or radiation. Radiation is not indicated in disease limited to the lungs. Since the Langerhans-cell is of hemopoietic origin, it has been suggested that Langerhans-cell histiocytosis is perhaps curable by ablating the patient's hemopoietic system and replacing it with donor bone marrow by bone marrow transplantation.

The overall prognosis is good in adults with pulmonary Langerhans-cell histiocytosis, with mortality rates of less than 5%. The prognosis is poor in patients with extensive cysts, large bullous type lesions, severe honeycombing, progressive obstructive airways disease, multiple pneumothoraces, severe hypoxemia, secondary pulmonary hypertension, markedly decreased diffusing capacity of lung for carbon monoxide, extensive multisystem disease, prolonged constitutional disturbance. Radiation therapy and chemotherapy to treat Langerhans-cell histiocytosis are associated with a 50% chance of inducing lung cancer and pulmonary lymphoma.

MISCELLANEOUS HEMATOLOGIC DISORDERS

Chronic anemia, in addition to its effects on cardiovascular hemodynamics, is known to produce a reduction in diffusing capacity of the lung for carbon monoxide. The diffusing capacity decreases approximately 7% for each gram per 100 mL decrease in hemoglobin. Before carbon monoxide diffusing capacity can be used to evaluate lung function, a correction for significant anemia should be made. Anemic patients demonstrate higher extraction of oxygen from blood, presumably as a result of increased work by the heart.

Paroxysmal nocturnal hemoglobinuria is a hematopoietic stem-cell disorder characterized by an increased sensitivity of blood cells to complement-mediated lysis. Vascular thrombosis of pulmonary vasculature and pulmonary hypertension have been described.

Autoimmune hemolytic anemia has been shown to be associated with pulmonary fibrosis in two patients, and a possible relationship between autoimmune hemolysis and fibrosing alveolitis has been suggested. Primary pulmonary hypertension has been described in association with microangiopathic hemolytic anemia and thrombocytopenia.

Bare lymphocyte syndrome is characterized by the absence of cell surface HLA-A, HLA-B, and sometimes HLA-C antigens and is a form of immunodeficiency in infants. The adult form of this syndrome, complicated by chronic sinusitis and bronchiectasis, has been described.

Hematopoiesis (extramedullary) in the thoracic cage may present as mediastinal process. A case of hematopoiesis occurring in bronchus has been described. Acute and rapidly fatal respiratory failure from pulmonary interstitial extramedullary hematopoiesis associated with myelofibrosis has been described. A Tc-99m sulfur colloid

bone marrow scan may show diffuse replacement of pulmonary interstitium with bone marrow, and bronchoscopic lung biopsy has shown interstitial involvement with increased numbers of megakaryocytes and other panhematopoietic staining elements.

Thoracic splenosis may present as a nodular or mass-like density in the thoracic cage or lung parenchyma. Past abdominal injuries in which splenic trauma is followed by migration of splenic fragments into the chest cage is usually responsible for this finding. The spleen is absent, usually due to splenectomy, and peripheral blood smear may be indicative of splenectomy.

Hereditary stomatocytosis is rare familial disorder of erythrocytes. Nine cases have been described with documented thrombotic complications after splenectomy. Three patients became severely ill with pulmonary hypertension.

PULMONARY DIAGNOSTIC PROCEDURES

The diagnostic approach to immunocompromised patients with pulmonary manifestations is discussed in detail in Chapter 55. Chest roentgenograph and computed tomography of the chest are invaluable in assessing the pulmonary complications in hematologic diseases. Specific findings on high-resolution computed tomography (HRCT) of the chest can be seen in pulmonary Langerhans-cell histiocytosis and bronchiolitis obliterans with organizing pneumonia. Computed tomography is frequently helpful in staging Hodgkin's and non-Hodgkin's lymphomas. Bronchoscopic needle aspiration of subcarinal, hilar, and paratracheal lymph nodes is facilitated by computed tomographic identification of the lymph nodes.

In patients with hematologic diseases who develop lung infiltrates, bronchoscopic examination is very useful to identify infectious organisms. A prospective study of 90 patients with hematologic malignancies (57 acute leukemias, six Hodgkin's disease, 15 non-Hodgkin's lymphomas, 12 other diseases) with fever (>38.4°C) and newly developed lung infiltrates employed bronchoscopy to obtain culture specimens. The results reveled that pneumonias caused by gram-negative bacteria (n = 38) and fungi (n = 34) were most frequent; sensitivity of bronchoscopy in diagnosing infectious episodes was 66%, but only four of 13 noninfectious lung infiltrates could be identified. Bronchoscopy was most effective in the diagnosis of *Pneumocystis carinii* and herpesvirus pneumonia, whereas sensitivity and specificity to detect fungal and bacterial pneumonia were low. Empiric antibiotic therapy was confirmed by evaluation of bronchoscopic samples in 25 of 90 cases, and treatment was changed in 34 of 90 cases. Early identification of causative pathogens had a significant impact on survival.

Bronchoscopy and diagnostic bronchoalveolar lavage are safe in patients with severe thrombocytopenia, other coagulopathies, and alveolar hemorrhage. Unless a bronchoscopic lung biopsy is planned, reversal of bleeding diathesis by transfusion of platelets, fresh frozen plasma, and vitamin K is usually unnecessary to obtain bronchoalveolar lavage. These procedures can be performed, with appropriate preparations and administration of supplemental oxygen, even in patients with significant hypoxemia.

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a distinct clinical course, and that bronchial lavage is a safe and useful test.

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Wiley JS, Firkin FC. Reduction of pulmonary toxicity by prednisolone prophylaxis during all-*trans* retinoic acid treatment of acute promyelocytic leukemia. Australian Leukaemia Study Group. *Leukemia* 1995;9:774–778. *All*-trans *retinoic acid induces complete remission in most cases of acute promyelocytic leukemia. Its use, however, is associated with potentially fatal pulmonary toxicity in approximately 25% of patients in the setting of a rapidly rising peripheral blood white cell count. This prospective multicenter study documents the efficacy of oral corticosteroid for prophylaxis against pulmonary toxicity.*

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CHAPTER

57 Renal Diseases

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INTRODUCTION

The respiratory and renal systems together maintain normal acid–base equilibrium. Failure of one system promptly elicits a compensatory response from the other. This close relationship is maintained not only in health but also in certain pathologic states. For example, in Goodpasture's syndrome, the alterations that occur in the alveolar basement membrane disease represent the reaction to the immunologic process that affects the glomerular basement membrane. Similar relationships exist for many of the disorders classified under the umbrella of “pulmonary–renal” syndromes. Many of the serious respiratory complications of kidney diseases described in the past are now uncommon because of the early diagnosis and treatment of renal disorders. The successful treatment, however, of renal failure by hemodialysis, peritoneal dialysis, and renal transplantation has led to several complications related to these treatments themselves. Elucidation of the basis for the pulmonary pathology in chronic hemodialysis has led to an understanding of some of the factors responsible for certain types of acute respiratory distress syndrome. Pulmonary complications after renal transplantation are well recognized. This chapter addresses the pleuropulmonary manifestations of kidney diseases (Table 1), renal transplantation, and pulmonary alveolar hemorrhage syndromes.

Pulmonary manifestation	Renal etiology
Hypoxemia	Hemodialysis Pulmonary edema Pleural effusion Pulmonary infections Pulmonary calcification Pulmonary–renal syndromes (see Table 2)
Pulmonary edema	Renal failure (acute and chronic) Acute glomerulonephritis Nephrotic syndrome Hemodialysis Renal transplantation
Pleural effusion	Renal failure (acute and chronic) Nephrotic syndrome Acute glomerulonephritis Hemodialysis Peritoneal dialysis Ureteral obstruction Hydronephrosis Perinephric abscess Pulmonary embolism Pulmonary–renal syndromes Renal transplantation
Pleuritis	Uremia
Pulmonary calcification	Hemodialysis Hemodialysis Transplantation
Sleep apnea	Chronic renal failure Chronic renal failure Hemodialysis, peritoneal dialysis
Infections	Hemodialysis Transplantation (Renal failure (Renal transplantation
Lymphoma, lung cancer	(Renal transplantation
Pulmonary–renal syndromes	(See Table 2)

TABLE 1. *Pulmonary complications in renal diseases*

RENAL FAILURE

Pulmonary Edema

Pulmonary changes may be associated with either acute or chronic renal failure. Pulmonary edema is the most serious complication of renal failure. The roentgenographic manifestations—variously referred to as *uremic lung, uremic pneumonia,* and *butterfly shadows* or *bat-wing shadows*—are manifestations of pulmonary edema. Similar features can occur in patients with left ventricular failure or noncardiogenic edema from various causes.

In chronic renal failure, pulmonary edema may develop without uremia, in part from sodium retention and increased blood volume. The pathogenesis of pulmonary edema in renal failure is unknown. Fluid overload, left ventricular failure, and increased capillary permeability from uremia are among the likely etiologic factors. Increased endothelial permeability to sodium and water and increased alveolar permeability to technetium-99m-labeled compounds before and during hemodialysis have been shown. Edema fluid sampled by endotracheal aspiration has shown an elevated protein content, suggesting increased vascular permeability to plasma proteins in renal failure. However, some studies have reported that there is no evidence of increased pulmonary endothelial permeability to the plasma protein transferrin in patients with pulmonary edema caused by renal failure.

The morphologic features of acute pulmonary edema caused by renal failure include septal swelling and edema, proteinaceous fluid in alveoli, and, in some cases, hyaline membrane formation. Lung in chronic pulmonary edema associated with renal failure shows round hyaline structures in alveolar septa that are well circumscribed and coated by a single layer of flat endothelial cells and organized casts of alveoli, alveolar ducts, and bronchioles, many revealing marked cellularity. Repeated episodes of uremic pulmonary edema may result in interstitial fibrosis and deposition of hemosiderin in the alveoli.

Pulmonary edema (Fig. 1) does not occur consistently in uremic patients, and its occurrence is unpredictable and cannot be correlated with the degree of azotemia. However, the clearing of chest roentgenographic abnormalities is usually paralleled by a reduction in total body fluid. Even when physical signs in the lungs are scant in comparison with the roentgenographic evidence of pulmonary edema caused by renal failure, the correction of fluid imbalance results in rapid symptomatic improvement in respiratory symptoms. The chest roentgenogram typically exhibits bilaterally symmetric densities extending laterally from the hilum, leaving clear apices and peripheral zones (Fig. 1 and Fig. 2). The reason for the central concentration of the abnormal shadows is unclear, but the severity of the changes increases with the degree of azotemia and acidosis. In acute glomerulonephritis, children may die so rapidly from pulmonary edema that the diagnosis may be made only at

postmortem.

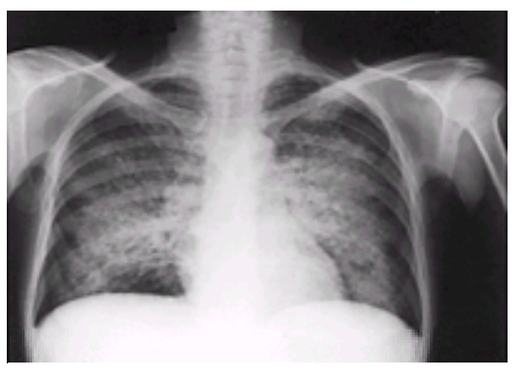

FIG. 1. Typical bat-wing (outer one-third of lungs) or butterfly (inner two-thirds of lungs) appearance in uremic pulmonary edema. Note sparing of both costophrenic angles.

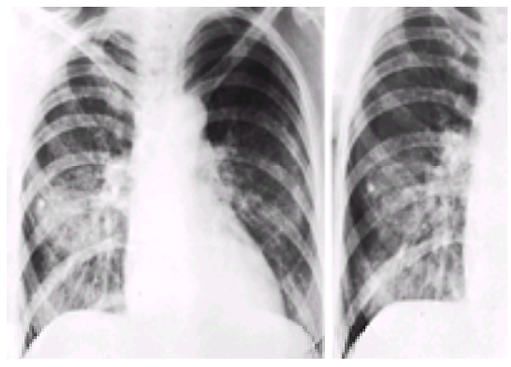

FIG. 2. Bilateral but asymmetric pulmonary edema in acute renal failure *(left).* Close-up shows clear demarcation of normal and abnormal lung.

Lung function studies in patients with severe renal failure have revealed significant decreases in diffusing capacity of lung for carbon monoxide (D_LCO), presumably from pulmonary edema. Improvement in midexpiratory flow and reduction in air trapping after hemodialysis have been described, and it has been suggested that these changes could be attributed to alleviation of peribronchial edema. The degree of restrictive lung dysfunction depends on the chronicity and severity of the renal failure. Muscle weakness, myopathy, and reduced aerobic muscle function are common in chronic renal failure and contribute to pulmonary dysfunction. Furthermore, diaphragmatic weakness caused by phrenic neuropathy is a frequent complication of uremia, and this contributes to the restrictive pulmonary dysfunction. Pulmonary function tests performed at least 12 hrs after the preceding hemodialysis in one group of patients revealed significantly reduced D_LCO, even after correction for anemia; there appeared to be no correlation between anemia and the severity of reduction in D_LCO.

Pleural Effusion

Pleural effusion is a common complication of renal diseases (Table 1). Hemodialysis, peritoneal dialysis, and renal transplantation are frequently associated with pleural effusion. Although hemodialysis can be associated with pleural effusion, the pleural effusion also resolves with hemodialysis (Fig. 3). Pleural effusion occurs in nearly half the children who develop acute glomerulonephritis. The effusions probably are secondary to hypervolemia and raised capillary hydrostatic pressures, and they are usually transudative. Many of these patients also exhibit edema and cardiomegaly.

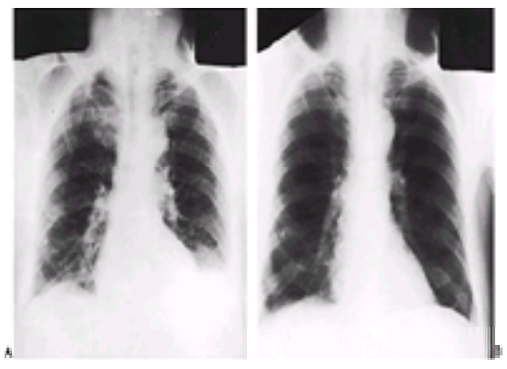

FIG. 3. Pulmonary edema and pleural effusion before **(A)** and after **(B)** hemodialysis for renal failure.

Nephrotic syndrome is one of the common causes of pleural effusion. The main factor leading to pleural transudation is the diminution of the plasma oncotic pressure, allowing easier transport of protein-poor fluid into the pleural space. The pleural fluid is usually a transudate with a low protein content. Pleural and pericardial effusions are seen in 20% to 25% of patients with the nephrotic syndrome. Usually bilateral and sometimes massive, the pleural effusions may produce significant respiratory distress. A peculiar feature of pleural effusions in patients with uremic syndrome is that the effusion tends to remain subpulmonic in location. A reason for this is that the pleuritis associated with uremia is reported to cause areas of adhesion between the parietal diaphragmatic pleura and the visceral pleura, thereby preventing the fluid from pushing the lung upward. Roentgenologically, subpulmonic effusions do not produce obliteration of the costophrenic angle (Fig. 4). The chest roentgenogram may show only an elevated hemidiaphragm on the side of pleural effusion. A lateral decubitus chest roentgenogram is often necessary to demonstrate free layering of the fluid (Fig. 4). Occasionally, pleural effusions are complicated by infections; fibrosing uremic pleuritis complicated by empyema has been described. Medical or surgical pleurodesis may be required in patients with recurrent or symptomatic effusions.

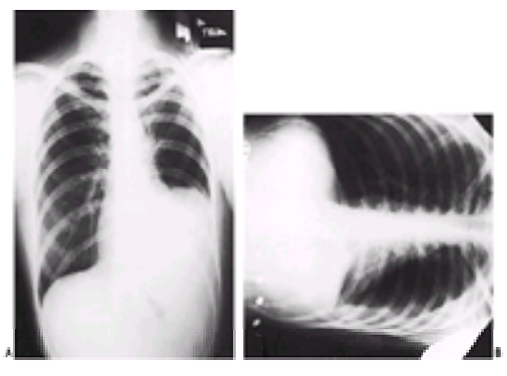

FIG. 4. Subpulmonic left pleural effusion on chronic renal failure demonstrates (A) maintenance of sharp costophrenic angle on the left and (B) free layering of the pleural effusion in the lateral decubitus position.

Fibrinous pleuritis is an uncommon but distinct entity and possibly a specific manifestation of uremia, although episodes of fibrinous pleuritis have been noted in patients on chronic hemodialysis. Clinical features consist of recurrent episodes of pleuritic chest pain, dyspnea, and low-grade fever. Pleural friction rubs are commonly heard on auscultation. In many patients, the fluid is an exudate containing high levels of protein and lactate dehydrogenase.

Patients undergoing chronic hemodialysis occasionally develop pleural effusions. The fluid usually is serosanguineous as a result of heparinization for the dialysis procedure. Correction of fluid balance by continued hemodialysis and improved renal function results in gradual clearing of the effusion. There are rare case reports of hemorrhagic effusion that resulted in fibrinous pleuritis and pulmonary restriction and required pulmonary decortication.

Ureteral obstruction from calculi, ureteral valves, malignancy, and gravid uterus may result in extravasation of urine into the pleural space and produce “urinothorax” or “urinoma.” Occasionally, retroperitoneal extravasation of urine as a result of hydronephrosis may lead to intrapleural urinomas and mediastinal widening. Urologic procedures, such as placement of ureteral stents, may cause pleural effusion. Perinephric abscess may be complicated by pleural effusions resulting from inflammation of the adjacent pleura. These rarely become infected. The pleural fluid in uninfected urinothorax is a transudate with a pH <7.30 and a creatinine concentration that is greater than serum creatinine.

The possibility that the pleural effusion is instigated by pulmonary embolism has to be considered because renal vein thrombosis is a known complication in nephrotic syndrome. One study observed pulmonary embolism in 22% (eight patients) of 36 adult patients with nephrotic syndrome.

The hemolytic–uremic syndrome may involve the respiratory system, and pleuritis and pericarditis associated with this syndrome have been described.

Although chylous ascites is known to be associated with nephrotic syndrome, chylous pleural effusion is rare. The edema of the intestines with resultant lacteal leakage or malabsorption may be responsible. Chylous pleural effusion has been described in a patient with nephrotic syndrome.

Pulmonary Calcification

Calcification of soft tissues can occur as “metastatic” calcification in which calcium salts are deposited in previously normal tissue or as “dystrophic calcification,” in which calcification occurs at anatomic sites altered by pathologic processes. The lung is the primary target of metastatic calcification in chronic renal failure and in patients on chronic hemodialysis. Although the pathogenesis of pulmonary calcification is not fully understood, some investigators have suggested that the disorder occurs when the product of calcium and phosphate ions exceeds the solubility constant in the blood (the product of plasma calcium and phosphate being greater than 75 mg/dl). Others have concluded that the product of calcium and phosphorus is more relevant to the *in vivo* situation.

Crystallographic, spectroscopic, and chemical studies have demonstrated two distinct types of calcium phosphate in tissues of patients with chronic renal failure. Calcifications found in the lungs are microcrystallites of magnesium, whitlockite, or an immediate precursor whose formation is promoted by the presence of magnesium. Preferential calcification of the upper lung zones may be induced by the higher ventilation–perfusion ratio in the apical regions of lung relative to the basal regions, resulting in a lower alveolar carbon dioxide tension and higher tissue pH (blood pH at the apex is approximately 7.51, compared with 7.39 at the base). The resultant relative alkalinity may favor precipitation of calcium phosphate. Chronic renal failure is complicated by the development of secondary hyperparathyroidism with hypercalcemia. The incidence of pulmonary calcification is greater in patients with hypercalcemia induced by secondary hyperparathyroidism of renal failure. Although pulmonary calcification is considered to be a common occurrence with chronic renal diseases, it usually is sparse and identifiable only on histologic examination of the lungs (Fig. 5). On the other hand, the pulmonary calcification that occurs in association with chronic hemodialysis is clinically more apparent (see below).

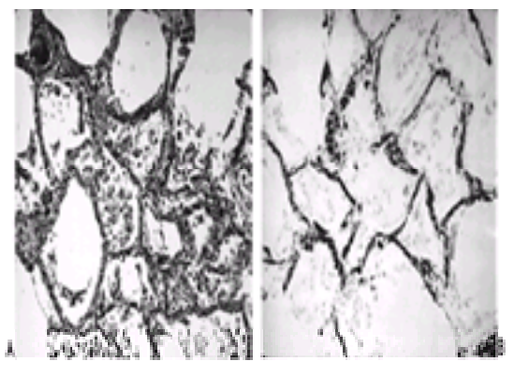

FIG. 5. Metastatic calcification associated with chronic renal failure or in patients on long-term hemodialysis. **(A)** Calcium is seen as deposits of dark and platelike material diffusely in alveolar walls. **(B)** A von Kossa stain for calcium shows diffuse black staining of calcium in alveolar walls.

The clinical manifestations of pulmonary calcification associated with chronic renal failure are nonspecific. Chest roentgenograms show calcifications that are either localized or diffuse. In most cases, they are identical to roentgenographic opacities produced by pneumonia or pulmonary edema, but sometimes definite punctate calcifications may be seen (Fig. 6). Upper lung zones are more commonly affected. A study of metastatic pulmonary calcification in seven patients (chronic renal failure in four, T-cell leukemia in one, multiple endocrine neoplasia type I syndrome in one, and idiopathic hypercalcemia in one) exhibited the following features in the computed tomographic scans of the chest: nodules were predominant in the upper lung zone in three cases, diffuse in three cases, and predominant in the lower lung zone in one case; calcification of the nodules was evident on the CT scans in four of the seven cases, and calcification of vessels in the chest wall was evident in six of seven cases. Even when pulmonary calcification cannot be demonstrated with certainty, the possibility should be considered in any case of renal failure if pulmonary infiltrates remain persistent. Pulmonary function tests may demonstrate a restrictive defect. Bone-seeking radionuclide (^{99m}Tc diphosphonate) lung scans have been used to establish an early diagnosis of pulmonary calcification (Fig. 7), especially in high-risk patients. An unusual form of focal, nodular pulmonary calcification has been reported in a patient with renal failure resulting from polycystic kidney disease.

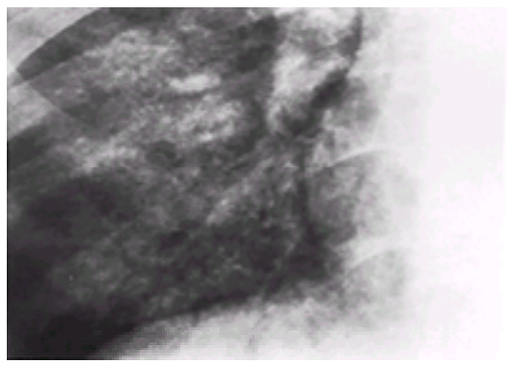

FIG. 6. Diffuse punctate clarification of pulmonary parenchyma in the right lower-lung zone in inadequately treated chronic renal failure.

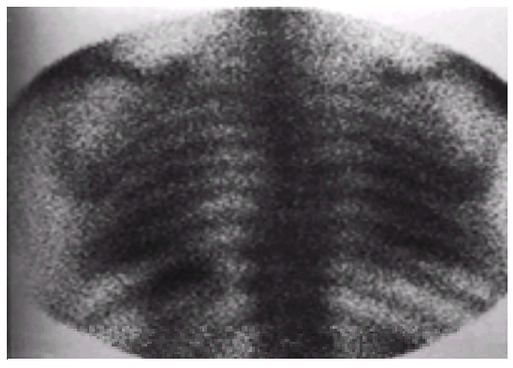

FIG. 7. A posterior view of ^{99m}Tc scan of lung in a patient with pulmonary calcification shows marked uptake of radionuclide by both lungs and the stomach (seen below the left lung).

HEMODIALYSIS

Hypoxemia

Hemodialysis-induced hypoxemia has been studied extensively. More than 85% of patients exhibit a 5 to 35 mmHg reduction in P_aO_2 from baseline as soon as the procedure is begun. This phenomenon persists for up to 60 min after the dialysis is terminated. The P_aO_2, however, seldom drops to below 70 mmHg. Several mechanisms are responsible for this phenomenon. Pulmonary arterial microembolization from certain types of the dialyzer membranes has been implicated in some studies. Dialysis membranes also can activate complement cascade, and the complement- and leukocyte-mediated leukostasis is capable of causing hemodialysis-induced hypoxemia. Cuprophane membrane activates complement cascade more than polyacrylonitrile or cellulose membranes. Larger falls in P_aO_2 have been associated with cuprophane dialysis membrane than with other types of membranes. The interaction of the dialysate and the dialysis membrane activates the alternate complement pathway by generating C3a and C5a within minutes of the dialysis procedure. The deposition of the complement fragments on the dialysis membrane induces aggregation of platelets and leukocytes on the membrane, from where they migrate to the pulmonary circulation to produce microembolization and hypoxemia. The hypoxemia occurs at the same time as the leukocyte sequestration in the pulmonary vasculature. Histologic analysis of lung tissue from animals undergoing hemodialysis have revealed severe pulmonary vessel leukostasis and interstitial edema. This pathologic process was prevented by preinactivation of complement but was reproduced by infusions of plasma in which complement was activated by zymosan. In a study of 34 patients undergoing dialysis, 15 were shown to have leukostasis or sequestration of leukocytes within the pulmonary vessels; leukopenia and impaired pulmonary function also were noted. The leukostasis-induced hypoxemia contributes minimally (<10%) to the development of hemodialysis-induced hypoxemia.

The main reason for the hemodialysis-induced hypoxemia appears to be the occurrence of dialysis-induced hypoventilation. Alveolar hypoventilation (compensatory hypoventilation) results from the substantial loss of carbon dioxide across the dialyzer membrane as well as a decrease in metabolic CO_2 production. Consumption of carbon dioxide in the oxidative metabolism of acetate has also been suggested as a mechanism for hypoventilation and hypoxemia. A study of patients undergoing hemodialysis with acetate as the dialysate found significant hypoxemia and diminished alveolar ventilation. Some studies have indicated that hypoxemia and reduced CO_2 production are most pronounced during acetate dialysis and are minimally affected during bicarbonate dialysis. Others have opined that whether acetate or bicarbonate is used in the dialysate does not seem to make a difference in dialysis-induced hypoxemia.

One study in hemodialysis patients has shown the occurrence of hypoxemia as a result of decreased minute ventilation without hypercapnia. It is hypothesized that the diminished minute ventilation is unrelated to alterations in traditional chemoreceptor output, which depends on changing arterial oxygen tension. Some have suggested that hypoventilation, localized ventilation– perfusion abnormalities related to changes in the pulmonary vascular volume during dialysis, and increases in arterial pH contribute variably to dialysis-induced hypoxemia.

Does the hemodialysis-induced hypoxemia have any clinical significance? The above discussions should be considered in the context of the timing of the detection of hypoxemia. Almost all studies on this topic were performed during hemodialysis. Almost every patient who undergoes hemodialysis is relatively immobile during the procedure because of the need to remain connected with the dialysis machine. Such a patient rarely exerts, physically that is, sufficiently to increase the work of breathing. Therefore, complaints of new or acute dyspnea or clinical detection of it is unusual in patients when they are undergoing hemodialysis. A clinical caveat is that arterial blood gas analysis should be avoided during active hemodialysis unless the patient develops respiratory symptoms and signs during the procedure. In patients with preexisting hypoxemia from diseases such as chronic obstructive pulmonary disease, cellulose or polyacrylonitrile filters and a bicarbonate bath are likely to minimize hemodialysis-induced hypoxemia.

A decreased D_LCO has been noted in both acetate-treated and bicarbonate-treated groups. Leukocyte sequestration in the pulmonary capillary network is perhaps one of the reasons for this phenomenon. A study of 25 uremic patients observed that hemodialysis-induced reductions in D_LCO in the majority of patients resulted from reduced pulmonary capillary volume brought on by hemodialysis. Another study recorded a significant fall in peak respiratory flow during the first 30 min of dialysis in 30% of patients. The improvements in flow rates ($FEF_{25–75}$) after hemodialysis suggested that peribronchial edema, which was present before hemodialysis, was responsible for the small airway dysfunction. Pulmonary dysfunction and eosinophilia have been noted in patients undergoing cuprophane dialysis.

Erythropoietin is effective in the treatment of anemia of chronic renal failure. In spite of improved hemoglobin concentration and quality of life following treatment with erythropoietin, peak oxygen uptake after erythropoietin therapy is not improved. In a study of eight patients with chronic renal failure undergoing regular hemodialysis, pre- and posterythropoietin tests suggested that this discrepancy results from two factors: first, the increase in hemoglobin produced by erythropoietin therapy is accompanied by a significant reduction in peak blood flow to exercising muscle, which limits the gain in oxygen transport; and second, even after restoration of hemoglobin, oxygen conductance from the muscle capillary to the mitochondria remains considerably below normal.

Pulmonary Calcification

The low rate of clinical occurrence and significance of metastatic pulmonary calcification in patients with chronic renal failure was discussed above. On the other hand, metastatic calcification of lungs in patients on long-term hemodialysis occurs more commonly and may cause clinically significant disease, including respiratory failure. Pulmonary calcification occurs more commonly in patients on chronic hemodialysis than in patients who undergo chronic peritoneal dialysis. Biochemical analysis of pulmonary parenchyma in patients with pulmonary calcification has shown the presence of magnesium whitlockite [$(CaMg)_3(PO_4)_2$] as the main constituent.

Ultrastructural studies of the lung parenchyma have shown linear or finely granular localization of the calcification along the alveolar septa. The extent of metastatic pulmonary calcification usually reflects the duration of hemodialysis (Fig. 6 and Fig. 7). Many patients who develop pulmonary calcification have been undergoing hemodialysis for more than 6 to 8 years. In a prospective study of 31 patients, of whom 15 died, postmortem studies revealed metastatic pulmonary calcification in nine. Such calcification has also occurred in patients with hyperphosphatemia who are being treated with a dialysate high in calcium.

The chest roentgenographs may not reveal obvious abnormalities in patients with pulmonary calcifications. Hazy, punctate, or speckled areas of density in upper and midlung zones may indicate pulmonary calcification. A pattern of persistent lung infiltrates despite adequate hemodialysis and normalization of fluid balance should suggest the possibility of metastatic pulmonary calcification. A high-resolution computed tomographic (HRCT) scan of the lung, as discussed above, may help in the diagnosis. As also noted above, a bone-seeking radionuclide (^{99m}Tc-diphosphonate) lung scan has been used to detect pulmonary parenchymal calcification. In a study of 18 children on maintenance dialysis without evidence of pulmonary calcification on chest roentgenograms, 22% had positive technetium bone scans. There were no significant differences between the groups with and without positive bone scans with respect to serum levels of calcium, phosphorus, bicarbonate, magnesium, and calcium–phosphorus product as well as parathyroid hormone and vitamin D levels. However, the two factors that influenced the presence of pulmonary calcification were the long-term duration of dialysis and high serum aluminum levels.

A literature review in 1979 noted that seven of 13 patients with pulmonary calcification died of respiratory failure.

Sleep Apnea

Hemodialysis is reported to increase the risk for developing sleep apnea. The association between end-stage renal failure and sleep apnea remains highly significant, though the cause for it remains unclear. This association seems not to be altered acutely by conventional hemodialysis treatment. In a report of 29 male patients maintained on outpatient hemodialysis, 12 had clinical features suggestive of sleep apnea, and polysomnography in eight of these patients documented obstructive

sleep apnea in six. In another study, sleep apnea was noted in nine of 15 patients on peritoneal dialysis and eight of 15 patients on hemodialysis; the incidence and severity of sleep apnea were similar in patients with end-stage renal disease being treated with chronic peritoneal dialysis and hemodialysis.

Autonomic neuropathy encountered in some patients with chronic renal failure may contribute to the occurrence of sleep-disordered breathing. Progressive dialysis encephalopathy as well as spells of sudden respiratory arrest, in close association with the episodic electroencephalographic abnormalities characteristic of the syndrome, have been reported.

Hemodialysis-Induced Asthma

Asthmatic episodes have been observed during hemodialysis, and some believe that bronchial reactivity is more pronounced in this group of patients. Hemodialysis-induced asthma has been attributed to the bronchospasm caused by acetate in the dialysate. Replacement of acetate by bicarbonate in the dialysate has resulted in resolution of this unusual problem. Others have inferred that hemodialysis does not commonly result in bronchial hyperactivity. In one study of six nonasthmatic patients who underwent histamine challenge testing before and after hemodialysis, no change was observed in reactivity, suggesting that hemodialysis does not commonly result in bronchial hyperreactivity in nonasthmatic individuals.

Asthmatic patients who take theophylline as a bronchodilator and are also hemodialysis-dependent need special care during dialysis. A shortened half-life of theophylline, from 5.7 hr to 1.6 hr, during hemodialysis has been described. However, hemodialysis clearance of theophylline varies substantially and may be dependent on the dialysis system, blood flow rate, and dialyzer used.

Pulmonary Embolism

Occlusion of the hemodialysis fistulas is a relatively common complication that requires therapy with thrombolysis and or thrombectomy. Pulmonary embolism is a potential consequence. A study of 31 patients with 43 acutely thrombosed hemodialysis fistulas observed perfusion lung scan abnormalities consistent with the diagnosis of pulmonary embolism in 59% of 22 patients studied. However, clinical signs or symptoms were absent in the majority of the patients.

Renal vein thrombosis is a known complication in nephrotic syndrome. Therefore, the risk of pulmonary embolism is increased. A study of 36 adults with nephrotic syndrome detected pulmonary embolism in eight patients (22%).

Pulmonary emboli (tumor emboli) from malignant tumors of the kidneys result from the extension of the tumor into the renal vein, from where the cancer cells exfoliate and travel to the pulmonary arterial bed. In a patient with renal cell carcinoma, onset of rapidly progressive dyspnea and diffuse interstitial pulmonary infiltrations with formation of Kerley's B-lines on chest roentgenographs of the chest should indicate the possibility of tumor emboli. Acute to subacute onset of secondary pulmonary hypertension can result from tumor emboli.

Postmortem studies in dialysis patients have shown a high incidence of pulmonary atherosclerosis, indicating chronic elevations in pulmonary artery pressure. However, clinical pulmonary hypertension is uncommon in patients with chronic renal failure or in those on chronic dialysis.

Miscellaneous Problems in Dialysis

The risk of infections caused by *Legionella* species is increased in patients on chronic hemodialysis. In some cases, these infections were believed to result from infection of the dialysis fistula by *Legionella* species. Patients receiving hemodialysis and renal transplant recipients are at an increased risk of developing pneumonia caused by *Legionella pneumophila.* The hemodialysis fistula can become infected by such organisms and cause *Legionella* pneumonia.

Tuberculosis

The risk of tuberculosis is increased in renal failure. A report from the United Kingdom estimated the risk to be nearly 70 times higher in non-Europeans with chronic renal failure than in the native population. The incidence of tuberculosis is also higher in patients on maintenance dialysis. Active tuberculosis occurs in 3.7% to 6.0% of patients followed longitudinally while on dialysis, an infection rate that is 12 to 15 times higher than normal. One study of 25 patients on dialysis detected tuberculosis in 28%; the majority were women, and extrapulmonary tuberculosis was common.

Isoniazid therapy to treat tuberculosis in patients with renal failure or those who are dialysis-dependent may be complicated by the enhanced risk of isoniazid-induced neurotoxicity. The increased sensitivity of the dialysis-dependent patients to isoniazid neurotoxicity results mainly from abnormal metabolism of pyridoxine, which results in low serum levels of the active metabolite, pyridoxal phosphate. The rapid clearance of pyridoxal phosphate by hemodialysis results in a pronounced deficiency of this active metabolite. In order to prevent the neurotoxicity associated with isoniazid therapy, a pyridoxine dose of 100 mg/day is recommended in hemodialysis patients who require isoniazid therapy.

PERITONEAL DIALYSIS

Many of the pulmonary complications associated with peritoneal dialysis are similar to those described for hemodialysis. However, several complications are peculiar to this group of patients. Chronic ambulatory peritoneal dialysis essentially produces iatrogenic ascites and the latter's attendant effects on pulmonary function. Acutely, the dialysate volumes of 2 to 3 liters will result in mild reductions in vital capacity and total lung capacity. The filling of the peritoneal cavity with the dialysate induces, in both the supine and upright positions, significant reductions in the maximal inspiratory pressure and diminished lung volumes. The diaphragmatic dysfunction observed during peritoneal dialysis is most likely the result of physical alterations resulting from infusion of the dialysate into the peritoneal cavity. The acute changes usually return to baseline within 2 weeks of initiation of the procedure as a result of the adaptation of the diaphragmatic and abdominal mechanics. A study of patients on continuous ambulatory peritoneal dialysis for more than 6 weeks indicated that the diaphragm may be capable of an adaptive rightward shift in its force–length relationship when it is chronically lengthened by continuous ambulatory peritoneal dialysis.

Patients on long-term peritoneal dialysis may develop extrapulmonary restrictive ventilatory defects. The D_LCO seems to diminish in patients who receive continuous ambulatory peritoneal dialysis. A study of 26 patients with chronic renal failure and continuous ambulatory peritoneal dialysis assessed the effects of the renal diseases on respiratory muscle function (P_{Imax} and P_{Emax}) before dialysis, 4 hr after the administration of 2 liters of dialysate into the peritoneal cavity, and just after the next drainage and concluded that respiratory muscle strength was preserved in the majority of the patients with chronic renal failure treated with continuous ambulatory peritoneal dialysis. However, lung volumes and respiratory muscle function, not strength, were decreased during dialysis.

The overall effect of long-term peritoneal dialysis on pulmonary function is minimal, even in the presence of mild lung disease from other causes. On the other hand, peritoneal instillation of large amounts of dialysate fluid in patients with severe chronic obstructive pulmonary disease may aggravate respiratory distress. The common occurrence of phrenic neuropathy in chronic renal failure may aggravate respiratory distress in patients with severe obstructive lung disease who undergo peritoneal dialysis.

Pleural effusion occurs in some patients who undergo peritoneal dialysis. A review of the literature noted 33 cases of pleural effusion associated with peritoneal dialysis. Interestingly, 28 of these cases occurred in women. Detection occurred within 48 hr of acute peritoneal dialysis. All cases were unilateral, and all but one were right-sided. The mechanism of fluid accumulation is similar to that in ascites. Instillation of large volumes of fluid intraperitoneally will further stretch the diaphragmatic defects and enable the dialysate to enter the pleural cavity. The pleural fluid can accumulate acutely and rapidly, within hours of initiating peritoneal dialysis, and produce respiratory distress. The effusions tend to recur on reinstitution of peritoneal dialysis. Massive hydrothorax occurring during continuous ambulatory peritoneal dialysis is a rare complication that may appear at any time during the course of the treatment. A case is reported in which peritoneopleural scintigraphy showed a rapid accumulation of the diagnostic agents over the right hemithorax, leading to the suspicion that a macroscopic diaphragmatic defect was responsible for the respiratory complication.

Disordered sleep occurs more frequently in patients receiving chronic peritoneal dialysis and hemodialysis than in the normal population. In a prospective study of 11 patients on chronic peritoneal dialysis, six were found to have obstructive sleep apnea; the amount of dialysate drained in the morning was negatively correlated with the minimum arterial oxygen saturation during the night. The association between dialysis and sleep apnea is discussed above.

Severe shifts in systemic pH that occur in patients undergoing peritoneal dialysis are usually acidemic shifts resulting from inadequate replacement of the kidney's ability to excrete acid and regenerate bicarbonate. Hypercapnia and acute respiratory acidosis have resulted from an increased carbohydrate load associated with peritoneal dialysis; lipogenesis following a carbohydrate load in patients with renal failure is associated with a respiratory quotient of 8.0, reflecting the much greater production of carbon dioxide per unit of oxygen consumed.

RENAL TRANSPLANTATION

Pulmonary problems in recipients of solid-organ transplants are a result of the transplant rejection process and the immunosuppressive therapy. The reader is referred to Chapter 55 for more detailed discussions regarding the respiratory complications of organ transplantation. A South African study of pulmonary complications in 110 consecutive renal transplant recipients on cyclosporine and low-dose steroid immunosuppression observed the following complications: acute pulmonary edema in 19 patients, pneumonia in 18, tuberculosis in nine, acute pulmonary embolism in five, and lung abscess in one. There were no pulmonary complications in 69 (63%) patients, and 69% of the complications occurred in the first 4 months after the transplant and were the most common cause of death in the first 3 years after the transplant.

Pulmonary infections are common in renal transplant recipients and are, as a group, the major cause of death. These infections may be caused by unusual bacteria or fungi, possibly favored by suppression of immune mechanisms by drugs and corticosteroids. The incidence of cytomegalovirus infection in cadaveric renal transplant patients is reported to be as high as 43% to 92%. Although many renal transplant patients remain asymptomatic during cytomegalovirus infection, pulmonary dysfunction is common. One report demonstrated that a decreased $D_L CO$ is common in virtually every patient with cytomegalovirus infection. An interesting finding was activation of the complement system (C3d and C3a) in many of these patients, suggesting a causal relationship between complement activation and diminished $D_L CO$. Earlier studies questioned whether cytomegalovirus played any role in the development of pneumonia among renal transplantation patients, but other reports show that cytomegalovirus pneumonia has become a leading cause of death in this patient group.

Study of pneumonia in renal transplant patients disclosed single-organism involvement by type 3 *Streptococcus pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli.* Nosocomial pneumonia caused by *Legionella pneumophila* has been described in renal transplant recipients. Systemic fungal infections with pulmonary involvement, particularly candidiasis and aspergillosis, are also common after renal transplantation.

Pneumocystis carinii infection carries a high mortality in renal transplant recipients. This infectious complication appears to be more common in older patients and unrelated to immunosuppressive therapy in them. A study compared 28 renal transplant recipients with *Pneumocystis carinii* pneumonia with a control group of 27 renal transplant recipients without any episodes of *Pneumocystis carinii* pneumonia. The mean age was higher in the former group (50 versus 38 years). No differences were in observed in basic immunosuppressive and rejection treatment or in antibiotic consumption, number of hospitalization days, and incidence of infection caused by cytomegalovirus. A study of seven renal transplant recipients who developed *Pneumocystis carinii* pneumonia noted a mean duration of 150 days before the diagnosis of the infection; six had at least one episode of acute graft rejection, and cytomegalovirus pneumonia was diagnosed in six of the patients. Overall mortality was 43%.

Prophylactic therapy to prevent *Pneumocystis carinii* pneumonia usually consists of long-term oral administration of trimethoprim–sulfamethoxazole. Up to 20% of patients, however, develop intolerance to this drug combination. A retrospective review of 17 kidney transplant recipients, all of whom were unable to take trimethoprim–sulfamethoxazole, reported that when aerosolized pentamidine was used for prophylaxis against *Pneumocystis carinii,* the aerosolized pentamidine was not only well tolerated but was also highly effective in the prevention of *Pneumocystis carinii* infection.

The increased rate of occurrence of tuberculosis in patients with chronic renal failure and those on chronic hemodialysis was alluded to above. Renal transplant recipients also are at increased risk of developing tuberculosis, which occurs in them as an opportunistic infection. The infection occurs with higher frequency in areas with high prevalence of tuberculosis. In a series of 400 transplant patients in a developed country, only five developed tuberculosis. A South African study of 857 renal transplant recipients noted 21 cases of confirmed or presumed *Mycobacterium tuberculosis* infections; the median time from transplantation to diagnosis of tuberculosis was 14 months. The chest roentgenographic findings included consolidation, miliary pattern, pleural effusion, tuberculoma, cavitation, and hilar lymphadenopathy; disseminated disease was less common than reported elsewhere. Several cases of pulmonary infection caused by *Mycobacterium xenopi* have been reported. Simple gastric aspirates are reported to be adequate in the diagnosis of pulmonary tuberculosis in renal allograft recipients. In a study of more than 200 renal allograft recipients suspected to have tuberculosis, gastric aspirates were more helpful than bronchoalveolar lavage in the identification of acid-fast bacilli; the acid-fast bacillus positivity was significantly greater than that in patients with abnormal chest roentgenographs compared with patients with normal chest roentgenographs.

The early diagnosis of pulmonary infections in renal transplant recipients is important so that optimal therapy is promptly instituted. Bronchoalveolar lavage is an important diagnostic procedure in renal transplant recipients who develop respiratory symptoms or chest roentgenographic abnormalities. A study of 70 renal transplant recipients among whom 48 patients underwent 58 bronchoalveolar lavages identified 39 etiologic organisms in 32 patients, with six patients having more than one infection; bronchoalveolar lavage was negative in 22 patients. Overall, the results of bronchoalveolar lavage altered therapy in more than 70% of cases.

Pulmonary calcification, at times fatal, also is seen in renal transplant recipients. One patient developed extensive pulmonary calcification 6 days after renal transplantation and died from respiratory failure on the seventh day. In a study of 17 pediatric patients, four developed pulmonary calcification and respiratory failure within 3 to 5 days of renal transplantation. Common clinical features included poor allograft function with persistent uremia requiring dialysis and evidence of moderate to severe hyperparathyroidism. Three patients had markedly elevated calcium–phosphorus product, to peak values of 122 to 147 mg/dl. This increase was noted at the time of onset of respiratory failure. All patients died of respiratory failure 5 to 58 days after transplantation.

Chronic immunosuppressive therapy in patients with renal transplants increases the risk of developing B-cell lymphoma and carcinoma of the lung. Non-Hodgkin's lymphoma has been observed in up to 2.5% of renal transplant recipients. Although rare, pulmonary involvement from Kaposi's sarcoma has been described in recipients of renal transplants.

Abnormal pulmonary function, particularly a reduced $D_L CO$, seems to persist even after renal transplantation. Subclinical pulmonary edema present in the pretransplantation period is presumed to progress to fibrosis before transplantation.

The incidence of pulmonary thromboembolism is increased in renal transplant recipients. Pulmonary embolism was the most frequent complication among 227 renal transplant recipients, observed in 60% of those with a noninfectious pulmonary process.

ALVEOLAR HEMORRHAGE SYNDROMES

Pulmonary alveolar hemorrhage syndromes are discussed in this chapter because many belong to the group of diseases sometimes referred to as *pulmonary–renal syndromes,* to denote simultaneous occurrence of pulmonary and renal diseases, usually by the same pathologic process. Indeed, it is now clear that many of the systemic vasculitides commonly involve the kidneys and the lungs. Because pulmonary alveolar hemorrhage is a common feature in most of the pulmonary–renal syndromes, the term *lung purpura* also has been used to describe these entities (Table 2). The mechanism of alveolar bleeding may vary from disease to disease. For instance, the bleeding in Goodpasture's syndrome is believed to be the result of pulmonary capillary wall damage caused by the destruction of type IV collagen by autoantibodies. The alveolar hemorrhage in mitral stenosis is the result of stress failure of the capillary wall, caused by a tremendous increase in capillary pressure. In vasculitic syndromes, capillaritis secondary to direct involvement by the vasculitic process leads to hemorrhage into the alveoli.

Goodpasture's syndrome
Churg–Strauss vasculitis
Wegener's granulomatosis
Polyarteritis nodosa
Microscopic polyangiitis
Systemic lupus erythematosus
Lymphomatoid granulomatosis
Henoch–Schönlein purpura
Hemolytic–uremic syndrome
Scleroderma
Rheumatoid arthritis
Mixed connective tissue disease
Drug-induced vasculitis
Granulomatous (giant-cell) arteritis
Hypocomplementemic urticarial vasculitis
Idiopathic rapidly progressive glomerulonephritis
Essential mixed cryoglobulinemia

TABLE 2. *Pulmonary–renal syndromes*

The common physiological defect in these disorders is the diminished alveolar gas volumes evidenced by reduced total lung capacity and vital capacity. Airflow

limitation is not a feature. Interestingly, D_LCO can be elevated if fresh alveolar hemorrhage is present. Theoretically, D_LCO may show a continual rise if measured repeatedly in a patient with continued alveolar hemorrhage because of the increased uptake of carbon monoxide by the erythrocytes newly introduced into the alveoli. This test has been used in anecdotal cases and is reported to be a sensitive and useful indicator of the presence or absence of recurrent intrapulmonary hemorrhage. My own experience in several patients has shown that repeated measurement of D_LCO for this purpose is unreliable. Furthermore, repeated testing is impractical because most patients with alveolar hemorrhage are markedly ill and may not be able to withstand the testing.

Quantitative measurement of macrophage hemosiderin content in the bronchoalveolar lavage effluent has been suggested as a useful test to determine the degree of alveolar hemorrhage. A better diagnostic test perhaps is the estimation of the percentage of siderophages (hemosiderin-laden macrophages) among the total alveolar macrophages recovered by bronchoalveolar lavage. A study of 240 bronchoalveolar lavages, stained by Prussian blue, performed in 194 immunocompromised patients diagnosed alveolar hemorrhage in 87 (36%) of the samples; the study considered the test to be positive for alveolar hemorrhage when the siderophages constituted at least 20% of the cells. Pulmonary alveolar hemorrhage was significantly associated with four parameters: thrombocytopenia (<50,000/mm^3), presence of other abnormal coagulation parameters, renal failure (creatinine ³2.5 mg/dl), and a history of heavy smoking. During bronchoalveolar lavage, incremental increase in the bloody discoloration of alveolar effluent is one strong indicator of alveolar hemorrhage. However, the possibility of bleeding induced by the procedure itself should be considered.

The antineutrophil cytoplasmic antibody (ANCA) test may aid in differentiating the various vasculitic syndromes (see Chapter 54). However, more data suggest that some patients with Goodpasture's syndrome also may exhibit perinuclear ANCA (see below).

Although the common feature of alveolar hemorrhage syndromes is the bleeding into alveolar spaces (Fig. 8), the disorders are diverse in etiology. However, many are immunologically mediated or belong to broad categories of vasculitides or collagenoses. Differential diagnoses of alveolar hemorrhage syndrome (with or without renal involvement) are listed in Table 3.

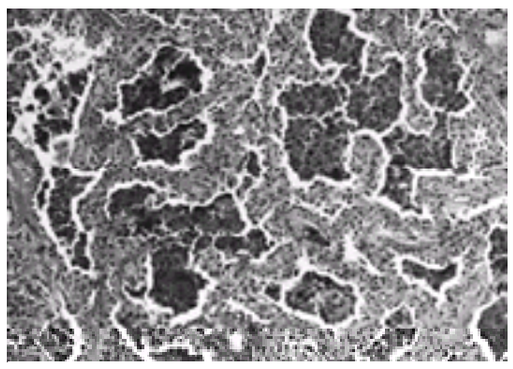

FIG. 8. Chronic pulmonary alveolar hemorrhage, regardless of cause, is seen as increased hemosiderin-filled alveolar macrophages associated with mild thickening and reactive changes in the surrounding alveolar walls.

TABLE 3. *Causes of pulmonary alveolar hemorrhage*

Goodpasture's Syndrome

Also known as antiglomerular basement membrane (anti-GBM) antibody disease, Goodpasture's syndrome is a typical example of the cytotoxic antibody-mediated (type II) reaction. It is an autoimmune disease causing rapidly progressive glomerulonephritis and pulmonary hemorrhage. The clinical manifestations are caused by autoantibodies that bind to a constituent, termed the Goodpasture autoantigen, of alveolar and glomerular basement membranes. This primary target antigen in glomerular and alveolar basement membranes is the a_3 chain of type IV collagen. The gene, COL4A3, has been encoded and localized to the q35–37 region of chromosome 2. In a postmortem study of a patient who died from Goodpasture's syndrome, the specificity of circulating, kidney-bound, and lung-bound autoantibodies against a variety of purified basement membrane constituents was studied. The results showed that the primary target for the circulating and tissue-bound autoantibodies is the NC1 domain of the a_3(IV) chain of type IV collagen; all the antibodies recognized a cryptic epitope(s) on the a_3(IV)NC1 hexamer. The results also indicated that tissue-bound and circulating antibodies compete with one another for overlapping epitopes on the antigen. Although the primary target of the antibodies to this antigen is the glomerular basement membrane of kidney, the lungs are affected by cross-reactivity.

Goodpasture's syndrome is characterized by the presence of circulating antiglomerular basement membrane (anti-GBM) antibodies and characteristic linear deposits of IgG and complement along the basement membranes of alveoli and glomerular basement membrane. The clinical manifestations correlate well with the presence of circulating anti-GBM autoantibodies.

Is the presence of anti-GBM antibody specific to Goodpasture's syndrome? This antibody has been described in patients without classic features of Goodpasture's syndrome. Indeed, some authors use the term *anti-GBM disease* to describe the syndrome when the clinical characteristics do not fit the classic Goodpasture's syndrome. In one study of 37 patients who tested positive for anti-GBM antibody or had linear IgG depositions, only 20 had typical Goodpasture's syndrome; 13 had anti-GBM glomerulonephritis alone, whereas two patients suffered solely from pulmonary hemosiderosis. Anti-GBM antibody has been detected in systemic lupus erythematosus, polyarteritis nodosa, Henoch–Schönlein purpura, hydrocarbon exposure, and following therapy with penicillamine.

The finding of ANCA with myeloperoxidase specificity in patients with Goodpasture's syndrome and other vasculitides (see Chapter 54) has introduced some confusion into the understanding of Goodpasture's syndrome and other alveolar hemorrhage syndromes. As a result, there is no universally accepted exact definition of Goodpasture's syndrome.

The etiology of Goodpasture's syndrome is unknown, but influenza virus, hydrocarbon exposure, penicillamine, and unknown genetic factors are known to stimulate anti-GBM antibody production. A review of the literature analyzed the data on 31 patients with hydrocarbon exposure and anti-GBM antibody-mediated nephritis and concluded that a causal relationship was present. Further, inadvertent exposure to hydrocarbons has resulted in the exacerbation of Goodpasture's syndrome. Goodpasture's syndrome has been described in identical twins. It is noteworthy, as noted above, that anti-GBM antibody has been detected in systemic lupus erythematosus, polyarteritis nodosa, Henoch–Schönlein purpura, hydrocarbon exposure, and penicillamine sensitivity. Azathioprine hypersensitivity, which depends on the nitroimidazole moiety of the drug, has been reported to mimic the pulmonary manifestations of Goodpasture's syndrome.

Tobacco smoking appears to have an association with Goodpasture's syndrome. In patients who develop Goodpasture's syndrome, a history of active cigarette smoking increases the risk of alveolar hemorrhage. In a study of 51 patients with glomerulonephritis related to anti-GBM antibody, 43 had pulmonary hemorrhage; of these, 37 were smokers, and all had pulmonary hemorrhage, as opposed to only two of ten nonsmokers. There was no significant difference between the titers of circulating anti-GBM antibody in smokers and nonsmokers.

Short-term exposure to certain solvents, such as halogenated hydrocarbons, petroleum distillates, ethylene glycol, ethylene glycol ethers, and diethylene glycol, may cause renal tubular necrosis, and tubular lesions with metabolic acidosis have been reported in addicts inhaling solvent vapor such as toluene. Goodpasture's syndrome may be induced by acute or subacute exposure to such solvents. Although adequate proof is lacking to suggest that repeated exposure to nonsubstituted organic solvents may lead to the development of different types of chronic glomerulonephritis and, possibly, Goodpasture's syndrome, the epidemiologic data suggest such an association. A fatal relapse of Goodpasture's syndrome 3 years after plasmapheresis has been described in a smoker who had been exposed to hydrocarbon solvents. Occult pulmonary hemorrhage followed by anti-GBM antibody-induced glomerulonephritis with normal renal function presenting as severe anemia was described in young woman who worked as a hairdresser; her exposure to chemicals in the products used for permanent waving of hair was considered to be responsible for the disease. Withdrawal of the suspected toxic hair spray was followed by both clinical remission and disappearance of the linear deposits of immunoglobulin from the renal glomeruli.

Penicillamine and carbimazole therapies for the treatment of rheumatoid arthritis and other diseases have been associated with Goodpasture's syndrome, circulating anti-GBM antibodies, and focal necrotizing glomerulonephritis with crescents. A study of 39 patients with anti-GBM antibody-mediated glomerulonephritis has suggested that HLA-B7-associated genes influence the severity of the renal disease but not that of the lung disease. In patients with Goodpasture's syndrome, a careful search should be made to ascertain the possibility of drug and toxin exposure.

A review in 1985 observed that since 1919, nearly 400 cases of Goodpasture's syndrome were published. Patients with anti-GBM antibody-mediated nephritis demonstrate two principal patterns of disease—young men presenting in their 20s with Goodpasture's syndrome (glomerulonephritis and lung hemorrhage) and elderly patients, especially women, presenting in their 60s with glomerulonephritis alone. In the classic form (in younger patients) of Goodpasture's syndrome, men are affected more often than women (male–female ratio 7:1), and the average age of onset is approximately 27 years. Recurrent hemoptysis, pulmonary insufficiency, renal involvement with hematuria and renal failure, and anemia are the classic features. Pulmonary hemorrhage almost always precedes renal manifestations. Frequent initial clinical features include hemoptysis, hematuria, proteinuria, and elevated serum creatinine.

Chest roentgenograms typically reveal bilateral, diffuse, symmetric perihilar infiltrates with sparing of the costophrenic angles and apices (Fig. 9). The diagnosis is made by correlating the clinical features, chest roentgenographic abnormalities, and characteristic renal pathology. Lung biopsy also will demonstrate the characteristic linear deposition of immunofluorescent material along the alveolar basement membrane (Fig. 10). Bronchoscopic lung biopsy has been used for diagnosis, but the diagnostic yield is approximately 30%.

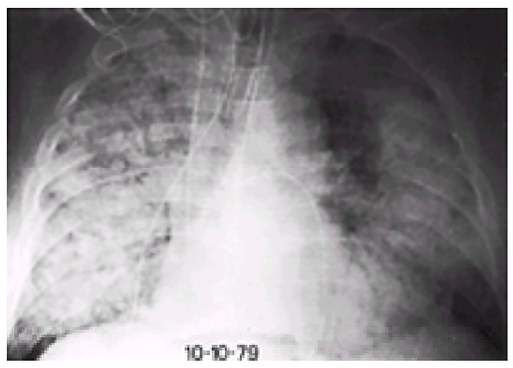

FIG. 9. Extensive dense alveolar infiltrates secondary to pulmonary alveolar hemorrhage in Goodpasture's syndrome. The costophrenic angles are spared.

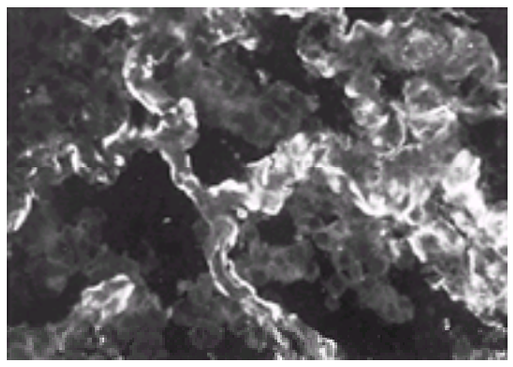

FIG. 10. Immunofluorescent staining of lung tissue in Goodpasture s syndrome reveals the characteristic linear deposits of IgG along alveolar basement membrane.

Plasmapheresis is the treatment of choice in patients with Goodpasture's syndrome. Although complete recovery can be expected in most patients who are treated with systemic corticosteroids, immunosuppressive agents, or plasmapheresis, relapses occur in up to 7% of patients.

Long-term follow-up data on 29 patients disclosed that 31% recovered totally and remained symptom-free with normal renal function for a mean of 206 weeks. In summary, the earlier therapy is associated with better outcome. Patients presenting early with a serum creatinine <200 µmol/L and without severe glomerular alterations gain the most benefit from therapy, indicating that outcome may be improved by early diagnosis.

Renal biopsies have been shown to be extremely valuable in predicting the progress and outcome of the disease. One study looked into the factors that affected the clinical course of 22 patients with Goodpasture's syndrome with renal impairment and reported that the most important features associated with a bad prognosis were total anuria or a very high percentage (>85%) of glomeruli showing crescents in the initial renal biopsy. In a retrospective study of 20 patients with Goodpasture's syndrome, indicators of poor prognosis were creatinine greater than 600 µmol/liter and crescent formation in more than 50% of the glomeruli on renal biopsy; the initial antibody titer and cigarette smoking were without predictive value. Recurrent Goodpasture's syndrome occurs in some patients. A fatal relapse 3 years after plasmapheresis has been described in a smoker who had been exposed to hydrocarbon solvents. A patient with Goodpasture's syndrome who was successfully treated with cytotoxic drugs, steroids, and plasma exchange exhibited, after an absence of 3 years, circulating anti-GBM antibodies. Long-term pulmonary function studies in patients who were treated for anti-GBM disease have found that a prior history of pulmonary hemorrhage significantly reduced the diffusing capacity of the lung for carbon monoxide without affecting other parameters of pulmonary function.

Glomerulonephritis

Rapidly progressive glomerulonephritis is a major cause of pulmonary alveolar hemorrhage. This disease is more common than reported, and more than 50% of cases are composed of Wegener's granulomatosis and microscopic polyarteritis. Additionally, rapidly progressive glomerulonephritis can occur in patients with Goodpasture's syndrome (anti-GBM antibody disease), lupus nephritis (immune complex disease), and pauci-immune and other vasculitides or idiopathic nephritis. In a series of 1500 renal biopsies demonstrating glomerulonephritis with crescent formation, 44% had immune complex deposition, 5% had anti-GBM antibody, and 51% had a pauci-immune pattern. In another review of alveolar hemorrhage syndrome associated with nephritis in 45 patients, the etiologies included anti-GBM disease (18%), a systemic vasculitis (56%), idiopathic glomerulonephritis (27%), and a variety of acute pulmonary complications, the most common being acute respiratory failure (29%); 7% died from fulminant lung hemorrhage. Follow-up studies in 22 patients 6 months after initial presentation indicated that although respiratory symptoms (14%) or pulmonary roentgenographic abnormalities (23%) were uncommon, the majority (73%) of patients had residual abnormalities on pulmonary function testing. Interstitial lung disease has occurred in association with glomerulonephritis caused by unusual vasculitic disorders such as Takayasu's arteritis. Other vasculitic syndromes—for instance, giant cell arteritis—can produce pulmonary problems without alveolar hemorrhage. Pulmonary hemorrhage is common in Behçet's disease.

Antineutrophil cytoplasmic antibodies (ANCA) have been detected in patients with idiopathic crescentic glomerulonephritis and alveolar hemorrhage syndrome. The presence of these antibodies may be associated with necrotizing vascular injury in the kidneys and the lungs. A study of 40 patients with biopsy-verified glomerulonephritis and overt hemoptysis or pulmonary infiltrates compatible with lung hemorrhage observed that 90% of patients exhibited antineutrophil cytoplasm antibodies (PR3-ANCA, myeloperoxidase-ANCA, or both in 27 patients, anti-GBM antibodies in nine). Among the patients with anti-GBM antibodies, the clinical

outcome was very poor (five irreversible renal failure; three deaths). On the other hand, despite no significant difference in clinical features or renal morphology when compared to patients with anti-GBM antibodies, 19 patients (70%) with ANCA recovered completely following treatment.

Intravenous immune globulin infusions have produced dramatic improvements in the necrotizing vascular injury produced by antineutrophil cytoplasmic autoantibodies, and a rapid reduction in the levels of these autoantibodies levels following intravenous immune globulin infusion has been observed in most patients.

Immunoglobulin A (IgA) nephropathy is rarely associated with pulmonary complications. The occurrence of fatal pulmonary hemorrhage in patients with IgA nephropathy is even rarer. An autopsy report described two patients with asymptomatic IgA nephropathy and a third patient with chronic renal failure caused by IgA nephropathy, all of whom died from an illness characterized by acute onset of dyspnea, hemoptysis, and pulmonary infiltrates. No infectious agent was identified, and in all three patients, the diagnoses of IgA nephropathy, idiopathic pulmonary hemorrhage, heavy alveolar hemosiderin-laden macrophages, and capillaritis were documented.

Collagenoses and Vasculitides

The disorders classified as collagenoses and vasculitides are two of the most important causes of pulmonary alveolar hemorrhage syndrome. In the former category, systemic lupus erythematosus is noteworthy, whereas in the latter, Wegener's granulomatosis and other vasculitic syndromes are significant. As a group, the vasculitic disorders are important in the etiology of alveolar hemorrhage syndrome. The clinical aspects of alveolar hemorrhage associated with these diseases are discussed in Chapter 53 and Chapter 54.

Idiopathic Pulmonary Hemosiderosis

It has become increasingly difficult to separate idiopathic pulmonary hemosiderosis from other causes of alveolar hemorrhage syndrome. The confusion stems from the inclusion of idiopathic pulmonary hemosiderosis with Goodpasture's syndrome and other causes of alveolar hemorrhage. Development of systemic vasculitis has been described several years after the diagnosis of idiopathic pulmonary hemosiderosis. For instance, the alveolar hemorrhage caused by microscopic polyarteritis (not to be confused with polyarteritis nodosa), associated with pauci-immune glomerulonephritis in combination with systemic small-vessel vasculitis but without granulomatous inflammation, has been labeled idiopathic pulmonary hemosiderosis. Furthermore, some have suggested that the term *idiopathic pulmonary hemorrhage* be used instead of idiopathic pulmonary hemosiderosis. Currently, idiopathic pulmonary hemosiderosis is a diagnosis of exclusion. The discussion here pertains to the traditional description of idiopathic pulmonary hemosiderosis.

Idiopathic pulmonary hemosiderosis is an uncommon disorder characterized pathologically by recurrent intrapulmonary hemorrhage, and clinically by the triad of hemoptysis, iron-deficiency anemia, and transient roentgenographic infiltrates. The etiology remains unknown, even though its origin has been attributed to several factors, including a heritable defect, an immunologic mechanism based on the presence of antibodies to cow's milk (Heiner's syndrome), cold agglutinins, and increased serum IgA, viral infections, a primary disorder of airway epithelial cells, and a structural defect of pulmonary capillaries. Familial occurrence has also been noted. Idiopathic pulmonary hemosiderosis has been described in association with idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia. A significant number of patients with idiopathic pulmonary hemosiderosis and nontropical sprue (celiac disease) have been described. The implication of these associations is unclear, although an immunologically mediated mechanism has been proposed. More recently, a pediatric form of pulmonary hemosiderosis, presumed to be caused by the toxins of a spore growing in humid basements, has been described.

The clinical findings are extremely variable. Although most patients previously described have been children or young adults, the condition has been recognized in older adults. Hemoptysis may be massive, with dyspnea, cough, and cyanosis, and recurrent bleeding may result in hypochromic anemia. Chest roentgenographic abnormalities include poorly defined, coarse infiltrates, more common in the lower lobes bilaterally. Cessation of symptoms correlates with roentgenographic clearing. Intrathoracic lymphadenopathy is seen in up to 25% of cases. The clinical course is characterized by remissions and relapses. Anemia results from sequestration of iron in the lung parenchyma, often in alveolar macrophages. Because they cannot be mobilized for synthesis of hemoglobin, usable body iron stores become depleted, but they can be mobilized and excreted by the use of synthetic chelating agents. Development of pulmonary fibrosis accounts for the chronic respiratory insufficiency evident in many patients with long-standing idiopathic pulmonary hemosiderosis.

Diagnosis is based on the clinical and roentgenographic features and the presence of significant number of hemosiderin-laden macrophages in the sputum or bronchoalveolar lavage (see above). Microscopically, there is marked capillary dilation with degeneration and hyperplasia of alveolar epithelial cells (see Fig. 8). Corticosteroid and immunosuppressive therapy have been utilized with varying results. Several cases of idiopathic pulmonary hemosiderosis that resolved with cyclophosphamide or chloroquine therapy have been reported. Resolution of idiopathic pulmonary hemosiderosis after institution of a gluten-free diet in patients with idiopathic pulmonary hemosiderosis and nontropical sprue has been reported.

Malignant Disease

Alveolar hemorrhage is an important complication of pulmonary malignancies, being more common in patients who develop hematogenous pulmonary metastasis, tumor emboli, or leukemic lung infiltrates. Autopsy studies in patients with leukemia frequently show alveolar hemorrhage that is occult during life. Twelve percent of focal and 78% of diffuse pulmonary infiltrates have been attributed to alveolar hemorrhage in leukemic patients. The alveolar hemorrhage is frequently related to other complications such as invasive aspergillosis or zygomycosis, which result from immunosuppression. Occasionally, nonfungal infections can also produce alveolar hemorrhage. In the majority of the documented cases, thrombocytopenia (platelet count of fewer than 20×10^9/L) has been noted. Irrespective of the etiology, alveolar hemorrhage usually is not suspected or diagnosed before death; hemoptysis occurs in fewer than one-fourth of patients. Many patients develop an immunocompromised state as a result of infections, neoplasms, cytotoxic chemotherapy, or for unknown reasons. The incidence of alveolar hemorrhage in this group of patients varies from 3% to 8%.

Pulmonary alveolar hemorrhage is also common in certain nonhematologic malignancies. In one study of 23 patients with bronchopulmonary Kaposi's sarcoma, occult alveolar hemorrhage was present in 16 (70%). Hematogenous malignancies with tumor emboli in the pulmonary vessels also cause alveolar hemorrhage (Fig. 11). Right atrial myxoma has caused pulmonary hemorrhage.

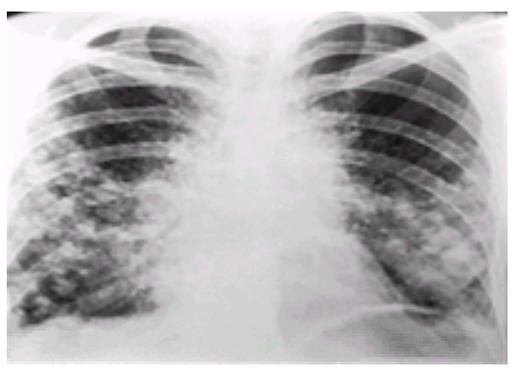

FIG. 11. Diffuse alveolar-nodular infiltrates caused by hematogenous tumor emboli originating in a hypernephroma resulted in clinically significant alveolar hemorrhage.

Bone Marrow Transplantation

Pulmonary alveolar hemorrhage is a significant cause of respiratory disease in recipients of bone marrow transplant (see Chapter 55). This serious complication occurs in up to 21% of patients, with a mortality ranging from 50% to 80%. A high incidence of alveolar hemorrhage has been noted in patients with Hodgkin's and non-Hodgkin's lymphoma treated with high-dose radiation and chemotherapy and autologous bone marrow transplantation. Acute respiratory failure secondary to alveolar hemorrhage occurred within 2 weeks after bone marrow transplantation in 26% of 77 consecutive patients thus treated; the mortality was 100%.

Hemoptysis is unusual in most cases of alveolar hemorrhage. The majority of patients exhibit clinical and roentgenologic signs of infection, including high fever, dyspnea, nonproductive cough, hypoxemia, and diffuse or focal alveolar infiltrates. The initial roentgenologic abnormalities develop within the first 2 weeks and precede the clinical diagnosis by an average of 3 days.

Mitral Stenosis

Although mitral valve disease is now an uncommon cause of alveolar hemorrhage in the developed countries as a result of prompt surgical therapy, it remains an important etiology of hemoptysis and alveolar hemorrhage in other countries. Earlier publications indicated that hemoptysis in mitral stenosis is caused by the rupture of dilated and varicose bronchial veins. Hemoptysis from this mechanism usually occurs early in the course of mitral stenosis and may be the presenting symptom. Other studies suggest that alveolar hemorrhage is the result of stress failure of pulmonary capillaries; the capillary wall stresses greatly increase when the capillary pressure is raised, and wall damage occurs at pressures of 40 mm Hg and higher. Recurrent episodes of alveolar hemorrhage may result in pulmonary calcification and even true ossification. Pulmonary fibrosis may be seen in some patients.

Toxic Alveolar Hemorrhage

D-Penicillamine

Alveolar hemorrhage is a rare manifestation of penicillamine toxicity. Several anecdotal case reports have suggested D-penicillamine as a cause of Goodpasture's syndrome. The daily dose of the drug was high (0.75 to 2.0 g) in almost all cases, and the duration of therapy preceding toxicity ranged from 10 months to 3 years. Uniformly severe alveolar hemorrhage occurred with glomerulonephritis, but other organs were not affected, and four deaths were recorded in a review of the subject in 1984. Immunopathologic features in these cases suggest immune-complex drug-induced disease with a granular pattern of immunofluorescence and with none of the hallmarks of Goodpasture's syndrome.

Trimellitic Anhydride

Trimellitic anhydride is a component of epoxy resin used in the manufacture of epoxy resin coatings, plastics, and paints. Inhalation of fumes or powder can lead to several clinical syndromes, among which pulmonary alveolar hemorrhage is the most serious. Workers exposed to this chemical have developed allergic-type lung disease as well as alveolar hemorrhage. Presence of antibodies against haptenized erythrocytes and human serum albumin suggests an immunologic basis. The illness is characterized by cough, hemoptysis, dyspnea, weakness, and nausea or vomiting. Anemia is a common finding; hence, the term *pulmonary disease–anemia syndrome* is sometimes used to describe this entity. A series of seven young men exposed to trimellitic anhydride developed typical symptoms, but all recovered quickly without treatment; light and electron microscopic studies of lung tissue showed extensive bleeding into alveoli, but no basement membrane deposits or anti-GBM antibodies were observed.

Isocyanates

Hemoptysis, dyspnea, and bilateral pulmonary opacities have been described in a patient who was exposed to spray paint that contained hexamethylene diisocyanate and toluene diisocyanate; high levels of IgG and IgE antibodies were detected against these isocyanates.

Anticoagulants

A case of rodenticide-induced diffuse alveolar hemorrhage has been reported in a patient who consumed brodifacoum (D-Con), a derivative of warfarin. Therapeutic use of anticoagulants is unlikely to cause alveolar hemorrhage unless the pulmonary parenchyma suffers trauma. Three cases were described in 1975, and the clinical features included dyspnea, unexplained acute anemia, and alveolar infiltrates, but hemoptysis was conspicuously absent; one patient died from massive pulmonary alveolar hemorrhage.

Lymphangiography

Lymphangiography has been complicated by pulmonary alveolar hemorrhage. Hemoptysis has been estimated to occur in only one in 3000 cases and is limited to blood-tinged sputum. A 1984 review of alveolar hemorrhage syndromes noted three reported cases of severe alveolar bleeding occurring 2, 5, and 10 days after the procedure, and one patient died.

Other Causes of Alveolar Hemorrhage

Ventilator-associated pneumonia is known to produce alveolar hemorrhage. A study of autopsy findings and premortem roentgenologic features of 69 patients with ventilator-associated pneumonia observed alveolar hemorrhage in 38% of cases; roentgenograms exhibited multiple air bronchograms in 29% and bilateral alveolar infiltrates in 30% of patients.

Pulmonary lymphangioleiomyomatosis is an uncommon cause of alveolar hemorrhage syndrome. Hemoptysis occurs as a presenting symptom in 7% of cases and in half the patients during the course of their illness. Alveolar hemorrhage is the result of venous obstruction and capillary hemorrhage caused by proliferation of muscle in the walls of the pulmonary veins.

Pulmonary venoocclusive disease is an uncommon disease. Alveolar hemorrhage occurs in a significant number of patients with this rare disorder. *Anticardiolipin antibody syndrome* (see Chapter 53) is another cause of alveolar hemorrhage.

Immunocompromised patients develop a variety of infectious and noninfectious pulmonary complications, as discussed in Chapter 55. Among the noninfectious respiratory manifestations, alveolar hemorrhage is an important consideration. Coexisting thrombocytopenia and invasive fungal infections greatly increase the risk of alveolar bleeding. Clinical features include progressive dyspnea, cough, and hypoxemia. Hemoptysis is distinctly uncommon. Chest roentgenologic abnormalities vary (Fig. 12 and Fig. 13).

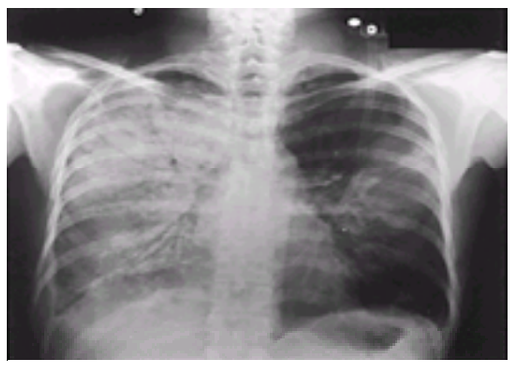

FIG. 12. Marked alveolar infiltrates in the right lung with only a patchy area of infiltrate in left midlung. Significant hemoptysis in this patient was caused by systemic lupus erythematosus complicated by renal failure. Not all cases of diffuse alveolar hemorrhage show bilaterally symmetric chest roentgenologic abnormalities.

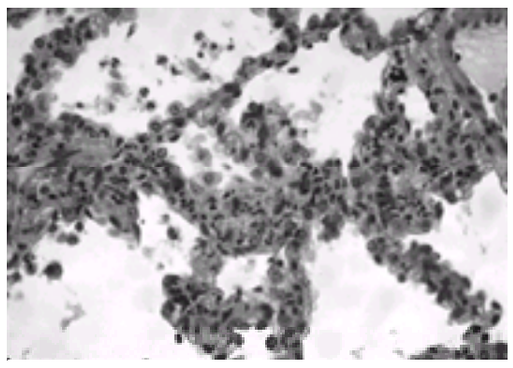

FIG. 13. Acute pulmonary alveolar hemorrhage showing infiltrates of neutrophils in the alveolar septa. The pattern here is nonspecific and could be seen in Goodpasture's syndrome, Wegener's granulomatosis, collagenoses, or vasculitis. In this particular case, a specific diagnosis could not be made.

MISCELLANEOUS RENAL DISEASES

Hemorrhagic diathesis associated with renal failure is the result of azotemia-induced platelet dysfunction. The platelet count is normal, but the bleeding time is abnormally elevated. This hemorrhagic diathesis is a relative contraindication to invasive pulmonary diagnostic procedures. When the serum creatinine level exceeds 3.0 mg/dl or serum urea exceeds 45 mg/dl, bronchoscopic lung biopsy carries an approximately 40% risk of bleeding.

Nephrobronchial fistula is a rare sequel of perinephric abscess and other inflammatory renal diseases. There are reports of nephrolithiasis and pyelonephritis complicated by obstruction leading to pyonephrosis, perinephric abscess, and nephrobronchial fistula that were treated successfully by nephrectomy. Inflammatory renal diseases may involve the perirenal space and spread contiguously to other organs in the abdomen as well as to the adjacent pleural space.

Acute respiratory distress has been described in a patient undergoing *nephrolithotripsy.* Absorption of a large volume of irrigating fluid during the procedure was responsible for this complication.

Pulmonary alveolar microlithiasis is an uncommon disease of unknown etiology, characterized by deposition of tiny calcispherites in the alveolar spaces. Although there is no relation between this disorder and nephrolithiasis, a case of pulmonary alveolar microlithiasis with pleural calcification and nephrolithiasis has been reported.

Renal cell carcinoma is one of the common tumors that produce endobronchial metastasis. Clinically, patients may present with segmental or lobar atelectasis, cough, hemoptysis, and expectoration of endobronchial tumor tissue. Pulmonary parenchymal metastases, usually the result of hematogenous spread of the tumor, may present as rounded nodules, frequently referred to as cannonball lesions. Resection of multiple bilateral pulmonary metastatic nodules is recommended by some. A study reported that in select patients with renal cell carcinoma with pulmonary metastasis who do not respond to nonsurgical therapy, surgical resection of residual metastatic disease may prolong life. The detection of such lesions may require computed tomography of chest. In a study, however, of 120 patients with renal cell carcinoma who underwent chest roentgenography and computed tomography of the chest, a follow-up at 24 months showed no significant impact as a result of the disagreement between the two imaging methods on the therapeutic decision or ultimate outcome. The study also indicated that in patients with a relatively small tumor (stage T_1), normal chest roentgenography suffices for pulmonary staging of the lung metastasis, and the indications for computed tomography of chest include a solitary nodule on chest roentgenograph before salvage resection of metastasis, respiratory symptoms suggestive of endobronchial metastasis, or extensive regional disease.

Interleukin-2 (IL-2) aerosolization therapy has been reported to be effective in controlling the progression of pulmonary metastases from renal cell carcinoma. In a study of 15 patients with pulmonary metastases from renal carcinoma, a trial of high-dose long-term inhalation of IL-2 (90% of IL-2 dose) demonstrated that none of the pulmonary metastases progressed during treatment; one complete response, eight partial responses, and six cases of stable disease were achieved in the lungs.

Renal metastases from primary lung cancer occur much more uncommonly than pulmonary metastases from renal cancer. Several cases of primary lung cancer with metastasis to kidney with resultant acute renal failure have been described, however. The renal changes included extensive bilateral parenchymal infiltration and replacement accompanied by tissue destruction, widespread vascular invasion and thrombosis resulting in ischemia, histologic evidence for foci of distal intratubular obstruction and pyelonephritis, and lymphatic renal metastases. Common findings in all six reported cases included bilaterally enlarged kidneys and progressive oliguria or anuria despite correction of prerenal or postrenal conditions.

Angiomyolipoma of the kidneys occurs commonly in patients with pulmonary lymphangioleiomyomatosis. In one study of 17 consecutive patients with pulmonary lymphangioleiomyomatosis, eight (47%) had renal angiomyolipomas that were found either at surgery or on computed tomographic scans of the abdomen. Therefore, patients with pulmonary lymphangioleiomyomatosis should undergo either ultrasonography or computed tomography of the kidneys. Furthermore, serial follow-up by ultrasonography or CT scanning is recommended to identify and monitor patients with renal lesions larger than 4 cm because such lesions present an increased risk for hemorrhage.

Rounded atelectasis, also known as *folded-lung syndrome* or *atelectatic pseudotumor,* has been described in patients with end-stage renal disease. It is usually caused by chronic pleural effusion or pleural disease. Uremic pleurisy or recurrent small pleural effusion associated with chronic renal disease may lead to rounded atelectasis.

Pulmonary fibrosis was reported in four of 19 patients with renal tubular acidosis. The explanation for the pathogenesis of this association is unclear. Hypoxemia and hemoptysis with life-threatening consequences have occurred after lithotripsy as a result of shock-wave–induced pulmonary contusion. Hemothorax has occurred as a complication of percutaneous renal biopsy.

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CHAPTER

58 Gastroenterologic Diseases

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INTRODUCTION

The common embryologic origin of the upper gastrointestinal tract and the tracheobronchial tree is responsible for their close anatomic proximity throughout life. The pathologic importance of this proximate relationship is evident in the knowledge that some diseases of the esophagus affect the tracheobronchial tree and vice versa. Furthermore, the intimate relationship between the tracheobronchial tree and the esophagus is evident in several congenital and developmental disorders including tracheoesophageal fistula, laryngotracheoesophageal cleft abnormalities, and incomplete development of the trachea and the esophagus. Among the acquired diseases, the aspiration of gastric contents as a result of gastroesophageal reflux into the respiratory system is an excellent example of the close relationship between the airways and the esophagus. Malignant neoplasms originating in the esophagus frequently invade or compress the tracheobronchial tree and cause respiratory embarrassment. Further, there is evidence to suggest the existence of local neuronal esophagolaryngotracheal reflexes in humans. Pulmonary involvement in hepatic and pancreatic diseases is well known. Respiratory manifestations in other gastroenterologic diseases, however, are less common and hence are not very familiar to all. This chapter discusses pulmonary manifestations in the common as well as the uncommon gastroenterologic diseases. The role of alcohol on lung function and disease also is included.

ESOPHAGEAL DISORDERS

Fistulas

Tracheoesophageal and bronchoesophageal fistulas may be congenital or acquired. Congenital fistulas are more commonly tracheal than bronchial. In 90% of congenital cases, there is a proximal blind-ending esophagus and usually a connection between the distal esophagus and the trachea (Fig. 1). In the remaining 10% of cases, an H-type fistula is seen. This latter congenital anomaly may remain undetected until adulthood, especially if the communication is small enough to prevent aspiration of large amounts of solids or liquids through the fistulous tract. Aspiration of small amounts of esophageal contents through the anomalous communication may lead to chronic cough, asthma-like symptoms, and recurrent respiratory infections. A fistula at a more distant site, such as an esophagobronchial fistula, can lead to recurrent infections and ultimately to the development of bronchiectasis. Occasionally, surgical resection of a chronically infected bronchiectatic segment of lung may disclose the presence of a previously undiagnosed fistula between the esophagus and the airway.

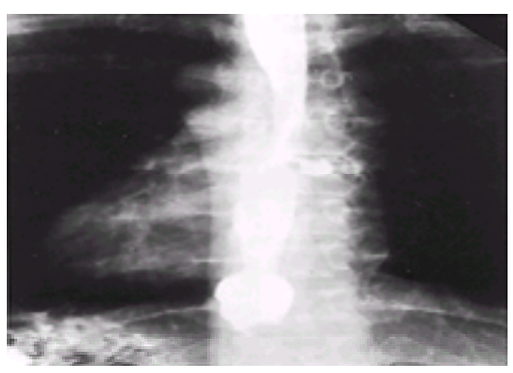

FIG. 1. Situs inversus and congenital fistula between esophagus and proximal left mainstem bronchus, presenting in adulthood as asthma and cough induced by ingestion of liquids.

Acquired tracheoesophageal fistulas as a result of malignancy in the trachea, esophagus, and mediastinum account for approximately 60% of fistulas in adults. The remainder are a consequence of infections, mediastinal granuloma secondary to histoplasmosis, broncholithiasis, silicotic lymph nodes, chemical corrosives, and trauma. Esophageal instrumentation (iatrogenic) is an important cause of tracheoesophageal fistula and acute mediastinitis. Esophagoscope and dilation procedures, inadvertent intubation of the esophagus during endotracheal intubation, rigid bronchoscopic procedures, and endoluminal laser therapy of tracheoesophageal lesions also may lead to the development of fistula. Radiation necrosis of malignancies involving the tracheoesophageal interphase is a relatively common cause of tracheoesophageal fistula. An uncommon cause of acquired tracheoesophageal fistula is Crohn's disease, which affects the esophagus in 0.3% of patients with the disease. Esophagography in patients with Crohn's disease of the esophagus has demonstrated stricture in 38% and ulceration in 32%; tracheoesophageal fistula has been observed in 6% of patients.

Symptoms depend on the location and size of the fistula, but, characteristically, there is coughing on swallowing liquids. Hemoptysis, recurrent pulmonary infection, wheezing, and bronchiectasis also are commonly encountered. A wrong diagnosis of chronic bronchitis or asthma is not uncommon. Diagnosis is documented by demonstrating, in the fistulous tract, contrast material introduced through the esophagus. Esophagoscope and bronchoscopy also are valuable in assessing the location and size of the fistula as well as in obtaining a biopsy from the edges of the fistula to exclude malignancy. Furthermore, bronchoscopy and esophagoscope are important in the insertion of a tracheobronchial or esophageal prosthesis (stent) to treat the fistula.

The possibility of satisfactory surgical correction depends on the cause and location of the fistula. Benign fistulous communications are amenable to surgical therapy. In patients with malignant fistulas, repeated aspiration and pneumonia lead to rapid deterioration and death. The prognosis is dismal, and curative resections and surgical bypass have been associated with 25% to 60% mortality. Insertion of endoprostheses (stents) by endoscopic methods carries perioperative mortality of 15% in these patients.

Gastroenteric Cysts

Gastroenteric cysts develop from the foregut and represent a failure of the originally solid esophagus to become a hollow tube. The cysts occur in the paraspinal region of the posterior mediastinum and usually are round or oval and homogeneous in density (Fig. 2). The majority of these cysts are detected incidentally when chest roentgenographs are obtained. The typical roentgenologic presentation is in the form of a mediastinal mass. Computed tomography helps in the diagnosis. It is uncommon for these cysts to enlarge greatly. Although the overwhelming majority of patients with gastroenterogenous cysts are asymptomatic, surgical resection is routine in most patients.

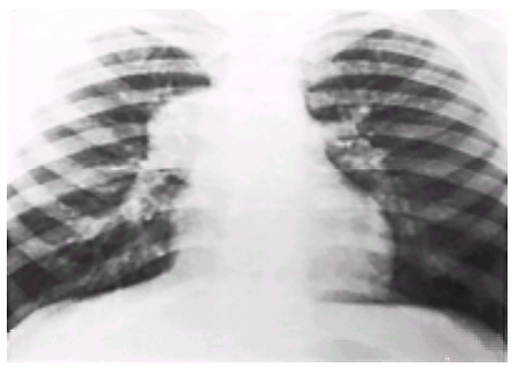

FIG. 2. A large gastroenteric cyst presenting as a posterior mediastinal mass. This was asymptomatic and was discovered during a routine examination.

Zenker's Diverticulum

A pharyngoesophageal diverticulum of Zenker may be large enough to be wrongly identified as a superior mediastinal mass on chest roentgenograms. Symptoms include dysphagia, chronic cough caused by aspiration, and recurrent aspiration pneumonia (Fig. 3).

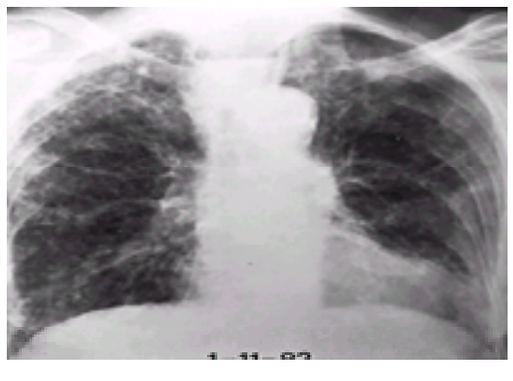

FIG. 3. Acute respiratory failure caused by aspiration from a large pharyngoesophageal diverticulum. Note the air–fluid level in the upper esophagus, just above the aortic arch.

Achalasia

Esophagomegaly (megaesophagus) secondary to achalasia can encroach on the upper airway and cause obstruction to airflow during the expiratory phase. It is not unusual for the enlarged esophagus in achalasia to appear as mediastinal widening or density on routine chest roentgenograms (Fig. 4). Aspiration pneumonia is a serious complication of achalasia and may lead to acute respiratory distress syndrome. Esophagobronchial fistula has been described in a patient with chronic achalasia.

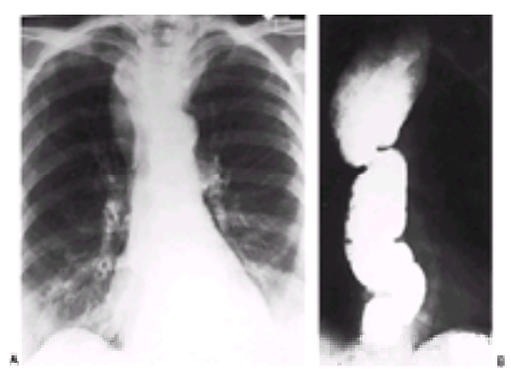

FIG. 4. Achalasia presenting as a superioposterior mediastinal mass. Posteroanterior chest roentgenogram **(A)** and barium contrast study **(B)** demonstrate the megaesophagus.

Mycobacterial infections caused by rapidly growing mycobacteria (*M. fortuitum, M. chelonae,* and others) occur more frequently in patients with achalasia and other esophageal disorders. This complication is more likely if lipoid pneumonia develops as a result of recurrent aspiration. Therapy of both the esophageal disease and mycobacterial infection may be necessary in patients who develop progressive respiratory problems.

Chagas' Disease

Chagas' disease, or American trypanosomiasis, is an infection caused by *Trypanosoma cruzi* and is characterized by an acute, often asymptomatic, illness with a prolonged latent period and chronic cardiac and gastrointestinal sequelae. In patients with predominantly esophageal involvement (chagasic megaesophagus), the pleuropulmonary problems include pleural effusion in 36%, pulmonary embolism in 22%, pneumonia in 35%, and aspiration pneumonia in a small percentage. All these complications are more common in patients with chagasic megaesophagus and cardiomyopathy than in those without esophageal involvement.

Esophageal Perforation

The majority of esophageal perforations are iatrogenic, and fewer than 15% represent spontaneous rupture. Esophagoscope, especially in the removal of foreign bodies, is the most common cause of iatrogenic perforation (Fig. 5). Other causes are the insertion of esophageal tubes, trauma, carcinomas of the esophagus or a Mallory-Weiss tear, Boerhaave's syndrome, mediastinal malignancy, radiation necrosis of the esophagus, foreign bodies, and external trauma.

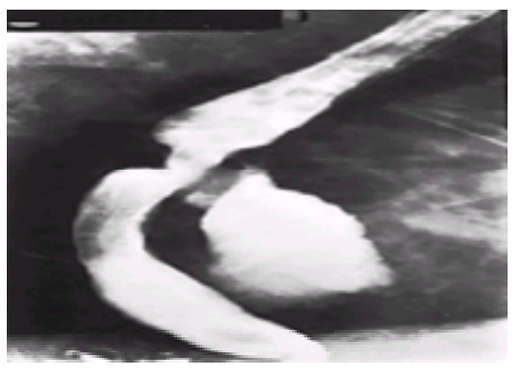

FIG. 5. Instrumental perforation of anterior midesophagus demonstrated by Gastrografin extravasation into the mediastinum.

Acute mediastinitis occurs as the most serious complication of esophageal perforation. Approximately 60% of patients with esophageal perforation develop pleural effusion, and nearly 25% will exhibit a pneumothorax. Pleural effusion usually is left-sided, and analysis will reveal a high protein content, high amylase level, low pH, and the presence of squamous epithelial cells and, occasionally, food particles. The amylase is derived from the salivary juices leaking into the pleural space. The extremely low pH results from the increased leukocytic and mesothelial metabolism as well as the localized acidosis. The diagnosis of esophageal perforation is made by the clinical findings of chest pain, severe back pain, dysphagia, acute fever, subcutaneous emphysema, and documentation of the tear by Gastrografin contrast studies of the esophagus. Boerhaave's syndrome and Mallory–Weiss tear of the esophagus can lead to acute mediastinitis.

Sclerotherapy of Esophageal Varices

Sclerotherapy of the esophageal varices is one therapeutic method used to control variceal hemorrhage. Either sodium morrhuate or ethanolamine oleate is used as the sclerosant and is injected into the varices under direct vision via the esophagoscope. Within 6 hrs of the injection, some patients develop mediastinal widening, presumably from chemical mediastinitis. The overall incidence of intrathoracic complications includes pleural effusion (0% to 50%), mediastinitis (63%), atelectasis (16%), bronchitis (8%), pneumonia (0% to 5%), and esophagopleural fistula (1% to 2%). Other complications such as esophagobronchial fistula, empyema, acute respiratory distress syndrome, pulmonary infarction, and late expectoration of sclerosant are described but rare. Acute pulmonary edema leading to respiratory distress syndrome within 8 to 36 hrs of sclerotherapy has been described. A study of 223 patients who underwent 390 esophageal variceal sclerotherapy procedures with either ethanolamine oleate or tetradecyl sulfate evaluated the pulmonary complications and reported the following: retrocardiac or mediastinal widening in 35%, pleural effusion in 27%, atelectasis in 12%, and pulmonary infiltrates in 9% of procedures. Respiratory insufficiency was noted after 14 sclerotherapy procedures. Most thoracic manifestations after variceal sclerotherapy are likely caused by a local inflammatory response to the sclerosant.

Injection of sodium morrhuate in sheep causes marked but transient pulmonary hypertension and an increased flow of relatively protein-poor lymph. The constituent unsaturated fatty acids may be responsible for the pathogenesis of pulmonary edema. The edema from sodium morrhuate may be another example of hydrostatic (low lymph protein) pulmonary edema caused by abrupt pulmonary hypertension without an increase in pulmonary capillary wedge pressure. Use of a Sengstaken tube immediately after sclerotherapy may increase the risk of pulmonary complications. On the other hand, acute respiratory failure resulting from sclerotherapy has resolved after aspiration of air via a Sengstaken tube.

The reductions in P_aO_2 and vital capacity soon after sclerotherapy have been attributed to pulmonary embolization of the sclerosant even though significant occurrence of pulmonary embolism has not been described.

Pleural effusion after endoscopic variceal sclerotherapy is reported in 50% of patients. The incidence of pleural effusion is related to the amount of sclerosant injected. The effusions are usually small; they are bilateral in a third, right-sided in a third, and left-sided in a third. They usually are exudative and transient. The pleural effusion is secondary to mediastinal pleuritis caused by the sclerosant. Chylothorax also has ensued after sclerotherapy.

GASTROINTESTINAL ENDOSCOPY

Transmission of infection by gastrointestinal endoscopy can occur if endoscopy instruments are contaminated. Organisms include *Salmonella* species, *Pseudomonas aeruginosa,* and *Helicobacter pylori.* A review of the literature disclosed 180 isolates causing disease in 67 cases and death in two as a result of infection transmitted by gastrointestinal endoscopy. Pulmonary aspiration is a fairly common complication during emergency upper gastrointestinal endoscopy. In a study of 30 patients who underwent upper gastrointestinal endoscopy for diagnosis and treatment of acute bleeding, six (20%) developed new pulmonary infiltrates after the procedure, and all but one exhibited fever, leukocytosis, and oxygen desaturation below 90%.

Percutaneous endoscopic gastrostomies for feeding have become the preferred method of providing enteral nutritional support. Pneumonia is a known sequel of this procedure and is reported to occur with an incidence of 10% at 30 days and 56% at 11 months. A study used 24-hr monitoring to demonstrate an increased prevalence of gastroesophageal reflux in patients who developed pneumonia following placement of percutaneous endoscopic gastrostomies.

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux is an extremely common phenomenon, occurring on a daily basis in 10% and intermittently in 50% of healthy individuals. Gastroesophageal reflux disease (GERD) is a syndrome that manifests as heartburn and the sequelae of esophagitis, ulceration, stricture, or Barrett's epithelium. Gastroesophageal reflux and GERD have assumed importance in the pathogenesis of certain lung diseases, particularly laryngospasm, chronic cough, and asthma. Strong evidence suggests that both reflux-induced asthma and otolaryngologic complications including subglottic stenosis, laryngitis, pharyngitis, or cancer can occur without esophagitis. Mechanical reflux of gastric acid into the tracheobronchial tree is another mechanism responsible for the pulmonary complications. A study of patients with chronic persistent cough or asthma suspected to be caused by reflux used distal and proximal pH monitoring to identify those with reflux-induced pulmonary problems and concluded that 17% of patients whose pulmonary symptoms responded to antireflux therapy would not have been recognized as having abnormal reflux if proximal pH

monitoring had not been done; indeed, the antireflux therapy achieved good to excellent success in relief of pulmonary symptoms in 71% of patients with reflux. Esophageal pH testing is of diagnostic significance if intermittent symptoms can be shown to be regularly associated with a decrease in the intraesophageal pH to less than 4.0 during testing.

Vagally mediated local neuronal esophagolaryngotracheal reflexes have assumed an important role in the etiology of many respiratory complications associated with GERD. Normal vagal reflexes in the respiratory tract include cough, laryngeal closure, forced inspiration, respiratory suppression, bronchoconstriction, and mucus secretion. Abnormal reflexes consist of laryngospasm, prolonged apnea, bronchospasm, and singultus (hiccup). There remains the question of whether gastroesophageal reflux is primary or secondary to the pulmonary disease. It is common knowledge that continuous coughing causes retching and vomiting. However, a study of 12 patients with chronic obstructive pulmonary disease employed esophageal manometry, 24-hr pH monitoring, esophageal acid clearance, and pulmonary function tests to determine that these patients do not have a bronchoconstrictive reflex to distal esophageal acidification and that their esophageal function was normal.

Reflux Laryngitis

The association of gastroesophageal reflux with chronic hoarseness and posterior laryngitis has been referred to as *reflux laryngitis* or *Cherry–Donner syndrome.* Twenty-four-hour esophageal pH monitoring has revealed that as many as 75% of patients with chronic hoarseness will exhibit an abnormal amount of gastroesophageal reflux. In a group of 33 patients referred for hoarseness, gastroesophageal reflux was found in almost 80%. Abnormal laryngeal reflexes can be elicited by acidic (pH < 4.5) solutions. GERD also contributes to the development of chronic throat clearing, cough, sore throat, contact ulcer and granuloma, globus pharyngeus, cervical dysphagia, subglottic stenosis, and cricoarytenoid arthritis.

Cough

Controlled studies have shown that chronic persistent cough that remains after a diagnostic evaluation is associated with increased episodes of otherwise asymptomatic gastroesophageal reflux. Four to 21% of chronic cough is estimated to be secondary to gastroesophageal reflux. Reflux should be considered an etiologic possibility in subjects with chronic persistent cough that remains unexplained after a standard diagnostic assessment. The adjusted odds ratio for the presence of gastroesophageal reflux in adults with unexplained chronic cough has been estimated to be 4.4. Indeed, cough may be the sole presenting manifestation of gastroesophageal reflux. Prolonged exposure of esophageal mucosa to gastric acid may cause cough by stimulating esophagolaryngotracheal reflexes. It has been suggested that in those with gastroesophageal reflux, a self-perpetuating mechanism may exist whereby acid reflux causes cough via a local neuronal esophageal–tracheobronchial reflex, and the cough in turn amplifies reflux via increased transdiaphragmatic pressure or by inducing transient lower esophageal sphincter relaxation. Impaired clearance of esophageal acid has been documented by 24-hr ambulatory monitoring of esophageal pH in patients with chronic cough. Postnasal drip also may irritate the receptors located in the pharynx and larynx and contribute to cough; this phenomenon should be excluded in patients who have nocturnal cough and gastroesophageal reflux. Cough caused by tobacco smoke may be aggravated by the lowered esophageal sphincter tone induced by the tobacco smoke.

Asthma

The association of asthma with GERD is well documented. As many as 45% to 65% of adults with asthma have been estimated to have gastroesophageal reflux. Both animal and clinical data suggest that gastroesophageal reflux serves as a trigger of bronchospasm, potentiates the bronchomotor response to additional triggers, or both. Patients with reflux-associated asthma may manifest symptoms of gastroesophageal reflux, either classic or atypical, but approximately 25% to 30% have clinically silent reflux. A questionnaire-based survey of 109 asthmatic patients recorded the presence of heartburn, regurgitation, and swallowing difficulties in 77%, 55%, and 24% of patients, respectively; at least one antireflux medication was required by 37% of asthmatics, and none of the asthma medications were associated with an increased likelihood of symptomatic gastroesophageal reflux. It is, however, important to recognize that asthmatic patients who take theophylline may develop gastroesophageal reflux because the drug is known to decrease lower esophageal sphincter tone and predispose to reflux. In addition, theophylline increases gastric acid secretion.

There is evidence that microaspiration does not play a significant role in esophageal acid-induced bronchoconstriction. The mechanism of bronchospasm in the setting of gastroesophageal reflux is unclear. Although reflux of acid into the airways is well known to produce bronchospasm, not all individuals with gastroesophageal reflux develop asthma. Asthma and gastroesophageal reflux are more common during sleep, but studies have shown that gastroesophageal reflux does not aggravate nocturnal asthma. It has even been questioned whether esophageal reflux is caused by asthma because treatment of asthmatics with esophageal reflux has resulted in diminished reflux symptoms. Nonetheless, compared to bronchitic patients with gastroesophageal reflux, asthmatics have exhibited more episodes and a shorter duration of gastroesophageal reflux.

One study provided the results of long-term experience (average follow-up of 7.9 years) with a group of 44 asthmatic patients with gastroesophageal reflux who underwent Nissan fundoplication: the gastroesophageal reflux cleared in 42 patients (95%), asthma was markedly improved or cured in 18 (41%), and the reflux improved in 29 (66%). There was a significant association between cure of asthma after fundoplication and the presence of nocturnal attacks, nocturnal tracheitis, intrinsic tracheitis, intrinsic asthma, or a clear history of reflux symptoms preceding the onset of asthmatic symptoms. A clinically useful finding was that the positive response to a trial of medical treatment helped identify patients who would be cured.

An opposite view of the role of gastroesophageal reflux in asthmatics was presented in a report on 90 nonasthmatic patients with adult-onset wheezing. A 90% prevalence of gastroesophageal reflux was noted during a study in which the patients were assigned randomly to receive cimetidine or a placebo for a 6-month trial. Those assigned to cimetidine or surgical therapy of gastroesophageal reflux improved significantly. The intake of pulmonary medicine for wheezing decreased significantly. Others have reported that antireflux treatment will provide only small improvements in asthma control in patients with a history of gastroesophageal reflux. Unfortunately, there is no acceptable diagnostic method to confirm the presence of gastroesophageal reflux-induced asthma, and controversy about this issue is likely to continue.

Although the otolaryngologic manifestations usually respond to antisecretory medications, reflux-induced asthma responds convincingly only to antireflux surgery. A number of studies have documented excellent long-term results of surgical treatment for reflux-induced asthma. However, such therapy should be reserved for cases of severe asthma poorly controlled by medications and complicated by severe reflux that leads to ulcerative esophagitis.

Aspiration Pneumonia

Aspiration pneumonitis caused by gastroesophageal reflux is a serious acute medical problem and may lead to acute respiratory distress syndrome. The risk of developing significant aspiration pneumonia increases when the volume of gastric contents aspirated exceeds 50 ml and the pH of the aspirate is below 2.5. Although the initial pathologic features are directly related to the damaging effects of gastric acid, aspiration pneumonia frequently is complicated by bacterial pneumonitis. Community-acquired aspiration pneumonia is extremely uncommon except in alcoholics, those with poor dental hygiene, and debilitated individuals. Nosocomial aspiration pneumonia is more likely to be complicated by bacterial pneumonitis. Debility and prolonged supine posture predispose to this complication. Studies using technetium-99 sulfur colloid labeling of gastric contents and subsequent measurements of endobronchial secretions in patients on mechanical ventilation have shown that the supine position, and particularly the length of time the patient is kept in this position, are potential risk factors for aspiration of gastric contents. The same microorganisms were isolated from stomach, pharynx, and endobronchial samples in 32% of studies done while patients were semirecumbent and in 68% of studies done while patients were in the supine position.

Alkalinization of gastric contents also can predispose to bacterial pneumonia, and gastric colonization by microorganisms is related to the degree of gastric alkalinization. A gastric pH exceeding 4.0 seems to be the most important factor favoring gastric colonization. Hospitalized patients, particularly those being mechanically ventilated, are systematically given antacids or histamine (H_2) blocking drugs, or both, to prevent the development of stress ulcers. Several studies have shown that the use of these drugs in critically ill patients is associated with a greater incidence of both nosocomial pneumonia and gastric and pharyngeal colonization. These studies also reported that the prophylactic use of a cytoprotective agent such as sucralfate does not alter gastric pH and thus prevents microbial colonization (see below). Others have shown that treatment with cimetidine is an independent risk factor for developing pneumonia in mechanically ventilated patients. Elevating the head of the bed to 45° is reported to reduce the risk of aspiration pneumonia significantly.

Many subjects who remain asymptomatic despite frequent aspiration may develop pulmonary complications after chronic aspiration. Typical examples of insidious aspiration-induced lung disease include mild basal pulmonary fibrosis and patchy infiltrates. Ingestion of oil-based compounds for laxative purposes or other reasons may result in lipoid pneumonia (Fig. 6).

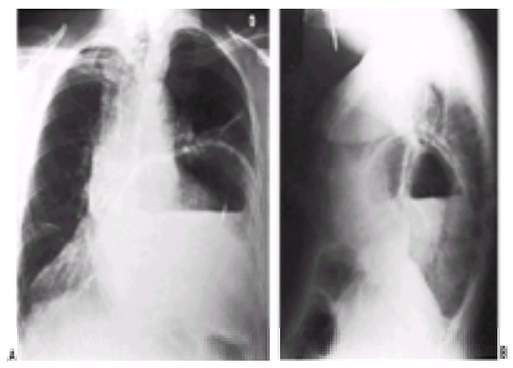

FIG. 6. A large hiatal hernia occupying most of the chest cavity. **(A)** Anterior view. **(B)** Left lateral view.

Gastric pH and Nosocomial Pneumonia

The clinical practice of neutralizing gastric acid to prevent aspiration pneumonia and nosocomial pneumonia in ventilator- and non-ventilator-dependent patients has been controversial. A gastric pH above 4.0 is crucial for overgrowth of gastric gram-negative but not gram-positive bacteria. Critically ill patients who receive ulcer prophylaxis with drugs to suppress or neutralize gastric acidity commonly demonstrate growth of intragastric gram-negative bacteria. Almost all patients receiving enteral feeding also are colonized in the stomach with gram-negative bacteria. Aspiration of these organisms is an important mechanism in the development of nosocomial pneumonia. In a study of 242 mechanically ventilated trauma patients, pneumonia occurred more frequently in patients with gram-negative retrograde colonization from stomach to trachea, even though this accounted for only 13% of all pneumonias. The presence of an endotracheal tube does not afford complete protection from aspiration of the gastric bacteria. A review of 269 articles including 63 randomized trials on the role of stress ulcer prophylaxis observed that prophylaxis with H_2-receptor antagonists decreased the incidence of overt gastrointestinal bleeding, but there was a trend toward an increased risk of pneumonia associated with H_2-receptor antagonists as compared with no prophylaxis. Sucralfate, however, was associated with a lower incidence of nosocomial pneumonia when compared with antacids and H_2-receptor antagonists. In a study of 242 patients who were randomized to sucralfate, antacid, and ranitidine, there was no statistically significant difference in pneumonia rates among the treatment groups during the first 4 days of therapy, although sucralfate appeared to decrease the incidence of nosocomial pneumonia after this period.

Other Complications of GERD

Several other complications have been described in relation to gastroesophageal reflux. These include singultus (hiccup), bronchitis, bronchiectasis, atelectasis, hemoptysis, pulmonary fibrosis, apnea, and seizures related to hypoxia. Many adults with obstructive sleep apnea suffer from gastroesophageal reflux. This may be related to lowered intrathoracic pressure caused by obstructive sleep apnea and increased arousal and repetitive body movement during sleep. Treatment of obstructive sleep apnea with nasal continuous positive airway pressure has been shown to decrease thoracic gastroesophageal reflux in these patients. The esophagus and central nervous system of asymptomatic volunteers have been shown to maintain an awareness of the presence and volume of intraesophageal acid, and the response time by the central nervous system is inversely related to acid volume. The larger volumes of acid in the esophagus are reported to create an afferent warning signal to the central nervous system to produce rapid arousal from sleep along with a shortened interval to the first swallow.

GASTRIC DISORDERS

Hiatal Hernia

In esophageal hiatal hernia, chest roentgenograms often show the herniated portion of the stomach directly behind the heart, suggesting the possibility of a posterior mediastinal mass lesion. The presence of an air–fluid level and a barium contrast study usually confirm the diagnosis. Symptoms originating from hiatal hernia may resemble those of cardiopulmonary disease; however, careful attention to the clinical history often helps in making the distinction. Occasionally, a large hiatal hernia may compromise pulmonary function by occupying a large area of the chest cavity (Fig. 7).

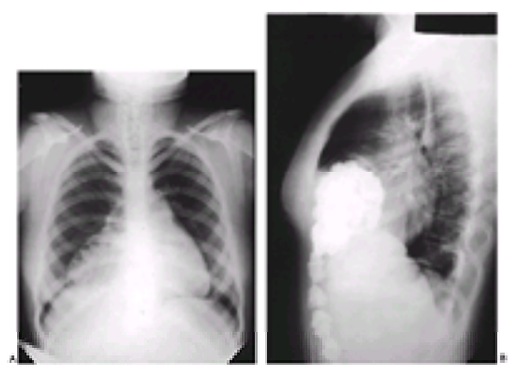

FIG. 7. (A) Foramen of Morgagni hernia presenting as an air-filled mass adjacent to the right heart border. **(B)** A left lateral chest roentgenogram shows that much of small intestine (containing barium contrast) has herniated through the foramen of Morgagni.

One of the most serious respiratory complications of hiatal hernia is the occurrence of aspiration pneumonia secondary to gastroesophageal reflux, as discussed previously. Roentgenologic and endoscopic investigations have reported that from 50% to 94% of patients with GERD have hiatal hernia. A study of 34 patients with endoscopically documented hiatal hernia recorded that, compared to normal volunteers, those with hiatal hernia had substantially higher reflux scores and reduced lower esophageal sphincter pressure.

Hernia Through the Foramina of Bochdalek and Morgagni

Hernia through the foramen of Bochdalek results from incomplete fusion of the posterolateral part of the diaphragm. Herniation is seen more frequently in children, and the abnormality is usually located on the left. Chest roentgenograms reveal a space-occupying mass lesion. Large herniations produce dyspnea, chest discomfort, and, occasionally, respiratory failure. Sometimes these hernias mimic pleural effusion, with the lateral chest roentgenogram disclosing free layering. Postmortem studies in infants with congenital diaphragmatic hernia have shown that the lungs are immature, especially the ipsilateral lung. Additionally, intraalveolar hemorrhage is reported to be a common complication of congenital diaphragmatic hernia. Hernia through the foramen of Morgagni tends to be on the right and anteriorly located. Herniation of the liver may occur, though herniation of intestinal segments is more likely (Fig. 8).

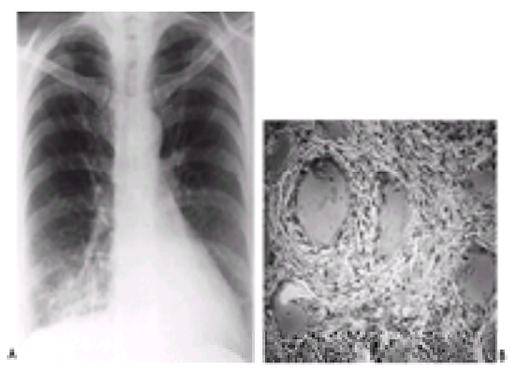

FIG. 8. (A) Chronic ingestion of mineral oil for laxative purposes resulted in an ill-defined mass in the right lower lobe. **(B)** Resected section of the abnormal lung revealed typical findings of lipoid pneumonia.

Peptic Ulcer Disease

Peptic ulcer disease has been found in 10% to 35% of study groups with chronic obstructive lung disease, contrasting with 3% in control groups. The increased incidence of ulcer disease has been explained, at least partly, by gastric hypersecretion because of increased arterial carbon dioxide tension and decreased arterial oxygen tension. This theory applies only to those who develop chronically persistent hypercarbia as a result of the lung disease. Peptic ulcers associated with chronic obstructive lung disease are more commonly duodenal than gastric. Often the peptic ulcer disease is not accompanied by pain and is recognized only after gastrointestinal hemorrhage calls attention to it. Perforation of a gastric ulcer occasionally may result in pleural effusion. Because many patients with obstructive lung disease are treated with corticosteroid preparations, the symptoms related to ulcer disease remain masked.

Acute upper gastrointestinal bleeding in patients with chronic obstructive pulmonary disease is reported to be associated with higher mortality than the upper gastrointestinal bleeding in patients without chronic obstructive pulmonary disease. A case-control study at a university teaching hospital observed that the mortality in patients with chronic obstructive pulmonary disease and ulcer bleeding was 32%, whereas for those with bleeding but without chronic obstructive pulmonary disease, mortality was 10% (odds ratio 4.3); the increased mortality was correlated to severity of chronic obstructive pulmonary disease.

Effect of Gastrectomy on Tuberculosis

Gastrectomy has an adverse effect on preexisting, active pulmonary tuberculosis, and elective surgery is best postponed until a reasonable period of antituberculous therapy has been completed. An increased incidence of pulmonary tuberculosis after subtotal or total gastrectomy and jejunal or ileal bypass has been noted. The incidence of tuberculosis after gastrectomy is estimated at 1% to 5%. The prevalence of prior gastrectomy in patients with tuberculosis has ranged from 1.7% to 20%, the higher incidence being more common in elderly patients. A poor response to treatment and an increased rate of reactivation have been noted in gastrectomy patients who develop infection caused by *Mycobacterium avium* complex. The relationship between gastrectomy and tuberculosis that develops several years later is uncertain. A plausible explanation for the increased incidence of tuberculosis in this group of patients is the decreased absorption of antituberculous drugs as a result of the gastrectomy. Pharmacokinetic studies have documented this phenomenon in anecdotal cases. All this notwithstanding, fear of tuberculosis should not be a factor in deciding on elective gastrectomy.

Total gastrectomy may predispose to the aspiration of esophageal reflux contents. A study concluded that this was the most important risk factor for recurrent pulmonary complications in patients who had undergone total gastrectomy. Among 186 patients who had undergone total gastrectomy, 16 patients had recurrent respiratory tract inflammation, and 45 had sporadic respiratory tract inflammation. The former group frequently showed symptoms related to esophageal reflux and the swallowing provocation test.

Gastrobronchial Fistula

Gastrobronchial fistula is extremely rare. A review in 1985 found only 13 cases. There are five causes for the development of these fistulas. The most common cause is the presence of a subphrenic abscess, which erodes through the diaphragm and leads to lung abscess. Traumatic rupture of the diaphragm, especially from penetrating injury, is the next most common cause. Perforated ulcer in an incarcerated hiatal hernia and necrosis of gastric tumors and areas of previous esophageal or gastric surgery are the other causes.

INTESTINAL DISEASES

Inflammatory Bowel Diseases

Both chronic ulcerative colitis and Crohn's disease (regional enteritis) are well known for their propensity to produce various extraintestinal manifestations. Pulmonary involvement is an uncommon extraintestinal manifestation of these inflammatory bowel diseases (Table 1). The pathogenesis of pulmonary disease in inflammatory bowel diseases is not known. A common systemic mechanism affecting both the bronchial and colonic epithelium may be responsible. It also has been speculated that similarities in the mucosal immune system of the lung and intestine are responsible for the bronchial hyperreactivity in some patients with active inflammatory bowel diseases. A variety of respiratory problems, including pulmonary vasculitis, apical fibrosis, chronic suppurative bronchitis, and bronchiectasis, have been reported (Fig. 9). However, in a series of 1400 patients with inflammatory bowel disease evaluated retrospectively, only three were found to have unexplained bronchopulmonary disease. In a separate review of clinical material on 1400 patients with inflammatory bowel diseases whose diagnoses were recorded in a computerized registry between 1930 and 1970, there were only six unexplained pulmonary diseases. However, publications in the 1980s and 1990s have reported higher prevalence rates of respiratory problems in inflammatory bowel diseases. For instance, abnormal pulmonary functions have been reported in 36% to 68% of patients with Crohn's disease.

TABLE 1. *Pulmonary abnormalities associated with intestinal diseases*

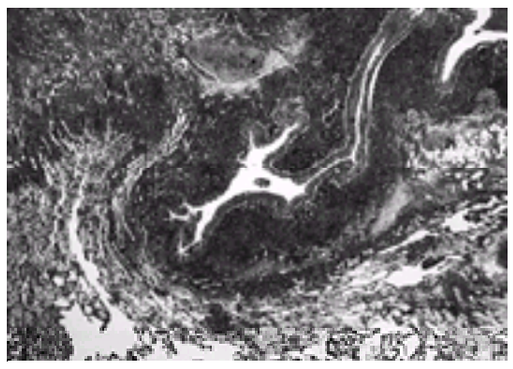

FIG. 9. Chronic bronchiectasis that was symptomatically steroid-responsive in this patient with ulcerative colitis. Dense infiltration of chronic inflammatory cells involving a small bronchus is shown.

A report on the data of an ongoing registry containing 33 cases of pulmonary complications in ulcerative colitis and Crohn's disease, of whom 23 were not on any therapy, noted that in 28 of the 33 cases, lung involvement followed the onset of intestinal diseases (eight of these 28 cases were postcolectomy), and in the others,

pulmonary features preceded the intestinal diseases. Airway manifestations included subglottic stenosis, chronic bronchitis, severe chronic bronchial suppuration, bronchiectasis, and chronic bronchiolitis. Bronchoscopy in these patients revealed exuberant inflammatory tissue and mucosal ulcerations and narrowed tracheal and/or bronchial lumen. Histologically, dense aggregates of inflammatory cells were noted. Interstitial lung disease consisted mainly of bronchiolitis obliterans with organizing pneumonia, pulmonary infiltrates, and eosinophilia. Neutrophilic necrotic parenchymal nodules were also noted. Corticosteroid therapy was more effective in resolving the parenchymal disease than in airway disease.

In another study, among ten nonsmokers with chronic ulcerative colitis, four had exertional dyspnea, four exhibited abnormal chest roentgenograms, and three had obstructive changes in their pulmonary function tests. Bronchial biopsies in four patients showed basal cell hyperplasia, submucosal inflammation, and thickening of the basement membrane, similar to the pathologic changes in the colonic mucosa. In a study of 18 patients with Crohn's disease and no pulmonary symptoms, bronchoalveolar lavage revealed lymphocytic alveolitis in 61%, with lymphocyte counts ranging from 18% to 79%. There was no apparent correlation between lymphocyte count in the lavage effluent and the pulmonary dysfunction observed in 11 patients. These studies suggest that most patients with Crohn's disease have a latent pulmonary involvement mediated by lymphocytes. In one study, 71% of patients with Crohn's disease demonstrated increased superoxide production, but the significance of this in the pathogenesis of lung disease is unclear.

Airways Disease

In one study, pulmonary function was assessed in patients with ulcerative colitis and Crohn's disease and compared with that of a healthy population, and no statistically significant differences were found among the three groups. However, in a prospective study of 58 patients with Crohn's disease and 44 patients with chronic ulcerative colitis, a high incidence of respiratory abnormalities was identified in both groups. Pulmonary function tests were abnormal in 50% of patients, with diminished flow rates (less than 50% of predicted forced expiratory volume in the first second, FEV_1) in 31% and decreased diffusing capacity (less than 75% predicted) in 26%. Abnormally low diffusing capacity was the only abnormality in 16 patients (eight with Crohn's). Four patients with Crohn's and two with colitis had interstitial processes on the chest roentgenograms.

A study disclosed that the prevalence of hay fever and asthma was raised among 242 patients with chronic ulcerative colitis and slightly higher among 45 patients with Crohn's disease. A report on 29 patients with Crohn's disease noted that the lungs are relatively unaffected by Crohn's disease. Bronchiolitis with organizing pneumonitis, sclerosing peribronchiolitis, and diffuse panbronchiolitis are the other abnormalities described in ulcerative colitis.

Ulcerative tracheobronchitis, with intense plasma cell infiltration of tracheal mucosa and submucosa and destruction of mucous glands, has occurred 4 and 8 years after total colectomy in patients with ulcerative colitis. Bronchoscopy in Crohn's disease has revealed small, diffuse, whitish granulations and erythematous mucosa, and biopsy of bronchial mucosa has shown ulcerative bronchitis and noncaseous tuberculoid granuloma.

Pulmonary Parenchymal Disease

Pulmonary function testing, in a study of 36 outpatients with inflammatory bowel diseases, revealed significantly reduced diffusing capacity for carbon monoxide (D_LCO) as compared with matched controls ($p < 0.01$). The reason for this reduction was not clear, though it was considered unlikely to be caused by sulfasalazine (salazosulfapyridine). A further study of the lung function of ten patients with Crohn's disease during and after an attack of the disease revealed that pulmonary volumes and D_LCO were not impaired but that functional residual capacity (FRC) was greater during the attack than during remission; it was also greater than in normal subjects. Disease activity, FRC values, and finger clubbing decreased concomitantly during remission. As noted above, some patients have exhibited low diffusing capacity as the only abnormality.

Although the association of apical fibrosis and ankylosing spondylitis is widely recognized, only one case has been reported in which fibrosis was associated with both spondylitis and ulcerative colitis. Dense basal pulmonary infiltrates responsive to steroid therapy have been reported in two patients: lung biopsy in one revealed changes similar to those in idiopathic pulmonary fibrosis, and the second had nondiagnostic findings. Pulmonary bullous lesions also are described in chronic ulcerative colitis. Hypoproteinemia is common in Crohn's disease. A case has been described of a 29-year-old man who presented with recurrent pulmonary edema and hypoalbuminemia. The diagnosis of Crohn's disease was made only after several episodes of pulmonary edema.

An investigation of pulmonary abnormalities in 26 children with acute or quiescent Crohn's disease revealed normal chest radiographs in all subjects. Even though no significant differences were found between acute and quiescent Crohn's for pulmonary volumes and expiratory flows, D_LCO was significantly decreased during the active phase of the disease as compared to remission (53 ± 15% versus 81 ± 19% predicted). An 11-year-old child who presented with terminal ileitis associated with pulmonary lesions showing periodic progression has been described; the initial thoracic disorder developed 2 years before roentgenographic evidence of the ileitis, the second episode coinciding with the diagnosis of the ileal lesion. Pulmonary lesions progressed simultaneously with the clinical signs of digestive tract disturbances, which eventually stabilized.

In patients with inflammatory bowel disease, biopsy of the affected segment of intestine may show granulomatous changes. Noncaseous and nonconfluent granulomas are found in 30% of patients with Crohn's disease. A report described three patients with classic chronic ulcerative colitis who developed histologically proved type III sarcoidosis during the course of their disease. A case of acute segmental inflammation of the terminal ileum in a female patient who presented with signs and symptoms of acute appendicitis is reported. The patient had associated bilateral pulmonary tuberculosis. The role of *M. tuberculosis* in the etiology of the segmental ileal disease is well known, but the relationship between tuberculosis and inflammatory bowel disease is not clear. Those with jejunal or ileal bypass exhibit an increased incidence of tuberculosis.

Other Pulmonary Complications

Pleuropericarditis may complicate ulcerative colitis and Crohn's disease. A review of the literature reveals approximately a dozen patients with ulcerative colitis and Crohn's disease who developed pleural effusions, bilateral in a third and left-sided in the rest. Many of these were associated with pericardial effusion. The pleuropericardial complications of inflammatory bowel disease may run an independent course and may be present at the time of inactive bowel disease.

Aspiration pneumonia has occurred from esophageal involvement in inflammatory bowel diseases. Crohn's disease is complicated by esophageal stricture in 38% and ulcerations in 32%. The most common presenting symptom in Crohn's disease of the esophagus is dysphagia, seen in more than two-thirds of patients. Cough and repeated bouts of pneumonia occur in a small number of patients.

Enteropulmonary fistulas may present as recurrent localized pneumonia. A case of one such fistula originating from the colon in a patient with Crohn's disease has been discussed. Esophagotracheal fistula has been described in 6% of patients. Histologic studies of these areas have shown submucosal fibrosis, lymphocytic infiltration, noncaseous granulomas, and hypertrophy of muscle.

Antineutrophil cytoplasmic antibodies (ANCA) have been reported in up to 87% of patients with primary sclerosing cholangitis with or without ulcerative colitis and in 68% of patients with only ulcerative colitis. A snow-drift-like perinuclear (p-ANCA) pattern has been described in up to 84% of patients with high disease activity in ulcerative colitis. The cytoplasmic ANCA (c-ANCA) seen in active Wegener's granulomatosis and p-ANCA with myeloperoxidase specificity seen in microscopic polyangiitis are distinctly uncommon in patients with ulcerative colitis. Nevertheless, c-ANCA positivity with typical histologic features and chest roentgenographic features of Wegener's granulomatosis has been described in a patient with ulcerative colitis who was treated with sulfasalazine. All these features resolved after the withdrawal of sulfasalazine.

Sulfasalazine, used in the treatment of inflammatory bowel diseases, is known to produce pulmonary infiltrates and dyspnea. A patient with ulcerative colitis receiving sulfasalazine therapy who developed interstitial pneumonitis and bronchiolitis has been described. Open-lung biopsy in a patient with chronic ulcerative colitis showed severe interstitial fibrosis and bronchiectasis. The pulmonary fibrosis progressed despite cessation of sulfasalazine therapy and a total colectomy. A child with chronic ulcerative colitis and hepatic cirrhosis developed progressive respiratory distress from desquamative interstitial pneumonitis despite cessation of sulfasalazine and institution of systemic corticosteroid therapy.

Mesalamine, one of the 5-aminosalicylate (5-ASA) drugs used to treat inflammatory bowel disease, has been implicated in the causation of bilateral pulmonary infiltrates, peripheral eosinophilia, and histologic findings consistent with acute pneumonitis characterized the lung injury. Nongranulomatous interstitial diffuse lung disease with an inflammatory lymphoid infiltration associated with some mild interstitial collagen fibrosis has been reported in a patient treated with mesalamine for Crohn's disease. Bilateral interstitial infiltrates and gas-exchange abnormalities were described in a patient who developed the pulmonary complication insidiously after 2 years of treatment with mesalamine.

Tobacco smoking and nicotine gum chewing are reported to have a beneficial effect on the severity of symptoms in patients with ulcerative colitis. Some reports have indicated that lifetime nonsmokers and former smokers have an increased risk of developing ulcerative colitis. In contrast, several studies have demonstrated a strong

association between Crohn's disease and smoking. The biological basis for these unusual associations remains unknown.

Nontropical Sprue

The association of nontropical sprue (celiac disease) and diffuse pulmonary disease has been reported in several cases. Although each of these disorders may be associated with abnormal immunologic phenomena, the pathogenesis remains unclear. However, studies of patients with this combination of diseases have identified avian protein precipitins in the sera. The influence of extrinsic factors seems to be prominent in cases of pulmonary fibrosis; in patients with the combination of nontropical sprue and pulmonary fibrosis, the presence of farmer's lung precipitins *(Micropolyspora faeni)* has been noted. It has been suggested that both nontropical sprue and extrinsic allergic alveolitis may be caused by a common immunologic mechanism, because extrinsic allergic alveolitis and nontropical sprue are both associated with HLA-D3, and an association has been reported between nontropical sprue and hypersensitivity pneumonitis in Europe. However, a study of 18 North American patients with nontropical sprue failed to corroborate this association. Nonetheless, a history of asthma or chronic cough was present in a higher proportion of the celiac than the control subjects, and the patients with nontropical sprue showed objective evidence of obstructive lung disease.

Interstitial lung disease has been diagnosed by lung function studies and chest roentgenograms. A case is reported of a 62-year-old woman who had celiac sprue and developed lymphocytic interstitial pneumonia followed by abdominal lymphoma. The patient presented with dyspnea, cough, weight loss, and bibasilar pulmonary infiltrates. Systemic corticosteroids resulted in improvement lasting 1 year. Whereas lymphocytic lymphomas are a well-known complication of sprue, lymphocytic interstitial pneumonitis is not. Postmortem examination of the respiratory system in a patient with nontropical sprue has revealed partial fibrous obliteration of small airways and dilation of larger airways.

Pulmonary hemosiderosis has been described in several patients with celiac disease. A study of seven patients with idiopathic pulmonary hemosiderosis revealed nontropical sprue in three patients and limitation to airflow and decreased D_LCO in five. Clinical documentation that treatment of celiac disease could lead to remission of idiopathic pulmonary hemosiderosis is worth noting. In the cases reported in the literature, six of ten patients showed improvement in both diseases with a gluten-free diet, although histopathologic improvement in the intestinal lesion was shown in only two patients. In patients with celiac disease, antibodies to reticulin and gliadin are found in 78% and 95%, respectively. It has been suggested that a positive serology for either reticulin or gliadin in a patient with idiopathic pulmonary hemosiderosis should lead to consideration of a gluten-free diet as part of the therapy.

Whipple's Disease

Whipple's disease is a chronic systemic infectious disease caused by *Tropheryma whippelii,* an organism closely related to actinomycetes. Whipple's disease typically involves the small intestine and causes malabsorption. Extraintestinal manifestations such as arthritis and fever are common and often exist before the onset of gastrointestinal symptoms. Involvement of the central nervous system can occur and lead to permanent sequelae. Weight loss, hyperpigmentation, and lymphadenopathy are frequent findings. A review of the literature demonstrates high prevalence of cardiac manifestations including constrictive pericarditis, valvular deformity, myocarditis, coronary arteritis, and congestive heart failure. The definitive diagnosis is made by biopsy of the small intestine mucosa which reveals infiltration of the lamina propria of the small intestine with periodic acid-Schiff positive macrophages. Electron microscopy reveals rod-shaped bacillary bodies which perhaps represent *Tropheryma whippelii.* Therapy with trimethoprim-sulfamethoxazole for 12 months usually results in clinical remission and an excellent prognosis. Several pulmonary complications have been described in patients with Whipple's disease.

Pleuropulmonary complications include pleuritic pain, pleural effusion, dyspnea, cough, lung infiltrates, and restrictive lung dysfunction. Respiratory involvement without other symptoms such as arthralgias and fever has occurred. Cough is noted in nearly half of these cases. Although intestinal and joint manifestations are attributed to intracellular infection, the pulmonary manifestations may be the result of an inflammatory reaction to locally deposited immune complexes containing bacterial antigens. Whipple's disease is known to simulate pulmonary sarcoidosis. One patient who developed chest roentgenographic features of sarcoidosis had noncaseous granulomas in the peripheral lymph nodes, pleura, and lung parenchyma. The pleuropulmonary disease resolved with appropriate treatment of Whipple's disease.

Endobronchial lesions and large pulmonary nodules have been described in Whipple's disease. In a 31-year-old man, Whipple's disease presented with large rapidly enlarging pulmonary nodules. A bronchoscopic examination showed several raised yellow endobronchial lesions mainly at the subcarinae of the lobar bronchi. Biopsies revealed multiple foamy macrophages that were PAS positive and diastase resistant without granulomas or giant cells. Interestingly, this patient had no gastrointestinal features. Whipple's disease presenting as pleuropericarditis in a 48-year-old woman exhibited peribronchiolar and perivascular histiocytic infiltrates in a patchy distribution with characteristic cytoplasmic bacilliform inclusions present in these cells.

Other Malabsorption Syndromes

Protein-losing enteropathy may predispose patients to developing pleural effusions, both transudative and chylous. Primary intestinal lymphangiectasia is a rare condition of uncertain etiology characterized by dilated small-bowel lymphatics and often complicated by anomalous lymphatics elsewhere, typically in the limbs. Protein-losing enteropathy secondary to intestinal lymphangiectasia has been reported to produce chylothorax.

The combination of yellow nails, lymphedema, and pleural effusions is known as the *yellow-nail syndrome.* Lymphedema can occur as a distinct entity or as a result of lymphatic obstruction or loss of chyle from various mechanisms. More than 20% of patients with primary lymphedema have a protein-losing enteropathy resulting from lymphangiectasia of the small bowel. With significant loss of protein, these patients develop hypoproteinemia as well as hypogammaglobulinemia. Persistent pleural effusions and recurrent pulmonary infections may ensue in this setting.

HEPATIC DISEASES

Diseases of the liver produce or are associated with multiple pulmonary problems (Table 2). Arterial hypoxemia in conjunction with hemoglobin desaturation, clubbing, pleural effusions secondary to ascites, hyperventilation, and platypnea-orthodeoxia are encountered in 15% to 45% of patients with cirrhosis. The pathologic mechanisms involved in these complications are varied. Pulmonary intravascular macrophages (phagocytes) are mainly responsible for the uptake of circulating particles by lung cells. Pulmonary intravascular phagocytosis has been detected in animal models of chronic biliary cirrhosis and in humans with liver diseases. In certain disease states, for instance, biliary cirrhosis, pulmonary phagocytes may develop in the pulmonary capillaries, placing the lungs at risk for pathogen localization and subsequent inflammation and respiratory distress.

TABLE 2. *Intrathoracic abnormalities in hepatic diseases*

Pleural Effusion

Pleural effusion, usually right-sided and occasionally massive and symptomatic, may occur in cirrhosis or peritonitis. Pleural effusion is found in 6% of patients who have hepatic cirrhosis associated with ascites. The fluid is usually a transudate, and its chemical characteristics are similar to those of ascitic fluid. There are three possible mechanisms for the development of pleural effusion in hepatic cirrhosis: hypoproteinemia, azygos hypertension, and transfer of peritoneal fluid to the pleural cavity via congenital defects in the diaphragm. Intraperitoneal injection of the radioisotope ^{99m}Tc-sulfur colloid has demonstrated the one-way transdiaphragmatic flow of fluid from the peritoneal to the pleural space, and thoracotomy has allowed identification of the diaphragmatic defects. In patients with massive pleural effusion secondary to ascites, drainage of pleural fluid for therapeutic purposes is usually futile because as long as the peritoneal cavity contains fluid, the pleural fluid will continue to reaccumulate. Treatment should be aimed at controlling the ascites. Pleural effusions also are seen with viral hepatitis. In a prospective Italian study of

hepatitis, 70% of 156 patients had some fluid in the pleural space.

Ascites, if large in volume, can interfere with normal pulmonary function by interfering with normal diaphragmatic excursion. Ascites and abnormal distension restrict full inflation of the lungs and thus reduce lung volume. This effect of ascites on the pulmonary system is mediated by the hydrostatic pressure exerted from within the peritoneal cavity on the diaphragm. However, this effect varies among patients and seems to be dependent on the intraabdominal hydrostatic pressure (thought of as a pressure in excess of the height of the anterior abdominal wall).

Large-volume paracentesis is a safe, rapid, and effective treatment of ascites and usually relieves respiratory symptoms caused by tense ascites. One study investigated the effect of large-volume (5 liters) paracentesis on pulmonary function parameters in eight hemodynamically stable patients with cirrhosis and tense ascites and absence of known lung disease or abnormal chest roentgenograms. Baseline lung volumes, diffusing capacity, and arterial PO_2 were reduced, but flow rates were normal. Following paracentesis, lung volumes increased significantly; diffusing capacity and arterial oxygenation did not change significantly.

Hepatopulmonary Syndrome

The hepatopulmonary syndrome denotes the arterial hypoxemia in patients with cirrhosis. Arterial hypoxemia is present in 30% to 50% of patients with hepatic cirrhosis. It also may occur in other chronic liver diseases, such as chronic active hepatitis and nonspecific hepatitis. The pathophysiological mechanisms include presence of low pulmonary vascular tone characterized by a poor or absent hypoxic pressor response, which results in a marked dilation of the pulmonary vasculature. Both the liver and the endothelial cells may play a critical role in the regulation of the pulmonary vascular tone in these patients. The abnormal pulmonary vascular tone causes *V/Q* mismatch and mild to moderate hypoxemia. As the hepatic damage progresses, the intrapulmonary venoarterial shunt becomes more severe, leading to serious limitation of oxygen diffusion and, finally, severe respiratory failure. Development of abnormal anatomic communications between pulmonary arteries and veins with bypassing of the capillary–alveolar interphase also contributes the hypoxemia. There may be other mechanisms at play in causing hypoxemia in association with liver cirrhosis. Injection of radioactive krypton into the spleen has shown definite portopulmonary anastomoses. In some instances, venous blood in the portal system may reach the left side of the heart through anastomotic channels with pulmonary veins. Intrapulmonary shunts can reach considerable proportions (20% to 70%) of the cardiac output. Blood gas analysis discloses moderate hypoxemia and respiratory alkalosis.

Orthodeoxia is hypoxemia that is produced by the assumption of an erect position and relieved by a recumbent position. Orthodeoxia in patients with hepatic cirrhosis results from the effect of the gravitational forces that increase the blood flow through intrapulmonary venoarterial shunts. When orthodeoxia is severe, patients develop increasing dyspnea while standing *(platypnea).* Although hypoxemia is common and multifactorial, severe hypoxia is unusual. In a large series of cirrhotic patients, 7% had an arterial oxygen tension of less than 60 mm Hg while breathing room air.

Chest roentgenographs in hepatopulmonary syndrome normally display bibasilar nodular or reticulonodular opacities. Conventional computed tomography reveals that these nodules portray dilated lung vessels. Imaging with ^{99m}Tc-MMA perfusion can be utilized to confirm intrapulmonary arteriovenous shunting. High-resolution computed tomography is valuable in eliminating pulmonary fibrosis as the reason for these opacities. Contrast-enhanced echocardiography appears to be the most sensitive diagnostic test for detecting intrapulmonary vascular dilations.

Therapy of hepatopulmonary syndrome with almitrine bismesylate, a somatostatin analog, indomethacin, and plasmapheresis has been disappointing. Large pulmonary arteriovenous shunts documented by pulmonary angiography have been treated by embolotherapy with improvement in hypoxemia.

Diffuse Pulmonary Disease

Diffuse interstitial lung disease, occasionally granulomatous, has been observed in patients with primary biliary cirrhosis. Primary biliary cirrhosis is a granulomatous liver disease characterized by chronic intrahepatic cholestasis. The etiology is unknown, and it is associated with the presence of non-organ-specific antibodies to mitochondria in more than 95% of patients. The frequency and nature of pleuropulmonary manifestations in primary biliary cirrhosis are poorly documented. Many of the cases of lung involvement in primary biliary cirrhosis have been characterized by lung parenchymal granuloma formation and mononuclear cell alveolitis mimicking pulmonary sarcoidosis. One study using bronchoalveolar lavage has shown an increase in the number of alveolar $CD4^+$ lymphocytes (22% versus 12% in alcoholic cirrhosis) and activated alveolar macrophages in 50% of patients. These data suggest that subclinical alveolar inflammation, involving T lymphocytes and activated alveolar macrophages and mimicking sarcoid alveolitis, is present in a high proportion of patients with primary biliary cirrhosis. Pulmonary nodules simulating pulmonary carcinomatosis and later documented to be lymphocytic interstitial pneumonitis was described in a 51-year-old woman. These changes were unrelated to the activity of primary biliary cirrhosis and underwent spontaneous resolution. Because sicca complex often is associated with primary biliary cirrhosis, part of the respiratory dysfunction noted in primary biliary cirrhosis may be related to sicca complex rather than to the liver disease.

A prospective study of hepatic and pulmonary function in 47 patients (nonsmokers) with primary biliary cirrhosis found a significant relationship between histologic stage of primary biliary cirrhosis and steady-state diffusing capacity, and between the Mayo risk score for disease severity and steady-state diffusing capacity. Progressive deterioration of steady-state diffusing capacity was associated with increasing severity of primary biliary cirrhosis. There was no relationship between pulmonary involvement and the presence of Sjögren's syndrome. No significant relationship was observed between expiratory airflow and severity of primary biliary cirrhosis.

In a prospective study of 170 patients with various types of chronic hepatic diseases, mottled pulmonary parenchymal infiltrates were noted in 6%. Decreased D_LCO was observed in 20%. Clubbing of nails seemed to occur with a higher frequency in those with liver disease and abnormal chest roentgenograms. Pulmonary edema as a result of passive congestion can be seen in patients with liver disease. There appears to be high incidence of low-pressure pulmonary edema and acute respiratory distress syndrome in patients with fulminant hepatic failure.

Pulmonary Hypertension

The association of hepatic cirrhosis and pulmonary hypertension was first observed more than three decades ago. In a study of 2459 patients with biopsy-proved cirrhosis and 1241 patients with cirrhosis diagnosed at autopsy, the incidences of idiopathic hypertensive pulmonary vascular disease were 0.6% and 0.73%, respectively, in contrast to 0.13% ($p < 0.001$) in all autopsies. The data from this study suggest an association between cirrhosis and the development of pulmonary hypertension. Whereas the prevalence of cirrhosis alone was highest in the fifth decade, the average age of the cirrhotics with pulmonary hypertension was 35 years, and they tended to be women. The mechanisms responsible for the development of pulmonary hypertension in hepatic cirrhosis are unknown. Recurrent embolization from portal to pulmonary circulation, primary vasoconstriction, *in situ* thrombosis of pulmonary vessels, increased pulmonary vascular resistance from vasoactive peptides released as a result of portal hypertension, dietary alterations, and recurrent pulmonary emboli have been implicated.

Although most cases of pulmonary hypertension have been reported in patients with cirrhosis, hepatic parenchymal disease or failure is not necessary for its development. The strongest association appears to be with portal hypertension, and portal hypertension nearly always precedes by several years the diagnosis of pulmonary vascular disease. Histologic features, including plexogenic arteriopathy, are similar to those in primary pulmonary hypertension. Autopsy studies reveal a high incidence of intravascular thrombosis in association with plexiform lesions.

Hepatitis C Virus Infection

Hepatitis C virus (HCV) infection has been suggested as a cause of idiopathic pulmonary fibrosis, based on a Japanese study in which a high prevalence of anti-HCV antibodies was detected. A British study, however, failed to confirm these results. A subsequent study observed that Italian patients with idiopathic pulmonary fibrosis recorded a 13% prevalence of HCV infection and viral replication; the prevalence of anti-HCV antibodies did not differ from that in patients with other lung diseases.

Bronchoalveolar lavage lymphocyte subsets from 13 patients (ten men) with active chronic hepatitis C virus infection, when compared with those from 13 healthy volunteers, showed no difference in total cell counts in lavage fluid between the two groups. However, lavage lymphocyte and eosinophil numbers were increased in patients with chronic hepatitis C, leading the authors to consider that HCV infection may trigger alveolitis.

Recombinant interferon-a is used to treat hepatitis C virus infection. There are many reports on the occurrence of diffuse interstitial lung infiltration, with acute respiratory failure in some, in patients with chronic hepatitis C virus infection following therapy with recombinant interferon-a. Bronchoalveolar lavage has shown an increase in lymphocytes, especially $CD8^+$ cells, and lung specimens have exhibited bronchiolitis obliterans with organizing pneumonia (BOOP). In the vast majority of patients, the pulmonary manifestations and chest roentgenographic abnormalities disappeared after interferon therapy was discontinued and corticosteroid therapy was given.

Liver Transplant

Pulmonary infections occur in 25% of transplant recipients. The organisms responsible for pulmonary infections include gram-negative bacteria, cytomegalovirus, *Candida* species, *Aspergillus* species, and *Pneumocystis carinii.* Interstitial pneumonia caused by herpes simplex virus type 1 (HSV-1) is a severe complication of orthotopic liver transplantation. Acyclovir together with mechanical ventilation and reduced immunosuppression has proved to be an effective treatment for HSV-1 pneumonia following orthotopic liver transplantation.

Cytomegalovirus (CMV) pneumonia is a relatively common occurrence in orthotopic liver transplant recipients and is associated with high mortality. A prospective analysis of 141 orthotopic liver transplant recipients observed CMV pneumonia in 13 (9%) patients during the first year posttransplant, and the mortality rate was 85% at 1 year compared with a 17% mortality in those without CMV pneumonia. Overall, a 67% mortality rate was attributed to CMV pneumonia within the first year after liver transplantation.

Noninfectious complications following orthotopic liver transplant are caused by prolonged general anesthesia, extensive upper abdominal surgery, and massive administration of blood products and colloids. Noninfectious complications include atelectasis, pleural effusion, acute respiratory distress syndrome, and pulmonary calcification. Although air embolism is common during liver transplantation, clinical sequelae are few.

Diaphragmatic paralysis that occurs after orthotopic liver transplantation may contribute to the postoperative pulmonary problems. A crush injury to the right phrenic nerve during transplantation is most likely the cause of right hemidiaphragmatic dysfunction. A prospective study of 48 adult liver transplant recipients assessed by ultrasound, pulmonary function tests pre- and postoperatively, and transcutaneous phrenic nerve conduction studies recorded right phrenic nerve injury and hemidiaphragm paralysis in 79% and 38% of patients, respectively; conduction along the right phrenic nerve was absent in 53% and reduced in 26%. Left phrenic nerve conduction and left hemidiaphragm excursion were unaffected. The abnormal findings, however, did not significantly influence either the time on the ventilator or the hospital stay. Complete recovery of phrenic nerve conduction and diaphragm function took as long as 9 months in some patients.

Metastatic pulmonary calcification (calcinosis) following orthotopic liver transplantation has been described. In a series of 91 patients who underwent orthotopic liver transplantation, chest roentgenographs of 77 patients were reviewed, and pulmonary calcification was observed in four (5%) patients. Pulmonary calcinosis is a form of dystrophic calcification. Pulmonary calcification, at times fatal, has been described in renal transplant recipients. Many of the renal transplant recipients had markedly elevated calcium–phosphorus product, to peak values of 122 to 147 mg/dl. In the four liver transplant recipients described above, significantly higher levels of serum phosphate and calcium were recorded postoperatively, and these patients had received more intraoperative platelets and other blood products containing exogenous calcium than other patients. Nonspecific and persistent pulmonary opacities should suggest the possibility of pulmonary calcification. High-resolution computed tomographic lung scan or bone-seeking radionuclide (^{99m}Tc-diphosphonate) lung scans can be used to establish an early diagnosis of pulmonary calcification.

Miscellaneous Hepatic Disorders

Pulmonary embolism caused by bile embolism is a rare, occasionally fatal complication following biliary trauma. Communications between the biliary tract and hepatic veins after biliary surgery have been shown to result in bile emboli in small pulmonary arteries. Among the nine cases reported in the literature up to 1983, five had malignancies encroaching on the biliary tree, and the rest had biliary trauma.

a_1*-Antitrypsin deficiency* predisposes to pulmonary emphysema, liver cirrhosis, and hepatocellular carcinoma. Liver disease or impaired liver function is not a clinically relevant problem in most adults with pulmonary emphysema caused by a_1-antitrypsin deficiency. Indeed, severe lung and liver disease rarely coexist in the same subject. A review of 19 adult patients with a_1-antitrypsin deficiency and chronic liver disease showed a late onset of symptomatic hepatic abnormalities; 13 patients were 60 years old or older when liver disease was discovered. Low levels of serum a_1-antitrypsin are more likely to be associated with cirrhosis of the liver in children than in adults; approximately 10% of children with PiZZ $a_1$antitrypsin deficiency develop significant liver dysfunction. Chronic liver disease in patients with a_1-antitrypsin deficiency is associated with a high prevalence of hepatic infection by viruses. It has been suggested that the viral infection of the liver, rather than the a_1-antitrypsin deficiency alone, may be the cause of the liver disease in such patients.

Hepatic amebiasis produces pleuropulmonary complications in 7% to 20% of patients with amebic liver abscesses and in 2% to 3% of those with invasive disease. The intrathoracic manifestations include sympathetic effusion over the infradiaphragmatic area of inflammation, rupture of the amebic abscess and amebic empyema, and rupture directly into the bronchial tree to produce hepatobronchial fistula (Fig. 10).

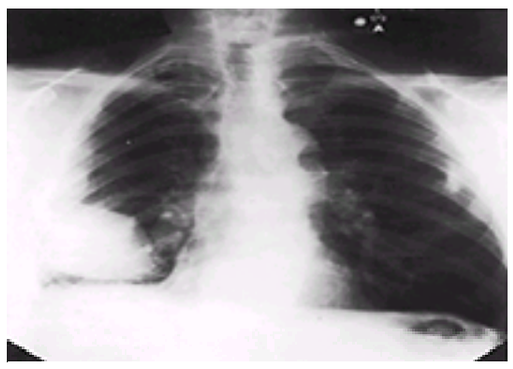

FIG. 10. Right-sided pleuropulmonary involvement by amebic abscess.

Pulmonary injury from *drugs* such as penicillamine, azathioprine, sulfasalazine, and mesalamine may occur in patients who are administered these drugs for therapy of various gastroenterologic diseases.

Alcohol and the Lung

Chronic alcohol consumption increases the risk of developing pulmonary tuberculosis, chronic bronchitis, aspiration pneumonitis, lung abscess, pulmonary complications of alcoholic cirrhosis, and pulmonary problems from alcoholic cardiomyopathy. The reported effects of alcohol on the respiratory system include diminished ciliary motion, decreased migration of alveolar macrophages, interference with surfactant production, and increased prevalence of oropharyngeal gram-negative bacilli.

Three large epidemiologic studies in the 1980s critically analyzed the effect of alcohol on respiratory function and found that alcohol has little, if any, effect on pulmonary function. The pulmonary functional abnormalities noted in earlier studies were apparently related to smoking, a common habit among subjects who consume alcohol. Further, a study of 27 alcoholic subjects in the United Kingdom concluded that the high prevalence of respiratory disease in alcoholics was largely attributable to their smoking habits and that there was no evidence of a specific pulmonary toxic effect of ethanol on the lungs. A population-based study, however, of more than 8750 persons, each of whom had consumed alcohol, 350 g/week or more, evaluated the effect of alcohol consumption on pulmonary function over a period of 5 years and reported that alcohol consumption significantly accelerated the loss of FEV_1 and forced vital capacity; these changes were comparable to the effect of smoking 15 g tobacco daily. Other reports have noted that short-term cessation of alcohol intake has no effect on pulmonary function parameters in cigarette-smoking alcoholics.

Impaired glottic reflex and cough reflex and oversedation induced by alcohol ingestion may play a role in causing community-acquired pneumonia. A case-control study concluded that high alcohol intake is the main risk factor for developing community-acquired pneumonia in middle-aged people. Compared with nonalcoholic patients, alcoholic patients with pneumonia exhibited more severe clinical symptoms, required longer intravenous therapy and longer hospital stays, and had multilobar involvement and pleural effusion as well as slower resolution of lung infiltrates. Pneumonia may also result from gastroesophageal reflux induced by alcohol ingestion. The effect of moderate amounts of alcohol (e.g., 120 mL Scotch whiskey, with 40% alcohol) on nocturnal esophageal reflux was studied in healthy volunteers. Monitoring of esophageal pH in ambulatory and supine postures revealed prolonged supine reflux episodes in 41%, whereas none in the control group had reflux. This study also found that there was a significant exposure of the distal esophagus to acid and that the normal acid clearance of the esophagus in the supine position was impaired after only moderate amounts of alcohol.

Klebsiella pneumoniae pneumonia with bacteremia is common and associated with a very high mortality in alcoholic subjects. In a study of 28 alcoholic patients (all men) with community-acquired pneumonia who were admitted to a referral medical center, all but a few were heavy smokers; bacteremic *Klebsiella pneumoniae*

pneumonia was diagnosed in 11 patients, all of whom required management and ventilatory support in the intensive care unit. Chest radiographs showed pleural effusion and roentgenographic spread of pneumonia in nearly 50% of patients. Acute renal failure and disseminated intravascular coagulation developed in six patients. Even though the overall mortality was 64%, all patients with *Klebsiella pneumoniae* died.

Acute respiratory distress syndrome (ARDS) is reported to occur with higher frequency in patients with a history of alcohol abuse. A prospective cohort study of 351 medical and surgical intensive care unit patients with one of seven at-risk diagnoses for the development of ARDS noted that the incidence of ARDS was significantly higher in patients with a history of alcohol abuse than in patients without such a history (43% versus 22%). In patients with sepsis, ARDS developed in 52% of the patients with a prior history of alcohol abuse compared with only 20% in patients without that history. In the subset of patients who developed ARDS, the in-hospital mortality rate was 65% in patients with a prior history of alcohol abuse. This mortality rate was significantly higher than the mortality rate in patients without a history of alcohol abuse.

Alcoholism is closely associated with tuberculosis, the prevalence of alcoholism being 49% in newly diagnosed tuberculous disease. Among 970 subjects in New York City with alcohol and drug addiction, the prevalence of tuberculosis was 0.91%, which was 28 times the age-matched rate for the population in the city; the screening of only those with a positive tuberculin test and cough substantially increased the yield of active tuberculosis to 7.2%, or 225 times the rate for the city. In view of the rising incidence of tuberculosis in the 1990s, screening for tuberculosis in the alcoholic population is highly recommended. A review of 23 patients with primary pulmonary sporotrichosis, presumably acquired by inhalation, revealed that this form of the disease affects middle-aged men with a history of alcoholism or chronic lung disease. Clinically and roentgenographically, the disease mimics chronic cavitary tuberculosis and histoplasmosis.

One study reported that low to moderate alcohol consumption by older persons is associated with a decreased risk of deep venous thrombosis and pulmonary embolism.

Alcohol asthma is the term applied to chest tightness and wheezing after alcohol ingestion; a small number of persons of Asian and Native American extraction have been reported to demonstrate this phenomenon.

Deficiency of IgG subclass has been reported in 70% of patients with alcoholic liver disease, and the deficiency was reported to be closely correlated with the number and type of bacterial respiratory infections.

PANCREATIC DISEASES

Pleural Effusion

Pleural effusion occurs in 4% to 17% of patients with acute pancreatitis. Roentgenographic abnormalities include free or loculated pleural effusion, elevation of a hemidiaphragm, and basilar atelectasis. The effusions are predominantly left-sided. Characteristically, the fluid is an exudate, contains elevated amylase level, and is hemorrhagic in 30% of patients. Massive pleural effusions can occur in association with asymptomatic pancreatic disease.

Pleuropancreatic fistula may produce chronic massive pleural effusions. Chronic massive pancreatic pleural effusion also may develop weeks, months, or years after an episode of acute pancreatitis, and, in most of these patients, there is no history of pancreatitis. Patients may present with dyspnea, cough, and chest pain. The pleural fluid amylase content is always markedly elevated. Chronic massive pancreatic pleural effusion is caused by posterior disruption of the pancreatic duct into the retroperitoneal space, with tracking of secretions from the pancreas along the esophagus or aorta upward into the mediastinum. The fluid can occasionally collect in the mediastinum and produce a mediastinal pseudocyst. Pericardial effusion and tamponade have been described. Very high levels of pleural fluid amylase also can be seen in pleural effusion secondary to esophageal perforation. The amylase in this situation results from leakage of salivary amylase.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is the most serious complication of pancreatitis and is reported to occur in 20% to 50% of patients. A prospective study to assess the incidence of pulmonary infiltrates in acute pancreatitis observed this complication in 26% of patients, but not all patients had ARDS. Pancreatitis-induced ARDS usually is attributed to the release of active enzymes and vasoactive substances from the pancreas. The mechanism of injury is unknown, but it is believed to be related to defective surfactant production. Lecithin is a main constituent of the pulmonary surfactant dipalmitoyl lecithin. The surfactant is split by a lecithinase, which is increased in acute pancreatitis. An experimental study suggests that pancreatic elastase plays a major role, by direct deleterious action on the pulmonary vasculature, in the development of pulmonary vascular injury after acute pancreatitis. In another experimental model, pancreatitis induced by injection of trypsin and sodium taurocholate into the pancreas, pulmonary injury was prevented by pretreatment of animals with trasylol, an antiprotease drug active toward trypsin and elastase.

Thoracic duct drainage has been used to remove pancreatic enzymes and vasoactive substances before they could reach the systemic circulation and cause adult respiratory distress syndrome. This method was used to collect the lymphatic effluent in six patients with severe acute pancreatitis; moderate lymph-to-plasma gradients were noted for IL-6, lipase, and trypsin, and similar levels in plasma and lymph were recorded for the other substances. These results suggest that cytokines as well as pancreatic enzymes could contribute to the development of the lung injury and that lymphatics are potential vectors of these mediators.

Ocreotide, a synthetic analog of somatostatin, is effective in the palliative therapy of vomiting associated with intraabdominal malignancies by reducing the volume of secretions. Intravenous administration of octreotide in patients with severe necrotizing pancreatitis has been shown to significantly reduce the frequency of the adult respiratory distress syndrome, circulatory shock, and mortality.

Acute hemorrhagic pancreatitis frequently is associated with acute respiratory failure with pulmonary edema, which is generally believed to be caused by increased alveolar membrane permeability. Hypoalbuminemia seen in pancreatitis may aggravate the tendency to develop pulmonary edema.

Pancreatic pseudocysts have been complicated by large intrathoracic fluid collections. Most, but not all, chronic or persistent pleural effusions are associated with, and caused by, a fistulous tract between the pseudocyst and the pleural space. Computed tomography is helpful in detecting the fistulous communication. Subdiaphragmatic collection of fluid is common and may play a role in the accumulation of pleural effusion; ultrasonography or computed tomography is necessary to exclude such fluid collections. Other pulmonary complications of chronic pancreatitis include bibasilar atelectasis, diaphragmatic elevation caused by pleural effusion or atelectasis, and pleural calcification. Mediastinal fat necrosis is another reported complication.

GASTROINTESTINAL MALIGNANCIES

Esophageal Cancer

Gastrointestinal malignancies play a major role in respiratory diseases. This is particularly true in esophageal cancer. Metastatic pulmonary involvement by esophageal cancer occurs in 20% of patients. However, an overwhelming majority of the metastases are the result of direct spread to the tracheobronchial tree because of the anatomic proximity of the esophagus to the airways. For this reason, some routinely perform bronchoscopy before surgical resection of the esophageal cancer. An important clinical caveat is that a positive cytology from bronchoscopic secretions in patients with esophageal carcinoma does not necessarily indicate airway involvement by cancer. Rather, the abnormal cytology is often the result of aspiration of cancer cells from the esophagus into the airways.

The respiratory manifestations can vary depending on the type of esophageal lesion and the degree of pulmonary involvement. An obstructing esophageal lesion can promote retention of food proximally, which in turn can lead to cough and aspiration pneumonia. Direct extension of the cancer into the airways can result in esophagotracheobronchial fistula. This too can cause aspiration pneumonia. Hemoptysis is another symptom of this. Extrinsic compression of the tracheobronchial tree may produce respiratory difficulty. Last, surgical resection of esophageal cancer may lead to respiratory complications.

A retrospective study of 309 resections for esophageal cancer (Ivor–Lewis resection for middle thoracic lesions was done in 182 cases, and the Akiyama resection for upper thoracic lesions in 127 cases) recorded overall mortality and morbidity rates of 9% and 37%, respectively. Mortality rate was four times higher, and morbidity was twice as high, after the Akiyama procedure than after the Ivor–Lewis procedure. Respiratory complications accounted for 64% of postoperative deaths. The Akiyama procedure had more respiratory complications, especially isolated bronchopneumonia and necrosis of the trachea or of the right or left main bronchus. Respiratory complications accounted for 53% of morbidity, mainly recurrent nerve paralysis with false passages and stasis in the transplant. Another mechanism for the formation of esophagus–airway fistula is necrosis of the esophageal tissue after surgery and/or high-dose radiation therapy for cancer.

Colon Cancer

Metastatic involvement of the lungs occurred in 11.7% of 22,715 patients who underwent colectomy for carcinoma in the U.S. Veterans Administration hospital system.

Of the 2659 (11.7%) patients who had pulmonary metastases, 514 had no prior or other metastatic sites. Of the 974 patients who underwent surgery for colorectal cancer during a 20-year period in Japan, pulmonary metastasis developed in 35 (3.6%) patients. Solitary or multiple lung nodules occur more frequently than other forms of pulmonary metastasis. Thus, colorectal carcinoma should always be considered when new or undiagnosed pulmonary nodules are encountered. Obviously, a documented history of previous malignancy of the colon and rectum increases the possibility of pulmonary metastasis. Even though the therapeutic approach to nodular lung metastasis from colon cancer has varied, surgical resection of pulmonary metastases from colorectal cancer in selected patients might improve prognosis. Indeed, significantly enhanced survival can be expected in patients with only intrapulmonary metastasis documented before thoracotomy.

Several large studies of patients who underwent resection of pulmonary metastases from colorectal cancer have recorded survivals of 20% to 41% at 5 years and 20% to 30% at 10 years. In the VA study quoted above, resections of pulmonary metastases were performed in 76 (2.9%) patients; the projected 5-year survival rate was 36%, mean survival was 8 months, and 30-day mortality rate was 3%. Of the 974 patients who underwent surgery for colorectal cancer during a 20-year period in Japan, the survival rate was 53% at both 3 and 5 years after resection of pulmonary metastasis.

Predictors of longer survival include total resection of metastatic lung disease, fewer than two pulmonary metastases, and a normal prethoracotomy serum carcinoembryonic antigen (CEA) level. In one study, the estimated 5-year survival rate of patients with a normal prethoracotomy serum CEA level was 60%, as compared with 4% in patients with elevated (>5 ng/mL) serum CEA. Sex, age, site of the primary tumor (colon or rectum), disease-free interval, size of metastases, and previous resection of hepatic metastases do not appear to be statistically significant prognostic factors.

Liver Cancer

Pulmonary metastasis in liver cancer may appear as small nodular lesions or, more likely, as interstitial infiltrations. Hepatocellular carcinoma is treated by hepatic artery chemoembolization therapy. One of the therapeutic agents contains iodized oil. In a retrospective study of 336 patients with hepatocellular carcinoma who underwent transcatheter oily chemoembolization of the hepatic artery, 14 patients were administered iodized oil in excess of 20 ml. In six of these patients, pulmonary symptoms including cough, hemoptysis, and dyspnea developed 2 to 5 days after chemoembolization therapy. The chest roentgenographs demonstrated diffuse bilateral pulmonary parenchymal infiltrates; P_aO_2 on ambient air ranged from 39 to 60 mmHg. All respiratory features resolved in 10 to 28 days, and five patients survived; one patient died 10 days after the procedure as a result of respiratory arrest with a progression of pulmonary infiltrate.

Of the 154 consecutive autopsies of patients with exocrine pancreatic cancer, 13 (8%) patients were found to have pulmonary metastases without hepatic metastasis.

OTHER GASTROENTEROLOGIC DISEASES

Subphrenic Abscess

With intraabdominal problems such as a rupture or perforation of a viscus and after intraabdominal surgery, subphrenic abscess is a common complication. The incidence of involvement of either side is approximately equal, as is involvement of the anterior and posterior subphrenic spaces. Roentgenographically, evidence of subphrenic abscess appears within the lung, in the pleural space, and in the subphrenic space. Blunting of the costophrenic angle is seen in nearly 90% of patients. Retroperitoneal abscess also can cause pleural effusion.

Abdominal Surgery

Changes in respiratory function after abdominal surgery have been well documented. Intraoperative testing of lung function has shown both diminished vital capacity and diminished residual capacity. Microatelectasis, seen commonly in postoperative states, is believed to be a major cause of persistent hypoxemia. Several mechanisms have been hypothesized to explain this, including diminished production of surfactant resulting from inhalation of high oxygen concentrations or from altered ventilatory patterns; alveolar collapse from complete resorption of alveolar gas following inhalation of 100% oxygen; and peripheral airways obstruction by bronchoconstriction in response to hypocapnia.

Upper abdominal surgery is commonly followed by postoperative pulmonary complications. Laparoscopic procedures are less likely to cause respiratory complications. A case-control study of laparoscopic (37 patients) and open cholecystectomy (58 patients) observed that the incidence of postoperative pulmonary complications was 2.7% after laparoscopic cholecystectomy and 17.2% after open cholecystectomy. Increased intraabdominal pressure during laparoscopic cholecystectomy causes a significant, but fully reversible, decrease in dynamic compliance. Prospective evaluation of pre- and postoperative spirometry, arterial blood gases, and chest roentgenographs in patients undergoing laparoscopic cholecystectomy has shown that the physiological derangements that occur are sufficiently small that all but the most severely impaired patients with pulmonary disease should be able to tolerate this operation.

Pleural effusions commonly occur after abdominal procedures. The amount of fluid accumulation, however, is small. In one study, pleural fluid could be detected in 49% of 200 patients 48 to 72 hr after operation. The incidence was higher after upper abdominal surgery and in patients with atelectasis on the same side as the operation. Thoracentesis in 20 patients revealed that the fluid was an exudate in 16 of them. Almost all the effusions resolved spontaneously.

Miscellaneous Disorders

Pulmonary embolism can be triggered by the act of defecation in patients with deep vein thrombosis. One retrospective chart review estimated that defecation-induced pulmonary embolism occurred in 6.8% of all patients with the discharge diagnosis of pulmonary embolism, and, of the nine patients with this combination, six died. Increased intraabdominal pressure (from the Valsalva maneuver) during defecation, followed by a sudden decrease in the pressure (vacuum effect), is hypothesized to dislodge clots from deep veins.

Ventral hernia and other abnormalities of the abdominal wall may interfere with normal pulmonary function. Large defects such as ventral hernia may produce respiratory embarrassment and therefore require surgical correction, especially in those with chronic obstructive lung disease.

Pneumatosis coli is a rare condition characterized by multiple gas-filled cysts within the bowel wall. A review of 25 cases (mean age 59 years; 15 women) treated over a period of 30 years observed its association with chronic lung disease in 20% of patients; oxygen therapy in nine patients always relieved the symptoms.

Strongyloides stercoralis infestation is postulated to be associated with asthma. A study, however, observed that there is no statistically significant difference in the prevalence of asthma between patients with *Strongyloides stercoralis* infestation and those without parasitic infection.

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CHAPTER

59 Endocrine and Metabolic Diseases

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INTRODUCTION

The lung, under certain conditions, may secrete or release various humoral substances that can produce specific endocrine syndromes or otherwise influence the functions of many organ systems. Ectopic endocrine syndromes, most often occurring with pulmonary malignancies, are the best known and most dramatic. It is not commonly recognized in clinical practice that the respiratory system can be involved in many of the endocrinologic diseases. In addition to the well-known respiratory compensatory mechanisms in metabolic acidosis and alkalosis, the pulmonary system may become involved in both common and uncommon metabolic disorders. This chapter deals with the pulmonary problems resulting from or associated with various endocrine and metabolic diseases. Pulmonary effects of the reproductive organs are discussed in Chapter 63.

PITUITARY DISORDERS

Pneumomegaly

The lungs are involved in the general visceromegaly of acromegaly, and, if an excess of growth hormone is present in adult life, the lungs are capable of additional growth. Total lung capacity in acromegaly is significantly increased from predicted values measured by body plethysmography. In one study, large lungs, defined as those with a vital capacity greater than 120% of predicted normal, were noted in 34% of 35 patients with acromegaly. Studies of pulmonary function in ten male patients with acromegaly and one male pituitary giant revealed tremendous increases in all lung volumes. There was no evidence of airflow obstruction or air trapping; lung compliance was increased, but lung elastic recoil was normal. Despite the large lung volumes, diffusing capacity of lung for carbon monoxide (D_LCO) was normal. However, others have reported D_LCO greater than 120% of normal in 22% of patients with acromegaly. Further, physiological studies in acromegalic patients indicate that lung growth is achieved by an increased alveolar number rather than size. There is disagreement among reports as to whether abnormal lung growth occurs in women with acromegaly. In children with hypopituitarism, the mechanical properties of the lung are consistent with the height-related rather than age-related variations.

Airways Obstruction

Extrathoracic airway narrowing has been noted in acromegalic patients. Even though the pulmonary function tests are normal in most, reduced airflow as a result of upper airway involvement has been noted in 50% of patients. Pulmonary function testing and roentgenographic assessment of the larynx and trachea in a group of 26 acromegalic patients demonstrated upper airway obstruction in 23%, whereas laryngeal tomography revealed marked narrowing of the true and false vocal cords in 54%.

The cause of the airway obstruction in acromegaly is believed to be related to osseous and soft-tissue changes surrounding the upper airway, which lead to narrowing and subsequent collapse during sleep. Macroglossia and hypertrophy of hypopharyngeal tissues, regressive after surgical therapy, have also been noted. Flexible bronchoscopy in acromegalic patients has revealed collapsible upper airways at the level of the soft palate, whereas at the base of the tongue, little, if any, dynamic narrowing occurs. The clinical importance of these observations is that attention to laryngeal anatomy is important in acromegalic patients scheduled for tracheal intubation and anesthesia. Thickened laryngeal mucosa has caused stridor and progressive dyspnea in acromegalic patients.

Sleep Apnea

Obstructive sleep apnea is a recognized complication in acromegaly. In one series of 11 patients, five had obstructive sleep apnea. Contributing factors include the large tongue and thickened tissues in the upper airways of acromegalic patients. The reduced ratio of airway space to tissue mass increases the resistance to airflow. As noted above, obstruction of the airways by the enlarged tongue further exaggerates the airway narrowing. However, bronchoscopic examination in some patients with sleep apnea and acromegaly has shown that, on inspiration, the soft tissue of the posterior and lateral hypopharynx invaginates into the lateral vestibule before there is any posterior movement of the tongue; thus, enlargement of the tongue does not appear to be a primary factor in causing sleep apnea.

Central sleep apnea occurs with greater frequency in patients with acromegaly. In a study of 53 patients with acromegaly, central sleep apnea was the predominant type of apnea in 33% of patients. Biochemical evidence of increased disease activity was associated with the presence of central apnea rather than with the degree of sleep apnea. Another study of 21 patients with sleep apnea and acromegaly suggested that the central sleep apnea in acromegaly may result from defective respiratory drive caused by the elevated growth hormone level. The resolution of sleep apnea after treatment of acromegaly indicates that it may indeed resolve after a normal level of growth hormone is restored. The hypercapnic ventilatory response remains normal and unaffected by the level of growth hormone.

The results of a case-control study of 11 patients with treated acromegaly who underwent nocturnal sleep studies, cephalometry, and endocrinologic studies revealed that nocturnal breathing abnormalities were present in ten acromegalic patients. The predominant breathing abnormality was periodic breathing with symmetrically waxing and waning respiratory effort without a major body movement component. Treated acromegaly was the most powerful predictor of breathing abnormalities, independent of the other significant predictors, age, and body mass index.

Cardiopulmonary complications are responsible for significant mortality in acromegalic patients. In one series of 194 patients with acromegaly, there were 55 deaths,

and nearly half of these were from cardiopulmonary complications.

Results of the clinical investigations suggest that acromegalic patients with sleep apnea should be treated for their pituitary tumor to reduce growth hormone before consideration of surgery to enlarge or bypass the upper airway. In a report on seven patients with both sleep apnea and acromegaly, four were treated by transsphenoidal hypophysectomy alone with a resolution of sleep apnea syndrome. One underwent hypophysectomy followed by postoperative radiation therapy, which reduced his apnea, and surgery was unsuccessful in three patients.

Octreotide, a somatostatin analog, has been shown to improve indices of sleep apnea severity in patients with acromegaly-induced sleep apnea.

THYROID DISORDERS

Goiter

Respiratory symptoms can result from both extrathoracic and intrathoracic goiters (Table 1). Intrathoracic goiter may be defined as any thyroid enlargement that has its greater mass inferior to the thoracic inlet. Although extension of goiter into the thorax is seen in only 1% to 3% of thyroidectomy patients, thyroid masses constitute a considerable percentage of anterior mediastinal tumors. In most of these, there is a direct connection between the retrosternal mass and a palpable thyroid gland in the neck. The masses usually consist of nodular colloid goiters, and thyrotoxicosis occurs in some cases. Malignant changes are extremely uncommon even though a rare case of tracheal invasion by a papillary carcinoma in an intrathoracic goiter has been reported. The intrathoracic location of the goiter does not alone predispose it to undergo malignant changes. Up to 80% of the intrathoracic goiters arise from the isthmus or lower pole and extend into the anterior mediastinum in front of the trachea. The rest arise from the posterior aspect of the thyroid gland and extend into the posterior mediastinum, behind the trachea, and almost always on the right.

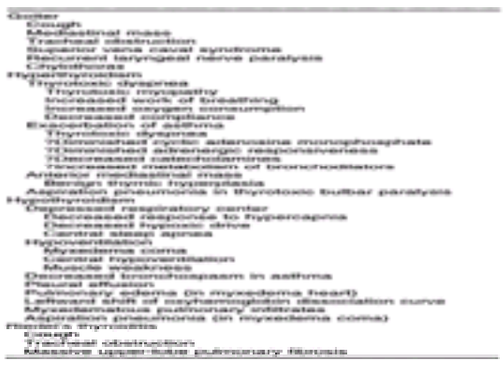

TABLE 1. *Pulmonary complications in thyroid diseases*

Of a total of 2908 goiters operated on over a 17-year period, 22 patients had severe or acute dyspnea, and four of them required immediate tracheal intubation. Chronic dyspnea without cyanosis was noted in 36 patients. In a study of 91 patients who underwent thyroidectomy, 29 had marked thyroid enlargement; 13 were unilateral (mean weight 122 g), and 16 were bilateral (mean weight 160 g). Of the 25 patients with symptoms of airway compression, 18 exhibited tracheal narrowing and/or displacement, 19 had substernal extension, and one had superior vena cava syndrome. Histologic analysis showed nodular goiter (11), adenoma (five), carcinoma (three), Graves' disease (five), and toxic multinodular goiter (five).

Most patients with intrathoracic goiters are women, and, in many, a previous history of thyroid surgery is present. From 50% to 96% of such patients have symptoms. The most common symptoms associated with intrathoracic goiters are dyspnea, stridor, dysphagia, hoarseness, coughing, wheezing, and cervical mass. A small percentage of intrathoracic goiters produce stridor and respiratory embarrassment. In a study of 273 patients with benign goiters, 33% had signs of tracheal compression, mostly from colloid goiters. Another study of 132 patients used flow–volume loops to evaluate upper airways and reported upper airway obstruction in 31% of those with goiters. The incidence of tracheoesophageal compression was higher (67%) in those with thyroiditis. Acute or subacute tracheal obstruction necessitated tracheostomy in 3% of these. Severe expiratory flow obstruction requiring surgical removal of goiter has been described. Acute life-threatening tracheal obstruction has been noted in patients with intrathoracic goiter. Histologic studies have shown that the acute problem is very likely related to the multiple foci of hemorrhage in the goiter.

Goiters may present with superior vena caval obstruction. Among 32 patients with superior vena caval syndrome, four had thyroid goiters. Recurrent laryngeal nerve paralysis is uncommon in benign goiters, having been discovered in fewer than 1% of 3279 goiters. A retrosternal goiter can compress the thoracic duct and brachiocephalic vessels and cause chylothorax. Intrathoracic goiter with hyperthyroidism, tracheal compression, superior vena cava syndrome, and Horner's syndrome has been described.

In the evaluation of chronic cough, thyroid disease usually is ignored as a cause. The close proximity of the thyroid gland to the laryngotracheal structures is occasionally responsible for distressing chronic cough. The cough usually disappears after the goiter is removed. Thyroiditis also may present with chronic cough.

Chest roentgenograms reveal a sharply defined, lobulated or smooth mass of homogeneous density displacing the trachea posteriorly and laterally if the goiter is located in the anterior mediastinum (Fig. 1). Calcification is very common (Fig. 2). The majority of intrathoracic goiters produce no symptoms and are discovered incidentally on a routine chest roentgenogram. A small percentage of patients have symptoms: inspiratory and expiratory stridor, hoarseness, and, rarely, respiratory distress. Radioisotopic studies (^{131}I thyroid scans) are diagnostic when positive, but these goiters are rarely, if ever, functioning. To evaluate the degree of tracheal obstruction caused by thyroid goiter or masses, flow–volume loops may be superior to conventional roentgenologic methods. Cine-CT and bronchoscopy provide dynamic assessment of the airway during all phases of respiration.

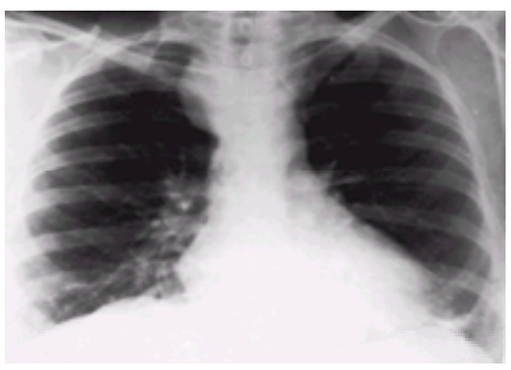

FIG. 1. Intrathoracic extension of thyroid goiter.

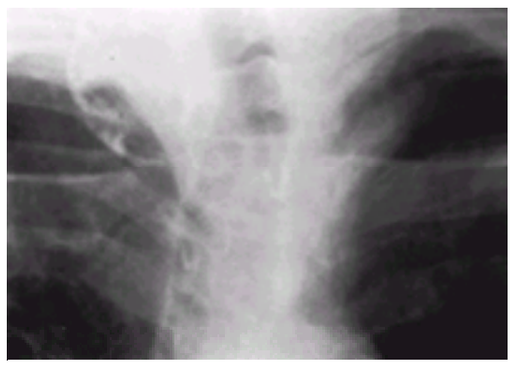

FIG. 2. Close-up view of upper middle chest demonstrating calcification within the intrathoracic goiter.

A retrospective study of 2908 goiters operated on over a 17-year period observed that the long-standing goiter did not preclude the possibility of compressive respiratory distress. Therefore, preventive removal of all large or substernal goiters should be considered. Thyroidectomy is the treatment of choice in patients with thyroid enlargement complicated by compression or displacement of the trachea. In patients who are inoperable, a bronchoscopically inserted tracheal prosthesis (stent) may provide airway patency.

Hyperthyroidism

Dyspnea at rest (thyrotoxic dyspnea) is a common symptom in patients with thyrotoxicosis. Proximal myopathy appears to play a major role because weakness of skeletal muscles has been reported in as many as 82% of thyrotoxic patients, and electromyographic evidence of myopathy is present in 93%. Significant decreases in both inspiratory and expiratory maximal pressures have been demonstrated. Reduced vital capacity and decreased compliance also may occur; however, the diffusing capacity of the lung for carbon monoxide is normal. Respiratory muscle strength is proportional to the degree of thyroid dysfunction, and the thyrotoxic myopathy is reversible with medical treatment. Thyrotoxic patients have higher ventilation than normal subjects during exercise. The increased ventilation is secondary to enhanced central drive, which is correlated to circulating thyroid hormone level, and this abnormal drive can be normalized by b-blockade. These findings suggest that the inappropriately increased ventilatory drive may be the result of enhanced adrenergic stimulation.

Dyspnea in thyrotoxic patients is also caused by decreased compliance, increased dead-space ventilation, and increased work of breathing. These are further aggravated by the greater oxygen requirement of the hypermetabolic body tissues. A study of 12 patients during hyperthyroid and euthyroid states indicated that the exercise intolerance in hyperthyroidism, despite elevated resting cardiac output, is the result of diminished work efficiency of skeletal muscles.

Hyperthyroidism occasionally may cause benign thymic hyperplasia. In most instances, the thymic enlargement is minimal and remains unnoticed. On rare occasions, thymic hyperplasia may present as an anterior mediastinal mass. The thymic enlargement associated with hyperthyroidism occasionally may produce dyspnea from extrinsic compression of the trachea, but usually the thymic hyperplasia is detected on computed tomographic scans performed for other reasons. Treatment of hyperthyroidism is followed promptly by regression of thymic hyperplasia. Bulbar palsy is a known complication of thyrotoxicosis; aspiration pneumonia and respiratory failure have been described in this setting.

Hypothyroidism

Hypothyroidism is associated with several respiratory problems because of a combination of factors, including hypoactive respiratory center, disturbed neuronal and neuromuscular transmission (hypothyroid neuropathy), respiratory muscle weakness, and changes in pulmonary alveolar capillary membranes.

Hypoventilation

Alveolar hypoventilation occurs in myxedema, and nearly 10% of patients with myxedema demonstrate diminished hypoxic drive. Myxedematous patients exhibit normal minute ventilation and oxygen and carbon dioxide tension in arterial blood. However, they demonstrate a decreased response to breathing higher concentrations of carbon dioxide. The hypoventilation is related to the depressed hypoxic ventilatory drive. This abnormal hypoventilatory response resolves with thyroid replacement therapy. A less-known mechanism is the myopathy that occurs in 30% to 40% of all hypothyroid patients. Dysfunction of diaphragm, in addition to weakness of other inspiratory and expiratory muscles, also occurs in these patients. Indeed, hypothyroidism can present as dyspnea secondary to phrenic neuropathy, which is reversible with therapy of hypothyroidism. Diminished muscle strength, as indicated by diminished maximum voluntary ventilation, has been observed in patients with hypothyroidism. Rapid resolution of hypercapnia with thyroid replacement despite persistent muscle weakness in some patients suggests that thyroid hormone deficiency is hierarchically more important than myopathy. It is also documented that the significantly diminished inspiratory and expiratory maximal strengths return to normal with thyroid replacement therapy. Prolonged hypothyroidism with gradual onset of respiratory failure and predominant hypercapnia has been described. Myxedema coma occurs usually in elderly, obese women; hypoventilation appears to be responsible for the coma in a third of the patients.

Sleep Apnea

Obstructive sleep apnea and oxygen desaturation are important complications in patients with hypothyroidism. However, in a study of 65 patients with documented obstructive sleep apnea, only two (3%) had hypothyroidism, and, among 20 patients with hypothyroidism, two showed moderate to severe obstructive sleep apnea. All hypothyroid patients in this study were snorers. Whereas obstructive sleep apnea without hypothyroidism is more common in men, obstructive sleep apnea associated with hypothyroidism is more common in women. Hypothyroidism can produce obstructive sleep apnea from the macroglossia and narrowing of the upper airways secondary to submucosal deposition of mucopolysaccharides and protein extravasation.

Central sleep apnea results from abnormalities in ventilatory control. Episodes of sleep apnea occur more frequently in hypothyroid patients who are obese than in the nonobese. The impaired respiratory drive is corrected by thyroid hormone replacement therapy. Thyroxine replacement therapy decreases apnea frequency, even without a change in body weight. Increases in the loaded respiratory effort and ventilation during thyroxine therapy have been demonstrated. Restoration of euthyroid status usually results in complete resolution of obstructive sleep apnea.

Pleural Effusion

Myxedema is an uncommon cause of pleural effusion, and the incidence of this complication in hypothyroidism is unknown. A review of the literature in 1983 revealed 13 cases, of which 11 were in women whose mean age was 52 years. The pleural effusions frequently were associated with ascites. Congestive heart failure also was noted in many patients. Usually, myxedematous patients with pleural effusion have a concomitant pericardial effusion. The pleural effusion associated with pericardial effusion is a transudate (Fig. 3). A report in 1990 reviewed the record of 60 patients with hypothyroidism and noted pleural effusion in 15 (25%), but the effusions in the majority of patients were caused by other diseases or hypothyroidism-related nonpulmonary complications. When this study was combined with another group of 13 for a total of 28 patients with pleural effusions associated with hypothyroidism, the study in 1990 found that only five patients (18%) had pleural effusions that could be ascribed to hypothyroidism; pleural fluid protein levels in four patients varied from 1.1 to 3.2 g/dl. Usually, effusions are evident only on roentgenographic examination, but rarely is one sufficiently large to cause symptoms. The observation that the pleural effusion disappears after treatment of myxedema supports an etiologic relationship with myxedema. Increased pulmonary or pleural capillary permeability may play a role in the collection of fluid in the pleural space.

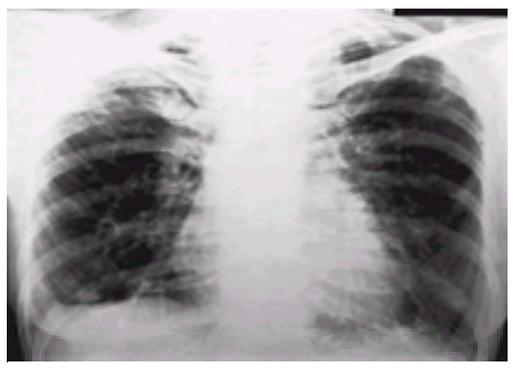

FIG. 3. Right-sided pleural effusion and pulmonary edema in a patient with severe myxedema. These findings resolved with thyroid replacement therapy.

Other Complications

A decrease in vital capacity in the absence of heart failure also has been noted in myxedema. Hypothyroidism is a good example of the leftward shift of the oxyhemoglobin dissociation curve; hence, the tissue supply of oxygen is worse than is indicated by hypoxemia alone. Soft, patchy, nodular infiltrates (myxedematous lesions) are reported to occur in myxedema. Roentgenographic clearing of these infiltrates has been reported following replacement therapy with thyroid hormone. The pathogenesis of these lesions is unknown, but studies have shown that thyroidectomized rats develop atelectasis related to decreased surfactant, and thyroxine therapy stimulates surfactant synthesis. Thyroxine is reported to promote lung maturation in fetal rabbit lungs.

Coexistence of autoimmune hypothyroidism with pulmonary hemosiderosis has been described in a patient. Pulmonary hemosiderosis has also been described in four patients with thyrotoxicosis.

Asthma and the Thyroid Gland

The relationship between thyroid function and bronchial asthma has very interesting clinical implications. However, the coexistence of asthma and thyroid diseases has been reported only sporadically. A retrospective cohort mortality study of 3696 women treated for thyrotoxicosis showed that asthma was the underlying cause of death in seven patients, compared with 2.6 expected deaths in the normal population. Another retrospective study of 1107 patients found only 12 with coexistent hypothyroidism and asthma. Treatment of hypothyroidism in three of these patients led to the worsening of their asthma. A similar experience has been described following administration of triiodothyronine for hypothyroidism. In contrast, some patients with coexistent intractable asthma and hyperthyroidism have exhibited prompt and striking improvement in asthma when their hyperthyroidism was treated. In a study, however, thyrotoxicosis that was induced by administering triiodothyronine (T_3) to subjects with mild asthma had no effect on lung function, airway responsiveness, or exercise capacity. One proposed mechanism for the worsening asthma in hyper-thyroidism is increased airways reactivity. Reduced b-adrenergic responsiveness and reduced b receptors (down-regulation of b receptors) in asthma may contribute to the worsening of bronchospasm. However, the positive therapeutic response to treatment of hyperthyroidism in asthmatic patients is not always uniform.

Nonasthmatic hyperthyroid patients exhibit an entirely opposite airway response. There appears to be an inverse relationship between the level of thyroid function and the b-adrenergic receptor responsiveness. Acute hypothyroidism has been reported to increase nonspecific bronchial reactivity in nonasthmatic subjects. However, a report on 11 hyperthyroid nonasthmatic patients concluded that hyperthyroidism actually reduced the severity of carbachol-induced changes in airways reactivity as measured by airway specific conductance (sG_{aw}).

It should be recognized that patients with hyperthyroidism may not demonstrate the therapeutic benefits of bronchodilator therapy. This is because of the accelerated metabolism of bronchodilators. b-Adrenergic blocking drugs such as propranolol used to treat thyrotoxicosis may exacerbate asthma. An asthmatic who develops hyperthyroidism should be closely monitored for deterioration of asthma. Similarly, even slow and cautious restoration of the euthyroid state in hypothyroid patients may lead to increasing problems with asthma.

Iodide-induced thyrotoxicosis is occasionally encountered after long-term administration of iodine or iodide-containing compounds to patients with preexisting thyroid disorders, particularly goiter. Interestingly, the saturated solution of potassium iodide (SSKI) was used in the past as an expectorant in asthmatic patients. Its use, in some patients, resulted in hyperthyroidism, which in turn aggravated the asthmatic condition. Currently, many clinicians use iodinated glycerol (Organidin) as a mucolytic agent in the treatment of chronic obstructive pulmonary disease; thyrotoxicosis induced by iodinated glycerol has been described.

Riedel's Thyroiditis

Riedel's thyroiditis is a rare disease characterized by extensive dense fibrosis of the thyroid gland, often extending into the strap muscles and adjacent structures in the neck. The condition is rare, 20 cases being discovered among 42,000 patients seen at a tertiary center. Respiratory symptoms result from tracheal compression. Massive fibrotic process has been described in both upper lobes of the lungs. Severe upper airway obstruction has been described in a patient with Hashimoto's thyroiditis. Lymphocytic interstitial pneumonitis has been described in four patients with autoimmune thyroiditis. The association of idiopathic pulmonary hemosiderosis and autoimmune thyroiditis has been noted.

Thyroid Cancer

Pulmonary involvement in thyroid carcinoma may be related to direct or contiguous spread with intraluminal extension into the airway, extrinsic compression of the trachea, or metastatic nodules in the lungs. The latter can be solitary or multiple. Tracheal obstruction can be life-threatening and require immediate bronchoscopically guided stent therapy or tracheostomy. Paralysis of the recurrent laryngeal nerve will increase the risk of aspiration pneumonia.

Pulmonary metastases are not uncommon in children and young adults with differentiated thyroid cancer. Metastases in the lungs may be overlooked unless near-total thyroidectomy is followed by total-body radioiodine scan in these patients. In a study of 209 patients younger than 25 years of age who were treated for thyroid cancer, 19 (9%) had pulmonary metastases at presentation, and all 19 had regional lymphadenopathy at the time of diagnosis. This study observed that the lung metastases almost always concentrate radioiodine diffusely and may be associated with a normal chest roentgenograph in almost half of the patients. Nevertheless, it is important to note that radioiodine uptake in the lung could also represent an uptake by unrelated pulmonary disease or by the breasts, or external contamination.

PARATHYROID DISORDERS

Parathyroid tumors rarely present as anterior mediastinal masses. They usually are small and encapsulated growths in the upper mediastinum. They may become large enough to widen the mediastinum, usually unilaterally. Mediastinal parathyroid tissue is identified in approximately 11% of patients who undergo surgical exploration and resection as therapy for primary hyperparathyroidism. In a study of 573 patients who underwent surgical exploration for therapy of hypercalcemia, mediastinal parathyroid glands numbered 68, of which 55 (81%) were enlarged, and 13 were of normal size. Preoperative levels of serum calcium have been observed to be higher in patients with mediastinal parathyroid tissue than in patients with hyperactive parathyroid glands in the neck. In patients who are suspected to have primary hyperparathyroidism, approximately 60% of the mediastinal glands are found on first exploration of the neck, and the rest (35%) usually require more than one surgical exploratory procedure for the detection and resection of the parathyroid tissue.

Ectopic parathyroid glands in the thoracic cavity have been detected with great accuracy with the use of sestamibi scintigraphy, whereas single-photon-emission CT (SPECT) has been helpful in distinguishing the adenomas located in the aortopulmonary recess from more common adenomas in the anterior mediastinum. Both CT and MR imaging studies also can enable this distinction.

Because most of these tumors are functioning, patients present with clinical hyperparathyroidism, which, along with hypercalcemic crises, has been reported to produce pulmonary edema. This, however, is uncommon. Hypercalcemic states also produce metastatic calcification or calcinosis (or calciphylaxis) of visceral organs. In the lungs, calcium deposits are found in bronchi, alveoli, and venous channels. A review of more than 7000 autopsies disclosed 13 cases of metastatic pulmonary calcification, and chronic renal disease and parathyroid abnormalities accounted for seven of them; the remainder were associated with malignancies. Roentgenograms in patients with metastatic pulmonary calcification reveal calcification of the bronchi and an amorphous, diffuse, and finely dispersed calcification of the lungs radiating from the hilar regions. Although primary hyperparathyroidism, malignancies, and chronic renal failure are the more common causes of the hypercalcemic state, metastatic lung calcification is seen also in recipients of renal and liver transplants and in those with hypervitaminosis D, sarcoidosis, and milk alkali syndrome as well as following intravenous calcium infusion.

In a study of 49 patients with persistent primary hyperparathyroidism caused by mediastinal parathyroid adenoma, angiographic ablation by injections of large doses of contrast material into the feeding artery was successful in long-term control of persistent primary hyperparathyroidism in 17 of 27 patients (63%); the unsuccessful cases were treated by surgical resection by median sternotomy.

Parathyroid carcinoma produces nodular metastasis in the lungs. Resection of pulmonary metastases in six patients with such lesions demonstrated that postoperative serum calcium level returned to normal after each thoracotomy in three patients who were alive and well 3, 8, and 12 years after the first thoracotomy, but the hypercalcemia persisted in the other three patients.

ADRENAL DISORDERS AND CORTICOSTEROIDS

Cushing's syndrome and long-term corticosteroid therapy can result in abnormal accumulation of fat in the upper mediastinum (mediastinal lipomatosis) and both pleuropericardial angles. Roentgenograms reveal a smooth, symmetric widening of the upper mediastinum (Fig. 4A) extending from the thoracic inlet to both hilar areas. Computed tomography (Fig. 4B) is diagnostic because of its ability to demonstrate the lipid density in the mediastinum.

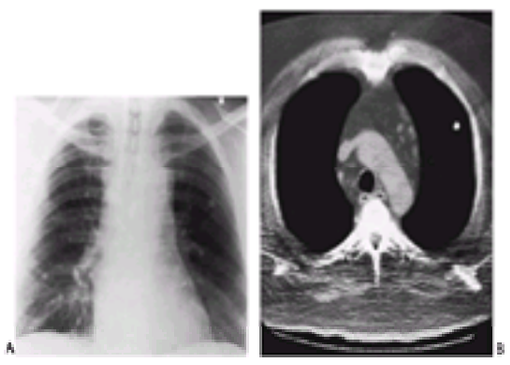

FIG. 4. (A) Cushing's syndrome with mediastinal widening. **(B)** Computed tomography in mediastinal lipomatosis reveals typical lipid density in the anterior mediastinum.

Cushing's syndrome can be the initial clinical presentation in patients with bronchial carcinoid tumors. In a study of 15 consecutive patients with Cushing's syndrome, all of whom were subsequently found to have bronchial carcinoid tumors, biochemical studies showed marked elevations of circulating corticotropin with a mean serum value of 156 ± 58 pmol/liter (normal 4 to 22 pmol/liter), hypokalemia in six patients, and glucocorticoid response to either high-dose dexamethasone or metyrapone in six of 13. These carcinoid tumors were frequently radiographically occult, with ten of 15 patients initially having normal chest roentgenographs. Computed tomography was successful in locating the lesions. Surgery resulted in complete remission in ten patients and partial remission in two; three patients continued to have symptomatic glucocorticoid excess caused by metastatic disease.

Long-term corticosteroid therapy suppresses some of the immune defense mechanisms of the body and predisposes the host to a number of unusual and opportunistic infections. Tuberculosis occurs with greater frequency in patients receiving long-term corticosteroid therapy. *Pneumocystis carinii* pneumonia is a serious complication in patients on significant doses of corticosteroid therapy for long periods. Endogenous Cushing's syndrome has been complicated by cryptococcosis. This syndrome, secondary to a hormonally active thymic carcinoid, has been noted to exist with *Pneumocystis carinii* infection. Patients with endogenous Cushing's syndrome who develop pulmonary infiltrates should be carefully evaluated to exclude the possibility of opportunistic infections.

Aerosolized corticosteroid therapy, particularly the megadose, in asthmatic patients has been of concern not only with regard to its increasing the risk of oropharyngeal candidiasis but also its ability to suppress adrenal function. In one report, it was noted that prolonged administration of 200 µg of inhaled budesonide daily to young children with severe asthma did not impair growth or pituitary–adrenal function.

Pheochromocytoma associated with a catecholamine-induced cardiomyopathy has led to the development of recurrent bilateral and unilateral pulmonary edema; special radionuclide studies indicated that oversecreted catecholamines influenced both the heart and lungs. Acute respiratory distress syndrome (ARDS) has been observed in a patient with pheochromocytoma. A surge of catecholamines from pheochromocytoma may provoke pulmonary edema in a manner similar to that in neurogenic pulmonary edema. Hemoptysis during paroxysms of hypertension caused by pheochromocytoma, and cured by surgical resection of the tumor, has been reported.

Paragangliomas (chemodectomas) are tumors of the extraadrenal paraganglion system. The most common paragangliomas are carotid body chemodectomas, the glomus jugulare tumors, and globus tympanicum. Para-ganglioma of the mediastinum is an indolent and slow-growing tumor. A review of the world literature noted 79 cases of mediastinal paraganglioma. The tumors were locally invasive and had a high local recurrence rate (56%) with a true metastatic capacity in 27%; the overall survival was 62% with a mean survival time of 98 ± 12 months. A retrospective study of 16 cases (ten men and six women; mean age 43 years) of mediastinal paragangliomas observed that 13 tumors were located in the posterior mediastinum, and three tumors were located in the anterior mediastinum. Some, however, have reported that these neoplasms usually are located in the anterior mediastinum (Fig. 5). In the thorax, these are usually located above the aortic arch near the subclavian arteries. Female preponderance, an average age at the time of diagnosis of 49 years, and an average tumor size of 7.5 cm are reported from a review of 40 patients. Nearly 50% of these patients are asymptomatic; the reported symptoms include hoarseness, cough, dysphagia, and chest pain. Distant metastasis were noted in 23% of the 40 cases reported in 1979. Surgical resection is recommended.

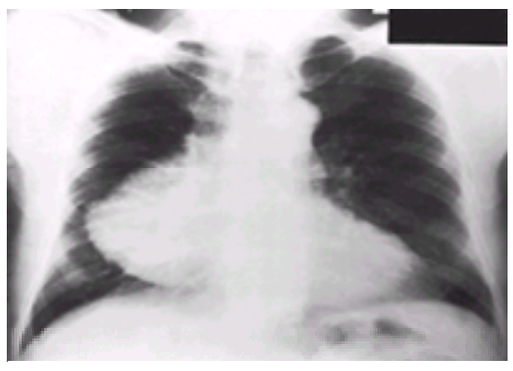

FIG. 5. Paraganglioma located in the lower anterior mediastinum.

Carney's triad is a syndrome of pulmonary chondroma, multicentric gastric epithelioid leiomyosarcoma, and extraadrenal paraganglioma. This triad has been described in over 35 patients since 1977. Several clinically important features of this unusual syndrome include the multicentricity of both the paragangliomas and the epithelioid leiomyosarcomas, the often indolent progression of metastatic leiomyosarcoma, the potential for late recurrences, and the importance of distinguishing intraadrenal from periadrenal catecholamine-producing tumors (paragangliomas). The majority of patients are women, and the average age has been 16.5 years. The most common clinical features are hematemesis and anemia as a result of the gastric lesion. Hypertension is the next most common finding. Multiple pulmonary tumors (two-thirds were uncalcified) and mediastinal widening are seen in the chest roentgenographs (Fig. 6). None of the reported patients had symptoms from the pulmonary lesions. If a new catecholamine-producing tumor is suspected, urine biochemical assays and computed tomography of the chest and abdomen are the first-choice localization procedures.

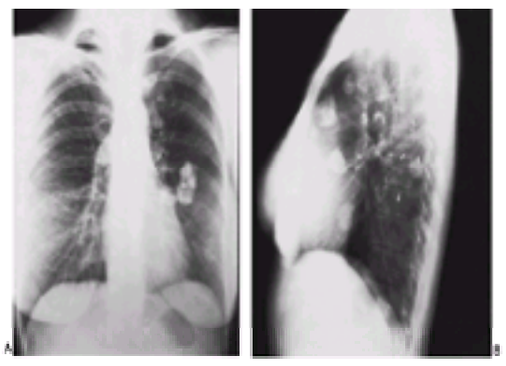

FIG. 6. Multiple pulmonary chondromas in the triad of multicentric gastric epithelioid leiomyosarcoma, functioning extraadrenal paraganglioma, and pulmonary chondroma.

The uncommon concurrence of duodenal epithelioid stromal sarcoma, pulmonary chondromatous hamartoma, and pancreatic islet cell tumor in a patient is described as a variant or an analog of Carney's triad. Gastric leiomyosarcoma and extraadrenal paraganglioma have been described in a 7-year-old child.

Adrenal carcinoma is rare. A review of the records of 24 patients with adrenal cortical carcinoma and pulmonary metastases over a 14-year period revealed that ten patients underwent pulmonary resection. The 5-year survival of seven patients in the surgical group was significantly longer than those not resected, with no one having survived for more than 3 years (median survival 11 months).

METABOLIC DISORDERS

Diabetes Mellitus

Diabetes mellitus is a common disease that often is complicated by the involvement of other “target” organs such as the eye, kidney, and peripheral nervous system. Based on the pathophysiological abnormalities observed in various studies, the lung also has been considered a “target” organ. The pulmonary pathologic changes such as thickened alveolar epithelial and pulmonary capillary basal laminae are considered to be secondary to pulmonary microangiopathy, akin to the diabetic vasculopathy encountered in retinal, renal, and other systemic vasculatures. Pulmonary complications may manifest clinically in different ways. Table 2 lists the reported complications in diabetes mellitus.

Reduced elastic lung recoil
Reduced diffusing capacity for carbon monoxide
Viral and bacterial infections
Tuberculosis
Mucormycosis
Pneumomediastinum
Pneumothorax
Acute pleuritic pain (in ketoacidosis)
Pulmonary fibrosis
Pulmonary edema (in ketoacidosis)
Mucous plugging of major airways (in ketoacidosis)
Central hypoventilation (in autonomic neuropathy)
Sleep apnea (with autonomic neuropathy)
Aspiration pneumonia (in diabetic gastroparesis)
Pulmonary xanthogranulomatosis
Respiratory alkalosis (in ketoacidosis)
Increased endogenous production of carbon dioxide

TABLE 2. *Pulmonary complications in diabetes mellitus*

Pulmonary Infections

Diabetes mellitus is often identified as an independent risk factor for developing lower respiratory tract infections. Carrier rates for aerobic gram-negative rods in pharyngeal secretions have been found to be higher for diabetics and alcoholics. Bacterial pneumonias are by far the most common type of respiratory infections. The causative agents include gram-negative organisms (*Escherichia coli, Klebsiella pneumoniae*) and gram-positive bacteria (*Staphylococcus aureus*). Infections caused by *Streptococcus pneumoniae, Legionella,* and influenza may be associated with increased morbidity and mortality. Nonbacterial lung infections (mycobacteria and *Mucor*) occur with an increased frequency.

Diabetics are particularly prone to develop tuberculosis, frequently to an advanced stage. Among 106 patients in whom both diseases occurred, the diabetes came first in 48, the tuberculosis was first in 40, and the two were diagnosed simultaneously in 18. The increased incidence of tuberculosis in patients with diabetes mellitus is paralleled by the incidence of diabetes in those with tuberculosis. Tuberculous infection of lungs in diabetics may present with infiltrates in any lobe (Fig. 7) rather than the traditional posterior-apical segments of upper lobes. A study of 20 patients with both pulmonary tuberculosis and diabetes mellitus showed lower-lobe involvement in 10% of patients.

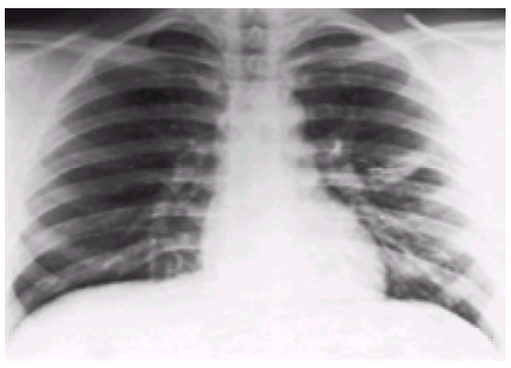

FIG. 7. Localized lesion secondary to *Mycobacterium tuberculosis* in a young patient with type I diabetes mellitus. The pulmonary lesion is located in the superior segment of the left lower lobe.

Diabetics also have been found to be more susceptible to mucormycosis. This is particularly true of patients with poorly controlled diabetes mellitus who have multiple complications (Fig. 8). In a literature review of 255 patients with pulmonary mucormycosis, diabetes mellitus was noted in 32%. Other associated medical conditions included leukemia or lymphoma, chronic renal failure, history of organ transplantation, or a known solid tumor. The overall mortality was 80%; the most common causes of death were fungal sepsis (42%), respiratory insufficiency (27%), and hemoptysis (13%).

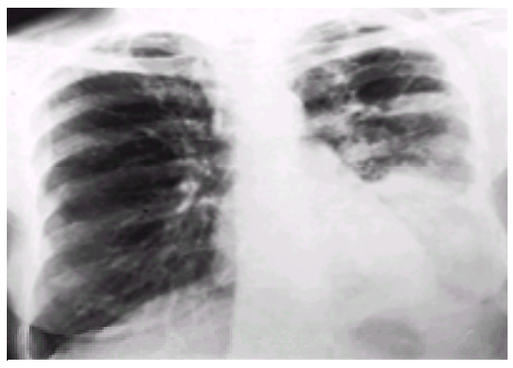

FIG. 8. Pneumonia of left lower lobe secondary to *Mucor* species in a patient with poorly controlled diabetes mellitus.

Diabetics with pulmonary mucormycosis have a striking tendency to develop lesions in major airways. Because of the propensity of the *Mucor* species to invade vascular structures, pulmonary infarction or massive hemoptysis can occur. Diagnostic features of major airways involvement include hoarseness, gross hemoptysis, or mediastinal widening on chest roentgenograms. Sudden, massive hemoptysis is a common fatal complication of endobronchial mucormycosis. The more usual roentgenographic findings of pulmonary zygomycosis represent a spectrum that comprises a normal chest roentgenograph, a lung abscess, subacute or chronic pneumonia that often evolves into a lung abscess, and rapidly progressive fatal pneumonia.

Pulmonary Dysfunction

Pulmonary dysfunction in diabetics is reported to be related to the severity of diabetes mellitus. A study of 284 diabetics reported that, on average, forced vital capacity (FVC) and FEV_1 were reduced by 334 ml and 239 ml, respectively, in insulin-treated diabetics and by 184 ml and 117 ml, respectively, in diabetics treated with oral hypoglycemic agents. An earlier study of 31,691 patients with diabetes mellitus observed pulmonary emphysema in 4.2%, asthma in 0.9%, and pulmonary fibrosis in 0.8%. Although the incidence of asthma and emphysema among diabetics was the same as in the total hospital population, the incidence of fibrosis was reported to be moderately elevated. Pulmonary function tests of 36 patients with insulin-dependent diabetes mellitus were compared with those of 40 nondiabetic controls, and the inspiratory vital capacity in the former group was found to be significantly reduced. The authors concluded that this abnormality may have been caused partly by the reduced capacity of the inspiratory muscles.

The significant lung function abnormalities have included reduced lung volumes in young (aged less than 25 years) insulin-dependent diabetic subjects, reduced pulmonary elastic recoil in both young and adult (aged greater than 25 years) diabetic subjects, and impaired diffusion caused by a reduced pulmonary capillary blood volume in the adult group. Nonenzymatic glycosylation-induced alteration of lung connective tissue is reported to be the most likely pathogenetic mechanism underlying mechanical pulmonary dysfunction in diabetic subjects, and the most tenable explanation for impaired diffusion is the pulmonary microangiopathy. Diminished total lung capacity in insulin-dependent diabetics has been ascribed to limited expansion of the ribs. The clearance of inhaled ^{99m}Tc-diethyltriaminepentaacetic acid (DTPA) aerosol from the lungs has been used to show that diabetic patients, particularly those with other diabetic complications, develop decreased epithelial permeability, which leads to pulmonary dysfunction. Other studies, however, have shown that insulin-dependent diabetes mellitus does not affect pulmonary function.

Physiological studies in juvenile diabetics have shown that the elastic lung recoil is significantly less than in normal individuals, and total lung capacity also is diminished. It is postulated that the disordered lung mechanics are manifestations of elastin and collagen abnormalities. In a study involving 40 adult insulin-dependent diabetics, all lifelong nonsmokers without evidence of lung disease and compared to a matched group of healthy controls, detailed pulmonary function tests demonstrated that the diabetics had mild abnormalities of lung elastic recoil and D_LCO as well as a reduction in pulmonary capillary blood volume. The degree of lung dysfunction was related directly to the duration of insulin-dependent diabetes mellitus.

Histopathologic studies of streptozotocin-induced diabetes in rats have shown ultrastructural alterations in the granular pneumocytes in the alveolar septum, nonciliated bronchiolar epithelial (Clara) cells, and collagen and elastin in the alveolar wall. Postmortem studies of diabetics also have documented thickening of epithelial and capillary basal laminae of alveoli, centrilobular emphysema, and diabetic microangiopathy in the capillaries of alveolar septa and the alveolar and pleural arterioles.

Diabetics with autonomic neuropathy have a higher threshold for the cough response to nebulized citric acid, thereby suggesting that vagal innervation of the bronchial tree is damaged by diabetic autonomic neuropathy. This is further supported by the observation that bronchoconstrictive response to cold air and methacholine is impaired in patients with diabetic autonomic neuropathy. Further studies in patients with diabetic autonomic neuropathy have demonstrated reduction in parasympathetic bronchomotor tone, resulting in increased basal airway caliber. Even though diaphragmatic dysfunction is reported to be common in type 1 diabetes, the impaired diaphragm function is not caused by phrenic neuropathy.

Physiological studies in insulin-dependent diabetic patients (type I diabetes) have shown that the endogenous opioid system does not respond to stress caused by breathing against fatiguing inspiratory resistive loads. Further, whereas resistive-loaded breathing caused a further increase in plasma b-endorphin concentration in the control group, absolutely no increase was found in the diabetic patients.

What are the clinical implications of these observations? Clinical experience suggests that the pulmonary parenchymal defects and pulmonary dysfunctions in insulin-dependent diabetics are insufficient to cause significant respiratory embarrassment in the vast majority of patients with diabetes mellitus. Despite the overwhelming information published in the medical literature on the subject, as is evident from the discussions here, clinically significant lung disease solely on the basis of diabetes-mellitus-induced pulmonary dysfunction is seldom encountered in clinical practice. Despite the extensive studies on pulmonary dysfunction in patients with diabetes mellitus, routine pulmonary function testing is not indicated in the absence of pulmonary symptoms or a history of smoking.

Pulmonary Edema

Pulmonary edema has been associated with diabetic ketoacidosis. It has been suggested that altered pulmonary capillary permeability is the cause of the extravascular leakage of fluids. The patient with diabetic ketoacidosis usually is administered large quantities of intravenous crystalloids over a short period. These solutions elevate the hydrostatic pressure and diminish oncotic pressure, thereby facilitating the development of pulmonary edema. Pulmonary vascular diabetic angiopathy may predispose some diabetics to pulmonary edema. Additionally, endogenous fluid shifts due to severe hyperglycemia may contribute to pulmonary edema. Recurrent episodes of acute alveolar and interstitial pulmonary edema have been noted on chest roentgenograms in anephric diabetics during periods of severe hyperglycemia. Clinical and chest roentgenographic resolution occurs immediately after insulin therapy and restoration of normoglycemia.

Disordered Sleep

Sleep-related breathing abnormalities occur with greater frequency in diabetic patients with autonomic neuropathy. The ventilatory and heart rate response to hypoxia are impaired in diabetics, whereas the ventilatory response to hypercapnia is well preserved. Although a diminished hypercapnic ventilatory response to progesterone therapy is described in a patient with diabetic autonomic neuropathy, detailed studies of the effect of this neuropathy on the respiratory system have shown that there is no difference in the ventilatory responses to hypoxemia and hypercapnia in patients with and without autonomic neuropathy. Diabetic microangiopathy of muscles, resulting in a myopathic process and muscle weakness and central hypoventilation, may cause hypercapnia and respiratory failure. Another explanation for the diminished ventilatory response to hypoxia is that medullary depression of ventilation by hypoxia is reported to be greater in diabetic patients than in control subjects. Others have reported normal breathing patterns in diabetics with severe autonomic neuropathy. A relationship has been shown between neuropathy and sleep-related breathing abnormalities in type I insulin-dependent diabetics.

Other Complications

Oxygen tension in arterial blood is usually high in patients with diabetic ketoacidosis. This is because of hyperventilation secondary to acidosis and the increased glucose load. Additionally, the production of endogenous carbon dioxide from the metabolic acidosis causes a higher respiratory quotient and thus a higher-than-expected increase in oxygen tension in arterial blood. Rarely, hypokalemic hypoventilation may complicate severe diabetic ketoacidosis.

Pleural effusion is reported to occur more commonly in diabetic patients, particularly in those with left ventricular failure. In a study of 40 patients with similar degrees of left ventricular dysfunction, pleural effusions were more common in diabetic patients, and, indeed, four of five diabetic patients who had persistent pleural effusions had no evidence of either cardiomegaly or congestive cardiac failure. Although several mechanisms, including those discussed above, were postulated to be responsible,

the exact mechanism remains unclear.

Pneumomediastinum has been reported in several cases of diabetic ketoacidosis. The cause remains obscure, although ketoacidosis is believed to change the pressure gradient within the lungs by the hyperpnea induced by acidosis, by severe vomiting, or by a combination of both. The prognosis is excellent, and the pneumomediastinum regresses promptly after correction of the ketoacidosis.

Mucous plugging of major airways has been described as a specific complication of diabetic ketoacidosis. Lethargy, altered vagal tone, and autonomic neuropathy are proposed as contributing factors responsible for occult mucous plugging. Reduced airway vagal tone and diminished cold responsiveness have been shown in nonsmoking, nonasthmatic diabetic patients with autonomic neuropathy.

Aspiration pneumonia secondary to recurrent vomiting caused by unsuspected gastroparesis has been observed in diabetic patients. This is of greater importance during anesthetic procedures.

Xanthogranulomatosis has been demonstrated in the perivascular spaces in lungs in 6% of diabetic patients (versus 2% in nondiabetics), but the effect of this abnormality on pulmonary function is unknown.

Acute pulmonary edema was observed in patients in whom hypoglycemic coma was induced as therapy (insulin shock therapy) for schizophrenia in the 1930s. In one series of seven patients treated with insulin shock, acute pulmonary edema ranked second to irreversible coma as the cause of death. Most of the patients were otherwise healthy and were younger than 35 years. Animal studies support the hypothesis that the pulmonary edema seen in hypoglycemic coma results from neurogenic causes.

Pulmonary maturation in the fetus has been linked to the level of maternal glucose control in diabetic pregnancies. Amniocentesis in pregnant diabetic women has shown that adequate glucose control may lower the risk of fetal pulmonary immaturity to that seen in the nondiabetic population.

Obesity

Pulmonary Dysfunction

Obesity, even when mild, is reported to significantly impair lung function. The most persistent pulmonary function abnormalities in obesity are decreased expiratory reserve volume and functional residual capacity (FRC). Among 144 men with mild obesity (mean weight 81.1 ± 9.0 kg), 63% exhibited diminished functional residual capacity (FRC), expiratory reserve volume, and arterial oxygen tension compared to 28 subjects of normal weight. Spirometric evaluation of lung functions in morbidly obese patients before severe weight loss programs has shown no significant abnormalities and no significant improvement in their lung functions after considerable weight loss. Several studies have reported decreases in forced expiratory flow in midcycle ($FEF_{25–75}$) and mildly decreased arterial oxygen tension. A study of 63 obese men without overt obstructive lung disease detected a subgroup with normal flow rates but significantly diminished maximum voluntary ventilation (MVV). These findings have been interpreted to show disease of the small airways.

Several studies in obese subjects have shown diminished tidal volume, vital capacity, and functional residual capacity but normal diffusing capacity. Another study has shown an increase in D_LCO in patients with weight-to-height ratios exceeding 0.6. It is postulated that the increase in D_LCO is the result of increased pulmonary blood volume, which accompanies the elevated cardiac output noted in obesity. These findings suggest that the diminished D_LCO in morbidly obese subjects indicates intrinsic pulmonary pathology. Abnormal ventilation–perfusion ratios have been demonstrated in the lung bases of obese patients with hypoxemia and low or normal carbon dioxide tension in arterial blood.

Altered respiratory function in obesity may result from a combination of mechanical impedance to breathing exerted by thoracic and abdominal fat and a ventilation–perfusion mismatch. Increased work of breathing and decreased efficiency of the respiratory system are also seen. Studies suggest greater diaphragmatic efficiency in the upright than in the supine position in a majority of obese subjects, a reversal of the normal response. Diaphragmatic overstretching may be an important mechanism in the development of hypoventilation in the morbidly obese. The overall incidence of postoperative pulmonary complications in a large group of obese patients undergoing abdominal surgery (ileojejunal bypass) was 25%.

Hypoventilation

The hypoventilation seen in obese patients with both hypoxemia and hypercapnia may result from one or more of the following proposed mechanisms: increased fat deposits around the chest wall and resultant increase in the work of breathing; extremely low ventilation–perfusion ratio at lung bases, promoted by lower expiratory reserve volume; upper airways obstruction; or a disturbance in the respiratory center itself, making it insensitive to carbon dioxide. Considerable weight loss may reverse the symptoms in many cases. However, in some instances, low arterial oxygen tension may persist, whereas in others there has been a significant reduction in the number of episodes of sleep-disordered breathing and nocturnal desaturation, lending support to the concept that obesity is the cause and not an effect of the sleep apnea syndrome in these patients.

Detailed discussions of sleep-disordered breathing in obese subjects can be found in Chapter 44.

Malnutrition

Clinically significant malnutrition is a common complication of long-term mechanical ventilation and in patients with severe emphysematous obstructive lung disease. These forms of malnutrition, as well as the malnutrition caused by starvation, affect the respiratory system. Prolonged starvation significantly alters the structure and function of the lung. Morphometric and ultrastructural changes similar to those observed in elastase-induced emphysema have been noted in hamsters subjected to starvation. Pulmonary defense mechanisms, as do those of other organ systems, depend on optimal nutritional status. Diminished respiratory clearance of microbial organisms, decreased number of pulmonary alveolar macrophages, and marked decreases in secretory IgA and other immunoglobulins (as a result of hypoproteinemia) may predispose these patients to infections caused by various organisms. Malnourished subjects also demonstrate reduced ventilatory drive from the effects of nutritional depletion on both the central nervous system and respiratory muscles. Diaphragmatic muscle mass is reduced in malnourished subjects.

The effects of starvation and renutrition on pulmonary function have been studies in patients with anorexia nervosa. In a study of 15 patients with anorexia nervosa, spirometry, lung volumes, arterial blood gases, and diaphragmatic functions were recorded on admission and days 7, 30, and 45. The mean body weight on admission was 37 ± 4.7 kg (63% ideal body weight) and increased significantly to 43 ± 4.6 kg by day 45. The VC and FEV_1 increased significantly by day 30; lung volumes were unchanged. The most significant change was in the diaphragmatic contractility, which was severely depressed initially but significantly increased with nutritional support by day 30. These results document earlier assertions that diaphragmatic function is markedly impaired in severely malnourished patients, even in the absence of lung disease, and that renutrition partially reverses the weakness.

Rachitic lung demonstrates roentgenographic abnormalities as lobar or segmental atelectasis, compression atelectasis, and interstitial pneumonitis. These changes are attributed to hypoventilation in a distorted, small chest along with chronic and recurrent pulmonary infections. Hypoventilatory failure has been described in these patients. In a study of a large group of children with vitamin A deficiency, the incidence of respiratory disease was twice that of normal children, and the risk of respiratory disease was more closely associated with vitamin A status than with general nutritional status.

Gaucher's Disease

Gaucher's disease is an autosomal recessive error of lipoprotein metabolism caused by a deficiency of glucocerebrosidase, the enzyme that catalyzes glucocerebroside metabolism. It is seen predominantly in Jewish women and occurs in a neurologic form, a visceral form, and an osseous form. Accumulation of glucocerebroside in cells of the reticuloendothelial system changes them to Gaucher's cells, which accumulate both there and in the lungs and other organs. Whereas pulmonary involvement and symptoms are common in the infantile form of Gaucher's disease, it is distinctly uncommon in the adult form (type I disease).

Pulmonary manifestations consist of interstitial infiltration of Gaucher's cells in the peribronchial, perivascular, and septal regions. Pulmonary hypertension has resulted from pulmonary capillary plugging by Gaucher's cells. Roentgenograms of the lung reveal a diffuse reticulonodular or miliary pattern. Microscopic examination indicates impressive consolidation of lung parenchyma by Gaucher's cells. Elevated levels of serum angiotensin-converting enzyme have been noted in this disease.

Of the 95 patients with type I Gaucher's disease studied in Israel, 68% had pulmonary function abnormalities; TLC was reduced in 22%, RV/TLC was elevated in 18%, and FEV_1 was reduced in one-third of the patients. Reduced FRC and transfer coefficient for carbon monoxide (KCO) were found in 45% and in 42% of the patients,

respectively. Male patients had a higher incidence of reduced expiratory flow than female subjects. Even though chest roentgenographic abnormalities were found in 17% of the patients, only 4% had significant symptoms. There was no association between abnormal pulmonary function and genotype or age.

In a patient with pulmonary involvement in type I Gaucher's disease, high-resolution CT demonstrated thickening of the interlobular septa and between four and six small nodules within secondary lobules, each probably corresponding to an acinus.

Intrathoracic extramedullary hematopoiesis in the form of a thoracic paravertebral mass is described in an asymptomatic woman with type I Gaucher's disease.

Replacement therapy with glucocerebrosidase has resulted in improved pulmonary status.

Niemann–Pick Disease

Niemann–Pick disease is characterized by an absolute or relative deficiency of the enzyme sphingomyelinase. Severe nodular pulmonary disease leading to cor pulmonale has been noted. Association of widespread pulmonary nodules, linear strands, and honeycombing has been reported. Large, multivacuolated foam cells (sea-blue histiocytes) can be found in pulmonary alveoli.

Angiokeratoma Corporis Diffusum (Fabry's Disease)

An X-linked sphingolipid storage disorder caused by the lack of a-galactosidase, Fabry's disease is reported to be associated with multiple angiomas of the tracheobronchial tree and bullous emphysema leading to hyperinflation of the lungs. Recurrent pulmonary infections and hemoptysis may indicate respiratory involvement. Bronchial inclusion bodies and alveoli filled with ceramide hexosidase have been observed in patients with obstructive lung disease secondary to Fabry's disease. The deposition of ceramide hexosidase in the bronchial tree may contribute to the intrinsic airways disease and functional airways obstruction.

Mucopolysaccharidosis

Lung involvement occurs in several mucopolysaccharidoses. Deposition of mucopolysaccharides in the tracheal wall of 56 patients with various mucopolysaccharidoses was noted to result in tracheal narrowing and airways compromise in nine patients. Pulmonary complications in 21 patients with mucopolysaccharidosis or mucolipidosis included (1) upper airway narrowing by hypertrophied tongue, tonsils, adenoids, and mucous membranes; (2) lower airway narrowing by glycosaminoglycan deposition within the tracheobronchial mucosa; and (3) decreased thoracic dimensions because of scoliosis and thoracic hyperkyphosis. The pulmonary consequences include the increased risk of developing respiratory tract infections, airway compromise during or after anesthesia or sedation, dyspnea on exertion, obstructive lung disease, obstructive sleep apnea, and cor pulmonale.

Hunter's syndrome is one of a group of heritable metabolic disorders caused by decreased activity of one or more of the lysosomal enzymes responsible for mucopolysaccharide catabolism, resulting in excessive deposition of mucopolysaccharides in skeletal and soft tissues. Airway obstruction is a frequent problem. Progressive obstruction sequentially involving the upper, mid-, and lower airway characterized by gradual deformation and collapse of the trachea (tracheobronchomalacia) has been described. Autopsy analyses have demonstrated anteroposterior flattening of the trachea and bronchi with submucosal thickening leading to structural alterations peculiar to this disease. Sleep apnea syndrome, atelectasis, recurrent pneumonia, and difficult endotracheal intubation are known to be associated with this rare disorders.

Hurler syndrome is a rare mucopolysaccharide storage disease that becomes clinically apparent during early childhood as mucopolysaccharide deposits form in skeletal and soft tissues. Progressive mucopolysaccharide deposition in the oropharynx and tracheal connective tissues leads to airway obstruction if untreated. Tonsillectomy, adenoidectomy, and tracheostomy have been utilized to provide symptomatic relief of upper airway obstruction. Treatment of tracheal lesions by carbon dioxide laser excision is an alternative method for the management of airway obstruction.

Hurler–Scheie syndrome is a genetic compound of two mucopolysaccharidoses, the Hurler and Scheie syndromes. The genetic error of metabolism caused by this syndrome produces intermediary systemic effects in the affected individuals. Lacking the enzyme a-L-iduronidase, glycosaminoglycans are deposited in the tissues, causing multiple systemic effects and airway lesions.

Morquio syndrome (mucopolysaccharidosis type IV A) is a rare inherited connective tissue disorder characterized by a distinct skeletal dystrophy (spondyloepiphyseal dysplasia), restrictive pulmonary disease, and normal intelligence. Tetraplegia secondary to subluxation of C1 over C2 because of marked odontoid dysplasia or hypoplasia is a common occurrence in these patients. Pulmonary function studies have noted the restrictive nature of the ventilatory defects. Upper airways collapse during head flexion may be an important cause of pulmonary disability in Morquio's disease.

Krabbe's leukodystrophy leading to rapidly progressive respiratory failure in an 8-week-old boy with has been described. Ultrastructural examination of lungs revealed the presence of numerous intraalveolar macrophages.

Sleep apnea is a common occurrence in patients with mucopolysaccharidoses. In the past, all reported cases of sleep apnea in these patients had been treated with tonsillectomy/adenoidectomy or tracheostomy. Some patients have been successfully treated with high-pressure nasal CPAP and supplemental oxygen. Bone marrow transplantation has resulted in effective metabolic correction as well as relief of obstructive apnea in Hurler syndrome.

Lipoid Proteinosis

A rare hereditary disorder of the autosomal recessive type, lipoid proteinosis involves multiple organs by deposition of an amorphous eosinophilic glycoprotein. Pulmonary abnormalities consist of infiltration of this anomalous glycoprotein into capillary walls. Roentgenograms reveal a diffuse reticulonodular pattern throughout both lungs.

Bronchoalveolar lavage in patients with pulmonary involvement from lipid storage disorders has shown presence of lipid-containing foamy cells, with the demonstration of both periodic acid–Schiff and Scharlach red stain-positive vacuoles in the cytoplasm of alveolar macrophages. These abnormal cells are the same cells found in bone marrow biopsy.

Lysinuric Protein Intolerance

Lysinuric protein intolerance is an autosomal recessive disorder caused by the defective transport of cationic amino acids. Pulmonary disease is a potentially fatal complication in these patients. A study of nine patients with lysinuric protein intolerance observed death in a 10-year-old patient as a result of severe respiratory insufficiency from alveolar proteinosis. The remaining patients were asymptomatic at the time of the study, although high-resolution CT scans revealed acinar nodules, inter- and/or intralobular thickening of the interstitial septa, and subpleural cysts in five of the patients. No abnormalities of pulmonary function were evident. Radionuclide studies showed an uneven distribution of perfusion and ventilation and confirmed the presence of segmental and/or diffuse pulmonary functional defects.

Acute Intermittent Porphyria

Acute intermittent porphyria results from an inborn error of metabolism. Occasionally, this entity may present as acute respiratory insufficiency or with neurologic, psychiatric, or gastrointestinal manifestations. With respiratory involvement, the mortality may be high. The pulmonary features usually are similar to those of Guillain–Barré syndrome, in which the disease process involves the respiratory muscles and produces alveolar hypoventilation. Acute intermittent porphyria should be considered in the differential diagnosis of respiratory failure.

Carcinoid Syndrome

Carcinoid tumors of the bronchus and lung are discussed fully elsewhere. The following is a review of pulmonary manifestations of the carcinoid syndrome, the classic form of which is caused by a hormonally active carcinoid tumor located most frequently in the terminal ileum. The tumor arises from the Kulchitzky (argentaffin) cells, which contain neurosecretory granules filled with serotonin (5-hydroxytryptamine). This hormone is responsible for most of the clinical features, which include episodic flushing, purplish cyanosis, diarrhea, bronchospasm, and valvular disease of the right side of the heart.

Among the 3718 cases of abdominal carcinoid tumors, 3.7% had symptomatic endocrine activity. In a Mayo Clinic series, the carcinoid syndrome was observed with

7% of gastrointestinal carcinoids and 2% of bronchial carcinoids.

Pulmonary manifestations of the syndrome may include hyperventilation and wheezing. Most frequently, however, patients do not have symptoms referable to the chest, and evidence of bronchoconstriction is found only during flushing attacks. The most prominent cardiac symptoms arise from stenosis of the pulmonic and tricuspid valves, and these lesions can lead to intractable right heart failure. Elevation of urinary 5-hydroxyindoleacetic acid is helpful in establishing the diagnosis.

Other Metabolic Disorders

Volume contraction is a common clinical problem, and its effects on pulmonary functions have been studied. During hypohydration induced by diuretics in normal volunteers, lung volumes increased significantly. In addition, peak expiratory flow rate, FEV_1, maximal voluntary ventilation, and flow rates at low lung volumes also increased but returned to normal on rehydration. D_LCO was unchanged. The mechanism is probably related to the loss of water in the airway walls or peribronchial space. The clinical significance of these findings is unclear.

Hypokalemia is a commonly encountered clinical problem. Respiratory muscle weakness may result from severe hypokalemia. Hypokalemic periodic paralysis has been associated with hypoventilation. Severe diarrhea, dehydration, and marked hypokalemia in a pediatric patient was followed by fatal respiratory failure as a result of respiratory muscle paralysis.

Hypophosphatemic states are known to produce respiratory failure secondary to muscle weakness. A decrease in the body phosphate level diminishes adenosine triphosphate and results in muscle weakness. Phosphate replacement therapy in such cases dramatically improves muscle function and reverses respiratory failure. Chronic hypophosphatemia produces a decrease in 2,3-diphosphoglycerate, which increases the affinity of oxygen for hemoglobin, thereby decreasing the delivery of oxygen to the tissues.

Hypomagnesemia may contribute to respiratory muscle weakness. Next to potassium, magnesium is the most abundant intracellular cation in the human body. It is required as a cofactor by many enzymes and is a cofactor in all transphosphorylation reactions. The incidence of hypomagnesemia varies from 30% in alcoholics to 2% in normal individuals. In patients with respiratory muscle weakness, hypomagnesemia should be sought as an etiologic factor because magnesium replacement therapy has been shown to improve all the indices of muscle power measured after treatment.

Hypermagnesemia as a result of excessive ingestion of antacids, bowel obstruction, and renal failure may be followed by respiratory depression and coma. These features can be reversed by lowering the magnesium level.

Metabolic alkalosis is a common acid–base disorder in hospitalized patients. The compensatory hypoventilation may lead to atelectasis, deterioration in the ventilation–perfusion relationship, and an increased alveolar–arterial oxygen tension difference. The resultant hypoxia can be corrected significantly by reversing alkalosis with administration of hydrochloric acid.

High carbohydrate loads have led to acute respiratory failure. This is a potential problem in those receiving total parenteral nutrition. The infused glucose is used as the primary energy source, which leads to substantial increases in carbon dioxide production and respiratory quotient. Respiratory failure is more likely to occur in patients with limited pulmonary reserve.

Total parenteral nutrition increases carbon dioxide production in patients on ventilation who cannot match their carbon dioxide excretion to the carbon dioxide load, leading to increased arterial carbon dioxide tension. This risk can be minimized by increasing minute ventilation before total parenteral nutrition is begun.

Hyperlipidemia is reported to produce falsely low D_LCO measurements as a result of interference with a hemoglobin-combining coefficient. This is of no clinical significance in healthy subjects.

Glycogen storage diseases predispose patients to bacterial infections. Staphylococcal infections may produce lung abscesses and pneumatoceles (Fig. 9).

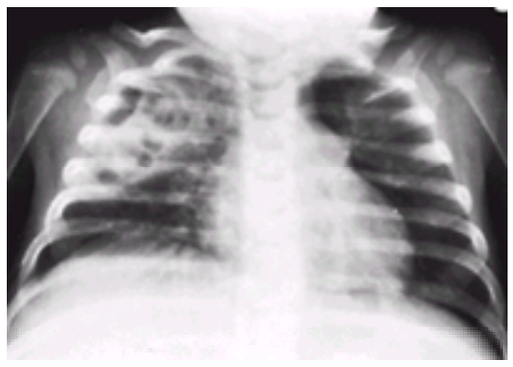

FIG. 9. Glycogen storage disease in an infant complicated by *Staphylococcus aureus*-induced abscesses in the right upper lobe.

Gouty tophi of the larynx and vocal cords have been described, with accompanying stridor, hoarseness, and signs of extensive gouty disease.

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CHAPTER

60 Neurologic Diseases

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INTRODUCTION

The central and peripheral nervous systems play significant roles in the normal functioning of the respiratory system. The central component of the respiratory system resides mainly in the respiratory centers located in the medulla oblongata. Internuncial pathways connect these centers with higher brain centers, which also play a role in the normal breathing mechanism. The peripheral nervous system is responsible for normal functioning of the respiratory musculature. Depending on the type and extent of injury to either the central or peripheral nervous system, the respiratory system may exhibit various abnormalities. In this chapter, the pulmonary manifestations of disease processes at various levels of the nervous system are discussed.

NEUROGENIC BREATHING DISORDERS

The most common respiratory feature noted in intracranial disorders is a change in the breathing pattern. Elevation of intracranial pressure is the main pathologic event responsible for the breathing abnormalities. When damage is limited to one hemisphere, breathing is often normal. In contrast, acute bilateral hemispheric injury commonly elicits abnormal pattern of breathing. Abnormal breathing patterns have been related to prognosis after brain damage. Abnormal breathing is equally common in each of three large groups of patients: those with head injury, intracranial tumor, or subarachnoid hemorrhage. Depending on the anatomic location of brain injury, patients may demonstrate hypoventilation, hyperventilation, or both at different times during their illness. In one report of 100 consecutive patients with severe head injuries who arrived at a major trauma center, hypoxia was noted in 30% and hypercapnia in 4%. Abnormalities in the rate and depth of respiration occur in approximately 40% of cases of cerebral hemorrhage. Extensive lesions, such as massive cerebral hemorrhage, major cerebral embolism, and those caused by severe head trauma, are accompanied by a higher incidence of abnormalities in breathing pattern.

Several types of breathing abnormalities, including periodic breathing, irregular breathing, and tachypnea, have been described in patients with central nervous system trauma, tumor, or cerebrovascular accidents. In one report of 227 patients with these types of abnormalities, 60% demonstrated some type of abnormal breathing. All patients with medullary lesions demonstrated respiratory abnormalities, whereas pontine lesions were associated with respiratory abnormalities in 60%–70% of patients. Poor prognosis was associated with respiration exceeding 25 breaths per minute and an arterial carbon dioxide tension ($PaCO_2$) of <30 mmHg (see discussion of hyperventilation below).

Cheyne-Stokes Breathing

Cheyne-Stokes breathing is characterized by regularly alternating phases of hyperventilation and apnea and usually persists for long periods. It occurs in approximately 25% of cases of cerebral embolism and nearly 10% of cases of cerebral infarction. This respiratory dysrhythmia is also seen in other clinical conditions, including lactic acidosis, diabetic ketoacidosis, and uremic coma. Instability of the ventilatory control system is the main cause of Cheyne-Stokes breathing. Another possible cause is

abnormal sensitivity of respiratory neurons to carbon dioxide, resulting in hyperventilation that is unduly prolonged by impairment of forebrain ventilatory inhibition. Patients with Cheyne-Stokes respiration exhibit a progressively increased tidal volume during the hyperpneic phase, with subsequent decreases without change in respiratory rate.

Patients with Cheyne-Stokes breathing in whom respiratory alkalosis develops have a higher mortality. Cardiac and pulmonary monitoring in 44 patients admitted within 48 hours of onset of stroke disclosed that the presence of intermittent Cheyne-Stokes breathing or tachypnea, seen in 88%, was associated with increased mortality. In one study reporting on 11 patients with a $PaCO_2$ of <35 mm Hg and a pH of >7.46, only one patient survived.

Ataxic Breathing

Ataxic breathing, sometimes known as *chaotic breathing,* comprises periodic hypoventilation, slow regular breathing, Biot's respiration, apneusis-like inspiratory pauses, and inspiratory gasps. Ataxic breathing is seen in lower pontine and medullary disorders, morphine poisoning, hypercapnic stupor, infarcts of the brainstem, meningitis, and tumors of the central nervous system.

Biot's respiration is another term that was employed in the past to describe some abnormal breathing patterns. The terms *ataxic breathing* and *Biot's breathing* are often used synonymously. The breathing pattern consists of irregular cycles of uniformly deep or shallow breaths separated by apnea. Biot's breathing can be seen in patients with lower pontine and medullary disorders, meningitis, lesions in the posterior fossa, morphine poisoning, and hypercapnic stupor.

Apneustic breathing refers to prolonged inspiratory “cramps” with cessation of breathing in the inspiratory phase. It is a rare clinical entity. Dissociation of cerebral pathways is believed to cause this. A report on five patients with achondroplasia, all of whom demonstrated apneustic breathing, speculated that compression of the lower medullary respiratory centers and afferent pathways in the spinal cord was responsible for the breathing abnormality. Apneustic breathing can be seen in patients with lower pontine and medullary disorders, brainstem infarction, hypercapnic stupor, meningitis, and hypoglycemia. A classic example of apneustic breathing has been described in a patient with Dandy-Walker syndrome, in which hydrocephalus associated with a cystic fourth ventricle, hypoplasia or agenesis of the cerebellar vermis, and atresia of the foramina of Luschka and Magendie are noted. Although the breathing pattern may revert to normal after a shunt procedure, respiratory failure is the major complication leading to death in infants with this syndrome.

Cluster breathing is characterized by clusters of normal breaths separated by irregular pauses. Cluster breathing is seen in patients with high medullary or low pontine lesions.

In *respiratory inhibitory apraxia,* the patient is unable to stop breathing voluntarily. However, voluntary spontaneous respiration is unaffected. This abnormal breathing pattern is often associated with other forms of apraxia or motor impersistence. Respiratory inhibitory apraxia has been described in association with lesions in the internal capsule and areas supplied by the middle cerebral artery.

Neurogenic Hyperventilation

A rare phenomenon, neurogenic hyperventilation is characterized by very regular, rapid breathing (24 to 38 breaths per minute, a rate three to six times greater than normal) for hours or days at a time. The diagnosis of central hyperventilation is based on the presence of normal PaO_2 (80 mmHg) and a volume of breathing that is increased out of proportion and beyond body needs. Lesions in the region of the midbrain and upper pontine tegmentum—as seen in brainstem infarctions, acute encephalitis, hypoglycemia, severe sustained anoxia, trauma, and carbon monoxide poisoning—may cause central neurogenic hyperventilation. The mortality is very high when central neurogenic hyperventilation or Cheyne-Stokes breathing is associated with respiratory alkalosis.

The mechanism of respiratory alkalosis in central neurogenic hyperventilation is unclear. Lessened sensitivity of peripheral chemoreceptors to hypoxia may allow the PaO_2 to fall to 45 mmHg, at which point central hypoxic drive produces hyperventilation and respiratory alkalosis. The presence of hyperventilation itself has been used as a diagnostic aid in patients with partial complex seizures. In a study of a large number of patients with partial complex seizures, hyperventilatory maneuvers evoked abnormal electroencephalographic discharges and clinical seizures in 11%. Central neurogenic hyperventilation has never been induced experimentally, and it is rare even in patients with severe neurologic problems.

Neurogenic Hypoventilation

Hypoventilation is defined as elevation in $PaCO_2$ of 45 mmHg. Neurogenic hypoventilation can be either central or peripheral in origin. The direct depressant effects of overdoses of narcotic medication are a well-known cause of centrally induced hypoventilation. Cerebral trauma, vascular accidents, and infections also may result in alveolar hypoventilation. Neurogenic hypoventilation, as result of microinfarctions of basal ganglia, has been described in patients with familial hemiplegic migraine. Patients with severe cerebrovascular disease show a reduced steady-state ventilatory response to hypercapnia. The mechanism for this phenomenon is unknown.

Ondine's curse or “true” central alveolar hypoventilation (i.e., hypoventilation without any neurologic, cardiopulmonary, or metabolic disorder) is extremely rare, with only a few cases having been reported. If, however, disorders such as syringomyelia, Parkinson's disease, schizophrenia, and mental retardation are included, approximately 50 cases of central alveolar hypoventilation have been described. Clinical features in these patients included cyanosis in all, polycythemia in one third, somnolence in one third, and headache in 25%. Frequent findings noted among these patients have included pulmonary hypertension and congestive cardiac failure. Bilateral phrenic nerve pacing has been tried with varying success. Pharmacologic agents, including medroxyprogesterone acetate and nocturnal administration of oxygen, have been used to stimulate respiration in patients with central hypoventilation.

Neurogenic Pulmonary Edema

The clinical occurrence of neurogenic pulmonary edema is uncommon. In a report of 2100 patients with serious head injuries and 132 with serious cervical spinal cord or spinal column injuries, there were only two clear examples of neurogenic pulmonary edema. In contrast, an autopsy study of 100 soldiers dying of combat wounds in Vietnam revealed pulmonary edema and alveolar hemorrhage in 89%, most commonly in those who died within 1 week of injury. Respiratory disease was discovered frequently, whether or not thoracic injury was present. Furthermore, pulmonary edema is a common postmortem finding in patients with bulbar poliomyelitis, hydrocephalus, tumors of the central nervous system, intracerebral hematomas, intraventricular and subarachnoid hemorrhages, and especially trauma to the central nervous system.

Sustained acute elevation of intracranial pressure is probably the most important factor in the pathogenesis of neurogenic pulmonary edema. Elevation of intracranial pressure stimulates hypothalamic centers, resulting in massive a-adrenergic sympathetic discharge. Damage to the hypothalamus probably initiates the response just discussed; indeed, the postchiasmatic area has been referred to as the *edematogenic center.* These events result in severe vasoconstriction of the systemic and pulmonary vessels. Additionally, increases in microvascular pressure attributed to changes in the distribution of lung perfusion are believed to play a major pathogenic role in pulmonary edema (Fig. 1). These hemodynamic events occur within seconds after injury to the central nervous system. The stiffening of the left ventricle further contributes to the development of pulmonary edema. Pulmonary edema develops during these hemodynamic alterations and persists after the vascular pressures return to normal. The persistence of edema is a consequence of pulmonary capillary endothelial damage caused by the abrupt changes in pressure and volume within the pulmonary vasculature. Protein also leaks into the alveoli.

FIG. 1. Mechanism of neurogenic pulmonary edema. [Modified from Robin TJ, ed. Speculations on neurogenic pulmonary edema (NPE). *Am Rev Respir Dis* 1976;113:405.].

Head trauma is one of the most common causes of severe but nonfatal neurogenic pulmonary edema. Analysis of a large autopsy database and head-injured patient database showed the incidence of neurogenic pulmonary edema in patients with isolated head injury dying at the scene to be 32%; in patients with isolated head injury dying within 96 hrs, the incidence was 50%. The implication of these findings is that neurogenic pulmonary edema begins very early following head injury. In a retrospective clinical and pathologic analysis of 78 cases of fatal subarachnoid hemorrhage, a pathologic diagnosis of pulmonary edema was made in 71%, and 31% of this group had a clinical diagnosis of pulmonary edema. Neurogenic pulmonary edema after subarachnoid hemorrhage carries a poor prognosis, and postmortem studies indicate the presence of pulmonary edema in 33%–71% of patients with fatal subarachnoid hemorrhage.

Severe cerebral hypoxia of any cause can lead to neurogenic pulmonary edema. The overall frequency of postictal edema is low; the literature yields approximately 100 cases. Postictal pulmonary edema has recurred in the same patient. It shows a predilection for young epileptic patients. It may develop immediately after an epileptic seizure or several hours later. Electric shock therapy for seizure disorder has resulted in fatal pulmonary edema. Guillain-Barré syndrome, old poliomyelitis, and meningitis have caused neurogenic pulmonary edema. In a report of the pathologic findings in 200 cases of fatal meningococcal meningitis, pulmonary edema was noted in 60%. Neurogenic pulmonary edema has followed trigeminal blockade.

The clinical features of neurogenic pulmonary edema include the obvious evidence of damage to the central nervous system, progressive respiratory distress, and chest roentgenographic distribution of asymmetric alveolar infiltrates (Fig. 2), although a generalized pattern has been observed in most cases. Delayed onset of edema is unusual, but it has been observed in a number of cases.

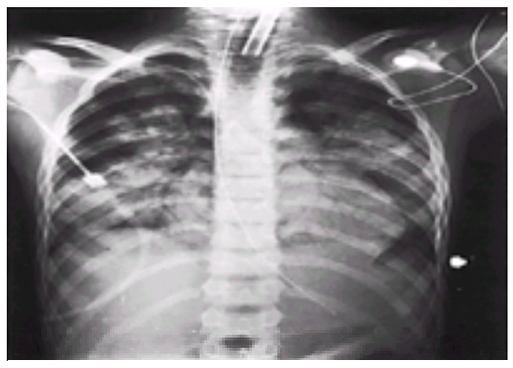

FIG. 2. Neurogenic pulmonary edema. Bilateral alveolar infiltrates with air bronchograms are noted.

ABNORMAL STATES OF CONSCIOUSNESS

Unconsciousness and Coma

Unconsciousness and coma predispose to the development of aspiration pneumonitis, nosocomial pneumonia, hypoventilatory respiratory failure, and pulmonary thromboembolism. Neurogenic pulmonary edema also is seen in these patients. Abnormal breathing patterns are common, especially at the lowest level of consciousness. However, no significant association has been found between a particular abnormal pattern and level of consciousness. The unconscious patient breathes more rapidly and regularly than a conscious patient. Increasing regularity of respiration correlates well with deepening coma and accurately reflects ultimate outcome, even when other clinical signs remain unchanged.

Aspiration pneumonia and nosocomial pneumonia resulting from infection with gram-positive, gram-negative, and anaerobic organisms are the major causes of morbidity and mortality in this group of patients. Approximately 50% of patients who are unconscious or comatose aspirate. Aspiration is significantly associated with reduced pharyngeal sensation, dysphagia, and stroke severity. Aspiration is common in the early period following acute stroke. Therefore, each patient admitted with acute stroke should be carefully tested for disordered pharyngeal sensation. Even though aspiration is a transient phenomenon in most cases of acute stroke, it is associated with a high incidence of lower respiratory tract infection. In a prospective study of 60 consecutive patients with acute stroke, videofluoroscopy detected aspiration in 42% of patients within 72 hours of stroke onset, and aspiration had resolved in all but three patients after 3 months. Aspiration was closely related to the presence of dysphagia, which itself resolved within 2 weeks in all but the persistent aspirators. Lower respiratory tract infection was more common in aspirators than in nonaspirators. In an analysis of 125 patients with closed head injury, development of early pneumonia was noted in 48% of the patients. Patients in whom early pneumonia developed were found to have a lower score on the Glasgow Coma Scale (5). In a study of 441 patients with recent stroke, videofluoroscopic barium swallow detected aspiration of thin liquids in 84 patients (19%), and aspiration pneumonia developed in 12% of this group.

Head Trauma

Neurogenic pulmonary edema and other complications also can result from closed head injury. The pulmonary complications depend on the degree of trauma, level of consciousness, and involvement of other organs. Closed head injury commonly requires endotracheal intubation and mechanical ventilation. A study of 109 initially comatose patients with isolated closed head injuries who were ventilated for 24 hours or more showed that closed head injury is associated with a high incidence of pneumonia and that pneumonia occurs earlier in patients with closed head injury than in other patient groups. Pneumonia usually does not occur after the first week of hospitalization in this group of patients.

Barbiturates are commonly administered to patients with cerebral edema. A prospective study in mechanically ventilated patients with brain edema discovered that the rate of nosocomial pneumonia was significantly higher in patients receiving barbiturates than in the control group, with those receiving higher doses being at greater risk for development of pneumonia. Colonization of the respiratory tract was observed in all barbiturate-treated patients and in 70% of the control group.

Epilepsy

Short periods of apnea almost always occur in *petit mal* seizures. Prolonged apnea also has been noted. Apneic periods have been observed in partial epilepsy, especially the temporal lobe type. However, respiratory changes only rarely appear to be the principal and important components of the seizure. Several cases of respiratory failure as a seizure phenomenon have been reported. The sudden death of epileptic patients, unexplained by autopsy, is reported to be relatively frequent. Such deaths have been attributed to acute functional disturbances in cardiorespiratory centers as a result of seizure discharges. It is theorized that acute respiratory failure develops from the propagation of seizure discharges that lead to brainstem dysfunction.

Laryngospasm has been noted as a presenting symptom in patients with temporal lobe seizures. Severe hypoxia and acidosis after local anesthetic-induced convulsions have been reported; the convulsions were induced by topical application of bupivacaine. Neurogenic pulmonary edema also occurs following epileptic seizures. Prolonged spasm of the respiratory muscles leading to ventilatory problems has been reported in patients with status epilepticus.

Phenytoin, used in the therapy of epilepsy, has been noted to predispose to immune deficiency (IgA) and frequent symptoms of respiratory disease. Phenytoin also is reported to cause mild lymphadenopathy.

Exaggerated vagal response has been described in 58 children in whom reflex anoxic seizures secondary to provoked cardiac inhibition (also known as *white breath-holding attacks*) were diagnosed. The seizures were diagnosed initially as epileptic in nature; however, it appears that these seizures resulted from vagally mediated reflex cardiac arrest.

SPINAL CORD DISORDERS

Damage to the cervical spinal cord can interfere with both afferent and efferent spinal pathways concerned with respiratory function. Transection or other severe injury to the cervical spinal cord at a high level causes weakness of the respiratory muscles and may result in ventilatory failure. Transection of the cord below the level of the fifth cervical vertebra results in intercostal muscle paralysis. In such an instance, although the accessory neck muscles of respiration are affected, diaphragmatic function is preserved, and so hypoventilation is rare. However, the work done by the diaphragm (work of breathing) is significantly exaggerated, and therefore most

patients with transection of the spinal cord experience dyspnea.

The term *hemiplegia* denotes loss of neuromuscular function on one side of the body, usually owing to a cerebrovascular accident on the contralateral side. The functional classification of spinal cord injuries includes *pentaplegia, quadriplegia* (*tetraplegia*), and *paraplegia.* In quadriplegia, the C4-8 levels are involved, with motor and sensory loss in the arms and legs. In respiratory quadriplegia, the spinal cord is involved at the second through third cervical vertebral levels, and findings include motor and sensory loss of the arms, legs, and diaphragm. Pentaplegia results when the lesion is located in the brain-stem to the first cervical vertebral level, with resultant motor and sensory loss of the neck, arms, legs, and diaphragm. In paraplegia, sensory and motor loss is noted in the legs as a result of involvement of the spinal cord between the levels of the first thoracic and first sacral vertebrae.

Quadriplegia (Tetraplegia)

In quadriplegic patients, the vital capacity (VC) is approximately two thirds of normal and the maximal breathing capacity is half of normal. A mean decrease in VC to 42% of the predicted value has been reported. The impaired ventilatory function in quadriplegic patients is caused by the elimination of supraspinal control of respiratory muscles innervated by spinal segments below the level of the lesion. The spastic paralysis results in decreased compliance of the chest wall and reduction of both inspiratory and expiratory reserve volumes. The decrease in VC is also caused by altered body posture. Duration of quadriplegia does not seem to alter the response to pulmonary function testing. In the early stages of quadriplegia, the intensity of the compensatory respiratory function of the sternomastoid muscle varies, and its development to full strength as an auxiliary force in the act of breathing may require some time and the use of systematic exercises. Indeed, the role of another accessory muscle, the pectoralis major, is such that its causes dynamic airway compression during expiratory efforts in a substantial proportion of tetraplegic subjects.

The most conspicuous feature of the respiratory mechanics of the supine quadriplegic patient is the paradoxical inward movement of the rib cage during inspiration. This results in functional deformity of the chest wall and increased work of breathing. In the sitting posture, the paradoxical inward motion disappears in the lower rib cage, whereas it is decreased but still present in the upper rib cage. The disappearance of paradoxical motion of the upper rib cage with time in quadriplegics has been attributed to the development of spasticity of the intercostal muscles, with better support of the rib cage preventing it from drawing in during inspiration.

The work done by the diaphragm in quadriplegic patients is estimated to be nine times greater than that in normal individuals. This increased work of breathing is associated with dyspnea, which is minimized by a decrease in the respiratory rate to an inadequate level, which is the basis for the chronic alveolar hypoventilation seen in such cases. Tracheostomy in these patients has been associated with a higher mortality. Radiofrequency electrophrenic respiratory pacing has been used to support quadriplegic patients in whom hypoventilation develops. Milder degrees of hypoventilation may respond to noninvasive ventilatory therapies, such as continuous positive airway pressure (CPAP). Mechanical ventilatory assistance is required in many.

A study evaluating the airway responsiveness to methacholine in subjects with spinal cord injury reported that smokers and former smokers with quadriplegia are hyperresponsive to methacholine and that the response is comparable with that found in persons who have never smoked. The airway hyperresponsiveness in these subjects is thought to represent loss of sympathetic innervation of the lung, leaving bronchoconstrictor cholinergic activity intact and unopposed.

Bronchorrhea (mucous secretion in excess of 100 mL/d) or bronchial mucous hypersecretion is reported to occur in 20% of quadriplegic patients, with the quantity of mucus produced occasionally exceeding 1.0 L/d. The sudden onset of and spontaneous recovery from quadriplegic bronchorrhea is probably a consequence of disturbed neuronal control of bronchial mucous gland secretions and the initial disappearance and later reappearance of peripheral sympathetic nervous system tone.

Most deaths that follow soon after acute quadriplegia are caused by pulmonary complications. Respiratory problems include hypoventilation, recurrent infections resulting from aspiration and ineffective cough, neurogenic pulmonary edema in the acute quadriplegic state, and an increased incidence of thromboembolic phenomena. In a prospective study of 22 consecutive patients with quadriplegia, a high mortality was noted during the first months; a 15%–40% mortality was seen in the first year. Most deaths were related to respiratory failure. A retrospective analysis of 22 quadriplegic patients showed a 41% mortality within 5 years after quadriplegia. With time, respiratory function improved in the survivors, especially diaphragmatic function.

Hemiplegia

In hemiplegia, spastic paralysis or weakness of the affected side of the body may affect the diaphragm and intercostal muscles. However, respiratory complications ordinarily are not regarded as a complication of hemiplegia, even though ipsilateral diaphragmatic dysfunction occurs frequently. The left diaphragm is more commonly involved in left hemiplegia than is the right hemidiaphragm in right hemiplegia. Forced vital capacity (FVC) and forced expiratory volume may be decreased to 60% of normal. Ventilatory failure becomes imminent when the VC is reduced to 25% or less of the predicted normal value. Spirometry has shown reduction of FVC and forced expiratory volume in 1 second (FEV_1) to approximately 60% and 70%, respectively, of the predicted values. Also, a mild restrictive pulmonary dysfunction occurs in patients with hemiplegia. The lack of significant clinical symptoms is attributed to the physical inactivity.

Paraplegia

Paraplegia usually is accompanied by a slight ventilatory restriction. Lung function tests have shown both VC and maximal voluntary ventilation (MVV) in the ranges of 60%–100% of predicted normal values. One study reported a VC diminished to 60% in patients with high thoracic transections and to 78% in patients with low thoracic lesions.

DIAPHRAGMATIC PARALYSIS

The diaphragm is the most important muscle of respiration, and therefore diaphragmatic paralysis can cause significant respiratory abnormalities. The paralysis can be unilateral or bilateral, transient or permanent. It may result from interruption of the nerve supply, from muscular atrophy, or transiently from diaphragmatic pleurisy. Acute unilateral diaphragmatic paralysis usually results from interruption of the phrenic nerve by bronchogenic carcinoma or another tumor in the mediastinum, whereas chronic unilateral paralysis usually is idiopathic. Unilateral or bilateral paralysis can be caused by motor neuron disease, paralytic poliomyelitis, high cervical cord injuries, infectious polyneuritis of Guillain-Barré, or peripheral neuritis associated with measles, tetanus, typhoid, or diphtheria. Diaphragmatic involvement is often a late manifestation of generalized neuromuscular disease. Diaphragmatic weakness has also been noted in patients with Charcot-Marie-Tooth disease. Diaphragmatic paralysis has been associated with Erb's palsy, which is a well-circumscribed complication of birth trauma to the shoulder and neck, with thoracotomy, and as a complication of central venous alimentation.

Unilateral phrenic nerve paralysis occurs in 2%–10% of patients who undergo cardiac procedures, most frequently with Blalock-Taussig shunts. Hypothermic cardioplegia, induced by placing ice around the heart before open heart surgery, is complicated by transient unilateral phrenic nerve palsy (“frost-bitten” phrenic nerve) that lasts for 6 to 8 weeks. In recipients of orthotopic liver transplants, crush injury to the right phrenic nerve during transplantation is most likely the cause of right hemidiaphragmatic dysfunction. A prospective study of 48 adult recipients of liver transplants recorded right phrenic nerve injury and hemidiaphragmatic paralysis in 79% and 38% of patients, respectively. Complete recovery of phrenic nerve conduction and diaphragmatic function took as long as 9 months in some patients.

The etiology of diaphragmatic paralysis remains undetermined in more than two thirds of cases. The majority of patients studied in clinical investigations were asymptomatic and remained so on follow-up examination. Approximately 25% of them regained diaphragmatic function after a period of several months to 3 years. In another study, of 247 patients with diaphragmatic paralysis, a cause was found in 42.5% of the cases, whereas no reason for the paralysis could be identified in the remaining 57.5% (142 patients). Among this group, left-sided paralysis was seen in 58%, right-sided involvement in 41%, and bilateral involvement in 1%. Intrathoracic malignant lesions were subsequently diagnosed in 3.5%, and progressive neurogenic atrophy was seen in one patient. During a 1-year period, two cases of bilateral diaphragmatic paralysis were found among 360 prospectively studied patients who underwent hypothermic cardioplegia; both patients had insulin-dependent diabetes mellitus. Phrenic nerve isolation and protection from hypothermia during surgery resulted in no case of phrenic paralysis in a group of 76 control patients, compared with an 18% incidence in 76 patients whose phrenic nerves were exposed to cold.

Parsonage-Turner syndrome, also referred to as *paralytic brachial neuritis, neuralgic amyotrophy,* or *brachial plexus neuropathy,* is characterized by sudden onset of pain in shoulder, chest, or upper arm followed by paresis of the shoulder girdle or upper arm. Although rare, both unilateral and bilateral diaphragmatic paralysis has been described in this syndrome. The diseases associated with diaphragmatic paralysis are listed in Table 1.

Cerebral hemispheric stroke
Spinal cord disorders
Trauma to the cervical spinal cord
Syringomyelia
Poliomyelitis
Motor neuron diseases
Peripheral neuropathies
Trauma to the phrenic nerve (surgery, radiation, tumor)
Phrenic nerve compression by tumor
Landry-Guillain-Barré syndrome
Brachial plexus neuritis
Nutritional or alcoholic neuropathy
Lead neuropathy
Postinfectious neuropathies
Diphtheria
Tetanus
Typhoid
Measles
Myasthenia gravis
Muscular disorders
Myotonic dystrophies
Duchenne muscular dystrophy
Metabolic myopathies
Polymyositis
Idiopathic

TABLE 1. *Causes of diaphragmatic paralysis*

Unilateral Diaphragmatic Paralysis

A diagnosis of unilateral diaphragmatic paralysis often is difficult to establish with certainty. Study of the motion of the abdominal wall and rib cage in the supine position with magnetometry has failed to show paradoxical movements of the abdomen in unilateral paralysis. This is in contrast to the findings in bilateral diaphragmatic paralysis, in which the anterior abdominal wall moves inward paradoxically with inspiration. Measurement of transdiaphragmatic pressure using two balloon catheters has shown that at rest and expiration, when the diaphragm is relaxed, the transdiaphragmatic pressure is zero. During maximal inspiration, the change in pressure exceeds 25 cm H_2O in normal individuals, whereas in patients with weakness of the diaphragm, this pressure is 6 cm H_2O.

Symptoms of unilateral phrenic paralysis are orthopnea and difficulty in inspiration. Significant arterial oxygen desaturation can occur in the supine position but is unusual. Carbon dioxide retention also is unusual. Roentgenographic findings include elevation of the diaphragm; diminished, absent, or paradoxical movements on inspiration; mediastinal shift on inspiration; and paradoxical movements of the diaphragm under conditions of augmented load, such as sniffing. Paradoxical motion of the affected diaphragm during a “sniff test” under fluoroscopic guidance is a widely accepted test to establish the diagnosis (Fig. 3). However, it should be noted that nearly 6% of normal people may demonstrate paradoxical movement of one hemidiaphragm or the other. It should be noted, however, that nearly 6% of normal people may demonstrate paradoxic movement of either hemidiaphragm. If paradoxical excursion during sniffing exceeds 2 cm and involves the whole leaf of the diaphragm as seen on the oblique view, it probably is pathologic, provided that the abdominal muscles are relaxed during the test. Measurement of transdiaphragmatic pressure or diaphragmatic electromyography are more reliable for the diagnosis. The diagnostic evaluation of respiratory muscle weakness primarily involves the assessment of diaphragmatic function. An algorithmic approach is depicted in Fig. 4.

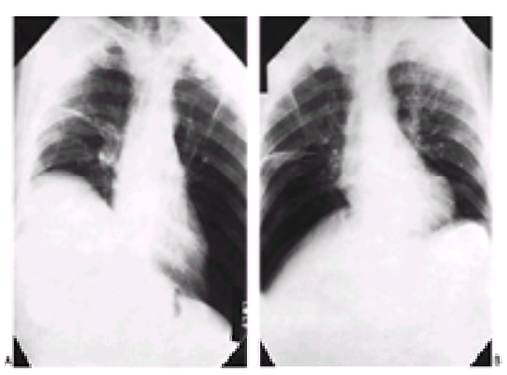

FIG. 3. Diaphragmatic motion in diaphragmatic paralysis. **A:** Paradoxical upward motion of the paralyzed right diaphragm during sudden inspiratory breathing. **B:** Paradoxical downward motion during expiration.

FIG. 4. Algorithm for approach to assessment of respiratory muscles. An incremental approach is used for most patients. For the remainder, comprehensive specialized tests are indicated. *VC,* vital capacity; *MIP,* maximal inspiratory pressure; *MEP,* maximal expiratory pressure; *SNIP,* sniff nasal inspiratory pressure; *Qs,* quadriceps; *MVC,* maximal voluntary contraction force. (Reproduced with permission from Polkey MI, Green M, Moxham J. Measurement of respiratory muscle strength. *Thorax* 1995;50:1131–1135.)

Pulmonary function studies in patients with unilateral diaphragmatic paralysis have shown total lung capacity (TLC) to be decreased by 37%, and VC and MVV to be decreased by 20%. The effects of posture on lung volume, airway closure, and gas exchange studied in eight patients with hemidiaphragmatic paralysis showed the mean VC in the sitting position to be 81% of the predicted normal value; in the supine posture it decreased by a further 19% in right-sided paralysis but by only 10% in left-sided paralysis. Diffusing capacity for carbon monoxide (D_LCO) was normal in all cases. Overall pulmonary function in the sitting position in 17 subjects with hemidiaphragmatic paralysis revealed VC, MVV, and FEV_1 to be reduced by an average of approximately 25%. Studies of regional lung function in the same body position have shown a considerable decrease in perfusion (19%), ventilation (20%), and lung volume (7%) in the diseased side as compared with reference values obtained in healthy volunteers.

Ipsilateral diaphragmatic dysfunction occurs frequently in hemiplegia. As stated previously, the left hemidiaphragm is more commonly involved in left hemiplegia than is the right hemidiaphragm in right hemiplegia. FVC and FEV_1 may be decreased to 60% of normal values in these patients. Ventilatory failure becomes immanent when the VC is reduced to 25% or less of the predicted normal value. Determination of maximal inspiratory and expiratory pressures is helpful in assessing respiratory muscle strength. Serial measurements aid in recognizing respiratory muscle fatigue or recovery of muscle strength. Unilateral diaphragmatic paralysis is associated with an abnormal pattern of use of the respiratory muscles during quiet breathing, characterized by the use of intercostal and accessory inspiratory muscles or compensatory use of abdominal expiratory muscles. A detailed physiologic study in one patient with right hemidiaphragmatic paralysis has suggested that to compensate for paralysis of a hemidiaphragm, a new pattern of inspiratory muscle recruitment develops, involving more rapid contraction of the remaining inspiratory muscles.

Bilateral Diaphragmatic Paralysis

Bilateral diaphragmatic paralysis is not as common as unilateral paralysis. Acute bilateral paralysis can be life-threatening. Bilateral paralysis or severe weakness of the diaphragm alone does not lead to respiratory failure unless weakness of other respiratory muscles is present. The most striking clinical feature is severe orthopnea in the absence of heart and lung disease. The VC is reduced to 50% of the predicted normal value in upright posture, with further decrease in the supine position accompanied by orthopnea. Lung compliance is reduced, especially in the supine posture, perhaps because of atelectasis. Although the $PaCO_2$ is usually normal in the

erect position, in some cases an elevated $PaCO_2$ in the supine position as well as during sleep has been observed. Bilateral diaphragmatic paralysis leads to chronic respiratory failure, with worsening of hypoxemia and hypercapnia during sleep.

An increased alveolar-arterial oxygen tension difference [$P(A\text{-}a)O_2$] and further mismatch of ventilation-perfusion relationships occur when the supine posture is assumed. The increased incidence of respiratory infection may be caused by chronic atelectasis and impaired mucociliary clearance. Radiofrequency electrophrenic pacing has been used successfully in some patients. Nocturnal ventilatory support, nasal CPAP, and chest cuirass have been used as therapies.

MYONEURAL AND MUSCULAR DISORDERS

Among these disorders are various neuromyopathies, demyelinating diseases, motor neuron diseases, and dystrophic muscle disorders. Although the etiology, pathogenesis, and nonrespiratory manifestations vary greatly in these diverse diseases, the main pulmonary problem relates to respiratory muscle weakness and chronic hypoventilation. In fact, respiratory failure may be the presenting symptom in many of these diseases (Table 2), and in their later stages, respiratory failure is common and frequently the cause of death.

Inherited muscular disorders
Muscular dystrophy
Duchenne muscular dystrophy
Myotonic dystrophy
Facioscapulohumeral muscular dystrophy
Limb girdle dystrophy
Oculopharyngeal dystrophy
Congenital myopathies
Nemaline (rod) myopathy
Centronuclear myopathy
Metabolic myopathies
Acid maltase deficiency
Mitochondrial myopathies
Periodic paralysis
Acquired myopathies
Inflammatory myopathies (polymyositis and dermatomyositis)
Systemic lupus erythematosus
Endocrine myopathies
Hyperthyroidism
Hypothyroidism
Hyperadrenocorticism and corticosteroid therapy
Acute steroid myopathy
Electrolyte disorders
Rhabdomyolysis

Reproduced with permission from Lynn DJ, Woods RP, Marshall JR. Respiratory dysfunction in muscular dystrophy and other myopathies. Clin Chest Med 1984; 5:661—674.

TABLE 2. *Myopathic diseases associatedwith respiratory dysfunction*

Myasthenia Gravis

Several pulmonary complications occur in myasthenia gravis. They can be categorized as complications of the disease itself and respiratory complications associated with therapy (Table 3). The respiratory muscles are involved in approximately 10% of patients with myasthenia gravis; the resultant respiratory failure may require prolonged ventilatory assistance. The risk for respiratory insufficiency is increased by surgery, infectious diseases, and the administration of corticosteroids or antimicrobial drugs. Untreated myasthenic patients show decreases in VC, TLC, dynamic lung volumes, and functional residual capacity (FRC), as well as in maximal inspiratory and expiratory forces. Patients with myasthenia gravis may have severe respiratory muscle involvement even when peripheral muscle weakness is mild. Repetitive surface electrode stimulation of the phrenic nerves is a useful and noninvasive method for identifying patients with myasthenia gravis in whom weakness of the diaphragm is suspected.

Reduced global respiratory muscle strength (reduced $P_{I_{max}}$ and $P_{E_{max}}$)
Reduced vital capacity (VC) as a result of
inspiratory muscle weakness, resulting in a reduction in inspiratory capacity
expiratory muscle weakness, resulting in a reduction in expiratory reserve volume
Fall in VC of >25% in supine position with severe diaphragmatic weakness
Increased residual volume (RV) in some patients
Decreased functional residual capacity (FRC)
Decreased transpulmonary pressure at FRC
Decreased maximal transdiaphragmatic pressure (Pdi_{max})
Rapid shallow breathing
Blunted ventilatory response to hypercapnia
Acute changes after anticholinesterase therapy
Improved global respiratory muscle function (increased $P_{I_{max}}$ and $P_{E_{max}}$)
Increased FRC because of greater respiratory muscle tone
Increased static compliance
Increased maximal transdiaphragmatic pressure
Minimal change in lung volumes
Improved ventilatory response to hypercapnia

$P_{I_{max}}$, maximal inspiratory pressure; $P_{E_{max}}$, maximal expiratory pressure.

Reproduced with permission from Zuwala JJ, Fleming RL. Respiratory dysfunction in myasthenia gravis. Clin Chest Med 1984; 15:683—691.

TABLE 3. *Effects of myasthenia gravison the respiratory system*

The patient with myasthenia gravis undergoing thymectomy presents special problems during and after anesthesia. In a study of 24 myasthenic patients who underwent thymectomy, assessment of four factors—duration of myasthenia, presence or absence of respiratory disease, pyridostigmine dosage, and VC—made it possible to predict in which patients postoperative mechanical ventilation would be needed and in which extubation could readily be performed. In addition, bulbar symptomatology and a prior history of respiratory failure should be considered in identifying patients who will need mechanical ventilation. Previous reports advocated tracheostomy in all instances to deal with complications in postoperative myasthenic patients. Others recommend that tracheostomy be performed if bulbar weakness is present, if the patient has a history of respiratory and myasthenic crises, or if the VC is 2 L. One study reported that repeated measurements of VC and blood gas parameters do not help to identify those in whom respiratory failure eventually develops. The anesthetic management of patients with myasthenia gravis is complicated by their increased sensitivity to nondepolarizing myoneural blocking drugs and resistance to depolarizing neuromuscular blocking drugs. Consequently, it is common practice to leave the endotracheal tube in place for 24 to 48 hours after surgery, and usually the patient's response to doses of anticholinesterase drugs is used as a guide to the progress of myasthenia after surgery. The major problems in myasthenic patients undergoing general anesthesia involve maintenance of adequate ventilation and provision of adequate relaxation and clearance of secretions.

Studies of the effect of administration of an anticholinesterase agent (pyridostigmine) on lung mechanics in eight patients with myasthenia gravis demonstrated impaired respiratory muscle function; the average VC increased by 14% after therapy. Pyridostigmine did not seem to modify specific airway conductance or the relationship between static lung recoil pressure and maximal expiratory flow. It did, however, markedly increase the peak expiratory flow and maximal inspiratory flow. This study suggested that the changes observed in patients were related solely to the increase in respiratory muscle force, and the major effect of the drug was an increase in the ability to inflate the lungs. Further studies using edrophonium chloride (Tensilon) have shown that this drug reduces the VC as well as the maximal inspiratory flows. Hence, the use of edrophonium chloride may be limited in patients with myasthenic crisis, especially those with obstructive lung disease. The increased airways resistance signals the limits of drug quantity that can be administered, especially in myasthenic patients who also have obstructive lung disease.

Plasmapheresis, immunosuppressive therapy, and thymectomy may prove effective in improving the respiratory function of some patients with myasthenia gravis. In a study of 22 patients who required prolonged mechanical ventilation because of respiratory failure secondary to myasthenia gravis, the most frequent cause of respiratory failure was surgery, and the most common type of procedure was thymectomy. All but one of the patients were weaned from the ventilator after 1 to 32 days of respiratory support.

Myasthenic Syndrome

Also known as *Eaton-Lambert syndrome,* myasthenic syndrome is a disorder of neuromuscular transmission in which the presence of IgG antibodies to presynaptic calcium channels causes them to be downregulated, thereby reducing the calcium-dependent, nerve impulse-evoked release of acetylcholine. Nearly 70% of patients with this syndrome have an underlying small-cell carcinoma of lung. In approximately half of all cases of myasthenic syndrome, a tumor is not detectable. The syndrome is characterized by proximal muscle weakness, tendency to fatigue, and progressive respiratory failure.

Myotonic and Progressive Muscular Dystrophy

Myotonic dystrophy and progressive muscular dystrophy can lead to insidious, chronic respiratory failure. This complication develops in approximately 10% of patients with myotonic dystrophy. Myotonic patients demonstrate decreased minute ventilation, hypoxemia, hypercapnia, and pulmonary hypertension, whereas patients with

nonmyotonic dystrophy exhibit a greater decrease in VC and maximal breathing capacity. FVC and MVV were decreased to 67% of predicted values and peak expiratory flow rate was reduced to 72% in 14 men with pseudohypertrophic muscular dystrophy. Pulmonary involvement in the form of respiratory muscle weakness is frequently observed in patients with limb girdle muscular dystrophy and occurs early in the disease. Children with nonmyotonic muscular dystrophy of the Duchenne type normally have well-preserved diaphragmatic function, but they commonly die of respiratory failure or pulmonary infection. Blunted respiratory drive is occasionally seen in congenital myopathies. Chronic alveolar hypoventilation has been reported in all major forms of muscular dystrophy. Studies of lung mechanics in patients with severe respiratory muscle weakness have shown that both maximal transpulmonary pressure and static expiratory compliance are low. The low compliance results from either microatelectasis or a generalized alteration of alveolar elastic properties.

Patients with muscular dystrophies face the same problems as those with other neuromyopathic diseases—namely, aspiration pneumonia, hypoventilation, and, in patients with dystrophic myocardial involvement, cardiomyopathy and pulmonary edema. The VC improves following vigorous respiratory therapy, including breathing exercises and intermittent positive-pressure therapy. A study of seven patients with mild myotonic dystrophy showed a consistently decreased hypoxic ventilatory response with a varying hypercapnic response. The high incidence of respiratory failure in such patients is most likely related to the decreased hypoxic ventilatory response, which occurs because of an underlying neurogenic deficit.

Daytime hypersomnolence is frequently reported by patients with myotonic dystrophy, and they often exhibit hypoxia during sleep. Obese patients with myotonic dystrophy are particularly at risk for the development of sleep apnea. These patients may demonstrate central apnea, an obstructive type of apnea, or a combination of the two. Detailed sleep studies in six young male patients with mild myotonic dystrophy and excessive daytime sleepiness showed evidence of sleep apnea syndrome, with high apnea indices in all. Other studies have shown no relation between hypoxic and hypercapnic ventilatory responses during wakefulness and sleep apnea indices. Both hypoxemia and hypercapnia worsen considerably during rapid-eye-movement (REM) sleep. Pulmonary and systemic arterial pressures are increased during sleep in these patients.

Ventilatory aids and mechanical respiratory assistance have been used in a domiciliary setting to support the respiratory function of such patients. They can have a meaningful life even though they require continuous mechanical ventilatory assistance. Spinal stabilization is one of the therapies available for patients with Duchenne muscular dystrophy. A retrospective study of 17 boys with Duchenne muscular dystrophy who underwent spinal stabilization found that the procedure altered neither the decline in pulmonary function nor survival. On the other hand, a study of 16 patients with spinal muscular atrophy who underwent surgical spinal stabilization demonstrated not only a reversal in the decline in lung function seen preoperatively but also a significant improvement at final follow-up.

Friedreich's Ataxia

Friedreich's ataxia is characterized by cardiac myopathy with decreased ventricular compliance, varying degrees of hypertrophy, and less frequently obstruction to ventricular outflow. Cardiopulmonary dysfunction is a primary cause of death in patients in whom the disease develops at a young age (average of 28 years). Progression of the neuromuscular disease leads to total respiratory failure. Three mechanisms contribute to the eventually fatal outcome: (1) Severe scoliosis, common in these patients, leads to respiratory failure; (2) neuromuscular dysfunction decreases the efficiency of the respiratory muscles; and (3) pulmonary edema occurs secondary to cardiomyopathy. Pulmonary function shows decreases in TLC and VC with elevation of the residual volume (RV) and FRC. Scoliosis itself may cause most of the respiratory difficulty in patients with Friedreich's ataxia.

A follow-up and a study repeated 3 years later in a group of 15 patients with classic Friedreich's ataxia showed striking decreases in RV and FRC. These changes could not be attributed entirely to the progression of scoliosis, as RV has been shown to be independent of the degree of scoliosis. Hence, it was concluded that the deterioration of cardiopulmonary function was multifactorial and that neuromyopathy appeared to be the main contributing factor to the deterioration in cardiopulmonary function, which is exacerbated by scoliosis and cardiomyopathy of varying degrees of severity. Another unusual feature in these patients is the low incidence of pulmonary infections.

Steinert's Myotonic Dystrophy

Steinert's myotonic dystrophy is a genetically transmitted (autosomal dominant) neuromuscular disease in which premature death is caused by cardiopulmonary complications. Both acute and chronic respiratory failure develop. Acute respiratory insufficiency is first diagnosed by the failure to generate the first postnatal breath, leading to a requirement for ventilatory support in the neonatal period. In adults with Steinert's dystrophy, acute respiratory disease can be precipitated during recovery from general anesthesia. Chronic respiratory complications include pneumonia, weakness of the respiratory muscles and hypoventilation, increased work of breathing, and altered central control of respiration. Both the blunted chemical drive of breathing and the respiratory muscle weakness have been cited in the pathophysiology of premature death in these patients. Studies have shown that the sensitivity of chemoreceptors in the respiratory centers is well preserved; however, the output to breathing is modulated by the impaired ventilatory mechanics, which causes tachypnea even in the absence of restricted lung volume.

Demyelinating Diseases

Multiple sclerosis, a relatively common demyelinating disease in Western countries, may lead to several types of respiratory complications (Table 4). The pulmonary complications, however, tend to be mild in the majority of patients. In a report of the natural history of multiple sclerosis in 840 patients, it was noted that involvement of the vital centers of the central nervous system was rare and confined to patients with acute disease who died within a few months of onset. This series included three deaths caused by respiratory failure, one of which occurred within 3 months of onset.

Abnormality	Anatomic localization	Clinical findings at bedside
Paralysis of voluntary respiration	Bilateral corticospinal tracts, brainstem, or upper cervical cord	Inability voluntarily to increase tidal volume or hold breath, automatic respirations intact
Paralysis of automatic respiration	Dorsomedial medulla, nucleus ambiguus, and medial lemnisci	Apnea during drowsiness, normal voluntary control of respiration while awake
Diaphragmatic paralysis (unilateral or bilateral)	Upper cervical cord (C1-4 level)	Paradoxical movements of chest wall and abdomen, use of accessory muscles, orthopnea
Apneustic breathing	Lower brainstem	Inspiratory apneusis, voluntary control between episodes
Paroxysmal hyperventilation	Lower brainstem	Apneic pauses after hyperventilation with or without bulbar "tonic spasms"
Obstructive sleep apnea	Tegmentum of medulla	Snoring, sleep apnea with or without hiccups
Neurogenic pulmonary edema	Medulla in region of nucleus tractus solitarii and floor of fourth ventricle	Pulmonary edema without signs of heart failure

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TABLE 4. *Patterns of respiratory involvement in multiple sclerosis*

In a report of four cases of respiratory failure associated with multiple sclerosis, the presence of lesions in high segmental sensory levels was emphasized. In these patients, respiratory failure was secondary to demyelinating lesions involving the bulbar area (especially the region of the respiratory center) and pyramidal tracts bilaterally and possibly the anterior horns. Severe involvement of the spinal cord by the demyelinating process may be complicated by respiratory failure. Hyperventilation, decreased response to carbon dioxide, irregular breathing, and sleep-induced apnea have been noted. Three cases of spontaneous pneumothorax were noted among 141 patients identified as incidence cases of spontaneous pneumothorax in an epidemiologic study. This occurrence was reported to be unlikely on the basis of chance alone. A statistically low incidence (less than expected) of pulmonary embolism has been noted. A study of 40 patients with multiple sclerosis concluded that descriptive clinical indices and clinical assessment were superior to spirometry as predictors of clinical illness; however, determination of MVV uncovered subtle respiratory muscle weakness.

Other Neuropathies

Charcot-Marie-Tooth disease encompasses a collection of chronic degenerative neuropathic conditions and includes cases of hereditary motor and sensory neuropathies. The major clinical feature is slowly progressive weakness, predominantly of the distal lower limbs. Diaphragmatic dysfunction has been described in several patients with this disease. Neuropathic changes characteristic of the disease have been observed in phrenic nerves.

Other Myopathies

Metabolic Myopathiesmaltase

Acid deficiency, also called *Pompe's disease,* is a type II glycogen storage disease known to cause respiratory failure. The deficiency of the enzyme acid maltase leads to engorgement of cellular vacuoles with glycogen excess. Acid maltase deficiency can present with respiratory failure. Proximal myopathy and weakness as well as diaphragmatic dysfunction occurs; isolated diaphragmatic paralysis also has been noted. Acid maltase deficiency classically affects infants and children, with a few sporadic cases appearing in adults.

Respiratory involvement, including ventilatory failure and diaphragmatic paralysis, has been described in various types of myopathies, including centronuclear myopathies (congenital myotubular myopathy), progressive congenital myopathy with type I fiber atrophy, Isaac's syndrome (myokymia, generalized muscular stiffness, and decreased tendon reflexes), and Kearns-Sayre syndrome (also known as *oculocraniosomatic neuromuscular disease,* characterized by a combination of all or some of the following: ptosis, external ophthalmoplegia, retinal degeneration, axial muscle weakness, deafness, ataxia, pyramidal tract abnormalities, small stature, mental retardation, endocrine abnormalities, and cardiac conduction defects). Mitochondrial myopathy leading to chronic respiratory failure with the need for mechanical ventilation has been described.

The porphyrias (acute intermittent porphyria, porphyria variegata, and hereditary coproporphyria) are disorders of porphyrin metabolism. Each of these may be associated with ascending paralysis and respiratory failure. The neuropathy in these diseases probably is caused by the toxic effect of the accumulated porphyrin precursors aminolevulinic acid and porphobilinogen.

Muscular weakness and respiratory failure have been noted in rhabdomyolysis (myoglobinuria), hypophosphatemia, hypokalemia, polymyositis-dermatomyositis, and familial periodic paralysis.

Toxic Myopathies

Organic phosphate poisoning is a common occurrence in certain regions of the world where these compounds are used as agricultural insecticides. Accidental or suicidal ingestion can lead to serious respiratory problems as a result of muscarinic and nicotinic effects. Organic phosphates cause muscle paralysis by inhibiting acetylcholinesterase. The pulmonary features include rhinorrhea, excessive bronchial secretions, pulmonary edema, laryngospasm, bronchospasm, respiratory muscle paralysis, and paralysis of the respiratory centers. In a report of 107 subjects in Taiwan exposed to organic phosphate or carbonate, respiratory failure developed in 40%, and 51% died. The use of pralidoxime did not reduce the incidence of respiratory failure. Importantly, aggressive treatment within the first 96 hours resulted in prevention of respiratory failure.

Botulism is a disorder of the neuromuscular junctions caused by the binding of neurotoxins elaborated by the bacterium *Clostridium botulinum.* Botulism characteristically causes multiple cranial motor neuropathies. Clinical findings include blurred vision, paralysis of pupillary muscles, ileus, dry mouth, and descending paralysis involving extraocular and bulbar muscles, with frequent progression to respiratory muscle weakness. Muscle weakness of the upper airways may result in dysphonia and nasal regurgitation. In a study of six patients with botulism, weakness of the ventilatory muscles was noted early in the course of poisoning in all patients, but recovery was the rule, although it took several months. Long-term follow-up in 13 patients revealed that residual symptoms, including dyspnea and fatigue, were common at 2 years after intoxication, even though lung function had returned to normal in all.

Summary of Respiratory Problems in Myoneural and Muscular Disorders

The main respiratory complications in neuropathies and dystrophic muscular diseases include hypoventilation with progressive respiratory failure, restrictive pulmonary dysfunction, aspiration pneumonia, recurrent infection, and cardiopulmonary problems in patients with cardiomyopathy-associated muscular dystrophies. Pulmonary embolism also occurs with greater frequency. Depending on the severity of the underlying disease, patients may have symptoms of anxiety, lethargy, headaches, dyspnea, and occasionally a sensation of suffocation. Severe hypoventilation leads to confusion, coma, cyanosis, severe hypoxemia, hypercapnia, and death. In patients with severe, protracted respiratory muscle weakness, marked alterations develop in the static mechanical properties of the lungs. Alveolar collapse produces low pulmonary compliance. Spirometric evaluation of lung function and assessment of respiratory muscle function by measurement of inspiratory and expiratory pressures aid in gauging the severity of respiratory involvement. A step-by-step approach to the evaluation and diagnosis of respiratory muscle weakness is important in the management of these patients (Fig. 4).

DISEASES OF PERIPHERAL NERVES AND ANTERIOR HORN CELLS

Poliomyelitis

Poliomyelitis is a typical example of an anterior horn cell disease that can lead to respiratory failure. Respiratory involvement from poliomyelitis may go undetected. Indeed, many patients remain in a state of chronic hypoventilation. Pulmonary function studies in patients who have recovered from poliomyelitis but who have residual muscle weakness have demonstrated that the majority experience exertional dyspnea and recurrent respiratory tract infections. Late onset of respiratory failure and polycythemia have been described in a significant number of patients with previous poliomyelitis. Respiratory failure is more common in poliomyelitis patients who have kyphoscoliosis and diaphragmatic paralysis. In a study of 55 patients with previous poliomyelitis, VC was reduced to approximately 20%–40% of the predicted normal values and TLC was correspondingly reduced in the majority of patients, but RV was within normal limits. The PaO_2 is usually normal despite severe reduction in VC. However, 60% of patients with a VC that is <50% of the predicted value have exhibited a PaO_2 of <80 mmHg. Hypercapnia is seen at some stage in 35% of patients. The decreased VC is a consequence of diminished compliance of the chest wall and lung parenchyma.

In patients with previous poliomyelitis and severe respiratory failure, long-term ventilatory assistance is required. Four years after the epidemic of poliomyelitis in Copenhagen in 1952, in which 264 patients underwent tracheostomy and 232 were treated with positive-pressure ventilation, 24 of 138 survivors were considered to be chronically respirator-dependent. Nine of these died during the next 17 years. Among the 24 chronically respirator-dependent patients, 13 were alive in 1975 and were receiving constant ventilatory assistance.

Guillain-Barré Syndrome

Guillain-Barré syndrome (acute polyneuritis) is the most common cause of acute paralysis and neuromuscular ventilatory failure. Guillain-Barré syndrome is probably the most common neuromuscular cause of acute respiratory failure. It is a demyelinating disease of motor neurons, and it is manifested clinically as symmetric ascending paralysis and a lack of cellular response in the cerebrospinal fluid despite an increase in protein concentration. A typical patient is younger than 26 years or between 45 and 60 years of age. Seasonal clustering (late summer and autumn) is a feature. However, atypical clinical features may make Guillain-Barré syndrome difficult to diagnose, and therefore a process of exclusion is necessary. Respiratory complications develop in nearly half the patients. The diaphragmatic and intercostal muscular paralysis produce progressive alveolar hypoventilation. The patient frequently is not disturbed by this weakness because of its gradual onset and slow progression. Indeed, significant respiratory muscle insufficiency can be present without being detected clinically. Paralysis of the ninth and tenth cranial nerves may lead to dysphagia, laryngeal paralysis, and aspiration. Neurogenic pulmonary edema has occurred in patients with Guillain-Barré syndrome.

The clinical course of Guillain-Barré syndrome is variable, but complete recovery can be expected in most cases. Systemic corticosteroids have been used as treatment, but because of the extremely variable course of the disease, it is difficult to evaluate their role. Treatment with plasma exchange and immune globulins has decreased the duration of mechanical ventilation by half. Respiratory failure requires mechanical ventilatory support in 10%–30% of patients. In a series of 79 patients with acute Guillain-Barré syndrome, 27% required admittance to the respiratory intensive care unit for 14 to 105 days, and nasotracheal intubation followed by tracheostomy and mechanical ventilation were required in 18%. The mortality was 4%. Repeated measurements of VC have been used as predictive parameters of the need for mechanical ventilation and weaning success. Up to 10% of patients remain seriously disabled, and approximately 5% die as a result of complications. Most deaths are caused by cardiopulmonary complications.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is the most common motor neuron disease in the United States. Destruction of the anterior horn cells in the spinal cord leads to atrophy and muscle weakness. The loss of anterior horn cells is most marked in the cervical, lumbosacral, and lower thoracic spinal segments. Most patients with amyotrophic lateral sclerosis exhibit progressive neurologic deterioration without remission, with an average life expectancy of 4 years after the onset of symptoms.

Respiratory muscle involvement can be detected in most patients before respiratory symptoms begin, and respiratory failure occurs as the initial manifestation in some. However, patients who have respiratory symptoms, decreased FVC, and an abnormal $PaO_2/PaCO_2$ ratio are more likely to exhibit increased phrenic nerve latencies or absent response than are patients with amyotrophic lateral sclerosis who have no respiratory problems. Irreversible hypoventilation leading to fatal respiratory failure is common in the later stages of the disease. Hypopnea during sleep as the presenting symptom has been described. Sleep and breathing were assessed in 18 patients with amyotrophic lateral sclerosis involving the bulbar muscles involvement and 10 controls. The patients had more arousals per hour, more stage 1 sleep, a shorter

total sleep time, and mild sleep-disordered breathing with a greater apnea-hypopnea index than did the control subjects. Eight patients had sleep-disordered breathing consisting of periods of hypoventilation, predominantly during REM sleep. No obstructive sleep apnea was observed.

Among 218 patients with amyotrophic lateral sclerosis, indications of abnormal lung function were detected in 94%. Decreased MVV and FVC were the significant findings. Severe diminutions of maximal inspiratory and expiratory pressures as well as MVV is observed in most, and the majority of patients have low lung volumes and unaltered RV volume and FRC. Some studies have found that TLC is well preserved even in an advanced stage of the disease, provided that diaphragmatic function is not grossly compromised. Obstructive pulmonary disease, although clinically not well recognized, has been noted in up to 19% of patients. Repetitive aspiration caused by bulbar incoordination perhaps is responsible.

The second major problem is aspiration pneumonia, as 25% of patients with amyotrophic lateral sclerosis have bulbar paralysis, which aggravates the problem of aspiration (Fig. 5). Respiratory insufficiency in patients with amyotrophic lateral sclerosis also may be a consequence of unilateral or bilateral diaphragmatic paralysis.

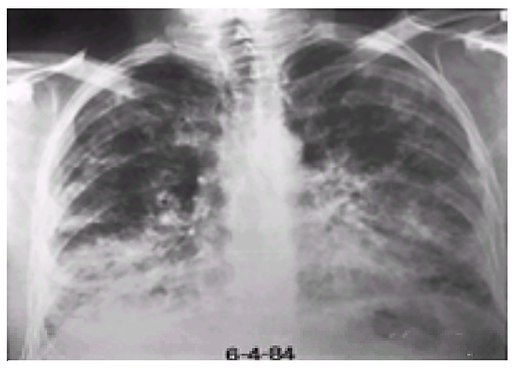

FIG. 5. Recurrent episodes of aspiration pneumonia secondary to bulbar involvement in amyotrophic lateral sclerosis.

The prognosis in the motor neuron diseases depends on the rapidity with which the underlying disorder progresses and the degree of respiratory muscle involvement. Aggressive, long-term ventilatory assistance and tracheostomy usually are not recommended because of the relentless progression of the disease. Selected patients, those who demonstrate slow progression of disease, are occasionally treated using CPAP or tracheostomy with ventilator assistance. In one study of 18 patients with amyotrophic lateral sclerosis, significantly prolonged survival was demonstrated in subjects who elected to receive noninvasive mechanical ventilation: In one study of 18 patients with amyotrophic lateral sclerosis, significantly prolonged survival was demonstrated in subjects who elected to receive noninvasive mechanical ventilation: 80 days for patients who had therapy versus 19 days for patients who did not. Prevention of aspiration pneumonia and nonaggressive palliative therapy are the prudent goals.

DYSKINETIC DISORDERS

Extrapyramidal diseases, such as parkinsonian syndrome, may produce severe, prolonged spasm of the respiratory musculature and consequent respiratory insufficiency. Respiratory abnormalities described in extrapyramidal diseases are now believed to involve the nigrostriatal dopaminergic system. In addition, these patients have episodes of respiratory spasms or tics associated with grunting, snorting, or puffing. It is postulated that the respiratory dyskinesias are related to destruction of mesencephalic and pontine respiratory centers governing the lower bulbar regions.

Parkinson's Disease

Parkinson's disease is a common dyskinetic disorder, and although pulmonary involvement is frequent and considered to be the common cause of death, it rarely is recognized clinically. Pneumonia and pulmonary embolism are the two most frequent causes of overall mortality in Parkinson's disease. Parkinson's disease is associated with pathologic changes in the reticular formation of the brainstem, and hence the afferent or efferent pathways involved in the control of respiration may be affected. More than 85% of patients have impaired ventilatory function, which is related to the severity of disease rather than to underlying lung disease. Patients with more severe disease tend to exhibit more pronounced pulmonary dysfunction. In a detailed study of 63 patients with Parkinson's disease, a restrictive ventilatory defect was noted in 54 patients, all of whom had an FEV_1/FVC ratio that was >80% of predicted.

The more common pulmonary function abnormality, however, is the obstructive type. It is been postulated that the obstructive lung disease in Parkinson's disease may be related to increased parasympathetic tone and infection. It is more likely that the airway abnormalities reflect involvement of the upper airway musculature.

Upper airways obstruction is relatively common in patients with Parkinson's disease. Among 31 patients with Parkinson's disease who underwent detailed pulmonary function testing, evidence of obstructive pulmonary function was identified in one third; lung function did not improve after therapy with levodopa. However, significant abatement of symptoms of Parkinson's disease was noted, and hence it was concluded that the obstructive pulmonary disease did not result from the Parkinson's disease. In contrast, 10 patients in another study exhibited a significant improvement in MVV following therapy with levodopa, but no correlation was found between clinical and pulmonary functional improvement.

An abnormal flow-volume loop contour is a frequent finding in patients with Parkinson's disease (Fig. 6). A study of the maximal inspiratory and expiratory flow-volume curves in 63 patients with different stages of Parkinson's disease, of whom 59 were undergoing treatment, showed that 31 patients (49%) had abnormal flow-volume curves. Physiologic evidence of upper airway obstruction was observed in three cases. The clinical aspects and duration of disease did not influence the pattern of the curve.

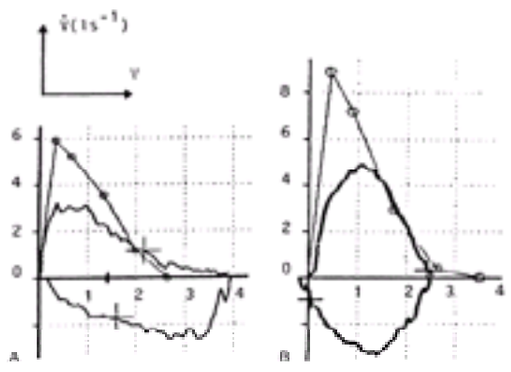

FIG. 6. Flow-volume loops described in patients with Parkinson's disease. **A:** Loop exhibits “saw-toothing” of both inspiratory and expiratory limbs, thought to result from rapid changes in laryngeal and supraglottic diameter. **B:** Loop exhibits a delay in achieving peak flow and a decrease in peak flow. (Reproduced with permission from Bogaard JM, Hovestadt A, Meerwaldt J, et al. Maximal expiratory and inspiratory flow-volume curves in Parkinson's disease. *Am Rev Respir Dis* 1989;139:610.)

Erratic breathing, also known as *chaotic breathing,* is common. The ventilatory defect is caused by rigidity and weakness of the respiratory muscles, which abate with treatment.

Levodopa is commonly used to treat Parkinson's disease. In patients with neuroleptic-induced tardive dyskinesia or levodopa-induced dyskinesia, acute dyspnea and chest pain may develop secondary to severe, involuntary muscle incoordination. Bromocriptine has been used in the treatment of Parkinson's disease. In a review of 123 patients treated with bromocriptine, six had pleurisy accompanied by effusion, pleural thickening, and pulmonary infiltrates. The daily dose of bromocriptine ranged from 20 to 90 mg, and the duration of treatment ranged from 6 to 27 months. Three of the patients were also taking levodopa with benserazide, from 400 to 800 mg/d. The pleuropulmonary complications are believed to have been caused by bromocriptine rather than levodopa. Similar complications have been noted in a patient

receiving cabergoline. Bromocriptine-induced myocardial infarction and secondary pulmonary edema should be considered in any patient using this drug, because bromocriptine is reported to cause coronary vasospasm and myocardial infarction; 24 such cases have been identified in the literature.

Respiratory Dyskinesia

The term *respiratory dyskinesia* has been used to describe extrapyramidal dysfunction with dyspnea that is not related to Parkinson's disease. It may mimic chronic psychogenic hyperventilation syndrome, and so it has been called *pseudopsychogenic hyperventilation.* Respiratory dyskinesia is probably related to destruction of mesencephalic and pontine respiratory centers governing the lower bulbar regions. When these areas of the brainstem are affected by pathologic process, irregular respiratory movements result. In both respiratory dyskinesia and chronic hyperventilation syndrome, abnormal respiratory movements worsen with stress and disappear with sleep.

In patients with respiratory dyskinesia, speech is interrupted by involuntary sounds or grunts, snorting, and puffing; respiration is awkward, and the patient appears distressed and anxious even when pain or dyspnea is absent. In a report of four patients with severe involuntary respiratory dyskinesia, respiratory findings included irregular respiratory rate, shortness of breath, and discomfort in the chest. Three of these patients had neuroleptic-induced tardive dyskinesia, and one had levodopa-induced dyskinesia. Many of these initially were believed to have cardiopulmonary disorders. Dopaminergic manipulation was successful in correcting the subjective discomfort and respiratory abnormalities in all these patients. Reserpine was used in three patients, and the dose of levodopa was lowered in another.

Tardive Dyskinesia

Tardive dyskinesia is a syndrome of involuntary movement characterized by facial involvement and temporal association with ingestion of neuroleptic drugs. Respiratory dyskinesia may well be a part of tardive dyskinesia syndrome. Patients with subjective tardive dyskinesia should undergo an assessment of respiratory function. Stiff-man syndrome is reported to be associated with progressive respiratory failure.

Respiratory tardive dyskinesia (clinical evidence of irregular respiration) was observed in 2% of a large group of continuously hospitalized patients with tardive dyskinesia and psychiatric illness. The prevalence of respiratory irregularities was significantly greater in patients with an organic mental disorder (11%) than in those without. None had respiratory symptoms.

CEREBELLAR DISORDERS

Arnold-Chiari Malformation

Arnold-Chiari malformation is a congenital anomaly characterized by caudal displacement of the inferior cerebellar vermis, kinking of the medulla oblongata, a small posterior fossa, a low tentorium cerebelli, and displacement of the fourth ventricle into the spinal canal. Coexistence of spina bifida, hydrocephalus, and other anomalies of the neural axis is common. The most common respiratory problem is the dramatic onset of laryngeal stridor, which appears precipitously and is closely correlated with increased intracranial pressure. Three vagally mediated mechanisms have been postulated: brainstem disease, compression of the vagus nerves at the level of the foramen magnum, and traction of the vagus nerves by caudal displacement of the brainstem. Respiratory obstruction and apnea with bilateral abductor vocal cord paralysis also has been described. Depressed ventilatory response to carbon dioxide has been observed. However, physiologic studies have shown that patients with uncomplicated Arnold-Chiari malformation have normal respiratory function.

Respiratory abnormalities, such as respiratory distress, apnea, vocal cord paralysis, and inability to swallow, are known complications of Arnold-Chiari malformation. Hemorrhages in the medulla oblongata in addition to compression or traction of the vagus and other lower cranial nerves may cause these symptoms. Respiratory problems result from impaired function of the ninth, tenth, and twelfth cranial nerves. In a study of 14 children who had Arnold-Chiari malformation, vascular lesions resulting in hemorrhage, hemorrhagic necrosis, or bland infarcts in the tegmentum of the medulla oblongata were found in 12 children with clinical abnormalities of respiratory function and dysfunction of the lower cranial nerves. Surgical decompression of the posterior fossa has been shown to relieve respiratory symptoms in some cases. Respiratory problems frequently cause death or markedly shorten the life expectancy of affected children.

Joubert's Syndrome

Joubert's syndrome, caused by agenesis of the cerebellar vermis, is characterized by abnormal eye movements, ataxia, retardation, and episodic hyperpnea. An abnormal respiratory pattern—namely, persistent tachypnea from birth—is the clinical hallmark of Joubert's syndrome and may be detectable *in utero,* thus permitting prenatal diagnosis. Peak respiratory rates in excess of 200 breaths per minute during wakefulness and of 150 breaths per minute with tachypneic episodes lasting up to 150 seconds have been described. Apneic episodes in non-REM sleep lasting 10 to 20 seconds, with a maximal duration of 45 seconds, have been observed.

PERIPHERAL CHEMORECEPTORS

Carotid Body Resection

Respiratory hypoxic drive is controlled primarily by peripheral chemoreceptors situated in the carotid bodies. Although the carotid bodies initiate the hyperpneic response to hypoxia, they have no part in ventilatory control in normal persons at sea level, either at rest or after exercise. Therapeutic carotid body resection has been advocated for bronchial asthma, but beneficial effects have not been proved. Bilateral carotid endarterectomy may abolish compensatory hyperventilation and cause hypoxemia. Furthermore, bilateral carotid body resection may preclude compensatory ventilation when hypoxemia develops. However, it has been reported that in patients who underwent bilateral carotid body resection for asthma, the ventilatory response to increased $PaCO_2$ was reduced, but hypoventilation did not occur. A patient with cough syncope has been described who was found to have carotid sinus hypersensitivity and mixed cardioinhibitory and vasodepressor responses. The cough syncope improved after denervation of the more hypersensitive carotid sinus.

Sympathectomy

Dorsal sympathectomy is performed for a wide spectrum of vascular diseases. Most patients have some shortness of breath during the first days after the operation. Pulmonary function tests in a group of 15 patients before and 1 to 3 months after upper dorsal sympathectomy showed significant decreases in all lung volumes and maximal expiratory flows. The reasons for these include a loss of diaphragmatic tone as a result of the surgical procedure, surgical transection of the scalenus anticus muscle leading to impairment of maximal inspiration and decreases in TLC and VC, and pulmonary constriction caused by sympathetic denervation.

DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Familial Dysautonomia (Riley-Day Syndrome)

The term *dysautonomia* denotes autonomic dysfunction. Both acquired and familial dysautonomia can lead to respiratory problems. Central and obstructive sleep apnea both occur in patients with dysautonomia. Familial dysautonomia is a mendelian recessive disease associated with a relative unresponsiveness to hypoxia and hypercapnia, believed to result from a defect in the carotid body. Breath-holding attacks have been seen in 66% of 210 children with familial dysautonomia, and fleeting episodes of hyperventilation followed by profound hypoxia have been observed. Hyperventilation followed by hypoxia, attributed to incoordinated central depression consequent to reduced cerebral blood flow, has been reported in these patients. Familial dysautonomia in 13 patients was associated with abnormal sleep patterns (decreased amounts of REM sleep and increased REM latencies) in all patients; the average number of apneic spells was 73 per night.

Acquired Dysautonomia

Dysautonomia is acquired as a result of diabetic autonomic neuropathy, amyloidosis, Shy-Drager syndrome, Arnold-Chiari malformation, botulism, generalized neuropathy, neoplasms, Parkinson's disease, bilateral cervical cordotomy, and bulbar poliomyelitis. A 6-year-old girl in whom sleep-induced hypoventilation and apnea with diffuse dysautonomic changes developed died 2 years later during sleep; detailed pathologic analysis revealed a ganglioneuroma originating in the sympathetic ganglia. This type of acquired progressive dysautonomia is rare. Dysautonomia can be associated with respiratory failure resulting from inability of the chemoreceptors to respond to hypoxia.

Aspiration pneumonia is a significant complication in patients with diabetic autonomic neuropathy. Studies of gastric volume and pH have shown solid, undigested food particles to be present more often in the gastric contents of diabetic patients with autonomic neuropathy than in diabetic patients without autonomic neuropathy.

MISCELLANEOUS NEUROLOGIC DISORDERS

Alzheimer's Disease

Pulmonary complications are being recognized more frequently in patients with progressive or advanced Alzheimer's disease. A prospective study of 25 patients with moderate or severe Alzheimer's disease employed videofluoroscopy to assess the incidence of oropharyngeal swallowing abnormalities. Six patients (28.6%) exhibited aspiration, and only four patients showed unequivocally normal performance. Swallowing abnormalities were associated significantly with duration of dementia, eating dependency, and abnormal oral praxis. A trend toward a higher incidence of aspiration in patients with more severe dementia was noted.

Cerebral Palsy

Patients with cerebral palsy are predisposed to respiratory infection because respiratory neuromotor control is affected. In one study of dynamic and static lung volumes in children with cerebral palsy, total capacity was significantly reduced, averaging 85% of the predicted normal values; a 50% decrease in VC was noted in subjects with dyskinesia, and a 67% decrease in patients with spasticity. The features of lung disease in these children were similar to those of chronic obstructive pulmonary disease. Breathing exercises in a study of 10 children with spastic cerebral palsy showed a mean increase in VC to 30% of pretest values, and this increase in VC nearly matched the normal predicted levels.

Migraine

Severe hyperventilation occasionally encountered in patients with migraine has led to diagnostic difficulties. In the reported cases, hyperventilation occurred at the peak of the migraine, making the attack seem worse to the patient. It is speculated that in these cases the migraine was exacerbated by the vasoconstrictor effect of hyperventilation. The term *pulmonary migraine* was suggested to describe a localized atelectasis of the lung associated with migraine headaches in a 14-year-old girl. Neuropathologic findings included deep areas of microinfarction in the basal ganglia and a remarkable sparing of brainstem nuclei associated with respiratory function.

Dystonia

Dystonia is a rare disorder characterized by involuntary sustained muscle contractions that frequently cause twisting and repetitive movements or abnormal postures. The disorder can be primary or secondary and may affect any muscle.

A combination of upper airway and diaphragmatic dysfunction has been described in these patients. The results of a study of 26 patients with dystonia indicated that dyspnea in dystonia appeared to be caused by excessive and/or desynchronized contractions of the upper airways and/or diaphragm, with usually normal gas exchange.

Reye's Syndrome

Reye's syndrome is characterized by encephalopathy and fatty accumulation in visceral organs, especially in children. Excessive lipolysis and mobilization of fat occur in this disorder, which has been shown to be associated with hypoxemia, hypocapnia, and tachypnea as well as interstitial pneumonitis, thickening of the alveolar walls, and the presence of intraalveolar foamy histiocytes.

Krabbe's Globoid Cell Leukodystrophy

Krabbe's globoid cell leukodystrophy is a hereditary degenerative brain disease caused by lack of the enzyme galactosylceramide galactosidase. The disease is characterized by the progressive development of retardation, failure to thrive, seizures, spasticity, and blindness, culminating in death by the age of 2 to 3 years. Symptoms begin at 4 to 8 months of age. In an 8-week-old boy who presented with rapidly progressive respiratory failure and died shortly thereafter, lung biopsy revealed numerous intraalveolar and a few interstitial macrophages containing intracellular structures that stained positively with periodic acid-Schiff.

Pulmonary Effects of Electroconvulsive Therapy

Electroconvulsive therapy is used in the treatment of major depressive disorders, schizophrenia, mania, and other conditions. Aspiration may occur, especially in elderly patients. Neurogenic pulmonary edema following electroconvulsive therapy has been observed in these patients.

Pulmonary Effects of Ventriculoatrial Shunt

Ventriculoatrial and ventriculoperitoneal shunts are placed to treat high-pressure hydrocephalus. The catheter tips occasionally become blocked or infected. Recurrent discharge of the proteinaceous debris from the catheter tip into the pulmonary circulation can produce recurrent embolic phenomena and secondary pulmonary hypertension. The onset of pulmonary hypertension in these patients is insidious and invariably leads to right ventricular failure. Empyema has been described as a complication of ventriculoperitoneal shunt.

Pulmonary Embolism in Neurologic Diseases

Pulmonary embolism is a common occurrence in patients with neurologic disorders and in those who undergo neurosurgery. A major etiologic factor is venous thromboembolism, especially in the lower extremities, as a result of stasis caused by significant immobilization. The risk for venous thromboembolism and pulmonary embolism is higher in patients with head trauma, stroke, spinal cord injury, brain tumor, and subarachnoid hemorrhage, and in patients who have undergone neurosurgical operations. In one study, spinal cord injury accounted for 31% of all pulmonary embolisms in the total trauma population of 2525 patients. Subacute or chronic neurologic disorders also are associated with a higher risk for pulmonary embolism. For instance, a review of the results of 60 complete autopsies performed in patients with parkinsonian syndrome revealed that pulmonary embolism was second only to pneumonia as the most common cause of overall mortality.

Anticoagulant therapy in patients with intracranial diseases is fraught with the risk of causing or aggravating hemorrhage in the brain or other areas within the cranium. Excessive anticoagulation has resulted in fatal intracerebral hemorrhage in patients with brain tumors. The risk for pulmonary embolism, however, exceeds the risk for severe or fatal bleeding from prophylactic or therapeutic anticoagulation. Studies have noted that prophylactic insertion of a filter in the inferior vena cava is effective in preventing pulmonary emboli in these patients.

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Teitelbaum JS, Borel CO. Respiratory dysfunction in Guillain-Barré syndrome. *Clin Chest Med* 1994;15:705–714. *A detailed review of pulmonary complications in Guillain-Barré syndrome, the most common cause of acute paralysis and neuromuscular ventilatory failure. The authors state that a good clinical outcome depends to a large extent on anticipation and management of ventilatory failure and its complications. The role of plasma exchange and immune globulins is discussed.*

Wilson JT, Rogers FB, Wald SL, Shackford SR, Ricci MA. Prophylactic vena cava filter insertion in patients with traumatic spinal cord injury: preliminary results. *Neurosurgery* 1994;35:234–239. *A retrospective, 5-year review of 111 patients with traumatic spinal cord injury; eight pulmonary emboli were documented in seven patients, and there were three fatalities. Six pulmonary embolisms occurred after discharge from the acute care facility. Spinal cord injury accounted for 31% of all pulmonary embolisms in the total trauma population of 2525 patients. After inferior venal caval filters were inserted in 15 patients, no case of deep venous thrombosis or pulmonary embolism occurred.*

Woratyla SP, Morgan AS, Mackay L, Bernstein B, Barba C. Factors associated with early-onset pneumonia in the severely brain-injured patient. *Conn Med* 1995;59:643–647. *Among 125 patients with closed head injury, pneumonia was diagnosed in 60%, and early pneumonia developed in 48%. Early pneumonia was more frequent in patients with a lower score on the Glasgow Coma Scale (5) and in those with swallowing disorders and evidence of aspiration. Patients with early pneumonia had prolonged intubation times, intensive care unit stays, and hospital stays.*

CHAPTER

61 Skeletal Diseases

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INTRODUCTION

The skeletal thorax is as much a part of the respiratory system as are the lungs, and hence it plays a major role in normal pulmonary function. Instability of the chest wall can lead to respiratory failure, as exemplified by ventilatory failure in patients with flail chest. Congenital and acquired defects and diseases of the thoracic cage may interfere with the normal respiratory mechanics. Occasionally, diseases of the extrathoracic skeleton may be associated with lung problems. An excellent example of this is the pulmonary parenchymal process that occurs in patients with ankylosing spondylitis. In this chapter, some common and uncommon skeletal diseases in which the respiratory system is involved are discussed. Certain disease entities, such as Marfan's syndrome, that are not primary skeletal diseases are nonetheless covered here, because skeletal abnormalities are clinically evident in such patients. The major spinal deformities are scoliosis, kyphosis, pectus excavatum, pectus carinatum, and straight-back syndrome. Discussions of respiratory complications in ankylosing spondylitis and several other skeletal disorders are also included.

KYPHOSCOLIOSIS

Scoliosis is deformity of the spine characterized by marked lateral curvature, kyphosis is the abnormally accentuated posterior curvature of the spine, and kyphoscoliosis is the combination of the two, which results in a lateral bending and rotation of the vertebral column. Pulmonary problems occur in both scoliosis and kyphoscoliosis (Fig. 1).

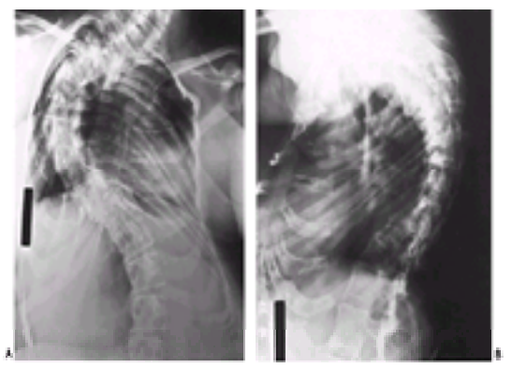

FIG. 1. Severe thoracic kyphoscoliosis. **A:** Posteroanterior view. **B:** Left lateral view.

Scoliosis is by far the most common spinal deformity. An incidence of 4/1000 population was found by a roentgenographic survey. Scoliosis is classified etiologically into five varieties: idiopathic, congenital, neuropathic (poliomyelitis, cerebral palsy, and syringomyelia), myopathic (muscular dystrophy, amyotonia, and Friedreich's ataxia), and traumatic. Scoliosis also is seen in mesenchymal disorders and in association with neurofibromatosis. In practice, 80% of cases of scoliosis are idiopathic. Among infants, the male-to-female ratio is 6:4, but among cases that begin in adolescence—the largest group—the ratio is 1:9, and overall it is 2:8. Infantile scoliosis is reported usually to involve a curvature toward the left, whereas scoliosis in adolescent girls is usually toward the right. A familial basis for idiopathic scoliosis exists. Among first-, second-, and third-degree relatives of children with idiopathic scoliosis, abnormal spinal curvature occurs 20 times as often as in a comparable group of the general population. In congenital scoliosis of early onset, there is failure of alveolar multiplication, whereas in idiopathic scoliosis, the alveoli do not enlarge normally.

Idiopathic scoliosis in adolescent girls usually involves 7 to 10 vertebrae. The curvature or angulation of a scoliotic spine is best measured by the Cobb method (Fig. 2). Pulmonary symptoms are not seen until the curvature exceeds 70°. Adolescent idiopathic thoracic curves of 60° to 80° have been observed to increase by an average of 30° during a period of 25 years after completion of growth. The Cobb angle has been traditionally employed in the clinical assessment and correlation of spinal deformity and pulmonary function tests. However, a study of 70 adolescents (mean age, 13.8 years) with idiopathic right thoracic scoliosis found that the mean values for the Cobb angle, vertebral rotational flexibility, kyphosis, and rib-vertebral angle asymmetry (in radiographs of standing as well as supine bending positions) differed significantly between patients with >80% of predicted vital capacity and those whose vital capacity was £60% of predicted values. Roentgenologic features indicative of better pulmonary function included rotational flexibility exceeding 55%, rib-vertebral angle asymmetry (standing) of <25°, and kyphosis of 15°. The two parameters of deformity, vertebral rotational flexibility and rib-vertebral angle asymmetry, provided a better prediction of respiratory function than the commonly used Cobb angle.

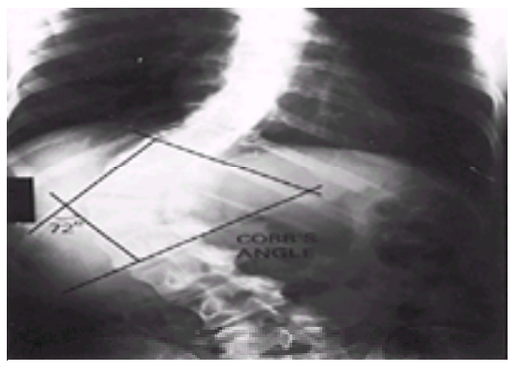

FIG. 2. The Cobb angle is determined by lines drawn perpendicularly to the tangents from the end plates of the most tilted superior and inferior vertebrae.

The scoliotic angle is an important predictor of respiratory failure. In a long-term study of 24 patients with unfused scoliosis, pulmonary function tests were performed 20 years apart, and respiratory failure occurred only in patients who had a vital capacity of 45% of the predicted value during the initial testing and an angle 110°; the initial vital capacity was the strongest predictor of the development of respiratory failure, followed by scoliotic angle. In a study of 29 patients with adolescent idiopathic thoracic scoliosis of 60°, maximal inspiratory pressure was found to be reduced, but maximal expiratory pressure was normal. The low maximal inspiratory pressure was attributed to the mechanical disadvantage resulting from the chest deformity.

Abnormalities of Pulmonary Function

The most common abnormality of pulmonary function is a reduction in static lung volumes, including vital capacity and total lung capacity. An inverse relationship exists between the angle of scoliotic curvature and the values (as a percentage of predicted values) for vital capacity, total lung capacity, functional residual capacity, residual volume, and static compliance of the total respiratory system. The ventilatory function may be impaired even in mild forms of scoliosis. The force developed by the respiratory muscles is a more important determinant of ventilatory defect than is the degree of spinal curvature. The decreased lung compliance is most pronounced in scoliotic patients with muscle weakness. In kyphoscoliosis, prediction of lung volume from body height results in significant underestimation, but arm span serves satisfactorily for this purpose. A method has evolved by which the theoretical height of these patients is predicted from the angle of scoliosis, length of spine, and actual height.

Even though restrictive lung dysfunction is typical in patients with severe scoliosis, obstructive airway disease and positive bronchodilator response are present. Extensive pulmonary function testing in 44 children (36 girls, 8 boys) between the ages of 10 and 18 years with idiopathic scoliosis before surgical correction showed significant restrictive defect in 41% of subjects, whereas air flow obstruction was noted in 7% of subjects. However, the ratio of total gas volume (by plethysmography) to functional residual capacity (by helium dilution) demonstrated moderate or severe gas trapping in 20 subjects (46%). Bronchodilator administration resulted in significant improvement in airway mechanics. Other studies of pulmonary function studies in children with idiopathic scoliosis have shown diminished vital capacity, 1-second forced expiratory volume, gas transfer, and maximal static expiratory airways pressure, but no significant diminution in total lung capacity or maximal inspiratory pressure.

The characteristic deformity seen in scoliosis causes one hemithorax to become smaller than the other. This inherent mechanical inefficiency of ventilation is the major factor in causing respiratory embarrassment. Patients with moderate to severe kyphoscoliosis have significant oxygen desaturation during exercise and should thus routinely be tested by oximetry during exercise for assessment of ambulatory oxygen therapy. Although hypoxemia often is present and has been attributed to alveolar hypoventilation resulting from small tidal volumes, arterial CO_2 tension ($PaCO_2$) usually is normal. In advanced cases, however, increased $PaCO_2$ is common and signifies the onset of serious respiratory insufficiency. Increased ratios of physiologic dead space to tidal volume (V_D/V_T) and elevated alveolar-arterial oxygen tension gradients [$P(A\text{-}a)O_2$] have been demonstrated. Studies employing xenon 133 have shown that the gas exchange abnormality in idiopathic scoliosis is primarily a consequence of ventilation-perfusion maldistribution resulting from deformity of the ribs. The proportion of ventilation, oxygen consumption, and volume on the side of convexity is less than on the side of concavity. However, a study with radionuclide methods did not find consistent differences in perfusion between the convex and concave sides of the curvature. Although adolescents with mild, asymptomatic scoliosis (thoracic curvature of 35°) demonstrate little or no impairment of lung volumes at rest, abnormal ventilatory patterns develop during exercise, hypoxia, or hypercapnia.

Clinical Features

Symptoms and signs of respiratory failure usually do not appear until the fourth or fifth decade. Cardiorespiratory failure is likely to occur when the vital capacity is 40% of the predicted normal value. Patients in whom cor pulmonale develops exhibit severely diminished total lung capacity. A retrospective survey of approximately 800 scoliotic subjects attending a chest clinic during a 25-year period revealed that cardiorespiratory failure attributable to scoliosis was the cause of death in 11 patients; in 10 of these the scoliotic curve had first been observed at 5 years of age, whereas the onset was during early adolescence (11 years) in only one.

The term *Quasimodo syndrome* is employed to describe severe kyphoscoliosis with abnormal sleep patterns. Sleep apnea and hypopnea occur more frequently in patients with kyphoscoliosis. Derangements in breathing pattern and arterial oxygen saturation apparently are unrelated to the degree of thoracic deformity, pulmonary function, $PaCO_2$, or chemical drives to breathe. Hypoventilation occurs in patients with kyphoscoliosis during sleep, particularly rapid-eye-movement (REM) sleep. Hypoventilation secondary to reduced chest wall movements is the main mechanism responsible for hypoxemia and hypercapnia during sleep. Pure obstructive sleep apnea caused by spinal deformity alone is uncommon.

An interesting observation has been the significant association between scoliosis and pulmonary infection with *Mycobacterium avium* complex. In an evaluation of 67 patients with pulmonary disease caused by *M. avium* complex, 52% of patients were discovered to have scoliosis. This skeletal abnormality was significantly more common among all patients with *M. avium* complex infection than among patients with *M. tuberculosis* infection or the general population. This increased risk for infection among scoliotic subjects is most likely related to structural bronchopulmonary abnormalities rather than to immunologic or other well-known risk factors.

Atelectasis of a lobe as a result of scoliosis-related bronchial stenosis has been described. Clinically significant bronchiectasis is a late complication in patients with severe kyphoscoliosis. Subclinical lung damage by this mechanism may predispose to secondary infections observed in some patients.

Treatment of Kyphoscoliosis

Significant improvements in pulmonary function test results is unlikely in the majority of patients who undergo corrective surgery. The aim of all therapies in this group of patients is to halt progression of the spinal deformity and thereby prevent further progression of pulmonary dysfunction. In a study of 14 adults who underwent anterior spinal surgery for correction of scoliosis, a follow-up evaluation 32 months later revealed a fall in mean forced vital capacity of 0.21 L despite improvement in the Cobb angle of 31%. The inference from this study is that in adults with reasonable lung function, the fall in forced vital capacity is small and clinically insignificant. Another study noted that whereas pulmonary function test values normalize in adolescent patients by 2 years after thoracoplasty, long-term pulmonary function in adults remains diminished. In advanced cases with hypercapnic respiratory failure, the treatment is mainly aimed at assisted ventilation to improve oxygenation and treat hypercapnia. It has been recommended that children with congenital scoliosis caused by multiple anomalies undergo surgery at an early age, before deformity becomes too severe.

Milwaukee brace or spinal fusion and reduction of the deformity by the posterior placement of Harrington's distraction strut bars have been the standard approaches to therapy of kyphoscoliosis. Many studies have shown no appreciable difference in lung function between patients with the Milwaukee brace and those with surgical correction. In severe respiratory failure resulting from kyphoscoliosis, cuirass respirators have been used with varying success. In a meta-analysis of five studies comprising a total of 173 patients, the Harrington's rod therapy resulted in an increase in mean vital capacity ranging from 2%–11% of predicted vital capacity.

Nighttime ventilatory support using continuous positive airway pressure is helpful in many patients with respiratory failure caused by secondary scoliosis. A comparison study of 13 clinically stable patients with kyphoscoliosis treated by nocturnal positive pressure ventilation via a nasal mask and 13 patients with kyphoscoliosis and acute respiratory insufficiency treated by nocturnal ventilation via tracheostomy concluded that both treatments are effective in the long-term management of respiratory failure in these patients. It appears that if nocturnal positive pressure ventilation via a nasal mask is initiated earlier in patients with chronic respiratory failure, the need to use an invasive technique, such as tracheostomy, is delayed.

Acute respiratory failure in adults with severe thoracic spinal deformity is associated with a higher mortality, but successful management of acute respiratory failure is

possible in the majority of patients. Pulmonary function deteriorates at a slower rate after acute respiratory failure in these patients, who tend to be middle-aged, than in patients in whom acute respiratory failure develops as a result of chronic obstructive respiratory disease.

Postoperative Respiratory Complications

Postoperative respiratory complications after spinal fusion are common in patients with nonidiopathic scoliosis who are 20 years of age or older, undergo anterior spinal fusion, are mentally retarded, and have relative arterial hypoxemia or obstructive pulmonary dysfunction. In a report of 32 pediatric patients (18 boys and 14 girls; mean age, 13 years) with severe restrictive lung disease (mean vital capacity, 31% of predicted normal), 54 reconstructive spinal surgical procedures were followed by pulmonary complications in six patients (19%). They included pneumonia, reintubation, pneumothorax, respiratory arrest, or the need for tracheostomy, with three patients requiring tracheostomy. Patients in whom thoracotomy or a thoracoabdominal approach was used had a significantly higher number of pulmonary complications. Lung function measurements in anesthetized young patients undergoing spinal correction have shown immediate and short-term deterioration of respiratory mechanics. However, in one study that assessed the effects of spinal fusion on pulmonary function test values in a homogeneous population of 42 women with idiopathic scoliosis by measuring lung function before and a minimum of 3 years (mean, 7.7 years) after surgery, the only significant preoperative abnormality found was vital capacity reduced to 81% of predicted. A scoliotic angle exceeding 50° was associated with a significantly lower vital capacity. Postoperative evaluations showed that vital capacity increased significantly, by 12%.

PECTUS DEFORMITIES

Pectus Excavatum

The congenital deformity pectus excavatum (also called *funnel chest*) is characterized by a depressed sternum (usually above the xiphisternal junction) and symmetric or asymmetric prominence of the ribs on either side. The origin of pectus excavatum is unknown, but it is believed to be caused by excessive diaphragmatic traction on the lower sternum or a more lateral displacement of the heart into the left hemithorax. A report of 10 cases of pectus excavatum noted pulmonary sequestration and other pulmonary abnormalities in nine patients and suggested a connection between pulmonary sequestration and the development of this deformity. However, when the common occurrence of pectus excavatum in clinical practice is considered, this incidence seems unusually high. Pectus excavatum usually occurs sporadically, although a dominant pattern of inheritance has been described. It may be associated with Marfan's syndrome and other connective tissue diseases. The majority of patients are asymptomatic, but some experience exertional dyspnea, precordial pain, palpitation, and a sensation of dizziness. Pulmonary function is usually normal, but with very severe deformity the vital capacity, total lung capacity, and maximal breathing capacity may be decreased.

Chest roentgenograms may reveal displacement of the heart to the left. The right parasternal soft tissues of the anterior chest wall give rise to the appearance of right middle lobe disease on posteroanterior roentgenograms (Fig. 3A). Sternal depression is best appreciated on lateral views (Fig. 3B). Paradoxical increase in cardiac size on inspiration has been described.

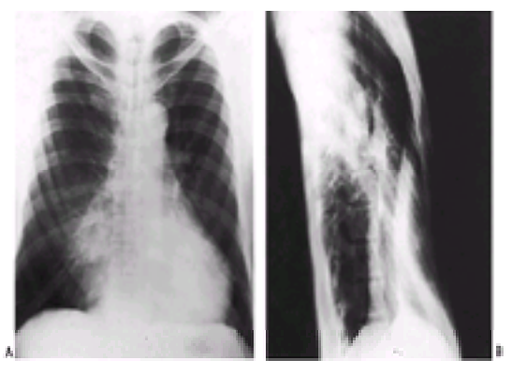

FIG. 3. Pectus excavatum. **A:** Right border of the heart is obliterated, and an infiltrate is apparent in the right middle lobe. The ribs on the right appear crowded. **B:** Right lateral view shows sternal depression.

In the study mentioned earlier, 27% of 67 patients with *M. avium* complex infection were found to have pectus excavatum deformity. By comparison, only 5% with *M. tuberculosis* infection had this skeletal abnormality. The prevalence of pectus excavatum among women with *M. avium* complex infection was significantly different from that among either the general population or patients infected with *M. tuberculosis,* whereas the prevalence of *M. avium* infection in male patients with pectus excavatum was significantly different from that in the general population but not from that in patients infected with *M. tuberculosis.* Possible mechanisms for this putative association include bronchopulmonary structural abnormalities secondary to pectus excavatum, impaired mucociliary function, impaired pulmonary lymphatic drainage, and altered alveolar macrophage function. It is unlikely that the skeletal abnormalities occurred as a result of mycobacterial infection, because there were no indications of chronic or past tuberculous infections.

An earlier study reported an apparent increase in infections of the lower respiratory tract among a series of U.S. Air Force recruits with pectus excavatum. Two cases of congenital bronchial atresia with pectus excavatum are reported; the authors indicate that costosternal retraction during the efforts to overcome the airway obstruction may have played a part in causing pectus excavatum.

In patients with significant pectus excavatum, pulmonary function tests usually show restrictive phenomena. The restrictive lung dysfunction does not appear to be related to age, severity of the deformity at physical examination, or pulmonary symptoms. In a study of 152 patients who underwent surgery for pectus excavatum at a mean age of 15 years, lung function was reevaluated after 8 years, and it was noted that the restrictive pulmonary dysfunction worsened despite a reduction in the symptoms of most patients and despite a significant increase in anteroposterior diameter of the chest.

Pectus Carinatum

Pectus carinatum is a congenital or acquired deformity of the chest cage characterized by protrusion of the sternum. It is a relatively rare chest deformity with an occurrence rate of 1 to 2/1000 population. Type I pectus carinatum, or “pigeon breast,” is caused by an overgrowth of rib cartilages, resulting in forward buckling of the sternum. Pectus carinatum type II, or “pouter pigeon breast” (Currarino-Silverman syndrome), is characterized by premature fusion of the manubriosternal joint and sternal segments, resulting in high carinate chest deformity. Both types of pectus carinatum deformities are frequently associated with congenital heart disease. The common cardiac anomalies in type I deformity are congenital atrial or ventricular septal defects. Conversely, nearly 50% of patients with those forms of heart disease have pectus carinatum. Some have reported that chronic and prolonged asthmatic attacks produce this deformity. Most patients with pectus carinatum are asymptomatic, but it has been suggested that they are subject to recurrent respiratory infections.

Pectus Deformatum

Pectus deformatum is the term used to describe an axially rotated sternum with an *S*-shaped frontal or sagittal plane. Among 80 patients with various abnormalities of the thoracic cage, pectus deformatum was noted in 13 (16%), and the incidence was identical to that of pectus carinatum. Pulmonary function abnormalities are usually mild, somewhat similar to those in pectus excavatum and pectus carinatum.

Surgical Correction of Pectus Deformities

Pectus deformities are surgically corrected for cosmetic reasons, to alleviate cardiopulmonary dysfunctions, and to prevent progressive postural deformities. In a study of 88 patients who underwent surgical correction of any of the pectus deformities just discussed, the operation appeared to have a favorable effect on chest roentgenologic indices but resulted in undercorrection in pectus excavatum and overcorrection in pectus carinatum. Furthermore, the study revealed that patients with preoperative lung function values that were 75% of predicted values experienced a functional improvement after corrective surgery. Interestingly, the pulmonary dysfunction worsened if lung function values were 75% of predicted. Another pulmonary function study of 138 patients before and after surgical correction of pectus excavatum reported that although the corrective procedures produced an excellent cosmetic result, there was no beneficial effect on pulmonary function. Among 227 children with pectus excavatum and 25 with pectus carinatum (195 boys and 57 girls) who underwent repair of pectus deformities, preoperative exercise limitation was reported by 51% and frequent respiratory infections or asthma were reported by 32%. Surgical repair through a transverse incision, with subperiosteal resection of the lower four or five costal cartilages from sternum to costochondral junction bilaterally, resulted in improvements in exercise tolerance, endurance, respiratory symptoms,

and cosmetic appearance in 98% of patients. The authors of this study recommend operation at an early age with routine use of substernal support.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis, also known by other names, including *rheumatoid spondylitis* and *Marie-Strumpell disease,* is a chronic disorder characterized by progressive inflammation of the spine and adjacent soft tissues. The sacroiliac, hip, and shoulder joints are commonly affected. The disease affects men (male-to-female ratio 10:1) 16 to 40 years of age but begins most often in the third decade. The cause is unknown. Ankylosing spondylitis may be inherited by a single autosomal dominant factor, with a 70% penetrance in men and a 10% penetrance in women. A high association exists between ankylosing spondylitis and the histocompatibility antigen HLA-B27. Extraskeletal manifestations are numerous and include incompetence of the aortic valve, varying degrees of heart block, acute anterior uveitis, fever, anemia, fatigue, and weight loss.

The most widespread involvement of the respiratory system occurs when ankylosing spondylitis causes chest wall pain, diminished chest wall movement, and a dorsal stoop. Although pulmonary involvement has been reported in 2%–70% of these patients in the clinical setting, only a small percentage (5%) demonstrate clinically discernible pulmonary problems. In a review of 2080 patients with ankylosing spondylitis, pleuropulmonary manifestations were noted in only 28 (1.3%). The most common chest roentgenologic finding was fibrobullous apical lesions in 26 patients. Other pleuropulmonary features included aspergilloma in five and pleural effusion with nonspecific pleuritis in three patients. A peculiar type of fibrotic process in the upper lobes characterized by nodular and linear lesions has been observed in 14%–30% of patients. The process initially appears as linear strands in the upper lobes, beginning medially and radiating laterally. When the spine resembles bamboo, these linear strands give rise to a “telephone pole” appearance. Occasionally, the linear strands are replaced by small nodules that show cavitation or appear cystic (Fig. 4). Computed tomography may reveal bullous changes, mycetomas, parenchymal fibrosis, and pleural thickening. The cystic spaces and cavities occasionally become infected by *Aspergillus* species, *M. avium* complex, *M. kansasii,* or *M. scrofulaceum.*

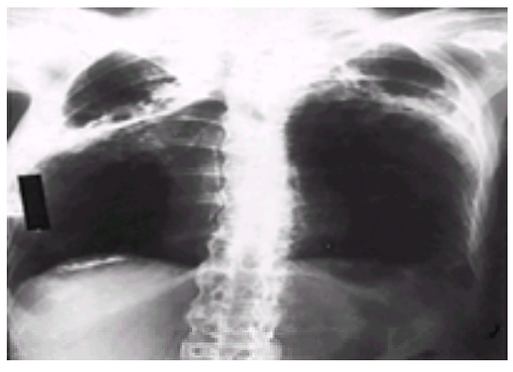

FIG. 4. Ankylosing spondylitis demonstrates “bamboo spine,” bilateral apical fibrous cavitary process, and right diaphragmatic calcification.

Diffuse interstitial pneumonitis and fibrosis are uncommon. Bronchoalveolar lavage and bronchial biopsies in patients with ankylosing spondylitis have failed to indicate subclinical alveolitis. Bilateral pleural effusion has been described in a patient with quiescent ankylosing spondylitis. A case of tracheobronchomegaly is reported in association with ankylosing spondylitis.

Upper airway involvement in the form of cricoarytenoid ankylosis occurs in some patients. Respiratory failure resulting from cricoarytenoid ankylosis has necessitated therapeutic tracheostomy in four patients. Calcification and ossification of cartilaginous structures may occur in the large airways. Obstruction by ossified arytenoid cartilage has been treated by endoscopic arytenoidectomy. Carcinoma of the upper lobes of lungs is another unusual long-term complication. Pathologic analysis of lung tissue in ankylosing spondylitis has demonstrated nonspecific fibrosis with lymphocytic infiltrates, dilated bronchi, and thin-walled bullae and cavities. Diaphragmatic calcification is seen in a small number of patients.

Ankylosing spondylitis alters lung function by modifying the mechanical properties of the thoracic cage. The ankylosis of the costovertebral joints rarely produces symptoms, even though pulmonary function test values are abnormal in these patients. Pulmonary function tests reveal diminished total lung capacity, vital capacity, and diffusing capacity for carbon monoxide. Increases in residual volume and functional residual capacity are the other findings, although in some studies the functional residual capacity was decreased. Lung function studies in 16 patients with ankylosing spondylitis recorded a mean total lung capacity of 83% of predicted and normal total respiratory resistance. Ventilation studies using xenon 133 have shown decreases in ventilation and gas volumes in the upper lobes; however, one study concluded that the upper zones of the lungs are not underventilated in patients with ankylosing spondylitis except in the presence of radiographically visible fibrosis. In a study of 32 patients with ankylosing spondylitis, pulmonary function test findings were compared with those of a control population. The patients had no lung symptoms, and their chest roentgenographic findings were normal. The main findings were reduced lung volumes, a raised closing volume-to-vital capacity ratio, and decreased airways conductance. The lung volume reduction correlated with disease duration, thoracic mobility, and degree of acute-phase reaction. The stiff spondylitic thorax probably was the main contribution to the impairment of lung function in these patients, but the findings in this study also suggested involvement of the small airways. Despite abnormal pulmonary function test findings, the majority of patients with ankylosing spondylitis are able to perform normal physical activities. Although diaphragmatic calcification occurs in some patients with ankylosing spondylitis, diaphragmatic function is unimpaired and compensates well for the minor restrictive changes found in tests of respiratory function.

In a report of the coexistence of seronegative spondyloarthropathy and sarcoidosis in 12 patients, the authors observed that the pelvic and spinal manifestations of sarcoidosis can mimic those of spondyloarthropathy. The coexistence of sarcoidosis and spondyloarthropathy is probably caused by chance, as there are no shared predisposing genetic factors and the number of reported cases is small.

Treatment is by mobilizing physiotherapy coupled with a home exercise program to encourage mobility and improve cardiovascular fitness. The role of medication is to ease symptoms and hence enable exercise. No treatments exist that can prevent the development of fibrobullous disease or halt its progression, although this may happen spontaneously. Treatment of established aspergillosis, especially when aspergillomas have formed, is unsatisfactory and carries substantial risks for morbidity and death.

CERVICAL HYPEROSTOSIS

Cervical hyperostosis of the spine is anatomically manifested by bony outgrowths arising from the anterior aspects of the vertebral bodies and extending over the disk spaces. Also known as *diffuse idiopathic skeletal hyperostosis* (*DISH*), the condition was observed in 12% of 215 routine autopsies. The abnormality is most common in men; the average age is 66 years. The pharyngeal masses formed by the bony outgrowths can be extensive and may occasionally be visualized or palpated at the time of physical examination. These hyperostotic spurs are known to cause dysphagia, foreign-body sensation, aspiration, respiratory distress, and dysphonia. Dysphagia occurs in 17%–28% of patients with this disorder.

Bilateral vocal cord paralysis with airways obstruction has been described in patients with DISH. The pathogenesis is infection superimposed on ulceration of the cricoid produced by laryngeal movement over a large, sharp osteophyte. Severe, acute airway obstruction caused by a cervical osteophyte pressing on the posterior trachea is described in a 68-year-old man; tracheostomy followed by resection of the osteophyte was therapeutically successful. Dysphagia and aspiration are the results of mechanical compression. Nonsteroidal anti-inflammatory drugs and antireflux precautions should be suggested for patients who have dysphagia. Surgical removal of the hyperostotic process is required in severe cases.

Cervical spondylosis can be associated with pressure symptoms in the neck area. Dyspnea and paresis of the left hemidiaphragm relieved by laminectomy are described.

OSTEOPOROSIS

Compression fractures of multiple thoracic vertebral bodies as a result of osteoporosis produce an anatomic anomaly akin to kyphosis. With severe compression fracture, a gentle (nonacute angle) thoracic gibbus or hyperkyphosis develops in some patients. Furthermore, a markedly shortened thoracic vertebral column leads to reduced lung volumes. A study of the effect of thoracic kyphosis on respiratory mechanics in 15 women with kyphosis resulting from spinal osteoporosis showed the vital capacity, inspiratory capacity, total lung capacity, and lateral expansion of the thorax to be lower in the osteoporotic group. These mechanical factors and the pain secondary to compression fracture have the potential to cause respiratory dysfunction. The pulmonary effects of significant osteoporosis are similar to those observed

in scoliosis. Seventy-four women referred for evaluation of osteoporosis were subjected to pulmonary function testing, and those with thoracic wedge compression fractures secondary to osteoporosis had a significantly lower predicted forced vital capacity than did those without fractures. The degree of hyperkyphosis as measured by the Cobb angle had an appreciable effect on this parameter. The study estimated that a fall of approximately 9% in the predicted forced vital capacity might be expected for each thoracic vertebral fracture.

STERNOTOMY

Median sternotomy is a common surgical procedure employed in the vast majority of cardiac surgeries, particularly coronary artery bypasses and valve replacement procedures. A restrictive ventilatory defect follows median sternotomy. Vital capacity, 1-second forced expiratory volume, and functional residual capacity may decline to as little as 40% of preoperative values 1 to 3 days after coronary artery bypass grafting. These changes are more pronounced after the use of internal mammary artery bypass than after saphenous vein grafting. This is reported to be related to disruption of the internal mammary artery-derived vascular supply of the phrenic nerves. The diminished lung function begins to reverse by the end of the first postoperative week, and recovery is almost total at 3 weeks. The causes of lung dysfunction include pain, atelectasis, pulmonary edema, pulmonary embolism, hemothorax, diaphragmatic paralysis (“frost-bitten” phrenic nerve), pleurotomy, and chest wall instability. A study of rib cage mechanics in 16 men before and 1 week and 3 months after median sternotomy for coronary artery grafting revealed that reduced and uncoordinated rib cage expansion contributed to the restrictive ventilatory defect. Pre-existing cardiopulmonary disease influences the reduction in lung volumes. Obviously, resection of pulmonary parenchyma will result in permanent loss of lung function contributed by the resected segment or lobe.

MARFAN'S SYNDROME

A heritable generalized disorder of connective tissue, Marfan's syndrome is manifested clinically by abnormalities of the skeletal system (excessive length of long bones), eyes (ectopia lentis), and cardiovascular system (aneurysm of the thoracic aorta, septal and valvular cardiac anomalies). Pulmonary abnormalities are observed in approximately 10% of patients with Marfan's syndrome and include generalized honeycombing of the lungs, spontaneous pneumothorax, and bronchiectasis (Fig. 5). Of these, spontaneous pneumothorax is the most common and is seen in nearly 5% of adolescents and adults. Spontaneous pneumothorax and bullae are causally related to Marfan's syndrome. Necropsy studies of four infants with this syndrome and pulmonary emphysema showed that the elastic fibers in alveolar ducts and sacs were irregularly thickened, wavy, fragmented, and clumped. Diffuse honeycombing of the lungs and spontaneous pneumothorax were reported as the presenting features of Marfan's syndrome in a boy. In two cases, bilateral bullous disease with spontaneous pneumothorax was reported. Fibrosis of the upper lobes also is reported in Marfan's syndrome. A report described three members of a family—a father and two sons, all afflicted with Marfan's syndrome—who had multiple bilateral episodes of pneumothorax that required repeated drainage procedures.

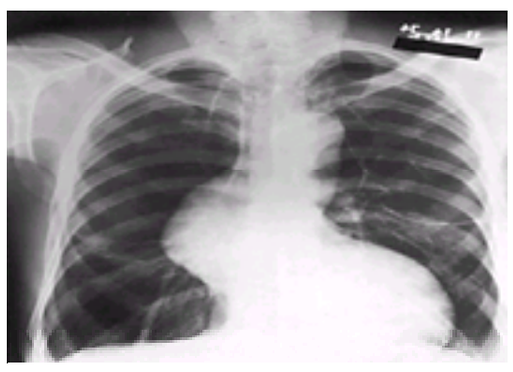

FIG. 5. Marfan's syndrome with hyperinflation, bullous changes, dilated tortuous aorta, and “tall” lungs.

Structural abnormalities of the right middle lobe have been described. Ciliary dyskinesia also has been observed in a patient with Marfan's syndrome. Additionally, deformities of the thoracic cage resulting from abnormalities of the vertebral column, ribs, and sternum are common in this syndrome and may occur in any combination and degree of severity. Both scoliosis and pectus excavatum occur and may cause pulmonary dysfunction. Tracheal weakness, presumably resulting from structural deficiency of the cartilages, has been reported in a patient.

A review of published reports disclosed nearly 50 patients with bullous lesions, lung cysts, or emphysema, 22 of whom were younger than 20 years and two thirds of whom were male. In the same review of an additional 100 patients with Marfan's syndrome, 11 had spontaneous pneumothorax, with recurrence in 10 and bilateral appearance in six, pneumonia or recurrent respiratory infections in eight, and bronchiectasis in two. Chest roentgenograms revealed emphysematous bullae in five, fibrosis of the upper lobes in four, and aspergilloma in two. Another review of 249 patients older than 12 years reported the frequency of pneumothorax to be 4.4%, with recurrent or bilateral pneumothorax in 3%. This review suggested that definitive surgical therapy should be considered at the first occurrence of pneumothorax because of the high rate of recurrence after treatment with a chest tube.

Pulmonary dysfunction occurs in the absence of thoracic cage abnormality. An important aspect of interpreting the pulmonary function test results is the recognition that the values are based on age, sex, and standing height. The unusually long length of the legs in patients with Marfan's syndrome contributes disproportionately to these calculations. Studies of pulmonary function in patients with Marfan's syndrome have revealed diminished total lung capacity and vital capacity and mildly lowered flow rates at low lung volumes, with decreased diffusing capacity and elastic lung recoil, but only minimal abnormalities of pulmonary function have been noted in some cases. A study involving 79 patients with Marfan's syndrome concluded that persons with this syndrome who have, at most, mild thoracic deformity do not have significant abnormalities of static pulmonary function, and thus the connective tissue defects in the lungs seem to have minimal clinical impact beyond the risk for pneumothorax. However, tests of dynamic lung function were not performed in this group of subjects. In a report of 11 children with Marfan's syndrome, airway reactivity as measured by methacholine challenge was noted in all children, even though only one patient had a diagnosis of asthma. An unusual case of Marfan's syndrome with hypercoagulability complicated by multiple pulmonary emboli has been described.

The prevalence of obstructive sleep apnea is higher in patients with Marfan's syndrome. Sleep apnea in these patients is not related to obesity. Indeed, patients with Marfan's syndrome usually are tall and thin rather than obese. Excessive collapsibility of the upper airway resulting from connective tissue defect has been postulated as one of the reasons. A more likely mechanism is related to the characteristically constricted maxilla and the high-arched palate. Measurement of nasal airway resistance by posterior manometry in patients with Marfan's syndrome has shown high resistance. The indices of maxillary constriction as determined by measurement of nasal airway resistance have been shown to correlate with the severity of sleep apnea.

ACHONDROPLASIA

Achondroplasia is the most common skeletal dysplasia resulting in short-limbed dwarfism. The disorder results from abnormal endochondral bone formation. Pulmonary complications are common in achondroplastic infants and children younger than 2 years. Factors that influence respiratory manifestations include associated deformities of the chest wall and involvement of respiratory centers at the level of the brainstem and upper cervical cord. The thoracic skeletal abnormalities include reduced chest cage measurements, pectus excavatum, accentuated thoracic kyphosis, or thoracic lordosis. Detailed physiologic abnormalities in 12 healthy subjects with achondroplasia showed that the reduction in vital capacity was out of proportion to what would be expected if these subjects had limbs of normal size; the other pulmonary function parameters were normal. In a study of 58 female and 44 male achondroplastic subjects between 7 and 60 years of age, the values for vital capacity were 68% and 72% of predicted normal values for normally proportioned men and women, respectively.

Upper airway involvement, nasal obstruction, hypoxemia, and obstructive sleep apnea are more common in younger achondroplastic subjects. The most important breathing disorder during sleep in children with achondroplasia is upper airway obstruction. The short cranial base and midfacial hypoplasia increase the risk for upper airway obstruction during sleep. Sleep apnea and death caused by acute or chronic compression of the lower brainstem or cervical spinal cord have been noted in infants with achondroplasia. One study found no relationship between apnea type and foramen magnum stenosis. Obstructive sleep apnea is reported to occur more often in older subjects with achondroplasia. Resolution of sleep apnea by tracheostomy in achondroplastic dwarfs has resulted in normalization of growth hormone release and normal growth. Apneustic breathing is a rare pattern of neurogenic breathing characteristic of some patients with achondroplasia. In a report of five patients with achondroplasia, all of whom demonstrated apneustic breathing, the authors speculate that compression of the lower medullary respiratory centers and afferent pathways in the spinal cord were responsible for the abnormal breathing pattern.

RIGID SPINE SYNDROME

In rigid spine syndrome, a rigid spine is associated with a myopathy predominantly affecting proximal limb muscles. Histologic analysis of skeletal muscles, including the diaphragm, may show the presence of autophagic vacuoles in muscle fibers. Although this syndrome is more common in children, respiratory failure secondary to respiratory muscle weakness has been described in adults. The cause of respiratory failure is extreme flattening of the chest and fixation of the thorax as a result of contracture of costovertebral joints. In almost all reported cases of rigid spine syndrome, the patients have died of respiratory failure. Respiratory muscle involvement is a significant feature of rigid spine syndrome, resulting in hypercapnic ventilatory failure in some patients. Investigation of thoracic abnormalities and respiratory muscle function in nine patients with rigid spine syndrome showed a severe restrictive chest wall defect and limited mobility of the spine. Most importantly, significant respiratory muscle weakness was present in all patients. Respiratory muscle strength and endurance were 60% of control values. Even though six of the patients were emaciated and one patient was underweight, no relationship was seen between body mass index and respiratory muscle strength. Patients with hypoventilation demonstrated more pronounced respiratory muscle dysfunction.

Nocturnal ventilatory assistance has been employed to assist patients with severe hypoventilation and respiratory failure.

CRANIOFACIAL DEFORMITIES

Several types of craniofacial deformities have been described. These structural aberrations frequently are associated with upper airway problems. Severe sleep apnea, sometimes necessitating tracheostomy, is a recognized complication of various craniofacial structural abnormalities. Different grades of respiratory distress resulting from obstructive sleep apnea have been described in adults with craniofacial dysostosis, achondroplasia, metatropic dwarfism, Hallermann-Streiff syndrome, and Treacher Collins syndrome. Sleep apnea is a well-recognized aspect of micrognathia and Pierre Robin syndrome (bird-face syndrome). Tracheostomy is recommended in pediatric cases of craniofacial abnormalities with sleep apnea before reconstructive surgery is undertaken.

Pierre Robin syndrome is characterized by mandibular hypoplasia (micrognathia) and glossoptosis, often associated with a cleft palate. Upper respiratory obstruction is commonly present in this disorder. The tongue is posteriorly displaced (glossoptosis) as a consequence of micrognathia and anterior insertion of the tongue to the mandible. Severe airways obstruction may persist for months but may improve with time.

Because of micrognathia, patients with Treacher Collins syndrome are at greater risk for development of obstructive sleep apnea. Surgical correction of the micrognathia may relieve sleep apnea.

GORHAM'S DISEASE

Gorham's disease or Gorham-Stout disease (disappearing or vanishing bone disease) is characterized by massive osteolysis. It generally appears in the second and third decades of life with an equal sex distribution. A report in 1994 recorded that 146 cases of Gorham's syndrome were documented in the literature. Although any skeletal bone can be affected, the commonly involved bones are the innominate bones, thorax, and spine. Clinically, patients present with dull aching and weakness in an affected extremity. Pain is usually caused by pathologic fractures, which are a prominent feature of this disease. Histologically, lymphangiomatous tissue is observed in the affected skeletal structures. The predominant feature is the lymphatic dysplasia in skeletal structures as well as the thorax.

Pleuropulmonary manifestations include pleural effusion and development of lymphangiomatous tissue in the mediastinum. Massive pleural effusions, sometimes chylous, with high mortality have been described. Of the 146 cases of Gorham's syndrome documented in the literature, chylothorax was diagnosed in 26 (17%) of patients. Pneumothorax may be associated with chylothorax and may be seen in conjunction with chylous pleural effusion. Pulmonary lymphangiectasia, described in patients with some of these skeletal abnormalities, may be responsible for the chylous pleural effusion. Reports of successful treatment of chylothorax by high-dose radiotherapy and bleomycin have been published.

ADULT STILL'S DISEASE

Adult Still's disease is characterized by high fever, arthritis, evanescent rash, serositis, lymphadenopathy, splenomegaly, leukocytosis, and absence of rheumatoid factor and antinuclear antibodies. Pleuropulmonary complications, such as pleuritis and pneumonitis, occur frequently. The incidence of pleuropulmonary complications is reported to be approximately 30%, but estimates of up to 60% are recorded. The most common symptom is pleurisy with or without effusion. Persistent or severe pulmonary parenchymal infiltrates are uncommon. Diffuse interstitial lung disease has been described in a patient with adult-onset Still's disease. Fatal adult respiratory distress syndrome complicated by opportunistic pulmonary infections has been described in a 65-year-old woman.

OSTEOGENIC SARCOMA AND OTHER SKELETAL NEOPLASMS

Pulmonary metastatic disease is a relatively common complication of osteogenic sarcoma and other soft-tissue sarcomas, including Ewing's sarcoma of bone, rhabdomyosarcoma, and synovial sarcoma. The pulmonary lesions almost always present as lung nodules, either solitary nodules or multiple bilateral nodules. Pulmonary metastases may appear with the primary tumor or follow it by several months to years after therapy of the primary tumor. The median doubling time for pulmonary metastatic nodules secondary to bone or soft-tissue sarcomas is estimated to be 35 days (estimated 95% range, 3.9 to 352 days). Follow-up chest roentgenography should be considered in the majority of these patients. Periodic computed tomography of the chest is more accurate in detecting smaller nodules than the plain chest roentgenogram. One of the unusual features of metastatic osteogenic sarcoma is calcification of the metastatic lung lesion.

Spontaneous regression of pulmonary metastatic osteosarcoma is extremely rare, even after curative therapy of the primary tumor. Therefore, pulmonary metastatectomy with or without adjuvant therapy is the accepted therapy. Up to 50% of patients with osteogenic sarcoma in whom pulmonary metastases develop can be satisfactorily treated with continued effective chemotherapy and pulmonary metastatectomies, as long as good local control is achieved in the primary tumor. The presence of bilateral, extensive, or recurrent disease is not a contraindication to thoracotomy, because aggressive resection of multiple nodules and improved chemotherapy appear to prolong survival of these patients in comparison with survival rates of historical control subjects. In patients presenting with simultaneous primary tumor and pulmonary metastatic disease, the cure rate is potentially as high as it is in those patients who present with primary tumor alone. Because the majority of patients are young and otherwise healthy, thoracotomy with resection of lung nodules—sometimes repeated and bilateral—is associated with low morbidity and mortality. Patients who undergo resection of pulmonary metastatic osteogenic sarcoma generally have a better prognosis than those with other soft-tissue tumors.

In a report of 152 patients (median age, 19 years; range, 5 to 33 years) who underwent 258 thoracic explorations for resection of metastatic Ewing's sarcoma (28), rhabdomyosarcoma (6), soft-tissue sarcoma other than rhabdomyosarcoma (42), and osteosarcoma (76), the thoracic procedures consisted of 218 wedge resections, 19 anatomic resections, 14 wedge and anatomic resections, 4 wedge and chest wall resections, and 3 wedge resections/other procedures. Complete resection was achieved in 121 patients (80%). The median survival from initial thoracotomy was 2.2 years. Unfavorable prognostic factors included three or more positive nodules, histology other than osteosarcoma, and incomplete resection. Predictors of shorter survival included the following: two or more metastatic lung nodules, left-sided thoracic location of metastatic lesion(s), age 14 years or older at diagnosis, or histology that depicted rhabdomyosarcoma. In a study of 36 patients with pulmonary metastatic osteogenic sarcoma, the 5-year survival rate following pulmonary metastatectomy was 23%.

In a study of 12 patients with Ewing's sarcoma of bone who relapsed with pulmonary metastases alone and were treated with surgical resection of the metastatic lesions but no additional radiotherapy or chemotherapy, five were continuously free of disease at follow-ups ranging between 3 and 14 years (mean, 9 years). The remaining seven patients died with uncontrolled disease 12 to 39 months (mean, 22 months) after thoracotomy. These results seem to indicate that an aggressive surgical approach should be considered for a selected group of patients with Ewing's sarcoma who relapse with only lung metastases.

Extraskeletal osteosarcomas are rare malignancies that account for about 1% of all soft-tissue sarcomas. One study of 40 patients (mean age, 51 years; male-to-female ratio, 1.9:1) with extraskeletal osteosarcoma found pulmonary metastases in 81%. The primary tumors originated in the lower limbs in 68% of cases and presented in 90% of patients as an enlarging soft-tissue mass; nine patients had a history of trauma. Morphologically, all were high-grade osteosarcomas. Distant metastases occurred, usually within 3 years, in 65%, but lung involvement was noted in 81%. The overall 5-year survival rate was 37%.

Benign giant-cell tumor of bone demonstrates the unusual ability to metastasize to the lungs. It is estimated that 9% of such tumors may metastasize to the lungs. Approximately 50 such cases have been reported. In a report of six patients with pulmonary metastasis of giant-cell tumor, one patient exhibited spontaneous regression and another died of pulmonary complications.

MISCELLANEOUS TOPICS

The increased risk for deep vein thrombophlebitis and pulmonary embolism in patients who undergo orthopedic procedures, particularly arthroplasty of the hip, knee, and other joints, is discussed elsewhere, as is the topic of fat embolism following fractures of bone and orthopedic procedures. Orthopedic procedures such as

intramedullary femoral nailing and arthroplasty in which chemical adhesive cement (methyl methacrylate) is used have been followed by pulmonary complications.

Femoral nailing after reaming has been shown to be associated with higher risk for development of adult respiratory distress syndrome in comparison with unreamed femoral nailing. The risk for respiratory complications is even higher in those with “borderline pulmonary status.”

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and five of whom also underwent posterior arthrodesis, were as follows: Cobb angle of the thoracic curve improved by 31% (from 59° to 39°), mean forced vital capacity decreased by 0.21 L, and decreases in mean 1-second forced expiratory volume and total lung capacity were also noted.

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CHAPTER

62 Dermatologic Diseases

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INTRODUCTION

Dermatologic manifestations of diseases that originate in other organs are commonly encountered in clinical practice. Frequently, the dermatologic sign is the initial signal of an internal illness. The best example of this is the presentation of paraneoplastic manifestations in the form of clubbing, dermatomyositis, acanthosis nigricans, bullous pemphigoid, and other external clinical features that point toward the possibility of an underlying malignancy. Among the malignant disorders, respiratory neoplasms are well known to cause paraneoplastic syndromes listed above. Many vasculitic syndromes and collagenoses also produce significant cutaneous lesions. These disorders are discussed in Chapter 53 and Chapter 54. Nonmalignant disorders such as pulmonary infections and pulmonary sarcoidosis may demonstrate unusual dermal response in the form of erythema nodosum or erythema multiforme. This chapter addresses several of these entities and the respiratory manifestations of primary dermatologic diseases. However, many of these disorders cannot be classified as primary dermatoses, though their clinical presentations with cutaneous lesions warrant their inclusion here. Because of the lack of connection among most of the diseases included here, which makes an appropriate classification difficult, the diseases are discussed in alphabetic order.

ACANTHOSIS NIGRICANS AND OTHER PARANEOPLASTIC DERMATOSES

Acanthosis nigricans is an uncommon cutaneous disorder characterized by hyperpigmentation and epidermal hypertrophy (Fig. 1). The paraneoplastic category of acanthosis nigricans is associated, in 90% of cases, with gastric adenocarcinoma and other intraabdominal malignancies. Skin changes and an underlying neoplasm appear together in 60% of cases, whereas the cutaneous changes appear before clinical evidence of carcinoma in 20% of patients. Acanthosis nigricans may be the presenting clinical feature of lung cancer, adenocarcinoma of the lung being the most common type of pulmonary malignancy associated with this skin disorder. Acanthosis nigricans has also been observed in a patient with bronchoalveolar cell carcinoma. The prognosis in patients with acanthosis and associated cancer is dismal. Progressive skin changes signify a higher mortality.

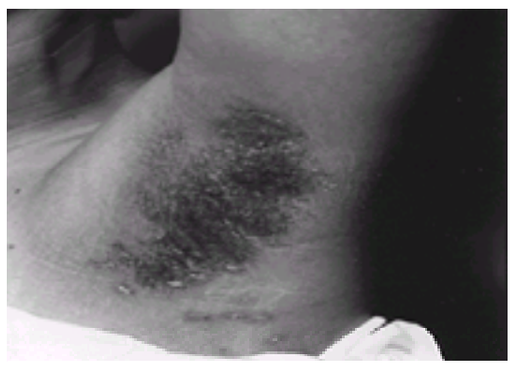

FIG. 1. Acanthosis nigricans involving left axilla in a patient with adenocarcinoma of the lung. Marked hyperpigmentation and epidermal hypertrophy are the pathologic features.

Tripe palms, sometimes called Bazex's syndrome, are characterized clinically by rugose, thickened, velvety palms with pronounced dermatoglyphic ridges and sulci. Tenderness around the fingernails also has been observed in this entity. Histologic examination reveals an undulant epidermis with hyperkeratosis, acanthosis, and papillomatosis. Over two-thirds of the patients with tripe palms exhibit associated acanthosis nigricans. More than 90% of patients with tripe palms have an associated cancer, most commonly involving the lung or the stomach. Among the 75 patients with tripe palms, the most common underlying neoplasm was lung cancer (in 53%), whereas patients with both tripe palms and acanthosis nigricans had gastric cancer (in 35% of cases) or lung cancer (11% of cases). Importantly, in over 40% of patients, tripe palms were the presenting feature of a previously undiagnosed malignancy. Therefore, any patient with tripe palms must have a complete cancer workup, especially for lung and stomach cancer.

Bowen's disease is a chronic dermatosis characterized by the development of *in-situ* epidermoid carcinoma of the skin. This disease has been linked to arsenic exposure in some cases; arsenic is a known carcinogen. The arsenic content of American tobacco was quite high until the early 1960s. This may explain some of the cases of lung cancer associated with Bowen's disease described in the past.

Paraneoplastic pemphigus is a syndrome in which patients have a severe mucocutaneous eruption with clinical features similar to those of both erythema multiforme major (Stevens–Johnson syndrome) and pemphigus vulgaris, in association with non-Hodgkin's lymphomas and other malignant neoplasms. A patient has been described in whom non-Hodgkin's lymphoma in apparent complete remission following autologous bone marrow transplantation developed bullous pemphigoid-like reaction and respiratory disease. Deposits of IgG were observed within the epithelium of the bronchial mucosa.

Tylosis or hyperkeratosis palmaris et plantaris, *epidermolysis bullosa, porphyria cutanea tarda,* and *acquired hypertrichosis lanuginosa* are among the other paraneoplastic cutaneous dermatoses associated with bronchogenic carcinoma. Many of these dermatoses precede the onset of the malignancy.

ACUTE FEBRILE NEUTROPHILIC DERMATOSIS

Acute febrile neutrophilic dermatitis (Sweet's syndrome) is an uncommon, recurrent, often dramatic cutaneous disease manifested by fever, painful erythematous plaque-forming inflammatory papules on the face, neck, and limbs and arthralgias and leukocytosis. Most cases are associated with a viral upper respiratory infection. Approximately 20% of patients have associated malignancies, particularly hematologic neoplasms.

Pulmonary involvement has been described in several cases. Chest roentgenograms have revealed patchy pulmonary parenchymal infiltrates. Histologic features in lung biopsies have included diffuse interstitial edema, neutrophilic interstitial and alveolar exudates, bronchiolitis obliterans with organizing pneumonitis, recent hemorrhages, and hyperplasia of type I and II cells. Pulmonary pathologic findings in one patient consisted of marked intraalveolar neutrophilic infiltrates similar to skin biopsy findings, chronic interstitial pneumonitis, and minimal fibrosis; resolution was reported after corticosteroid therapy. A report on a 54-year-old woman with myelodysplasia described severe dyspnea and pulmonary infiltrates associated with recurrent episodes of Sweet's syndrome. Lung and skin biopsies revealed a sterile infiltration of the interstitial tissues by mature neutrophils. Although corticosteroid therapy resulted in rapid clinical improvement, recurrent episodes became increasingly resistant to therapy, and she ultimately died from respiratory failure. Rare cases of primary lung cancer have been described in association with Sweet's syndrome.

ANHIDROTIC ECTODERMAL DYSPLASIA

Anhidrotic ectodermal dysplasia is a hereditary, usually X-linked disorder characterized by insufficient sweating, sparse hair, and scanty teeth. Predisposition to severe bronchitis has been observed. The common upper respiratory infections occur often in these patients and have been ascribed to scanty mucus and deficient cilia. Absence of mucous glands in the tracheobronchial tree and increased incidence of asthma are the other respiratory features described in this disorder.

ATAXIA-TELANGIECTASIA

Also known as Louis–Bar syndrome, ataxia-telangiectasia is characterized by a progressive cerebellar ataxia, oculocutaneous telangiectasia, and recurrent sinopulmonary infections. This disorder is associated with deficiency of IgA and IgE and the development of lymphoreticular malignancies. In addition, granulocytopenia, noted in many of these patients, is a factor in frequent infections. Repeated sinopulmonary infections are noted in three-fourths of patients with ataxia-telangiectasia, usually starting at approximately 4 to 6 years of age. Infection in nonrespiratory organs is uncommon. Severe neurologic impairment, bronchiectasis, and pulmonary fibrosis are usually progressive, leading to death by the time of adolescence. Roentgenologically, abnormalities are similar to those in cystic fibrosis, and both diseases also manifest chronic paranasal sinusitis. Upper airway dysfunction, identified by abnormal maximum inspiratory and expiratory flow–volume loops, has been described in patients with olivopontocerebellar atrophy.

BLUE RUBBER BLEB NEVUS SYNDROME

More than 40 cases of the blue rubber bleb nevus syndrome (Bean's syndrome), which is characterized by the presence of rubbery blue hemangiomas of the skin and gastrointestinal tract associated with gastrointestinal hemorrhage, have been reported in the literature. The rubbery angiomas of skin are variable in size, compressible, and refill on release of pressure. Hemangiomas may occur in other organs, including the pleura. Those of the gastrointestinal tract cause profuse hemorrhage, whereas hemothorax has resulted from pleural hemangiomas. Hemothorax and hemopericardium are described in a patient with this syndrome. Histologic examination of pleural specimens has shown features similar to those in the skin.

CHEST WALL LESIONS

Confusion arises when chest roentgenograms reveal unusual abnormalities caused by lesions located in the chest wall. Initially diagnosed as pulmonary parenchymal lesions, many of these undergo extensive diagnostic testing. Good physical examination with a posteroanterior stereo chest roentgenogram and a lateral view will exclude an intrathoracic lesion. Unusual density, significant calcification, and association with skin lesions in areas other than the thoracic cage assist in excluding an intrathoracic lesion (Fig. 2 and Fig. 3).

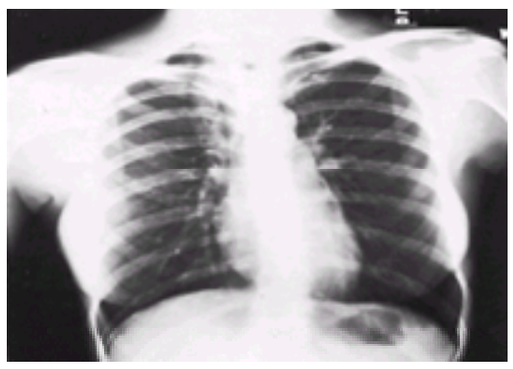

FIG. 2. Thick braid of hair masquerading as a superior mediastinal mass in the right paratracheal region.

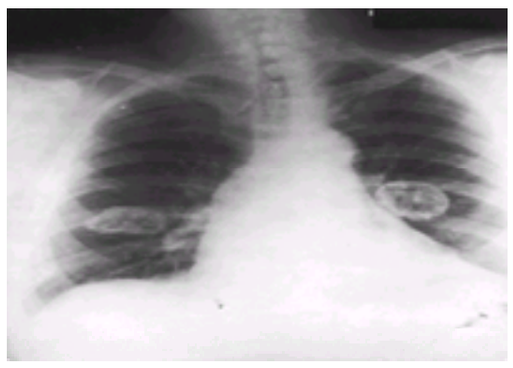

FIG. 3. Calcified skin lesions appearing as intrapulmonary lesions on a single posteroanterior view.

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Mucocutaneous candidiasis is an uncommon disorder associated with certain immunologic defects. Deficiency of the IgG_2/IgG_4 subclass and absence of antibodies against pneumococcal and *Hemophilus* polysaccharide occurs in patients with this disorder. Detailed studies of a pediatric patient with mucocutaneous candidiasis and recurrent pulmonary infections revealed a severe defect in cell-mediated immunity, but humoral immune responses were normal. The disease may be complicated by candidiasis involving the larynx, trachea, bronchi, and esophagus. Symptoms consist of hoarseness, hemoptysis, and dysphagia. Bacterial pneumonia, bronchopneumonic infiltrates, and bronchiectasis are some of the pulmonary manifestations described.

COGAN'S SYNDROME

Cogan's syndrome is a disease of unknown origin characterized by audiovestibular symptoms, nonsyphilitic interstitial keratitis, and systemic manifestations that include fever, anemia, elevated sedimentation rate, leukocytosis, and thrombocytosis. Complications include deafness, blindness, vasculitis, aortic insufficiency, and

death. Variable cardiovascular involvement leading to aortic insufficiency or orificial stenosis of coronary or aortic arch vessels is a common complication.

Respiratory involvement is present in approximately 20% of patients and includes mild, sometimes transient, chest roentgenologic abnormalities and pleuropericarditis. An upper respiratory tract infection precedes onset of the syndrome in approximately 40% of patients. A review of 78 patients noted transient pulmonary infiltrates and pleuritis in 9% and 5%, respectively. Recurrent lung infiltrates have been described.

CUTIS LAXA

Cutis laxa (generalized elastolysis) is a rare systemic disorder of connective tissue in which the elastic fibers become fragmented, disorganized, and fewer in number. A congenital (X-linked recessive) as well as an acquired variety have been described. The acquired cases manifest in midlife, and their origin, genetic or otherwise, is unknown. The dermatologic abnormalities in cutis laxa seem to result mainly from a developmental defect of the elastic network in the papillary dermis. Both the congenital and acquired varieties exhibit identical clinical, physiological, and pathologic abnormalities. Cutaneous pathologic findings are characterized by the disappearance of elastic fibers of the skin (Fig. 4). The skin changes lead to an appearance of early senility. Because the disease affects connective tissues all over the body, the clinical manifestations can be varied. Cutis laxa (loose skin), emphysema, aortic aneurysms, diverticula of bowel, and hernias are some of the complications. This disorder is distinct from Marfan's syndrome, Ehlers–Danlos syndrome, and pseudoxanthoma elasticum.

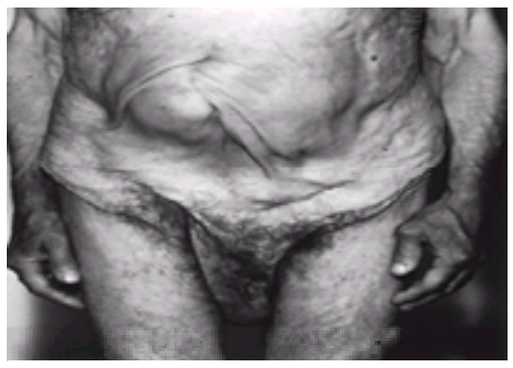

FIG. 4. Cutis laxa (generalized elastolysis) shows loss of skin elasticity over lower trunk and external genitalia. This patient also had severe emphysema.

The respiratory system ranks second only to the skin as the most commonly affected organ. The most frequent and serious pulmonary problem associated with cutis laxa is panlobular emphysema. Markedly elevated activity of an elastase-like serum enzyme, observed in some patients with cutis laxa, may predispose to the development of emphysema. Severe and rapidly progressive emphysema leads to early cor pulmonale, which is the most common cause of death among patients with the congenital variety. Emphysema also occurs in nearly 5% of patients with acquired cutis laxa. Other respiratory complications include pneumothorax, pulmonary fibrosis, pulmonary artery stenosis, eventration of the diaphragm, recurrent pulmonary infections, bronchiectasis, tracheobronchomegaly, and aneurysms of the thoracic aorta.

EHLERS–DANLOS SYNDROME

Ehlers–Danlos syndrome is a group of inherited disorders in which connective tissue diseases result from disorganization of collagen fibers. Deficiency of type III collagen may be responsible for the respiratory complications. Ultrastructural and biochemical analysis of the lung tissue have revealed a marked decrease in type III collagen and the production of less type III procollagen relative to type I procollagen by fibroblasts cultured from the abnormal lung. Electron microscopic examination of the lung tissue has shown dilated endoplasmic reticulum of the fibroblasts with normal collagen. Of the nine subtypes of Ehlers–Danlos syndrome, which generally are too difficult to distinguish from one another, only types I and IV are reported to be associated with a substantial risk of arterial rupture. Specifically, type IV, which is also known as the vascular or ecchymotic type, is associated with many serious complications. The disorder is clinically characterized by abnormal skin flaccidity, hyperextensibility of the joints, bleeding tendencies, atrophic scars, easy skin bruising, and pseudotumors.

Pulmonary involvement in Ehlers–Danlos syndrome results from weakness of the collagen in the lung tissue. Respiratory complications recorded include pneumothorax and bullous lung disease. Severe panacinar emphysema of lungs has been observed, and transient pulmonary cysts have been reported with this syndrome. Bronchiectasis resulting from weakened bronchial walls also has been reported. A dilated trachea, similar to that in Mounier–Kuhn syndrome, was noted in a patient with this disorder. Weakness of the pulmonary arterial wall may result in rupture and hemoptysis. Massive recurrent hemoptysis over a 6-year period followed by fatal lung hemorrhage has been described in a 27-year-old man. Pulmonary artery regurgitation and pulmonary valvular stenosis are described as well. An 18-year-old patient with Ehlers–Danlos syndrome, type IV, who developed recurrent large, thick-walled lung cavitary lesions, probably a manifestation of focal lung rupture, has been described. A patient with Ehlers–Danlos syndrome who presented acutely with clinical and roentgenologic features suggestive of aortic dissection was found to have mediastinal hematoma with no evidence of aortic dissection and was treated conservatively with no complications.

EOSINOPHILIC FASCIITIS

The syndrome of eosinophilic fasciitis consists of symmetric thickening of the deep fascia between muscle and subcutis of the arms, legs, and torso. Skin biopsy reveals a normal epidermis and an inflammatory infiltrate in the deep fascia. More than 200 cases of this unusual syndrome have been reported. Visceral involvement is generally mild or absent. Clinically, the affected skin is thickened and indurated.

When the skin around the thoracic cage becomes involved, the work of breathing is increased by the constricting effect of the thickened noncompliant skin (“hidebound chest”). Physical examination may reveal marked induration of the thoracic integument with a severely limited chest wall excursion. This extrapulmonary thoracic restriction has led to progressive respiratory limitation, documented by pulmonary function tests. Pulmonary parenchymal disease is not a feature, even though the diffusing capacity of carbon monoxide ($D_L CO$) in some patients with this disorder has been found to be reduced to a very low level.

EPIDERMOLYSIS BULLOSA DYSTROPHICA

Epidermolysis bullosa represents a group of rare hereditary bullous disorders marked by blister formation following relatively minor trauma. Three types of the disease occur depending on the site of disruption within the skin: simplex (above the basement membrane), dystrophic (below the basement membrane), and junctional (at the lamina lucida). Epidermolysis bullosa dystrophica generally presents in newborns and is characterized by noninflammatory bullous lesions that may affect the tracheobronchial mucosa and cause respiratory distress. Postmortem analysis of the airways in a 29-month-old boy who died from laryngeal obstruction secondary to this disorder showed intense mucosal inflammation and swelling of the seromucinous glands in the supraglottic airway. Localized subglottic edema and the formation of an inflammatory membrane in the trachea has led to chronic subglottic stridor. Even minimal trauma is reported to result in stricture formation. In one series of five children, three required tracheostomies acutely, and one died of airway obstruction. The laryngeal cysts are distinct from the cutaneous bullae or bullous pemphigoid.

ERYTHEMA MULTIFORME

Erythema multiforme is a systemic disorder characterized by generalized eruptions of red or violaceous macules similar to urticaria, papules, vesicles, or bullae, involvement of various internal organs, and fever. The most characteristic skin lesion is known as a target or bull's eye. A more severe form is generally described as Stevens–Johnson syndrome, in which mucocutaneous ulcerations are seen.

Although the association of erythema multiforme with respiratory infection caused by *Mycoplasma pneumoniae* is well known, the most common association of this disorder is with bacterial pneumonias caused by streptococci, *Pseudomonas* species, pneumococci, *Legionella* species, and *Hemophilus influenzae.* Erythema multiforme is also seen in association with histoplasmosis and blastomycosis. Noninfectious causes of erythema multiforme include penicillin, antipyretics, barbiturates, and sulfonamides. A literature review of 70 cases of *Mycoplasma* pneumoniae infections associated with the Stevens–Johnson syndrome recorded that none of the cases exhibited erythema multiforme. Most patients had prodromal symptoms of an upper respiratory tract infection before the onset of the eruption and an underlying pneumonia. These findings led the authors to conclude that *M. pneumoniae* is the most common infectious agent associated with the Stevens–Johnson syndrome and that the infection is not associated with erythema multiforme. Another report noted that four of seven cases of erythema multiforme were caused by *M. pneumoniae*

infection.

Respiratory complications include bronchopneumonic infiltrates, massive pneumonic consolidations, miliary lesions, hilar lymphadenopathy, and, uncommonly, pleural effusions. Clinically, the pulmonary manifestations are indicated by laryngotracheobronchitis, cough, hemoptysis, dyspnea, and cyanosis. In a 46-year-old woman with active systemic lupus erythematosus, severe Stevens–Johnson syndrome developed 8 hr after intravenous urography with the nonionic contrast medium iopamidol. The illness included erythema multiforme, intrahepatic cholestasis, pulmonary infiltrates, and acute renal failure, which led to her death. Rapidly progressive and fatal bronchiolitis obliterans was observed in a middle-aged woman. Stevens–Johnson syndrome with supraglottic laryngeal obstruction has been described.

The diagnosis and management of erythema multiforme and Stevens–Johnson syndrome are complex and controversial. Systemic corticosteroids have been used successfully in many instances.

ERYTHEMA NODOSUM

Erythema nodosum is a self-limited cutaneous disorder characterized by inflammatory nodules in the dermis and subcutaneous tissues, commonly along the extensor aspects of the legs. This form of panniculitis is clinically characterized by pain in the anterior tibial area, followed by development of tender pink nodules on the shins. The lesions normally resolve spontaneously over a period of several weeks. The appearance is so characteristic that biopsy is seldom required. Erythema nodosum is most likely a hypersensitivity reaction to a broad variety of disorders, especially drug reactions and infection by viruses, bacteria, and fungi. The cause of erythema nodosum remains unknown in approximately half the patients.

Sarcoidosis is one of the common diseases associated with erythema nodosum. Erythema nodosum has been observed in 13% of two large series of patients with sarcoidosis. Erythema nodosum can be the presenting manifestation of sarcoidosis. The presence of erythema nodosum in patients with sarcoidosis is associated with a good prognosis, and an acute onset of sarcoidosis with erythema nodosum signifies a good prognosis and spontaneous resolution. In a retrospective study of 818 patients with sarcoidosis, 16% of patients presenting with erythema nodosum followed a chronic course. Bronchoalveolar lavage in patients who had an acute inflammatory onset of sarcoidosis and erythema nodosum has demonstrated high CD4/CD8 lymphocyte ratios and a higher proportion of T lymphocytes than in patients presenting with respiratory complications after erythema nodosum resolved. Erythema nodosum in conjunction with non-Hodgkin's lymphoma that presents as a solitary pulmonary nodule has also been described.

Histoplasmosis and coccidioidomycosis are common causes of erythema nodosum in the United States. Pulmonary blastomycosis associated also with erythema nodosum has been described. Among 305 children with postprimary tuberculosis, erythema nodosum was observed in 37 (12%) children. As in sarcoidosis, erythema nodosum in association with these infections denotes a good prognosis because such a combination confirms the development of antibodies or hypersensitivity to the pathogenic antigens. Erythema nodosum was observed in 28% of 88 cases of tularemia in northern Finland, and pulmonary tularemia was present in 27% of the patients. Erythema nodosum was seen more often in patients with pulmonary tularemia than in other forms of the disease.

FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean fever, also known as periodic disease, is an autosomal recessive inherited disorder characterized by recurrent episodes of fever accompanied by inflammation of the peritoneum, pleura, synovial membranes (recurrent polyserositis), and skin. The disorder predominantly affects persons of Mediterranean origin (Sephardic Jews, Armenians, and Arabs) and is rare in other groups. The most serious complication of the disease is amyloidosis, which is the cause of death in a substantial proportion of adult patients. Abdominal pain, which occurs in more than 95% of patients, is an important aspect of the disease. Acute arthritis occurs in 17% to 75% of patients.

Pulmonary manifestations commonly occur in the form of pleuritic chest pain in 35% to 85% of patients. Recurrent pleuritic chest pains are common and may be associated with small pleural effusions. Right-sided effusions are reported to be more common. Pulmonary hypertension and pulmonary amyloidosis have been described in familial Mediterranean fever.

Asthma is reported to occur less commonly in patients with familial Mediterranean fever. A study of 148 parents of patients with familial Mediterranean fever and of 148 ethnically matched control persons demonstrated an apparently reduced prevalence of asthma in the heterozygotes compared with the control subjects (three versus six). The authors of this study concluded that their data were in agreement with previous studies that demonstrated decreased asthma prevalence in patients with familial Mediterranean fever.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease) is an autosomal dominantly inherited disorder characterized by telangiectasia of the skin and mucous membranes and intermittent bleeding from arteriovenous malformations and fistulas. The prevalence of simultaneous hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformation during a 10-year period in one Scandinavian county of more than 429,207 inhabitants was 2.6 per 100,000. The male–female ratio was 1:2. Telangiectasias of the skin and oral, nasal, and conjunctival mucosa manifest in the second and third decades of life. They appear bright red, punctate or linear, and blanch under pressure. Gastrointestinal bleeding occurs in approximately 15% of patients.

Hereditary hemorrhagic telangiectasia is the most common cause of pulmonary arteriovenous fistula. In a study of seven families that participated in screening for pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia, 36 (80%) of the 45 screened family members were found to have hereditary hemorrhagic telangiectasia, and 13 (36%) of the 36 family members with hereditary hemorrhagic telangiectasia were proven to have pulmonary arteriovenous malformations by pulmonary angiography. A report on 53 patients with pulmonary arteriovenous malformations observed that 42 (79%) patients had associated hereditary hemorrhagic telangiectasia.

The rate of occurrence of pulmonary arteriovenous fistulas is determined by the mutations in endoglin. In a genetic study, members of families with the mutation in endoglin (the locus has been designated ORW1) exhibited a 29% prevalence of pulmonary arteriovenous malformations compared to a prevalence rate of 3% in families in which ORW1 was excluded. A genetically determined location for a second ORW locus with linkage to chromosome 12 has been identified in patients with significantly reduced incidence of pulmonary involvement.

Pulmonary arteriovenous malformation is a rare cause of cyanosis in the newborn. Among the nine previously reported neonatal cases, typical signs at presentation included cyanosis, murmur, and congestive cardiac failure. Chest roentgenographs commonly exhibited cardiomegaly, oligemia, and focal pulmonary density. The majority of pulmonary fistulas are detected in the third and fourth decades of life. The pulmonary fistulas usually occur in the lower lobes of lungs and are multiple in nearly 35% of patients. Typically, chest roentgenograms show the pulmonary arteriovenous fistulas as oval or round homogeneous nodular lesions that measure from a few millimeters to several centimeters in diameter. These fistulas tend to evolve and continue to enlarge over long periods, sometimes as long as 24 years. A standard chest roentgenogram may show a nodular shadow but can easily obscure small afferent and efferent vessels attached to the fistula (Fig. 5). The risk of relying solely on the standard chest roentgenogram becomes apparent when a transthoracic needle aspiration is performed, with resultant serious hemorrhage. Simple tomography generally discloses an artery entering the fistula and a vein leaving it (Fig. 6). Pulmonary angiography confirms the diagnosis in virtually all cases and is required before embolotherapy or surgical resection of a fistula is undertaken (Fig. 7). Cases of spontaneous pneumothorax and hemothorax secondary to intrapleural rupture of an arteriovenous fistula have been observed. Endobronchial mucosal or submucosal telangiectases are distinctly uncommon. They may come to light when bronchoscopy is performed to investigate hemoptysis. Telangiectasia of the nasal mucosa occurs more frequently than does endobronchial fistula and leads to recurrent bouts of epistaxis.

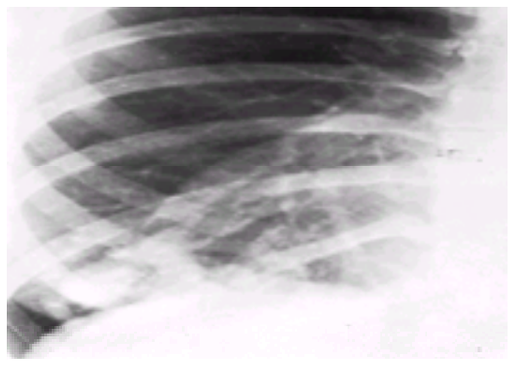

FIG. 5. Pulmonary arteriovenous malformation in right lower lobe of a patient with hereditary hemorrhagic telangiectasia reveals afferent and efferent vessels attached

to the fistula.

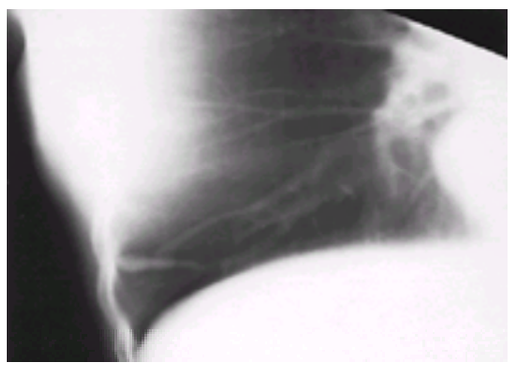

FIG. 6. Localized tomography sometimes is necessary to identify pulmonary arteriovenous malformation, especially when the fistula is small.

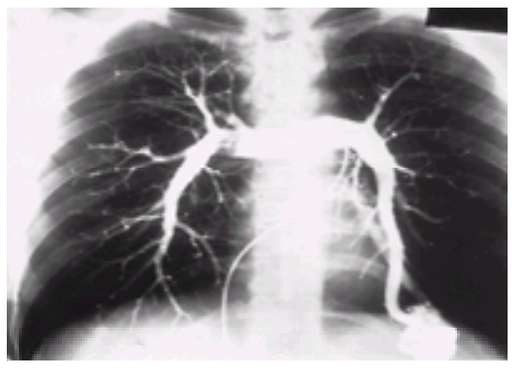

FIG. 7. Pulmonary angiogram in hereditary hemorrhagic telangiectasia shows a large arteriovenous malformation in the left lower lobe.

Dyspnea and hemoptysis are the two common symptoms. The severity of dyspnea depends on the degree of right-to-left shunting. Although dyspnea is present in nearly 60% of patients, hemoptysis (occurring in 10% to 20%) is the most common presenting symptom. This can be brisk but usually is not life-threatening. In a study of 143 patients with pulmonary arteriovenous malformations associated with hereditary hemorrhagic telangiectasia, 11 (8%) patients (seven women and four men) had a history of either massive hemoptysis or hemothorax; one patient died as a result of the pulmonary hemorrhage. Among the seven women, three had pulmonary hemorrhage during pregnancy. The increased risk of bleeding from the arteriovenous malformations during pregnancy has been reported in several cases.

Clinical examination may reveal cyanosis, clubbing of fingers, and a bruit or a continuous vascular noise or hum over the site of the fistula. Pulmonary artery catheterization generally reveals diminished arterial oxygen tension and saturation but normal pulmonary artery pressure. Echocardiography is a less invasive method for detecting extracardiac right-to-left shunts. After venous injection of indocyanine green dye or agitated saline, the characteristic contrast flow pattern consists of a markedly delayed appearance of echoes in the left ventricle. However, this type of assessment does not calculate the degree of shunt. Physiological shunt calculation is accomplished by administering 100% oxygen and obtaining blood samples for measurements of gas tensions.

Paradoxic embolism is a common and serious complication of pulmonary arteriovenous fistulas; the occurrence of this complication has been noted at presentation in more than one-third of patients. A report on 53 patients with pulmonary arteriovenous malformations observed that 19 (36%) patients had neurologic problems compatible with paradoxic embolization. Among 67 patients with pulmonary arteriovenous malformations associated with hereditary hemorrhagic telangiectasia, strokes and transient ischemic attacks were recorded in 37%. Another report observed that four of five patients with asymptomatic small or moderately sized pulmonary arteriovenous malformations presented with stroke caused by paradoxic embolism. A review of the English literature in 1990 disclosed 52 cases of neurologic complications, but not all were caused by paradoxic emboli originating in pulmonary arteriovenous fistulas. Indeed, among a series of more than 200 reported patients with hereditary hemorrhagic telangiectasia and associated neurologic sequelae, 61% developed neurologic lesions secondary to pulmonary arteriovenous fistula, whereas 36% of the patients with neurologic manifestations exhibited vascular malformations of the brain and spinal cord.

Various neurologic manifestations are reported in up to 30% of patients. Brain abscess, estimated to occur in approximately 1% of patients, can be the presenting feature of hereditary hemorrhagic telangiectasia. Mental obtundation, headache, visual disturbances, hemiplegia, and seizures are the most common presenting features of paradoxic embolism to the neurologic system. Leukocytosis and fever are not prominent features, and blood cultures are generally sterile. However, in patients with brain abscesses, anaerobic and microaerophilic streptococci are the most common pathogens isolated. In a series of 31 patients with hereditary hemorrhagic telangiectasia and neurologic involvement, 13 patients died, and patients without abscess drainage or with delayed diagnosis had a higher mortality.

Unusual complications described in patients with hereditary hemorrhagic telangiectasia include high-output congestive cardiac failure, portosystemic encephalopathy (from hepatic arteriovenous malformations), and disseminated intravascular coagulation. In a report on 47 patients with documented hereditary hemorrhagic telangiectasia, disseminated intravascular coagulation was observed in 51%.

The treatment of choice is pulmonary artery embolo-therapy (therapeutic embolization) using coils and other intravascular devices. The aim of such treatments is to reduce right-to-left shunts. As new fistulas evolve in the same patient, or recanalization occurs in the embolized fistulas over a period of time, repeated embolizations may be necessary (Fig. 8 and Fig. 9). A publication on embolo-therapy in 67 patients with pulmonary arteriovenous malformations associated with hereditary hemorrhagic telangiectasia reported that the physiological improvements remained stable for 5 years after embolotherapy, complications were minimal, and surgery was not required in any patient. In another report on 11 patients with pulmonary arteriovenous malformations, lung function tests before embolotherapy disclosed normal vital capacity and FEV_1/FVC ratios, reduced D_LCO (mean 71% of predicted; range 36% to 123%), a resting supine arterial oxygen saturation of 86% (range 67% to 95%), mean shunt fraction of 33% (range 15 to 47%), and well-preserved exercise capacity. Six months after therapy, the mean shunt fraction decreased from 33% to 19%, and resting arterial oxygen saturation increased from 86% to 92%. A consistent improvement in D_LCO was also seen. There were no long-term complications following embolotherapy. In another report, 32 patients with 92 pulmonary arteriovenous malformations (with feeding arteries >3 mm) were treated by coil embolization and followed up for a mean period of 25 months, and the mean shunt fraction decreased from 16.6% to 7.4%; treatment was incomplete in two patients, one of whom was subsequently treated surgically. Others also have documented the immediate improvement in respiratory symptoms, exercise capacity, and gas exchange at rest and during exercise as a result of the embolization-induced reduction in right to left shunt. Even though hypoxia induced by right-to-left shunt does not respond to oxygen therapy, many patients subjectively feel better with supplemental oxygen.

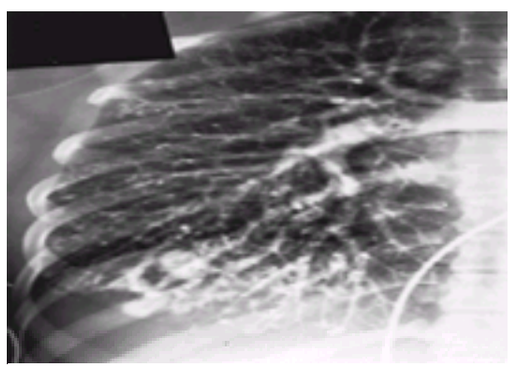

FIG. 8. Multiple arteriovenous malformations the right lower lobe. This patient had multiple bilateral arteriovenous malformations.

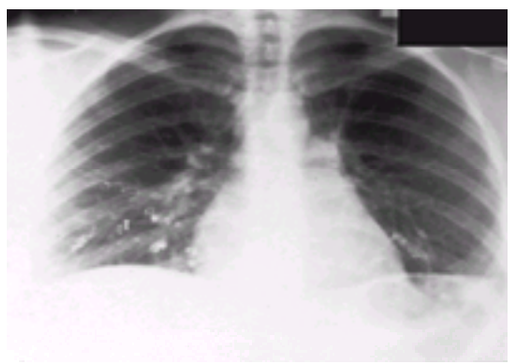

FIG. 9. Chest roentgenogram of the patient shown in Fig. 8 after multiple steel-coil embolizations. This patient has required several embolizations for recurrent arteriovenous malformations.

Complications of coli embolization therapy have been noted in 10% of procedures. They have included potentially serious problems such as systemic coil embolization, cerebrovascular accident, and myocardial puncture.

Large arteriovenous fistulas (diameter of efferent vessel exceeding 10 mm) may require surgical resection. The life expectancy of patients with hereditary hemorrhagic telangiectasia is not reduced provided treatable complications are diagnosed and treated promptly.

HYPERHIDROSIS

Hyperhidrosis, or abnormally excessive production of sweat, can signify an underlying malignancy. Unilateral hyperhidrosis of the chest cage has been described in patients with lung cancer. In most reported cases, hyperhidrosis has been limited to the same side as the tumor. It is speculated that direct irritation of nerves may excite the autonomic efferent fibers. The presence of hyperhidrosis indicates a poor prognosis. Resection of a cervical rib may abolish the hyperhidrosis.

Anhidrosis or abnormally diminished production of sweat can be encountered as part of the paraneoplastic syndrome. An example of this is the anhidrosis seen in Horner's syndrome, in which the other features include ipsilateral miosis and ptosis. These changes as well as anhidrosis occur on the same side as the pulmonary neoplasm.

MALIGNANT ATROPHIC PAPULOSIS

Malignant atrophic papulosis (Degos' disease) is a rare multisystemic disorder characterized by typical skin and gastrointestinal symptoms. Many patients demonstrate a rapidly fatal course. The presenting clinical feature is the appearance of crops of asymptomatic oval skin lesions ranging from 2 to 8 mm in diameter. A review of 60 reported cases of Degos' disease found that 17 included intrathoracic abnormalities, most of which were found incidentally at postmortem. The most common intrathoracic findings were pleuritis and pericarditis. Bilateral hemorrhagic pleural effusions, pleural plaques, pulmonary infarcts, and pulmonary abscesses also were noted.

MASTOCYTOSIS

Systemic mastocytosis, or mast cell disease, is an uncommon disorder characterized by urticaria pigmentosa, hepatosplenomegaly, osteosclerotic bone lesions, and diarrhea, nausea, vomiting, and flushing. Respiratory manifestations include interstitial lung disease and extensive peribronchial and alveolar infiltration with mast cells. There are several reports of systemic mastocytosis associated with mediastinal germ cell tumors.

NEUROFIBROMATOSIS

Neurofibromatosis (von Recklinghausen's disease) is a common disease of variably expressive autosomal dominant inheritance characterized by café-au-lait spots, freckling, and neurofibromas of skin and internal organs. Its incidence is one per 3000; approximately half the cases occur sporadically. Cutaneous lesions are the result of the maldevelopment of neural crest cells. The number of dermal neurofibromas varies from individual to individual. Large plexiform neurofibromas develop along peripheral nerves and involve deeper tissues. Extracutaneous (visceral) involvement may not be apparent during life unless such lesions produce symptoms.

Respiratory involvement occurs in 10% to 15% of patients with neurofibromatosis. Although neurofibromatosis is a congenital disorder, the lung involvement does not become evident until adulthood. Up to 20% of patients older than 35 years develop diffuse interstitial fibrosis. Diminished perfusion and ventilation to apices of the lungs has been documented by radionuclide studies in a patient with cutaneous neurofibromatosis. Bullous lung disease may occur alone or in combination with diffuse pulmonary fibrosis. Pulmonary fibrosis usually is seen in the basal areas of the lungs, whereas the bullous lesions occur predominantly in the apical areas (Fig. 10). Cystic lung disease resembling honeycomb lung also has been described.

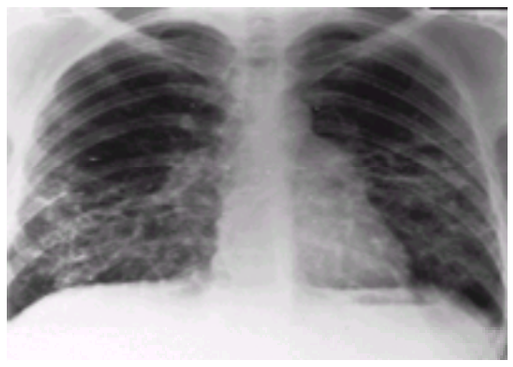

FIG. 10. Neurofibromatosis with pulmonary manifestations showing bullous changes in the upper lung zone and honeycomb changes in the lower lungs.

The pulmonary parenchymal disease is attributed to a mesenchymal defect resulting in primary deposition of collagen. The histologic features mimic those of idiopathic pulmonary fibrosis. Ultrastructural studies have shown fragmentation of collagen fibers in the lung. The clinical manifestations are mild, usually consisting only of exertional dyspnea, but a restrictive pattern of pulmonary function and diminished diffusing capacity often are observed.

Intrathoracic neurofibromas and meningoceles may be associated with a dermal form of neurofibromatosis, but these usually remain undetected because they rarely are symptomatic (Fig. 11). An earlier review of the literature reported 27 cases of intrathoracic meningoceles with neurofibromatosis. Since then, more than a dozen such associations have been reported. When these lesions are situated in the posterior mediastinum, as they commonly are, they may represent so-called dumbbell tumors with intraspinal extension. Magnetic resonance imaging of the involved spinal area is helpful in assessing the anatomic extent of such tumors.

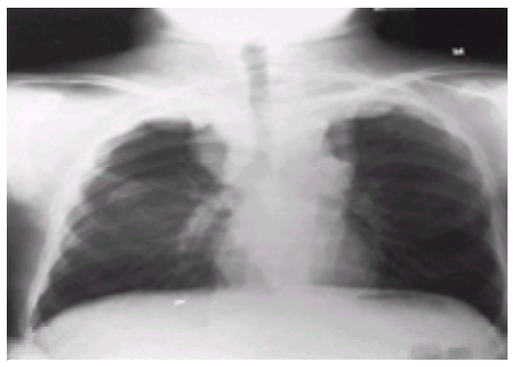

FIG. 11. Neurofibromatosis with intrathoracic neurofibromas.

Neurofibromatosis can involve the mediastinum. A 44-year-old woman with a dumbbell-shaped mediastinal mass developed a large pleural effusion, respiratory failure, and fatal hemoptysis. Autopsy revealed systemic neurofibromatosis involving the mediastinum and pleura. Mediastinal and pleural hemorrhage probably occurred as a result of an eroded thoracic artery. Primary pulmonary parenchymal neurofibromas are rare. Benign neurogenous tumors arising in the trachea are also uncommon. A report described a patient with neurofibromatosis who presented with dyspnea caused by endotracheal neurofibroma. Hoarseness may result from recurrent laryngeal nerve involvement.

Primary or secondary malignancy in the lung has been overlooked in two patients with generalized neurofibromatosis because of roentgenographic confusion caused by overlying cutaneous lesions (see above regarding chest wall lesions). Neurofibromatosis is associated with an increased incidence of malignancy, ranging from malignant tumors of the central nervous system to Wilms' tumor, rhabdomyosarcoma, leukemia, and pheochromocytoma. In 5% of patients, the neurofibromas in neurofibromatosis undergo transformation to malignant degeneration and commonly metastasize to the lungs. Scar cancer of the lung has been reported as a complication of the chronic pulmonary process in neurofibromatosis.

NONSUPPURATIVE PANNICULITIS

Sometimes referred to as *Weber–Christian disease,* nonsuppurative panniculitis is characterized by cutaneous nodular fat necrosis of the panniculus adiposum. Tender, erythematous subcutaneous nodules appear over the extremities and trunk.

A review in 1976 reported pulmonary involvement in only five cases. Pulmonary manifestations include pulmonary fat emboli and infarcts, lipogranulomatous pneumonitis with nodules measuring 0.8 to 3 cm in diameter, and fluffy roentgenographic densities bilaterally. Recurrent pneumonia and pleural effusion also occur. Interestingly, a_1-antitrypsin deficiency has been found in some patients with acute panniculitis. There is no report of emphysematous lung disease occurring as a result of this.

OCULOCUTANEOUS ALBINISM

Sometimes called *pulmonary ceroidosis* or the *Hermansky–Pudlak syndrome,* oculocutaneous albinism is an autosomal recessive disorder characterized by oculocutaneous tyrosinase-positive albinism, platelet pool disease with moderate bleeding tendency, and ceroid-like inclusions in the reticuloendothelial system. A review of the literature in 1989 recorded more than 200 cases of the Hermansky–Pudlak syndrome, the most striking feature of which is the presence of clinically recognizable oculocutaneous albinism. However, the most frequent clinical complication is hemorrhage, and epistaxis is the most common hemorrhagic manifestation.

Respiratory involvement is a recognized complication in oculocutaneous albinism. The primary disease affects men and women equally, but the incidence of lung disease is twice as high in women as in men. The pulmonary disease is similar to idiopathic pulmonary fibrosis and usually begins in the third or fourth decade of life. Bronchoalveolar lavage in asymptomatic patients has shown that the concentration of platelet-derived growth factor-related peptides is six times greater in patients with Hermansky–Pudlak syndrome than in normal subjects. These peptides are important in the initiation of alveolar remodeling in the fibrotic lung disorders and are perhaps involved in the pathogenesis of lung disease in this syndrome.

Clinically, constant nonproductive cough and progressive dyspnea are the chief symptoms. Dyspnea can develop suddenly over several weeks or gradually over years, and the respiratory disease can progress to end-stage fibrosis and death. The pulmonary pathology in oculocutaneous albinism is compatible with oxidant injury as it parallels pathologic alterations seen with pulmonary oxygen toxicity. Bronchoalveolar lavage may show alveolar macrophages containing typical ceroid-like material. Brown-pigmented histiocytes have been demonstrated in the alveolar spaces. Increased levels of immunoglobulins, numbers of IgG- and IgA-secreting cells, and normal percentages of helper and suppressor T cells are observed. The pulmonary fibrosis is an irreversible and progressive process. No specific therapy is available for the lung disease.

Pulmonary ceroidosis occurs in many of the approximately 30 disorders in which systemic or localized deposition of ceroid occurs. Sea-blue histiocytosis syndrome is an example of ceroidosis, and lung involvement is present in 11% of these patients. Idiopathic pulmonary ceroidosis may represent pulmonary alveolar deposition of ceroid-like material in the absence of clinical or biochemical data characteristic of any specific ceroid storage disease. Interestingly, deposition of ceroid-like pigment in the pulmonary alveolar macrophages has been reported in eight patients with carcinoma of the stomach.

PEMPHIGOID

The association of bullous pemphigoid with lung cancer was discussed earlier. Cicatricial pemphigoid, however, is a nonparaneoplastic chronic vesiculobullous disease of the mucosal epithelium that primarily involves the oral cavity and the eyes. This chronic mucosal blistering disorder exhibits a predilection for subsequent scar formation. Airway obstruction and laryngeal stenosis, several of which required tracheostomy, have been described in patients with cicatricial pemphigoid. An unusual case of a 20-year-old woman who died of respiratory failure and was noted to have cicatricial pemphigoid of the bronchi is reported. A case of a 22-year-old man with cicatricial pemphigoid in whom severe stenosis of the left mainstem bronchus developed 2 years after onset of the disease is described; therapy by sleeve resection and end-to-end anastomosis was successful. Pulmonary hemorrhage associated with bullous pemphigoid of the lung has been described. Stenosis of the nasopharynx or larynx has resulted in obstructive sleep apnea.

PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum is a rare disorder characterized by fragmentation and calcification of elastic fibers in skin, blood vessels, and retina. Both autosomal dominant and recessive forms have been described. The basic defect is unknown. One patient with pseudoxanthoma elasticum has been reported in whom the lung biopsy showed widespread deposition of calcium in the walls of some arteries, arterioles, and venules, with swollen, short, irregularly clumped elastic fibers and irregularity of the elastic laminae.

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is a painful, chronic, destructive, and ulcerating skin disease of unknown origin. The occurrence of this disorder in intestinal diseases is well known. In a report on 86 patients with this disease, inflammatory bowel disease was present in 36%. Asthma or chronic obstructive pulmonary disease was noted in 5%. Pulmonary abscess has been described in a patient with pyoderma gangrenosum, but the relationship between pyoderma gangrenosum and pulmonary disease remains unclear. Pyoderma gangrenosum of the skin and trachea has been described in a 9-month-old boy.

TUBEROUS SCLEROSIS

Tuberous sclerosis (Bourneville's disease) is an autosomal dominant disease of mesodermal development characterized clinically by epilepsy and mental retardation and pathologically by congenital tumors and malformations of the brain, skin, and viscera. The classic clinical triad in tuberous sclerosis consists of adenoma sebaceum, mental retardation, and seizures. Skin lesions, in addition to adenoma sebaceum or dermal angiofibroma, include ash leaf spots (a hypopigmented skin lesion, the earliest to appear in tuberous sclerosis), shagreen patches (hamartomas of connective tissue seen in 50% of patients and located over the lumbosacral area), and periungual fibromas (benign pink fibrous neoplasms adjacent to the nails and seen in 15% to 20% of patients). Poliosis, or hypopigmentation of the scalp

hair or eyelashes, also is seen. Extracutaneous manifestations include seizure disorder, electroencephalographic abnormalities, or both in 80% to 90%, mental retardation of wide-ranging severity, a hamartomatous lesion of the central nervous system, retinal phakomas, angiomyolipomas of the kidney, renal and bone cysts, and cardiac rhabdomyomas.

Some consider tuberous sclerosis and pulmonary lymphangioleiomyomatosis to be the same clinical entity because of the many striking similarities in clinical, roentgenologic, and pathologic features. However, the presence of hormonal (estrogen, progesterone) receptors in lymphangioleiomyomatosis may distinguish it from tuberous sclerosis, although not all patients with lymphangioleiomyomatosis exhibit these receptors. Chylous effusion is more common in lymphangioleiomyomatosis, whereas angiomyolipomas are much more common in tuberous sclerosis. The difficulty of separating these two entities as distinct diseases is further enhanced by the observation that several patients reported in the literature with the diagnosis of tuberous sclerosis have responded favorably to hormonal therapy that is used to treat pulmonary lymphangioleiomyomatosis. Furthermore, the clinical features are not overt in many patients; indeed, a study of nine patients with pulmonary tuberous sclerosis noted that there was an average delay of 8 years before the correct diagnosis was made. Details on pulmonary lymphangioleiomyomatosis are included in Chapter 63.

Morphologic analysis of the lungs affected by tuberous sclerosis reveals multiple cysts measuring a few millimeters in diameter. The walls of the cysts are formed of hypertrophied smooth muscle cells. The compression of the bronchioles caused by the hypertrophied smooth muscles leads to obstruction, air trapping, bulla formation, and pneumothorax. The compression of the pulmonary venules results in venous congestion and hemoptysis, whereas the compression of the pulmonary arterioles may lead to pulmonary hypertension. The same mechanism, when it involves the lymphatic channels, causes chylothorax. Ultrastructural morphologic analysis of the lung in tuberous sclerosis has shown findings identical to those in lymphangioleiomyomatosis. Cystic disease of the lung with focal adenomatoid proliferation is among the least common pathologic features of tuberous sclerosis.

Pulmonary function tests demonstrate obstructive pulmonary dysfunction despite the nodular interstitial appearance of lungs on the chest roentgenograms. Obstruction to airflow is caused by the compression of the smaller airways by the smooth muscles that undergo hyperplasia. This mechanism also contributes to the increased lung volumes and thoracic hyperinflation. Air-space lesions, however, are reported to be more important than muscular proliferation in bringing about these physiological abnormalities.

Respiratory disease is seen in fewer than 2% of patients with tuberous sclerosis. Often, there is a delay in the diagnosis of pulmonary disease, and many patients are treated for asthma or emphysema. A review of the literature in 1971 noted that there were only 31 cases of pulmonary tuberous sclerosis. Pulmonary tuberous sclerosis usually involves other organs. Indeed, in the largest series of nine patients with pulmonary tuberous sclerosis reported in 1995, seizure was the most common presenting feature. The pulmonary disease tends to develop in adult life, occurs much more commonly among women of childbearing age (between 18 and 34 years) who do not have mental retardation and epileptic seizures. Lung disease has been observed in a mother and daughter from a family with tuberous sclerosis for four generations. Only two male patients with pulmonary tuberous sclerosis are described; neither had pathologic documentation of lung disease. The disease may be rapidly fatal after the onset of respiratory symptoms. Exertional dyspnea is the most common respiratory symptom and may progress to the point of disability. Hemoptysis occurs in up to 25% of patients. The diffuse pulmonary interstitial process may progress to honeycombing and cyst formation, spontaneous pneumothorax, and cor pulmonale (Fig. 12). An earlier review of the literature revealed 19 cases of spontaneous pneumothorax secondary to tuberous sclerosis, with eight patients dying of this complication. Chylous pleural effusion secondary to lymphatic obstruction from mediastinal lymphadenopathy can occur. Significant pulmonary hypertension also has been reported.

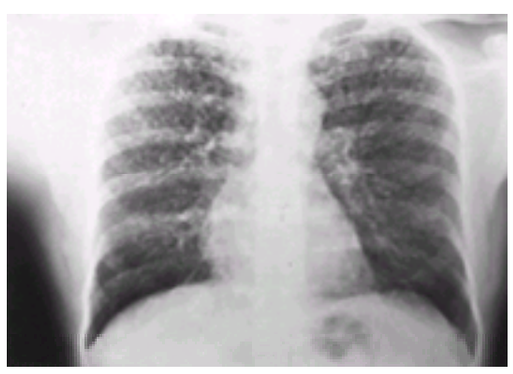

FIG. 12. Tuberous sclerosis with extensive reticulonodular infiltrates with some sparing of lower lung zones.

Chest roentgenograms in tuberous sclerosis may show diffuse interstitial infiltrates in later stages of the disease. In the early stages, reticular or reticulonodular changes are found. Bullous changes and hyperinflation of lungs are also common. Spontaneous pneumothorax is common. Pleural effusion may be secondary to pneumothorax or to chylous effusion. In up to 25% of patients, normal chest roentgenograms may contribute to missed diagnoses. In such cases, a high-resolution computed tomographic (CT) scan of the lung is helpful. High-resolution CT scans of lungs in tuberous sclerosis have shown thin-walled cysts less than 20 mm in diameter scattered randomly in all parts of the lungs, with normal-appearing lung tissue between cysts. The CT findings are identical in tuberous sclerosis and pulmonary lymphangioleiomyomatosis (Fig. 13). The CT findings correlate better with D_LCO than do chest roentgenograms.

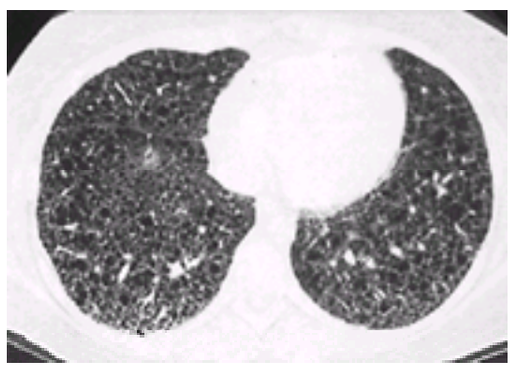

FIG. 13. Tuberous sclerosis of lung evaluated by high-resolution computed tomography, showing typically diffuse fine honeycombing.

Therapy has included to hormonal manipulations including progesterone, tamoxifen, and oophorectomy. Lung transplantation is an option in patients with progressive respiratory failure. Hypoxemic patients benefit from supplemental oxygen therapy. Complications such as pneumothorax and chylothorax require chest tube drainage and/or pleurodesis. Overall survival among nine patients (average age 33 years) with pulmonary tuberous sclerosis followed for an average of 17 years was 78%; two patients died of respiratory failure at 46 and 53 years of age. Presence or absence of lung involvement in tuberous sclerosis does not seem to affect the mortality rate. Pneumothorax, however, has been associated with higher mortality. In a review of 34 patients reported in the literature up to 1971, the average time between the onset of respiratory symptoms and death was approximately 5 years; the cause of death was pulmonary involvement in 86% of patients, 59% of whom died from cor pulmonale and 41% from pneumothorax. Only 25% of affected children live beyond their 20th year.

YELLOW NAIL SYNDROME

The term yellow nail syndrome was first employed in 1964 to describe yellow discoloration of the fingernails in association with lymphedema in 13 patients (Fig. 14). Further experience with more than 150 patients portrayed in the literature has demonstrated the association of yellow nails with pleural effusion and bronchiectasis. Lymphedema of the breasts has been described in many patients with the yellow nail syndrome. The origin of yellow nail syndrome is unknown, although a few cases seemed to follow episodes of pneumonia. The mechanism of nail discoloration is undefined, and the nail changes are not present in all patients. Histopathologic changes in the nail matrix and bed demonstrate dense, fibrous tissue replacing subungual stroma with numerous ectatic, endothelium-lined vessels that mimic pleural alterations in this syndrome. Based on these findings, it is hypothesized that primary stromal sclerosis may lead to lymphatic obstruction and lymphedema.

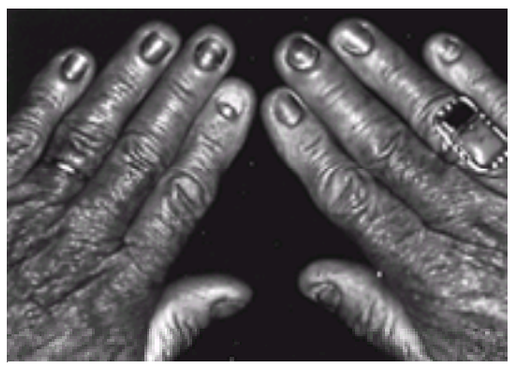

FIG. 14. Yellow nail syndrome with characteristic yellow discoloration of nails.

Among 97 patients with yellow nail syndrome, most developed the disease in early middle age; the male-to-female ratio was 1:1.6. Yellow nail syndrome has been described in an 8-year-old. Whereas more than half the patients develop nail changes, the majority do not notice the nail discoloration because its onset is subtle. Nails of both hands and feet are affected, becoming thickened, excessively curved along both axes, very slow growing, and of yellowish-gray hue; cuticle and lunula are usually absent, and onycholysis generally is evident. Nail discoloration may precede or follow pleural effusion and lymphedema. Lymphangiography of the lower extremities has shown hypoplasia or aplasia of the lymphatics, similar to that occurring in primary lymphedema.

The recurrent pleural effusions are most likely the result of lymphatic hypoplasia. Measurements of the rate of pleural fluid turnover have indicated that accumulation of pleural fluid in yellow nail syndrome results from defective lymphatic drainage rather than excess production. Histologic examination of the pleura shows thickening with fibrosis, chronic inflammatory infiltration, and dilation of lymphatic capillaries in the visceral pleura. The pathologic process affects not only the lymphatic system but also the pleural capillaries. Ectasia of lymphatic capillaries has been documented by electron microscopy. Pleural effusion may precede the onset of nail changes by several years. The fluid may be an exudate or a transudate. In some patients, the pleural fluid glucose level may be reduced. Pleural effusions range from small, unilateral, and asymptomatic to large, bilateral, recurrent, and debilitating. The pulmonary symptoms depend on the size of the pleural effusion and the severity of associated bronchiectasis. Empyema thoracis has been reported as a complication of the yellow nail syndrome.

Bronchiectasis of lower lobes is now included in the definition of yellow nail syndrome. Bronchiectasis limited to upper lung zones has been noted in a patient, but the mechanism responsible for its development is unknown. Many patients develop sinus infections. Among 17 patients with yellow nail syndrome, 14 (83%) suffered severe rhinosinusitis that predated nail changes in four, coincided with yellow nails in six, and occurred later in the remaining patients. In general, patients responded poorly to conventional medical and surgical treatment, with the exception of endoscopic sinus surgery.

Even though several cases have been described in association with carcinomas of breast, lung, and larynx, there is no clear indication that yellow nail syndrome is a paraneoplastic process. Nevertheless, the nail changes have resolved with successful treatment of the malignancy. There has been one report of a case of yellow nail syndrome following penicillamine therapy that resolved after discontinuation of the drug. A report of eight patients with proved diagnoses of the acquired immunodeficiency syndrome (AIDS) and *Pneumocystis carinii* pneumonia described yellow discoloration of the distal portions of the nails in four patients, with some showing ridging, loss or decrease in size of lunulae, and opaqueness. Yellow nail syndrome has been described in association with rheumatoid arthritis in three patients as well as in two mentally retarded siblings.

Nonpulmonary complications of yellow nail syndrome include keratosis obturans involving the external ear and excess cerumen, chylous ascites, hypoalbuminemia, chyluria, intestinal lymphangiectasia, pericardial effusion, giant-cell interstitial infiltrates, lymphedema of the eyelids, nephrotic syndrome, and Raynaud's phenomenon.

Large, recurrent, or debilitating pleural effusions require repeated thoracentesis, pleuroperitoneal shunting, medical or surgical pleurodesis, or pleurectomy. Chylous effusions are more difficult to cure, although successful therapy has been achieved with dietary restriction of fat and supplements of medium-chain triglycerides. Treatment of pulmonary disease (bronchiectasis and sinus infections) also may resolve the nail changes. There are reports of resolution of the nail changes following topical vitamin E solution. There also are reports of spontaneous resolution of nail discoloration without change in the patient's respiratory status.

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CHAPTER

63 Obstetrics, Gynecology, and Reproductive Organs

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INTRODUCTION

The respiratory system is affected by the normal anatomic and physiologic alterations that take place throughout pregnancy, parturition, and early postpartum. A healthy pregnant woman experiences minimal or tolerably mild respiratory symptoms. A pre-existing pulmonary problem, however, can be exacerbated by pregnancy. On the other hand, the normal course of the pregnancy can be adversely affected by pre-existing respiratory disorders to the point of threatening the pregnancy itself. In pregnancy, the clinical course of primary pulmonary diseases such as asthma, sarcoidosis, and certain infectious processes may vary from that in the nonpregnant patient. Likewise, the treatment of pulmonary disease in the pregnant patient may differ because some of the drugs normally used may interfere with pregnancy or cross the placental barrier and adversely affect the fetus. The pulmonary system can also be involved by pathologic processes exclusive to pregnancy, such as amniotic fluid embolism and trophoblastic pulmonary emboli that can occur after removal of a benign hydatidiform mole. The various pulmonary complications described in pregnancy and the postpartum are listed in Table 1. In this chapter, the physiologic changes noted in normal pregnancy, lung involvement by obstetric and gynecologic pathology, as well as the pulmonary manifestations in the disorders of the reproductive organs are included.

Pulmonary complications	Obstetric causes
Dyspnea of pregnancy	Mechanical Hormonal (biochemical) Hemodynamic changes Pulmonary disease (see below)
Pneumothorax and pneumomediastinum	Valsalva maneuver (second stage of labor)
Pulmonary edema	Aspiration pneumonia Eclampsia Tocolytic therapy Pulmonary embolism Amniotic fluid embolism Disseminated intravascular coagulation Trophoblastic embolism Transfusion reactions Sepsis (septic abortion)
Pleural effusion	Postpartum Eclampsia Pulmonary edema (see above) Pulmonary embolism Amniotic fluid embolism
Pulmonary embolism	Metastatic choriocarcinoma Thromboembolism Amniotic fluid embolism Septic embolism (septic abortion)
Pulmonary hypertension	Unknown Recurrent pulmonary embolism Trophoblastic emboli

Note: Sarcoidosis, mumps, asthma, coccidioidomycosis, tuberculosis, and cystic fibrosis, though not complications due to pregnancy, may be present in conjunction with, and thereby affect, pregnancy, and vice versa.

TABLE 1. *Pulmonary complications in pregnancy*

PREGNANCY

Dyspnea

Dyspnea due to mechanical, biochemical, and hemodynamic factors during pregnancy is common. By the twelfth week of pregnancy, more than 20% of women experience dyspnea at rest, whereas nearly two-thirds are dyspneic on exertion. The incidence of dyspnea increases from 15% in the first trimester to 50% by the 19th week and 75% by the 31st week of gestation. Upward displacement of the diaphragm by the enlarging uterus results in slightly diminished lung volumes in the second half of pregnancy. Diaphragmatic fatigue following prolonged contractions, particularly before and during labor, may contribute to dyspnea. Late pregnancy is commonly associated with a decrease in expiratory reserve volume, a mild decrease in functional residual capacity, and a slightly reduced total lung capacity. Airway closure is too insignificant to cause clinical problems. Diffusing capacity during early pregnancy is unchanged or slightly increased over nonpregnant values in the same patient and then diminishes to a plateau during the latter half of pregnancy.

Resting ventilation and, to a lesser extent, oxygen consumption are increased at rest and during exercise in pregnancy as well as during labor. Hyperventilation is a common feature of pregnancy, but the overall pH remains relatively intact because of increased renal excretion of bicarbonate. Severe hyperventilation, however, during labor has resulted in tetany. Arterial oxygen tension (PaO_2) is elevated because of the hyperventilation. However, an abnormally high alveolar-arterial oxygen tension difference near term, possibly because of small airways closure, partially offsets the high PaO_2 . Changes in concentrations of progesterone are also important in producing the ventilatory changes in pregnancy.

Smoking in Pregnancy

Studies in children have demonstrated a clear association between passive exposure to maternal smoking and frequency of acute respiratory illness and chronic pulmonary conditions such as wheezing or asthma. Infants of mothers who smoke during pregnancy have reduced respiratory function and are more likely to develop wheezing. In a study in which healthy infants born to women who smoked during pregnancy were compared to infants born to women who did not smoke during pregnancy, maternal smoking was associated with significant reductions in forced expiratory flow in their young offspring. Maternal smoking during pregnancy may impair *in utero* airway development or alter lung elastic properties and these effects may be important factors predisposing infants to the occurrence of wheezing illness

later in childhood. In another study, respiratory-function data from 461 infants showed that *in utero* smoke exposure, a family history of asthma, and maternal hypertension during pregnancy were associated with reduced respiratory function after birth. This led the authors to speculate that these factors adversely affect lung development *in utero.* A study of the relationship between maternal smoking during pregnancy and lung function in 493 white and 383 black schoolchildren 9 to 11 yr of age in three areas of Philadelphia observed that maternal smoking during pregnancy was associated with significant deficits in FEF_{25-75} and FEV_1/FVC and the observed deficits were larger for black children than for white children, and they were larger for boys than for girls. Suburban white schoolchildren whose mothers smoked during pregnancy had significantly reduced lung function.

Barotrauma

Spontaneous pneumothorax and pneumomediastinum may appear during pregnancy, but these are more likely to occur during the second stage of labor. Repeated Valsalva maneuvers are the most frequent cause of these problems. Pneumomediastinum is a rare complication of pregnancy, and symptoms usually are not noted until after delivery.

Pulmonary Edema

Obstetric causes of pulmonary edema include aspiration pneumonia, sepsis, transfusion reactions, allergic reactions, disseminated intravascular coagulation, amniotic fluid embolism, toxemia of pregnancy, tocolytic therapy, and eclampsia, the latter being the most common cause of pulmonary edema in pregnancy. In a report on 32 obstetric patients who required admission to a critical care unit, preeclampsia was the most common reason (22%). Eclampsia remains the leading cause of maternal mortality in developing countries. A study of 126 patients with eclampsia showed acute respiratory insufficiency in 24% and a mortality of 6%. Morphologic changes in the lungs include intravascular coagulation, fibrin deposition, and intraalveolar hemorrhage. Focal areas of bronchopneumonia also may occur. Hemodynamic studies have shown reductions in colloid osmotic pressure, pulmonary capillary leak, and left ventricular failure. Left ventricular dysfunction is common enough that echocardiography has been recommended to evaluate all pregnant women who develop pulmonary edema. Decreased venous tone and venous resistance have been suggested as the reasons for iatrogenic pulmonary edema. Surgical procedures, pyelonephritis, and other infections during pregnancy pose an increased risk for the development of pulmonary edema and acute respiratory distress syndrome.

Tocolytic therapy, employed to arrest uterine contractions, is associated with the development of pulmonary edema in up to 4.5% of pregnant women who are thus treated. Women with twin gestations are more likely to develop this complication, and the syndrome can occur within 12 hours postpartum. The mechanisms responsible for tocolytic therapy-induced pulmonary edema likely include a combination of volume overload, decreased colloid oncotic pressure, and increased hydrostatic pressure.

A review of tocolytic therapy-induced pulmonary edema from 1966 to 1988 revealed 58 cases. Terbutaline, a b adrenergic agonist was the most commonly used tocolytic agent, in 41% of patients, following by isoxsuprine in 33%, ritodrine in 17%, and salbutamol in 10%. The mean duration of tocolytic therapy was 54 hours. Symptoms included dyspnea (76%), chest pain (24%), and cough (17%), and these occurred before delivery in 70% of cases. The mean PaO_2 was 50 mmHg. Chest roentgenograms showed bilateral alveolar infiltrates and a normal-sized heart. The response to diuresis was rapid, with full recovery over a period of 24 hours, but there were 2 deaths.

Pleural Effusion

Pleural effusions occur with toxemia of pregnancy, preeclampsia, pulmonary edema, pulmonary embolism, choriocarcinoma, and amniotic fluid embolism. Small pleural effusions are common in the postpartum period in normal pregnancy. In a retrospective study of 112 pregnant women who underwent normal delivery, pleural effusion was noted in 46%, where as a prospective study of 30 normal pregnancies revealed pleural effusion in 67%. These effusions were noted within 24 hours of delivery, and all were asymptomatic and small. The factors that promote pleural effusion include increased blood volume and decreased colloid osmotic pressure normally seen in pregnancy and the impaired lymphatic drainage secondary to elevated systemic venous pressure from Valsalva maneuvers during the second stage of labor. Pleural effusion as an uncommon complication of ureteral obstruction by the gravid uterus has been described in a patient. Several cases of transudative pleural effusion in connection with severe preeclampsia are reported.

Pulmonary Embolism

Pulmonary embolism is a rare complication of pregnancy, but it is second only to abortion as a cause of maternal death. It occurs with higher frequency during the postpartum period, especially after a difficult labor and an abnormal postpartum hemorrhage. An earlier review of several series observed the incidence of deep vein thrombosis to be 0.29 per 100 deliveries. Among the 32,337 pregnancies reviewed at the Mayo Clinic, superficial phlebitis was seen in 12 per 1000 patients and deep phlebitis was seen in 2 per 1000 pregnancies. The prepartum and postpartum incidences of thrombophlebitis were 1 in 1902 patients and 1 in 622 patients, respectively. More than 75% of phlebitic episodes occurred during the first month after delivery, especially within the first 3 days postpartum. Calf veins were involved in 50%. Pulmonary embolism was noted to have an incidence of 0.4 per 1000 persons (13 of 32,337 pregnancies), and 10 of these occurred during the first postpartum month. The incidence of pulmonary embolism is increased also during the first trimester.

The factor V Leiden mutation which leads to activated protein C resistance is an important risk factor for thrombophlebitis and pulmonary embolism during pregnancy (especially the first trimester), after pregnancy, or during oral contraceptive use. A study of 50 women who had deep venous thrombosis and/or pulmonary embolism identified 10 women with activated protein C resistance caused by factor V Leiden mutation. First-trimester deep venous thrombosis and/or pulmonary embolism developed in 6 of the 10 women with the mutation compared with 3 of 40 women without the mutation. Another coagulopathy that plays a significant role in pregnancy-associated thrombophlebitis and pulmonary embolism is the presence of antiphospholipid antibody syndrome. Also known as lupus anticoagulant syndrome or anticardiolipin antibody syndrome, the antiphospholipid antibody syndrome is characterized by the presence of antiphospholipid antibodies in serum. Obstetric complications attributed to this syndrome include recurrent (three or more) miscarriages, fetal death in utero, intrauterine growth restriction, preterm delivery, early or severe eclampsia, and abruptio placentae. Thrombophlebitis and pulmonary embolism are common.

Coumarin drugs, unlike heparin, cross the placenta and may cause fetal hemorrhage and congenital malformations, with a perinatal mortality of 18%. Treatment of antepartum thrombophlebitis or pulmonary embolism should start with intravenous heparin, followed by coumarin after the first trimester. Coumarin should be replaced by intravenous heparin at the thirty-seventh week of gestation. All anticoagulants are withheld from the time of labor to 6 hours after delivery. Then heparin and coumarin should be resumed as in conventional patients. The availability of low-molecular heparin for prophylactic use in patients with high- or known-risk for development of thromboembolic diseases has been shown to be effective. The use of prophylactic low molecular weight heparin therapy during part of their pregnancy in 24 women carrying 27 pregnancies with known risk of veno-pulmonary thromboembolic diseases showed that none of the treated women developed clinical signs of thromboembolic diseases during pregnancy or 6 weeks postpartum. All the babies were born healthy and none of the women had any side effects due to the treatment.

Pulmonary Hypertension

The incidence of primary pulmonary hypertension in pregnancy is higher than that in nonpregnant nubile women. A review of 602 cases of primary pulmonary hypertension from 51 medical centers recorded that 4.5% of the cases were associated with pregnancy. Another analysis of 73 women with primary pulmonary hypertension showed that 8% of the cases were related to pregnancy. A rigorous screening of these patients (all of whom were referred for heart-lung transplantation) to detect an underlying etiology for the pulmonary hypertension failed to disclose evidence of thromboembolic disease. Recurrent noncardiogenic pulmonary edema has been described in patients with pregnancy-induced hypertension. The reason for the increased incidence of primary pulmonary hypertension in pregnancy remains unknown.

Amniotic Fluid Embolism

Amniotic fluid embolism is an uncommon complication of parturition. In the United States, the incidence is in the range of 1 in 20,000 to 30,000 deliveries. Amniotic fluid embolism carries an exceedingly high mortality, with a fatal outcome in 86% of cases. Nearly 10% of maternal deaths in the 1960s were attributed to this complication. As the frequency of other causes of mortality in pregnancy has diminished, the percentage of deaths due to amniotic fluid embolism has risen, and it is reported to be second only to pulmonary thromboembolism.

The average age at occurrence of amniotic fluid embolism is 32 years, and the risk factors include multiparity, very strong (tetanic) uterine contractions during labor, a large fetus, a dead fetus, and large quantities of particulate matter, including meconium. In one study of 40 cases of amniotic fluid embolism, the occurrence of abruptio placentae and placenta previa was noted in 45%. Rupture of the cervix (in 54% to 60% of cases), amniocentesis, and legal abortions also have caused amniotic fluid embolism.

Originally, the pathogenesis was attributed to an anaphylactoid reaction, but there has been no proof of this. The pathogenesis probably comprises a combination of three factors including pulmonary microvascular obstruction with subsequent systemic hypotension, pulmonary hypertension with acute cor pulmonale, and

ventilation-perfusion inequality. Detailed studies have shown that left ventricular failure is the only consistent abnormality.

Clinically the patient develops, during labor or immediately postpartum, chills, shivering, cough, cyanosis, convulsions, and profound shock. The survivors almost always develop disseminated intravascular coagulopathy, resulting in excessive uterine hemorrhage. The diagnosis is made on a clinical basis presumptively and definitively at postmortem. The diagnosis also can be made by identifying mucin and squamous cells in a blood smear taken from a central venous line such as a pulmonary artery catheter.

Pathologic examination of the lungs show overwhelming obstruction of the pulmonary arteries are by amniotic fluid contents—namely, mucin, fetal squamous cells, vernix fat globules, meconium, and lanugo hairs (Fig. 1). Mucin is almost always present, and the cellular elements are seen 80% of the time, with special stains and immunoperoxidase. Treatment is supportive, as the use of corticosteroids and anticoagulants has not changed the course of the disease.

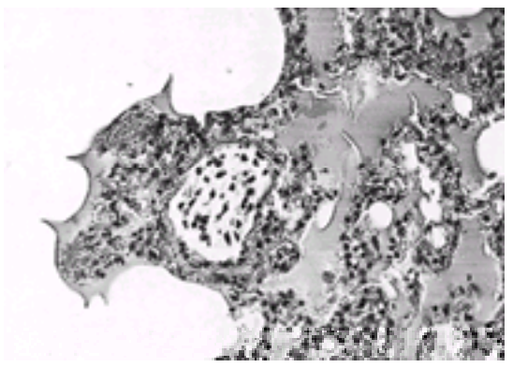

FIG. 1. Amniotic fluid embolism. Pulmonary arteriole occluded by fetal cells, vernix, and mucin.

Asthma

Asthma is encountered in pregnancy with an estimated frequency of 0.4% to 1.3% and is reported to complicate gestation in approximately 1% of pregnant women. Publications have reported both an improvement and worsening of asthma during pregnancy in approximately 5% to 46% of women. A study of 31 asthmatic women reported that mild to moderately severe asthmatics exhibit an improvement in asthma in the last trimester, but in more than one-third there may be a postpartum deterioration. In contrast, a prospective study of 198 pregnancies among 181 asthmatics reported that asthma caused no emergencies during labor and there was no difference between asthmatic and control subjects with regard to length of gestation, birth weight, incidence of perinatal deaths, low Apgar scores, neonatal respiratory difficulties, hyperbilirubinemia, or malformations. However, the study observed that severe asthma or systemic corticosteroid treatment (or both) during pregnancy increased the incidence of preeclampsia in the mother and hypoglycemia in the infant. Another significant finding was that among the asthmatic women, 28% of births were by cesarean section, compared with 17% in the control group.

Two cross sectional community studies indicated that asthmatic mothers were more likely to have a preterm delivery than nonasthmatic mothers and that asthmatic mothers did not have an increased risk of delivering small, growth retarded babies. Maternal asthma, paternal asthma, and premature birth, in that order, increased the risk of later childhood respiratory morbidity. Another study analyzed the hormonal factors and clinical and physiologic parameters during the preconception period (in 20 asthmatic women) and after conception and delivery (in 16 of 20 women), and noted that both airway responsiveness and asthma severity showed statistically and clinically significant improvements during pregnancy and returned toward preconception levels postpartum. A significant association between pregnancy-induced hypertension and asthma during pregnancy has been observed. It also appears that there is a significant upward trend in the incidence of asthma during pregnancy in women without, with moderate, and with severe pregnancy-induced hypertension. The reasons for this relationship is not obvious.

The improvement in asthma during pregnancy may be induced by progesterone- and other hormone-induced reduction in the contractility of airway smooth muscle, increased free serum cortisol, and the steroid's prolonged duration of action. The latter explanations are supported by the observation that other inflammatory conditions, such as rheumatoid arthritis also improve during pregnancy. The effect of mechanical factors responsible for dyspnea in nonasthmatic pregnant, discussed above, is also important in the deterioration of asthma during pregnancy.

Management of asthma during pregnancy is similar to that in the nonpregnant patient. In a prospective study of 181 asthmatic women with 198 pregnancies, 40% of the patients were managed during pregnancy with the same antiasthmatic medications as before pregnancy, 18% required less medication, and 42% needed more. Theophylline therapy at term did not influence labor or delivery. During the second and third trimesters until term, moderate doses of theophylline are safe. However, the safety of theophylline treatment during the first trimester with regard to teratogenicity remains to be determined. b-agonists are also safe, but an increased risk of fetal malformation has been mentioned with the use of epinephrine. Catecholamines inhibit uterine contractions. Corticosteroids may cause fetal adrenal insufficiency, but this risk is believed to be negligible. Hypoglycemia in the infant is a complication of maternal corticosteroid therapy, and therefore plasma glucose must be carefully monitored in the newborn. Status asthmaticus unresponsive to medical therapy during pregnancy may necessitate termination of the pregnancy. Respiratory distress can complicate pregnancy in women with severe obstructive pulmonary disease. Endotracheal intubation and mechanical ventilation in the postpartum period may be required. Bronchiectasis, if mild, does not seem to pose special problems for the pregnant patient. The National Institute of Health (NIH) has indicated that undertreatment of pregnant asthmatics, partially because of unfounded fears of adverse pharmacologic effects on the developing fetus, remains the major problem in the management of asthma during pregnancy in the United States.

Tuberculosis

The annual incidence of tuberculosis among pregnant women has varied depending on the period during which the data were collected. A report in 1972 recorded an incidence of tuberculosis among pregnant women in New Orleans of 4.8%. The rate of tuberculosis among American women of childbearing age (15 to 45 years) declined from 3.8 per 100,000 in 1977 to 2.35 per 100,000 in 1987, then increased to 2.5 per 100,000 in 1989 among Hispanic white women.

Pregnancy neither predisposes to the development or progression of tuberculosis nor alters the clinical presentation of the disease. A study of 1565 pregnancies during which tuberculosis was active showed no evidence of a negative consequence of pregnancy on tuberculosis during gestation, although most of the relapses developed in the postpartum period. A corollary to this is that tuberculosis neither affects nor complicates the course of pregnancy or the type of delivery. However, mother-to-fetus or -newborn transmission of tuberculosis is an important clinical consideration in the management of the pregnant tuberculous patient. The modes of spread of *tubercle bacilli* from mother to fetus or newborn include hematogenous or lymphogenous spread, transmission through placenta, and tuberculous endometritis during pregnancy. A detailed review of the topic concluded that despite the potential for transmission *in utero,* the newborn is at greater risk of acquiring tuberculosis postpartum than congenitally, particularly if born to a mother whose sputum contains *tubercle bacilli* and whose condition remains undiagnosed and untreated.

Radiation hazard from repeated chest roentgenography should be minimized in pregnant women. In those suspected of having tuberculosis, a chest roentgenogram should be obtained after the 12th week of gestation with proper shielding of the abdomen, and it should be performed only when a positive result of a tuberculin skin test requires exclusion of active pulmonary tuberculosis. However, it may be necessary sooner if the patient has symptoms that are highly suggestive of pulmonary tuberculosis. Tuberculin skin testing is not contraindicated in pregnancy as it does not affect pregnancy or the fetus. The tuberculin response in pregnancy is no different from that in nonpregnant woman. Induced sputum and gastric washings on a repeated basis are valuable.

Active pulmonary tuberculosis diagnosed during pregnancy should be treated promptly, the initial drug combination being isoniazid (300 mg/day) and rifampin (600 mg/day) for at least 9 months. Ethambutol may be used if the clinical situation warrants addition of the third or alternate drug. Because of their potential to cause fetal toxicity, pyrazinamide, streptomycin, and other aminoglycosides should be avoided. Active disease detected at the time of delivery should be treated. During the postpartum period, antituberculous drugs are continued until the prescribed treatment period is completed. Antituberculous therapy is not a contraindication to breast-feeding. Other precautions—namely, the isolation precautions, study of contacts, and preventive therapy for the infant and close contacts—is similar to the approach in nonpregnant tuberculous patients. Tuberculosis is not an indication for routine therapeutic interruption of pregnancy.

Sleep Apnea

Even though several cases of obstructive sleep apnea in pregnancy are reported, the prevalence of sleep apnea in pregnancy is unknown. The effects of pregnancy on the severity of pre-existent sleep apnea also are unknown. More important is the effect of obstructive sleep apnea-induced hypoxemia on fetal maturation. Chronic

hypoxemia induced in an animal model has caused fetal polycythemia, but the heart rate and respiratory movements were not greatly affected. Intrauterine growth retardation in maternal obstructive sleep apnea has been reported and may be present even if external cardiotocography shows normal fetal heart rate reactivity to fetal movements despite apneic episodes and periods of desaturation in the pregnant woman. Early recognition and treatment of obstructive sleep apnea in pregnancy might prevent problems with fetal development. Nasal continuous positive airway pressure (CPAP) treatment and other nonhormonal therapies pose no threat to the development of the fetus, but careful monitoring of fetal status and maternal cardiopulmonary condition is imperative.

Molar Pregnancy

Thoracic complications can occur after removal of a benign hydatidiform mole. The incidence of trophoblastic pulmonary emboli varies between 2% and 11%. Clinically, a wide spectrum of pulmonary findings occur, including the development of pulmonary hypertension and pulmonary edema. Among 128 women who underwent evacuation of hydatidiform mole, 9.4% developed acute, severe respiratory distress, and trophoblastic embolism was identified in 7 patients. The incidence of respiratory complications increased from 0 at less than 16 weeks' gestation to 27% when the uterus had developed beyond 16 weeks. In a review of 60 patients with benign trophoblastic disease, 5 developed pulmonary complications, with 2 progressing into acute respiratory distress syndrome from pulmonary edema. Possible etiologies for the respiratory manifestations include trophoblastic emboli, hypervolemia, and intravascular coagulation. Chest roentgenograms may reveal rounded lesions.

Choriocarcinoma

Choriocarcinoma is most often preceded by molar pregnancy. It is a fetal neoplasm that invades maternal tissue and it occurs in 1 in 20,000 pregnancies. Pulmonary metastases occur frequently in patients with gestational choriocarcinoma. The interval between pregnancy and pulmonary metastases varies from 1 to 60 months. Pulmonary metastases have been reported in 68% of patients with choriocarcinoma. The pulmonary lesions may be multiple, discrete, calcified, and associated with pleural effusion. Hemoptysis is seen in patients with chest roentgenographic abnormalities. In a series of 179 patients, 36 presented with pulmonary symptoms, and all but 1 had abnormal chest roentgenograms. Among 131 patients with gestational trophoblastic tumor, 57% had pulmonary metastases detected on plain chest roentgenography. Pulmonary involvement was commonly extensive, with 43% having more than 10 pulmonary metastases and 60% having a pulmonary lesion more than 5 cm in diameter. Eleven percent developed early respiratory failure requiring mechanical ventilation within one month of presentation. Other pulmonary features included greater than 50% lung opacification in 25 patients, mediastinal involvement in 25 patients, and pleural effusion 36 patients.

Most patients with pulmonary metastasis from choriocarcinoma achieve remission with chemotherapy alone. The major aspect of management of patients with high-risk, metastatic gestational trophoblastic tumors includes polychemotherapy. Therapeutic regimen employing etoposide, high-dose methotrexate, actinomycin D, cyclophosphamide and vincristine, is reported to result in complete response rates of 80% to 94% and survival rates of 82% to 100%. The factors that determine poor response to treatment are metastases to sites other than the lung and vagina, more than eight metastases, previous failed chemotherapy and a World Health Organization (WHO) score over 8. Tumor emboli and hemothorax also can occur. Gestational choriocarcinoma has presented as an endobronchial lesion. The indications for surgical resection of lung metastasis are limited, but in appropriately selected patients, resection of a lesion resistant to chemotherapy can be curative.

Miscellaneous Obstetric Disorders

Sarcoidosis

Sarcoidosis does not seem to have any adverse effects on the course of pregnancy. Pregnancy, on the other hand, is reported to lead to improvement of sarcoidosis in some patients. In patients whose chest roentgenograms demonstrate disease resolution before pregnancy, a normal chest roentgenogram is likely to persist through the prenatal period and gestation. Patients with active sarcoidosis usually experience partial or complete resolution of chest roentgenographic abnormalities during pregnancy, although many in this group will experience exacerbation of sarcoid within 3 to 6 months after delivery. Those with a fibrotic process secondary to sarcoidosis are likely to show no changes in their chest roentgenograms. One possible explanation for the frequent ameliorating effect of pregnancy on sarcoidosis is the increased serum levels of corticosteroids.

Rhinitis

Rhinitis occurs frequently during pregnancy, and although many causes, including altered vagal function, hormonal imbalance, and others, have been proposed, the rhinitis of pregnancy may not be a distinct entity.

Varicella

Varicella pneumonia seems to occur more commonly in pregnant women. A review of the literature in 1980 noted that approximately 10% of all reported cases of varicella pneumonia were in pregnant women, and the maternal mortality rate was approximately 45%. A study in 1996 of 28 pregnant women with varicella infection observed the incidence of pneumonia to be 3.6% and reported that pregnant women are not at increased risk of developing varicella pneumonia. Furthermore, all pregnant patients recovered uneventfully and no congenital anomalies or perinatal complications were noted in the infants of the 26 mothers who were followed up.

Coccidioidomycosis

Coccidioidomycosis shows a propensity to disseminate during pregnancy. One report on 50 pregnant women observed a 50% rate dissemination. The risk of dissemination was higher in those who contracted the infection during pregnancy, particularly in the second and third trimesters. Amphotericin B, the drug of choice in disseminated coccidioidomycosis, has no detrimental effects on pregnancy and poses minimal risk to the fetus.

Cystic Fibrosis

Cystic fibrosis poses special problems in pregnancy. As women with cystic fibrosis are living longer, pregnancy is becoming increasingly common in this group of women. Premature labor and delivery remain a significant risk for pregnant women with cystic fibrosis, contributing to a high rate of perinatal death. Maternal illness and death result from deteriorating pulmonary function. In a study of 11 pregnancies among 8 women with cystic fibrosis, the maternal condition deteriorated during and after pregnancy and did not return to the pregravid state. Prepregnancy FEV^1 appears to be the most useful predictor of important outcome measures in pregnancies in women with cystic fibrosis. A retrospective study of 22 pregnancies in 20 patients with cystic fibrosis noted that 18 pregnancies were completed producing healthy, noncystic fibrosis infants (12 female). Even though there was a 13% decrease in FEV^1 and 11% decrease in FVC during pregnancy, these values returned to normal after labor.

Systemic Lupus Erythematosus

Systemic lupus erythematosus may be exacerbated during pregnancy. Several cases of lupus pneumonitis developing during the postpartum period have been described.

Wegener's Granulomatosis

Wegener's granulomatosis is reported to relapse during pregnancy. A review noted that there were 15 pregnancies recorded in 10 women with Wegener's granulomatosis. Among these, the diagnosis of Wegener's granulomatosis was documented during pregnancy in 4 cases and during postpartum period in 3 cases. Eight pregnancies occurred in women with known Wegener's granulomatosis and the disease relapsed during 5 pregnancies. Two cases ended with maternal death.

Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations associated with hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome) pose several additional pulmonary problems. Pregnant women with this syndrome face the risk of increased hypoxemia due to elevation of the intrapulmonary shunt fraction. In a report of a case, the pregnancy was terminated at 35 weeks' gestation because of life-threatening hypoxemia; the increased shunting was the result of the physiologic increase in blood volume during pregnancy. There are several reports of the arteriovenous fistulas enlarging during pregnancy and rupturing into the lungs or pleura and causing serious complications such as massive hemothorax and increasing hypoxia.

Diaphragmatic Rupture

Diaphragmatic rupture leading to respiratory failure is another rare but potentially lethal complication of pregnancy.

GYNECOLOGIC DISORDERS

Several gynecologic diseases produce pulmonary complications. Some of these represent a peculiar association of pulmonary and gynecologic disorders rather than complications. Table 2 lists the pulmonary complications of the gynecologic diseases.

Pulmonary complication	Gynecologic etiology
Pneumothorax, pneumomediastinum (catamenial)	Pleural endometriosis
	Air entry via genital tract into pleural space
Hemoptysis	Endobronchial endometriosis
Pulmonary nodules or atelectasis	Endobronchial endometriosis
	Benign metastasizing leiomyoma
	Pulmonary lymphangioleiomyomatosis
Pleural effusion	Ovarian neoplasm (Meigs-Salmon syndrome)
	Pulmonary lymphangioleiomyomatosis
	Uterine fibroids
	Pleural endometriosis
Premenstrual exacerbation of asthma	Hormonal imbalance (?)

TABLE 2. *Pulmonary complications in gynecologic diseases*

Thoracic Endometriosis

A literature review in 1996 of 110 cases of thoracic endometriosis observed the following clinical features: pneumothorax in 73%, hemothorax in 14%, hemoptysis in 7%, and lung nodules in 6%. The right hemithorax was involved in more than 90 percent of all manifestations except for nodules. Hemothorax was more often associated with presence of pleural and pelvic endometriosis compared with other manifestations.

Catamenial Pneumothorax

Catamenial pneumothorax is a syndrome of spontaneous recurrent pneumothorax occurring within 48 to 73 hours of the onset of menses. Pleural disease is associated more frequently with pelvic endometriosis. Until pneumothorax recurs, it is impossible to determine clinical coincidence from the specific syndrome of catamenial pneumothorax. Catamenial pneumothorax is the most common thoracic complication of endometriosis. A review in 1990 noted that there were approximately 100 cases in the literature. Among 196 cases of spontaneous pneumothoraces in women younger than 50 years, 5.6% were catamenial. Usually seen in women between the ages of 30 and 35 years, catamenial pneumothorax is almost always (90% to 95%) right-sided and small. The majority of patients present with chest pain or mild dyspnea, though the syndrome can be asymptomatic.

Pneumothorax is believed by some to be caused by pleural endometriosis (Fig. 2). However, clinical and pathologic evidence of pelvic endometriosis is demonstrated in only 22% to 37% of cases. Pleural or diaphragmatic endometrial implants have been visualized at thoracotomy in 23% to 35% of patients. Air originating in the genital tract is believed to make its way through defects in the diaphragm. Examination at the time of thoracotomy for treatment of catamenial pneumothorax has revealed defects in the diaphragm, and closure of these defects has resulted in the absence of recurrent pneumothorax. However, such diaphragmatic defects or fenestrations have been found in only 19% to 33% of the cases explored. The diaphragmatic defects have been observed with thoracoscopy using a bronchoscope.

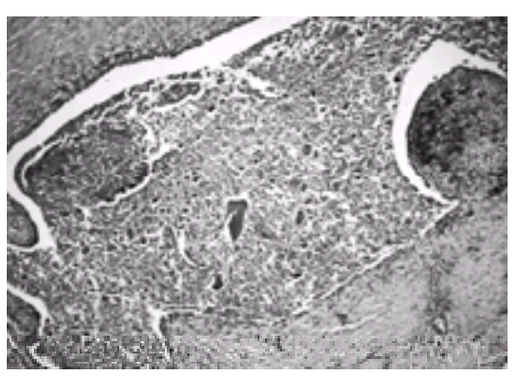

FIG. 2. Pleural endometriosis causing pneumothorax.

Pulmonary Endometriosis

Pulmonary endometriosis is rare. The endometrial tissue in the lung is presumed to originate from hematogenous spread or celomic metaplasia. Pleural endometriosis is believed to spread from pelvic or peritoneal deposits. Another possibility is the hematogenous metastasis of viable endometrial tissue after uterine surgery or cesarean section. This argument is supported by the finding that pulmonary endometriosis is almost always detected in the lower lung, which receives a higher blood supply. Pathologic analysis of pleuropulmonary tissue in patients with thoracic endometriosis generally shows changes typical of endometriosis.

Pulmonary parenchymal endometriosis appears later (mean age, 39 years) and is associated with pelvic endometriosis in only 10% of cases, catamenial hemoptysis in 82%, and catamenial pain and dyspnea in 18%. A literature review in 1996 of 110 cases of thoracic endometriosis observed the lung nodules in 6%. Endobronchial endometriosis has been reported to cause catamenial hemoptysis and airways obstruction with segmental atelectasis. Other symptoms include chest pain, dyspnea, or pleural effusion. Asymptomatic pulmonary density is another manifestation. Chest roentgenograms have revealed solitary pulmonary nodules in parenchymal endometriosis.

Ovulation-suppressing agents such as danazol sometimes are helpful in preventing recurrent pneumothorax. A case of catamenial pneumomediastinum that responded to danazol has been described. Spontaneous pneumothorax has also been described in a patient with carcinoma of the cervix.

Premenstrual Asthma

Premenstrual worsening of asthma (premenstrualasthma) has been reported in several publications. Severe asthmatics are reported to be more prone to premenstrual deterioration of asthma. In a study involving 126 consecutive women aged 14 to 46 years who attended an outpatient asthma clinic, a detailed questionnaire and twice-daily peak expiratory flow (PEF) measurements revealed premenstrual deterioration of asthma in 40%. The falls in peak flow were modest and of a degree that would not be expected to result in increased dyspnea. No correlations were found between premenstrual exacerbation of asthma and symptoms of premenstrual tension, consumption of aspirin, use of the contraceptive pill, cycle length, or behavior of asthma during pregnancy. Even mild asthmatics who were previously unaware of premenstrual asthma have been shown to observe a premenstrual deterioration of asthmatic symptoms and PEF rate without showing any significant changes in spirometry or airway reactivity.

The mechanism of premenstrual exacerbation of asthma is unclear. Progesterone level reaches a peak approximately 7 days before menstruation and rapidly falls almost to zero at the onset of the period. It is known that progesterone is a smooth-muscle relaxant in the gastrointestinal tract, genitourinary system, and vascular tree, and the fall in progesterone concentration in the late luteal phase might be associated with the withdrawal of a relaxant effect on bronchial smooth muscle. There are earlier reports on treatment of ovarian asthma by irradiation of the ovaries and progesterone preparations. Progesterone is a well-known respiratory stimulant and is

known to cause hyperventilation, which may heighten the sensation of breathlessness. However, the peak serum concentrations of progesterone are reached several days before symptomatic deterioration of asthma, and therefore, progesterone-induced hyperventilation is an unlikely explanation for premenstrual exacerbation of asthma. Analysis of clinical data from 182 nonpregnant, adult females with asthma aged 13 years to menopause showed a 4-fold variation in asthma presentations during the perimenstrual interval, indicating that the monthly variations in serum estradiol levels may influence the severity of asthma in adult females.

Estrogen Replacement Therapy

Estrogen replacement therapy may play a role in the pathophysiology of asthma. Long-term use and/or high doses of postmenopausal hormone therapy may increase subsequent risk of asthma. A prospective study of a cohort of pre- and postmenopausal women 34 to 68 years of age during 582,135 person-years of follow-up documented 726 new cases of asthma. Postmenopausal women who were never users of replacement hormones had a significantly lower age-adjusted risk of asthma than premenopausal women. Those who had 10 or more years' of replacement hormones had twice the age-adjusted risk of asthma compared with women who never used postmenopausal hormones.

Ozone (O_3) exposure during the follicular phase of the menstrual cycle is reported to elicit enhanced airway response and lead to airway inflammation. One study noted while the socioeconomic status appeared to affect FEV_1 responsiveness to ozone, with the middle socioeconomic group being the most responsive to ozone, the phase of menstrual cycle did not have an impact on individual responsiveness to ozone.

Effect of Menses on Respiration

Menses also affect normal respiration in nonasthmatic women. The respiratory-stimulating effect of progesterone was mentioned above. The level of progesterone varies during the menstrual cycle in adult women. In a study of 30 healthy female adults, respiratory muscle function, measured by maximal static inspiratory and expiratory pressures, was assessed during the midfollicular and midluteal phases of the menstrual cycle; the results showed that inspiratory muscle endurance was 26% higher in the midluteal phase than in the midfollicular phase, whereas the respiratory muscle strength and pulmonary function were unchanged. Other studies have shown that resting ventilation, ventilatory response to hypoxia or hypercapnia, and resistance to genioglossal activity are elevated during the luteal phase. These findings imply that the high inspiratory muscle endurance in the midluteal phase may be related, at least in part, to high plasma progesterone levels. A study of variations in carbon monoxide diffusing capacity (D_LCO) during the menstrual cycle in 14 healthy women (8 were using oral contraceptives) with a mean age of 29 years observed the D_LCO to vary significantly during the menstrual cycle, with the highest values occurring prior to menses and the lowest values occurring on the third day of menses, with a mean difference between them of 9%.

Metastasizing Benign Leiomyoma

Metastasizing benign leiomyoma is an oddity in pulmonary diseases and an oxymoron. Uterine fibroleiomyomas (also called well-differentiated leiomyosarcoma) are known to be associated with multiple pulmonary fibroleiomyomas. Although slow-growing, these are believed to be pulmonary metastases—hence the term metastasizing benign leiomyoma. A review of 23 reported cases revealed the following: The age span among patients studied was 30 to 74 years (mean, 47 years), three-fourths had uterine leiomyomas, and all but 2 were white. Most cases were discovered during routine chest roentgenographic examination. The lesions were nodular, bilateral in 15, recurrent in 3, and increased in size in 7 patients. Roentgenographically, these nodular densities may range from 0.5 to 4.5 cm in diameter (Fig. 3 and Fig. 4) and, occasionally, pleural effusion is also seen. Nodules may grow in premenopausal women and remain stationary in postmenopausal women.

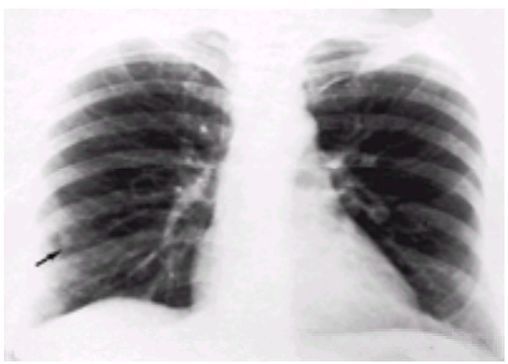

FIG. 3. Benign metastasizing leiomyoma in the lungs. Arrows point to small nodules in the lungs.

FIG. 4. Benign metastasizing leiomyoma in right upper lobe (RUL); cavitation as a result of secondary infection is demonstrated.

REPRODUCTIVE ORGANS

Diseases of the reproductive organs are occasionally associated with pulmonary problems. The main entities included in this discussion are Meigs-Salmon syndrome, Klinefelter's syndrome, Turner's syndrome, and Young's syndrome. Lymphangioleiomyomatosis is also included here although it is not a primary gonadal disease, it responds to ovarian hormones. Pleuropulmonary metastases are common in patients with malignancies of the reproductive organs.

Meigs-Salmon Syndrome

Meigs-Salmon syndrome, also known as Meigs-Salmon-Cass syndrome, is characterized by the coexistence of ovarian fibroma or other solid ovarian tumors, ascites, and pleural effusion. Pleural effusion occurs in 3% of patients with ovarian neoplasms that measure more than 6 cm in diameter. A variant of this syndrome is described in which the clinical features were highly suggestive of Meigs-Salmon syndrome but the ovary showed degenerative changes without tumor. The pleural effusions in this syndrome are more common on the right, are transudative chemically, and may become voluminous. The transportation of fluid from the peritoneum to the pleural space is via the diaphragmatic lymphatics. Massive edema of the ovary without neoplastic changes has been reported to cause hydrothorax and ascites. Very large ovarian tumors are capable of producing respiratory failure by upward push on the diaphragm. The effusions and ascites usually disappear with removal of the ovarian tumor.

Uterine Fibroids

Uterine fibroids have been responsible for the occurrence of pleural effusion in several cases. These patients were between the ages of 30 and 45 years and presented with abdominal distension and mass. There were no menstrual abnormalities. The pleural effusions were right-sided in 75% and hemorrhagic in 1 patient. Both transudates and exudates have been described. The pathogenesis of the pleural effusion in these patients and in Meigs-Salmon syndrome is unknown, although there

exists the possibility of active exudation of fluid by the tumors or inflamed peritoneum and lymphatic or venous obstruction.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a rare disorder that affects women of childbearing age and is characterized by progressive dyspnea, spontaneous pneumothorax, chylothorax, and hemoptysis caused by diffuse cystic changes in the pulmonary parenchyma and marked proliferation of peribronchial smooth muscle in a lymphatic distribution. Lymphangioleiomyomatosis is an uncommon pulmonary condition of unknown origin and pathogenesis. Although the oral contraceptive pill has been implicated in the pathogenesis of pulmonary lymphangioleiomyomatosis, a case control study of 23 patients with the disease did not support this hypothesis. However, many consider this a primarily an ovarian disorder with predominantly respiratory manifestations. The rationale for this assumption is that first, the disease generally presents in women during their childbearing years. Second, there is exacerbation of the disease during menses and pregnancy. Third, estrogen and progesterone receptors are present in lung tissue. And, fourth, clinical improvement has been documented following treatment with progesterone or oophorectomy. There have been reports of only 6 women older than 55 years developing symptomatic pulmonary lymphangioleiomyomatosis. Patients who develop pulmonary lymphangioleiomyomatosis are less likely to have been pregnant or to have had children.

Lymphangioleiomyomatosis is sometimes discussed with tuberous sclerosis because of the similarities noted in the pulmonary pathologic specimens. Further, lymphangioleiomyomatosis and tuberous sclerosis have been reported to co-exist in some patients. Nevertheless, the usual presence of clinical features such as mental retardation, development of angiomyolipomas, adenoma sebaceum, subungual fibromas, and other various skin lesions in patients with tuberous sclerosis distinguish these two entities. The absence of angiomyolipomas is not always the case in lymphangioleiomyomatosis. Indeed, in a report on 17 patients with pulmonary lymphangioleiomyomatosis, 47% were found to have renal angiomyolipomas.

The majority of the clinical features are the result of abnormal proliferation of smooth muscles in the lung parenchyma. The hypertrophied bundles of smooth muscle encircle and obstruct airways, pulmonary arterioles and venules, and the lymphatic channels. These changes result in obstructive airway disease, hemoptysis, and accumulation of chylous pleural effusion. Clinical features include progressive dyspnea resembling that of ordinary chronic obstructive lung disease, recurrent pneumothorax (in more than 60%), unilateral or bilateral chylous pleural effusions (in 25%), and hemoptysis (in 50%) in nubile women. The around the distal airways causes venular congestion and disruption, resulting in hemoptysis and alveolar hemosiderosis. Abdominal and thoracic lymphatics as well as lymph nodes may become involved. Chylous ascites and a doughy abdomen are sometimes the presenting features.

Histologically, two types of pulmonary lesions have been observed; a predominantly cystic type and a predominantly muscular type. Patients with predominantly cystic pattern of disease are reported to have a poorer prognosis compared with those who have muscular type of disease.

Chest roentgenograms show diffuse reticulonodular infiltrates in 50% to 80% of patients (Fig. 5). Normal chest roentgenography that is noted in some patients may lead to the wrong diagnosis of asthma or obstructive lung disease. Lung hyperinflation is observed in up to 25%. Cystic spaces measuring 0.5 to 1.5 cm in diameter and bullous changes are seen in 12% to 40% of patients. Pneumothorax (50% to 80%) and pleural effusion (30% to 40%) may be present. The smooth-muscle proliferation around the distal airways leads to alveolar destruction and development of cystic changes and pneumothorax. Likewise, the smooth-muscle proliferation around the pulmonary lymphatics produces lymphatic obstruction and development of chylothorax. Despite the presence of the above-noted typical clinical and roentgenologic features, the diagnosis was delayed by an average of 44 months (range, 1 to 219 months) in a series of 32 patients with lymphangioleiomyomatosis. Bronchoscopic lung biopsy may be adequate, or an open-lung biopsy may be required for the diagnosis. However, typical clinical features combined with characteristic findings depicted by high-resolution computed tomography may establish the diagnosis (Fig. 6). Histopathologic features of lung parenchyma include accumulation of smooth-muscle bundles in the alveolar walls, especially around bronchioles and venules (Fig. 7). Ultrastructural and immunofluorescent examination of these smooth-muscle bundles has shown higher glycogen content of muscle cells and smooth-muscle antigens. There are no serologic (antibody) tests to identify these antigens.

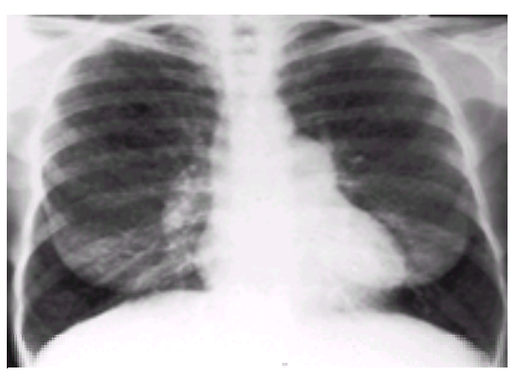

FIG. 5. Lymphangioleiomyomatosis of lungs. Diffuse nodular infiltrates, relative sparing of lower lung zones, and hyperinflation of lungs can be seen.

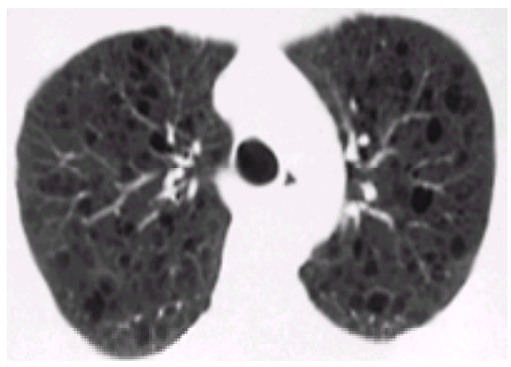

FIG. 6. Lymphangioleiomyomatosis of lungs imaged with high-resolution computed tomography showing typical cystic spaces.

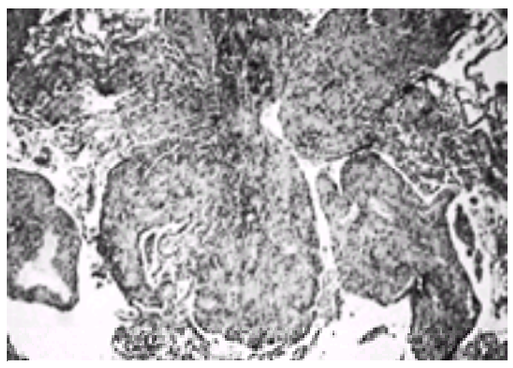

FIG. 7. Lymphangioleiomyomatosis in the lung tissue showing hypertrophy of bronchial smooth-muscle bundles.

Compression of the airways by the hypertrophied smooth muscles is responsible for the severe obstructive pulmonary dysfunction. Studies of pulmonary mechanics in 8 women with lymphangioleiomyomatosis showed increased total lung capacity (114% of predicted) and residual volume (207% of predicted), reduced ratios of 1-second forced expiratory volume to forced vital capacity (62% of predicted), moderately reduced retractive force at total lung capacity (67% of predicted), increased static compliance (128% of predicted), and markedly elevated pulmonary flow resistance (266% of predicted). Maximal flow-static recoil curves demonstrated changes

secondary to predominantly airway narrowing rather than loss of lung elastic forces. Lymphangioleiomyomatosis is one of the rare diseases in which even though the chest roentgenogram suggests a restrictive type of process (nodular or interstitial), the pulmonary function tests reveal characteristics of obstructive pulmonary disease.

Treatment should be initiated as soon as the diagnosis is established because of the progressive nature of the disease. Patients should be advised against pregnancy and the use of estrogen preparations. Treatment options for lymphangioleiomyomatosis continue to evolve. A meta-analysis of 30 cases reported in the literature noted that although eight treatment regimens were used, progesterone or oophorectomy or both were the most effective treatments, resulting in improvement or stabilization of the disease in the majority of cases. Another report on 8 women with lymphangioleiomyomatosis treated by various antiestrogen therapies concluded that without a control group, it was difficult to ascertain whether the treatments were responsible for the apparent improvement of the disease. Medroxyprogesterone is given in doses equivalent to at least 10 mg/day on either a daily or monthly basis. Rapidly progressive cases should be considered for both progesterone therapy and oophorectomy. Tamoxifen therapy and tetracycline pleurodesis have been used success fully to control recurrent chylothorax. However, tamoxifen therapy is reported not only to lack evidence of proved effectiveness but also to be closely associated with the recurrence of pneumothoraces and exacerbation of the disease. Persistent chylothorax may require surgical pleurodesis or placement of a pleuroperitoneal shunt. Single or double lung transplantation has become a therapeutic option for refractory cases. Progressive respiratory distress and death within 10 years has been noted in refractory cases.

Klinefelter's Syndrome

Klinefelter's syndrome is the most common example of male hypogonadism in phenotypic men, characterized by the presence of two or more X chromosomes, the most common karyotype being XXY. It is morphologically manifested by varying degrees of seminiferous tubular failure and decreased Leydig cell function. Clinical features include small and firm testes, infertility, decreased testosterone level, gynecomastia and, frequently, eunuchoid features and mild mental retardation. Respiratory disease is known to be more prevalent in these patients than in the population at large. Pulmonary manifestations described have included asthmatic bronchitis, recurrent pulmonary infections, bronchiectasis, pectus excavatum, kyphoscoliosis, pulmonary cysts, respiratory infections, and emphysema. Restrictive lung dysfunction is attributed to chest wall abnormalities, even though pulmonary restriction has been demonstrated in the absence of parenchymal or musculoskeletal abnormalities. A detailed physiologic study of 13 patients with Klinefelter's syndrome reported that none exhibited chest wall restriction, but 4 patients demonstrated significantly reduced lung compliance. The authors concluded that the likely cause of pulmonary restriction, noted in 8 patients (62%), was a decrease in the compliance of the lung matrix, probably related to the absence of testosterone.

Turner's Syndrome

Turner's syndrome is a disorder of sex differentiation. Its clinical features include an XO sex chromosome constitution, dwarfism, sexual infantilism, webbing of the neck, and cubitus valgus. Thoracic manifestations consist of square and shield-like chest, pleural effusions, coarctation of the aorta, and rib notching.

Young's Syndrome

Young's syndrome, or obstructive azoospermia, denotes primary infertility in men who have normal spermatozoa in the epididymides but none in the ejaculate. This entity differs from the well-known links between infertility and lung diseases noted in ciliary dysmotility syndromes and cystic fibrosis. Unlike the immotile cilia syndrome, Young's syndrome has no demonstrable ultrastructural ciliary disorders and, unlike cystic fibrosis, normal sweat and pancreatic functions are present. Indeed, electron microscopy of nasal cilia in 12 patients with Young's syndrome has confirmed normal ciliary ultrastructure. Young's syndrome is estimated to have a prevalence rate comparable to that of Klinefelter's syndrome and higher than that of either cystic fibrosis or the immotile cilia syndrome.

The underlying abnormality in Young's syndrome is unknown, although it is presumed to be a mucous defect. Mucociliary clearance, as determined by nasal ciliary beat frequency, is shown to be abnormal in Young's syndrome. It is not clear whether this is the cause or effect of sinusitis. The relative disorientation of distal ciliary axoneme in patients with Young's syndrome may be due to a structural defect but is more likely a consequence of abnormal mucus. However, use of mucoregulatory agents in these patients has not been helpful.

Mercury intoxication has been proposed as an etiologic factor in the development of Young s syndrome. Calomel (mercurous chloride) was removed from teething powders and worm medication in the United Kingdom in 1955. An interesting study of 274 men with obstructive azoospermia undergoing epididymovasostomy observed that the incidence of Young's syndrome fell significantly from 114 of 227 men born up to 1955 to eight of 47 men born since then. This decline in incidence of Young's syndrome in those born after 1955 was similar to that observed with pink disease (mercury intoxication).

More than half the patients in the original series had severe chest disease in childhood. In a study of 34 infertile men with obstructive azoospermia and normal controls, the following abnormalities were noted in those with Young's syndrome: grossly abnormal sinus roentgenograms (59%), sinusitis (56%), repeated otitis media (32%), chronic bronchitis (35%), abnormal chest roentgenograms (53%), and bronchiectasis (29%) (Fig. 8). Airflow obstruction was observed in 15 patients. Although this controlled study confirmed that a significant excess of sinopulmonary disease exists in this group, the reason for the relationship between obstructive azoospermia and lung disease remains undefined.

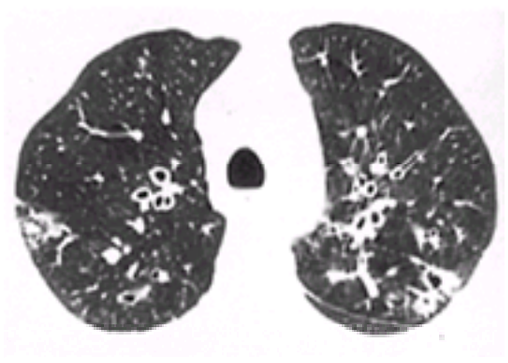

FIG. 8. Young's syndrome with bronchiectasis documented by high-resolution computed tomography showing bilateral bronchiectasis.

Sexual Activity and the Lung

The coital act is physically strenuous even in healthy humans. The presence of chronic respiratory disease affects this function in many patients in the form of functional impotence or lack of libido. Although a considerable number of patients with respiratory diseases are concerned about their inability to have normal sexual intercourse, very few mention this aspect of their health to their physicians. Part of the reason is the patients' embarrassment in bringing up this medically irrelevant topic, and part is due to physicians' failure to inquire about it. Several medications, particularly b-blocking agents, cause impotence. However, none of the drugs used in chronic obstructive pulmonary disease or other common lung diseases is known to affect sexual function. Medroxyprogesterone used in some patients with central sleep apnea may result in impotence after long-term therapy. In hypoxemic patients, supplemental oxygen therapy during sexual intercourse may be helpful.

Coital Hemoptysis

Coital hemoptysis has been described in a patient with coronary artery disease. Despite recurrent episodes of hemoptysis that necessitated several visits to his physician, the patient did not provide the history of sexual activity in relation to hemoptysis. Increased cardiovascular demands and left ventricular dysfunction brought on by sexual activity were concluded to be physiologic reasons for the hemoptysis. Postcoital catamenial pneumothorax not associated with endometriosis has also been reported.

Postcoital Asthma

Postcoital asthma and rhinitis (honeymoon rhinitis) brought on by sexual activity have been described in several patients. A study of 3 men and 1 woman with post-coital asthma or rhinitis observed clinically significant attacks of asthma or rhinorrhea during and immediately after sexual intercourse; indeed, 1 man required several visits to the emergency department and hospitalization on one occasion. All had a previous history of asthma, and anxiety was noted to be a predominant feature in the patients and their sexual partners. Sexual excitement, rather than exercise, may have caused asthma in one of the patients who developed asthmatic

symptoms before sexual intercourse. Allergy to human seminal plasma in female subjects has also been reported to cause postcoital asthma.

Reflux Dyspareunia

Reflux dyspareunia denotes heartburn occurring during sexual intercourse. In a prospective study of 100 women with known gastroesophageal reflux, 77% suffered from reflux symptoms (severe in 6, moderate in 22, and mild in 49) during sexual intercourse. The supine position and increased intraabdominal pressure may account for the reflux symptoms during sexual intercourse. Although the number of women with hiatal hernia was not mentioned, the presence of gastroesophageal reflux during coitus is as important as other factors in causing reflux dyspareunia. No mention has been made in the literature on reflux dyspareunia-related aspiration.

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de Veciana M, Towers CV, Major CA, Lien JM, Toohey JS. Pulmonary injury associated with appendicitis in pregnancy: who is at risk? *Am J. Obstet Gynecol* 1994;171:1008–1013. *This case-control study of 49 patients with appendicitis during pregnancy noted 7 cases of pulmonary edema or infiltrates in 7 and adult respiratory distress syndrome in 2 patients. By multivariate analysis, the following factors were estimated to predict 99% of the pulmonary complications: a fluid overload 4 L, respiratory rate 24 breaths/min, maximum temperature 100.4°F, and tocolytic usage.*

Edenborough FP, Stableforth DE, Webb AK, Mackenzie WE, Smith DL. Outcome of pregnancy in women with cystic fibrosis. *Thorax 1995;50:170–174. A retrospective study of 22 pregnancies in 20 patients with cystic fibrosis noted that 18 pregnancies were completed producing healthy, non-cystic fibrosis infants (12 female). Mothers lost 13% of FEV1 and 11% of FVC during pregnancy, most of which was regained. Microbiological status remained unchanged. Four mothers died up to 3.2 years following delivery. FEV1 (%) showed the best correlation with maternal weight gain, gestation, birth weight, and maternal survival.*

Eliasson AH, Phillips YY, Tenholder MF. Treatment of lymphangioleiomyomatosis. A meta-analysis. *Chest* 1989;96:1352–1355. *A comprehensive review of the literature revealed 30 cases of lymphangioleiomyomatosis treated with eight regimens of treatment. Evaluation with predetermined criteria (meta-analysis) showed that administration of progesterone or oophorectomy or both are the most effective treatments, resulting in improvement or stabilization of the disease in the majority of cases.*

Friedman KJ, Teichtahl H, De Kretser DM, Temple-Smith P, Southwick GJ, Silverman LM, Highsmith WE Jr, Boucher RC, Knowles MR. Screening Young syndrome patients for CFTR mutations. *Am J Respir Crit Care Med* 1995;152:1353–1357. *An evaluation of 13 patients with Young syndrome, including screening for more than 30 different mutations within the CFTR gene, revealed normal sweat chloride concentration in all patients. The incidence of CFTR mutations (1 in 26) did not differ significantly from the expected carrier frequency in this population. The authors concluded that it is unlikely that the typical Young syndrome patient has a clinical disease associated with CFTR mutation on both alleles.*

Grodstein F, Stampfer MJ, Goldhaber SZ, Manson JE, Colditz GA, Speizer FE, Willett WC, Hennekens CH. Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996;348:983–987. *In this prospective study through questionnaires sent every 2 years (1976-92) to 11,259 women, 123 cases of primary pulmonary emboli (no identified antecedent cancer, trauma, surgery, or immobilization) were recorded. In current users of oral contraceptives, the risk of primary PE was about twice that in non-users. However, past use showed no relation to PE.*

Handelsman DJ, Conway AJ, Boylan LM, Turtle JR. Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections. *N Engl J Med* 1984;310:3–9. *A study of 29 men with Young's syndrome, a combination of obstructive azoospermia and chronic sinopulmonary infections. Men with this syndrome have only mildly impaired respiratory function and normal spermatogenesis; the azoospermia is due to obstruction of the epididymis by inspissated secretions.*

Hankins GD, Harvey CJ, Clark SL, Uckan EM, Van Hook JW. The effects of maternal position and cardiac output on intrapulmonary shunt in normal third-trimester pregnancy. *Obstet Gynecol* 1996;88:327–330. *Ten normotensive nulliparas between 36 and 38 weeks' gestation underwent pulmonary hemodynamic measurements sequentially in the left lateral, right lateral, supine, knee-chest, sitting, and standing positions. Directly measured Qs/Qt averaged 15.3% in left lateral, 15.2% in right lateral, 13.9% in supine, 12.8% in knee-chest, 13.8% in sitting, and 13.0% in standing positions. Authors concluded that this is the first report of directly measured Qs/Qt in normal pregnant women in the third trimester and that Qs/Qt values reported in pregnancy are higher than those reported in nonpregnant individuals.*

Heffner JE, Sahn SA. Pleural disease in pregnancy. *Clin Chest Med* 1992;13:667–78. *A detailed review of pleural effusion, pneumothorax, and other pleural disorders in pregnancy. The incidence, clinical manifestations, and, where appropriate, therapeutic options of these disorders are discussed.*

Hendry WF, A'Hern RP, Cole PJ. Was Young's syndrome caused by exposure to mercury in childhood? *BMJ* 1993;307:1579–1580. *An interesting study of 274 men with obstructive azoospermia undergoing epididymovasostomy observed that the incidence of Young's syndrome fell significantly from 114 (50%) of 227 men born up to 1955 to eight (17%) of 47 men born since then. This decline in incidence of Young's syndrome in those born after 1955 was similar to that observed with pink disease (mercury intoxication).*

Hirsch DR, Mikkola KM, Marks PW, Fox EA, Dorfman DM, Ewenstein BM, Goldhaber SZ. Pulmonary embolism and deep venous thrombosis during pregnancy or oral contraceptive use: prevalence of factor V Leiden. *Am Heart J* 1996;131:1145–1148. *A study of 50 women who had deep venous thrombosis (DVT) and/or pulmonary embolism (PE) identified 10 women with activated protein C resistance caused by factor V Leiden mutation. First-trimester DVT and/or PE developed in 6 of the 10 women with the mutation compared with 3 of 40 women without the mutation. Authors conclude that the factor V Leiden mutation is an important risk factor for DVT and/or PE during pregnancy (especially the first trimester), after pregnancy, or during oral contraceptive use.*

Hornby PJ, Abrahams TP. Pulmonary pharmacology. *Clin Obstet Gynecol* 1996;39:17–35. *This article reviews the basic principles of pharmacodynamics and pharmacokinetics, with a special emphasis on the pharmacologic considerations that must be taken into account when treating the patient with respiratory disease who is also pregnant or nursing the neonate. A description of the four classes of therapeutic agents used for COPD is given with a discussion of the scientific evidence for their safety during pregnancy.*

Hughson WG, Friedman PJ, Feigin DS, Resnik R, Moser KM. Postpartum pleural effusion: a common radiologic finding. *Ann Intern Med* 1982;97:856–858. *A retrospective study of 112 patients and a prospective study of 30 patients and 30 controls to ascertain the incidence of postpartum pleural effusion noted pleural effusion on chest radiographs in 51 patients (46%) in the retrospective study, and 20 patients (67%) in the prospective study. There was no difference between patients with effusion and those without in age, race, parity, antepartum complications, method of delivery, fetal outcome, or postpartum complications.*

Jones WB, Romain K, Erlandson RA, Burt ME, Lewis JL Jr. Thoracotomy in the management of gestational choriocarcinoma. A clinicopathologic study. *Cancer* 1993;72:2175–2181. *Among 9 patients with choriocarcinoma metastatic to the lung who underwent 11 thoracotomies, 6 patients achieved complete remission for periods ranging from 3 months to 18 years, and three patients died of their disease.*

Joseph J, Sahn SA. Thoracic endometriosis syndrome: new observations from an analysis of 110 cases. *Am J Med* 1996;100:164–170. *An analysis of data on 110 patients with thoracic endometriosis syndrome described in the literature showed that the peak incidence for pelvic endometriosis was between 24 and 29 years and the peak incidence for thoracic endometriosis was between 30 and 34 years. Thoracic complications included pneumothorax in 73%, hemothorax in 14%, hemoptysis in 7%, and lung nodules in 6% of patients.*

Kelly YJ, Brabin BJ, Milligan P, Heaf DP, Reid J, Pearson MG. Maternal asthma, premature birth, and the risk of respiratory morbidity in schoolchildren in Merseyside. *Thorax* 1995;50:525–530. *Two cross sectional community studies of 1872 children (5-11 years) in 1991 and 3746 children in 1993 indicated that asthmatic mothers were more likely to have a preterm delivery than non-asthmatic mothers and that smoking was a separate risk factor for preterm delivery. Asthmatic mothers did not have an increased risk of delivering small, growth retarded babies. Maternal asthma, paternal asthma, and premature birth, in that order, increased the risk of later childhood respiratory morbidity.*

Kent NE, Farquharson DF. Cystic fibrosis in pregnancy. *Can Med Assoc J* 1993;149:809–813. *A total of 20 reports citing cases of pregnancy in women with cystic fibrosis were reviewed. Of 217 pregnancies in 162 women, spontaneous abortion occurred in 10 (4.6%), Pregnancy progressed beyond 20 weeks in 81.6% of cases; 24.3% of the deliveries were preterm. The maternal death rate did not exceed that among age-related women with CF who were not pregnant. Poor outcomes were associated with a weight gain of less than 4.5 kg and a forced vital capacity of less than 50% of the predicted value.*

Kitaichi M, Nishimura K, Itoh H, Izumi T. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. *Am J Respir Crit Care Med* 1995;151:527–533. *The clinical and pathologic features of 46 patients from Japan, Korea, and Taiwan with pulmonary lymphangioleiomyomatosis showed reduction of FEV1/FVC ratio. This and an increase in TLC correlated with a poor prognosis at 2, 3, and 5 yr after the first examination. Histologically, two types of pulmonary lesions were observed; a predominantly cystic type and a predominantly muscular type.*

Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. *Am J Respir Crit Care Med* 1995;152:427–455. *This state of the art review with 482 references includes discussions on physiologic changes, fetal oxygenation, drug therapy, mechanical ventilation, eclampsia, amniotic fluid embolism, and pulmonary edema as they relate to critical illness and critical care in the pregnant patient.*

Lehrer S, Stone J, Lapinski R, Lockwood CJ, Schachter BS, Berkowitz R, Berkowitz GS. Association between pregnancy-induced hypertension and asthma during pregnancy. *Am J Obstet Gynecol* 1993; 168:1463–1466. *This study noted a significant association between pregnancy-induced hypertension and asthma during pregnancy. In addition, there was a significant upward trend in the incidence of asthma during pregnancy in women without, with moderate, and with severe pregnancy-induced hypertension. The authors conclude that both pregnancy-induced hypertension and asthma might be caused by a factor/s affecting smooth muscle reactivity.*

Mabie WC, Hackman BB, Sibai BM. Pulmonary edema associated with pregnancy: echocardiographic insights and implications for treatment. *Obstet Gynecol* 1993;81:227–234. *A prospective study of 45 pregnant or recently postpartum women admitted to an obstetric intensive care unit with pulmonary edema used echocardiography between 1 and 4 days after the onset of pulmonary edema and detected decreased systolic function in 19, normal systolic function but increased left ventricular mass and presumed diastolic dysfunction in 17, and normal hearts in 9 patients. The authors recommend echocardiography to evaluate all pregnant women with pulmonary edema.*

Masson RG. Amniotic fluid embolism. *Clin Chest Med* 1992;13:657–665. *This paper is devoted to the review of amniotic fluid embolism. The author indicates that amniotic fluid embolism is the most unpredictable and catastrophic complication of pregnancy, accounting for 10% to 20% of maternal deaths and the pulmonary edema commonly seen in this syndrome is probably due primarily to alveolar capillary leakage and may be potentiated by high maternal extracellular volume, low colloid osmotic pressure, and, in some patients, by depressed myocardial function.*

Neville E, Brewis R, Yeates WK, Burridge A. Respiratory tract disease and obstructive azoospermia. *Thorax* 1983;38:929–933. *A study of 34 infertile men with mechanical azoospermia noted that 19 patients (59%) had grossly abnormal sinus radiographs, 19 (56%) gave a history of sinusitis; of these, six (18%) had sinus operations, 11 patients (32%) had histories of repeated otitis media, 10 patients had bronchiectasis, and the chest radiograph was abnormal in 18 patients.*

Pauli BD, Reid RL, Munt PW, Wigle RD, Forkert L. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. *Am Rev Respir Disease* 1989;140:358–362. *This study of 11 asthmatics and 29 normal control subjects indicated that asthmatics not previously aware of premenstrual activation of asthma will record a premenstrual worsening of asthma symptoms and peak expiratory flow rates. These changes were not related to a deterioration in spirometry and airway reactivity or to the absolute levels of circulating progesterone and estradiol.*

Pauzner R, Mayan H, Hershko E, Alcalay M, Farfel Z. Exacerbation of Wegener's granulomatosis during pregnancy: report of a case with tracheal stenosis and literature review. *J Rheumatol* 1994;21:1153–1156. *This review of 15 pregnancies recorded in 10 women with Wegener's granulomatosis reported that pregnancy may significantly contribute both to the relapse of Wegener's granulomatosis and to its appearance. The article also describes a woman with Wegener's granulomatosis who relapsed twice during 2 pregnancies and developed tracheal stenosis. A therapeutic abortion was performed during the second pregnancy.*

Pisani RJ, Rosenow EC III. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989;110:714–718. *Fifty-eight case reports served as the database for this review article on tocolytic pulmonary edema. Authors note that women at risk were receiving or had recently received sympathomimetic agents to arrest uterine contractions, with or without steroids. The incidence of the syndrome is higher in women with twin gestations.*

Rasmussen C, Wadt J, Jacobsen B. Thromboembolic prophylaxis with low molecular weight heparin during pregnancy. *Int J Gynaecol Obstet* 1994;47:121–125. *Prophylactic low molecular weight heparin therapy during part of their pregnancy in 24 women carrying 27 pregnancies with known risk of veno-pulmonary thromboembolic diseases showed that none of the treated women had clinical signs of thromboembolic diseases during pregnancy or 6 weeks postpartum. All the babies were born healthy and none of the women had any side effects due to the treatment.*

Rizk NW, Kalassian KG, Gilligan T, Druzin MI, Daniel DL. Obstetric complications in pulmonary and critical care medicine. *Chest* 1996;110:791–809. *In this extensive review with 196 references, the authors discuss the physiologic changes and pulmonary disorders including tuberculosis, thromboembolism, pneumonia, peri- and postpartum hemorrhage, and other respiratory complications.*

Robinson CA, Rose NC. Tuberculosis: current implications and management in obstetrics. *Obstet Gynecol Survey* 1996;51:115–124. *This review article discusses the issues of diagnosis and treatment of asymptomatic infection and active tuberculosis in pregnant women, the need for universal screening of all prenatal patients and the benefit and potential perinatal toxicity of chemotherapy in both immunocompetent patients and those infected with human immunodeficiency virus.*

Sansores RH, Abboud RT, Kennell C, Haynes N. The effect of menstruation on the pulmonary carbon monoxide diffusing capacity. *Am J Respir Crit Care Med* 1995;152:381–384. *A study of variations in DLCO during the menstrual cycle in 14 healthy women (8 were using oral contraceptives) with a mean age of 29 years observed the DLCO to vary significantly during the menstrual cycle, with the highest values occurring prior to menses and the lowest values occurring on the third day of menses, with a mean difference between them of 9%.*

Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, Saunders B, Porreco R, Sperling W, Kagnoff M, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. *Am J Respir Crit Care Med* 1995;151:1170–1174. *A study of 486 pregnant (28 wk) women with asthma and 486 pregnant nonasthmatic controls with normal pulmonary function found no significant differences in incidences of preeclampsia, perinatal mortality, preterm births, low-birth-weight infants, intrauterine growth retardation, or congenital malformations in the pregnancies of the asthmatic women as compared with the matched controls.*

Seal E Jr, McDonnell WF, House DE. Effects of age, socioeconomic status, and menstrual cycle on pulmonary response to ozone. *Arch Environ Health* 1996;51:132–137. *In this study, 372 healthy white and black young adults, between the ages of 18 and 35 y, were exposed only once to 0.0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm ozone for 2.3 h. Prior to and after exposure, pulmonary function tests were obtained. The results indicated that the decrements in FEV1 decreased as the subjects' ages decreased; socioeconomic status, as reflected by education of fathers, also appeared to affect FEV1 responsiveness to ozone, with the middle socioeconomic group being the most responsive. The phase of menstrual cycle did not have an impact on individual responsiveness to ozone.*

Skobeloff EM, Spivey WH, Silverman R, Eskin BA, Harchelroad F, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Intern Med* 1996;156:1837–1840. *Analysis of clinical data from 182 nonpregnant, adult females with asthma aged 13 years to menopause showed a 4-fold variation in asthma presentations during the perimenstrual interval, when serum estradiol levels decreased sharply after prolonged peak. Authors concluded that the monthly variations in serum estradiol levels may influence the severity of asthma in adult females.*

Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax* 1996;51:411–414. *A study of 504 pregnant asthmatic subjects who were prospectively followed and treated showed that patients with inadequate inhaled anti-inflammatory treatment during pregnancy run a higher risk of suffering an acute attack of asthma than those adequately treated with an anti-inflammatory agent. Authors concluded that if the acute attack of asthma is relatively mild and promptly treated, it does not have a serious effect on the pregnancy, delivery, or the health of the newborn infant.*

Stenius-Aarniala BS, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. *Chest* 1995;107:642–647. *A case-control study in which 212 pregnant asthmatics with theophylline treatment were compared with findings in 292 pregnant asthmatics without theophylline and 237 nonasthmatic pregnant control subjects. Authors concluded that during the second and third trimesters until term, moderate doses of theophylline are safe but the safety of theophylline treatment during the first trimester with regard to teratogenicity remains to be determined.*

Stick SM, Burton PR, Gurrin L, Sly PD, LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996;348:1060–1064. *Respiratory-function data from 461 infants showed that* in-utero *smoke exposure, a family history of asthma, and maternal hypertension during pregnancy were associated with reduced respiratory function after birth. The authors speculate that these factors adversely affect lung development* in utero.

Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Crit Care* Med 1995;152:1183–1188. *This prospective study of a cohort of pre- and postmenopausal women 34 to 68 yr of age during 582,135 person-years of follow-up documented 726 new cases of asthma.*

The authors concluded that estrogen plays a role in the pathophysiology of asthma and that long-term use and/or high doses of postmenopausal hormone therapy increase subsequent risk of asthma.

VanWinter JT, Nichols FC III, Pairolero PC, Ney JA, Ogburn PL Jr. Management of spontaneous pneumothorax during pregnancy: case report and review of the literature. *Mayo Clin Proc* 1996;71:249–252. *Report of a case of recurrent spontaneous pneumothorax during the third trimester of pregnancy that necessitated surgical intervention; at thoracotomy, a large bulla was excised from the lower lobe of the right lung; abrasive pleurodesis was subsequently done. Clinical aspects of 22 nonmalignancy-related spontaneous pneumothoraces during pregnancy are discussed.*

CHAPTER

64 The Normal Adult Pulmonary Circulation

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INTRODUCTION

The survey of the adult pulmonary circulation that follows in the next few chapters emphasizes the interplay between structure and function in determining the behavior of the normal and abnormal pulmonary vascular bed. We especially emphasize the clinical course of patients with pulmonary hypertension and cor pulmonale (right ventricular failure on the basis of lung disease). This chapter is devoted to a description of the anatomy, physiology, and biochemistry of the pulmonary vascular bed. We also consider aspects of the physiology of lung extravascular water homeostasis, the physiological–anatomic basis for pulmonary edema, and the function of pulmonary endothelia. In addition, we consider the normal function of the bronchial circulation. Finally, we consider the physiology of pulmonary hypoxic vasoconstriction.

PULMONARY VASCULAR ANATOMY

General Considerations

The principal function of the lungs is to transport the respiratory gases O_2 and CO_2 into and out of the bloodstream. In the mammalian lung, this is done by a remarkable system of air- and blood-containing vessels, folded together in an elastic structure in such a way that these vessels are in intimate contact, yet their contents do not physically mix. The normal adult human requires the transfer of 200 to 250 ml/min of O_2 into the body at rest. However, the transport of O_2 can increase to 3000 to 4000 mL/min at maximum exercise. In diseased lungs, O_2 transport capacity can be limited, which in turn limits the transport of O_2 into peripheral tissues, the ultimate target.

To accomplish its task, the pulmonary vasculature affords a capillary surface area (i.e., blood vessels exposed to air-containing compartments) measuring 50 to 80 m^2 and only some 300 nm thick. In normal lungs, which receive all the output from the right ventricle (approximately 5 L/min), there is 290 ± 50 mL/m^2 volume in the pulmonary circulation. Of this pulmonary blood volume, approximately 50 mL/m^2 is found in the gas-exchanging vessels, the capillaries. Any given red cell normally spends approximately 0.75 sec in air-exchanging vessels, which affords ample time for gas exchange across the wall of the vessel by the process of diffusion.

Several differences between systemic and pulmonary circulations should be emphasized. First, the major site of flow resistance in the pulmonary circulation is in alveolar capillaries, as opposed to precapillary vessels in the systemic circulation. Second, pulmonary microvascular pressures are extremely variable within the lung, depending on the anatomic location of the vessel (dependent versus independent regions), the site of the vessel within the parenchyma (intraalveolar versus extraalveolar), and the state of lung inflation. Third, the systemic vessels within the lung (bronchial circulation and pleural vessels) drain into the same venous bed as the pulmonary vessels by a network of anastomoses that constitute potential shunts from one bed to another.

Careful morphometric analysis of the pulmonary vascular tree reveals that there are more arteries than airways. After a few generations, pulmonary arteries lose their muscular media, and the most peripheral branches consist only of endothelium and internal elastic membrane. This flimsy structure is very susceptible to direct mechanical interactions, either compression or tethering open, by surrounding lung parenchyma. Extension of muscular coats from arterial generations that normally have them (diameter 100 to 500 µm) into peripheral arteries that normally do not is one of the prime histologic manifestations of pulmonary hypertension. The muscular coat in pulmonary arterioles is relatively smaller (3% to 4% of cross-sectional diameter) than that in systemic arterioles (40% to 50% of cross-sectional diameter). Sympathetic and parasympathetic innervation of pulmonary vessels is sparser than that of systemic vessels. The pulmonary circulation has no valves. Pulmonary veins are also relatively more thin-walled than systemic veins of the same diameter. These factors mean that the pulmonary circulation normally has an enormous capacity to accommodate increased blood flow by either distention or recruitment of pulmonary vessels (see section on Pulmonary Capillaries), with little increase in pressure.

Pulmonary Capillaries

The pulmonary capillary network is different from that in the systemic circulation. Systemic arterioles give rise to successive generations of capillaries as in a spreading brush, which reunite on the venous side. One can trace the connection between systemic arterioles and the capillaries to which they give rise. The situation is different in the pulmonary system. Pulmonary capillaries in the alveolar walls form a dense hexagonal network of cylindrical tubes into and out of which conducting vessels are connected. Other, more complicated models have been proposed to account for biological irregularity and to make mathematical analysis feasible. Some of these models postulate sheet-like flow in capillaries rather than tube flow. In this situation, classic laminar flow does not apply.

It is useful to distinguish among three types of vessels in the pulmonary microvasculature: intraalveolar, alveolar corner, and extraalveolar vessels. *Intraalveolar* microvessels are contained within and virtually fill the walls between separate adjacent alveoli. They are subject to changes in intraalveolar pressure, being compressed when alveolar pressure increases relative to pleural pressure (lung inflation) and vice versa. They are also subject to the effects of alveolar surface tension. Thus, capillary morphology depends on lung volume, vascular pressures, and alveolar surface forces.

Corner vessels are found at the junction of three alveoli. They are contained within folds of the endothelium, or pleats, beneath sharp curvatures of the alveolar surfactant film. In this way, corner vessels are contained within a space surrounded by smooth curved tissue surfaces, which protect them from perturbations of alveolar pressure. Hence, when intraalveolar pressure is increased, thus shutting off flow through alveolar walls, flow can continue from arterial to venous channels, even when there are swings in alveolar pressure.

Extraalveolar vessels are small vessels not exposed to alveolar pressure and are surrounded by a connective tissue sheath. They are exposed to interstitial pressure, which decreases as the lungs inflate (i.e., as intraalveolar pressure increases relative to pleural pressure). Hence, lung inflation tends to open extraalveolar vessels while closing intraalveolar vessels. The differing behavior of intraalveolar and extraalveolar vessels accounts for lung volume-dependent changes in pulmonary vascular volume and resistance.

Pulmonary capillaries have an average diameter of approximately 5 µm. Although the diameter of erythrocytes is larger (7 to 8 µm), these cells are extremely deformable because of their biconcave shape and lack of nucleus. This means they normally pass freely through the capillary. However, if deformability is severely reduced, as might occur, for example, with sickle cell disease, then erythrocytes will be sequestered in the precapillary and capillary vessels. Similarly, the neutrophil is approximately 700 times less deformable than the erythrocyte because of its viscous cytoplasm and the presence of a nucleus. This means that the tendency to be

trapped and sequestered is far greater for neutrophils than for erythrocytes.

PULMONARY VASCULAR PRESSURES

The pulmonary vascular bed is a low-pressure, low-resistance bed that accommodates all the cardiac output. Normally, pulmonary vascular pressures are measured relative to atmospheric pressure and are zero-referenced to a level 5 cm below the angle of Louis in the supine patient (approximate level of the right atrium). Normal limits for pressure values in the pulmonary circulation are given in Table 1. Pulmonary arterial pressure contours resemble those seen at the aortic root, with a dicrotic notch (Fig. 1). However, pulmonary arterial pressures recorded from bedside balloon-tipped catheter systems may not resemble those recorded under ideal conditions. Under ideal conditions, the frequency response of the catheter transducer system used to record pulmonary arterial pressure should be flat to approximately 80 Hz. The presence of bubbles in the line or, as is common in long indwelling catheters used in critical care units, fibrin clots at the catheter tip can severely dampen this response such that high-frequency components of the signal are damped and the signal can resemble a mean. Other causes of damped recording include tubing kinks, an excessive number of stopcocks, and cracked fittings. On the other hand, pulmonary artery catheters may demonstrate excessive high-frequency components, sometimes caused by vibration or knocking of the catheter, which may make interpretation difficult. Finally, pulmonary arterial pressure is subject to transmitted changes in intrathoracic pressure. With normal quiet breathing (i.e., under catheterization laboratory conditions), these are small. However, in the presence of abnormal ventilatory patterns (e.g., airway obstruction or positive-pressure ventilation), these may be considerable. In such cases, referencing pulmonary vascular pressures to atmosphere may be confusing at best and misleading at worst. Many investigators and clinicians overcome this problem by referencing intravascular pressure to esophageal pressure as an estimate of intrathoracic pressure.

Pulmonary arterial pressure	
Systolic	22–30 mmHg
Diastolic	6–12 mmHg
Mean	10–12 mmHg
Left ventricular end-diastolic pressure (left atrial mean)	6–12 mmHg
Right ventricular end-diastolic pressure (right atrial mean)	0–6 mmHg
Cardiac index	2.7–3.5 liters/min per m^2
Pulmonary vascular volume	290 ml/m^2
Capillary blood volume	80–120 ml
Pulmonary vascular resistance	150–200 $dynes/cm^2$

TABLE 1. *Approximate normal pulmonaryhemodynamic values for adults*

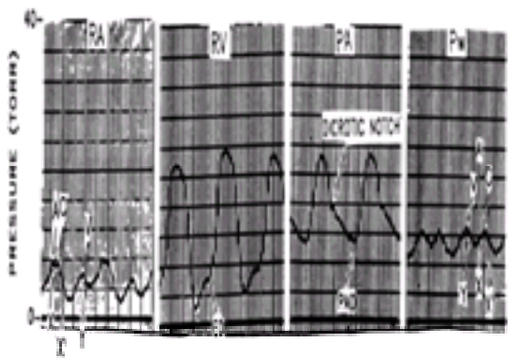

FIG. 1. Normal pulmonary and right heart pressures. These were measured using a standard saline-filled balloon-tipped catheter and are of particularly excellent quality for this type of system. Note mean right atrial (RA) pressure is equal to right ventricular (RV) end-diastolic (ED) pressure. Pulmonary arterial diastolic (PAD) pressure is equal to mean pulmonary wedge pressure (P_w), which, under most circumstances, is equal to left ventricular end-diastolic pressure. (Courtesy of Dr. Gary Friedman.)

Pulmonary venous pressure is equal to left atrial (LA) pressure. Both left and right atrial (RA) pressures exhibit three waveforms per beat, the *a, c,* and *v* waves (see Fig. 1). The *a* wave coincides with atrial contraction and peaks approximately 80 msec after the P wave on the surface electrocardiogram (ECG). The *v* wave is caused by atrial filling during ventricular systole, aided by descent of the atrioventricular (AV) valve ring. The origin of the *c* wave, a minor deflection, is not as well established but may be related to bulging of the AV valves into the atria at the onset of ventricular systole. The pressure descent following the *a* wave is called the *x* descent, that following the *c* wave is the *x'* descent, and the *y* descent follows the *v* wave. The right ventricular (RV) waveform is characterized by a gradual upsloping curve during diastole (ventricular filling) with a rapid steep upstroke at the onset of ventricular systole. The RV end-diastolic pressure is normally equal to mean RA pressure because there is no flow across the open tricuspid valve.

During diastole, there is normally no flow across the pulmonary bed. Hence, there is no pressure gradient from pulmonary artery to vein, and so pulmonary artery end-diastolic pressure is normally equal to pulmonary venous and left atrial pressure. Because mean LA pressure is normally equal to left ventricular (LV) end-diastolic pressure, pulmonary artery end-diastolic pressure becomes a measure of LV filling pressure. Of course, if pulmonary vascular resistance is elevated (see below), then flow continues throughout diastole, and pulmonary artery end-diastolic pressure is greater than pulmonary venous pressure. If a catheter is wedged into a small pulmonary vessel such that flow ceases through the vessel, then there is no longer a pressure drop from catheter tip to pulmonary vein, and the pressure recorded from the wedged catheter is equal to LA and LV end-diastolic pressure, provided the catheter is wedged in a so-called zone 3 portion of the lung (defined below). A similar recording can be made by using a balloon-tipped catheter in a small branch of the pulmonary artery to stop flow. The pressure recorded often is called the *capillary wedge pressure,* although it has very little to do with pulmonary capillary pressure when blood is flowing. Pulmonary *occlusion* pressure is a better term. Of course, if there are mitral valve problems, then pulmonary occlusion pressure is not equal to LV end-diastolic pressure.

PULMONARY CAPILLARY PRESSURES

Pulmonary capillaries are interposed between arterioles and veins. Capillary hydrostatic pressure provides the gradient for filtration of fluid into the interstitium and alveoli (pulmonary edema). Thus, one would ideally want to measure this in clinical situations where pulmonary edema is a consideration. For any given arterial-to-venous channel, capillary pressure depends on the longitudinal distribution of resistance along the channel as well as on flow. Capillary pressure (P_c) is related to blood flow through the channel ($\dot{Q}_c$), venous resistance (R_v), and pulmonary venous pressure (P_{pv}) by the laminar flow equation:

$$P_c = P_{pv} + \dot{Q}_c R_v$$

Because flow is related to inflow pressure (P_{pa}) and arterial resistance (R_a) for each channel, P_c can be shown to be related to P_{pa} and to the ratio of venous to arterial resistance (R_v/R_a):

$$P_c = [(R_v/R_a)P_{pa} + P_{pv}]/[1 + (R_v/R_a)]$$

This is easily derived from laminar flow relationships. Thus, pulmonary capillary pressure is, in part, a function of the ratio of venous to arterial resistance (R_v/R_a), downstream pressure (P_{pv}), and arterial pressure (P_{pa}).

A number of techniques have been devised to measure capillary pressure. The arterial occlusion technique has been proposed as clinically useful. This technique is based on the assumption that most pulmonary vascular compliance between a catheter tip in a branch of the pulmonary artery and venous outflow is located in

pulmonary capillaries. When arterial flow in the branch is stopped by wedging the catheter tip distally or inflating a balloon just proximal to the catheter tip, pressure immediately falls to the level in the pulmonary capillaries (no flow, no pressure gradient). Then, as the capillary reservoir empties, pressure falls exponentially to that of the pulmonary veins. Thus, two phases can be distinguished in the wedged catheter: first an initial fall to the level of pulmonary capillary pressure, and then a slower fall leading to equilibration with the pulmonary venous pressure and with the usually measured wedge pressure. Unfortunately, a number of theoretical and practical problems remain before this technique can be recommended as a routine clinical measure.

PULMONARY BLOOD FLOW

Although the pulmonary circulation receives all the cardiac output, the distribution of blood flow within the lung is far from uniform. Physiologists frequently speak about *upstream* and *downstream* loci in a vascular bed. These terms are relative and connote an orientation more toward the arterial (upstream) or more toward the venous (downstream) side of the circulation. In the upright human, there is a hydrostatic gradient down the lung as a result of gravitational effects on the column of blood (approximately 30 cm H_2O, the approximate height of the adult human lung). West and co-workers conceived of the distribution of blood flow within the lung according to the relation between pulmonary arterial (P_{pa}), alveolar (P_{alv}), and venous (P_{pv}) pressures. Pulmonary hydrostatic pressures increase from apex to base of the upright lung because of the gravitational acceleration and are equal to r*gh,* where r is fluid density (1.05 g/cm^3 for blood), *g* the gravitational acceleration constant (980 cm/sec^2 on the planet Earth at sea level), and *h* the vertical distance down the lung. Because r and *g* remain constant, vascular pressure increases approximately 1 cm H_2O for each centimeter down the lung.

With a mean P_{pa} of 20 cm H_2O, P_{pa} falls to zero 20 cm from the bottom of the lung. With a mean P_{pv} of 10 cm H_2O, P_{pv} falls to zero 10 cm from the bottom of the lung. With the lung at rest and the glottis open, alveolar pressure (P_{alv}) is constant throughout the lung (P_{alv} = 0). This distribution of pressures results in three zones of flow within the lung (Fig. 2). In zone 1 (more than 20 cm from the bottom of the lung), both P_{pa} and P_{pv} are less than zero (= P_{alv}). Pulmonary vessels are collapsed, and flow is zero. In zone 2 (in our example, 10 to 20 cm from the bottom of the lung), P_{pa} exceeds P_{alv}, which exceeds P_{pv}. Flow is thus determined by the gradient between P_{pa} and P_{alv}, *not* the gradient between P_{pa} and P_{pv}. In zone 3 (less than 20 cm from the lung base in our example), P_{pa} is less than P_{pv}, which is less than P_{alv}. Here, flow is determined by the gradient between P_{pa} and P_{pv}, as in standard ohmic resistances. According to this scheme, the distribution of blood flow is explained by a series of simple Starling resistors (collapsible tubes with a pressure surrounding the collapsible segment). In fact, the theory predicts that when P_{pa} is greater than P_{alv}, which, in turn, is greater than P_{pv} (zone 2), raising and lowering P_{pv} would have little effect on pulmonary blood flow because the effective back pressure to flow is P_{alv}, not P_{pv}. Only as P_{pv} is raised above P_{alv} does P_{pv} become the effective back pressure to flow.

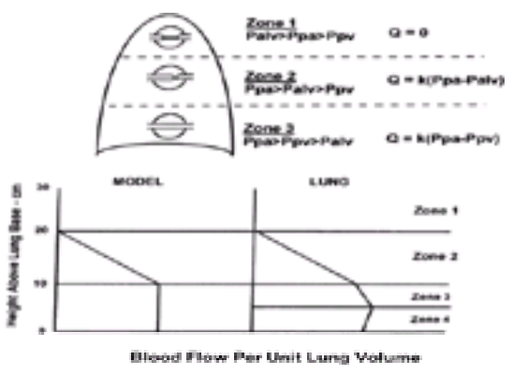

FIG. 2. Model of three lung zones based on relationships among pulmonary arterial (P_{pa}), alveolar (P_{alv}), and pulminary venous (P_{pv}) pressures. *Q* is flow; *k* is a proportionality constant with units of conductance. In the *lower panel* are shown representations of the theoretical (model) and actual (lung) changes in blood flow from apex to base in the upright human. Note that the appearance of zone 4 is not predicted on the basis of the simple model depicted in the *upper panel*. See text for discussion.

As with most models, the simple Starling resistor model does not explain all experimental results, as illustrated in Fig. 2. As expected, in zone 1 there is no blood flow. Flow in zone 2 increases down the lung because the gradient ($P_{pa} - P_{alv}$) increases one to one with decreasing height. Further increases in flow are not expected in zone 3 because both P_{pa} and P_{pv} increase one to one down the lung, and the gradient for flow ($P_{pa} - P_{pv}$) thus remains constant. However, actual flow does increase in zone 3, although at a slower rate than in zone 2. Further, a new zone, zone 4, is found—especially at low lung volumes—in which flow actually decreases toward the base. Flow may increase down the lung in zone 3 because pulmonary vascular resistance decreases with either distention of vessels or recruitment of closed vessels. The explanation for zone 4 may be that with increased capillary pressure, there is an increased hydrostatic gradient for transudation of fluid into the interstitium, possibly decreasing the diameter of microvessels in the interstitium. On the other hand, at low lung volume, the tendency for extraalveolar vessels to be held open is less, which would result in increased pulmonary vascular resistance toward the lung base because transpulmonary pressure decreases toward the lung base as well.

Finally, there are other factors, which are as yet poorly defined, that influence the distribution of blood flow within the lung that are independent of gravity. Recently, it has been demonstrated that for zone 3 conditions, gravity actually plays little role in determining the intralobar distribution of blood flow. One possibility is that the fractal geometry of the pulmonary vascular system explains the heterogeneity and small effect of gravity on flow in zone 3 conditions.

During normal spontaneous ventilation, most lung is in zone 3, with little of the lung in zone 1. In supine patients, there is practically no lung in zone 1 conditions. With hypovolemia, pulmonary vascular pressures fall, which leads to an increased proportion of the lung in zone 1, manifest as an increase in measured anatomic dead space. With positive-pressure mechanical ventilation, alveolar pressures can increase relative to vascular pressures, especially at high levels of positive end-expiratory pressure (PEEP). This leads to an increased proportion of the lung in zones 1 and 2 and increased numbers of lung units with high ventilation–perfusion ratios. Conversely, when pulmonary vascular pressures increase, as in congestive heart failure or pulmonary hypertension, the proportion of the lung in zone 3 increases, thus making blood flow more uniform within the lung. Of course, as blood flow increases in the apex, zone 1 diminishes. Because the apices receive relatively poor ventilation, units with decreasing ventilation–perfusion relationships could be created, thus contributing to hypoxemia in congestive heart failure. As previously indicated, there is normally a large reserve in the pulmonary vascular bed. A significant portion of the bed is underperfused (zone 1), thus allowing substantial reserve for recruitment of new vessels. In addition, there may be a significant reserve for distention of already perfused vessels. For these reasons, P_{pa} normally does not rise substantially with pneumonectomy provided the pulmonary vasculature is normal. With exercise, pulmonary blood flow (cardiac output) can increase considerably with only small increases in P_{pa}. This is because, with passive dilation of the pulmonary vascular bed, the resistance to blood flow through the pulmonary vascular bed decreases passively. We consider next the factors that actively regulate pulmonary vascular resistance.

PULMONARY VASCULAR RESISTANCE

The pulmonary bed often is modeled as a straightforward Poiseuille type of system where flow ($\dot{Q}$) is laminar and is determined by the gradient between mean P_{pa} and left atrial pressure (P_{la}) and a resistance term called *pulmonary vascular resistance* (PVR):

$$\dot{Q} = (1/\mathrm{PVR})(P_{pa} - P_{la})$$

If pulmonary blood flow were truly laminar and the pulmonary vascular bed were a simple ohmic resistance, then plotting the pressure drop across the bed as a function of flow would yield a straight line. Actual data demonstrate that $P_{pa} - P_{la}$ rises in a hyperbolic manner, with $\dot{Q}$ illustrating that PVR, calculated in the classic manner, *decreases* with increasing flow. As we have seen, the gradient ($P_{pa} - P_{la}$) is the driving pressure only for zone 3 lung. Thus, measurements of PVR by the usual equation or plot of $P_{pa} - P_{la}$ against $\dot{Q}$ fail to differentiate between changes in cross-sectional area from recruitment or from distention and critical closing pressure (usually approximately alveolar pressure).

As noted earlier, the presence of a gradient that develops between pulmonary arterial end-diastolic and pulmonary venous pressure (i.e., wedge pressure) is indicative of flow at end-diastole. The magnitude of this gradient increases with increased pulmonary vascular resistance, compliance, and blood flow.

A number of workers have performed studies plotting P_{pa} against $\dot{Q}$ When these plots are extrapolated to zero flow, the critical closing pressure of the vascular bed may be measured as the pressure at zero flow. The slope of the line is the true laminar flow resistance such that:

$$\dot{Q} = (1/\mathrm{PVR})(P_{pa} - P_c)$$

where P_c is the critical closing pressure of the bed when P_c exceeds P_{la} (zone 2). Although alveolar pressure can function as the critical closing pressure (when P_{alv} exceeds P_{la}), any pressure surrounding the pulmonary vessels can act similarly, whether caused by vasomotor tone or even increased interstitial pressure, as might occur in pulmonary edema. These plots sometimes lead to surprising conclusions. For example, Fig. 3 shows pulmonary pressure–flow curves obtained in dogs. With oleic-acid-induced pulmonary edema, a model of adult respiratory distress syndrome, there was an increase in the critical downstream pressure compared to a time-dependent control, which suggests that an increase in critical closing pressure of the pulmonary vascular bed is an important contributor to increased P_{pa} in this form of edema.

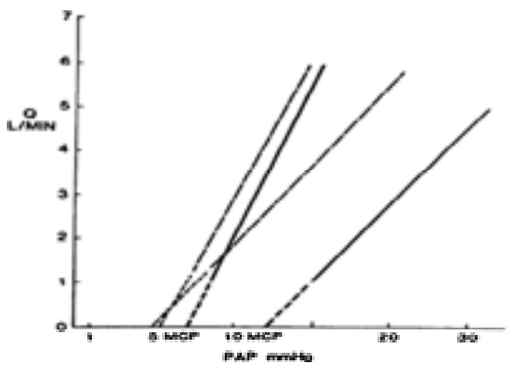

FIG. 3. Mean pressure–flow curves before and during oleic-acid-induced pulmonary edema. *Dashed lines* represent controls at time zero and at 5 hr. *Solid lines* represent before and 5 hr after oleic acid infusion. With time alone, there is a decrease in the slope (conductance) of the dashed lines but no change in the zero intercept, which represents the critical closing pressure of the pulmonary bed. With pulmonary edema, a similar decrease occurs in conductance *(solid lines).* However, note that the zero-intercept pressures also increase, suggesting an increase in the critical closing pressure of the vascular bed. $\dot{Q}$, volume of regular blood flow; PAP, pulmonary artery pressure; MCP, mean circulatory pressure. (Reprinted with permission from Prewitt RM, Ducas J. Hemodynamic management of acute respiratory failure. In: Scharf SM, Cassidy SS, eds. *Heart–Lung Interactions in Health and Disease.* New York: Marcel Dekker, 1989;906.)

Hydralazine and pulmonary emboli also lead to changes in critical closing pressure. Differentiating between effects on critical closing pressure and resistance of the pulmonary vascular bed has implications for the interaction between cardiac and pulmonary causes of pulmonary hypertension. For example, if pulmonary hypertension is produced by increased critical closing pressure, changes in P_{la} would have little effect on upstream pressure or flow. On the other hand, vasodilators such as hydralazine, which lower critical closing pressure, could make upstream pressures or flow *more* sensitive to fluctuations in P_{la}. Thus, it must be obvious that calculating the ratio $(P_{pa} - P_{la})/\dot{Q}$ may not give adequate information to infer the caliber of pulmonary resistance vessels or the state of vasomotor tone. This is because of the effects of passive dilation of the pulmonary bed (recruitment or distention), the intrapulmonary distribution of blood flow (percentage flow in any given lung zone), and the differential effects of resistance versus critical closing (or alveolar) pressure.

Pulmonary Vascular Impedance

The usual laminar flow approximations governing pulmonary resistance calculations assume that pulmonary vessels have rigid walls and that flow is nonpulsatile ($\dot{Q}$ = mean flow). We have already noted that the vessels are markedly distensible and that flow is pulsatile, being zero at end-diastole. Thus, calculations of PVR based on laminar flow profiles may be misleading, even taking into consideration the factors previously discussed.

It has been suggested that the calculation of input impedance (z) at the pulmonary arterial root is a better way of assessing the total hydraulic load placed on the right ventricle. Input impedance is the ratio of instantaneous pressure to instantaneous flow at a given frequency. Pressure and flow signals are analyzed, usually by Fourier transformation, and broken down into their respective harmonic series, each harmonic being a sine wave characterized by a frequency (a multiple of the heart rate, the dominant frequency), amplitude (called the *modulus*), and a phase angle. The pressure modulus is divided by the flow modulus to calculate impedance magnitude, and the phase angles are subtracted to yield the impedance phase. One advantage of using impedance analysis is that it takes into account two major determinants hindering RV ejection (i.e., two major determinants of RV afterload). These are the flow-resistive and capacitative behavior of the pulmonary bed. The development of electromagnetic catheter-tipped measurements of instantaneous flow velocity has enabled impedance measurements to be made in humans.

Effects of Lung Volume on Pulmonary Vascular Resistance and Blood Volume

The responses of intraalveolar and extraalveolar vessels to lung inflation are different. With increased transpulmonary pressure, intraalveolar vessels are compressed, whereas extraalveolar vessels are exposed to expanding forces. The net effect on pulmonary vasculature is biphasic, such that vascular capacitance is maximal at lung volumes close to functional residual capacity (FRC). As lung volume decreases below FRC, vascular capacity diminishes as a result of compression of extraalveolar vessels. As lung volume increases above FRC (as with ventilation with PEEP or in obstructive airways disease), vascular capacity diminishes from compression of intraalveolar vessels. As lung volume increases, the tendency for pulmonary edema to form around intraalveolar vessels diminishes because of increased interstitial pressure, whereas the tendency for edema formation increases around extraalveolar vessels because of decreased interstitial pressure. The balance of these tendencies may even lead to increased rate of edema formation as lung volume increases in noncardiogenic pulmonary edema. Biphasic compressive effects on the pulmonary circulation lead to biphasic effects of lung inflation on calculated PVR. As lung volume decreases below FRC, PVR rises, and as lung volume increases above FRC, PVR also rises. At high lung volumes, increased PVR caused by intraalveolar compression can lead to a substantial increase in RV afterload, especially in the presence of pulmonary edema.

PULMONARY VASOMOTION

The normal pulmonary vascular bed has very little resting vasomotor tone, PVR is low, and infusion of potent vasodilators rarely leads to decreases in baseline resistance. Whether the normally low PVR is the baseline natural state or reflects the continued chronic production of vasodilator substances is a matter of controversy. Nevertheless, it is clear that there are many influences capable of regulating pulmonary vasomotor tone. These include endogenously produced vasoconstrictors and vasodilators (Table 2), changes in autonomic tone mediated by central nervous system reflexes, a variety of pharmacologic agents, and changes in arterial blood gases, such as hypoxia, hypercapnia, and changes in pH. Changes in pulmonary vasomotor tone should be viewed on three levels: (1) global effects, or changes in overall PVR; (2) regional effects, or changes in the distribution of blood among various parallel channels (e.g., pulmonary hypoxic vasoconstriction); and (3) changes in longitudinal distribution of resistance, which could affect microcirculatory pressure gradients responsible for edema formation.

Vasoconstrictors	Vasodilators
α-Adrenergic agonists: norepinephrine, phenylephrine	Histamine (in preconstricted bed)
Angiotensin II	Prostacyclin (PGI_2)
Thromboxane A_2	β-Agonists: isoproterenol
Serotonin	Bradykinin
Histamine (in relaxed bed)	Prostaglandins E_1 and E_2
Prostaglandins $F_{2\alpha}$, E_2, and D_2	Platelet-activating factor (PAF, preconstricted bed)
Leukotrienes C_4 and D_4	Nitric oxide (endothelium-derived relaxing factor)
Interleukin-2	Adenosine
Tumor necrosis factor	
Endothelin-1	
Endothelium-derived constricting factor	

TABLE 2. *Some vasoactive mediators in the pulmonary circulation*

The state of initial vasomotor tone is important in determining the action of a given vasoactive agent. An example is histamine, which acts as a constrictor on dilated vessels and a dilator on constricted vessels.

Pulmonary Vasomotor Mediators

Vasoactive mediator substances (Table 2) are produced by many cell types within the lung, including interstitial mast cells and neutrophils, interstitial monocytes, alveolar macrophages, marginated neutrophils, and pulmonary endothelium. Many mediator substances are hypothesized to be released in response to acute lung injury and pulmonary embolism, which are responsible for changes in vasomotor tone (usually vasoconstriction) and vascular permeability. Among the most potent vasoactive substances are the eicosanoids, derived from arachidonic acid. Arachidonic acid is a 20-carbon polyunsaturated fatty acid released from tissue by the deacylation of cellular phospholipids. It may be metabolized by one of two pathways. The *cyclooxygenase* pathway leads to the production of the prostanoids—prostacyclin (PGI_2), thromboxane A_2, prostaglandin D_2 (PGD_2), PGE_2, and PGF_{2a}—and it is inhibited by a variety of pharmacologic agents including nonsteroidal antiinflammatory agents (e.g., aspirin and indomethacin). The *lipoxygenase* pathway leads to the production of the leukotrienes. Just as the prostenoids have been recognized as powerful vasoactive agents, the leukotrienes are also vasoactive agents. This allows for cross-talk between endothelium-derived factors such as PGE_2 and neutrophil-derived factors such as leukotriene D_4 in the regulation of vasomotor tone and permeability. A number of pharmacologic uses have been found for naturally occurring mediators. For example, prostacyclin, a powerful vasodilator, has been used in the treatment of primary pulmonary hypertension, and infusion of PGE_2 or PGE_1 can maintain patency of the ductus arteriosus of newborns.

Nitric Oxide

Since its discovery in 1980, the endothelium-derived relaxing factor, either the free radical NO or a related species, has been the subject of a great deal of basic and clinical research. This short-lived species (half-life 6 to 10 sec) is rapidly deactivated by hemoglobin bound to haptoglobin. This provides a mechanism to limit the action of NO downstream from the site of production and allows the actions of NO to be localized. Nitric oxide is derived from the terminal guanidino nitrogen atom of L-arginine, yielding NO and citrulline (see Fig. 4). The oxygen radical probably is provided by molecular oxygen. This reaction is catalyzed by a group of isoforms termed NO synthases (NOS). All NOSs can be inhibited to some degree by N^G-substituted L-arginine analogs. All contain four prosthetic groups: flavin-adenine dinucleotide, flavin-adenine mononucleotide, tetrahydrobiopterin (BH_4), and a heme complex, iron protoporphyrin IX. All NOS isoforms are dependent on calmodulin and NADPH. The brain isoform (bNOS) is found in the central and peripheral nervous system and functions as an intracellular messenger.

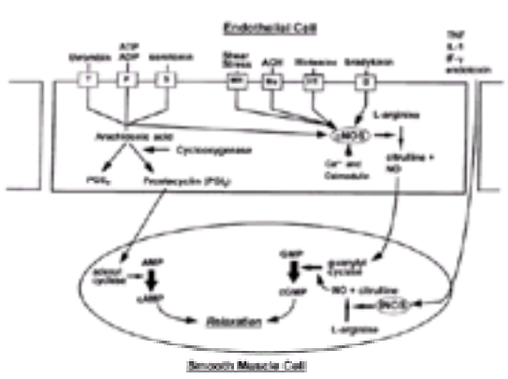

FIG. 4. Schematic depiction of endothelial cell–smooth muscle cell interactions leading to vasodilation. Endothelial cell receptors are shown as *square boxes* in the wall of the endothelium. T, thrombin receptor; P, purine receptor; S, serotonin receptor; MR, mechanoreceptor; Mu, muscarinic receptor; H1, histamine receptor; B, bradykinin receptor; TNF, tumor necrosis factor; IL-1, interleukin-1; IF-g, inteferon; cNOS, constitutive nitric oxide synthase.

Endothelial cell NOS (eNOS or cNOS), a constitutive isoform, is calcium and calmodulin dependent. The eNOS is a monomer with molecular mass of 133 kDa, bound to the cell membrane by a myristoylate bridge linked to the N-terminal glycine of the enzyme. The localization of the enzyme favors the formation of NO in high local concentration. As can be seen in Fig. 4, there are a number of receptor sites on endothelial cells that lead to activation of eNOS formation of NO. Endothelium-derived NO diffuses into the cytosol of vascular smooth muscle and leads to the activation of guanylyl cyclase. This in turn leads to the formation of cyclic guanosine monophosphate (cGMP). Increased cGMP triggers a reduction of calcium concentration by enhancing extrusion and sequestration of Ca^{2+}, which leads to smooth muscle relaxation. The eNOS-derived NO also has other actions such as regulation of adhesion and activation of circulating blood elements, cell killing, and increasing microvascular permeability.

Inducible NOS (iNOS) is an isoform not usually found in cells but is induced by inflammatory mediators such as bacterial endotoxin or the cytokines TNF-a, IL-1, or interferon-g. The role of NO derived from iNOS in systemic inflammatory response syndrome is a matter of extreme clinical interest. The iNOS is active as a dimer consisting of two 131-kDa units. In contrast to bNOS or eNOS, iNOS binds calmodulin so tightly that it does not require further addition of exogenous calmodulin to synthesize NO. Hence, iNOS is not regulated by intracellular Ca^{2+}. Nitric oxide formation catalyzed by iNOS located in vascular smooth muscle leads to relaxation, as does eNOS.

Because NO is a gas and highly soluble in water, inhaled NO acts readily on the pulmonary circulation. Because NO has such a short half-life, administering NO by inhalation leads to local effects on the pulmonary circulation with little in the way of systemic side effects. Thus, NO is being investigated as a local pulmonary vasodilator in a variety of clinical situations.

Other Functions of Pulmonary Endothelium

As suggested above, the vascular intima and its main constituent cell, the endothelium, can no longer be considered a simple layer of cells interposing a tissue barrier between the blood and vascular smooth muscle. Because the pulmonary circulation receives the entire cardiac output, it is an ideal location for performing a number of biological operations on the entire vascular system. Pulmonary endothelium contains a number of receptors for vasoactive substances or their precursors (see Fig. 4 and Fig. 5). For example, the potent vasoconstrictor angiotensin II is manufactured in the pulmonary endothelium from the precursor angiotensin I by a reaction catalyzed by angiotensin-converting enzyme.

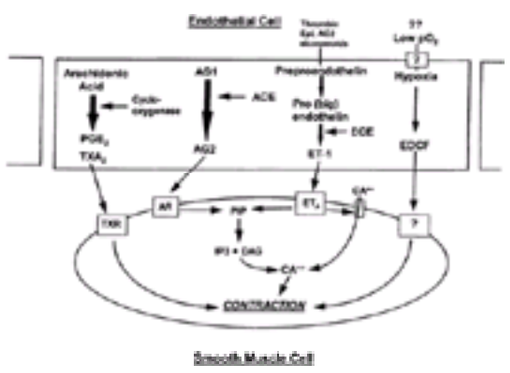

FIG. 5. Schematic depiction of endothelial cell–smooth muscle cell interactions leading to vasoconstriction. Epi, epinephrine; TXA_2, thromboxane A_2; AG1, angiotensin I; AG2, angiotensin II; ACE, angiotensin-converting enzyme; ECE, endothelin-converting enzyme; ET-1, endothelin-1; EDCF, endothelium-derived constricting factor; ET_A, endothelin-A receptor; TXR, thromboxane receptor; AR, angiotensin II receptor; PIP, phosphoinositol bisphosphate; IP3, inositol trisphosphate; DAG,

diacylglycerol.

The vasoconstrictor endothelin-1, a 21-amino-acid peptide, is the most potent vasoconstrictor currently known. It has a serum half-life of 2 min and hence has primarily local effects. Endothelin-1 is manufactured from pro- or big endothelin by endothelin-converting enzyme. Endothelin-A receptors are localized on vascular smooth muscle and mediate vasoconstriction. Endothelin-B receptors are located on vascular endothelium and are linked to vasodilation. When endothelin-1 binds to endothelin-A receptors, there is a biphasic rise in intracellular Ca^{2+}. The initial rise results from mobilization of intracellular Ca^{2+} stores by activation of phospholipase C, leading to generation of inositol trisphosphate and diacylglycerol (Fig. 5). The subsequent sustained rise in intracellular Ca^{2+} is from influx of extracellular Ca^{2+}. Endothelin release is stimulated by thrombin, epinephrine, calcium ionophore, angiotensin II, and some of the eicosanoids.

Endothelium-derived constricting factor is released from endothelial cells in response to hypoxia. The role of this substance in hypoxic vasoconstriction is being debated. Prostacyclin and PGE_2 are produced by pulmonary endothelium. Serotonin is extracted by pulmonary capillary endothelium. Angiotensin-converting enzyme also metabolizes the vasodilator bradykinin; thus, inhibition of angiotensin-converting enzyme would lead to increased systemic vascular resistance by inhibiting the formation of the vasoconstrictor angiotensin II and leading to the accumulation of the vasodilator bradykinin. The lung is a frequent site of injury in systemic inflammatory syndromes. Because of the interactions between pulmonary endothelial cells and a number of vasoactive mediators associated with inflammation, it is easy to understand why this should be so.

As discussed, the pulmonary endothelium interacts with vascular smooth muscle to produce contraction or relaxation by a variety of humoral mechanisms. Among the external forces acting on vascular endothelium are mechanical forces, probably acting via shear stress. Endothelial cells also secrete several growth factors that can regulate smooth muscle and fibroblast proliferation. These include growth-factor-like substances and a growth-inhibiting substance. The cross-talk between endothelium and surrounding lung tissue provides a series of mechanisms whereby chronic abnormalities in pulmonary vascular mechanics, i.e., chronically elevated pulmonary arterial pressures, can lead to remodeling of the pulmonary vasculature.

Autonomic Vascular Reflexes

The role of autonomic reflexes in controlling pulmonary vascular tone is less well understood than that for the systemic circulation. One should bear in mind that interspecies differences occur that may partially account for varying results in the literature. Relatively little is known about these responses in humans. In a number of species, both adrenergic and cholinergic nerve endings can be demonstrated in the pulmonary arterial bed, in the adventitia of large and small intrapulmonary arteries. Further, a- and b-adrenergic responses can be demonstrated after administration of exogenous selective a- or b-adrenergic agonists. Blocking of these responses by specific blockers can be demonstrated as well. Electric stimulation of pulmonary sympathetic nerves (i.e., by stimulating the stellate ganglion) causes pulmonary vasoconstriction, which has been variously manifest as an increase in pulmonary resistance or a decrease in pulmonary vascular compliance, primarily of large pulmonary arteries. Stimulation of the vagus nerve is more complex because it contains both sympathetic and parasympathetic fibers. According to some, sympathetic effects predominate with low baseline tone and cholinergic effects predominate with high baseline tone. Stimulation of muscarinic receptors by vagal stimulation or acetylcholine leads to vasodilation by release of NO.

A number of efferent brain–pulmonary vascular connections have been identified that may be responsible for the sympathetic component of the response to elevated cerebrospinal fluid pressure (Cushing's reflex). The ultimate change in PVR with autonomic stimulation depends on the interaction of sympathetically mediated pulmonary vasoconstriction, cholinergic vasodilation, resting tone, and concomitant changes in venous return and cardiac output, which lead to passive dilation of the bed. The role of neural control in maintaining oxygenation by matching ventilation and perfusion is not well known; nor are the mechanisms understood by which pathologic central nervous system stimulation may lead to abnormal water exchange, as in neurogenic pulmonary edema.

Finally, there are a number of afferent reflexes from pulmonary vasculature that lead to changes in ventilatory pattern. The existence of mixed venous CO_2-sensitive receptors that can regulate ventilation has been the subject of considerable controversy. These receptors have been postulated to contribute to the hyperpnea of exercise. The mixed venous CO_2 receptor may be identical to slowly adapting stretch receptors in the lung. However, a role for vagally carried bronchopulmonary C fibers has been postulated as well.

There is a large body of literature reporting that pulmonary vascular congestion can reflexively evoke systemic hypotension, bradycardia, and tachypnea. Unmyelinated C-fiber-innervated receptors in the interstitium of the lung may be stimulated by congestion of pulmonary microcirculation. Whether these *J-receptors* (for “juxtacapillary”) play a role, via vagally carried fibers, in mediating the tachypnea accompanying many pulmonary disorders such as pulmonary edema, pulmonary embolus, and fibrosis remains controversial, with evidence on each side of the argument. Whether these fibers are stimulated directly by vascular congestion or by release of a mediator substance is not known.

A number of chemical substances lead to the triad of bradycardia, hypotension, and apnea. This pulmonary chemoreflex can occur with the injection of certain naturally occurring mediators such as prostaglandins I_2 and E_2 and opiate peptides. Numerous other substances, including iced saline, when injected into the pulmonary artery through balloon-tipped catheters, are capable of causing this reflex.

Effects of Altered Gas Exchange on Pulmonary Circulation

It would be in the interest of preserving pulmonary ventilation–perfusion relationships if there were a mechanism allowing local vascular control by regional gas tensions such that areas of poor ventilation receive less blood flow. Hypoxic, hypercapnic, or acidotic lung regions would thereby undergo local vasoconstriction, shunting blood away from diseased areas. Both severe hypercapnia and acidosis are capable of causing vasoconstriction. Hypoxic pulmonary vasoconstriction has been most extensively studied. It should be noted that there are interspecies differences in the strength of, and possibly the mechanisms involved in, hypoxic vasoconstriction; these should lead to caution in comparing studies in different species. Failure of hypoxic vasoconstriction is probably a cause of hypoxemia seemingly out of proportion to the estimated size of a pulmonary lesion, as seen in pneumonia and atelectasis.

Graded decreases in alveolar P_{O_2} produce graded increases in pulmonary vascular resistance. The curve relating PVR to $P_{A_{O_2}}$ is roughly sigmoid in shape with a marked rise in the slope at $P_{A_{O_2}}$ » 60 torr. When hypoxia is confined to a local area of lung, then hypoxic vasoconstriction (HPV) is a mechanism for flow diversion from that area. For small segments, flow diversion is an effective means for shifting flow from hypoxic to normoxic lung regions. However, as the area of hypoxic lung gets larger, flow diversion becomes less effective. With whole-lung hypoxia, flow diversion does not occur. At this stage, elevated pulmonary arterial pressures may lead to redistribution of flow from bases to apices. This will lead to lower ventilation–perfusion ratios in the bases. This unfavorable effect on the distribution of ventilation–perfusion relations within the lung may even exacerbate systemic hypoxemia. Further, there is a point at which the gain in arterial P_{O_2} is offset by increased right ventricular afterload produced by HPV.

It is generally agreed that the site of pulmonary HPV is in the small muscular precapillary pulmonary arteries, which suggests that the site of O_2 sensing is not confined to alveolar capillaries alone. Interestingly, changing $P_{A_{O_2}}$ leads to a parallel shift in the pulmonary pressure–flow curve. This suggests a primary effect on critical downstream pressure rather than overall vessel diameter *per se* as discussed above.

A number of factors are known to modify the strength of HPV in different animal species. With very severe hypoxia (P_{O_2} < 25 torr), vasodilation may be seen. Other mediators that modify the vigor of HPV include estrogen, prostacyclin, pregnancy (although this response may be variable), glucocorticoids, and neural stimuli. More work is needed to define these factors in humans, especially as relates to clinical situations.

It would seem strange that after all the investigation of HPV, there is no universal agreement as to the mechanisms involved. There are two major schools of thought. One is that acute hypoxia elicits HPV via release of mediators from surrounding lung and/or endothelial cells. The other states that HPV is a direct effect of regional hypoxia (either in air or blood) on pulmonary vascular smooth muscle.

Regarding the mediator hypothesis, many previously postulated candidates are no longer thought to be viable alternatives as primary mediators, although they may certainly act as modifiers. These include catecholamines, potassium, histamine, serotonin, angiotensin II, certain arachidonic acid metabolites, and various neurotransmitters. Endothelin-1 and endothelium-derived constricting factor are being considered for roles as primary mediators of HPV. One interesting hypothesis concerns the role of NO in HPV. Because NO is released tonically into the pulmonary circulation, inhibition of NOS could result in vasoconstriction. In fact, NOS inhibition can enhance the pulmonary pressor response to hypoxic challenge. This in turn suggests that NO plays a role modulating the vigor of the pulmonary pressor response to hypoxia. However, NOS inhibition does not abolish HPV, indicating that there is another primary mechanism at work.

Direct effects of hypoxia on the pulmonary vasculature are considered in the context of a three-part model: a hypoxia sensor, a transducer, and an effector. The effector is clearly vascular smooth muscle. The sensor is most likely located anatomically in precapillary arterioles. Because the presence of an intact endothelium is necessary for HPV, it is possible that this cell, with its potential to produce vasoconstrictors and vasodilators, acts as the primary sensor. The identity of the sensor within cells is likewise unknown. Possibilities include the mitochondrial oxidative phosphorylation system and cytochrome P_{450}. The transducer is likewise not universally agreed on; however, any one of a number of endothelium-derived vasoconstrictors could be a candidate (Fig. 5). Finally, an intriguing observation is that small pulmonary arteries exhibit membrane depolarization and action potential generation on exposure to hypoxia, suggesting that hypoxia may act directly on the vessel wall of these vessels. This work is consistent with the notion that there is a role for potassium influx and change in potassium channel conductance in the genesis of HPV.

In addition, the effect of local hypoxia on regional blood flow is the end result of a number of factors besides regional gas tensions. These effects include local compression or malformation of vessels as well as the systemic effects of hypoxemia. Thus, systemic adrenergic stimulation could add to the local mechanisms involved in hypoxic vasoconstriction.

Chronic hypoxemia, as occurs in high-altitude dwellers, is associated with structural changes in the pulmonary vascular bed in addition to the vasospasm of acute hypoxia. We have already alluded to the cross-talk between pulmonary endothelium-derived growth factors and smooth muscle, which may be responsible for architectural remodeling, including hyperplasia and hypertrophy of pulmonary arterial and arteriolar walls (i.e., smooth muscle and medial layers). In chronic high-altitude dwellers who move to sea level, pulmonary arterial pressures remain elevated, and dilatory reserve remains limited for an extended period of time, because of structural changes in pulmonary vasculature.

Pulmonary Edema Formation and Prevention in the Lung

Exchange of nutrients and fluids occurs at the capillaries, arterioles, and small veins, vessels that may be lumped under the term *microvasculature.* Fluid exchange at the microvascular level occurs by filtration, diffusion, and micropinocytosis. Filtration and diffusion are passive processes in which substances flow down a potential energy gradient.

The Starling Equation

In 1896, Starling described the balance of forces that regulate the flow of fluid (filtration) across microvasculature into and out of the interstitium. The force driving fluid *out* of microvasculature is the hydrostatic pressure gradient across the vessel wall, and that driving fluid *into* the microvessels is the colloid oncotic (or osmotic) pressure gradient across that wall. The classic relationship may be written:

$$\dot{Q}_f = K_f[(P_m - P_{is}) - k(\pi_m - \pi_{is})]$$

where $\dot{Q}_f$ is fluid flow across the microvessel, P_m is microvasculature hydrostatic pressure, P_{is} is interstitial hydrostatic pressure, p_m is microvascular plasma oncotic pressure, and p_{is} is interstitial oncotic pressure. The constant k is the reflection coefficient, which represents the degree to which proteins can move across the vessel wall. If $k = 0$, then protein moves freely, and there can be no oncotic gradient driving fluid back into the microvasculature. If $k = 1$, then the vessel wall is impermeable to protein. Constant k is usually close to 1. K_f is the filtration coefficient, which is made of terms representing the filtration constant of the microvascular membrane, membrane surface area, filtrate viscosity, and the distance across the vessel wall; it thus represents the conductance for fluid flux across the membrane. It can be seen that with a large K_f, even a small balance of forces in favor of fluid movement results in a large volume flow of fluid.

Plasma and interstitial fluid each contain approximately 280 mmol of crystalloid, which is freely interchangeable between the two compartments. Thus, the osmotic forces governing transvessel fluid exchange are dominated by the protein concentration gradient, approximately 7 g/100 mL, giving a plasma osmotic (oncotic) pressure of 28 mmHg. Pulmonary interstitial protein content is not known for certain and is often assumed to be close to zero. Thus, the edemagenic potential of the lung depends on the balance of forces, which is not necessarily constant but is related to regional variations in vascular and interstitial compartments. In addition, the lung is richly endowed with a lymphatic system, which can drain the interstitium (Fig. 6).

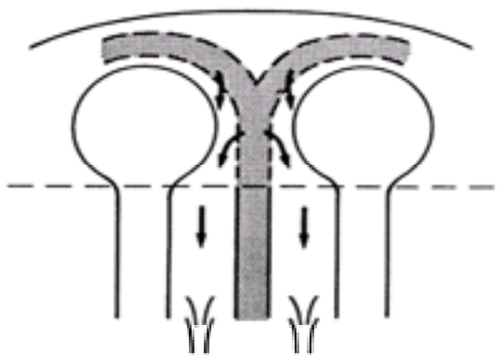

FIG. 6. Representation of the lung as three concentric compartments: airway, vascular, and interstitial. *Arrows* indicate the net filtration volume. Lymphatics drain the interstitium. (Reprinted with permission from Oppenheimer L, Goldberg HS. Pulmonary circulation and edema formation. In: Scharf SM, Cassidy SS, eds. *Heart–Lung Interactions in Health and Disease.* New York: Marcel Dekker, 1989;93–130.)

We have already considered most of the factors that govern microvascular filtration pressure. It should be noted that both extraalveolar and intraalveolar vessels contribute to edema formation, and the gradients across the walls of these vessels may be very different depending on the state of lung inflation. In general, microvascular filtration pressure increases from less to more dependent lung regions, and, for any given arterial pressure, microvascular filtration is greater as the ratio of arterial to venous resistance decreases. Thus, it is difficult to consider *the* capillary filtration pressure within the lung as if it were a unique entity, although various techniques have been used to estimate the overall mean filtration pressure for any given set of conditions.

It is important for preservation of normal gas exchange that the pulmonary interstitium, particularly in the intraalveolar compartment, remain dry—that is, without free fluid. Pulmonary interstitium, far from being a space, is composed of cellular elements, elastin, collagen, glycosamines, and proteoglycans and probably has a consistency similar to gelatin. Like microvascular pressure, interstitial pressure varies locally between extraalveolar and intraalveolar compartments, with lung inflation, along hydrostatic gradients and from hilum to parenchyma. In general, interstitial pressure is *less* than pleural pressure, is more negative in the extraalveolar than in the intraalveolar compartments, and is more negative in hilar than in peripheral lung regions. This leads to different transmicrovascular fluid pressure gradients within the lung such that the edemagenic potential varies within the lung, leading to a sequence of edema formation. Edema forms initially in the connective tissue of the alveolar septa. Following pressure gradients, it then accumulates around arterioles and bronchioles in the form of cuffs of fluid and travels to the interstitium around larger arteries, veins, and airways. This leads to the perivascular and peribronchial cuffing sign seen on chest roentgenograms. Ultimately, fluid may penetrate into the alveolar space to cause alveolar flooding.

Like other interstitial areas, the pulmonary interstitium has a biphasic pressure–volume curve. At low levels of hydration (low free fluid volume), large changes in fluid pressure produce small changes in volume. This stiff portion of the pressure–volume curve is found when interstitial pressure is negative and protects against edema formation because large pressure gradients, such as might be produced by lung inflation, are tolerated with little change in fluid volume. As water accumulates and the matrix opens up, the pressure–volume curve becomes more compliant, such that relatively small changes in pressure produce large volume changes. This allows the interstitium to soak up considerable amounts of fluid, thereby buffering against alveolar flooding.

Finally, pulmonary lymphatics, which drain into the systemic venous system, act as sump drains, removing excess interstitial fluid. Lymphatic flow increases with either increased microvascular pressure or increased microvascular permeability. With high microvascular pressures resulting in transudation of fluid, lymph is essentially an ultrafiltrate of plasma and has a low protein content. With increased vascular permeability, however, macromolecules usually leak through, and the protein content of lung lymph becomes high. Injection of substances that damage pulmonary microvessels often demonstrates two phased alterations of lung lymph. In stage 1, lymph protein content is low, although lung lymph flow is increased. This is consistent with elevation of pulmonary microvascular filtration pressure with little change in

vascular permeability. In phase 2, lung lymph flow is also increased, but protein content is high, consistent with permeability or leaky-capillary-type pulmonary edema.

Although the overall Starling balance for the lung is difficult to ascertain, estimates of microvascular fluid filtration pressure usually hover around 15 mmHg, albeit with considerable variation. Interstitial hydrostatic pressure is subatmospheric, approximately –8 mmHg. This gives a 23-mmHg (15 to –8 mmHg) gradient for outward fluid movement, which is more than counterbalanced by the inward-acting oncotic pressure gradient of 28 mmHg. Therefore, the overall balance of forces is approximately 5 mmHg in favor of movement of fluid out of the interstitium into the microvasculature. This does not leave much room for increases in microvascular filtration pressure, as might well occur with physiological maneuvers (i.e., exercise). Thus, the other mechanisms discussed that keep the interstitium fluid-free assume greater importance.

The Bronchial Circulation

The bronchial circulation is the systemic vascular supply to the airways, arising from the bronchial arteries, intercostal arteries, and aorta. The bronchial circulation constitutes the major nutritive blood supply to the bronchi down to the level of the respiratory bronchioles. Below this level, the pulmonary circulation performs this function. There is considerable anatomic variation in the origin of the bronchial arteries, which has practical importance in clinical situations where embolization of the bronchial circulation is used to treat massive hemoptysis. The bronchial circulation also sends branches to mediastinal and other extrapulmonary structures, including hilar lymph nodes and pleura (Fig. 7). The extrapulmonary bronchial circulation drains via the azygos and hemiazygos veins, whereas the intrapulmonary bronchial circulation drains via the pulmonary veins. There is evidence for anastomoses or potential anastomoses between bronchial and pulmonary circulations at every level of the vasculature, including arteries, capillaries, and veins. To supply airways to the level of the terminal bronchioles, the bronchial circulation forms two plexuses, one inside the airway in the submucosa and one outside the airway in the peribronchial tissue.

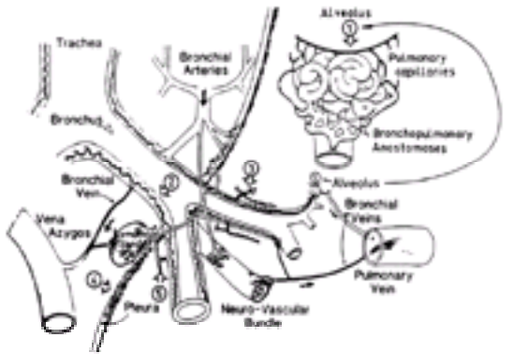

FIG. 7. Schematic depiction of the bronchial circulation. The *numbers* indicate possible sites of absorption of edema fluid. Note the many intra- and extrapulmonary sites supplied by the bronchial circulation. (Reprinted with permission from Deffeback ME, Butler J. The bronchial circulation and lung edema. In Scharf SM, Cassidy SS, eds. *Heart–Lung Interactions in Health and Disease.* New York: Marcel Dekker, 1989;131–154.)

The bronchial circulation normally constitutes only 1% to 2% of the cardiac output. However, this belies its potential importance. Because of its location and extensive networking, total bronchial blood volume is considerable; hence, bronchial blood velocity is slow. Thus, the bronchial circulation is well situated to participate in fluid and even gas exchange in the lung. When there is pulmonary vascular obstruction, bronchial blood flow via anastomoses to the pulmonary circulation helps maintain inflow from surrounding pulmonary networks and acts to prevent infarction. Of particular importance may be the role of the bronchial circulation in airway inflammation, when bronchial blood flow increases considerably.

Clearly, the bronchial circulation is important when considering the edema, bronchospasm, and inflammatory changes found in airways in a variety of disorders. In addition, the bronchial circulation acts to condition air in the bronchial tree that is not conditioned in the upper airways. The blood vessels of the airways may act to minimize heat loss during hyperventilation such as that induced by exercise. During exhalation, heat and water would be given back to the air, cooling the airway surface but minimizing heat loss to the outside. Similarly, the bronchial circulation plays an important role in regulating airway water, which can influence the rheology of mucus and thus affect the clearance of particulate matter from the lung as well as change the osmolality of the mucous lining layer. The latter is believed to affect airway smooth muscle tone, especially in asthmatic patients. Finally, in pathologic situations—most notably bronchiectasis, tumor, and lung abscess—local bronchial circulation increases considerably, in part because of opening of previously closed bronchial–pulmonary anastomoses. The hypertrophied bronchial circulation is responsible for hemoptysis in these situations, which may be life-threatening. Conditions associated with bronchial arterial hypertrophy and proliferation may be associated with right-to-left extracardiac shunting, hypoxemia, and increased cardiovascular load. Left-to-left shunts have been demonstrated, but only when the expansion of the bronchial circulation is large. Interestingly, these conditions are often associated with the clinical sign of digital clubbing.

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CHAPTER

65 Pulmonary Hypertension: Pathophysiology and Clinical Disorders

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INTRODUCTION

As reviewed in the previous chapter (Chapter 64, The Normal Adult Pulmonary Circulation) the normal pulmonary circulation is a low-pressure, high-flow vascular bed that accommodates the entire cardiac output with each heartbeat. Increased cardiac output, a normal response to exercise, does not significantly increase pulmonary arterial pressure. The reasons for the high capacitance of the pulmonary circulation are recruitment of underperfused microvessels and distension of patent vessels in response to increases in blood flow. In addition, the tone of the smooth muscle in the media of pulmonary arterioles is lower, and the smooth muscle layer of pulmonary resistance vessels is thinner than that of most systemic vascular beds. The causes of the normally low tone of pulmonary arteriolar smooth muscle probably include both enhanced responsiveness to endogenous vasodilators and decreased responsiveness to vasoconstrictors.

Pulmonary hypertension occurs when pulmonary arterial pressure is inappropriately high for a given level of blood flow through the lungs. A useful clinical definition of pulmonary hypertension is a pulmonary artery pressure (P_{pa}) >25 mmHg at rest or >30 mmHg during exercise. Pulmonary hypertension may occur as a primary disorder of the pulmonary circulation, or it may be secondary to other heart or lung diseases. Examples of primary disorders of the pulmonary circulation include those in which pulmonary vessels are obstructed by thrombosis (i.e., recurrent pulmonary thromboembolism) or by vasoconstriction (i.e., idiopathic or primary pulmonary hypertension). Secondary pulmonary hypertension occurs as a complication of other disorders, such as pulmonary hypertension as a consequence of chronic hypoxia caused by chronic bronchitis. In this chapter we discuss the pathophysiology of pulmonary hypertension in the context of abnormalities of the normal mechanisms that maintain low pulmonary vascular pressure. We survey clinical disorders manifested by pulmonary hypertension, and we review the approach to diagnosis and treatment of pulmonary hypertensive disorders.

PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION

In order to understand the pathogenesis of pulmonary hypertension, it is necessary to review the determinants of normal pulmonary vascular tone. As illustrated in Fig. 1, pulmonary vascular resistance is a function of inflow (pulmonary arterial) and outflow (left atrial or pulmonary venous) pressures and is inversely proportional to cardiac output. As noted above, the normal structure and function of pulmonary arterioles are those of a low-resistance circulation. Pulmonary arterial pressure increases with increases in cardiac output and with increases in left atrial pressure. Because of the remarkable capacity of the pulmonary circulation, acute changes in flow and venous pressures do not ordinarily cause significant pulmonary hypertension. However, if these conditions persist in a chronic state (weeks to months), then vasoconstriction, vascular remodeling, and subsequent narrowing of the vessels occur, as discussed below. Thus, conditions characterized by sustained increases in pulmonary blood flow, such as left-to-right intracardiac shunts, may result in secondary pulmonary hypertension. Similarly, conditions characterized by long-standing increases in left atrial and pulmonary venous pressures, such as mitral valvular stenosis, may also cause secondary pulmonary hypertension.

PULMONARY VASCULAR RESISTANCE

$$PVR\ (mmHg \cdot mm \cdot L^{-1}) = \frac{\bar{P}_{PA} - \bar{P}_{LA}}{\dot{Q}}$$

POISEUILLE'S LAW

$$R = \Delta P/\dot{Q} = \frac{8\mu \cdot l}{\pi \cdot r^4}$$

FIG. 1. Pulmonary vascular resistance (PVR) is calculated from the ratio of differences in pressure across the pulmonary vasculature to blood flow; P_{PA}, mean pulmonary arterial pressure (mmHg); P_{LA}, mean left atrial (or pulmonary venous) pressure (mmHg); *Q,* cardiac output (blood flow, L/min). The PVR may be expressed in units of dyne-seconds per cm^5 by multiplying this ratio by 80. Poiseuille's law indicates that the vascular resistance in a tube, the ratio of the pressure drop across the tube (D *P*) to blood flow (*Q*), is determined by blood viscosity (h), the length of the vessel (*l*), and the radius (*r*) of the vessel.

The factors that modulate pulmonary vascular resistance are delineated by Poiseuille's law, which describes resistance to flow through rigid tubes (Fig. 1). Pulmonary vascular resistance is directly proportional to the viscosity of blood and is inversely proportional to the radius to the fourth power of the aggregate cross-sectional area of the pulmonary vascular bed. Thus, conditions that increase blood viscosity, such as erythrocytosis, may exacerbate pulmonary hypertension. Most importantly, conditions that decrease the luminal area of the pulmonary circulation significantly increase pulmonary vascular resistance and arterial pressure.

Figure 2 illustrates conditions in which the aggregate cross-sectional area of the pulmonary circulation may be diminished. Loss of aggregate cross-sectional area occurs after surgical resection of lung tissue. Ordinarily, even pneumonectomy does not cause resting pulmonary hypertension because of the enormous reserve of the pulmonary circulation. Indeed, more than half of the pulmonary circulation must be removed before pulmonary hypertension is observed at rest. However, because cardiac output increases with exercise, pulmonary hypertension may occur after pneumonectomy. Similarly, if there is some other underlying disorder decreasing pulmonary arterial cross-sectional area, then further loss of area after lung resection may cause resting pulmonary hypertension. Another common cause of loss of pulmonary vascular luminal area is the destructive lung disease, emphysema. In emphysema, destruction of alveolar capillary septa results in loss of pulmonary capillaries and microvessels.

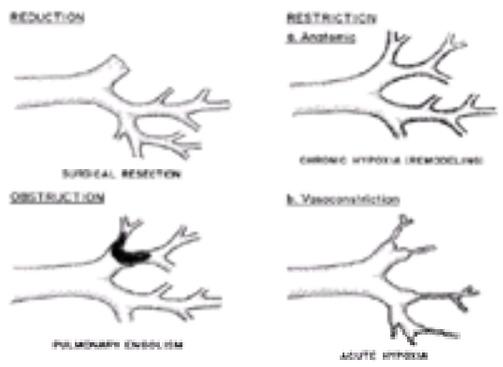

FIG. 2. Several commonly occurring mechanisms by which the aggregate cross-sectional area of the pulmonary vasculature may be reduced.

The luminal area of the pulmonary circulation may also be decreased by obstruction of vessels, such as occurs after pulmonary thromboembolism. Because of the huge cross-sectional area of the normal pulmonary circulation, acute pulmonary thromboembolism rarely causes sustained pulmonary hypertension unless there is massive embolization resulting in obstruction of more than half of pulmonary arteries. However, if there is an underlying disorder that has diminished the luminal area, then submassive thromboembolism may cause pulmonary hypertension. Also, recurrent thromboembolism with multiple small clots accumulating over a period of months to years causes sustained pulmonary hypertension. Other vascular obstructive causes of pulmonary hypertension include schistosomiasis, foreign body emboli as a result of intravenous drug abuse, and sickle cell disease.

Widespread narrowing of pulmonary vascular lumina is an important cause of loss of cross-sectional area. Narrowing may be caused by anatomic changes in the vascular wall structures, such as the vascular remodeling seen after chronic hypoxia or in primary pulmonary hypertension. Contraction of vascular smooth muscle causes vasoconstriction, another cause of decreased luminal area. Although a variety of mediators cause pulmonary arterial vasoconstriction, the most important cause of pulmonary vasoconstriction is acute alveolar hypoxia. Vasoconstriction and remodeling frequently occur simultaneously, as in conditions characterized by long-standing hypoxia, such as chronic mountain sickness or chronic bronchitis. Long-standing increases in intrathoracic pressure, as may occur with COPD, may also decrease vascular area by compression of pulmonary vessels.

Thus, increases in pulmonary blood flow, left atrial or pulmonary venous pressure, and blood viscosity and decreases in pulmonary arterial lumen area all increase pulmonary arterial pressure. These mechanisms of pulmonary arterial hypertension are summarized in Table 1 with clinical examples of characteristic disorders resulting in pulmonary hypertension. Some of these mechanisms, such as increased blood viscosity, exacerbate pulmonary hypertension but rarely, if ever, cause clinically significant disease by themselves. In many clinical disorders, more than one mechanism of pulmonary hypertension may be operant. For example, in primary pulmonary hypertension, vasoconstriction, structural remodeling, and *in situ* thromboses are all likely contributors to increased pulmonary vascular resistance. In chronic bronchitis, hypoxic vasoconstriction, structural remodeling, increased intrathoracic pressure, secondary erythrocytosis, and increased blood volume may all be present and contribute to pulmonary hypertension. In conditions of sustained increases in pulmonary blood flow, such as congenital left-to-right intracardiac shunts, sustained increases in flow eventually cause increased vasomotor tone and vascular remodeling that exacerbate and may perpetuate pulmonary hypertension. Thus, regardless of the original insult, the mechanism of sustained pulmonary hypertension is usually multifactorial. In subsequent sections of this chapter, we discuss in more detail the effects of acute and chronic hypoxia and clinical disorders of pulmonary hypertension, with correlation of pathologic and physiological changes and clinical manifestations.

Mechanism	Clinical example
Increased blood flow	Atrial septal defect
Increased venous pressure	Mitral stenosis
Increased blood viscosity	Erythrocytosis
Decreased vascular area	
Surgical resection	
Obstruction	Thromboemboli
Obliteration	Emphysema
Extrinsic compression	Interstitial pulmonary fibrosis
Vasoconstriction	Acute hypoxia
	PPH
Vascular remodeling	Chronic hypoxia
Increased intrathoracic pressure	COPD

TABLE 1. *Mechanisms of pulmonary hypertension*

PATHOPHYSIOLOGY OF PULMONARY VASOMOTOR CONTROL

As noted above, the normal pulmonary circulation is a low-pressure, high-flow circuit maintained in a relative state of vasodilation as compared to the systemic circulation. Endogenous pulmonary vasodilators and vasoconstrictors are described in Chapter 64. Loss of normal balance among these substances can cause contraction of vascular smooth muscle and restriction of the pulmonary vascular bed, resulting in pulmonary hypertension. An example of such loss of balance in patients with primary and secondary pulmonary hypertension is the reported increase of the vasoconstrictor prostaglandin thromboxane A_2 relative to the vasodilator prostaglandin prostacyclin. Because the pulmonary endothelium is a site of synthesis and/or metabolism of many vasoactive mediators such as prostaglandins, it is possible that endothelial cell injury or dysfunction may cause or perpetuate pulmonary hypertension. In support of this idea, reduced expression of endothelial cell nitric oxide synthase has been reported in lungs of patients with pulmonary hypertension. This enzyme is responsible for synthesis of the potent vasodilator nitric oxide, also known as endothelial cell-derived relaxing factor. Similarly, enhanced expression of the potent vasoconstrictor endothelin-1 has been reported in pulmonary arterial endothelial cells in lungs of patients with pulmonary hypertension. However, it is not clear at this time whether changes in vasoactive mediator balance are primary

causes of or responses to abnormalities in pulmonary vascular tone.

Another potential cause of abnormal pulmonary vascular tone is enhanced responsiveness of vascular smooth muscle to vasoactive substances. Evidence in support of this idea comes from animal studies that show changes in pulmonary vascular reactivity after lung injuries. Depending on the cause of injury, vasoreactivity may be increased or decreased. In addition, patients with acute lung injuries, such as the adult respiratory distress syndrome, may have increased pulmonary vascular tone. Causes of pulmonary vascular smooth muscle dysfunction are not clear, but direct effects of cytokines and oxidants have been demonstrated *in vitro.*

The most important physiological stimulus for pulmonary vasoconstriction is the acute hypoxic pressor response. Diseases that cause alveolar hypoxia are characterized by vasoconstriction, which is at least partially ameliorated by administration of oxygen. As noted in the previous chapter, the site of acute hypoxic vasoconstriction is the precapillary arteriole. The mechanism of hypoxic vasoconstriction is not known. The magnitude of hypoxic vasoconstriction is enhanced by acidosis, which may be important in lung diseases characterized by hypoventilation and respiratory acidosis. There is significant variability among individuals in the magnitude of hypoxic vasoconstriction. This variation, which may be genetic in origin, may explain differences in the degree of pulmonary hypertension complicating lung diseases.

PATHOPHYSIOLOGY OF PULMONARY VASCULAR REMODELING

In 1958, Heath and Edwards described a histologic classification of vascular changes associated with pulmonary hypertension, encompassing a progression of changes from grade 1 to 6 (Table 2). These grades represent a continuum of abnormalities, with grade 1 being the most potentially reversible and grade 6 least likely to be reversible. Examples of these changes are illustrated in Fig. 3 and Plate 1 and Plate 2. In 1973, the World Health Organization proposed that causes of pulmonary hypertension could be characterized by distinct pathologic patterns—plexogenic pulmonary arteriopathy, thrombotic pulmonary arteriopathy, and pulmonary venoocclusive disease. It has subsequently been learned that there is considerable overlap among these pathologic patterns in given diseases. Indeed, it is not possible to diagnose a given cause of pulmonary hypertension with certainty from the pathologic pattern alone.

Grade	Pathology	Cause
I	Medial hypertrophy	Chronic hypoxia
II	Cellular intimal proliferation	Venous hypertension
III	Luminal occlusion caused by intimal hyperplasia ("onionskinning")	Primary PH
IV	Angiomatoid formation ("plexiform lesion")	Primary PH
V	Fibrinoid necrosis	Vasculitis

TABLE 2. *Heath and Edwards classification of progressive pulmonary vascular changes in pulmonary hypertension*

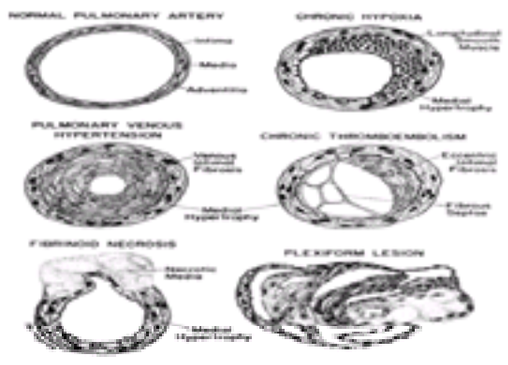

FIG. 3. Normal structure of the muscular pulmonary artery and pathologic changes that may occur in various pulmonary vascular diseases.

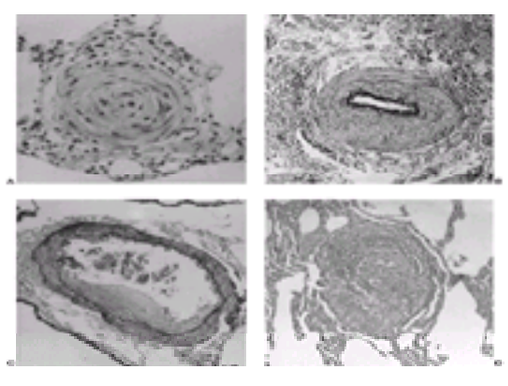

PLATE 1. (A) Small muscular pulmonary artery showing almost complete occlusion by myointimal hyperplasia and fibrosis. This is also termed concentric laminar intimal fibrosis or an onionskin lesion (H&E). (Courtesy of Dr. G. Pietra.) **(B)** Medium-sized pulmonary artery showing medial muscular hypertrophy between the external muscular coat and the internal elastic lamina (elastic stain). (Courtesy of Dr. D. Dantzker.) **(C)** Muscular pulmonary artery demonstrating eccentric intimal fibrosis, which is suggestive of remote thromboembolism (H&E). (Courtesy of Dr. G. Pietra.) **(D)** Plexiform lesion. *See Color Plate 20.*

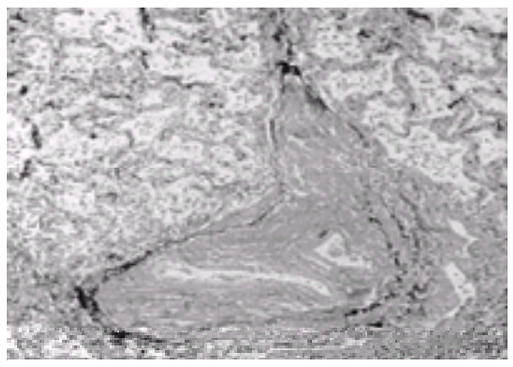

PLATE 2. Medium-sized pulmonary vein in a case of venoocclusive disease demonstrating intraluminal fibrosis and variably sized intravascular channels, suggesting recanalization of prior thrombosis. (Courtesy of Dr. D. Dantzker.) *See Color Plate 18.*

The pioneering work of Lynne Reid and her associates has yielded important insights into the pathogenesis of pulmonary hypertension based on pathologic studies of

human diseases and on studies of the pathogenesis of animal models of pulmonary hypertension. These investigators have shown that the process of pulmonary vascular remodeling results in restriction of the pulmonary vascular bed and consequent pulmonary hypertension, as noted above. Examples of causes of pulmonary vascular remodeling include chronic hypoxia; sustained increased blood flow, such as that caused by congenital right-to-left intracardiac shunts; and repeated endothelial cell injury. There are some differences among models and diseases in the degree of endothelial cell injury, inflammatory reactions, and patterns of muscle hypertrophy. However, the process of remodeling is strikingly similar regardless of the inciting stimulus, suggesting a stereotypic response to vascular injury. The best studied of the experimental models of remodeling is the response to chronic hypoxia.

Unlike large vessel atheromata in the systemic circulation, remodeling of the pulmonary vasculature occurs primarily in microvessels (<500 µm diameter). Restriction is caused both by reduction in vessel number and by wall thickening that encroaches on the vascular lumen. Each of the cell types of the vascular wall can participate in the process. Endothelial cell swelling, necrosis, or hypertrophy may narrow the vascular lumen (Color Plate 1A). In addition, endothelial cells may direct the synthesis of noncellular matrix with ensuing increases in intimal thickness (Color Plate 1C). Smooth muscle cell hypertrophy and hyperplasia are seen (Color Plate 1B). A very important role of vascular smooth muscle is the synthesis of matrix material, such as elastin, which contributes to hypertrophy of vascular media. In precapillary segments, hypertrophy and hyperplasia of pericytes and intermediate cells cause vascular narrowing. These cells may also undergo phenotype shifts toward smooth muscle cells with characteristic changes in contractile and synthetic properties. Adventitial fibroblasts undergo hyperplasia and markedly increase collagen production, resulting in dramatic increases in adventitial thickness (Color Plate 1B), which may impair responsiveness to vasodilators.

The mechanism of pulmonary vascular remodeling is a subject of intense research interest. It is thought that enhanced vasoconstriction may predispose to remodeling, perhaps stimulated by changes in shear forces. Growth factors, such as transforming growth factor-b (TGF-b), are involved in modulation of extracellular matrix production. Endothelial cell injury may be an important stimulus to the remodeling response. Hypoxia may play a direct role by stimulating production of other cytokines, such as vascular endothelial growth factor. Reduced production of inhibitors of vascular cell replication and synthetic functions may also be important. An example of such an inhibitory substance is endothelial cell-derived heparan sulfate. Inflammatory cells may contribute to remodeling by producing cytokines and growth factors, which, in turn, stimulate vascular smooth muscle cell replication. Emerging understanding of the genetic regulation of vascular cell replication and phenotype holds the promise of therapies that may delay or prevent vascular remodeling.

Perpetuation of structural changes, continued cell replication, and matrix accumulation suggest that control of normal reparative processes may be impaired in the process of vascular remodeling. The role of processes that cause involution of tissue, such as apoptosis (programmed cell death) or proteolysis of extracellular matrix, is not known at this time.

CLINICAL SYNDROMES OF PULMONARY HYPERTENSION

Clinical syndromes of pulmonary hypertension may be classified as those that primarily alter the pulmonary blood vessels and those that are secondary to underlying heart or lung diseases.

DISEASES OF THE PULMONARY BLOOD VESSELS

Diseases that primarily affect the pulmonary arteries include primary pulmonary hypertension, AIDS-related pulmonary hypertension, pulmonary vasculitides, and thromboembolic pulmonary hypertension. Pulmonary venoocclusive disease is probably a disease of both pre- and postcapillary vessels, distinguished by involvement of the pulmonary veins. We describe primary pulmonary hypertension in detail because it provides a useful background for consideration of the other pulmonary vascular diseases and pulmonary hypertension secondary to underlying heart or lung diseases.

PRIMARY PULMONARY HYPERTENSION

Definition

Primary pulmonary hypertension is a clinical syndrome of pulmonary hypertension that progresses rapidly to right ventricular failure and death. Primary pulmonary hypertension (PPH) is also known as unexplained or idiopathic pulmonary hypertension to distinguish this disorder from other syndromes of pulmonary hypertension that arise from underlying heart or lung diseases or are clearly complications of clotting or other systemic diseases, such as collagen vascular diseases. The diagnosis of PPH is based on the presence of clinical manifestations of pulmonary hypertension, demonstration of pulmonary hypertension by direct measurement of pulmonary artery pressure and vascular resistance, and exclusion of causes of secondary pulmonary hypertension. Although PPH is not a common disease, it is important to understand because the pathophysiology, signs, and symptoms are characteristic of pulmonary vascular disease *per se* and not of other underlying disorders. Primary pulmonary hypertension was first described by Dresdale in 1951; detailed pathologic descriptions were provided by Wagenvoort and Wagenvoort in 1970; and in 1973, the World Health Organization described three major pathologic types of disease. The Primary Pulmonary Hypertension Registry of the NHLBI collected important data on the natural history and prognosis of PPH in the 1980s. Since the advent of lung transplant for therapy of PPH and the application in the 1990s of molecular biological approaches to identification of potential mediators of the disease, additional information regarding pathology and pathogenesis has accumulated. However, knowledge of pathogenesis is still primitive. Indeed, it is likely that what is now called PPH is a clinical syndrome secondary to multiple diseases of distinct etiologies that can be recognized only at an end stage in the pathogenetic sequence because of lack of an easily applicable screening test for early diagnosis.

Demographics of Patients with PPH

The frequency of diagnosis of PPH among patients undergoing right heart catheterization has been reported to be about 1%; thus, PPH is probably not a common disease in the general population. The disease is generally considered to be a disease of younger people, with greatest incidence between the ages of 20 and 45 years. However, PPH has been reported among the elderly (age >65 years). It is particularly difficult to diagnose in older age groups because of the increased incidence of potentially confounding intercurrent heart or lung diseases. Thus, the diagnosis of PPH may be delayed in these individuals while other, more common disorders, such as coronary artery disease or COPD, are treated. In the PPH Patient Registry, the ratio of women to men was 1.7:1 regardless of age at diagnosis.

Pathology

The PPH Registry sponsored by the NHLBI investigated the pathology of 38 cases meeting clinical criteria for the diagnosis of PPH, with 33 patients exhibiting primary pulmonary arteriopathy and five exhibiting pulmonary venoocclusive disease in addition to arterial lesions. Among the histologic patterns observed in the 33 cases of pulmonary arteriopathy were plexiform lesions (Plate 1D), thrombotic lesions, medial hypertrophy with intimal fibrosis (Plate 1C), and isolated medial hypertrophy (Plate 1B). Thus, the vascular lumina were narrowed by both intimal and medial changes. These results and the work of preceding investigators suggest that *in situ* or embolic thromboses contribute to remodeling of the pulmonary circulation in PPH. In addition, the association of venoocclusive changes with pulmonary arteriopathy suggests that venoocclusive disease may be a syndrome resulting from multiple injuries to the entire pulmonary vascular tree rather than a single disease that primarily affects the pulmonary veins (see below).

Subsequent pathologic studies of lungs of patients undergoing lung transplantation for treatment of PPH have revealed increases in adventitial thickness, increased expression of mRNA of the connective tissue proteins collagen and elastin, and foci of inflammation associated with plexiform lesions. Thus, pathologic studies suggest that the pathogenesis of PPH involves sustained cell proliferation, extracellular matrix protein production, inflammation, and thrombosis.

Pathogenesis

Table 3 lists some of the disorders or conditions associated with PPH, which range from familial causes to exogenous toxins, such as the appetite supressant fenfluramine. It is evident that PPH is a heterogeneous group of disorders of differing pathogenetic sequences, culminating in the recognizable clinical syndrome. There are several factors that play a role in the pathogenesis of PPH. These factors include genetic predisposition, endothelial cell dysfunction, abnormalities in vasomotor control, thrombotic obliteration of vascular lumen, and vascular remodeling through cell proliferation and matrix production. This complex interaction is illustrated in Fig. 4. It is important to note that PPH likely results from both inherited and acquired conditions.

Familial
Menarche
Pregnancy
Autoimmune phenomena, e.g., Raynaud's phenomenon, positive antinuclear antibody
Hepatic cirrhosis
Appetite suppressants, e.g., aminorex, fenfluramine
Crack cocaine inhalation
Toxic oil (rapeseed oil) syndrome
HIV infection

TABLE 3. *Conditions associated with primarypulmonary hypertension*

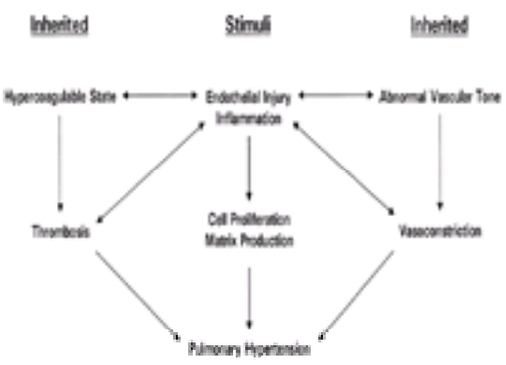

FIG. 4. Inherited and acquired factors that are likely to be important in the pathogenesis of PPH.

Not all individuals with associated disorders, such as hepatic cirrhosis, develop PPH. Thus, there may be inherited abnormalities of the pulmonary circulation that predispose to the development of PPH. In support of this contention, families have been described in which PPH occurs in an autosomal dominant pattern with a 2:1 female:male ratio but with differing degrees of disease expression. In addition, associations have been described among familial cases of PPH, autoantibodies, and major histocompatibility (MHC) loci, suggesting that some cases of familial PPH may be caused by inherited autoimmune causes. Thus, the search is ongoing for as yet unidentified gene(s) causing familial PPH.

As noted above, reports have been published of changes in endothelial cell expression of vasoactive mediators, such as nitric oxide, endothelin-1, and prostacyclin/thromboxane A_2, in patients with pulmonary hypertension, including patients with primary pulmonary hypertension. This has led to the hypothesis that PPH might originate as an endothelial cell injury. In support of this idea, animal models of PPH, such as that caused by monocrotoline, are characterized by endothelial cell dysfunction early in the course of injury. Furthermore, other animal models of repeated endothelial cell injury, such as that related to a-naphthylthiourea, ultimately cause sustained pulmonary hypertension. However, similar changes in endothelial cell-derived vasoactive mediators have been reported in patients with secondary pulmonary hypertension. Thus, it is also possible that reported changes in endothelial cell-derived vasoactive mediators are not causes of pulmonary hypertension *per se* but are markers of some other, underlying, more fundamental abnormality.

Changes in vasomotor tone and vascular reactivity are thought to occur in patients with PPH and to contribute to constriction of the pulmonary vascular bed. In support of this, there have been numerous reports of decreases in pulmonary vascular resistance in PPH in response to pharmacologic vasodilators, which provides the rationale for vasodilator therapy. However, not all patients with PPH respond to vasodilators. It is possible that these “nonresponsive” patients represent a more advanced stage of disease and/or that vascular remodeling has progressed to the point that their vessels are no longer capable of vasodilator responses.

As noted, above, pathologic studies of PPH have shown that thrombosis of pulmonary arteries is a frequent finding. Thus, it is likely that *in situ* thrombosis is an important contributor to pulmonary hypertension in this disease. In support of this, there have been reports of prothrombotic conditions in patients with PPH that may have been inherited or acquired. In addition, anticoagulant therapy may improve the prognosis of PPH.

Finally, vascular remodeling and subsequent restriction of the pulmonary vascular cross-sectional luminal area are a cause of pulmonary hypertension in PPH. The cause of remodeling is not known and likely differs among the various etiologies of PPH. Studies in animal models suggest that endothelial cell dysfunction may play a role. The presence of perivascular inflammatory cell foci in lungs of patients with PPH suggests that inflammation and inflammatory mediators, such as cytokines and oxidants, are also potential causes or perpetuators of the remodeling response.

Clinical Presentation of PPH

The PPH Patient Registry of the NHLBI has provided important information regarding the clinical presentation and natural history of PPH. Dyspnea was the most common presenting symptom, being noted in 60% of patients. Less commonly encountered symptoms were fatigue, chest pain, syncope, leg edema, and palpitations. At the time of diagnosis, the functional class of patients varied from NYHA Class II to severely disabled Class IV. The average time between onset of symptoms and diagnosis was 2 years.

The physical examination of patients with PPH is similar to that of patients with pulmonary hypertension of other causes. Signs of right heart strain and/or failure may be observed, including RV parasternal heaves, right-sided third and fourth heart sounds, tricuspid regurgitant murmurs, and pulmonary ejection and regurgitant murmurs.

The chest roentgenogram (Fig. 5) typically reveals enlargement of the main and hilar pulmonary arteries. A diameter of the right lower lobe pulmonary artery >17 mm is diagnostic of pulmonary hypertension. Pruning of the peripheral vasculature is common. The lung parenchyma is free of infiltrates in primary pulmonary hypertension, as contrasted with pulmonary hypertension secondary to interstitial lung disease. Right ventricular enlargement may be observed when the right ventricle occupies more than one-third of the retrosternal space on the lateral chest x-ray.

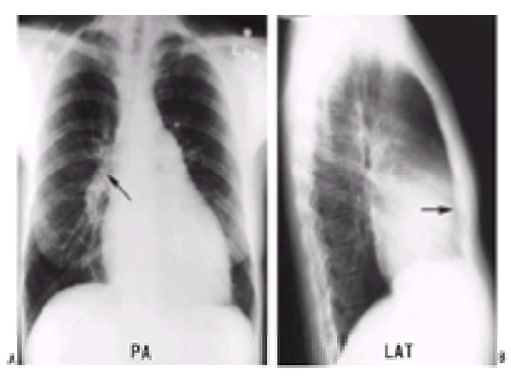

FIG. 5. Chest radiograph of a 47-year-old woman with idiopathic pulmonary hypertension (P_{pa} = 104/40 mm Hg). The hilar vessels *(arrow)* are enlarged on the posteroanterior (PA) view, and there is relative oligemia in the lung periphery. The heart is enlarged, and on the lateral (LAT) view there is filling of the retrosternal air space, indicating right ventricular enlargement.

In most patients, the electrocardiogram shows signs of right heart strain or enlargement, including right axis deviation, right ventricular hypertrophy, and right atrial enlargement. Although atrial fibrillation and other supraventricular tachyarrhythmias are common among patients with cor pulmonale secondary to lung disease, atrial fibrillation was not reported among patients admitted to the PPH Patient Registry.

An echocardiogram showed right ventricular enlargement in 75% of patients, although left ventricular dimensions were normal. Paradoxic septal motion and partial systolic closure of the pulmonic valve are other commonly observed echocardiographic abnormalities. However, some patients may not have signs of pulmonary hypertension on chest x-ray, ECG, or echocardiogram. Thus, these tests are relatively insensitive diagnostic tools. Echocardiography is also important in excluding other causes of pulmonary hypertension, such as mitral stenosis. Transesophageal echocardiography is useful in excluding atrial septal defect as a cause of flow-induced pulmonary hypertension. In addition, Doppler echocardiography may be used to estimate pulmonary artery pressure noninvasively when there is a regurgitant tricuspid jet.

Pulmonary function tests in patients with PPH may be normal but commonly reveal mild restrictive defects and decreases in the diffusing capacity for carbon monoxide. The changes in diffusing capacity may reflect obliteration of pulmonary microvessels by the remodeling process. The critical role of pulmonary function tests is to exclude significant obstructive or restrictive lung disease.

Arterial blood gases typically show mild to moderate arterial hypoxemia and respiratory alkalosis. The hypoxemia is caused by ventilation–perfusion mismatching and a small degree of right-to-left shunt, exacerbated by decreased cardiac output and mixed venous hypoxemia. Some patients may display more significant hypoxemia because of right-to-left shunting through a patent foramen ovale.

Positive tests of “autoimmunity,” such as antinuclear antibodies and rheumatoid factor, and the presence of Raynaud's phenomenon may be observed in patients with PPH. In the PPH Registry, 29% of patients had positive antinuclear antibody tests. These findings suggest an “autoimmune” pathogenesis for at least some cases of PPH.

Perfusion lung scans may be normal or may reveal diffuse patchy areas of decreased perfusion in patients with PPH. The presence of lobar or segmental abnormalities in lung scans suggests major vessel thromboembolism and should prompt further diagnostic investigation for that disorder, such as performance of pulmonary arteriograms.

Hemodynamic Features

Right heart catheterization is necessary for the definitive diagnosis of PPH. Patients in the PPH Patient Registry had severe pulmonary hypertension with increased mean pulmonary artery pressure (60 ± 18 mmHg, range 28 to 127 mmHg), mild to moderate increases in right atrial pressures (9 ± 6 mmHg, range 0 to 29 mmHg), and mildly reduced cardiac indices (2.27 ± 0.9 L/min per m^2, range 0.8 to 7.9 L/min per m^2). Pulmonary capillary wedge pressures were, by definition, normal.

Approach to Diagnosis

The diagnosis of PPH depends on exclusion of other disorders that may secondarily cause pulmonary hypertension. The general approach to diagnosis of the cause of pulmonary hypertension is outlined in Fig. 6.

FIG. 6. This schema illustrates the steps in diagnosis of PPH.

The clinical suspicion of PPH is raised by symptoms of dyspnea on exertion in the absence of other known underlying heart or lung diseases. Physical examination may suggest the presence of pulmonary hypertension by increased intensity of the pulmonic component of the second heart sound or by findings suggestive of right ventricular strain or failure. However, it should be noted that in early cases of PPH, these findings may not be present.

Chest x-ray is important in screening for infiltrative lung diseases and hyperinflation suggestive of COPD. High-resolution chest computed tomography may be useful in screening for occult interstitial lung diseases. Pulmonary function tests are important to exclude moderate or severe degrees of lung restriction or airways obstruction. Arterial blood gas analysis is useful to screen for hypoventilation and hypoxemia as causes of secondary pulmonary hypertension. Oxygen saturation during sleep may be necessary to exclude obstructive sleep apnea.

Echocardiography should be done to exclude mitral valvular disease and to assess RV and LV function. An ECG is useful to assess for signs of RV hypertrophy.

A ventilation–perfusion lung scan should be done to exclude major vessel thromboembolism. In some cases, pulmonary arteriography may be necessary to exclude chronic thromboembolism syndrome as a cause of pulmonary hypertension (see below). Although complications of arteriography are said to be increased in patients with pulmonary hypertension, if the procedure is performed with care by experienced operators, pulmonary hypertension *per se* is not a contraindication.

Right heart catheterization is necessary to confirm the diagnosis of primary pulmonary hypertension and to obtain important prognostic data—right atrial pressure and cardiac index. During catheterization, samples of blood from the superior vena cava, right atrium, right ventricle, and main pulmonary artery should be obtained for measurement of oxygen saturation to exclude left-to-right intracardiac shunting as a cause of pulmonary hypertension. A normal pulmonary capillary wedge pressure measurement excludes left ventricular failure as a cause of pulmonary hypertension.

In some patients, open lung biopsy may be necessary to exclude occult interstitial lung disease or pulmonary vasculitis or to confirm the presence of venoocclusive disease.

Finally, it is useful to obtain exercise studies in order to assess response to treatment in individuals with PPH. The 6-min walk is a simple and useful test, with measurement of the duration and distance of walking as well as changes in oxygen saturation with exercise.

Management of PPH

The pathology of PPH suggests possible areas for therapeutic intervention. The presence of *in situ* thromboses may certainly exacerbate and perpetuate increases in pulmonary vascular resistance. Indeed, a retrospective study suggested that mortality was improved in individuals treated with oral anticoagulation. In addition, mortality was improved in nonresponders to vasodilator therapy who were treated with oral warfarin. Thus, it seems reasonable to treat PPH with warfarin. Animal studies suggest that anticoagulant therapy with heparin-based agents may be more effective in that heparin may inhibit proliferation of medial vascular smooth muscle hypertrophy. However, variability in effectiveness of the antiproliferative properties of heparin preparations precludes routine use of these agents at this time.

Although moderate degrees of hypoxemia have been reported in patients with PPH, there are no firm data that oxygen therapy improves survival with PPH. However, hypoxia may exacerbate pulmonary hypertension via hypoxic vasoconstriction, and hypoxemia is associated with cardiac arrhythmias. Chronic hypoxemia can further exacerbate pulmonary hypertension via secondary erythrocytosis and vascular remodeling. Thus, hypoxemic patients with PPH should be given low-flow oxygen

therapy according to guidelines developed for patients with COPD (see Chapter 43).

Treatment of right heart failure is aimed at relieving symptoms. Diuretics may relieve peripheral edema and hepatic congestion. One should be careful to avoid development of metabolic alkalosis, which could depress ventilation and thereby exacerbate hypoxemia. In addition, because right ventricular function is highly dependent on preload, care must be taken to avoid excessive diuresis and decreased venous return to the right ventricle, with resultant decreased cardiac output and loss of responsiveness to vasodilators. Digitalis is not likely to be of benefit because of potential pulmonary vasoconstrictor effects.

The rationale for vasodilator therapy in PPH is the presence of potentially reversible vasoconstriction as an important cause of pulmonary hypertension. Even small reductions in right ventricular afterload might substantially improve RV output. Vasodilators decrease pulmonary arterial pressures and increase cardiac output in many patients with PPH. In the 1980s there was considerable interest in defining vasodilator responsiveness as a measure of severity and reversibility of PPH and interest in potential long-term beneficial effects of vasodilator therapy. Because all available vasodilators are effective in both the systemic and pulmonary circulations, a problem in vasodilator use has been the frequent complication of systemic hypotension. In addition, most vasodilators increase cardiac output with only mild decreases in pulmonary arterial pressures. Thus, definition of vasodilator effectiveness is problematic—both calculated pulmonary vascular resistance (see Fig. 1) and pulmonary arterial pressures have been used. We favor the conservative approach of defining a vasodilator response as a greater than 30% decrease in calculated pulmonary vascular resistance combined with a greater than 10% decrease in mean pulmonary arterial pressure. The PPH Patient Registry found that about one-third of patients undergoing vasodilator trials had both an increase in cardiac output and a decrease in mean pulmonary arterial pressure, whereas more than half had a decrease in total pulmonary resistance alone.

Some investigators have reported that acute vasodilator-induced decreases in pulmonary vascular resistance are associated with improved survival in PPH. However, long-term therapy with vasodilators was not associated with improved survival among patients in the PPH Registry.

More recent studies have suggested that long-term therapy with high doses of calcium blockers (nifedipine or diltiazem) or continuous infusions of epoprostenol (also called prostacyclin or prostaglandin I_2) may be associated with improved survival. In addition, 12 weeks of continous infusion of epoprostenol improved hemodynamics, symptoms of dyspnea, exercise capacity, and survival in patients with PPH, as compared to patients treated with “conventional therapy.” Thus, there may be a role for vasodilators in relieving symptoms and maintaining patients who are awaiting heart–lung transplantation. Vasodilator therapy should be instituted only after drug effectiveness and safety have been confirmed with right heart catheterization.

Continuous intravenous infusion of epoprostenol currently offers the most effective and best-studied mode of vasodilator therapy. However, infusional therapy is not without complications, mostly related to catheters, such as sepsis, thrombosis, and acute dyspnea associated with interruption of infusion. Other modes of vasodilator delivery may also prove effective, such as inhaled NO or aerosolized epoprostenol.

Heart–lung transplantation or single-lung transplantation offers the best hope for long-term therapy for PPH at this time. Unfortunately, limited donor organs make this therapy unavailable to many patients with PPH. It is reasonable to explore this option if clinical deterioration occurs or if hemodynamic parameters suggest a poor prognosis. However, optimism regarding transplantation must be tempered with recognition of complications of rejection and the potential for recurrence of primary pulmonary hypertension in the transplanted lung.

Survival and Prognosis

Median survival of patients in the PPH Registry was 2.8 years, with 34% of patients alive after 5 years. Thus, PPH is a disease with a poor prognosis.

Several factors were associated with poor survival. Mortality correlated best with measures of right ventricular hemodynamic function. Mean pulmonary arterial pressures over 85 mmHg, mean right atrial pressures over 20 mmHg, and cardiac indices less than 2 liters/min per m^2 were associated with poor survival. Thus, the presence of right ventricular failure indicated a poor prognosis. Accordingly, the risk of death was higher among patients with NYHA functional Class III or IV than among those with Class I or II function at the time of diagnosis. Indeed, survival was only 6 months for those with Class IV function.

Interestingly, the presence of Raynaud's phenomenon was associated with a worse prognosis for unclear reasons. In addition, decreased diffusing capacity also correlated with increased risk of mortality. Recent short-term studies suggest that drug therapy with intravenous infusions of epoprostenol may improve survival (3-month follow-up).

The most frequent causes of death in patients with PPH are progressive right ventricular failure and sudden death. Pneumonia is often fatal because alveolar hypoxia may cause pulmonary vasoconstriction and exacerbate pulmonary hypertension, with resulting inadequate cardiac output and cardiogenic shock. Some possible mechanisms for sudden death in PPH include bradyarrhythmias and tachyarrhythmias, acute pulmonary embolus, pulmonary hemorrhage, and sudden right ventricular ischemia.

PULMONARY HYPERTENSION ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

Pulmonary hypertension may be associated with several connective tissue disorders, including scleroderma, mixed connective tissue disease, systemic lupus erythematosus, and rheumatoid arthritis. The incidence of pulmonary hypertension varies significantly among connective tissue disorders, but when it occurs, it may be devastating. In these disorders, pulmonary hypertension may occur in association with concomitant lung parenchymal disease, but it is also frequently observed in the absence of significant parenchymal lung disease.

As noted above, there is overlap between primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. Female preponderance, similar symptoms on presentation (dyspnea and fatigue), and the frequent presence of restrictive changes in lung volumes, sometimes in the presence of a normal chest x-ray, are findings shared by both groups of patients. Raynaud's phenomenon and elevated rheumatoid factor and ANA titers are also frequently observed in both groups of patients. Despite these similarities, there are notable clinical differences between PPH and pulmonary hypertension associated with connective tissue disease. Patients with connective tissue disease and pulmonary hypertension tend to be older women and to have a much higher incidence of Raynaud's phenomenon. Pulmonary function tests may demonstrate the presence of more severe restrictive disease in patients with connective tissue disease who have concomitant pulmonary parenchymal disease.

Pathology

In addition to the clinical overlap noted above, the connective tissue disease disorders and primary pulmonary hypertension also show similar pathologies. Plexogenic arteriopathy is observed in both groups, suggesting a similar underlying pathogenesis. Intravascular thrombosis, possibly secondary to a hypercoagulable state, may contribute to pulmonary hypertension. An example of such a hypercoagulable state is the presence of circulating antiphospholipid antibodies. Vasculitis, with inflammatory cell infiltrate, has been reported in patients with pulmonary hypertension complicating SLE.

Pathogenesis

The pathology of pulmonary hypertension associated with connective tissue diseases suggests that restriction of the pulmonary circulation by remodeling and obstruction of the microvessels by thromboses are important in its development. Acute hypoxic vasoconstriction and compression of pulmonary vessels by abnormal lung parenchyma may also contribute to the magnitude of the pulmonary hypertension. Responsiveness to vasodilators and spontaneous fluctuation in levels of pulmonary hypertension in some patients suggest that vasoconstriction may also contribute to increased pulmonary vascular resistance.

There is little information available concerning the precise mechanisms of pulmonary hypertension at the cellular level. Elevated plasma levels of endothelin-1 in scleroderma suggest that this potent vasoconstrictor may contribute to pulmonary hypertension in that vasospastic disorder. Circulating anti-endothelial-cell antibodies have been reported in SLE complicated by pulmonary hypertension, suggesting an immunologic pathogenesis. Circulating factors that are toxic to endothelial cells have been reported in scleroderma.

Clinical Presentation

In general, the different connective tissue diseases have similar clinical presentations of pulmonary hypertension. Dyspnea is the most common symptom. Immunologic evaluation is not helpful in distinguishing which patients have pulmonary hypertension or will subsequently develop the condition. Right ventricular enlargement and prominent pulmonary arteries on chest x-ray and ECG findings of right axis deviation and right ventricular hypertrophy may suggest pulmonary hypertension. A severe decrease in diffusing capacity should raise the suspicion of pulmonary hypertension.

Features of Specific Disorders

Scleroderma is the connective tissue disorder in which pulmonary involvement is most frequent and pulmonary hypertension is most commonly observed. Although the exact incidence is not known, clinical studies have demonstrated that in patients with scleroderma undergoing right heart catheterization, the frequency of pulmonary hypertension is approximately 50%. The development of severe pulmonary hypertension culminating in cor pulmonale and death is highest in the CREST variant of scleroderma. The most common pulmonary parenchymal manifestation in this disease is interstitial fibrosis, but the magnitude of the pulmonary hypertension does not correlate well with the degree of fibrosis. In fact, again most notably in the CREST variant, patients may die of malignant pulmonary hypertension without significant pulmonary fibrosis. In accord with the high incidence of pulmonary hypertension by cardiac catheterization, pulmonary vascular pathology is frequently found on pathologic examination. Interestingly, there is a notable absence of plexogenic arteriopathy in the lungs of patients with scleroderma and pulmonary hypertension. This is in contrast with the findings in other connective tissue diseases, which are more similar to those of primary pulmonary hypertension. Endothelial cell injury, intimal and medial cell proliferation, and fibrosis of small arteries and arterioles are the major pathologic lesions. Vasculitis is unusual.

Several studies have confirmed that pulmonary vasoconstriction occurs when the hands of scleroderma patients are immersed in cold water. This has been described as Raynaud's phenomenon of the pulmonary vasculature and is additional evidence of a generalized disorder of vasospasm in these patients.

Mixed connective tissue disease is a syndrome consisting of features of systemic lupus erythematosus, scleroderma, Sjögren's syndrome, and polymyositis. Involvement of the respiratory system in this syndrome occurs in the majority of patients (82%). Pulmonary hypertension and cor pulmonale occur infrequently but are well described and may dominate the clinical course, leading to a fatal outcome. Although pulmonary function tests commonly suggest the presence of interstitial lung disease, pulmonary vasculopathy is typically more prominent than interstitial disease on pathologic examination of lung tissue. This vasculopathy is characterized by intimal thickening and medial hypertrophy of pulmonary arteries and arterioles and the presence of plexiform lesions.

Systemic lupus erythematosus (SLE) involves the respiratory system in 50% to 70% of patients, but the incidence of pulmonary hypertension is significantly lower, ranging from rare to »14%. Noninvasive measurement of pulmonary arterial pressures by repeated Doppler echocardiography studies in patients with SLE suggests that the prevalence of pulmonary hypertension may increase with time after diagnosis of SLE to as high as 43%. When pulmonary hypertension is present, it tends to be mild, with pulmonary artery systolic pressures generally less than 40 mmHg. The pathologic features include intimal and medial hypertrophy and plexiform lesions in more advanced cases. Vasculitis is unusual. The frequent association of antiphospholipid syndrome and SLE suggests that microvascular thrombosis may be an important cause of pulmonary hypertension in SLE.

Rheumatoid arthritis and polymyositis/dermatomyositis may also be complicated by pulmonary hypertension.

Diagnosis

Although decreased diffusing capacity is a sensitive pulmonary function test marker for the presence of pulmonary vascular disease, it is also a nonspecific marker because it may be abnormal in the presence of parenchymal lung disease without a pulmonary vascular component. Because it may be difficult to determine the presence and severity of pulmonary hypertension by clinical assessment and noninvasive laboratory testing alone, right heart catheterization is usually required for definitive diagnosis. However, because there is little evidence for beneficial effects of vasodilator therapy, it is difficult to justify invasive testing merely to document the presence of pulmonary hypertension. Doppler echocardiography is useful as a noninvasive means of estimating pulmonary arterial pressure in patients with regurgitant tricuspid jets.

Treatment

Pulmonary hypertension associated with connective tissue disorders does not typically respond to vasodilator therapy. However, a recent report documented a significant acute vasodilator response to the combination of oxygen and diltiazem administration in a patient with mixed connective tissue disease. Significant beneficial effects were achieved without major adverse side effects and were sustained over 1 year of follow-up. This approach with combined therapy warrants further investigation. Beneficial effects of therapy with corticosteroids and other forms of immunosupressive therapy in isolated case reports suggest some hopeful avenues for future clinical research. Patients with antiphospholipid antibodies and pulmonary hypertension should be treated with anticoagulation, and consideration should be given to plasmapheresis and immunosuppressive therapy as well.

In view of limited evidence of documented efficacy of most approaches to treatment of pulmonary hypertension associated with connective tissue disease, it is important to determine the response to supplemental oxygen administration in individual patients. The contribution of acute hypoxic vasoconstriction to pulmonary hypertension is sometimes difficult to determine from the clinical features alone. This was underscored by recent findings of a substantial reduction in pulmonary artery pressure and resistance following administration of oxygen in patients with scleroderma. These patients were found to have a significant vasodilatory response to oxygen administration compared to the patients with primary pulmonary hypertension, who demonstrated no response to oxygen administration.

PULMONARY HYPERTENSION ASSOCIATED WITH THROMBOEMBOLIC DISEASE

Acute pulmonary thromboembolism rarely causes significant pulmonary hypertension except in the case of massive embolism in which more than half of the pulmonary vascular bed is occluded. In patients with underlying pulmonary or cardiac disease, less vascular obstruction (30% occlusion) may be sufficient to cause pulmonary hypertension. The causes of acute pulmonary hypertension after thromboembolism include vascular obstruction, hypoxic vascoconstriction, and vasospasm caused by vasoactive mediators released from platelets. Most frequently, an embolized clot resolves within 3 weeks of the acute event, and acute thromboembolism rarely causes sustained pulmonary hypertension. The reader is referred to Chapter 66 for a more complete discussion of acute pulmonary thromboembolism.

However, in a minority (perhaps 2%) of patients with pulmonary thromboembolism, there may be repeated episodes of thromboemboli or failure of resolution of clot. These patients may progress to sustained pulmonary hypertension.

An interesting variant of thromboembolic pulmonary disease is chronic thromboembolic pulmonary hypertension (CTEPH). This disorder is characterized by incomplete resolution of proximal pulmonary arterial thrombotic obstruction, with residual recanalized clot and/or scarring. It is thought to result from undiagnosed (and therefore untreated) thromboemboli, with an estimated incidence of 0.5% of patients suffering an acute embolic event.

Pathology and Pathogenesis

Proximal pulmonary arteries are obstructed by fibrotic (“organized”) clot, which may extend to more peripheral vessels in a branching pattern. Pathologic studies of lung biopsies obtained at the time of thromboendarterectomy also revealed involvement of small pulmonary arteries, even in areas of lung unobstructed by proximal clot. The full range of pulmonary hypertensive lesions was demonstrated, including plexiform lesions. Thus, the development of sustained pulmonary hypertension in this disorder results from obstruction to flow in major arteries from proximal, incompletely resolved clot and also remodeling of small resistance arteries. How proximal obstruction causes vascular remodeling is not known.

The hemodynamic consequences of unresolved thromboembolic obstruction to the pulmonary vascular bed are increased pulmonary vascular resistance, leading to pulmonary hypertension and diminished right ventricular contractility. The specific consequences in an individual patient are dependent on the presence of preexisting cardiopulmonary disease.

Clinical Presentation

The clinical presentation of patients with chronic thromboembolic pulmonary hypertension is relatively nonspecific. Clinical suspicion may be raised by repeated episodes of acute thromboembolism, unexplained dyspnea, atrial fibrillation, syncope, or pulmonary hypertension. The presence of underlying cardiopulmonary disease is associated with a higher incidence of unresolved acute pulmonary emboli 1 year after an acute event.

Diagnosis

The diagnosis of chronic thromboembolism must be confirmed with radionuclide ventilation–perfusion lung scans and pulmonary angiography. Ventilation–perfusion lung scans demonstrate at least segmental or larger mismatched defects. This is in contrast to primary pulmonary hypertension, in which ventilation–perfusion scans are normal or demonstrate only patchy, subsegmental defects. Angiographic findings include pouch defects, webbing, banding, and intimal irregularities. These are different from what is most often observed with acute thromboembolic obstruction of the pulmonary circulation, and it is therefore helpful to alert the angiographer of the clinical suspicion of CTEPH. Performance of angiography in the setting of increased pulmonary artery pressure is reasonably safe if only small amounts of nonionic

contrast material and/or selective angiographic injections are used to minimize dye load. This is particularly important in patients with right ventricular failure, which is a recognized risk factor for sudden death during angiography.

Treatment

The clinical importance of recognizing CTEPH is that pulmonary thromboendarterectomy can produce dramatic improvement in hemodynamics and functional status in selected patients. Patients in New York Heart Association functional Class III or IV status can move to Class I or II following operative intervention. However, pulmonary thromboendarterectomy is a technically demanding procedure performed in only a small number of centers. Patients must be carefully selected for optimum results. Overall mortality from this procedure is as high as 10%, even in referral centers. Reperfusion pulmonary edema in areas of clot removal and pulmonary vascular steal (blood flow diversion to areas of lung opened after thromboendarterectomy) may cause postoperative hypoxemia.

All patients must be maintained on lifelong anticoagulant therapy, and some require vena cava interruption as well.

Other Causes of Embolic Obstruction of the Pulmonary Circulation

Schistosomiasis, sickle cell disease, and fat, tumor, and amniotic fluid embolism are other examples of embolic syndromes affecting the pulmonary vascular bed that may cause pulmonary hypertension.

Schistosomiasis is a common cause of pulmonary hypertension in endemic areas and among immigrant populations. Pulmonary hypertension results from a combination of physical obstruction to the pulmonary vascular bed and vasculitis caused by the immunologic response to the foreign protein of the parasite.

Sickle-cell disease and other *mixed hemoglobinopathies* (S-C disease, S-b-thalessemia) commonly involve the pulmonary circulation either acutely or on a chronic basis. The chronic pulmonary vascular manifestations of this disease are most commonly observed in individuals who are long-term survivors. These patients most frequently seek medical attention as a result of the development of the “acute chest syndrome” consisting of fever, pleuritic chest pain, dyspnea, leukocytosis, hypoxemia, and pulmonary infiltrates. Pulmonary vascular occlusions caused by *in situ* thromboses in the pulmonary microcirculation are a frequent component of this syndrome. Accurate differentiation of infection from pulmonary vascular occlusion and/or infarction may be difficult. Mild pulmonary hypertension in this setting may be related to volume overload as a secondary consequence of chronic anemia and changes in blood viscosity. Survivors of the acute chest syndrome may develop chronic pulmonary disease consisting of pulmonary fibrosis, pulmonary hypertension, and cor pulmonale because of the cumulative effects of pulmonary vascular occlusion. This obstructive vasculopathy is thought to be the end result of several key events, notably emboli of necrotic bone marrow, *in situ* thromboses, and endothelial cell damage. In addition to hydration and prompt treatment of infection, the key principle for management of the pulmonary vascular complications of sickle cell disease is maintenance of an adequate oxygen tension. Anticoagulants have no documented role in the management of the *in situ* pulmonary vascular occlusion in these disorders and may be dangerous because of increased risk of spontaneous bleeding in these patients. Exchange transfusions are often used to treat refractory life-threatening hypoxemia. Individuals with sickle trait rarely develop manifestations of pulmonary vascular complications, although anecdotal reports of an increased risk of sudden death during strenous exercise highlight the need for further work in this area.

Fat embolism is a syndrome of pulmonary microemboli of bone marrow occurring most commonly in the setting of trauma and fracture of the pelvic or long bones of the thigh. The pulmonary microvascular disease has been described as a “toxic vasculitis” secondary to the effects of circulating free fatty acids. Although pulmonary hypertension has been reported in these patients, typically gas-exchange (ARDS) and central nervous system abnormalities dominate the clinical picture and the management of this disorder. The same is true for amniotic fluid embolism seen after placental membrane rupture, spontaneous delivery, or cesarean section. Septic pulmonary emboli may complicate bacterial and nonbacterial sepsis but rarely produce clinically significant pulmonary hypertension requiring specific therapy.

Pulmonary granulomatosis associated with intravenous drug use is a syndrome that appears to be increasing in frequency and worldwide distribution. This syndrome is specifically seen in individuals who inject aqueous suspensions of medications intended for oral use. These suspensions contain insoluble materials such as talc that may lodge in the pulmonary microvessels. The lungs of these patients demonstrate the presence of a diffuse vascular and perivascular granulomatous reaction. There is variable occlusion of pulmonary vessels by thrombosis or fibrosis, and plexogenic arteriopathy may be observed in severe cases. Over time, there may be transvascular migration of the foreign body emboli with the formation of interstitial granulomas, interstitial fibrosis, and pulmonary hypertension. The initiating factor is thought to be endothelial injury induced by the foreign body microemboli, such as talc. Other substances, including cotton fibers, cornstarch, and cellulose may also play a role. Clinically, these patients present with progressive dyspnea, diffuse reticular-nodular infiltrates on chest x-ray, and either obstructive or restrictive changes in PFTs with a low diffusing capacity. Only a small percentage of patients with this syndrome go on to develop clinically significant pulmonary hypertension.

PULMONARY VENOOCCLUSIVE DISEASE

Pulmonary venoocclusive disease (PVOD) is an unusual disorder of unknown etiology that is characterized by clinical and pathologic evidence of occlusion of postcapillary veins and venules; it may account for about 10% of cases of pulmonary hypertension of unknown etiology. This idiopathic disorder occurs in children and young adults, but its rarity has hampered the study of its epidemiology and demographics.

Pathology

Pulmonary venoocclusive disease is characterized by organized and recanalized thrombi in pulmonary veins and venules with eccentric fibrosis of the intima and medial hypertrophy and arterialization of veins (Fig. 3 and Color Plate 2). Alveolar capillaries are congested with blood. There are findings consistent with long-standing hydrostatic pulmonary edema, such as lymphatic dilation and interstitial edema. Because precapillary arterioles may also demonstrate intimal fibrosis and fibrinoid necrosis of media, it is possible that this disease is actually a more generalized obstructive angiopathy.

Pathophysiology

Obstruction of the pulmonary venous system in venoocclusive disease increases pulmonary artery pressure and resistance in the absence of an elevation of left ventricular end-diastolic pressure. Passive increases in venous pressure, thrombotic obstruction of microvessels, and remodeling of pulmonary arteries all contribute to pulmonary hypertension in PVOD.

Clinical Presentation and Diagnosis

Patients usually present with dyspnea. The major clinical challenge is establishing the diagnosis of PVOD and distinguishing it from other, more common conditions. Pulmonary venoocclusive disease may simulate congestive heart failure with interstitial and alveolar edema and pulmonary vascular congestion on chest x-ray. The absence of distended upper lobe veins or left ventricular enlargement are important clues to the presence of PVOD as a cause of pulmonary edema. Other causes of pulmonary venous obstruction, such as fibrosing mediastinitis and congenital venous atresia or stenosis, should be excluded. In addition, it may be difficult to distinguish PVOD from primary pulmonary hypertension. In many patients with PVOD, pulmonary capillary wedge pressure is normal with elevated P_{pa}, suggesting that the site of obstruction is in venules rather than large veins. Finally, the presence of basilar rales and interstitial infiltrates on chest x-ray in some patients with PVOD may lead to an incorrect diagnosis of interstitial fibrosis. Because of these difficulties in distinguishing among these conditions, open lung biopsy is necessary to unequivocally diagnose PVOD.

Treatment

There is no documented effective treatment for PVOD. Uncontrolled case reports suggest that anticoagulants, aspirin, steroids, azathioprine, calcium channel blockers, or prostacylin may have some benefit. Vasodilators are probably not indicated in these patients. Pulmonary vasodilation in the presence of venous obstruction may cause an increased pulmonary blood volume and pulmonary microvascular pressures and the development of pulmonary edema.

In addition to the idiopathic form of pulmonary venoocclusive disease, there are sporadic reports of other clinical associations. An acquired variant of this disorder is drug-induced pulmonary vascular disease (e.g., caused by bleomycin, BCNU, or mitomycin) with typical findings of pulmonary venoocclusive disease on pathologic exam. Other reported clinical associations include bone marrow transplantation, malignancy, and an unexplained genetic predisposition for this disorder, suggested by the finding of documented cases of pulmonary venoocclusive disease in siblings.

PULMONARY HYPERTENSION ASSOCIATED WITH HIV INFECTION

Pulmonary hypertension was first reported as a complication of human immunodeficiency virus infection in 1987. Since then, over 50 patients have been reported with

this complication of HIV infection from all causes. The estimated incidence of pulmonary hypertension in patients with HIV infection (0.5%) is higher than the estimated incidence of primary pulmonary hypertension (0.02%) in the general population, suggesting that the viral infection itself is somehow causally linked to the development of pulmonary hypertension. A direct or indirect effect of the virus on either pulmonary arterial smooth muscle cells or endothelial cells has been postulated. However, no clear evidence of arterial wall infection with HIV virus has been found in a small number of carefully examined cases.

In a recent review of published reports, only 33% of patients with HIV-associated pulmonary hypertension had AIDS. Most patients are normoxic, and CD4 lymphocyte cell counts may be normal. Thus, the pulmonary hypertension is not caused by concomitant respiratory infections. Patients with HIV-associated pulmonary hypertension demonstrate pathologic changes similar to primary pulmonary hypertension, including plexigenic arteriopathy.

Comparison of the clinical characteristics of patients with HIV-associated pulmonary hypertension with those of patients with primary pulmonary hypertension has demonstrated very few distinguishing characteristics. Although the magnitude of the pulmonary hypertension may be less severe at the time of presentation in HIV-associated pulmonary hypertension, the presence of Raynaud's phenomenon and the percentage of patients who respond to vasodilator therapy appear to be similar in both groups. Overall survival is poor in both groups of patients. Because of these similarities, HIV testing should be considered in cases of PPH for which no other associated cause is evident.

There has not been sufficient therapeutic experience in patients with HIV-associated pulmonary hypertension to make any definitive recommendations. Obviously, hypoxemia and concomitant lung infections should be treated aggressively.

PULMONARY HYPERTENSION ASSOCIATED WITH CARDIAC DISEASE

In general, pulmonary hypertension associated with heart disease is caused by increased pulmonary venous pressure or by increased pulmonary blood flow, both of which passively increase pulmonary artery pressure (see Chapter 67). Increased vascular reactivity to vasoconstrictors may result from long-standing increased flow or pressure. Eventually, the pressure or flow abnormalities cause pulmonary vascular remodeling, which perpetuates increased vascular resistance by further narrowing the pulmonary arterial cross-sectional area. In addition, pulmonary thromboemboli may complicate low-flow states or the sedentary life style that may be associated with cardiac disease. Thus, several factors may contribute to pulmonary hypertension associated with heart diseases.

Left Ventricular Failure

Left ventricular failure is the most common form of pulmonary venous hypertension in both adults and children. Causes of left ventricular failure include coronary artery disease and cardiomyopathies.

Left ventricular failure passively increases pulmonary artery pressure because of altered pressure–flow relationships in the pulmonary circulation, which occur in stages. The first stage begins with an increase in left ventricular end-diastolic pressure, which increases pulmonary blood volume until the pulmonary vascular bed is fully recruited. At this point, any additional increase in left ventricular end-diastolic pressure will increase pulmonary artery pressure. If pulmonary artery pressure rises to the point at which the critical microvascular pressure (~25 mmHg) is exceeded, fluid accumulates in the pulmonary interstitial compartment. As this process continues, alveolar edema formation begins with loss of lung volume and a further increase in pulmonary vascular resistance related to compression of small pulmonary vessels by the accumulating alveolar edema fluid. Localized hypoxic vasoconstriction may also contribute to the increase in pulmonary artery pressure at this stage. These acute changes are readily reversible with resolution of the left ventricular dysfunction, assuming there has been no overt damage to the pulmonary vascular bed.

Mitral stenosis secondary to rheumatic heart disease is also associated with pulmonary hypertension caused by sustained increases in pulmonary venous pressure. Pulmonary hypertension results from passively increased pulmonary artery pressure and from remodeling of pulmonary arteries and veins. Pathologic changes include medial hypertrophy and fibrosis of pulmonary arteries and veins. The pulmonary hypertension associated with this acquired cardiac condition is usually reversed after valve replacement.

Congenital Cardiac Disease

Pulmonary hypertension is a common manifestation of congenital heart disease. The unifying pathogenetic feature in these congenital abnormalities (ventricular septal defect, atrial septal defect, patent ductus arteriosus) is that there is a chronic increase in blood flow through the pulmonary vascular bed as a result of left-to-right shunting (“high-flow states”). Over time, if the primary defect is not corrected, pulmonary vascular resistance progressively increases following structural changes in the pulmonary arteries. The elevation of pulmonary vascular resistance ultimately may reverse the direction of shunt blood flow, with subsequent development of cyanosis and severe exercise intolerance (Eisenmenger's syndrome).

The morphologic changes in pulmonary vessels are initiated by the primary pathologic increase in pulmonary blood flow through the shunt. The progression of pathologic changes correlates with the increase in pulmonary vascular resistance (see Table 2). Reversible changes include the development of medial hypertrophy and intimal hyperplasia (grades I and II). As pulmonary vascular resistance increases, the vascular lumen is occluded by progressive intimal hyperplasia and, ultimately, by formation of plexiform lesions (grades III and IV). Plexiform lesions and fibrinoid necrosis represent advanced, irreversible changes (grades IV and V). Recent work has emphasized an important relationship between the development of the changes in the pulmonary vascular bed and altered lung growth. Thus, the early pathologic effects of chronic high-flow states on the pulmonary vasculature are now recognized as changes in the normal pattern of pulmonary vascular growth and development. Medial smooth muscle hypertrophy or extension of vascular smooth muscle into peripheral pulmonary arteries, diminished size and number of peripheral pulmonary arteries, and an increase in intercellular connective tissue proteins in the vessel walls are all aspects of an altered pattern of pulmonary vascular growth. It appears that both microvascular endothelial cells and smooth muscle cells produce factors that modulate cell growth in response to pulsatile flow and that may be altered by shear stress from increased blood flow.

A detailed discussion of the treatment of congenital cardiac disease is beyond the scope of this chapter. The basic treatment is surgical repair of the lesion before severe pulmonary hypertension occurs. The rapidity with which pulmonary hypertension develops in these syndromes is dependent on the anatomic site of the left-to-right shunt. Pulmonary hypertension develops only after many years in patients with atrial septal defects, whereas ventricular septal defects are associated with the development of pulmonary hypertension in early childhood. In addition, variability in the rapidity of the development of pulmonary hypertension with a specific cardiac defect among different patients suggests a genetic predisposition for the risk of development of pulmonary vascular disease. Other factors in addition to blood flow, such as increased pressure and shear stress, probably interact and contribute to the development of pulmonary vascular disease and pulmonary hypertension in this patient population. Detection of congenital cardiac abnormalities before the development of severe pulmonary vascular disease is a key component of care. Patients who have already developed severe pulmonary vascular disease may not be helped by surgery at a late disease stage. In fact, they may experience further clinical deterioration following surgery related to the presence of advanced pulmonary vascular disease.

Diagnosis

Pulmonary hypertension caused by cardiac disease usually presents with symptoms and signs referrable to the underlying disease. Dyspnea on exertion, syncope, and arrhythmias may all be seen. Echocardiography is an effective means of screening for the presence of heart disease, with examination of mitral valvular and left ventricular function. Transesophageal echocardiography may be useful in diagnosis of septal defects. A Doppler flow study, in conjunction with infusion of saline or bubbles, may reveal transseptal shunts. As noted above, sampling of blood for oxygen saturation at the time of right heart catheterization is necessary to exclude left-to-right intracardiac shunts. Increased pulmonary vascular wedge pressures and decreased cardiac output are diagnostic of pulmonary hypertension associated with left ventricular failure.

PULMONARY HYPERTENSION ASSOCIATED WITH LUNG DISEASE

Lung diseases are the most common causes of pulmonary hypertension. Patients with pulmonary hypertension associated with lung disease typically present with symptoms and signs related to the underlying lung disease. This form of secondary pulmonary hypertension is not generally observed until the lung disease is severe, as assessed by pulmonary function testing. The prognosis is generally determined by the underlying lung disease, although the presence of pulmonary hypertension is an unfavorable prognostic sign.

Chronic Obstructive Pulmonary Disease

Several mechanisms contribute to the development of pulmonary hypertension in patients with chronic obstructive pulmonary disease. The most important initiating factor, discussed earlier in this chapter, is alveolar hypoxia leading to acute hypoxic vasoconstriction and a resultant elevation in pulmonary artery pressure and resistance. Global alveolar hypoxia causes generalized vasoconstriction, which may help to recruit additional parts of the underutilized pulmonary vascular space for participation in gas exchange. Sustained alveolar hypoxia causes vascular smooth muscle hypertrophy and remodeling of the pulmonary circulation (Fig. 3 and Color

Plate 1B). If the elevated pulmonary artery pressure is sustained, then sustained increased right ventricular work is required to maintain cardiac output at the same normal level over time.

Several other mechanisms contribute to the development of pulmonary hypertension in COPD. Destruction of the pulmonary vascular bed decreases pulmonary cross-sectional area as a direct result of the disease process and thereby contributes to the elevation in pulmonary artery pressure. Increased lung volume has complex effects on pulmonary vessels. Pressure in the extraalveolar vessels (vessels not exposed to alveolar pressure) may actually fall with the increase in lung volume related to the “tethering effect” of being pulled open by the hyperinflated lung. However, the net effect of increased lung volume is increased pulmonary artery pressure and vascular resistance as a result of compression of alveolar vessels by the raised intraalveolar pressure. Potentiation of hypoxic vasoconstriction by additional vasoconstrictor stimuli, such as acidosis associated with hypercapnia, increased blood viscosity that may accompany polycythemia, and increased platelet aggregation within the pulmonary vasculature, may also contribute to pulmonary hypertension.

Pulmonary hypertension in patients with COPD is multifactorial in origin, with sustained alveolar hypoxia being the most important initial stimulus triggering the acute and chronic events culminating in an elevated pulmonary artery pressure. In general, pulmonary hypertension in patients with COPD correlates with the severity of the underlying lung disease. There is no significant correlation between pulmonary hypertension and resting P_aO_2 or P_aCO_2. Pulmonary artery pressure also increases during exercise, indicating a limited ability of the structurally compromised pulmonary vascular bed to accommodate the normal increase in pulmonary blood flow during exercise. The contribution of this exacerbation of pulmonary hypertension during exercise to morbidity and mortality in patients with COPD is not well defined.

Another factor that may exacerbate the development of pulmonary hypertension in COPD is worsened hypoxemia during sleep. Nocturnal oxygen desaturation is very common in this patient population; the most severe episodes occur during REM sleep. Although the cause of the hypoxemia during sleep is probably multifactorial, the most important contributing factor is centrally mediated hypoventilation during REM sleep. Nocturnal hypoventilation is thought to reflect the diminished contribution of the rib cage to ventilation secondary to hypotonia of the intercostal muscles. In addition to hypoventilation during REM sleep, these patients also commonly demonstrate a significant reduction in normal central regulation of ventilation, with decreased ventilatory response to hypoxia and hypercapnia. There may also be a familial component to the postulated altered sensitivity of this brainstem control of ventilation, which can be exacerbated by drugs or alcohol. Other possible contributing factors to sleep-related hypoxemia are decreased lung volume (FRC) and worsening of ventilation–perfusion imbalance.

The net result is that diminished alveolar ventilation during sleep may cause profound oxygen desaturation for prolonged times on a recurring basis (“episodic hypoxia”) in association with a significantly increased pulmonary artery pressure. In the available studies that have actually measured the changes in pulmonary hemodynamics during sleep, episodes of oxygen desaturation were accompanied by increases in pulmonary artery pressure ranging from 10 to 20 mmHg. The increases in pulmonary artery pressure were reversed when oxygen saturation returned to baseline, linking oxygen desaturation to the altered pulmonary hemodynamics. Thus, sustained pulmonary hypertension in COPD may be caused by these recurring episodes of oxygen desaturation, which further increase pulmonary artery pressure. Studies in animal models lend support to the notion that intermittent, cyclic decreases in oxygen saturation may increase pulmonary artery pressure more than continuously decreased saturation. Nevertheless, the overall contribution of the alterations in pulmonary hemodynamics during sleep to the magnitude of pulmonary hypertension and the overall clinical course of patients with COPD remain undefined.

The clinical manifestations of pulmonary hypertension in COPD are synonomous with the signs and symptoms of cor pulmonale discussed in detail in Chapter 67. It is important to remember that the clinical signs of cor pulmonale, including evidence of right ventricular enlargement and pulmonary hypertension, may be obscured by the presence of severe lung disease, specifically hyperinflation. Auscultation of a right-sided S_3 or a loud P_2 may be difficult to appreciate in the patients with overdistended lungs. Similarly, right ventricular enlargement on chest x-ray may be obscured by hyperinflation. Hyperinflation may displace a normal liver, which may be mistaken for hepatic enlargement compatible with passive congestion on physical exam.

Determining whether the etiology of increased dyspnea in an individual patient is secondary to left heart failure or an exacerbation of airways disease is always a challenge. Finally, chest pain secondary to right ventricular ischemia and syncope are two additional symptoms associated with pulmonary hypertension that may also occur in patients with cardiac disease.

Restrictive Lung Disease

In this category we consider diseases of the lung parenchyma, such as idiopathic pulmonary fibrosis, asbestosis and other pneumoconioses, and a group of heterogeneous disorders that share the common feature of loss of lung volume that is not the direct result of a primary disease process affecting the lung parenchyma. This latter category includes thoracic cage deformities, diaphragm weakness, neuromuscular disorders, and diseases of the spinal cord.

The mechanisms leading to the development of pulmonary hypertension in chronic interstitial lung disease are similar to those discussed above for obstructive disease. Hypoxic vasoconstriction, compression and/or obliteration of lung vessels by fibrosis with loss of lung volume, and destruction of vascular surface area all contribute to pulmonary hypertension. The relationship between lung volume and pulmonary vascular resistance in parenchymal restrictive lung disease is well defined. Typically, vital capacity <50% of predicted is associated with the presence of pulmonary hypertension at rest, whereas vital capacity between 50% and 80% of predicted is associated with the development of pulmonary hypertension only during exercise. In restrictive parenchymal disease, the major anatomic site of this increase in pulmonary arterial pressure and vascular resistance is the extraalveolar vessels, which are no longer tethered open as lung volume falls.

There are two important mechanisms for the development of pulmonary hypertension in thoracic cage deformities, diaphragmatic disorders, neuromuscular disease, and spinal cord injury. In all of these disorders, loss of lung volume imposes a mechanical or anatomic limitation on the patient's respiratory system. Critical loss of lung volume can cause alveolar hypoventilation, with consequent decreases in alveolar oxygen tension and hypercapnia providing the stimuli for pulmonary vasoconstriction and pulmonary hypertension. In addition, superimposed conditions, such as atelectasis or infection, alter ventilation–perfusion relationships and help to maintain hypoxic vasoconstriction. In many thoracic cage disorders (kyphoscoliosis, thoracoplasty, or restrictive pleural disease), there is compression of lung vessels related to loss of lung volume, which also increases pulmonary artery pressure and resistance, as described under obstructive disease. Long-standing hypoxia causes remodeling of the pulmonary circulation, as described above, which also contributes to loss of pulmonary vascular cross-sectional area.

Treatment

Treatment of patients with secondary pulmonary hypertension should be focused on correction of the underlying respiratory system abnormality.

Supplemental oxygen can correct arterial hypoxemia and reduce pulmonary arterial pressure and vascular resistance associated with both obstructive and restrictive lung diseases. The rationale for this therapy emerged from the findings of several studies demonstrating that the overall prognosis and survival of patients with chronic obstructive pulmonary disease are correlated with the presence and severity of pulmonary hypertension. Patients with a pulmonary vascular resistance greater than 550 dyne-sec-cm^{-5} have an overall prognosis that is the equivalent of inoperable lung cancer.

The finding that the acute administration of supplemental oxygen to patients with advanced COPD reduced pulmonary artery pressure opened a new chapter in the use of oxygen as a therapeutic agent on a chronic basis. The acute administration of oxygen to patients with COPD produces significant, moderate reductions in pulmonary artery pressure and resistance. Pulmonary artery pressure does not return to normal immediately in many patients, probably because of morphologic changes in the walls of blood vessels and obliteration of the pulmonary vasculature secondary to the disease process. The efficacy of prolonged oxygen therapy for chronic bronchitis and emphysema has been unequivocally established in clinical trials by the Nocturnal Oxygen Therapy Trial Group and the British Medical Research Council Working Party. Reductions in pulmonary artery pressure and vascular resistance and long-term mortality were observed in both studies, although the reductions in pulmonary vascular resistance were modest.

These latter findings suggest that the survival benefit cannot be attributed solely to changes in pulmonary hemodynamics. The basis for this survival benefit remains undefined, but oxygen therapy is the only approach to date that has been shown to prolong life in patients with COPD. Supplemental oxygen administration does not change lung function. Maximal vasodilatory effects are observed with continuous oxygen administration (>16 hrs/day), especially during sleep. Prolonged administration of oxygen for weeks further decreases mean pulmonary artery pressure, suggesting that supplemental oxygen therapy not only reverses hypoxic vasoconstriction but may partially reverse some of the morphologic changes in the pulmonary vessels. The indications for home oxygen therapy are discussed in Chapter 43.

The long-term efficacy of supplemental oxygen administration in restrictive lung disease has never been validated in prospective clinical trials. There are far fewer patients with advanced restrictive disease who develop pulmonary hypertension and cor pulmonale, perhaps because of advanced underlying lung disease culminating in death. Many of the mechanisms of pulmonary hypertension are undoubtedly similar. Therefore, in the absence of evidence that this approach is contraindicated or ineffective, it is reasonable to administer supplemental oxygen to appropriately hypoxemic patients with restrictive lung disease.

Obviously, patients with chest wall disorders causing restriction and hypoventilation require treatment of hypoventilation, including (potentially) mechanical ventilation.

There is continuing controversy regarding the benefits of vasodilator treatment of pulmonary hypertension secondary to pulmonary disease. On the one hand, pulmonary hypertension often worsens during an exacerbation of chronic obstructive pulmonary disease in relation to superimposed acute hypoxemia and hypercarbia and may contribute to the deterioration of right heart function and symptoms of right heart failure. This rationale for pharmacologic treatment of pulmonary hypertension in COPD patients is weakened by the lack of selective pulmonary vasodilators and the potential for worsening of the matching of ventilation and perfusion, resulting in further decreased arterial oxygen tension. In addition, systemic hypotension and tachycardia may be significant side effects. Thus, vasodilator therapy is not recommended for pulmonary hypertension secondary to COPD or restrictive lung disease.

PULMONARY HYPERTENSION ASSOCIATED WITH SLEEP-RELATED BREATHING DISORDERS AND PRIMARY DISORDERS OF HYPOVENTILATION

Many patients with severe obstructive sleep apnea demonstrate periodic elevations in pulmonary artery pressure that are preceded by oxygen desaturations. These reversible oscillations of pulmonary artery pressure are initiated by decreased oxygen tension and thus represent examples of acute hypoxic vasoconstriction. Despite these periodic oscillations of pulmonary artery pressure, sustained pulmonary hypertension does not develop in the majority of patients with obstructive sleep apnea alone. Development of sustained daytime pulmonary hypertension also does not correlate with the severity of the sleep-related breathing disorder alone (i.e., the number or frequency of apneic events). Several studies have demonstrated that sustained pulmonary hypertension requires the presence of daytime hypoxemia and hypercapnia. Thus, the patients with obstructive sleep apnea who are at greatest risk for the development of resting, daytime pulmonary hypertension are those with underlying obstructive or restrictive lung disease, associated abnormalities of ventilatory control, or obesity.

The most important etiologic factors that contribute to the initiation and maintenance of pulmonary hypertension in these patients are hypoxic vasoconstriction and the added vasoconstrictor stimulus of respiratory acidosis from hypercapnia. Another potential contributor to pulmonary hypertension is increased venous return caused by generation of significant negative intrathoracic pressure during breathing with an obstructed airway. The development of pulmonary hypertension in primary alveolar hypoventilation or the obesity hypoventilation syndrome is also dependent on the development of alveolar hypoxia and acidosis, as noted above for obstructive sleep apnea. Correction of the primary process leading to oxygen desaturation and/or hypoventilation will reverse pulmonary hypertension in these disorders.

SUMMARY

The pathophysiology of pulmonary hypertension includes both functional and structural changes in the pulmonary circulation. Functional alterations that increase pulmonary vascular resistance include increases in blood flow, pulmonary venous pressure, and blood viscosity and increased reactivity of vascular smooth muscle to vasoconstrictor and decreased reactivity to vasodilator stimuli. Factors that decrease aggregate pulmonary arterial cross-sectional diameter also increase pulmonary vascular resistance; these include vascular obstruction, vasoconstriction, vessel obliteration, and vascular remodeling. Pulmonary hypertension is the end result of one or more of these pathophysiological changes that occur in response to primary or secondary pulmonary vascular diseases. Thus, the diagnostic approach to the patient with suspected pulmonary hypertension is to evaluate for underlying heart or lung diseases that might cause pulmonary hypertension. The diagnosis of “primary” pulmonary hypertension can be made only in the absence of secondary causes. Therapy is directed at the underlying heart or lung disease in patients with secondary pulmonary hypertension. Oxygen is the treatment of choice for hypoxemic patients. Patients with primary pulmonary hypertension may benefit from treatment with anticoagulants, lung transplant, or, in selected cases, vasodilator therapy.

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CHAPTER

66 Thromboembolic Syndromes

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INTRODUCTION

Pulmonary embolism results in death in approximately 150,000 patients per year in the United States and contributes to death in another 150,000 patients. After acute myocardial infarction and stroke, pulmonary embolism is the third most common cause of cardiovascular death. It is the most common preventable cause of death in hospitalized patients. Venous thromboembolism (pulmonary embolism and/or venous thrombosis) frequently develops in hospitalized patients with one or more comorbid disorders, but this condition may also develop in otherwise healthy individuals who have undergone orthopedic surgery or trauma or who are pregnant. Although effective prophylaxis is available for most of these situations, venous thromboembolism can occur unexpectedly in ambulant patients, particularly if they have been exposed to risk factors in the preceding months. When venous thromboembolism occurs, it is important that appropriate objective testing be performed so that an accurate diagnosis can be established and treatment can be instituted immediately. A massive pulmonary embolus may be the first indication that venous thromboembolism has occurred. This can, unfortunately, be fatal within a short time in up to a third of patients.

This chapter highlights practical approaches to the diagnosis and treatment of venous thromboembolism. It covers the use of anticoagulants, thrombolysis, embolectomy, and vena cava filters.

PATHOGENESIS OF VENOUS THROMBOEMBOLISM

Factors that predispose an individual to the development of venous thromboembolism are shown in Table 1. Deep venous thrombosis usually arises in the deep veins of the calf muscles or, less commonly, in the proximal deep veins of the leg. When deep venous thrombosis remains confined to the calf veins, it is associated with a low risk of clinically important pulmonary embolism. However, without treatment, approximately 20% of calf-vein thrombi extend into the proximal venous system, where they may pose a serious and potentially life-threatening disorder. Untreated proximal venous thrombosis is associated with a 10% risk of fatal pulmonary embolism and at least a 50% risk of pulmonary embolism or recurrent venous thrombosis. In addition, the postphlebitic syndrome is associated with extensive proximal venous thrombosis and carries its own long-term morbidity. Pulmonary emboli in most cases (90%) originate from thrombi in the deep venous system of the legs. Less common sources of pulmonary embolism include the deep pelvic veins or renal veins, the inferior vena cava, the right heart, and occasionally the axillary veins. The clinical significance of pulmonary embolism depends on the size of the embolus and the cardiorespiratory reserve of the patient.

Clinical risk factors
Surgical and nonsurgical trauma
Previous venous thromboembolism
Immobilization
Malignant disease
Heart disease
Leg paralysis
Age (>40)
Obesity
Estrogens
Parturition
Inherited or acquired abnormalities
Activated protein C resistance
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Anticardiolipin syndrome
Heparin-induced thrombocytopenia

TABLE 1. *Factors predisposing to the development of venous thromboembolism*

Venous thromboembolism is generally considered to be a single disorder. Therefore, the diagnostic approach may initially focus on the legs or the lungs, and testing starts with the least invasive methods and proceeds to more invasive methods. The treatment of venous thrombosis or pulmonary embolism is basically the same.

CLINICAL FEATURES

The clinical features of venous thrombosis include leg pain, tenderness and swelling, a palpable cord, discoloration, venous distention and prominence of the superficial veins, and cyanosis. None of the symptoms or signs is unique, and each may be caused by nonthrombotic disorders. This makes the clinical diagnosis of venous thrombosis highly nonspecific. Some patients with relatively minor symptoms and signs may have extensive deep venous thrombi. Other patients may have florid leg pain and swelling suggestive of extensive deep venous thrombosis, but objective testing may produce negative results. Thus, objective testing is mandatory to confirm or exclude a diagnosis of venous thrombosis.

Pulmonary embolism may present clinically in various ways, depending on the size, location, and number of emboli and on the patient's underlying cardiorespiratory reserve. In general, the clinical manifestations of acute pulmonary embolism can be divided into several syndromes that overlap considerably. There may be (1) transient dyspnea and tachypnea in the absence of other associated clinical manifestations; (2) the syndrome of pulmonary infarction or congestive atelectasis (also known as ischemic pneumonitis or incomplete infarction), including pleuritic chest pain, cough, hemoptysis, pleural effusion, and pulmonary infiltrates on the chest x-ray; (3) an assortment of less common and highly nonspecific clinical features such as confusion and coma, pyrexia, wheezing, resistant cardiac failure, and unexplained arrhythmia; or (4) acute massive pulmonary embolism.

In patients with acute massive pulmonary embolism, there is usually a dramatic presentation: a sudden onset of severe shortness of breath, hypoxemia, and right ventricular failure. Symptoms include central chest pain (often identical to angina), severe dyspnea, and, frequently, syncope, confusion, or coma. Examination reveals

a patient in severe distress with tachypnea, cyanosis, and hypotension. The marked increase in pulmonary vascular resistance leads to acute right ventricular failure with the presence of large A waves in the jugular veins and a right ventricular diastolic gallop. When pulmonary hypertension is present, there is marked right ventricular dilation with a shift of the intraventricular septum, decreasing cardiac output, and a further decreasing coronary perfusion. This frequently results in cardiorespiratory arrest. If patients with a massive pulmonary embolus survive, they are acutely threatened by any further pulmonary thromboembolism.

It is now widely accepted that the clinical diagnosis of pulmonary embolism is highly nonspecific. Multiple studies indicate that this diagnosis is not confirmed by objective testing in more than half of all patients with clinically suspected pulmonary embolism.

Patients given a clinical diagnosis of either deep vein thrombosis or pulmonary embolism have been assessed for clinical probabilities of the diagnosis before objective testing. Although such pretest probabilities have been useful in the hands of experienced clinical investigators, they still require further assessment by prospective studies before their use can be generalized. At the present time, algorithms involving objective tests must be used to establish the diagnosis for a large proportion of patients with suspected venous thromboembolism.

LABORATORY FEATURES

A number of laboratory abnormalities have been associated with venous thromboembolism. These include increased levels of fibrinopeptide A and fibrinogen degradation products, thrombin–antithrombin complexes, prothrombin fragment 1.2, and D-dimer. Patients with venous thromboembolism frequently have other comorbid conditions including cancer, recent surgery or trauma, infection, and inflammation. Also, many of the laboratory changes associated with venous thromboembolism are highly nonspecific.

The D-dimer assay has been evaluated in several studies of patients who had clinically suspected deep vein thrombosis that was later confirmed by objective testing. D-dimers can be measured by ELISA or by latex agglutination assays. When the appropriate cutoff is used, the negative predictive value of these tests is very high in patients with suspected venous thromboembolism. Several of these assays have a rapid turnaround time, and some of them are quantitative, so that they can now be studied in a prospective fashion in patients with suspected venous thromboembolism.

OBJECTIVE TESTS FOR THE DIAGNOSIS OF VENOUS THROMBOEMBOLISM

Ancillary Tests

Various ancillary tests such as the chest x-ray, arterial blood gas measurement, and the electrocardiogram, as well as laboratory tests for fibrinopeptide A, D-dimer, and serum lactate dehydrogenase, have a role in the diagnosis of venous thromboembolism, but they all lack sensitivity and specificity. The main role of these tests is to rule out other conditions that may mimic pulmonary embolism. Such conditions are acute myocardial infarction, pneumonia, or pneumothorax. In the case of venous thrombosis, objective tests include B-mode ultrasound, duplex ultrasonography, color flow ultrasonography, impedance plethysmography (IPG), and ascending venography. For the diagnosis of pulmonary embolism the objective tests include ventilation/perfusion lung scanning and pulmonary angiography.

Ultrasonography

Venous imaging using real-time B-mode ultrasound, with or without Doppler assessment, is a promising technique for evaluating patients with clinically suspected deep venous thrombosis. As shown in prospective studies, the single criterion of vein compressibility is highly sensitive and specific for proximal venous thrombosis (sensitivity and specificity both greater than 95%). Other criteria, such as echogenicity or change in venous diameter during a Valsalva maneuver, are less useful: the visualization of an echogenic band is highly sensitive but nonspecific (specificity 50%), and the percentage of change in venous diameter during a Valsalva maneuver is both insensitive and nonspecific.

Real-time B-mode venous ultrasound is insensitive for isolated calf-vein thrombosis, and, as with IPG, serial testing is required to detect patients who develop proximal extension. B-mode venous ultrasound may fail to detect isolated iliac vein thrombi. This is a practical clinical limitation in patient groups in whom isolated iliac-vein thrombosis is not uncommon, such as the pregnant patient with clinically suspected venous thrombosis. Color flow imaging and other technological advances have improved the ability of B-mode venous imaging to detect isolated iliac-vein thrombi and calf-vein thrombi.

Doppler ultrasound is highly sensitive and specific for diagnosing proximal venous thrombosis in symptomatic patients. Doppler ultrasound is more sensitive than IPG in symptomatic calf-vein thrombosis and in proximal venous thrombosis in patients with increased central venous pressure or with arterial insufficiency. Doppler ultrasound can be used in a patient whose leg is in a plaster cast or externally fixed, who is in traction, or who has had a leg amputated. Ultrasonography lacks both sensitivity and specificity for the detection of asymptomatic venous thrombosis in postoperative patients. Ascending venography remains the only reliable test for the detection of venous thrombosis in the high-risk patient or for clinical trials.

Impedance Plethysmography

Impedance plethysmography (IPG) is sensitive and specific for proximal venous thrombosis in symptomatic patients, but it is insensitive for calf-vein thrombosis. In patients with clinically suspected venous thrombosis, positive IPG results can be used to make therapeutic decisions as long as no clinical conditions known to produce false-positive results are present. A normal result essentially excludes the diagnosis of proximal venous thrombosis but does not exclude calf-vein thrombosis. This potential limitation can be overcome by performing serial IPG, which is based on the concept (now confirmed by clinical observation) that calf-vein thrombi are clinically important only when extension into the proximal veins occurs; at this point, detection with IPG becomes possible.

The effectiveness and safety of IPG have been evaluated by prospective clinical trials in patients with clinically suspected venous thrombosis. From these studies the following recommendations can be made: (1) a positive result by IPG is highly predictive of acute proximal vein thrombosis (positive predictive value greater than 90%), and (2) it is safe to withhold anticoagulant therapy in symptomatic patients who remain negative by serial IPG for 10 to 14 days.

As does ultrasonography, IPG lacks sensitivity for the detection of asymptomatic venous thrombosis after surgery. False-positive results may occur in disorders that interfere with arterial inflow or venous outflow. Such disorders include severe congestive cardiac failure, constrictive pericarditis, severe arterial insufficiency, hypotension, and external compression of the veins. Most of these disorders are readily recognized on clinical grounds.

Venography

Venography is accepted as the standard objective method for the diagnosis of venous thrombosis. Venography is a difficult technique to perform well, and accurate interpretation requires considerable experience. A number of venographic abnormalities have been defined as criteria for the diagnosis of acute deep vein thrombosis. The most reliable of these is an intraluminal filling defect that is present on all films and can be seen in a number of projections. Other venographic abnormalities, such as nonfilling of a segment of the deep venous system or nonfilling of the entire deep venous system above the knee, may be caused by technical artifacts, particularly if the dye is injected too far proximally into the dorsal foot vein. Such artifacts may then be interpreted either to indicate a thrombus because the vein is not filled or as normal because a filling defect is not seen. The common femoral, external iliac, and common iliac veins may not be adequately filled by ascending venography. This can lead to an incorrect diagnosis because of inadequate venography. In the case of nonfilling of an entire segment of the deep venous system, the diagnosis of acute or recurrent venous thrombosis must depend on the use of other tests such as IPG or ultrasound.

There are a number of problems related to venography. Even in the best of circumstances, it may be impossible to cannulate a vein on the dorsum of the foot, and so ascending venography may be impossible on one or both legs. If there is inadequate filling of the common femoral or iliac systems, it may be necessary to perform a femoral venogram.

Venography is associated with a number of clinically troublesome side effects. Pain may occur in the foot while dye is being injected, or there may be delayed pain in the calf 1 or 2 days after injection. The procedure may be complicated by superficial phlebitis and even deep vein thrombosis in a small percentage of patients with normal venograms (1% to 2%). Other, less common complications of venography include hypersensitivity to the radiopaque dye and local skin or tissue necrosis as a result of extravasation of dye at the site of injection. Both nonionic and high-ionic contrast media may cause or aggravate renal insufficiency in patients at high risk for these complications (patients with established renal disease, hypertension, heart failure, diabetes, or multiple myeloma, for example). The risks of venography must be carefully weighed in such circumstances and reviewed with the patient before venography is performed.

Ventilation/Perfusion Lung Scanning

Perfusion lung scanning is the key diagnostic test for patients with suspected pulmonary embolism. A normal perfusion scan excludes significant pulmonary embolism.

An abnormal perfusion scan, however, is nonspecific and may occur in conditions that produce either increased radiographic density (such as pneumonia, atelectasis, and pleural effusion) or a regional reduction in ventilation (such as chronic obstructive lung disease, acute asthma, bronchial mucous plugging, and bronchitis, which are frequently associated with normal radiography).

Ventilation imaging improves the specificity of an abnormal perfusion scan by differentiating between embolic occlusion of the pulmonary vasculature and perfusion defects occurring secondary to a primary disorder of ventilation. Recent prospective clinical trials have shown that the basic premise, that perfusion defects that ventilate normally (ventilation/perfusion mismatch) result from pulmonary embolism but that matching ventilation/perfusion abnormalities are due to other conditions, has been shown to be incorrect.

Ventilation lung scanning is helpful only if the perfusion defect is segmental or larger and is associated with ventilation mismatch. Pulmonary angiography shows that such patients have a high probability (³86%) of pulmonary embolism. Other abnormal findings on lung scans, such as matching ventilation/perfusion defects (either segmental or subsegmental), subsegmental defects with ventilation mismatch, or perfusion defects that correspond to an area of increased density on the chest radiograph (nondiagnostic perfusion scan), are associated with a 20% to 40% frequency of pulmonary embolism. Therefore, further investigations, including pulmonary angiography and objective tests for venous thrombosis, must be carried out in patients with nondiagnostic ventilation/perfusion scan findings. Pulmonary angiography and/or venography should be used when other approaches are unavailable or inconclusive. The morbidity associated with these tests is substantially less than that arising from unnecessary anticoagulant therapy and inappropriate hospitalization.

At least 80% of patients with pulmonary embolism have thrombi that originate in the lower leg veins. Prospective studies in patients with nondiagnostic lung scan findings who have adequate cardiorespiratory reserve have indicated that serial noninvasive leg testing is a simple and safe alternative to pulmonary angiography. If the noninvasive leg test is positive initially or on serial screening, anticoagulant treatment can be instituted. On the other hand, if noninvasive leg testing remains negative for 10 to 14 days, anticoagulant therapy can be safely withheld. Pulmonary angiography is required in patients with decreased cardiopulmonary reserve and nondiagnostic lung scan findings.

Pulmonary Angiography

Pulmonary angiography is the accepted diagnostic reference standard for pulmonary embolism. The diagnosis is established if there is an intraluminal filling defect that is present on multiple films or if there is abrupt termination (cutoff) of a vessel greater than 2 to 5 mm in diameter that is visible on multiple films in different projections. Other abnormalities, such as oligemia, vessel pruning, and loss of filling of small vessels, are nonspecific and occur in a variety of conditions, including pneumonia, atelectasis, bronchiectasis, emphysema, and pulmonary carcinoma.

In recent years, the diagnostic resolution of pulmonary angiography has been markedly improved, and the risk to the patient decreased, by the use of selective catheterization with repeated injections of small volumes of dye. This is a safe technique in the absence of severe chronic pulmonary hypertension or severe cardiac or respiratory decompensation. Clinically significant complications including tachyarrhythmias, endocardial or myocardial injury, cardiac perforation, cardiac arrest, and hypersensitivity reactions to contrast medium occur in fewer than 3% to 4% of patients.

TREATMENT OF VENOUS THROMBOEMBOLISM

The objectives of treatment in patients with venous thromboembolism are (1) to prevent death from pulmonary embolism, (2) to prevent recurrent venous thromboembolism, and (3) to prevent the postphlebitic syndrome.

The accepted anticoagulant therapy for venous thromboembolism is a combination of continuous intravenous heparin and oral warfarin sodium. The use of heparin and warfarin simultaneously has become the standard clinical practice for all patients with venous thromboembolism who are medically stable. Exceptions include patients who require immediate medical or surgical intervention such as thrombolysis or insertion of a vena cava filter or patients at high risk for bleeding. The length of the initial intravenous heparin therapy has been reduced to 5 days, thus shortening the hospital stay and leading to significant cost saving.

Heparin Therapy

The anticoagulant activity of unfractionated heparin depends on a unique pentasaccharide that binds to antithrombin III (ATIII) and potentiates the inhibition of thrombin and activated factor X (X_a) by ATIII. Heparin also catalyzes the inactivation of thrombin by another plasma cofactor, heparin cofactor II, which acts independently of ATIII. Several other effects of heparin are (1) the release of tissue factor inhibitor, (2) the binding to numerous plasma and platelet proteins, endothelial cells, and leukocytes, and (3) increased vascular permeability. The anticoagulant response to a standard dose of heparin varies widely among patients. It is necessary, therefore, to monitor the anticoagulant response of heparin by measuring either the activated partial thromboplastin time (aPTT) or heparin levels, and to titrate the dose to the individual patient.

The laboratory test most commonly used to monitor heparin therapy is the aPTT. The traditional approach has been to adjust the heparin infusion dose to maintain the aPTT within a defined “therapeutic range.” Over the years, this therapeutic range has evolved as a result of clinical custom to the use of upper and lower limits (an aPTT ratio of 1.5 to 2.5 times control). The clinical practice of adjusting the heparin dose to maintain the aPTT response within this range is based on two concepts: (1) that maintaining the aPTT ratio above the lower limit of 1.5 will minimize recurrent venous thromboembolic events and (2) that maintaining the aPTT ratio below the upper limit of 2.5 will minimize the risk of bleeding complications.

It has been established, from experimental studies and clinical trials, that the efficacy of heparin therapy is dependent on achieving a critical therapeutic level of heparin within the first 24 hr of treatment. Patients receiving heparin, by either continuous intravenous infusion or intermittent subcutaneous injection, who do not achieve therapeutic aPTT values during initial therapy have an increased risk of recurrent venous thromboembolism over the subsequent 3 to 12 weeks. The critical therapeutic level of heparin, as measured by the aPTT, is the one that will produce 1.5 times the mean control value or the upper limit of the normal aPTT range. This corresponds to a heparin blood level of 0.2 to 0.4 mL by the protamine sulfate titration assay and 0.35 to 0.70 u/mL by the anti-factor-X_a assay. However, the aPTT and heparin blood levels determined with reagents from different manufacturers and even with different batches of the same reagent vary widely. It is therefore vital for each laboratory to establish the minimal therapeutic level of heparin, as measured by the aPTT, that will provide a heparin blood level of at least 0.2 units/ml using the protamine titration assay for each batch of thromboplastin reagent being used, particularly if the reagents are provided by different manufacturers.

Although there is a strong correlation between subtherapeutic aPTT values and recurrent thromboembolism, the relationship between supratherapeutic aPTT and bleeding (aPTT ratio 2.5 or more) is less definite. Indeed, bleeding during heparin therapy is more closely related to underlying clinical risk factors than to aPTT elevation above the therapeutic range. Recent studies confirm that age greater than 65 years and female gender increase the risk of bleeding on heparin.

Numerous audits of heparin therapy indicate that administration of intravenous heparin is fraught with difficulty and that the clinical practice of using an *ad hoc* or intuitive approach to heparin dose titration frequently results in inadequate therapy. For example, an audit of physician practices at three university-affiliated hospitals showed that 60% of patients failed to achieve an adequate aPTT response (ratio ³1.5) during the initial 24 hrs of therapy. Furthermore, 30% to 40% of patients remained subtherapeutic over the next 3 to 4 days.

The use of a prescriptive protocol for administering intravenous heparin therapy has been evaluated in two studies in patients with venous thromboembolism. In one clinical trial of the treatment of proximal venous thrombosis, patients were given either intravenous heparin alone, followed subsequently by warfarin sodium, or intravenous heparin and simultaneous warfarin sodium. This heparin nomogram is summarized in Table 2 and Table 3. Only 2% and 1% of the patients were subtherapeutic for more than 24 hrs in the heparin and warfarin group and the heparin group, respectively. Recurrent venous thromboembolism (objectively documented) occurred infrequently in both groups (7%), rates similar to those previously reported. These findings demonstrated that subtherapy was avoided in most patients and that the heparin protocol resulted in effective delivery of heparin therapy in both groups.

1. Initial intravenous heparin bolus: 5000 units
2. Continuous intravenous heparin infusion: commence at 42 ml/hr of 20,000 units (1000 units/hour) in 500 ml of two-thirds dextrose and one-third saline (a 24-hr heparin dose of 40,320 units), except in the following patients, in whom heparin infusion will be commenced at a rate of 31 ml/hr (1240 units/hr) (i.e., a 24-hr dose of 29,760 units):
   a. Patients who have undergone surgery within the previous 2 weeks.
   b. Patients with a previous history of peptic ulcer disease or gastrointestinal or genitourinary bleeding.
   c. Patients with recent stroke (i.e., thrombotic stroke within 2 weeks previously).
   d. Patients with a platelet count < 150 × 10^9 per liter.
   e. Patients with miscellaneous reasons for a high risk of bleeding (e.g., hepatic failure, renal failure, or vitamin K deficiency).
3. Heparin dose adjusted using the aPTT. The aPTT is performed in all patients as outlined below:
   a. 4 to 6 hr after commencing heparin: the heparin dose is then adjusted according to a nomogram (Table 3).
   b. 4 to 6 hr after implementing the first dosage adjustment.
   c. The aPTT is then performed as indicated by the nomogram for the first 24 hr of therapy.
   d. Thereafter, the aPTT will be performed once daily, unless the patient is subtherapeutic, in which case the aPTT will be repeated 4 to 6 hr after increasing the heparin dose.

[a] Reproduced with permission from Hull RD, Raskob GE, Pineo GF, et al. Optimal therapeutic level of heparin therapy in patients with venous thrombosis. *Arch Intern Med* 1992; 152:1589.

TABLE 2. *Heparin protocol*[a]

aPTT	Infusion i.v. Rate change (ml/hr)	Infusion i.v. Dose change (U/24 hr)[b]	Additional action
≤45	+6	+5760	Repeated aPTT[c] in 4–6 hr
46–54	+3	+2880	Repeated aPTT in 4–6 hr
55–85	0	0	None[d]
86–110	-3	-2880	Stop heparin sodium treatment for 1 hr; repeated aPTT 4–6 hr after restarting heparin treatment
>110	-6	-5760	Stop heparin treatment for 1 hr; repeated aPTT 4–6 hr after restarting heparin treatment

[a] aPTT indicates activated partial thromboplastin time. Reproduced with permission from: Hull RD, Raskob GE, Rosenbloom D, et al. Optimal therapeutic level of heparin therapy in patients with venous thrombosis. *Arch Intern Med* 1992; 152:1589.
[b] Heparin sodium concentration, 20,000 U in 500 ml = 40 U/ml.
[c] With the use of Actin-FS thromboplastin reagent (Dade, Mississauga, Ontario).
[d] During the first 24 hr, repeated aPTT in 4 hr (-1 hr. Thereafter, the aPTT will be determined once daily unless subtherapeutic.

TABLE 3. *Intravenous heparin dose-titration nomogram for aPTT*[a]

In the other clinical trial, a weight-based heparin-dosing nomogram was compared with a standard care nomogram (Table 4). In the weight-adjusted group, 89% of patients achieved the therapeutic range within 24 hrs compared with 75% in the standard-care group. The risk of recurrent thromboembolism was more frequent in the standard-care group. This study included patients with unstable angina and arterial thromboembolism in addition to venous thromboembolism, indicating that the heparin protocol used for the treatment of venous thromboembolism in otherwise normal individuals was generalizable to other clinical conditions.

Initial dose	80 U/kg bolus, then 18 U/kg per hr
aPTT < 35 sec (<1.2 × control)	80 U/kg bolus, then 4 U/kg per hr
aPTT, 35–45 sec (1.2–1.5 × control)	40 U/kg bolus, then 2 U/kg per hr
aPTT, 46–70 sec (1.5–2.3 × control)	No change
aPTT, 71–90 sec (2.3–3.0 × control)	Decrease infusion rate by 2 U/kg per hr
aPTT > 90 sec (>3.0 × control)	Hold infusion 1 hr, then decrease infusion rate by 3 U/kg per hr

[a] Reproduced with permission from: Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. *Ann Intern Med* 1992; 117:674–681.

TABLE 4. *Weight-based nomogram*[a]

Complications of Heparin Therapy

The main side effects of heparin therapy include bleeding, thrombocytopenia, and osteoporosis, with rarer complications being hypersensitivity, hypoaldosteronism, and elevated liver enzymes. Approximately 5% of patients on continuous intravenous heparin experience major bleeding. Patients at particular risk are those who have had recent surgery or trauma or other predisposing comorbidities such as peptic ulcer, occult malignancy, liver disease, or hemostatic defects. Age greater than 65 years and female gender predispose to bleeding on heparin.

The management of heparin-related bleeding depends on the location and severity of bleeding, the risk of recurrent venous thromboembolism, and the level of the aPTT. Heparin should be discontinued temporarily or permanently. Patients with recent venous thromboembolism may be candidates for insertion of an inferior vena cava filter. If urgent reversal of the heparin effect is required, protamine sulfate can be administered.

Heparin-induced thrombocytopenia is a well-recognized complication of heparin therapy, usually occurring within 5 to 10 days after the start of heparin treatment. Approximately 1% to 2% of patients receiving unfractionated heparin will experience a fall in platelet count to less than the normal range or a 50% fall in the platelet count within the normal range. In the majority of cases, this mild to moderate thrombocytopenia appears to be a direct effect of heparin on platelets and is of no consequence. However, approximately 0.1% to 0.2% of patients receiving heparin develop an immune thrombocytopenia mediated by IgG antibody directed against a complex of PF4 and heparin. The development of thrombocytopenia may be accompanied by arterial or venous thrombosis. This may have serious consequences, such as death or limb amputation. The diagnosis of heparin-induced thrombocytopenia, with or without thrombosis, must be made on clinical grounds because the assays with the highest sensitivity and specificity are not readily available and have a slow turnaround time.

When the diagnosis of heparin-induced thrombocytopenia is made, heparin in all forms must be stopped immediately. In those patients who require ongoing anticoagulation, several alternatives exist: warfarin therapy, insertion of an inferior vena cava filter, the use of the defibrinogenating extract of snake venom, Arvin (Ancrod), the heparinoid Danaproid sodium (Organon), and, more recently, the specific antithrombins hirudin and Argatroban. Most of the reports in case series have included the use of Arvin or Danaproid, but clinical trials are currently under way to assess the efficacy and safety of the specific antithrombin agents.

Osteoporosis has been reported in patients receiving unfractionated heparin in doses of 20,000 units per day or more for more than 6 months. Demineralization can progress to the fracture of vertebral bodies or long bones, and the defect may not be entirely reversable.

Other complications of heparin therapy, such as hypersensitivity, elevated liver enzymes, and hyperkalemia secondary to hypoaldosteronism, are rare and of little clinical consequence.

Low-Molecular-Weight Heparin

Heparin currently in use clinically is polydispersed unmodified heparin and has a mean molecular mass ranging from 10 to 16 kDa. In recent years, low-molecular-weight derivatives of commercial heparin have been prepared that have a mean molecular mass of 4 to 5 kDa.

Low-molecular-weight heparins have a number of advantages over unfractionated heparin: they have greater bioavailability when given by subcutaneous injection; the duration of anticoagulant effect is greater, permitting once- or twice-daily administration; the anticoagulant response (anti-X_a activity) to low-molecular-weight heparin correlates highly with body weight, permitting administration without laboratory monitoring; and there is less bleeding with equivalent antithrombotic effect.

Several different low-molecular-weight heparins and one heparinoid are available for the prevention and treatment of venous thromboembolism in various countries. In North America, three low-molecular-weight heparins have been approved for clinical use, two in the United States and three in Canada. A large number of clinical trials of deep vein thrombosis prophylaxis have been carried out in general and in orthopedic surgery in both Europe and North America. Meta-analyses indicate that low-molecular-weight heparins are at least as effective as unfractionated heparin or warfarin in the prevention of postoperative deep vein thrombosis, and they have the added convenience of once-daily administration. However, the incidence of postoperative bleeding may be somewhat higher than with low-dose unfractionated heparin or warfarin. Low-molecular-weight heparin has become the prophylaxis of choice for patients undergoing high-risk surgery, such as total hip or total knee replacement.

Subcutaneous, unmonitored, low-molecular-weight hep- arin has been compared with continuous intravenous heparin in a number of clinical trials for the treatment of proximal venous thrombosis. In one clinical trial conducted in North America, there was a significant decrease in major bleeding and in mortality rate in patients treated with low-molecular-weight heparin compared with unfractionated heparin (Fig. 1). There was also a trend to decreased recurrent thromboembolism. Four other clinical trials, which also used long-term follow-up as an outcome measure, showed that low-molecular-weight heparin was at least as effective and safe as unfractionated heparin, although the differences were not significant. When all five studies were combined, low-molecular-weight heparin demonstrated a significant advantage with respect to recurrent venous thromboembolism, major bleeding, and mortality. Data from ongoing studies indicate that low-molecular-weight heparin is equally effective in the treatment of patients presenting with pulmonary embolism.

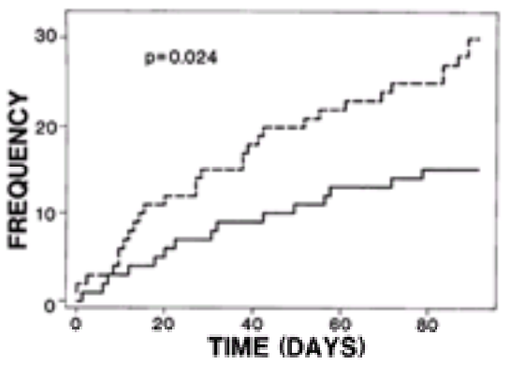

FIG. 1. Time-to-event analysis for patients who had recurrent venous thromboembolism or died (*solid line,* low-molecular-weight heparin; *dashed line,* unfractionated heparin). Fifteen of 213 patients receiving low-molecular-weight heparin (7%) had objectively documented recurrent venous thromboembolism or died, compared with 30 of 219 patients receiving intravenous heparin (13.7%) (p = 0.024). In each group the majority of these events occurred within the first 6 weeks. (From Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992;326:975–988.)

Two recently completed randomized clinical trials show that low-molecular-weight heparin can be used safely to treat selected patients with venous thromboembolism as outpatients. Cost analyses indicate that low-molecular-weight heparin is cost effective in both the prevention and treatment of venous thromboembolism compared with standard treatment. When these agents become more available for treatment, they will undoubtedly replace intravenous unfractionated heparin in the initial management of patients with venous thromboembolism as well as in the management of other patients in whom intravenous heparin is currently used.

If patients experience bleeding while receiving low-molecular-weight heparin, protamine sulfate has been shown to reduce clinical bleeding, presumably by neutralizing high-molecular fractions of heparin, which are thought to be most responsible for it.

Oral Anticoagulant Therapy

The most common oral anticoagulant is a 4-hydroxycoumarin derivative, warfarin sodium. Warfarin exerts its anticoagulant effect by inhibiting the vitamin-K-dependent g-carboxylation of coagulation factors II, VII, IX, and X. This results in the synthesis of immunologically detectable but biologically inactive forms of these coagulation proteins. Warfarin also inhibits the vitamin-K-dependent g-carboxylation of proteins C and S. Protein C circulates as a proenzyme that is activated on endothelial cells by the thrombin–thrombomodulin complex to form activated protein C. Activated protein C inhibits activated factor VIII activity directly and, in the presence of protein S, also inhibits activated factor V. Therefore, vitamin K antagonists such as warfarin create a biochemical paradox by producing an anticoagulant effect through inhibition of procoagulants (factors II, VII, IX, and X) and a potentially thrombogenic effect by impairing the synthesis of naturally occurring inhibitors of coagulation (proteins C and S). Heparin and warfarin treatment should be overlapped by 4 to 5 days when warfarin treatment is initiated in patients with thrombotic disease.

The anticoagulant effect of the vitamin K antagonists is delayed until the normal clotting factors are cleared from the circulation, and the peak effect does not occur until 36 to 72 hr after drug administration. During the first few days of warfarin therapy, the prothrombin time reflects mainly the depression of factor VII, which has a half-life of 5 to 7 hrs. Equilibrium levels of factors II, IX, and X are not reached until about 1 week after the initiation of therapy. The use of small initial daily doses (10 mg, for example) is the preferred approach for initiating warfarin treatment. The dose–response relationship to warfarin therapy varies widely among individuals, and, therefore, the dose must be carefully monitored to prevent overdosing or underdosing. There is some evidence that elderly subjects are more sensitive to the effects of warfarin, and greater caution is required in establishing maintenance doses in order to prevent overanticoagulation.

A number of drugs interact with warfarin. Critical appraisal of the reports of such interactions indicates that the evidence substantiating many of the claims is limited. Nonetheless, patients must be warned against taking any new drugs without the knowledge of their physician.

Laboratory Monitoring and Therapeutic Range

The one-stage prothrombin time is the laboratory test most commonly used to measure the effects of warfarin. The prothrombin time (PT) is sensitive to reduced activity of factors II, VII, and X but insensitive to reduced activity of factor IX. Confusion about the appropriate therapeutic range has occurred because the different tissue thromboplastins used to measuring the PT vary considerably in their sensitivity to the vitamin-K-dependent clotting factors and in response to warfarin. Rabbit brain thromboplastin, which is widely used in North America, is less sensitive than standardized human brain thromboplastin, which has been widely used in the United Kingdom and other parts of Europe. A PT ratio of 1.5 to 2.0 using rabbit brain thromboplastin (the traditional therapeutic range in North America) is equivalent to a ratio of 4.0 to 6.0 using human brain thromboplastin. Conversely, a two- to threefold increase in the PT using standardized human brain thromboplastin is equivalent to a 1.25- to 1.5-fold increase in the PT using a rabbit brain thromboplastin such as Simplastin or Dade-C.

In order to promote standardization of the PT for monitoring oral anticoagulant therapy, the World Health Organization (WHO) has developed an international reference thromboplastin from human brain tissue and has recommended that the PT ratio be expressed as the *International Normalized Ratio* (INR). The INR is the PT ratio obtained by testing a given sample using the WHO reference thromboplastin. For practical clinical purposes, the INR for a given plasma sample is equivalent to the PT ratio obtained using a standardized human brain thromboplastin known as the Manchester Comparative Reagent (which has been widely used in the United Kingdom). The currently recommended therapeutic range for the treatment of venous thromboembolism is an INR of 2.0 to 3.0. The only possible exception is in the treatment of thrombosis complicating the anticardiolipin syndrome. In this case, retrospective reviews suggest that an INR of 2.5 to 3.5 may be more effective.

Warfarin is administered in an initial dose of 5 to 10 mg/day for the first 2 days, and the daily dose is then adjusted according to the INR. Heparin therapy is discontinued on the fourth or fifth day after initiation of warfarin therapy, provided the INR is prolonged into the therapeutic range (INR 2.0 to 3.0). The selection of the correct dosage of warfarin must be individualized because some individuals are either fast or slow metabolizers of the drug. Therefore, frequent INR determinations are required initially to establish therapeutic anticoagulation.

Once the anticoagulant effect and patient's warfarin dose requirements are stable, the INR should be monitored weekly throughout the course of warfarin therapy. However, if there are factors that may produce an unpredictable response to warfarin (concomitant drug therapy, for example), the INR should be monitored more frequently to minimize the risk of complications resulting from poor anticoagulant control.

Long-Term Treatment of Venous Thromboembolism and Pulmonary Embolism

Patients with venous thromboembolism (proximal venous thrombosis or pulmonary embolism) require oral anticoagulants for a period of 3 months to prevent recurrent disease. Attempts have been made to shorten the treatment period to 12 or 6 weeks, but outcomes in terms of recurrent disease are superior when oral anticoagulants

are used for 3 to 6 months. There may be an exception in patients who develop venous thromboembolism in association with an obvious and transient risk factor, such as trauma, orthopedic surgery, or bed rest. In these patients, the recurrence rate is lower than that in patients who have idiopathic venous thromboembolism, even when shorter courses of anticoagulants are used. Patients with continuing risk factors (such as malignancy, paralysis, or prolonged bed rest) may require long-term therapy until the risk has decreased. Patients with irreversible risk factors, such as deficiency of antithrombin III or activated protein C resistance, may require anticoagulant treatment indefinitely after an episode of venous thromboembolism. Patients with a first recurrence of venous thromboembolism have been treated empirically for 12 months, whereas those with a second recurrence usually receive lifelong anticoagulants. Clinical trials are currently under way to establish the most appropriate duration of anticoagulation in some of these clinical situations.

Adverse Effects of Oral Anticoagulants

The major side effect of oral anticoagulant therapy is bleeding. Bleeding during well-controlled oral anticoagulant therapy is usually caused by surgery or other forms of trauma or by local lesions such as peptic ulcer or carcinoma. Spontaneous bleeding may occur if an excessive dose of warfarin sodium is given and results in marked elevation of the INR. Such bleeding may be severe and even life-threatening. The risk of bleeding can be substantially reduced by adjusting the warfarin dose to achieve a less intense anticoagulant effect than has traditionally been used in North America (INR 2.0 to 3.0).

Nonhemorrhagic side effects of oral anticoagulants differ according to whether the coumarin derivatives (warfarin sodium, for example) or indanediones are administered. Nonhemorrhagic side effects of anticoagulants occur infrequently with the coumarin derivatives but more frequently with the indanedione derivatives; these include skin necrosis, dermatitis, and a syndrome of painful blue toes. Hypersensitivity reactions have been reported to occur in 1% to 3% of patients receiving indanedione derivatives and include rash, fever, hepatitis, leukopenia, renal failure, and diarrhea. These side effects may be fatal. In many patients, the indanedione derivatives also produce red discoloration of the urine, which may be confused with hematuria.

Coumarin-induced skin necrosis is a rare but serious complication and requires that oral anticoagulant therapy be stopped immediately. It usually occurs 3 to 10 days after therapy starts, is more common in women, and most often involves areas of abundant subcutaneous tissues such as the abdomen, buttocks, thighs, and breast. The mechanism of coumarin-induced skin necrosis, which is associated with microvascular thrombosis, is uncertain. It does, however, appear to be related, at least in some patients, to the depression of protein C, and patients with congenital deficiencies of protein C or S may be particularly prone to its development. To avoid the development of skin necrosis in patients with protein C or S deficiency who require anticoagulant therapy, intravenous heparin should be started, and then warfarin should be initiated without a loading dose. The heparin should be continued until the INR is therapeutic for at least 2 consecutive days.

Oral anticoagulants cross the placenta, and their use during pregnancy may cause fetal malformations. Two specific fetopathic syndromes are associated with oral anticoagulant administration during pregnancy. Treatment with oral anticoagulants during weeks 6 to 12 gestation may induce the syndrome of warfarin embryopathy in the fetus, that is, skeletal abnormalities ranging from stippled epiphyses to frank skeletal hypoplasia. Although most reported cases have occurred in infants of mothers receiving warfarin, it has also been reported to result from phenindanedione or acenocoumarin administration. Oral anticoagulant administration during the second or third trimester of pregnancy may result in central nervous system abnormalities in the fetus, including abnormalities of the ventricular system (Dandy–Walker malformation), dorsal midline dysplasia, and optic atrophy. Therefore, the use of oral anticoagulants is contraindicated at any time during pregnancy, and they should not be used in women planning a pregnancy. Adjusted-dose twice-daily subcutaneous unfractionated heparin is the anticoagulant of choice for venous thromboembolism occurring in pregnancy.

Antidote to Oral Anticoagulants

The antidote to the vitamin K antagonists is vitamin K_1. If the INR is increased excessively, treatment will depend on the level of the INR and whether or not the patient is bleeding. If the increase is mild (INR < 6.0), and the patient is not bleeding, no specific treatment is necessary other than reduction of the warfarin dose; the INR can then be expected to decrease during the next 24 hrs. If there is a more marked increase in the INR in patients who are not bleeding, treatment with small doses of vitamin K_1, given either orally or by subcutaneous injection (2.5 to 5.0 mg), should be considered. If there is a very marked increase in the INR (INR > 10.0), vitamin K_1 should be given, particularly to a patient who is either actively bleeding or at risk of bleeding.

Second-generation rodenticides, known as “super warfarins,” have an extremely long half-life. Accidental or intentional consumption of these agents requires repeated injections of vitamin K and fresh-frozen plasma for up to 1 to 2 years to overcome their effects completely.

The reported side effects of vitamin K include flushing, dizziness, tachycardia, hypotension, dyspnea, and sweating. Intravenous administration of vitamin K_1 should be carried out with caution to avoid inducing an anaphylactoid reaction. The risk of an anaphylactoid reaction can be reduced by giving vitamin K_1 slowly, no faster than 1 mg/min i.v. In most patients, i.v. administration of vitamin K_1 produces a demonstrable effect on the INR within 3 to 4 hrs and corrects the prolonged INR within 6 to 8 hr. Because the half-life of vitamin K_1 is less than that of warfarin sodium, a repeat course of vitamin K_1 may be necessary. If bleeding is very severe and life-threatening, vitamin K therapy can be supplemented by using concentrates of factors II, VII, IX, and X.

TREATMENT OF ACUTE MASSIVE PULMONARY EMBOLISM

The emergency management of massive pulmonary embolism includes the use of intravenous heparin, the use of oxygen, with or without mechanical ventilation and positive end-expiratory pressure (PEEP), volume resuscitation, and the use of inotropic agents and vasodilators. In addition to these supportive measures, specific treatment options for acute massive pulmonary embolism include (1) thrombolysis, (2) pulmonary thrombectomy, with or without cardiopulmonary bypass support, (3) transvenous catheter embolectomy or clot dissolution, and (4) insertion of an inferior vena caval filter.

Thrombolytic Therapy

Randomized clinical trials have demonstrated that the mortality rate from venous thromboembolism can be decreased by anticoagulant treatment. A mortality rate of less than 5% can be achieved with intravenous heparin and oral anticoagulants. This can be further reduced with the use of low-molecular-weight heparin. However, patients who present with acute massive pulmonary embolism and hypotension have a mortality rate of approximately 20% even when anticoagulants and other supportive measures are used. For such patients, the appropriate use of thrombolytic agents has a role. A high percentage of acute pulmonary emboli occur within 10 to 14 days of surgery and, therefore, are excluded from treatment protocols that use thrombolytic agents. These patients may be candidates for local infusion of low-dose thrombolytic agents.

In several randomized clinical trials, thrombolytic drugs have been compared with heparin for the treatment of pulmonary embolism. These trials compared urokinase (UK) with heparin, streptokinase (SK) with heparin, or tissue plasminogen activator (t-PA) with heparin. The dosage regimens used either a bolus or chronic infusion up to 72 hr. Outcome measures for accelerated thrombolysis included quantitative measures on repeat pulmonary angiograms, quantitative scores on repeat pulmonary perfusion scans, and measures of pulmonary vascular resistance. Although all studies demonstrated the superiority of thrombolysis (in particular with t-PA) in terms of resolution of both radiographic and hemodynamic abnormalities when measured within the first 24 hr, this advantage was short-lived. Repeat perfusion scans at 5 to 7 days revealed no significant difference between the patients treated with thrombolytic agents and those with heparin. Furthermore, the trials demonstrated neither a difference in mortality rate nor one in resolution of symptoms. Measurement of diffusion capacity and capillary volumes at 2 weeks and 1 year after treatment showed that those receiving thrombolytic therapy had higher diffusion capacity and lung capillary volumes than did patients receiving heparin. Follow-up of the same group of 23 patients an average of 7 years after thrombolytic treatment showed that patients who had been treated with thrombolytic therapy had lower pulmonary artery pressure and pulmonary vascular resistance than patients who had received heparin. The clinical relevance of these findings, however, must await further prospective studies.

Several randomized clinical trials have compared different thrombolytic agents using different treatment protocols: SK versus UK, UK with UK, t-PA with t-PA, and t-PA with UK. These studies again demonstrated resolution of angiographic, echocardiographic, and perfusion scan abnormalities as well as reduction of pulmonary pressure, but there was little or no difference between the regimens being compared. Again, the clinical relevance of the changes requires further study.

In weighing the risks and benefits of thrombolytic therapy, the main concern is bleeding. The incidence of major bleeding has decreased, particularly with the use of bolus or short-term infusions and with the use of newer thrombolytic agents. However, intracerebral hemorrhage continues to occur more frequently than with heparin.

At this time, the role of thrombolytic agents in the management of acute massive pulmonary embolism remains controversial. Although there is a more rapid dissolution of venous thromboemboli, the risk of serious bleeding is still a concern. Until there is a clearly demonstrated reduction in both morbidity and mortality from well-controlled prospective randomized clinical trials, the question of risk/benefit will remain. In the meantime, the use of thrombolytic agents has become simpler through the use of high-probability ventilation–perfusion scans or echocardiography to confirm the diagnosis, the use of short-term or bolus infusion of thrombolytic agents into peripheral veins rather than the pulmonary artery, the elimination of laboratory monitoring, and treatment on the medical ward rather than the intensive care unit. The fact that a high percentage of acute massive pulmonary emboli still occur after surgery, even though effective prophylactic regimens are available against

venous thromboembolism, indicates that greater efforts must be taken to ensure that these prophylactic measures are being applied in a more uniform fashion.

Thrombolytic therapy may benefit selected patients with acute massive venous thrombosis, such as those with phlegmasia cerulea dolens. In most patients with acute deep-vein thrombosis, however, the indication for thrombolytic therapy remains controversial, and most patients do well with unfractionated heparin or low-molecular-weight heparin. At present, randomized clinical trials have yielded no definitive evidence that thrombolytic therapy is associated with improved benefit by the prevention of postphlebitic syndrome.

Pulmonary Embolectomy in Massive Pulmonary Embolism

Pulmonary embolectomy is occasionally indicated in the management of massive pulmonary embolism. This is usually defined as the sudden occurrence of a massive embolus that produces severe cardiovascular decompensation with severe hypotension, oliguria, and hypoxia refractory to aggressive treatment. A somewhat more liberal set of indications are (1) an obstruction of more than 50% of the pulmonary vasculature, (2) arterial oxygen tension less than 60 mmHg, (3) systolic blood pressure less than 90 mmHg, and (4) urine output of less than 20 mL/hr. In some centers, patients who have contraindications to thrombolytic therapy or who have failed a trial of thrombolytic therapy are considered candidates for thrombectomy. On the other hand, others would argue that a patient who survives the first 2 hrs after an acute massive pulmonary embolus will probably survive with adequate medical management if no further pulmonary emboli occur. It will not be possible to perform a randomized trial comparing thrombolytic therapy with pulmonary embolectomy, and it is difficult to compare one case series of pulmonary thrombectomy with another because the case material often differs.

Early experience with the Trendelenburg procedure revealed unacceptably high mortality rates (>50%). Mortality rates between 16% and 57% have been reported with the use of cardiopulmonary bypass (CPB) support. In a review of 651 patients undergoing emergency pulmonary embolectomy, the survival rate was 59.3% with CPB support and 47.7% without CPB support. Patients with chronic pulmonary hypertension, other medical disorders, or with symptoms of more than 7 days' duration have higher mortality rates. Patients who have sustained a cardiac arrest before embolectomy also have a higher mortality rate. Greater care to avoid vasodilation at the initiation of anesthesia has decreased mortality rates. Pulmonary hemorrhagic infarction with reperfusion has been reported after pulmonary embolectomy. Other causes of death after embolectomy include cardiogenic shock, infection, and hypoxic brain damage. Pulmonary embolectomy is usually accompanied by insertion of a vena cava filter.

The role of pulmonary embolectomy remains unclear and will depend in part on the ready availability of a surgical team. Patients who are not candidates for thrombolysis (after recent surgery, for example) or who have not responded to maximal medical therapy may be candidates for pulmonary embolectomy. However, the recent report of successful thrombolysis with intrapulmonary UK in patients treated within 10 days of surgery casts further doubt on the need for this somewhat radical procedure.

Percutaneous Clot Extraction or Disruption in the Treatment of Acute Massive Pulmonary Embolus

In patients who have contraindications to anticoagulants or thrombolysis, pulmonary embolectomy via a catheter suction device inserted into the jugular or femoral vein under local anesthesia has been used in the treatment of acute massive pulmonary embolism. Mortality rates of 27% and 28% were observed. The most common cause of death was cardiac arrest from ventricular arrhythmia, right heart failure, and pulmonary hemorrhage. Some patients in whom clot extraction was not possible responded successfully to pulmonary embolectomy while on CPB. Inferior vena cava filters should be used in conjunction with catheter embolectomy.

Attempts have been made to fragment pulmonary emboli using conventional cardiac catheters or a catheter guide wire in conjunction with pulmonary thrombolytic therapy. Mechanical disruption of experimental pulmonary emboli in animals has been attempted using catheter-operated mechanical devices.

Catheter clot extraction is currently confined to a few centers with the required expertise. This procedure cannot be used in patients who suffer cardiac arrest. The exact future role of catheter clot extraction is unclear.

Inferior Vena Caval Interruption in the Treatment of Pulmonary Thromboembolism

The insertion of an inferior vena caval filter is indicated in:

The patient with acute venous thromboembolism and an absolute contraindication to anticoagulant therapy.

The rare patient with massive pulmonary embolism who survives but in whom recurrent embolism may be fatal.

The very rare patient who has objectively documented recurrent venous thromboembolism during adequate anticoagulant therapy.

Characteristics of an ideal filter include one that is easily and safely placed percutaneously, is biocompatible and mechanically stable, is able to trap emboli without causing occlusion of the vena cava, does not require anticoagulation, and is not ferromagnetic (does not cause artifacts on magnetic resonance images). Although there is at present no ideal filter, several devices have proved to be useful. These include the Greenfield stainless steel filter and titanium filter, the bird's nest filter, the Vena Tech filter, and the Simon–Nitinol filter. In experienced hands these devices can be quickly and safely inserted under fluoroscopic control. One novel filter can be inserted temporarily when needed, used in conjunction with thrombolytic therapy, and then removed. At present, the Greenfield filter (titanium version) has had the best performance record, and any future comparative studies should use this filter as the standard.

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CHAPTER

67 Pulmonary Heart Disease

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INTRODUCTION

The heart and the respiratory system are closely connected such that disorders of one system influence the function of the other. In the 1800s, Laennec described patients with pulmonary emphysema and associated right heart enlargement. In the 1930s, Paul Dudley White recognized that, although left heart disease is the most common cause of right ventricular enlargement and dysfunction, enlargement of the right ventricle (RV) can result from lung disease in the absence of left heart failure. He coined the term *cor pulmonale* to describe this condition, also known as *pulmonary heart disease* (PHD). With the advent of technological advances in cardiovascular physiology and diagnosis, there has been an impressive advance in our knowledge of the manner in which disordered respiratory function affects the heart, especially the RV. Uniformly accepted criteria for defining PHD do not exist; hence, precise estimates of its prevalence are difficult to ascertain. However, heart failure on the basis of PHD probably constitutes at least 15% to 20% of all cases of heart failure and 7% to 10% of all heart disease. Some 40% of patients with severe chronic obstructive pulmonary disease demonstrate clinical or pathologic evidence of PHD. This is especially important because PHD implies a grave prognosis. Only approximately one-third of patients with lung disease and PHD will be alive 4 years after diagnosis, as opposed to 64% of those without PHD.

DEFINITIONS

Pulmonary heart disease is heart disease caused by dysfunction of the lungs leading to altered pulmonary vasculature. McGinn and White used the term *acute cor pulmonale* to describe right heart strain resulting from acute pulmonary hypertension. This is in contrast to *chronic cor pulmonale,* which has been defined by the World Health Organization as an alteration in structure or function of the RV resulting from disease affecting the structures and function of the lung except when this alteration results from disease of the left heart or congenital heart disease. This definition, based on alterations in structure, has been challenged in favor of more functional definitions containing elements of clinical syndromes, i.e., right heart failure. However, these definitions are similarly imprecise, and there seems no reason to depart from the classic definition. Thus, PHD may be associated with varying degrees of clinically apparent heart failure or abnormalities in pulmonary hemodynamics or may, in many cases, be clinically silent.

In this chapter, we review some of the factors that characterize acute and chronic PHD. Because PHD is a disease of the RV, we briefly describe normal RV function and the response of the RV to imposed mechanical loads. We consider the interactions between the RV and the LV because these are so important to the normal functioning of the heart. We then consider the clinical and pathophysiological features of acute and chronic PHD. Details of pulmonary circulation and pulmonary hypertension have been reviewed in previous chapters.

NORMAL RIGHT VENTRICLE

The RV develops embryologically from two separate components of the primitive cardiac tube. The bulbus cordis is incorporated into the conus (outflow tract), and the sinus venosus is incorporated into the sinus (inflow tract). Normal RV contraction preserves the functional distinction of its dual embryologic origin. Right ventricular systole occurs by sequential contraction, beginning at the inflow tract and extending to the outflow tract, and is almost peristaltic in nature, with approximately 25 msec separating contractile activity of the two components. In fact, with increased sympathoadrenal activation, a pressure gradient can develop between the inflow and outflow tract within the ventricular cavity. This mode of contraction makes the RV ideally suited for its job as a high-volume low-pressure pump.

The RV is normally thin (less than 0.5 cm thick) and crescent shaped. Therefore, determination of its volume from limited numbers of dimensions that can be assessed using standard imaging techniques is more difficult than for the left ventricle (LV). The difficulty in measuring RV volume using simple imaging techniques (as for the LV) is further compounded by the fact that, with dilation, its shape becomes more ellipsoidal. Thus, changes in loading conditions can lead to changes in shape. This in turn may be responsible for the fact that in many circumstances there is a poor or nonexistent correlation between end-diastolic and end-systolic pressures and corresponding RV volumes.

RIGHT- AND LEFT-VENTRICLE FUNCTION COMPARED

The fact that the RV free wall may be ablated or surgically replaced with a dacron patch with no change in resting cardiac output initially led workers to believe its importance to circulatory homeostasis is minimal. However, when there is an increase in pulmonary arterial pressure or venous return, as with exercise or other stress, normal RV functioning is essential for maintenance of normal circulatory status. It is commonly stated that the RV is a “volume pump,” whereas the LV is a “pressure pump,” implying some sort of qualitative difference between the ventricles. It is certainly true that the thin-walled RV is less able to generate pressure than the muscular LV (Table 1). However, compared to its normal physiological pressure range, the RV is capable of increasing maximum pressure generation proportionally to the same degree or even more than the LV. During acute constriction of the pulmonary artery, maximum RV pressure can increase to 55 to 60 torr (almost three times the normal peak systolic pressure) before circulatory failure ensues.

TABLE 1. *Diseases that have been associated with pulmonary hypertension and/or pulmonary heart disease*

The determinants of RV function are the same as those of LV function, namely, preload, afterload, and contractility. Figure 1 illustrates the pressure–volume history of RV contraction. During diastole, the RV fills along the diastolic or relaxation pressure–volume curve. At end-diastole (EDP), isovolumic contraction occurs. The RV pressure increases until the level of pulmonary artery (PA) diastolic pressure (PADP) is reached, at which point shortening occurs. Shortening ceases when the pressure–volume point reaches the curve describing the maximum end-systolic pressure–volume relationship, at which time isovolumetric relaxation occurs. The point labeled EDP in Fig. 1 represents the stress on the RV at the onset of contraction (preload). The stress on the RV during contraction represents the afterload. The slope of the end-systolic pressure–volume curve represents a load-independent measure of contractility and is sometimes called the maximum systolic elastance. These concepts, developed and validated for the LV both in isolated load-clamped heart preparations and in *in situ* preparations, also apply to the RV with some slight modifications. First, pulmonary arterial pressure represents only part of the hydraulic load placed on the RV (afterload) during contraction. A substantial part of the total hydraulic load is represented by the elastance of the pulmonary arterial circulation. The total hydraulic load placed on the RV is more properly represented by the input impedance of the pulmonary circulation (see Chapter 64). Second, end-systole is more difficult to define for the RV than for the LV. This is because for the LV, end-ejection and end-contraction correspond fairly well. For the RV, there is dyssynchrony in that the ventricle continues to eject for a short time after end-contraction. Further, there are slight differences in end-systolic volume depending on whether contraction is isovolumetric or isotonic.

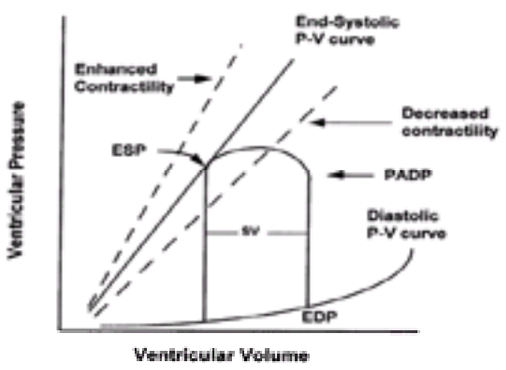

FIG. 1. Ventricular pressure–volume diagram. EDP, end-diastolic pressure; PADP, pulmonary arterial end-diastolic pressure; ESP, end-systolic pressure; SV, stroke volume. See text for explanation.

Practically speaking, however, these quantitative differences do not negate the concept of the end-systolic pressure–volume curve being an important measure of ventricular contractile function. Often the end-systolic point is defined in terms of a specified time interval, often 100 msec from end-diastole, in analyses of RV mechanics. In general, however, RV and LV contraction behave remarkably similarly. When normalized for peak pressure, the time courses of RV and LV isovolumetric pressure development are practically superimposable. Just as for the LV, RV contraction can be viewed as a series of time-varying elastances, a concept that had been developed for the LV. For the RV, as for the LV, the instantaneous pressure–volume relationship may be expressed as:

$$P_t = E_t(V_t - V_0)$$

where P_t is the pressure at any given time in the cardiac cycle, E_t is the slope of the pressure–volume curve at time *t,* V_t is ventricular volume at time *t,* and V_0 is the volume intercept of the regression line. E_t at end-systole is a measure of ventricular contractility that is relatively independent of pre- or afterload.

RIGHT-VENTRICLE RESPONSE TO ACUTELY INCREASED AFTERLOAD: THE PHYSIOLOGY OF ACUTE PHD

Investigators have assessed the ability of the RV to tolerate increased afterload by graded occlusions of the pulmonary artery or injection of glass beads or other small particles into the distal pulmonary bed. These two models are not strictly comparable because the hydraulic load produced by main pulmonary arterial constriction is greater than that produced by microvascular embolization. However, the principles governing load tolerance are the same. Relevant clinical conditions include acute massive pulmonary embolism and large increases in lung volume (high levels of positive end-expiratory pressure) in the presence of adult respiratory distress syndrome. Figure 2 illustrates the results of a typical series of experiments. The RV systolic pressure could be increased to approximately 60 torr with little evidence of circulatory decompensation, although there were decreases in cardiac output and blood pressure. However, a further small increase in the degree of pulmonary arterial constriction brought about sudden dramatic circulatory collapse accompanied by RV dilation and increased RV end-diastolic pressure. Because RV dilation occurred primarily at the time of circulatory collapse, this might suggest that the Frank–Starling mechanism plays little role in maintaining RV output against an increase in afterload. However, other studies have shown that there is a role for the Frank–Starling mechanism in RV afterload tolerance, although it is not the primary determinant. Because the right coronary artery, which supplies the RV free wall, originates in the aorta, coronary blood flow to the RV free wall depends on aortic blood pressure. One hypothesis for the sudden deterioration of the RV with increased afterload is that the balance between RV myocardial O_2 demand and supply suddenly tips in the direction of increased demand, resulting in RV ischemia. Other studies suggest that RV failure does not result from ischemia but, rather, that ischemia is secondary to circulatory collapse. Either way, RV failure with severe pulmonary hypertension appears to be the result of a vicious cycle in which decreased RV output causes decreased LV output. This in turn leads to decreased aortic pressure, which limits the degree to which coronary flow can increase commensurate with O_2 demand. With inadequate coronary flow relative to O_2 demand, RV contractility decreases, which in turn decreases cardiac output. Limitation of right coronary flow is further enhanced by increased RV intramyocardial pressure during systole, which may produce endocardial ischemia.

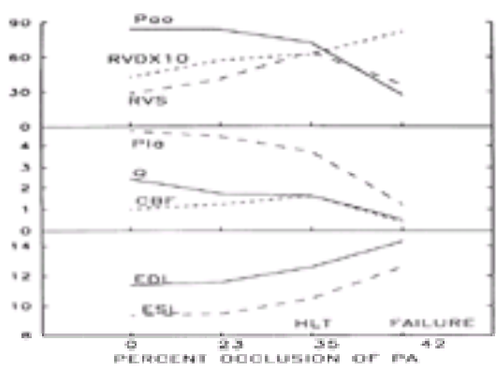

FIG. 2. Summary of hemodynamic changes with acute graded constriction of the pulmonary artery. P_{ao}, aortic pressure; RVD, RV end-diastolic pressure; RVS, RV end-systolic pressure; P_{la}, left atrial pressure; *Q,* cardiac output; CBF, coronary blood flow; EDL, RV end-diastolic segmental length; ESL, RV end-systolic segmental length; HLT, highest load tolerable; failure, circulatory collapse. (Reproduced with permission from Scharf SM. Right ventricular function and cor pulmonale. In: Scharf

SM, ed. *Cardiopulmonary Physiology in Critical Care.* New York: Marcel Dekker, 1992;239–247.)

Supportive Therapy of Acute PHD

The issues discussed above have direct clinical relevance in the assessment and treatment of acute PHD. First, sustained RV pressures greater than approximately 60 torr mean that pulmonary hypertension cannot have been acute because the normal RV cannot sustain systolic pressures greater than this level. Second, whether ischemia is involved or not, one should view RV failure in the light of the balance between myocardial O_2 supply and demand. Resuscitative maneuvers, such as the administration of isoproterenol or even massive fluid resuscitation, could act to increase RV myocardial O_2 demand and unfavorably influence the supply–demand relationship. Although we favor volume infusion in patients who are dehydrated and/or in whom the central venous pressure is low, massive volume infusion when RV afterload is severely elevated may actually worsen failure and produce circulatory decompensation. Support measures should be directed toward maintaining aortic pressure and hence coronary flow. In this setting, vasoconstrictor agents such as phenylephrine or norepinephrine are preferred over agents that increase myocardial contractility and heart rate while producing arterial vasodilation, such as isoproterenol or dobutamine. Diagnosis and specific therapy (thrombolytic agents in massive pulmonary embolism) should be instituted as rapidly as feasible while supportive measures are being instituted.

Right-Ventricle–Left-Ventricle Interactions

The ventricles exhibit two major types of interactions, “series” and “parallel.” Series interactions refers to effects of RV output on LV filling and output. Parallel interactions refers to those interactions arising from the fact that the two chambers are part of one structure, contain common muscle bands, share a common septum, and are covered by a single pericardial sac. It has been amply confirmed that the function of one ventricle depends on that of the other. Many studies have verified the diastolic interactions of the ventricles. When diastolic filling of one ventricle is increased, that of the other is impaired. This diastolic interaction is mediated largely through the interventricular septum. However, the degree of diastolic interaction is amplified approximately fourfold by the presence of the pericardium. Anything that increases the stiffness of the pericardium (pericardial fibrosis, tamponade) increases the degree of diastolic interdependence. These considerations may explain the fact that with acute massive overload of the RV, LV end-diastolic volume decreases, and LV end-diastolic pressure either remains the same or increases. Indeed, bulging of the interventricular septum into the LV is a sign of severe RV overload (see below) and is a reflection of diastolic interaction.

The ventricles also interact during systole. This interesting interaction arises because the ventricles share common fiber bundles, contract toward a common center of gravity, are found within a common pericardial sac, and share a common septum. This means that rather than impairing the function of the opposite ventricle, contraction of one ventricle actually enhances the function of the other. Although the low-pressure RV does little to enhance pressure generation in the LV, as much as 40% to 60% of the pressure generated in the RV is attributable to LV contraction! Systolic interaction is mediated largely through the septum but is substantially enhanced by increasing the elasticity of the RV free wall. This is yet another mechanism by which LV systolic pressure (arterial pressure) increases RV afterload tolerance.

CLINICAL FEATURES OF ACUTE PULMONARY HEART DISEASE

The clinical manifestations of acute PHD are nonspecific and include dyspnea, orthopnea, and cough. Physical examination may reveal distended neck veins with prominent *a* and *v* waves, pulsus paradoxus, and peripheral cyanosis. Inspection of the precordium may demonstrate RV lift, whereas palpation of the cardiac impulse may reveal a parasternal or subxyphoid heave. On cardiac auscultation, an S3 gallop and a loud pulmonic component of the second sound are usually present. A holosystolic murmur along the left parasternal border, accentuated during inspiration, suggests tricuspid regurgitation, often seen with acute or chronic pulmonary hypertension. Auscultation of the lung fields may be normal or may reveal bilateral basilar crackles. Although the patient's history and a carefully performed physical examination may suggest acute PHD, additional diagnostic studies may be necessary to confirm the diagnosis.

CHRONIC PULMONARY HEART DISEASE

Chronic PHD develops when pulmonary disease is bilateral, diffuse, and chronic. Causes of pulmonary hypertension are discussed in previous chapters. Table 1 lists many of the causes of chronic PHD. Chronic obstructive pulmonary disease is by far the most commonly seen cause of chronic PHD in the developed world. Pulmonary heart disease is especially seen in patients with the features of the so-called blue and bloated (type B) syndrome, consisting of hypoxemia, hypercapnia, and peripheral edema. Although the true incidence of chronic PHD is probably unknown, 10% to 30% of hospital admissions in the United States for congestive heart failure are caused by PHD. As discussed in previous chapters, hypoxemia and subsequent vascular remodeling are probably the most important correctable features seen in chronic PHD. Although destruction of peripheral pulmonary vessels can contribute to increased pulmonary arterial pressure, this factor appears to be minor.

Recent studies using computed tomography to quantify the extent of parenchymal obstruction have demonstrated a similar extent of emphysema in patients with the “blue and bloated” syndrome (hypoxia, hypercapnia, edema, polycythemia) as in the so-called “pink and puffing” syndrome (normoxic, breathless). Another recent study has demonstrated that RV weight correlates with peripheral airway narrowing and not with emphysema. Thus, peripheral vascular destruction probably plays a minor role in the genesis of pulmonary hypertension and PHD in patients with COPD, the major role being hypoxemia with secondary vascular narrowing and remodeling. In patients with COPD, there is a positive correlation between arterial PCO_2 and pulmonary arterial pressure. This suggests additive effects of hypercapnia and acidosis in these patients. Peripheral pulmonary vascular obstruction may be a more important mechanism for the genesis of PHD in diseases such as pulmonary fibrosis when peripheral vascular obstruction may be extensive, although these conditions have been less well studied than COPD.

Right Ventricle in Chronic PHD

Chronic PHD leads to uniform hypertrophy of the RV. The ventricular wall cross-sectional area increases, as does myocardial fiber thickness. It should be remembered that dilation of the RV may actually be associated with a greater increase in muscle mass than hypertrophy without dilation because of the increase in RV surface area. Baseline coronary flow increases in proportion to muscle mass. The RV end-diastolic pressure increases only in the later stages of pulmonary hypertension and RV hypertrophy. Because of increased muscle mass, RV myocardial O_2 demand is increased, thus rendering the RV more susceptible to demand and supply imbalance.

In contrast to acute PHD, RV systolic pressure in chronic PHD can be very high, even approaching systemic levels. Cardiac output at rest is usually normal but may be elevated in patients with chronic PHD. Patients with progressively decreasing cardiac output have a poor prognosis. This suggests that maintaining peripheral blood flow is an important adaptive response to chronic tissue hypoxemia. Polycythemia develops in many patients with chronic PHD, and this may augment peripheral O_2 delivery in the setting of a decreased cardiac output. However, polycythemia increases blood viscosity, thereby increasing pulmonary vascular resistance according to the laminar flow equation. The development of polycythemia may therefore be maladaptive, as it may contribute to further decreases in cardiac output. Patients who maintain normal or slightly elevated cardiac output with pulmonary hypertension tend to be those who do not become polycythemic, supporting the notion that polycythemia in COPD is a maladaptive response.

Patients with chronic PHD frequently experience syncope during exercise. The cause is multifactorial. Increased venous return during exercise leads to increased RV pressure and volume, thus increasing O_2 demand. This could produce RV myocardial O_2 supply–demand imbalance and even ischemia as discussed above. In addition, during exercise, systemic vascular resistance normally falls. If, because of poor RV function, cardiac output fails to increase proportionally, this will result in a fall in blood pressure, in contrast to the usual increase in systemic arterial pressure observed with exercise. Decreased systemic arterial pressure could limit RV coronary blood flow and contribute to circulatory collapse as well as lead to poor cerebral perfusion and syncope.

Pathophysiological Features

The pulmonary hemodynamics of patients with COPD has been thoroughly investigated. In the early stages, pulmonary arterial pressure is either normal or only slightly elevated. However, pulmonary arterial pressure almost invariably increases with exercise in patients with PHD. This is because of the lack of recruitable or distensible pulmonary vessels in the patient with pulmonary vasculopathy. As the disease progresses, pulmonary arterial pressure is increased even at rest. If the disease remains untreated, even with no changes in pulmonary mechanics, as hypoxemia worsens with time, pulmonary arterial pressures increase, although the rate of increase may be slow. Data on the progression of pulmonary arterial pressure in patients enrolled in the British Medical Research Council (MRC) trial on domiciliary O_2 therapy showed an increase of mean pulmonary arterial pressure of 3 torr per year. In smaller trials, other authors have found the rate of increase of pulmonary arterial pressure in untreated COPD patients to be either somewhat greater or less than this. Differences in initial disease state, degree of hypoxemia, or other patient selection factors may have accounted for the differences found.

Although pulmonary hypertension progresses slowly in patients with COPD, its presence is a poor prognostic sign. Mortality in patients with pulmonary hypertension

and PHD may be increased two- to threefold over that of comparable patients without PHD. Some studies have demonstrated that in untreated COPD, progression of pulmonary hypertension is associated with progressively worsening hypoxemia. The relationship between RV contractile function and clinical features of PHD is not clear. Some authors have found that RV function deteriorates during exercise in patients with PHD. Others have failed to show a correlation between changes in RV contractile function and clinical features of heart failure such as peripheral edema, ascites, and increased right atrial pressure. Finally, progressive decreases in systemic arterial pressure have been demonstrated in patients with pulmonary hypertension. This suggests that decreased LV afterload may help buffer the effects of pulmonary hypertension. However, as discussed above, decreased LV systolic pressure could decrease the ability of the RV to generate pressure against increased afterload. Variable results have been found regarding the changes in cardiac output with time in COPD patients with PHD.

Left-Ventricle Function in Chronic PHD

As discussed above, with RV dilation, ventricular interdependence acts to inhibit LV filling, as mediated through a leftward shift in the interventricular septum and pericardium. Indeed, decreased compliance of the LV has been demonstrated in some patients with chronic PHD. There has been a great deal of debate in the literature as to whether chronic RV overloading leads to structural and functional changes in the LV as well. In experimental studies, banding the pulmonary artery in animals led to LV as well as RV hypertrophy, supporting the concept of the whole-heart theory of PHD. Indeed, LV hypertrophy accompanies RV hypertrophy in approximately 30% of patients with COPD. Others have reported depressed LV function in patients with COPD in the absence of identifiable causes of LV failure such as coronary heart disease. On the other hand, a number of studies have failed to find evidence of LV dysfunction in patients with COPD and PHD in the absence of known causes of LV failure. More recent studies have demonstrated LV myocardial fibrosis and cellular hypertrophy in patients with COPD dying of heart failure in whom there was no identifiable cause of LV disease. It must be remembered that in addition to RV hypertrophy and dysfunction, acute-on-chronic respiratory failure is accompanied by hypoxemia, hypercapnia, and probably increased blood catecholamine levels, which could produce these changes.

There are a number of causes of impaired LV filling in patients with COPD and other obstructive airways diseases. Patients with airflow obstruction may generate large negative inspiratory swings in intrathoracic pressure, especially during exercise. Such swings increase venous return during inspiration, further dilating the RV and leading to greater diastolic interdependence effects. This may explain the early inspiratory decrease in LV preload observed in many studies. This effect is partly or wholly responsible for decreased stroke volume in early inspiration and thus contributes substantially to the pulsus paradoxus observed in many types of airway obstruction. In addition, patients with COPD often demonstrate pulmonary hyperinflation. By direct mechanical heart–lung interactions, an increased volume of the lower lobes of the lung can hinder LV filling. Finally, hypoxemia itself can impair LV relaxation.

In addition, there are factors contributing to possible LV systolic dysfunction. Large decreases in intrathoracic pressure, especially if sustained, can impair LV ejection (i.e., increase LV afterload). If intrathoracic pressure decreases more than aortic pressure during inspiration, then LV systolic transmural pressure, one measure of LV wall stress or afterload, may increase. Although sustained decreases in intrathoracic pressure increase LV afterload, the importance of this mechanism in influencing LV function with intermittent (inspiratory) exaggerated decreases in intrathoracic pressure in obstructive airways disease remains controversial.

Finally, many patients with COPD have concomitant coronary artery, valvular, or hypertensive heart disease. These conditions certainly affect LV function and contribute to further deterioration of RV function through the mechanism of backward series interaction.

Diagnosis of Chronic PHD

Both the clinical history and physical examination are critical in the diagnosis of PHD. There are several noninvasive methods that can aid in the assessment of secondary pulmonary hypertension and its cardiac complications.

Clinical Presentation

Patients with chronic PHD exhibit signs and symptoms of the underlying disease. Dyspnea is a frequent symptom and often occurs concurrently with hypoxemia and hypercapnia. However, in many patients, especially those with infiltrative or fibrotic lung disease or vascular obstruction, dyspnea is not associated with hypoxemia and is not completely relieved with oxygen therapy. In these cases, dyspnea may be caused by reflexes originating in the lungs or chest wall.

Patients with chronic PHD may present with syncope, especially during exercise, as a result of mechanisms discussed above. A type of chest pain called pulmonary artery pain has been described in patients with chronic severe PHD. This pain is anginal in character but lasts longer and is not responsive to nitrates. Stretching of the pulmonary artery or actual RV ischemia may be the cause of pulmonary artery pain. On the other hand, this type of pain may in fact represent classic coronary heart disease.

Hemoptysis may be associated with pulmonary hypertension because of leakage of blood from the vascular to the alveolar space in dilated pulmonary capillaries that rupture. It must be emphasized that hemoptysis should not be attributed to PHD until other diagnoses such as tumor, bronchiectasis, or pulmonary infarction are excluded.

Right upper quadrant fullness, early satiety, and nausea and vomiting are not uncommonly seen in patients with PHD. These symptoms are signs of chronic passive congestion of the liver. The liver may even be tender to palpation. Neurologic symptoms such as headache and mental obtundation are often seen, changes possibly attributable to decreased cardiac output and altered arterial blood gas tensions. Occasionally, hoarseness is observed, which may be caused by enlargement of the left pulmonary artery as it passes contiguous to the aorta and presses on the left recurrent laryngeal nerve.

Tachypnea at rest is often found in patients with chronic pulmonary vasculopathy, chronic pulmonary fibrosis, or infiltrative disease, but usually not in patients with stable chronic bronchitis. As in acute PHD, there may be a loud pulmonic component of the second heart sound and a RV heave and gallop. A holosystolic murmur along the left sternal border that is exacerbated on inspiration (Carvallo's sign) may be present with tricuspid regurgitation. Elevated neck veins with prominent *a* and *v* waves are associated with congestive heart failure.

Peripheral Edema in PHD

Peripheral edema is part of the congestive heart failure syndrome. Edema may extend into the abdominal wall and sacrum. The simplest explanation for edema is that elevated pulmonary artery pressure leads to elevated right atrial pressure, which in turn raises peripheral venous and capillary pressure. This leads to an increased hydrostatic gradient for fluid transudation. However, many patients with peripheral edema have normal right atrial pressures. Thus, the explanation for edema must be sought elsewhere.

There are data demonstrating that chronic hypoxia and hypercapnia can lead to abnormal renal excretion of sodium and water. Hypoxia can lead to decreased glomerular filtration and decreased filtration of sodium. Retention of bicarbonate by the kidney is a mechanism for maintaining arterial pH in cases of chronic respiratory acidosis. Because bicarbonate is retained with Na^+, this constitutes an additional edemagenic mechanism. Hypoxemia may also stimulate the production of arginine vasopressin (AVP) and lead to decreased free water excretion. Alternatively, AVP production may be stimulated by the renin–angiotensin system, specifically angiotensin II, which is activated by a reduction in renal blood flow that is seen with hypoxia. Catecholamines, often elevated in COPD patients, can also lead to renin release from the kidneys and promote sodium absorption.

Atrial natriuretic peptide (ANP) is, as expected, elevated in patients with COPD and edema. It has been demonstrated that these patients exhibit normal responsiveness to ANP following water loading. However, the response to ANP, which acts to buffer edemagenic mechanisms, is not sufficient to overcome them in the most severe patients. Finally, circulating L-dopa is filtered at the glomerulus and enters renal tubular cells under the influence of sodium. Here, L-dopa is converted into dopamine by the enzyme L-dopa decarboxylase. Stimulation of dopamine receptors promotes natriuresis and renal arterial vasodilation. Thus, dopamine may act to buffer the edemagenic effects of PHD in some patients. In summary, although the precise nature of the mechanisms leading to peripheral edema formation in PHD is not completely understood, it is clear that edema results from a complex series of interactions between pulmonary and peripheral hemodynamics along with alterations in salt and water balance at the level of the kidney.

Electrocardiogram

The electrocardiographic (ECG) abnormalities in PHD depend on its etiology. Patients with COPD have a characteristic ECG pattern as a result of major structural changes of the thorax and its contents. The resulting ECG patterns, such as shifts of the P wave and QRS axis, will then be superimposed on the changes caused by PHD. The ECG criteria for PHD listed in Table 2 illustrate the common patterns associated with COPD as well as with other parenchymal lung diseases. In general, ECG criteria are fairly specific but not terribly sensitive for the detection of PHD. The absence of all criteria for RV hypertrophy excludes approximately 95% of cases without RV hypertrophy. Esophageal electrocardiography is even more sensitive and specific for RV hypertrophy.

ECG criteria for cor pulmonale without obstructive disease of the airways
1. Right-axis deviation with a mean QRS axis to the right of +110°
2. R/S amplitude ratio in V_1 > 1
3. R/S amplitude ratio in V_6 < 1
4. Clockwise rotation of the electric axis
5. P-pulmonale pattern
6. S_1, Q_3 or S_1, S_2, S_3 pattern
7. Normal voltage QRS
ECG changes in chronic cor pulmonale with obstructive disease of the airways
1. Isoelectric P waves in lead I or right-axis deviation of the P vector
2. P-pulmonale pattern (an increase in P-wave amplitude in II, III, AVF)
3. Tendency for right-axis deviation of the QRS
4. R/S amplitude ratio in V_6 < 1
5. Low-voltage QRS
6. S_1, Q_3 or S_1, S_2, S_3 pattern
7. Incomplete (and rarely complete) right bundle-branch block
8. R/S amplitude ratio in V_1 > 1
9. Marked clockwise rotation of the electric axis
10. Occasional large Q wave or QS in the inferior or midprecordial leads, suggesting healed myocardial infarction

TABLE 2. *Electrocardiographic changesin cor pulmonale*

One problem with the ECG diagnosis of RV hypertrophy is that the electrical activity of the RV is considerably less than that of the LV. Thus, small changes in RV forces may be “lost” in the preponderance of leftward-acting forces. An increase in anteriorly directed forces may occur with RV hypertrophy, but this may also be a sign of posterior LV infarction. Mitral stenosis and PHD may meet the QRS criteria for apical, lateral, and posterior infarction. Severe RV hypertrophy may lead to Q waves in the precordial leads, falsely suggesting anterior myocardial infarction. However, if the precordial leads are moved down one interspace, Q waves will be abolished in RV hypertrophy but persist with LV anterior wall myocardial infarction.

In addition, many rhythm disturbances may be present in PHD. These range from premature atrial contractions to supraventricular tachycardia of all types, including paroxysmal atrial tachycardia, multifocal atrial tachycardia, atrial fibrillation, atrial flutter, and junctional tachycardia. Arrhythmias are frequently observed in patients undergoing acute-on-chronic respiratory failure. These are often secondary to acute RV overload, electrolyte abnormalities, hypoxemia, and acidosis or may be secondary to therapy with b-agonists, methylxanthines, or diuretics. Interestingly, red cell magnesium has been found to be decreased in patients with COPD in whom arrhythmias are observed. Although the overall incidence of arrhythmias is in the range of 20% to 70%, the range of the reported incidence of ventricular arrhythmias is considerably lower (7% to 24%). Patients with pure pulmonary vasculopathy such as primary pulmonary hypertension rarely demonstrate arrhythmias, suggesting that the increased incidence of arrhythmias in COPD is caused by other factors besides RV hypertrophy or pulmonary hypertension.

Figure 3 shows an ECG from a patient with severe pulmonary hypertension and PHD.

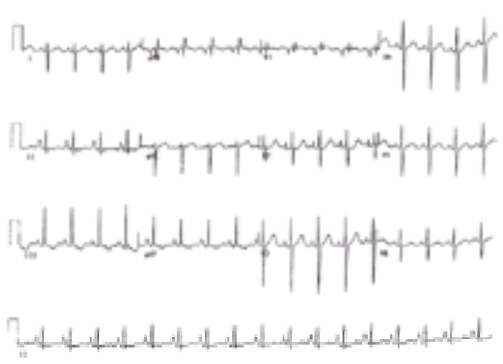

FIG. 3. Example of an electrocardiogram from a 37-year-old woman with chronic PHD related to chronic bronchiectasis. Note right-axis deviation and p-pulmonale in lead 2 along with persistent right axis forces (RS) in the lateral precordium (V_5–V_6).

Chest Roentgenogram

Routine chest radiography demonstrating a right descending pulmonary artery more than 16 mm in diameter or a left artery more than 18 mm in diameter indicates pulmonary hypertension. The RV enlargement on the posteroanterior view results in displacement of the heart shadow to the right and in an increased transverse diameter of the heart. In the lateral view, RV enlargement leads to filling of the retrosternal air space. There may be pruning of peripheral pulmonary vessels. In patients with COPD or chest wall deformity, changes in mediastinal and chest wall configuration may render the correlation of x-ray signs with RV weight unreliable. The National Institutes of Health Registry demonstrated enlarged main pulmonary arteries in 90%, enlarged hilar pulmonary arteries in 80%, and peripheral pulmonary vascular pruning in 51% of patients with primary pulmonary hypertension or chronic pulmonary thromboembolic disease. Heart size was enlarged in 94% of these patients.

Figure 4 demonstrates typical roentgenographic signs of PHD.

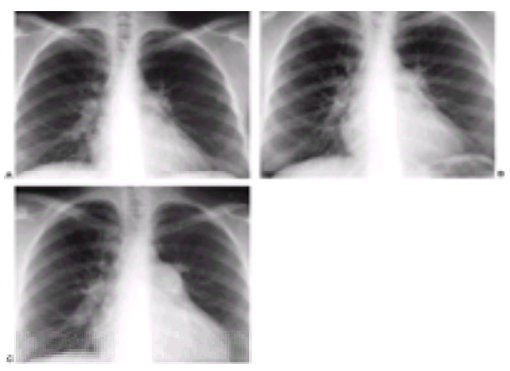

FIG. 4. Progression of chest x-ray in a 34-year-old woman with a primary pulmonary hypertension-like syndrome associated with human immunodeficiency virus syndrome. **A:** Chest x-ray taken in 1991. **B:** Chest x-ray taken in 1992. **C:** Chest x-ray taken in 1994. Note the progressive dilation of the main pulmonary arteries and cardiac dilation over the years.

Ultrafast Computed Tomography

Ultrafast, ECG-gated CT scanning has recently been evaluated for studying global and regional systolic and diastolic RV function. Good correlations between RV and LV stroke volumes have been obtained, and RV ejection fraction (RVEF) can been reliably estimated. Further, the stop-action mode of ultrafast CT has been shown to yield estimates of RV wall mass that correlate to actual mass in both animals and human studies. As these techniques improve, it is expected that they will be utilized increasingly in the evaluation of the progression of chronic PHD.

Echocardiography

The diagnostic application of M-mode echocardiography in evaluating the RV is limited. Because the right-sided cardiac structures are anatomically situated posterior to the echo-dense sternum, accurate assessment is technically difficult. Pulmonary hyperinflation and excessive chest motion in patients with COPD also impose

limitations to this technique.

Two-dimensional (2-D) echocardiography provides multiple cross-sectional views of the heart, improves visualization of right-sided cardiac structures, and is useful in assessing RV hypertrophy in patients with PHD. In addition, multiple cross-sectional views can be employed to obtain relatively accurate estimations of RV volume using the Simpson's rule approximation technique. Measurements of right atrial and RV size by 2-D echocardiography distinguish normal patients from those with RV volume overload and correlate with measurements made at cardiac catheterization.

There have been correlations made between indices of RV size and/or mass and pulmonary hemodynamics. One measurement called the RV index is equal to (TA × RV + AW/BSA), where TA is the inner tricuspid annulus diastolic dimension, RV is RV short-axis dimension, AW is RV anterior wall thickness, and BSA is body surface area. This index has been shown to correlate reasonably well with mean pulmonary arterial pressure.

The use of velocity measurements (Doppler echocardiography) has allowed noninvasive estimation of the pulmonary arterial pressure. One convenient method utilizes the fact that, because of dilation of the tricuspid annulus, most patients with RV overload develop some degree of tricuspid regurgitation. The pressure gradient across the tricuspid valve during systole can be estimated from the maximum velocity of the regurgitant jet and the modified Bernoulli equation:

$$PG = 4\ V^2$$

where *PG* is pressure gradient across the valve and *V* is the maximum velocity of the regurgitant jet. If right atrial pressure is measured by another technique (e.g., by neck vein distention on physical exam) or a value is assumed, then this value is added to the value for *PG.* Thus, RV and pulmonary arterial systolic pressure may be estimated. Other techniques for estimating pulmonary arterial pressure using Doppler measurements of pulmonary arterial velocity also exist and may be employed when tricuspid regurgitation is not present.

Chronic RV overload leads to RV dilation, especially during inspiration, when venous return is maximized. These changes can result in changes in RV configuration and impairment of LV diastolic filling by ventricular interdependence. Because these effects are mediated through the interventricular septum, they may be detected by echocardiogram. Normally, the septum is concave toward the LV, resulting in a relatively circular LV shape in the axial plane during diastole. During systole, there is symmetric inward motion of the ventricular walls, resulting in constriction of the LV while it maintains its circular shape. Thus, the septum functions as part of the LV during systole. With RV volume overload, the septum may become flattened or even reverse its curvature so as to become concave toward the RV. In extreme cases, the septum may bulge into the LV during diastole. During systole, the septum may demonstrate so-called paradoxic motion, defined as motion away from the LV posterolateral wall and toward the RV free wall. The septum effectively functions as part of the RV in these cases. With a sufficient degree of leftward shift of the septum, LV end-diastolic volume may become compromised enough to lead to decreased cardiac output. Finally, from echocardiographically derived estimates of wall thickness and chamber size, estimates of RV muscle mass may be made.

Figure 5 shows an example of an echocardiogram in a patient with primary pulmonary hypertension and PHD.

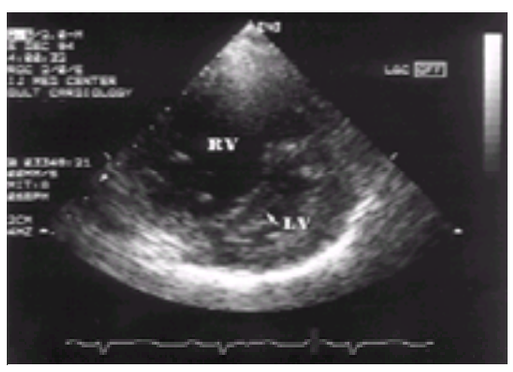

FIG. 5. Example of echocardiogram from the patient illustrated in Fig. 4 at the time of the most recent chest x-ray. This short-axis view shows severe dilation of the RV, bulging of the septum to the left in diastole, and a small LV chamber. The RV was noted to be severely hypokinetic. The *arrow* points to the interventricular septum. RV, right ventricle; LV, left ventricle. (Courtesy of Scott Roth, M.D., Division of Cardiology, Long Island Jewish Medical Center, New Hyde Park, NY.) *See Color Plate 19.*

Radionuclide Techniques

The equilibrium-gated blood-imaging technique allows continuous monitoring of RV performance by tagging erythrocytes with technetium-99m. Ejection fraction is calculated by comparing counts at end-systole with those at end-diastole over approximately 10 min. Although equilibrium-gated blood pool imaging allows continuous monitoring of RV performance and provides reliable measurements of RV ejection fraction (RVEF), RV dimensions are difficult to evaluate because the ventricular borders are obscured by the presence of background counts in other cardiac chambers and the lungs. The “first-pass” technique also involves labeling with technetium-99m but is based on principles of indicator dilution theory, whereby counting is done sequentially over each cardiac chamber as a function of time. The advantage of the first-pass technique is that data are gathered over only a few heartbeats. Further, the large number of counts relative to background allows definition of the RV borders and estimates of diastolic and systolic size. Both first-pass and equilibrium-gated techniques can be used to evaluate ventricular function at rest and during exercise. The first-pass techniques allows patients to be studied in the supine or upright position, which is a major advantage. The 30° right anterior oblique position is optimal for assessing the RV. It should be noted that although radionuclide studies can detect severely elevated pulmonary arterial pressure, they cannot accurately assess mild pulmonary hypertension. The prediction of the actual level of mean pulmonary arterial pressure from radionuclide measurements is also difficult.

Right ventricle function in COPD depends on the cause, duration, and severity of PHD. The correlations between pulmonary arterial pressure and RVEF and, similarly, those between pulmonary vascular resistance and RVEF have generally been weak. Exercise studies appear to enhance the detection of decreased RVEF by radionuclide techniques.

Thallium-201 is another radionuclide used for imaging the RV. Thallium is taken up by myocardial tissue, in contrast to technetium, which images the blood pool. Although visualization of the RV at rest is not common in normals, the thickened RV myocardium present in patients with chronic PHD allows RV visualization in these patients. Thallium imaging techniques are most sensitive for detecting RV hypertrophy when mean pulmonary arterial pressure is greater than 30 torr.

Radionuclide scanning can be combined with tomographic techniques to yield images of RV blood pool and RV myocardial perfusion. Single-photon-emission computed tomography (SPECT) can be used to reconstruct three-dimensional surface images of the ventricles, which permit visualization of atrial and ventricular movements in humans. This exciting dynamic technique will undoubtedly prove to be extremely useful in the evaluation of RV function and the interactions of RV and LV function in patients during the progression of PHD.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) allows the noninvasive evaluation of RV free wall mass. With this technique, mean RV free wall mass has been shown to be greater in patients with chronic PHD than in normals. A modified short-axis section of the heart imaged by MRI appears to provide valid clinical configurational information concerning the RV on which the noninvasive diagnosis of PHD may be entertained.

In summary, with the increasing availability of noninvasive techniques for evaluating ventricular function, invasive procedures are often not indicated for the routine diagnosis of PHD. However, if unexplained RV dysfunction presents in a patient without previously diagnosed pulmonary disease, other diagnoses such as primary pulmonary vascular disease, pulmonary embolism, or left heart failure should be considered. Right heart catheterization and pulmonary angiography may be indicated in these cases.

THERAPY OF CHRONIC PHD

Of course, specific disease-directed therapy is always part of the therapeutic regimen. This may include treatment of infection and bronchodilation in COPD, treatment with steroids or other immunosuppresive agents in chronic infiltrative and fibrotic disorders, and anticoagulation in chronic thromboembolic diseases. In this section we

review some of the principles of supportive therapy that apply to cases of chronic PHD.

Oxygen Therapy

Oxygen therapy is the only mode of therapy shown to improve long-term prognosis in patients with COPD and hypoxemia. It is the only drug that causes long-term pulmonary vasodilation and halts the progression of pulmonary vasoconstriction in COPD patients with chronic PHD. However, the use of oxygen in treating causes of PHD other than COPD has not been as firmly established. There are no large randomized controlled trials of O_2 therapy in diseases such as pulmonary fibrosis and pneumoconioses as there are for COPD. However, in diseases such as pulmonary fibrosis, pneumoconioses, cardiac failure, and terminal cancer, O_2 therapy certainly appears to offer significant symptomatic relief and should not be withheld even though patients do not meet the currently accepted criteria for long-term O_2 therapy used in COPD. Further, many patients are normoxic at rest (O_2 saturation >92%) but become severely hypoxic either at night or during exercise. Although the administration of O_2 has not been unequivocally demonstrated to improve long-term prognosis in these patients, many patients derive significant functional benefit from the administration of O_2 during times of hypoxemia. For example, many patients with idiopathic pulmonary fibrosis and exercise-induced hypoxemia will demonstrate increased exercise tolerance and less exercise-induced dyspnea if portable O_2 is administered during activities of daily living.

Short-Term Effects of O_2 Therapy

Many patients presenting to the hospital with acute-on-chronic respiratory failure are hypoxemic, and treatment with oxygen leads to substantial clinical improvement, e.g., diuresis, decreased dyspnea, and improved mental functioning. Even though arterial O_2 content increases with short-term O_2 therapy, O_2 delivery to the periphery has not uniformly been reported to increase. This is because as arterial O_2 content increases, sympathoadrenal stimulation decreases, which may lead to reductions in cardiac output. However, in the most severely ill patients (P_aO_2 £ 40 torr), cardiac output may be fixed even with O_2 administration. In these patients, increasing arterial O_2 will increase peripheral O_2 delivery.

Hypoxia causes pulmonary vasoconstriction. Thus, the presence of pulmonary arterial hypertension is inversely correlated with arterial O_2 saturation in COPD. However, most clinical studies have documented either no change or only slight decreases in pulmonary arterial pressure associated with the acute administration of O_2 to COPD patients with acute-on-chronic respiratory failure. This suggests that increased pulmonary vascular resistance in most of these patients is a result of pulmonary vascular remodeling rather than hypoxic vasoconstriction. However, the demonstration that at least some of these patients respond to other vasodilators suggests that other factors such as sepsis, acidosis, and hypercapnia modulate the acute vasodilating effects of hypoxemia. Similarly, short-term O_2 therapy does not substantially change RV or LV function in most patients with acute-on-chronic respiratory failure. Therefore, the substantial clinical benefits of short-term O_2 therapy appear to derive primarily from effects on peripheral circulatory function rather than on improvement in cardiac function.

Long-Term Effects of O_2 Therapy

Modern recommendations concerning the administration of long-term domiciliary O_2 to patients with COPD derive from two major clinical trials. The British Medical Research Trial (MRC) consisted of 87 patients with severe COPD randomized to O_2 therapy (42 patients) or no therapy (45 patients). The two groups were clinically matched and had similarly severe stable pulmonary function (FEV_1 £ 1.5 liters, P_aO_2 £ 60 torr, and peripheral edema with or without hypercapnia). The treatment group was given nasal O_2, 2 liters/min or O_2 sufficient to increase P_aO_2 to at least 60 torr, for at least 15 hr per day. After 5 years, survival was 50% greater in the O_2-treated group than in the untreated group. Interestingly, pulmonary arterial pressure did not decrease in the treated group. However, the increase of 3 torr/year in mean pulmonary arterial pressure noted in the control group was not seen in the treated group. Pulmonary vascular resistance increased by 27% in the untreated patients and decreased by 11% in the treated group. However, this decrease occurred only after 6 months of treatment. This suggests that oxygen therapy reversed some of the structural changes in the pulmonary vasculature associated with chronic hypoxemia. This notion is supported by follow-up studies demonstrating less severe structural abnormalities in the pulmonary vasculature of the treated patients and is consistent with animal studies demonstrating resolution of structural abnormalities in hypoxia-induced pulmonary hypertension with removal of the hypoxic stimulus.

The nocturnal oxygen therapy trial (NOTT) sponsored by the National Institutes of Health in the United States compared 24-hr (“continuous”) and 12-hr (“intermittent”) O_2 therapy in patients with severe COPD. The study was stopped after 18 months because of the enhanced survival in the patients treated for 24 hrs (approximately double that of the 12-hr group). This continuous group actually used O_2 for a mean of 17.7 hr/day (56% took it for >19 hr). Pulmonary vascular resistance increased by 6.5% in the 12-hr group but decreased by 11% in the treated group. Long-term follow-up of patients in the NOTT trial showed that an improvement in resting and exercise RV stroke volume and a decrease in pulmonary vascular resistance predicted survival.

The conclusion from these trials was that long-term O_2 therapy in patients with hypoxic COPD can enhance survival. Little survival benefit was derived from 12 hr/day; maximum benefit was to be derived from 24 hr/day use. Table 3 presents some of the accepted criteria used by physicians and third-party payers for providing long-term domiciliary O_2 in the United States. As noted in the table, there are patients who do not meet the strictest criteria for home O_2 therapy who are nevertheless candidates for such therapy. Controlled trials of these patients do not exist, and the indications for therapy are primarily by inference, physiological considerations, and small trials. Clinical features of PHD such as secondary polycythemia, elevations in pulmonary arterial pressure and pulmonary vascular resistance, and peripheral edema are poor prognostic signs. Thus, it is reasonable to institute therapy when these are present, even though a spot check of resting P_aO_2 does not meet the strictest criteria. Often exercise testing or monitoring of O_2 saturation during sleep provides documentation of arterial desaturation to allow for the prescription of home O_2 therapy payable by third-party payers.

P_aO_2 ≤55 torr or O_2 saturation ≤88% on room air at rest in nonrecumbent position
P_aO_2 >55 torr or O_2 saturation ≤88% with evidence of secondary polycythemia (hematocrit ≥55), RV hypertrophy, impaired mental or cognitive function
P_aO_2 ≤55 torr or O_2 saturation ≤88% during exercise with demonstrable improvement in exercise performance with O_2 therapy
P_aO_2 ≤55 torr or O_2 saturation ≤88% during sleep especially associated with fragmentation of sleep, cardiac arrhythmias or ischemia, or pulmonary hypertension

TABLE 3. *Indications for long-term oxygen therapyin COPD*

Stability of Respiratory Failure and Long-Term O_2 Therapy

Long-term O_2 therapy has been shown to be of benefit only in COPD patients with stable chronic respiratory failure. Thus, the decision to institute long-term therapy should not be based on pulmonary function and arterial blood gases taken immediately after a bout of acute-on-chronic respiratory failure. Of course, this does not mean that patients presenting to the hospital who are discharged with resting hypoxemia should not be treated with O_2 for a few weeks while their pulmonary function is allowed to improve. Rather, these patients should be assessed for long-term O_2 use when they have become clinically stable. Studies have demonstrated that following acute-on-chronic respiratory failure, approximately 30% to 40% of patients will improve sufficiently with 3 weeks of standard therapy using bronchodilators and antibiotics to obviate the need for chronic O_2 therapy. There is no reliable means of predicting which patients will improve to the point of not needing O_2 therapy. Thus, at least 3 weeks of optimum standard care should be instituted in hypoxemic COPD patients before initiation of long-term O_2 therapy. Only if the accepted criteria are met after optimal standard care should therapy be instituted with O_2.

Patients who smoke should be *required* to stop smoking as a precondition for receiving a prescription for O_2. Aside from the obvious danger of having a lighted

cigarette in the flow stream of O_2 and the philosophical concerns of self responsibility, the presence of elevated carboxyhemoglobin in the blood from smoking will largely obviate the effects of O_2 on arterial O_2 content.

Nocturnal Hypoxemia

Many patients with COPD are hypoxic primarily at night and may under go severe desaturation during sleep, especially during rapid eye movement (REM) sleep. Reasons for this include nocturnal hypoventilation, ventilation–perfusion imbalance from loss of tonic skeletal muscle tone, and coexisting congestive heart failure and Cheyne–Stokes respiration and/or obstructive sleep apnea. There is no firm evidence that episodes of nocturnal desaturation *per se* lead to clinical harm; however, a number of workers believe that nocturnal desaturation may have significant clinical consequences. Nocturnal hypercapnia may lead to resetting of the central ventilatory controller and predispose to daytime hyperventilation. Nocturnal events may account for the development of clinical signs of PHD in COPD patients with daytime O_2 saturations in the normal range. Clearly, the combination of COPD and concomitant disease such as obstructive sleep apnea (overlap syndrome) predisposes to severe nocturnal hypoxemia. Both conditions must be dealt with to successfully relieve nocturnal hypoxemia.

Clinical PHD is seen in some 5% to 12% of patients with obstructive sleep apnea. Echocardiographic studies have demonstrated an association between RV hypertrophy and the occurrence of obstructive sleep apnea in children as well as adults. Figures range from 50% to 90%. Nocturnal hypoxemia and increases in pulmonary arterial pressure during apneas may contribute to PHD in these patients. Another possible mechanism is that during obstructive apneas, there are large increases in venous return during inspiration compared to expiration, which may lead to flow overload of the RV. When upper airway obstruction is relieved in these patients, improvement in RV function is almost always noted.

Other causes of nocturnal desaturation related to hypoventilation at night include chest wall deformity, severe muscle weakness or paralysis, Ondine's curse, and obesity-hypoventilation syndrome. Many of these patients will benefit greatly from nocturnal ventilation with resulting normalization of O_2 saturation.

Exercise Hypoxemia

Some relatively normoxic COPD patients become hypoxemic while exercising. Although this may not lead to increased resting pulmonary arterial pressures or increased mortality, the administration of O_2 during exercise can increase exercise tolerance and thus lead to an improved quality of life. During the NOTT trial, those patients receiving continuous O_2 may have done better not simply because they received O_2 for a greater proportion of the day but because they were better oxygenated during exercise. Similarly, in other hypoxic pulmonary conditions, O_2 administered during exercise may lead to improved quality of life. Exercise testing should be performed to document improved exercise tolerance during administration of O_2 on a case-by-case basis, and O_2 should be prescribed for patients with exercise hypoxemia in whom objective evidence of improved function can be documented.

Pulmonary Vasodilator Therapy in PHD

The demonstrated benefit of pulmonary vasodilator therapy in at least some patients with primary pulmonary hypertension has led to numerous attempts to treat PHD secondary to other conditions, most notably COPD, with vasodilator regimens. This topic has been covered thoroughly elsewhere. Various classes of vasodilators including, b-adrenergic blockers, b-agonists, calcium channel blockers, nitrates, and angiotensin-converting enzyme inhibitors have been tried. In general, vasodilator therapy has failed to demonstrate sustained therapeutic benefit in patients with COPD, and its use cannot be recommended on a routine basis. Methylxanthines lead to improved RV performance in patients with COPD, perhaps through a vasodilatory mechanism. b_2-specific agonists also act as pulmonary vasodilators in addition to their well-known effects on bronchomotor tone and mucociliary clearance. Finally, there are some individuals who will derive benefit from specific pulmonary vasodilator therapy; agents may be tried on a case-by-case basis before this form of therapy is undertaken for the long term.

Cardiac Glycosides

The utility of cardiac glycosides in PHD has been clearly documented only in the presence of concomitant LV dysfunction. There are few data to support therapeutic benefit from cardiac glycosides in isolated PHD. This, plus the fact that acute hypoxemia may increase toxicity of these agents, either directly or through secondary mechanisms such as sympathoadrenal stimulation, makes it difficult to recommend cardiac glycosides for routine treatment of PHD.

Phlebotomy and Diuretics

Reduction in intravascular volume could lead to improved function. Extravascular lung water may increase during episodes of acute-on-chronic respiratory failure associated with PHD by mechanisms discussed above. Reduction of extravascular lung water may therefore be of substantial clinical benefit. Too great a reduction in vascular volume could reduce mean circulatory pressure and lead to unwanted reductions in cardiac output and renal blood flow. In addition, care must be taken to avoid the hypokalemia that can accompany diuresis. Hypokalemia can produce metabolic alkalosis, which, when combined with possible contraction alkalosis with overdiuresis, can lead to decreased respiratory drive. Thus, adequate diuresis for clinically apparent edema is clearly beneficial, but care should be taken to maintain a normal volume state.

Blood viscosity increases sharply as the hematocrit exceeds approximately 55. This may lead to increased pulmonary vascular resistance according to the laminar flow equations and eventually to increased RV afterload. Because secondary polycythemia is a sign of hypoxemia, it should theoretically be preventable with adequate long-term O_2 therapy. However, with persistently elevated hematocrit (>55), phlebotomy should be considered. The increase in cardiac output that accompanies reduction of blood viscosity often increases peripheral O_2 delivery even though blood hemoglobin is reduced.

Almitrine Bismesylate

Almitrine bismesylate is a triazine derivative that increases the sensitivity of peripheral arterial chemoreceptors to hypoxia. Doses in the range of 50 to 100 mg twice daily have been shown to lead to increased arterial Po_2 without the need for additional O_2 therapy. Nocturnal arterial oxygenation has also been shown to be increased in patients with COPD and sleep apnea. One possible mechanism for the observed improvement in arterial oxygenation is a reduction in ventilation–perfusion mismatching. However, elevations in pulmonary arterial pressure and pulmonary vascular resistance have been reported, and it has been suggested that increasing pulmonary vasomotor tone with almitrine could worsen PHD. Further, some patients on almitrine demonstrate increased dyspnea, perhaps related to increased sensitivity to O_2. Thus, the role of this interesting agent in treating hypoxic respiratory failure and PHD remains unclear.

Lung Transplantation

Although lung transplantation was originally introduced for treatment of end-stage restrictive lung disease, the indications and eligible age range for this procedure are being widened. Patients with end-stage obstructive and vascular diseases are now considered candidates for transplantation. Patients with PHD who undergo lung transplantation may demonstrate improvement in RV function and resolution of pulmonary hypertension. Unfortunately, this mode of therapy will be limited by organ donor availability.

Lung Reduction Surgery

Currently, lung reduction surgery for patients with severe pulmonary emphysema is a promising new mode of therapy that may bring improvement in mechanical function of the lungs. Severe PHD is presently considered to be a contraindication for this surgery, primarily because of the associated increased peri- and postoperative mortality. However, the long-term effects of lung reduction surgery on pulmonary hemodynamics still need to be evaluated. Improved oxygenation and decreased mechanical distortion of pulmonary vessels postoperatively may lead to improved pulmonary hemodynamics.

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CHAPTER

68 Bronchogenic Carcinoma

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INTRODUCTION

Lung cancer is presently the most common and deadly malignancy in the United States and throughout the world. According to the American Cancer Society, bronchogenic carcinoma will be responsible for 160,400 cancer deaths in the United States in 1997. This compares with 140,890 deaths from colorectal cancer, breast cancer, and prostate cancer combined. In 1993, lung cancer was responsible for 28% of all cancer deaths in the United States, and 6.5% of all deaths. Almost 600,000 deaths from lung cancer occurred worldwide in 1995; it is projected that this figure will continue to rise well into the next century. Fifty percent more women will die of lung cancer than of breast cancer in the United States in 1997 (66,000 vs. 43,900). This is true despite the fact that breast cancer will be diagnosed this year in 225% more women than will lung cancer (180,200 vs. 79,800).

An examination of epidemiologic trends demonstrates that the sharp rise in lung cancer death rates is sufficient to account for the increase in overall mortality from cancer in this country. The only encouraging news is that the age-adjusted lung cancer mortality rates have declined 3.6% between 1990 and 1995. Nonetheless, aging of the population and increases in population size have contributed to the grim fact that the absolute number of new cases of lung cancer and the absolute number of lung cancer deaths have increased every year during at least the last half century. To date, public health measures and therapeutic advances have failed to reverse the

inexorable trend of increased lung cancer mortality in our society.

DETERMINANTS OF LUNG CANCER RISK

Cigarette Smoking

In 1604, in “A Counterblast to Tobacco,” King James I of England declared that the use of tobacco products represented “. . . a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs.” Although tobacco products were introduced in Europe shortly after the discovery of the New World, lung cancer was a distinctly uncommon disease until well into the twentieth century.

In 1912, Adler first suggested that inhalation of cigarette smoke might be a cause of lung cancer. However, he also made note of the fact that a “nearly complete consensus of opinion” existed “that primary malignant neoplasms of the lungs are among the rarest forms of the disease.”

In 1920, lung cancer comprised approximately 1% of all malignancies in the United States. The development of the technology to mass produce cigarettes early in this century coupled with the generosity of the American Red Cross in providing free cigarettes to those serving in World War I greatly contributed to a marked increase in smoking prevalence.

In 1938, the first scientific report appeared that pointed out an association between cigarette smoking and an increased risk for premature death. However, it was not until 1950 that Doll and Hill clearly demonstrated an epidemiologic association between cigarette smoking and increasing lung cancer mortality, an observation that was confirmed shortly thereafter by Wynder and Gardner in 1951.

Because of the indisputable link between cigarette smoking and a dramatic increase in lung cancer risk, bronchogenic carcinoma is without doubt the most preventable of the common cancers in our society. In one study of 3070 patients with lung cancer from Edinburgh, only 2% of cases occurred in lifelong nonsmokers. In the United States, current estimates indicate that 87% of all cases of lung cancer are directly attributable to cigarette smoking. This includes 90% of lung cancers in men and 79% of cases in women.

It is well-known that the relative risk for lung cancer in long-term cigarette smokers is dramatically increased versus that of lifetime nonsmokers, with estimates varying from 10- to 30-fold. The lifetime risk for development of lung cancer in a nonsmoker is probably about 1% or less. In dramatic contrast, the cumulative lung cancer risk may be as high as 30% in heavy smokers. It has been estimated that a 35-year-old man has a 9% chance of dying of lung cancer before the age of 85 if he smokes <25 cigarettes per day, and an 18% chance of dying of lung cancer if he smokes >25 cigarettes per day.

The major evidence linking cigarette smoking to human lung cancer has primarily been based on an enormous body of prospective and retrospective epidemiologic research. Well-established criteria, based on observational evidence, have been used for the attribution of causality. These criteria are based on five factors, which include (1) the consistency, (2) strength, (3) specificity, (4) temporal relationship, and (5) coherence of the association between a disease and exposure to the disease-associated variable (e.g., smoking). Applying these criteria to a huge body of observational data, the Surgeon General definitively concluded that “cigarette smoking is the major cause of lung cancer.”

Until recently, the evidence linking cigarette smoking to lung cancer has been primarily indirect. However, a direct link between tobacco and lung cancer has recently been established. Employing genetic amplification techniques, it was demonstrated that a specific metabolite of benzo[*a*]pyrene, a chemical constituent of tobacco smoke long suspected of being directly involved in carcinogenesis, damages three specific loci on the p53 tumor suppressor gene that are abnormal in about 60% of primary lung cancers. This finding was described as the “smoking gun” or “missing link” that definitively demonstrates the causal relationship between cigarette smoking and lung cancer.

Studies have demonstrated that lung cancer susceptibility in cigarette smokers can be substantially modified by a wide variety of environmental agents and host characteristics. Many of these factors have also been demonstrated to be independent risk factors for the development of lung cancer.

Occupational and Environmental Carcinogens

Asbestos

Numerous occupational and environmental carcinogens are known to increase lung cancer risk in cigarette smokers. The best-studied of these factors are asbestos and radon; additional factors include arsenic, bis(chloromethyl) ether, chromium, ionizing radiation, nickel, polycylic aromatic hydrocarbons, and vinyl chloride.

It has been demonstrated that the risk for development of lung cancer is substantially increased by previous asbestos exposure. Asbestos workers' risk for dying of lung cancer is increased 16-fold if they have smoked more than 20 cigarettes per day and 9-fold if they have smoked less than 20 cigarettes per day, compared with asbestos workers who have never smoked regularly. When cigarette smokers are considered as a group, a history of asbestos exposure increases the risk for dying of lung cancer about fivefold.

Moreover, the risk of lung cancer in those exposed to asbestos and cigarette smoking is multiplicative. If age-adjusted lung cancer death rates for those without exposure to asbestos or cigarette smoking is arbitrarily defined as 1, the relative risk for cigarette smokers not exposed to asbestos is 11. For those with asbestos exposure and no smoking history, the relative risk is 6. However, for cigarette smokers with a history of asbestos exposure, the relative risk is 59. For any individual patient, the relative risk fluctuates according to the level of smoking and degree of asbestos exposure.

The magnitude of risk for lung cancer caused solely by asbestos depends somewhat on the type of asbestos fiber. Lung cancer risk appears to be considerably higher for workers exposed to amphibole fibers than for those exposed to chrysotile fibers, controlling for the amount of exposure. The magnitude of lung cancer risk in workers with an occupational exposure to asbestos is dose-dependent.

Radon

In recent years, there has been considerable public concern about the possible risks for lung cancer caused by radon exposure. Radon is a decay product of uranium 228 and radium 226; it damages respiratory epithelium via interactions with alpha particles. It is present in soil, rocks, and groundwater, and can accumulate in homes. The risk for lung cancer related to radon exposure has been studied in underground uranium miners who were occupationally exposed to radioactive radon and its decay products. In this setting, an increased risk for lung cancer has been established. An interaction between radon exposure and cigarette smoking has also been demonstrated.

The risks associated with household exposure to radon remain uncertain. These risks have been assessed in eight case-control studies, three of which showed statistically significant associations and five of which did not. A recent meta-analysis of these eight studies reported a greater risk for lung cancer associated with higher levels of indoor radon. Moreover, the summary exposure-response trend was statistically significant, suggesting that the overall relative risk for lung cancer among those exposed to household radon was 1:14.

Family History and Genetic Determinants

Family history has received insufficient attention as a risk factor for lung cancer. One case-control study reported that relative risk for lung cancer mortality among smoking relatives of lung cancer patients was twofold to 2.5-fold greater than that of smoking relatives of controls. Even among nonsmoking relatives, lung cancer risk was higher among relatives of patients than of controls. Other studies have demonstrated that the first-degree relatives of lung cancer patients have a twofold to threefold higher risk for lung cancer.

Recent data indicate that the genetic component of lung cancer risk is greater than has been previously estimated. Indeed, there exists a genetic susceptibility to the effects of tobacco smoking that is inherited on the basis of mendelian codominance. Lung cancer risk was 2.4-fold greater among first-degree relatives of 336 deceased lung cancer probands compared with 307 controls (consisting of probands' spouses). A case-control study reported that a history of lung cancer in a parent was associated with a 5.3-fold increased risk for development of lung cancer. A recent review concluded that a consistent pattern of increased prevalence of lung cancer exists among relatives of lung cancer patients even after adjusting for the effects of age, sex, and smoking habits, with the average excess risk being about twofold.

Benign Lung Disease

The coexistence of a number of benign lung diseases increases lung cancer risk in cigarette smokers. Emphysema, bronchitis, and pulmonary fibrosis have all been demonstrated to increase lung cancer risk. Individuals with diffuse pulmonary interstitial fibrosis have a 14-fold increased risk for lung cancer, even when age, sex, and smoking history are taken into consideration. A case-control study demonstrated that chronic obstructive pulmonary disease (COPD) was associated with an overall doubling of the lung cancer risk. A statistically significantly higher risk of lung cancer has been demonstrated in a group of individuals having COPD compared with a cohort not having COPD (matched for age, sex, occupation, and smoking history).

The increased lung cancer risk in individuals exposed to asbestos has been discussed above. It appears that lung cancer is much more likely to develop in asbestos workers with asbestosis (interstitial fibrosis) than in those without asbestosis. In one study of 138 asbestos workers who died of lung cancer, fibrosis was microscopically present in the lung tissue of all sampled patients.

Dietary Factors

Dietary factors have been shown to influence lung cancer risk. An extensive body of literature suggests that certain antioxidant vitamins, particularly derivatives of vitamin A and vitamin E, may help to prevent lung cancer. Indeed, there is substantial evidence for a reduction in lung cancer risk by the regular ingestion of fruits and vegetables.

More than 100 epidemiologic surveys have demonstrated that individuals with high levels of beta carotene in their diet or blood have a lower risk for cancer in general and lung cancer in particular. Case-control or cohort studies have consistently shown that certain antioxidant vitamins decrease the risk for lung cancer. In 30 of 32 studies, the risk for lung cancer was reduced among those who consumed substantial quantities of fruits, vegetables, or both. Existing data suggest that an increase in consumption of fruit, green and yellow vegetables, and possibly some micronutrients can meaningfully decrease lung cancer risk among cigarette smokers.

Results from randomized trials have been much more inconsistent and less encouraging. The Alpha-Tocopherol Beta Carotene Lung Cancer Prevention Study, a population-based randomized trial involving almost 30,000 male cigarette smokers in Finland, suggested a possible adverse effect on lung cancer risk among those randomized to beta carotene. Similarly, the Beta Carotene and Retinol Efficacy Trial (CARET), a randomized trial comparing beta carotene and retinyl palmitate with placebo among 18,000 men and women at high risk for lung cancer, also found a higher lung cancer incidence and mortality in the experimental group. The Physicians' Health Study, which involved approximately 22,000 male physicians, reported no significant differences between groups randomized to beta carotene or placebo. A beneficial effect of beta carotene on cancer risk was suggested by the Chinese Cancer Prevention Trial, a randomized trial involving almost 30,000 participants. Finally, a trial in which patients who had undergone resection for stage I non–small-cell lung carcinoma were randomized to either retinyl palmitate or no further treatment demonstrated a reduction in the number of second primary lung cancers in those randomized to adjuvant high-dose vitamin A therapy. The definitive answer regarding the effects of dietary factors on lung cancer risk is not yet known.

Molecular Genetic Factors

The most influential determinants of lung cancer risk may be molecular genetic factors. Progress in molecular epidemiology has led to the realization that certain population subsets have a much greater risk for development of lung cancer caused by exposure to environmental carcinogens, possibly because the response to the carcinogen is modulated by genetic and acquired susceptibility factors. Unfortunately, it is not yet possible to assess the cancer risk in an individual on a molecular level. More than one genetic factor is likely important. It may soon be possible to develop a risk profile for an individual that integrates exposure to environmental carcinogens with such constitutional factors as altered proto-oncogenes and tumor suppressor genes, as well as susceptibility to DNA damage and mechanisms of DNA repair.

SMOKING AND RISK FOR LUNG CANCER

The risk for lung cancer is proportional to total lifetime cigarette consumption. The relative risk for development of lung cancer increases in proportion to the number of cigarettes smoked per day, as well as to the duration of smoking. Additional smoking-related factors that may influence risk include age at onset of smoking, degree of inhalation, tar and nicotine content of cigarettes, and use of unfiltered cigarettes. There exists no safe level of cigarette consumption, because even low levels of smoking increase lung cancer risk.

The age at which the increased risk of cigarette smokers for development of lung cancer becomes apparent is the middle to late forties. Subsequently, this age-specific relative risk increases steadily to a peak in the late seventies.

Environmental Tobacco Smoke

A great deal has appeared in the literature in recent years relating passive smoking to the risk for lung cancer. The concentration of carcinogenic constituents in environmental tobacco smoke (ETS) is far less than in smoke inhaled by a cigarette smoker. However, exposure to ETS usually begins much earlier in life than does cigarette smoking. Therefore, duration of exposure to environmental carcinogens occurs during a longer period of time.

Epidemiologic studies of nonsmokers with a history of high-level exposure to ETS demonstrates an increased risk for development of lung cancer compared with those having lower cumulative exposures. A dose-response relationship between intensity of exposure and relative risk has been reported.

Decreasing Prevalence of Smoking in Adults

Despite the increasing number of lung cancer cases, smoking prevalence among the adult population has been steadily decreasing for decades. A National Cancer Institute (NCI) survey conducted in 1955 demonstrated that nearly 60% of men and 28% of women were current cigarette smokers. When *Smoking and Health,* the first Surgeon General's report, was published in 1964, 70 million Americans used tobacco products. In the mid-1960s, 42% of adults in the United States smoked cigarettes on a regular basis. This proportion has steadily declined since that time, and was 37% in 1974, 33% in 1980, 29% in 1987, 26% in 1991, 25% in 1993, and 23% in 1995 (Fig. 1). The number of cigarette smokers in the United States was 50 million in 1965, 53 million in 1983, and 46 million in 1991. In 1993, there were estimated to be 46 million current and 46 million former smokers in this country.

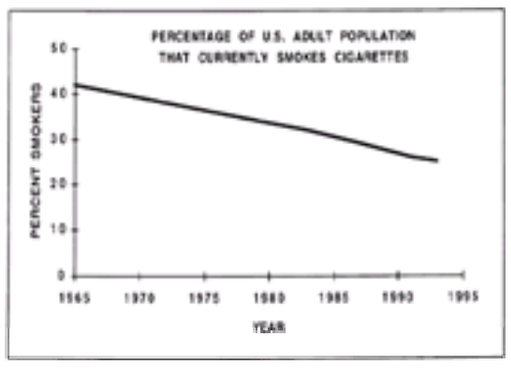


FIG. 1. Percentage of U.S. adult population that currently smokes cigarettes.

The U.S. Public Health Service had set a goal that smoking prevalence fall to 15% by the turn of the century. Unfortunately, indications are that this goal will not be reached. In the late 1980s, smoking prevalence was declining at a rate of about one percentage point per year, and in 1987 stood at 29%. However, in the 1990s, the cessation rate has slowed to about one-half percentage point per year. It has been projected that the percentage of Americans who continue to smoke will remain at 19%–20% in the year 2000.

Patterns of smoking prevalence vary markedly among different segments of the population. The prevalence of smoking in adult men in the 1930s to 1950s exceeded

50%, whereas about a third of women were regular smokers during much of that period. The percentage of men who smoke steadily declined to about 30% in the 1980s. However, there was a modest increase in the percentage of women who smoke during much of this period, with a reversal of the trend occurring only in the 1980s.

A number of surveys have demonstrated that the “quit ratio” for cigarette smoking has been steadily increasing among both men and women since 1965, although it has been consistently higher among men. In 1965, the quit ratio was 28% in men and 19% in women. In 1991, it was 52% in men and 45% in women. Nonetheless, although smoking cessation among men has been greater than among women, smoking prevalence continues to be higher in men than in women.

As white men were successful in decreasing their smoking prevalence, smoking prevalence among black men increased. This has translated into lung cancer mortality rates that in 1990 were about 30% higher among African-American men than among Caucasians. Smoking prevalence in Hispanics, particularly Hispanic women, is relatively low.

Increasing Prevalence of Smoking in Children and Adolescents

In contrast to some of the encouraging trends in smoking prevalence among adults, overall smoking prevalence among young people has not changed substantially since 1980. The prevalence of cigarette smoking among high school students in 1995 was 35% higher than in 1991 and 1993 (Fig. 2). It is estimated that 3000 children and adolescents become regular cigarette smokers every day. Nationwide, 71% of high school students have experimented with cigarette smoking. Approximately 3 million adolescents in this country currently smoke cigarettes. If current smoking trends among youth are not reversed, it is predicted that more than 5 million premature deaths may occur among those currently under 18 years of age.

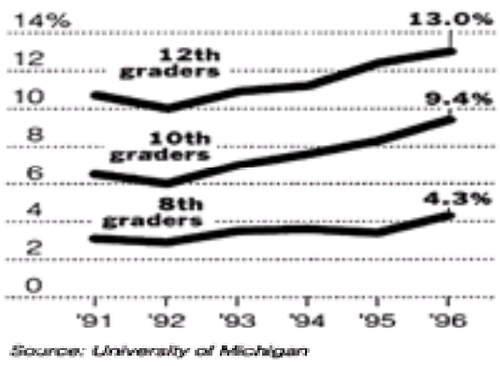


FIG. 2. Percentage of U.S. adolescents who have smoked half a pack of cigarettes a day at an early age. (Reprinted with permission from *The New York Times,* April 20, 1997.)

There are substantial racial differences in smoking prevalence in young people. A 1993 survey of smoking behavior among U.S. high school seniors reported the “phenomenal success” of black teenagers in stopping smoking; only 4% of black seniors described themselves as current smokers in 1993. This compared with 27% of blacks who smoked in 1976, an 84% drop in smoking behavior among black teens. In contrast, 23% of white high school seniors surveyed in 1993 described themselves as current cigarette smokers. This represented a 3% increase compared with 1984.

Cessation of Smoking and Lung Cancer Risk

As cigarette smoking is the major determinant of lung cancer risk, it is important to understand how smoking cessation effects risk for bronchogenic carcinoma among long-term smokers. Five large cohort studies and 10 case-control studies have attempted to quantify the magnitude of risk reduction associated with smoking cessation. Many of these data have been summarized in a 1990 Surgeon General's report.

Smoking cessation clearly decreases lung cancer risk among former smokers compared with that of persons who continue to smoke. Estimates of the extent of risk reduction vary from 20%–90%, depending on duration of abstinence. Lung cancer risk progressively declines with increasing duration of abstinence, and risk reduction is evident within 5 years of quitting. Reduction in lung cancer risk with smoking cessation is observed in both men and women and in users of both filtered and unfiltered cigarettes for all histologic subtypes of lung cancer.

There is an apparent increase in lung cancer risk within the first few years of abstinence, possibly reflecting symptoms of illness that led to smoking cessation before diagnosis. Even with a reduction in risk after quitting, former smokers continue to have a 10%–80% greater risk for development of a lung neoplasm than persons who never smoked, so that a substantial lung cancer risk remains even with prolonged periods of abstinence. This is in marked contrast to other smoking-related diseases, such as coronary artery disease, in which the beneficial effects of smoking cessation are apparent much sooner after quitting.

Although a large number of men quit smoking in the mid-1960s, shortly after the first Surgeon General's report, it took 20 years before lung cancer incidence started to decrease in men. Indeed, as smoking prevalence among adults decreases, lung cancer is increasingly becoming a disease of former smokers.

EARLY DETECTION OF LUNG CANCER

The current standard of care directed toward a reduction of lung cancer mortality in our society is well expressed by the 1980 position statement of the American Cancer Society, which did not recommend any test for the early detection of cancer of the lung but urged a focus on primary prevention. The statement added that “people with signs or symptoms of lung cancer should consult their physicians.” Between 1980 and 1995, lung cancer incidence and mortality in the United States increased by 45% and 55%, respectively (Fig. 3).

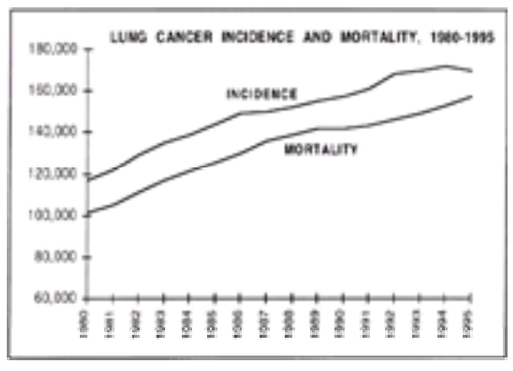


FIG. 3. Annual incidence and mortality of lung cancer based on annual statistics of the American Cancer Society, 1980–1995.

Screening for the early detection of lung cancer is not recommended. In addition to the American Cancer Society, the American College of Radiology, the National Cancer Institute, the U.S. Preventive Services Task Force, and the Canadian Task Force on Periodic Health Examination all continue to recommend that lung cancer screening not be done. The basis of this universal recommendation is that no randomized controlled trial has ever demonstrated a significant reduction in lung cancer mortality as a result of screening.

However, a reappraisal of all randomized trials on lung cancer screening raises serious questions about the proper interpretation of these trials. Although mortality reductions have not been demonstrated, significant advantages in stage distribution, resectability, survival, and fatality have been shown. Accordingly, the critical

question is related to how the benefit of screening is measured in randomized controlled trials.

It is believed that all outcome parameters other than mortality may be confounded by certain biases that are integrally related to early-detection trials. Accordingly, judgments regarding the effectiveness of screening based on parameters that include stage distribution or survival/fatality can be misleading, because of the potentially confounding influences of lead-time bias, length bias, selection bias, or overdiagnosis bias.

Unlike other outcome parameters, mortality is not subject to confounding by any of these screening biases. Accordingly, mortality is considered to represent the strongest evidence that supersedes all other outcome parameters. If a statistically significant reduction in disease-specific mortality in a randomized study were achieved, there would be general agreement that the screening strategy used should become the standard of care. However, what has been poorly understood is that mortality can be confounded by other effects in randomized controlled trials.

Randomized Trials of Lung Cancer Screening

Four randomized controlled trials including 37,724 participants have evaluated lung cancer screening. Because they were all initiated in the 1970s, before the epidemic of lung cancer in women became so obvious, each of these trials was limited to male cigarette smokers. Accordingly, no randomized controlled trial has evaluated the efficacy of lung cancer screening in women, despite the fact that lung cancer is now the most common cause of cancer death in women.

The National Cancer Institute sponsored three of the randomized controlled trials in the context of the Cooperative Early Lung Cancer Detection Program. In the Memorial Sloan-Kettering Lung Project and the Johns Hopkins Lung Project, participants were randomized at study entry to a “dual-screen” group (in which patients underwent chest roentgenography annually and a sputum cytologic examination every 4 months) or to a “single-screen” group (in which annual chest roentgenographic screening was performed).

In the Memorial Sloan-Kettering Lung Project (Table 1), 10,040 men were randomized. A total of 288 lung cancers were detected. More than 40% of the cases detected had stage I disease, and these stage I cases achieved a 76% 5-year survival. Overall, 5-year survival for all cases was 35%. Comparison of the dual-screen and single-screen groups demonstrated no differences with regard to stage distribution, resectability, survival, fatality, or disease-specific mortality. Similarly, in the Johns Hopkins Lung Project, there were no differences in outcome among 10,387 men randomized to a dual-screen or single-screen group. Eight-year survival in both groups was 20%.

Smoking status and duration of abstinence in former smokers (years)	Mortality ratio[b]			
	Men		Women	
	1–20 cigarettes/day	>21 cigarettes/day	1–20 cigarettes/day	>21 cigarettes/day
Never	1.0	1.0	1.0	1.0
Current	18.8	26.8	7.3	16.3
Former				
<1 yr	25.7	50.7	7.8	34.3
1–2 yr	22.4	33.2	9.1	10.5
3–5 yr	16.5	20.9	2.9	14.6
6–10 yr	8.7	15.0	1.0	5.1
11–15 yr	6.0	12.6	1.5	5.9
>16 yr	3.1	5.5	1.4	2.6

[a] A Report of the Surgeon General, The Health Benefits of Smoking Cessation. USDHHS, 1990 (Reprinted with permission)
[b] Lung cancer mortality ratios in men and women for never, current, and former smokers. Mortality ratio defined as 1.0 for never smokers.

TABLE 1. *American Cancer Society cancer prevention study II*[a]

Accordingly, the Memorial Sloan-Kettering and Johns Hopkins Lung Projects demonstrated no benefit by adding sputum cytology to annual chest roentgenography. As randomized comparisons, these trials were designed to assess the benefit of sputum cytology rather than chest roentgenography. However, all participants in these studies did undergo annual chest roentgenographic screening for the early detection of lung cancer.

In this regard, it is perhaps noteworthy that long-term survival rates in experimental and control populations in both the Memorial Sloan-Kettering and Hopkins studies were approximately three times better than that observed in the National Cancer Institute Surveillance Epidemiology and End Results for men in whom lung cancer was diagnosed during the same epoch. Accordingly, these studies provide some support that annual chest roentgenographic screening, which was performed in all participants, contributed to the improved outcome. In any case, it is impossible to reconcile the design of these randomized controlled trials (in which all participants underwent annual chest radiographs) and the results of these trials (in which long-term survival rates were threefold higher than those observed in the general population) with existing public policy mandating no screening whatsoever.

Although the Memorial Sloan-Kettering Lung Project and the Johns Hopkins Lung Project do not directly address the effectiveness of chest roentgenographic screening for lung cancer, the Mayo Lung Project (Table 2) and the Czechoslovak Study (Table 3) do provide direct evidence regarding the efficacy of chest roentgenographic screening for lung cancer. Although neither study had an untreated control group, both studies compared regular rescreening with periodic chest roentgenography in an experimental group with infrequent, sporadic, or in some cases no rescreening in a control group.

	Dual screen group	X-ray-only group
Population	5072	4968
Incidence	144	144
Resectability	53%	51%
Five-year survival	35%	35%
Mortality	90	92

TABLE 2. *Memorial Sloan–Kettering lung project*

	Experimental group	Control group
Population	4618	4593
Incidence	206	160 ($p = 0.016$)
Resectability	46%	32%
Five-year survival (actuarial)	33%	15%
Fatality (actual)	59%	72% ($p = 0.016$)
Mortality	122	115

TABLE 3. *Mayo lung project: Incidence screening*

In the Mayo Lung Project, 10,933 participants underwent a prevalence screen, consisting of a chest roentgenogram and sputum cytology. Ninety-one prevalence cases (0.83%) were detected. Chest roentgenography detected 59 cases (of which 64% were resectable), sputum cytology detected 17 (94% resectability), and 15 cases were detectable by both chest roentgenogram and sputum cytology (20% resectability). Overall, the resection rate among these 91 prevalence cases was 54%. Although there was no control group for prevalence cases, there was a contemporary "comparison group" of 3104 patients matched for age and sex who were being treated during the same time at the Mayo Clinic. In the "comparison group," only 29% of cases were resectable. Five-year survival for all prevalence cases was 40%, which was more than double that observed in the "comparison group." Fifty-four percent of prevalence cases had either occult or stage I disease, and the 5-year survival in this subgroup was 70%.

Among those free of cancer in the prevalence screen, 4618 were randomized to an experimental group in which chest roentgenography and sputum cytology were performed every 4 months, whereas 4593 were assigned to a control group in which no specific screening was conducted (although control patients were advised to undergo annual chest roentgenography and sputum cytology).

Throughout the trial, lung cancer incidence was higher in the screened than in the control population. The trial lasted for an average of 9 years, during which time those in the experimental group underwent an average of 6 years of screening and 3 years of observation, whereas those in the control group were observed for 9 years. At the completion of the study, there were 206 cases of lung cancer detected in the experimental group, compared with 160 control cases. Accordingly, the cumulative incidence of lung cancer in the experimental and control populations was 4.5% and 3.5%, respectively, indicating a 1% incidence discrepancy. The proportion of early-stage cancers and resectability was higher in the experimental group. Moreover, actuarial 5-year survival was more than double, 33% compared with 15% (Fig. 4). Mayo investigators did not report whether survival differences were statistically significant, because they believed that these differences reflected certain screening biases. However, there was a statistically significant advantage in the lung cancer fatality rate among those randomized to screening (59% vs. 72%; $p = .016$).

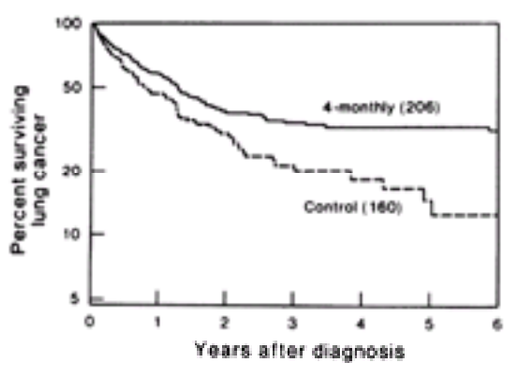


FIG. 4. Mayo Lung Project survival of patients with lung cancer diagnosed during experimental or observation period. (Reprinted with permission from Fontana R, Sanderson DR, Woolner LB, et al. Screening for lung cancer: a critique of the Mayo Lung Project. *Cancer* 1991;67:1155–1164.)

Nonetheless, despite statistically significant advantages in stage distribution, resectability, and survival/fatality, there were 122 lung cancer deaths in the screened group and 115 among the controls. Accordingly, there was a statistically insignificant mortality advantage favoring the control group.

The Czechoslovak Study on Lung Cancer Screening was a randomized trial that enrolled 6364 male smokers between the ages of 40 and 64 years. As in the Mayo study, all participants underwent a prevalence screen, consisting of a chest roentgenogram and sputum cytology. The experimental group then underwent chest roentgenography and cytology every 6 months for 3 years, whereas the control group underwent no screening until the end of the third year, when another chest roentgenogram and cytology were performed. Subsequently, both groups underwent chest roentgenography at the end of the fourth, fifth, and sixth years.

During the initial 3-year experimental period (excluding the scheduled screening at the end of the third year), 36 lung cancers were diagnosed in the study group and 19 in the control group. Resectability was 25% in the experimental group and 15% in the control group. Survival was superior in the study group, with no survivors beyond 3 years among controls and a 5-year survival of 23% in the study group, a difference that was highly statistically significant ($p = .0001$). However, there were 28 lung cancer deaths in the study group and 18 in the control group, so mortality was higher in the study group.

During the entire 6-year period of the trial, a total of 108 cancers were detected in the study group and 82 in the control group. Overall, there were 85 lung cancer deaths in the study group and 67 in the control group. Accordingly, relative mortality was 27% higher in the study population, although this difference was not statistically significant ($p = .16$).

Both the Mayo Lung Project and the Czechoslovak Study (during the experimental period) found advantages in experimental populations with regard to stage distribution, resectability, and survival/fatality. Nonetheless, there were also statistically insignificant mortality disadvantages for the screened groups in both studies.

Furthermore, in both the Mayo and Czechoslovak studies, cumulative lung cancer incidence was higher in the experimental group. In the Mayo Lung Project, the incidence difference was statistically significant at the end of this 9-year study ($p = .016$), whereas in the Czechoslovak Study it approached significance at the end of 6 years ($p = .065$). It therefore becomes important to determine why these incidence differences were observed.

Because of the relationship between mortality and incidence, it is critical to understand the nature of these incidence discrepancies. Disease-specific mortality is proportional to disease incidence and fatality. The numerator in a mortality calculation represents the number of cancer deaths. The only candidates for lung cancer mortality are those with lung cancer, who constitute the incidence group. The number of deaths then depends on the proportion of cancer deaths among these cases, which is the definition of fatality.

Screening Biases

Four screening biases, selection bias, lead-time bias, length bias, and overdiagnosis bias, which are inherent to the evaluation of screening programs, may confound proper interpretation of randomized controlled trials. It has been understood for decades, indeed before any population-based randomized controlled trials of cancer screening were initiated, that certain of these biases are likely to increase the rate of detection of cancer in an experimental group. An increased cancer detection rate in an experimental group would confound survival and fatality comparisons. Accordingly, it is assumed that one or more of the biases must provide the answer for the anomalous findings of superior survival/fatality but inferior mortality in the experimental populations of the Mayo and Czechoslovak studies. The question, however, is whether this assumption is correct.

Selection bias cannot explain differences in cumulative incidence. Although selection bias determines participation in screening trials in the first place, the process of randomization eliminates selection bias as a determinant of whether participants are assigned to experimental or control groups. Selection bias may still determine compliance with screening guidelines. It is important to understand that the elimination of selection bias in group assignment is the only direct result of randomization. Because selection bias has been eliminated, it is assumed that experimental and control populations are identical, except in regard to whether screening is conducted.

Lead-time predicts for an initial excess of cases, because cancer is detected during a preclinical phase rather than by symptomatic presentation. Indeed, if screening is to improve outcome, the opportunity provided by lead-time must be exploited. Because cancers are detected earlier on the basis of lead-time, survival and fatality are improved during this lead-time interval. This is the definition of lead-time bias. It is critical to distinguish the effects of lead-time from the effects of lead-time bias. The only effects that can be ascribed to lead-time bias are increased incidence and improved survival/fatality during the lead-time interval. Lead-time bias does not influence stage distribution, nor does it inflate long-term survival comparisons after the lead-time effect dissipates.

The concept of lead-time assumes that all cancers are clinically important lesions that eventually become life-threatening if not effectively treated. Accordingly, after screening is discontinued in the experimental group (or offered to the control group), the number of control cases should catch up to the number in the experimental group.

In the Mayo Lung Project, intensive screening in the experimental group continued for 6 years but was followed by a period of observation that on average lasted 3 years. At the end of the 6 years, there were 56 more cases in the screened group. During the first 18 months of observation, this discrepancy narrowed to 31, but by the end of observation, it had increased again to 46. The widening incidence discrepancy at the end of the observation period is not explainable on the basis of

lead-time bias.

In the Czechoslovak Study, screening in the control group at the end of the third year should have led to a compensatory number of cases that had previously been detected in the experimental group, but this did not occur. Before screening in the control group, the incidence difference was 17, but it narrowed to nine when those cases of lung cancer detected at the planned rescreening at the end of the third year were included. During the subsequent 3-year period, when both groups underwent annual screening chest roentgenography, the discrepancy in cumulative incidence increased to 26 cases. Incidence discrepancies, which increased when experimental and control groups were treated in effect as a single screened population, cannot be explained on the basis of lead-time bias.

Accordingly, lead-time bias cannot account for the cumulative incidence discrepancies noted by the completion of the Mayo Lung Project and the Czechoslovak Study. Moreover, significant advantages in stage distribution and long-term survival rates can never be attributed to the effects of lead-time bias.

Length bias refers to the tendency of screening to detect indolent tumors, which are likely to have a better prognosis. Prevalence cases are most likely to be affected by length bias, because they are likely to have been present for a considerable period of time. Comparison of case detection rates and survival of prevalence and incidence cases in the Mayo Lung Project indicates that the magnitude of length bias is small in that study. Screening the control population in the Czechoslovak Study eliminates length bias as a determinant of outcome in that trial.

That leaves only overdiagnosis, among the conventional screening biases. Overdiagnosis refers to the detection by screening of lesions that are not clinically important and would never adversely affect the lifespan of the patient. Indeed, overdiagnosis bias has been widely accepted as the most likely explanation for the observed incidence differences, at least in the Mayo Project. For example, Eddy concluded that the results of the Mayo Lung Project are “consistent with the hypothesis that many of the lesions detected by screening and labeled as cancers were not clinically important in the sense that they would never have become clinically evident during the time of the trial and follow-up.”

Although from a purely statistical point of view overdiagnosis in an experimental group can plausibly cause an increase in cumulative incidence in a corresponding control group, overdiagnosis would appear to lack biologic plausibility. As the most virulent of all the common cancers, lung cancer would appear to be an unlikely candidate for overdiagnosis through screening. Nonetheless, despite hypothetical considerations, evidence for overdiagnosis can be sought indirectly in two ways.

One is to determine if a substantial proportion of individuals have “latent” lung cancer detected incidentally at autopsy, similar to what has been documented to exist in prostate cancer. Multiple studies have repeatedly documented that approximately a third of men over the age of 50 and two thirds of men over the age of 60 have evidence of latent prostate cancer at autopsy. In contrast, the finding of lung cancer unexpectedly at autopsy is extremely uncommon. In the only series that has focused exclusively on this issue, “surprise” lung cancer was documented in 1% of 3000 autopsies conducted at Yale. Moreover, most of these “surprise” cases were not reminiscent of “latent” cancers. Indeed, two thirds of “surprise” cases were found to have metastatic disease, and up to a third of patients with “surprise” cancers may have died of lung cancer.

The second line of evidence relates to the hypothesis that if screening results in overdiagnosis of lung cancer, then many lesions detected on chest roentgenograms should remain clinically silent for prolonged periods, even if untreated. Indeed, therapy becomes irrelevant to outcome. Consequently, a substantial number of patients not undergoing resection should be long-term survivors. Data in prostate cancer might provide a model for this phenomenon. For example, a meta-analysis of six series demonstrated that 828 patients from six studies managed initially with observation enjoyed an actuarial 10-year survival of 87% among men with grade I or II tumors. However, in dramatic contrast, a pooled analysis from six studies of 239 lung cancers detected in the context of prospective screening programs that were not treated with curative resection (but were often treated by other methods) indicates that 5-year survival was 4%. Included among these six series is the report that focused on the importance of surgical resection for patients with stage I non–small-cell lung cancer identified in the context of the Mayo, Memorial, and Hopkins Lung Projects. Among 331 stage I patients, 45 did not undergo surgery (because of patient refusal or medical contraindication). Among the 45 nonsurgical patients, there were only two 5-year survivors. Among 286 resected stage I patients, actuarial 5-year survival was 70%.

The reason that “surprise” lung cancer is such an uncommon autopsy finding is that the vast majority of patients with lung cancer die of lung cancer. The only exception exists for patients with resectable early-stage disease who actually undergo curative resection. Approximately 90% of those with resectable early-stage disease who do not undergo curative resection die of lung cancer within 5 years.

In the Mayo Lung Project, higher cumulative incidence coupled with improved stage distribution, resectability, and long-term survival is, in theory, consistent with overdiagnosis. However, careful analysis of existing data conclusively demonstrates that overdiagnosis is not the answer. In the Czechoslovak Study, differences similar to those observed in the Mayo Project between experimental and control populations were observed regarding incidence, stage, resectability, and survival/fatality. However, in the Czechoslovak Study overdiagnosis cannot be implicated, because the study design incorporated regular screening in the control group during the second half of the study.

Accordingly, none of the screening biases credibly accounts for the hypothetical “missing cases” in the Mayo Lung Project and the Czechoslovak Study. This is a conclusion of enormous importance, because prevailing dogma regarding the ineffectiveness of chest roentgenographic screening for lung cancer has depended completely on these screening biases, and in particular overdiagnosis. Indeed, if screening does not lead to the overdiagnosis of lung cancer, then survival comparisons indicating that the proportion of long-term survivors is twofold to threefold higher than that observed in the general lung cancer population would indeed accurately reflect the effectiveness of screening.

Population Heterogeneity

If none of the screening biases accounts for the missing cases in the Mayo and Czechoslovak studies, what does account for them? Population heterogeneity represents the most plausible explanation for differences in cumulative incidence in these trials.

In population-based randomized controlled trials focusing on cancer, the target disease develops in only a small proportion (typically in the range of 1%–5%) of participants during the course of the study. Factors relevant to balance in such trials include population size, number of covariates influencing disease risk, and magnitude of risk modification by each variable. As previously noted, the only direct result of randomization is the elimination of selection bias.

However, when many covariates are relevant to disease risk, the elimination of selection bias may not be the obstacle to balance in population-based randomized controlled trials. Support for this hypothesis must come from an analysis of population-based randomized controlled trials evaluating screening for other diseases. In fact, analysis of 18 randomized controlled trials focusing on screening for breast cancer, colorectal cancer, and lung cancer demonstrates that substantial population heterogeneity often persists despite randomization. This in turn confounds the ability of mortality to reflect screening effectiveness accurately.

All participants in the Mayo Lung Project and Czechoslovak Study were cigarette smokers. However, there is abundant evidence that certain cigarette smokers are much more susceptible than others to the development of lung cancer. If randomization did not result in groups with equivalent lung cancer risk, mortality comparisons would not accurately reflect the benefit of screening.

Symptomatic Versus Screen-Detected Lung Cancer

The current standard of care directed toward a reduction of lung cancer mortality in our society is well expressed by the 1980 position statement of the American Cancer Society, which declared it “does not recommend any test for the early detection of cancer of the lung, but urges a focus on primary prevention.” Moreover, it added that “people with signs or symptoms of lung cancer should consult their physicians.”

Unfortunately, when patients consult their physicians because of “signs or symptoms of lung cancer,” 85%–90% already have advanced-stage disease. Moreover, 90%–95% will die of their lung cancer, usually within 2 years of diagnosis.

As early detection strategies are not advocated, it is predictable that the vast majority of patients with lung cancer are symptomatic at the time of diagnosis. Among 678 patients with lung cancer admitted to Yale-New Haven Hospital or the West Haven Veterans Administration Hospital between 1953 and 1959, only 6% were asymptomatic at the time of diagnosis. In contrast, 27% of patients had symptoms directly related to the primary tumor, 32% had symptoms of metastatic disease, and 34% had systemic symptoms of cancer. Five-year survival of these three groups of symptomatic patients was 12%, 6%, and 0, respectively. In the asymptomatic group, 5-year survival was 18%. Five-year survival for the entire group was 7%.

Among 702 patients from the Medical University Hospital and the Veterans Administration Hospital in Charleston, South Carolina, only 12% of patients were asymptomatic at the time of diagnosis. In contrast, 64% of patients presented with cough, 55% with weight loss, 53% with pain, and 44% with sputum production. Similar to the results reported from Yale, 5-year survival of the entire group was 7%.

Even in apparently early-stage disease, symptoms represent a significant determinant of prognosis. For example, the presence of symptoms at the time of diagnosis of stage I non–small-cell lung cancer adversely influenced survival among 289 resected stage I patients from Duke University. There was a 74% 5-year survival in 189 asymptomatic patients, compared with 41% in 100 patients who were symptomatic at presentation ($p < .001$).

In Japan, screening for the early detection of lung cancer is routinely practiced, and screening chest roentgenograms have been covered by health insurance by legal mandate since 1987. Outcome was compared between the 381 screen-detected and the 239 symptom-detected patients undergoing resection at Okayama University between 1980 and 1989. In the screen-detected group, 55% of patients had tumors of 3 cm, whereas in the symptom-detected group, it was 25%. In contrast, in the screen-detected group, only 11% of tumors were 5 cm, compared with 32% in the symptom-detected group. The proportion of patients with stage I and stage III non–small-cell lung cancer in the screen-detected group was 65% and 22%, respectively, whereas in the symptom-detected group, it was 32% and 48%, respectively. Overall 5-year survival in the screen-detected group was 56%, compared with 25% in the symptom-detected group ($p < .001$).

Similarly, a report from Uppsala, Sweden, indicated that lung cancers diagnosed incidentally during a general health survey, which included biennial chest roentgenographic screening for tuberculosis, had a far superior survival than those detected by symptoms. During the survey period, a total of 244 lung cancers were detected. Of these, 28 (11%) were detected on a survey chest roentgenogram, 31 (13%) were found accidentally, and 185 (76%) were noticed by symptoms. Resectability among cases detected in the survey chest roentgenogram, accidentally, and by symptomatic presentation was 75%, 74%, and 20%, respectively, whereas 4-year survival in the three groups was 39%, 33%, and 7%, respectively. If only squamous cell carcinoma or adenocarcinoma is considered, 4-year survival was 42% if the cancer was survey-detected and 10% if symptom-detected ($p < .001$). Although only a small proportion of total lung cancers were detected by survey chest roentgenogram, chest roentgenography was performed only every other year, an interval that would not be appropriate if the objective were screening for lung cancer.

In the NCI-sponsored lung screening studies, the majority of the 784 cancers detected among populations randomized to either chest roentgenography alone or chest roentgenography and sputum cytology were detected on a routine screening examination. Fifty percent of 322 lung cancers detected in groups randomized to chest roentgenography alone in the Memorial Sloan-Kettering or Hopkins studies were detected on screening radiographs, whereas the other 50% were interval cancers. Among 452 cancers detected among patients randomized to chest roentgenography and sputum cytology in the Mayo, Memorial, and Hopkins studies, 39% were detected by chest roentgenography, 13% by cytology, and 4% by both methods. Only 44% of cancers in the dual-screen groups were interval lesions detected following normal screening examinations.

Lung Cancer Screening Reconsidered

Disease-specific mortality has long been believed to be the best measure of outcome in screening trials. However, when one analyzes the data, not a single example from the 18 population-based randomized controlled trials, which included 870,593 participants, can be cited as definitive proof of the effectiveness of any screening strategy. Indeed, screening cannot be justified for any cancer on the basis of consistent reductions in mortality in randomized controlled trials.

Lead-time bias, length bias, and overdiagnosis bias may confound stage distribution and survival/fatality comparisons in randomized controlled trials. However, failure to distinguish the effects of lead-time from the effects of lead-time bias and misconceptions regarding the true nature of overdiagnosis have interfered with proper interpretation of these trials.

In lung cancer, randomized controlled trials consistently demonstrate that periodic chest roentgenographic screening is associated with statistically significant advantages in stage distribution and long-term survival. Moreover, these advantages are also clinically important, because they cannot be attributed to the effects of any conventional screening bias. Extrapolation of such long-term survival advantages from randomized controlled trials to the national stage in the 1990s would likely translate into tens of thousands of additional lung cancer survivors every year in the United States.

However, such an interpretation of the data depends completely on how screening effectiveness is measured. Because of the enormous public health importance of this issue, and the considerable fiscal implications of a change in public policy, the question of whether periodic chest roentgenographic screening should be recommended for those at high risk for lung cancer deserves reconsideration by organizations responsible for formulating public policy.

However, pending a formal reappraisal of screening guidelines, sufficient evidence currently exists to justify an annual screening chest roentgenogram among asymptomatic individuals at high risk for lung cancer. Early detection leading to early treatment is of key importance if we are to impact favorably on the appalling epidemic of lung cancer mortality among cigarette smokers and the growing population of former smokers in our society.

PATHOLOGY AND CLASSIFICATION

The histologic classification for primary lung cancer was originally developed by the World Health Organization (WHO) in 1967 and modified in 1981. It remains the international standard at the present time, and is currently undergoing its third revision (Table 4). The four major histologic subtypes of lung cancer, which cover approximately 95% of all primary bronchogenic carcinomas, include squamous cell (epidermoid) carcinoma, adenocarcinoma, large-cell carcinoma, and small-cell (or oat cell) carcinoma. Bronchoalveolar cell carcinoma is classified as a subtype of adenocarcinoma. Although a specific histopathologic classification is highly desirable, the distinction between small-cell carcinoma (SCLC) and non–small-cell lung carcinoma (NSCLC) is most critical in guiding therapy.

	Experimental group	Control group
Population	3172	3174
Incidence	36	19
Resectability	25%	15%
Five-year survival (actuarial)	23%	0% ($p = 0.0001$)
Mortality	28	18

TABLE 4. *Czechoslovak study: Incidence screening*

Today, pathologists most frequently make an initial diagnosis of lung cancer by cytologic techniques alone. More than 80% of all lung cancers are diagnosed by bronchial brushings, washings, or directed fine-needle aspiration (FNA). Thus, as thoracoscopic techniques have improved, the role of cytology and FNA has dramatically increased during the past decade, gradually replacing the less sensitive induced sputum cytology as a method of diagnosis. These methods of obtaining cellular specimens suitable for definitive diagnosis are safe and inexpensive compared with the cost and morbidity of invasive surgical techniques. The diagnostic yield of cytologic specimens can be enhanced with such techniques as immunocytochemistry and electron microscopy.

Relationship of Histologic Type to Smoking

Although the relationship between cigarette smoking and squamous cell carcinoma and small-cell carcinoma has long been clear, the relationship between smoking and adenocarcinoma and large-cell carcinoma has been more ambiguous. Although the older literature suggests that smoking is unrelated to adenocarcinoma of the lung, more recent data indicate that each of the major histologic subtypes is directly related to smoking, although to differing degrees. The degree of lung cancer risk as a function of total exposure to tobacco differs with cell type and is strongest for small-cell carcinoma, less strong for squamous cell carcinoma, weaker still for adenocarcinoma, and absent for large-cell carcinoma. Adenocarcinoma is the most common histologic type seen in nonsmokers.

The role of cigarette smoking in the pathogenesis of bronchoalveolar carcinoma has been less clear, although more recent studies do support a clear-cut association between smoking and bronchoalveolar carcinoma. Two case-control studies suggest an association between smoking intensity and bronchoalveolar carcinoma. In one case-control study of 87 patients with bronchoalveolar carcinoma, only 10% of men and 25% of women were lifelong nonsmokers.

Squamous Cell Carcinoma

In the past, squamous cell carcinoma was the most common histologic subtype of all lung cancers. In the 1970s, squamous cell carcinoma comprised approximately half of all lung cancers, but by the mid-1980s, the percentage had decreased to approximately 30%–40%. These cancers occur almost exclusively in cigarette smokers and are much more common in men than in women. The decrease in frequency appears in part to be related to the decreased prevalence of smoking in men.

About two thirds of squamous cell carcinomas occur centrally in the lung; most of the rest present as peripheral or subpleural masses (Fig. 5). They tend to be relatively slow-growing neoplasms and spread along the bronchial wall, directly invading the peribronchial lymph nodes and adjacent pulmonary parenchyma. Peripheral squamous cell carcinomas often invade the chest wall. Central tumors tend to arise at the bifurcation of segmental or subsegmental bronchi. Squamous cell cancers have a tendency to become necrotic and cavitary.

FIG. 5. Central squamous cell carcinoma of left lung with cavitation. This tumor eroded into the adjacent pulmonary artery (*probe*), causing fatal hemorrhage. (Reprinted with permission from Morgan WKC, Hales MR. Bronchogenic carcinoma. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* 3rd ed. Boston: Little, Brown; 1983.)

Squamous cell cancer is frequently preceded by a preinvasive lesion of squamous dysplasia or carcinoma *in situ* and can be detected by biopsy and cytology. These tumors tend to be relatively slow-growing (Fig. 6 and Fig. 7). It has been estimated that the average time from the development of carcinoma *in situ* to clinically apparent tumor is approximately 3 to 4 years.

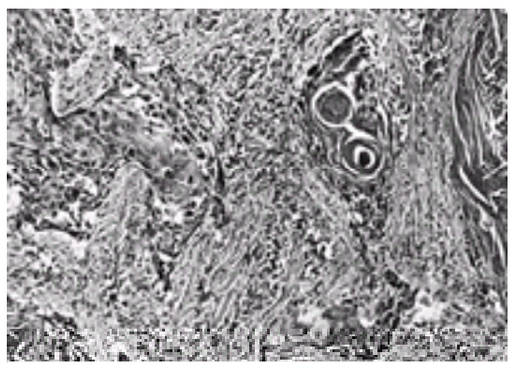


FIG. 6. Well-differentiated squamous cell carcinoma with two keratinized epithelial pearls. There are numerous lymphocytes and plasma cells in the desmoplastic stroma. (Reprinted with permission from Morgan WKC, Hales MR. Bronchogenic carcinoma. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* 3rd ed. Boston: Little, Brown; 1983.)

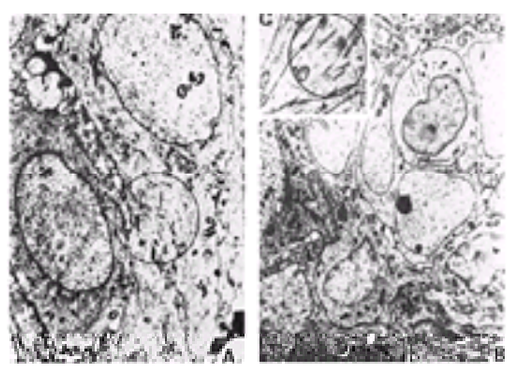


FIG. 7. Squamous cell carcinoma. **A,B:** Note the overall low-power ultrastructural appearance of a squamous cell carcinoma, with prominent nucleoli and evenly dispersed nuclear chromatin. Note (*within the circle*) the well-formed desmosomes joining apposing outpouchings of adjacent cells and clusters of tonofilaments in the neighborhood of intercellular junctions, as well as in paranuclear location (A). ×10,000. Note that only a few scattered bundles of tonofilaments are identifiable (B). ×7500. **C:** Note the well-formed desmosomes joining apposing cellular membranes and nearby clusters of tonofilments. ×22,000. (Reprinted with permission from Herrera, et al. Ultrastructural characterization of pulmonary neoplasms. *Surv Synth Pathol Respir* 1984;3:520.)

Adenocarcinoma

During the past two decades, adenocarcinoma has emerged as the most common histologic subtype of all lung cancers. Adenocarcinomas arise predominantly in the periphery of the lung, often in relation to focal scars or in regions of interstitial fibrosis. Adenocarcinoma usually does not arise within the bronchi, and it involves the bronchi only through local invasion or submucosal lymphatic spread. Because of their peripheral location, adenocarcinomas are associated with pulmonary symptoms less commonly than centrally located squamous cell carcinomas. Although often presenting as a solitary pulmonary nodule, they are not infrequently multicentric.

Although adenocarcinomas are the most common histologic subtype in women and nonsmokers, most adenocarcinomas occur in persons with a smoking history. Adenocarcinomas tend to be slow-growing. However, they invade lymphatic and blood vessels relatively early in their natural history, and for this reason they have a higher propensity for distant metastasis than squamous cell carcinomas. This property helps explain why they are associated with a poorer survival than are squamous cell carcinomas.

Adenocarcinomas are characterized by glandular formation, the development of papillary structure, or the production of mucin (Fig. 8). Well-differentiated adenocarcinomas are characterized predominantly by acinar formation, whereas poorly differentiated adenocarcinomas may appear as solid sheets of tumor cells that may exhibit a slight tendency to form small acini and less prominent glandular differentiation. Immunohistochemically, adenocarcinomas express low-molecular-weight cytokeratins, carcinoembryonic antigen (CEA), and epithelial membrane antigen. The major value of determining CEA levels is to distinguish adenocarcinomas, which are usually CEA-positive, from mesotheliomas, which are CEA-negative.

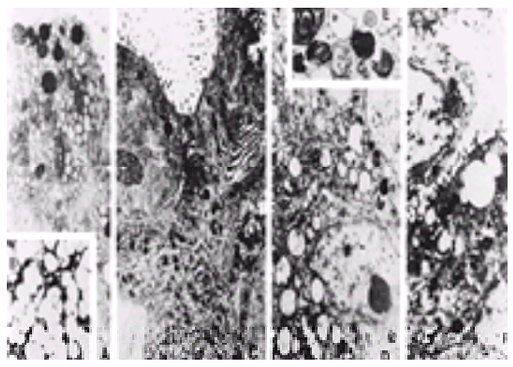


FIG. 8. Adenocarcinomas. **A:** Note the poorly formed surface microvillous border and the collections of coalescent mucin vacuoles. ×13,000. **B:** Coalescent mucin vacuoles are better illustrated at this magnification. ×22,000. **C:** Note the dark, electron-dense granules, typical of Clara cell adenocarcinomas. Also note the better-developed microvillous border. ×10,000. **D:** Note the collections of typical lamellar bodies, indicative of pneumocyte type II differentiation. ×7500. **E:** Note the details of the lamellar bodies. ×28,000. **F:** Note a combination of coalescent mucin vacuoles and Clara cell granules within the same cell, indicative of a mixed adenocarcinoma. ×13,000. (Reprinted with permission from Herrera, et al. Ultrastructural characterization of pulmonary neoplasms. *Surv Synth Pathol Respir* 1984;3:520.)

The WHO classification divides adenocarcinoma into four subtypes: acinar, papillary, solid tumor with mucin production, and bronchoalveolar cell carcinoma. When these tumors are resectable, solid tumor with mucin production is associated with the poorest prognosis, and bronchoalveolar carcinoma with the most favorable. Bronchoalveolar carcinoma tends to occur in younger patients than do other histologic NSCLC subtypes.

Large-Cell Carcinoma

Large-cell carcinoma constitutes approximately 10% of all lung cancers. These tumors tend to occur as bulky masses and are most often located in the periphery of the lung. They usually present as solitary masses with associated necrosis and no cavitation. They tend to metastasize widely, in a manner similar to that of adenocarcinomas.

Large-cell carcinoma is so classified because at the level of the light microscope it lacks both the glandular formation of adenocarcinomas and the keratinization or intracellular bridges indicating squamous differentiation (Fig. 9A and Fig. 10). By electron microscopy, some large-cell carcinomas contain intracytoplasmic tonofilaments, mucin droplets, or electron-dense granules, which indicate neuroendocrine differentiation. Most large-cell carcinomas have ultrastructural features consistent with either poorly differentiated squamous cell carcinomas or adenocarcinomas.

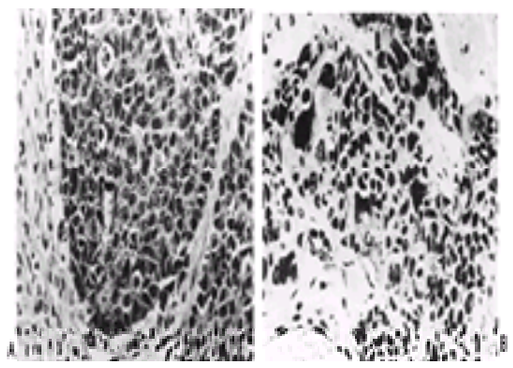


FIG. 9. A: A large-cell carcinoma not showing any mucin production or stratification, an example of group 4 in the WHO (1981) classification of undifferentiated large-cell carcinomas. **B:** A tumor with large, pleomorphic cells. This is another area from the tumor, illustrated as an example of a small-cell carcinoma of intermediate type. Such large-celled areas do not preclude the diagnosis of small-cell carcinoma, but they may pose problems when a diagnosis is based on small biopsy specimens. H&E stain, ×320. (Reprinted with permission from Smith JF. *The Management of Lung Cancer.* London: Edward Arnold; 1984.)

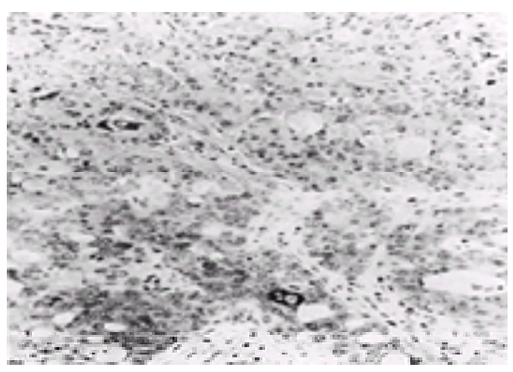


FIG. 10. Photomicrographs of a large-celled anaplastic carcinoma with mucin production. **A:** Most of the mucin was cytoplasmic or in pools, as shown by period acid-Schiff staining after diastase digestion. No clear ductal structures or acini were formed. **B:** The same tumor stained immunocytochemically for keratin. Most cells contained keratin-like immunoreactive material, and occasional mononuclear and multinucleated cells were strongly positive. ×250. (Reprinted with permission from Carter RL. *Precancerous States.* New York: Oxford University Press; 1984.)

In recent years, the entity of large-cell neuroendocrine carcinoma has been the focus of considerable interest. It has been recognized that tumors that are otherwise typically squamous cell carcinomas, adenocarcinomas, or large-cell carcinomas may show evidence of neuroendocrine differentiation when examined by electron microscopic or immunohistochemical techniques. Large-cell neuroendocrine carcinomas cannot be distinguished from large-cell carcinomas without the use of these techniques. The prognostic significance of this entity is presently unclear, but there is some evidence that they may respond better to chemotherapy than other large-cell carcinomas. Giant cell carcinoma is recognized as another distinct clinical entity with a very adverse prognosis.

Small-Cell Carcinoma

In the past, small-cell carcinoma represented about 25% of all cases of lung cancer. However, the proportion of lung cancers classified as SCLC has declined in recent years in the United States, and SCLC currently represents approximately 20% of primary lung neoplasms. However, SCLC remains relatively more prevalent in other parts of the world. There is a very strong relationship between SCLC and cigarette smoking.

The majority of SCLCs are located centrally, arise in the peribronchial tissues, and infiltrate the bronchial submucosa (Fig. 11). SCLC is believed to arise from basal neuroendocrine Kulchitsky cells. As with adenocarcinoma of the lung, a preinvasive form of SCLC has not been identified.

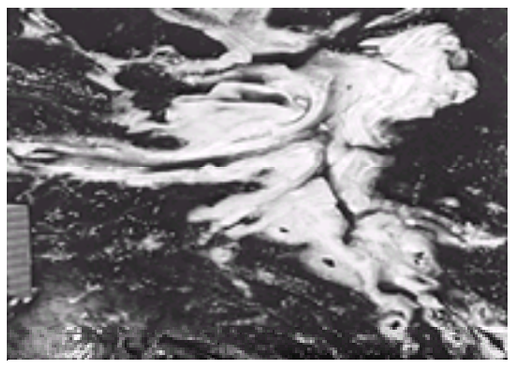


FIG. 11. Small-cell anaplastic carcinoma arising in the distal portion of the right intermediate bronchus and extending both proximally and distally along the bronchial vascular rays. Although small in mass, this tumor was responsible for widespread metastases, causing inappropriate secretion of ACTH, adrenal cortical hyperplasia, and death from severe, intractable hypokalemia. (Reprinted with permission from Morgan WKC, Hales MR. Bronchogenic carcinoma. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* 3rd ed. Boston: Little, Brown; 1983.)

SCLC disseminates early and widely into regional lymph nodes, and this histologic subtype is the most common cause of superior venal cava syndrome in adults. SCLC behaves much more aggressively than other lung cancers, exhibiting very rapid growth and early dissemination.

These tumors are characterized by a proliferation of highly malignant small cells, about two to three times the size of lymphocytes (Fig. 9B). They contain hyerchromatic nuclei with finely dispersed chromatin, indistinct nucleoli, and scanty cytoplasm. The nuclei of these cells mold or conform to the cytoplasm of adjacent cells in well-preserved specimens. There is often extensive smearing of the fine chromatin of these delicate cells, producing a characteristic “crush”-like artifact in poorly preserved specimens. Mitotic figures are common, and the tumor grows in sheets without a specific pattern.

Small-cell carcinoma has traditionally been subdivided into a classic oat cell and intermediate cell types. Oat cell carcinomas consist of lymphocyte-like cells growing in sheets or nests in a sparse connective-tissue stroma. The intermediate cell type is comprised of polygonal or fusiform cells that are much larger in size, with more abundant cytoplasm. These cells form rosettes.

Two other, less common histologic subtypes have also been described. One is the mixed small-cell and large-cell variant, which comprises about 4% of SCLCs. Some early studies had demonstrated that this subtype had a lower response rate to chemotherapy and a lower survival compared with “pure” small-cell subtypes, although this claim has been disputed. The other subtype that has been described is combined small-cell with squamous cell or adenocarcinoma. The significance of this subtype is not completely clear. In one series, 2% of SCLCs also had histologic features of adenocarcinoma or squamous cell carcinoma, and such tumors tended to be more localized, were occasionally resectable, and seemed to be associated with a better prognosis than pure SCLC.

However, the predominance of evidence at the present time suggests that there are no real differences in outcome between the four SCLC subtypes. Accordingly, stage distribution, metastatic potential, response to therapy, and survival appear to be similar when the oat cell or intermediate cell subtype is considered on the one hand, and the mixed cell or combined subtype on the other.

PROGNOSTIC FACTORS IN NSCLC

The anatomic extent of the cancer, as reflected by the stage of disease, is the most important determinant of prognosis in NSCLC. Indeed, the objective of cancer staging is to provide a prognostically useful classification based on the anatomic distribution of disease. In NSCLC, patients with resectable stage I or II disease have a prognosis superior to that of patients with more advanced disease. The significance of most nonanatomic determinants of prognosis is not as important, especially in the setting of overt distant metastases, because stage IV NSCLC is invariably fatal.

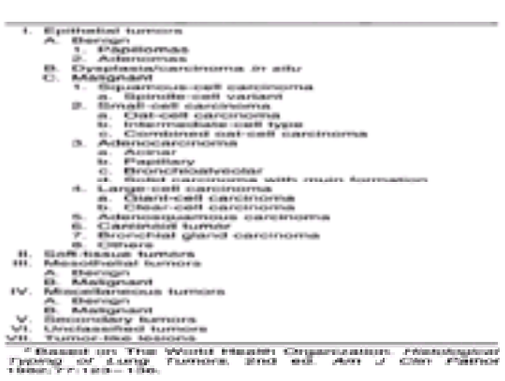
Nonetheless, a variety of clinical and pathologic factors can significantly contribute to an assessment of prognosis, particularly in patients with resectable disease. Moreover, numerous biologic or molecular markers of prognosis have been identified in recent years. Because a substantial proportion of patients with resectable NSCLC have biologically virulent cancers, the use of prognostic factors can contribute to an assessment of outcome among those with early-stage disease.

Performance Status and Weight Loss

Although many clinical factors have been reported to be predictive of outcome in lung cancer, the two most important variables are weight loss and performance status. It has long been established that poor performance status predicts a short survival in those with localized stage I and II NSCLC. A multivariate analysis of 651 patients demonstrated that weight loss and poor performance status were significant adverse indicators of outcome independent of stage, histology, and treatment.

Lymph Node Involvement

The critical importance of regional node involvement in NSCLC is recognized in the International Staging System (ISS) for NSCLC, which was introduced in 1986 and modified in 1997 (Table 6 and Fig. 12). In this system, the definition of stages I, II, IIIA, and IIIB largely depends on the presence or absence of nodal involvement at specific sites. The prognostic significance of the level and extent of nodal involvement in NSCLC has led to the development of a thoracic lymph node map (Fig. 13). Involvement at specific nodal stations has great prognostic significance.



I. Epithelial tumors
A. Benign
1. Papillomas
2. Adenomas
B. Dysplasia/carcinoma in situ
C. Malignant
1. Squamous cell carcinoma
a. Spindle cell variant
2. Small cell carcinoma
a. Oat cell carcinoma
b. Intermediate cell type
c. Combined oat cell carcinoma
3. Adenocarcinoma
a. Acinar
b. Papillary
c. Bronchioloalveolar
d. Solid carcinoma with mucin formation
4. Large cell carcinoma
a. Giant cell carcinoma
b. Clear cell carcinoma
5. Adenosquamous carcinoma
6. Carcinoid tumor
7. Bronchial gland carcinoma
8. Others
II. Soft tissue tumors
III. Mesothelial tumors
A. Benign
B. Malignant
IV. Miscellaneous tumors
A. Benign
B. Malignant
V. Secondary tumors
VI. Unclassified tumors
VII. Tumor-like lesions

[illegible] on the World Health Organization Histological Typing of Lung Tumors. 2nd ed. Am J Clin Pathol 1982; 77:123–136.

TABLE 5. *WHO II lung cancer classification*[a]

Primary tumor (T)
TX: Tumor [illegible] or [illegible] by presence of malignant cells in [illegible] but not visualized by imaging or bronchoscopy
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor [illegible] in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than lobar bronchus (i.e., not in the main bronchus)
T2: Tumor with any of the following features of size or extent:
More than 3 cm in greatest dimension
Involves main bronchus, 2 cm or more distal to the carina
Invades visceral pleura
Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3: Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium
Associated with atelectasis or obstructive pneumonitis of the entire lung
Separate tumor nodule(s) in the same lobe
T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina
Separate tumor nodule(s) in a different ipsilateral lobe
Associated with malignant pleural or pericardial effusion

Regional lymph node (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar nodes and intrapulmonary nodes involved by primary tumor extension
N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

Metastasis (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis present

Stage groupings of TNM subsets

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1,2,3	N2	M0
Stage IIIB	any T	N3	M0
	T4	any N	M0
Stage IV	any T	any N	M1

[illegible] on Staging of Lung Cancer. Chest 1997; 111:1710–1717.

TABLE 6. *TNM descriptors*[a]

TABLE 6. *International staging systemfor lung cancer*[a]

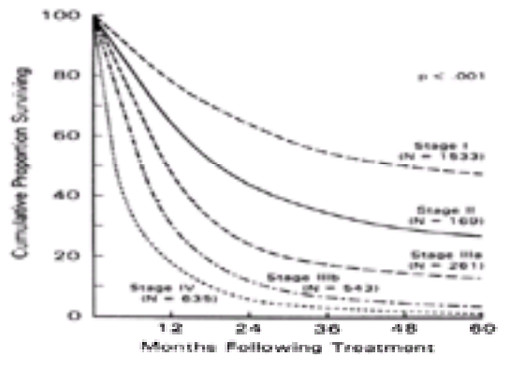


FIG. 12. Cumulative proportion of patients surviving 5 years by clinical stage of disease. (Reproduced with permission from Mountain CF. A new international staging system for lung cancer. *Chest* 1986;89:225S.)

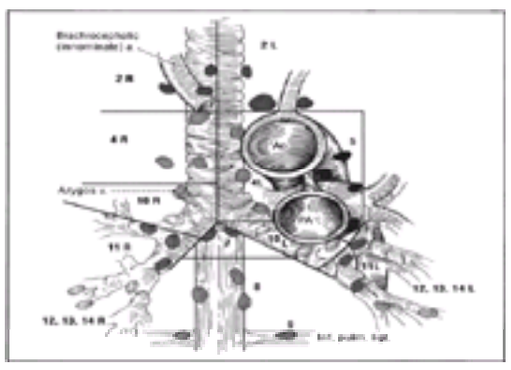


FIG. 13. Classification of mediastinal lymph nodes. (Reprinted with permission from the Lung Cancer Study Group, courtesy of Bristol-Myers Squibb.)

Stage I disease is defined by the absence of regional nodal involvement. In stage II disease, lymph node involvement is limited to ipsilateral intrapulmonary (hilar, peribronchial, lobar) nodes. A modification of the ISS, introduced in 1997, subdivides stages I and II into IA/IB and IIA/IIB subcategories, primarily based upon tumor size (Table 6). Stage IIIA is defined by the presence of ipsilateral mediastinal nodes or subcarinal lymph nodes. Stage IIIB disease is defined by the presence of contralateral mediastinal or hilar nodal involvement, or ipsilateral or contralateral supraclavicular nodal involvement by tumor.

In patients with stage II NSCLC, the number and/or location of involved N1 nodes is a significant determinant of outcome. At Memorial Sloan-Kettering, the overall 5-year survival was reported to be 39% in stage II NSCLC, and the number of involved N1 lymph nodes was an important predictor of survival. In a Japanese series, overall 5-year survival was 49% in stage II disease, but survival was 65% in patients whose N1 involvement was limited to lobar nodes, compared with only 40% when hilar nodes were involved ($p > = .014$).

The location of specific involved nodal groups may also have prognostic significance in patients with stage IIIA or IIIB disease. It appears that patients with resected right-sided lung cancers have a worse prognosis if the involved N2 nodes include superior mediastinal nodes compared with inferior mediastinal nodes. For left-sided tumors, involvement of inferior mediastinal nodes by tumor carries a worse prognosis. Patients with single-level mediastinal nodal involvement do better than those with multilevel metastases.

In addition to the location of nodal involvement, the size and number of involved nodes have been demonstrated to be important prognostically. Moreover, the presence of extracapsular extension outside involved nodes has adverse prognostic significance.

Tumor Size

Tumor size has consistently been an important determinant of outcome in stage I NSCLC. Nine studies of stage I NSCLC have shown that T1 tumors are associated with superior survival compared with T2 tumors (Table 6). Survival in patients with T1N0 tumors varies from 64% to 85% and is more variable in those with T2N0 tumors, ranging from 36%–68%. The magnitude of survival differences between T1 or T2 subsets in individual studies is quite variable, ranging from 8%–38%. The modification to the ISS, introduced in 1997, subdivides stage I into stage IA (TIN0M0) and stage IB (T2N0M0) subcategories.

Despite the consistency of the finding that tumor size is an important prognostic factor, T status may not be the dominant prognostic factor in stage I NSCLC. Other important factors include the degree of tumor differentiation (well, moderate, poor) and DNA ploidy (diploid, aneuploid).

In stage II or II NSCLC, one study from Memorial Sloan-Kettering did demonstrate that patients whose tumors were <3 cm had a significantly superior survival compared with those whose tumors were >5 cm. However, tumor size has not consistently been an important prognostic variable in stage II and III NSCLC. Once the tumor has progressed beyond the primary site, the existence of nodal or distant metastases represents the major determinant of outcome.

Histologic Subtype

There is conflicting information relating to the prognostic importance of histologic subtype in resectable NSCLC. Two studies from the Lung Cancer Study Group (LCSG) reported that squamous cell carcinoma had a superior outcome compared with other histologic types. In one series of 392 stage I patients, long-term survival was 77% in squamous cell carcinoma and 66% in adenocarcinoma and large-cell carcinoma ($p = .014$). Similarly, in 572 patients with T1,N0 lesions, the recurrence rate was 12% in squamous cell carcinoma, compared with 26% in those with adenocarcinoma, large-cell carcinoma, or bronchoalveolar cell carcinoma. When only squamous cell carcinoma and adenocarcinoma were compared, the probability of recurrence was significantly lower in patients with squamous cell carcinoma ($p < .001$). However, studies from the Mayo Clinic, Memorial Sloan-Kettering, Duke University, and Japan reported no significant differences in survival based on histologic subtype of NSCLC. In the Japanese series, 5-year survival trends favored those who had nonsquamous histologies over those with squamous cell carcinoma (71% vs. 77%; $p = .076$).

Finally, a report on the prognostic significance of histopathologic subtyping of adenocarcinoma of the lung based on the WHO classification indicated that those with solid carcinomas and mucus formation had a significantly worse outcome than those with the three other histologic subtypes. In 137 patients, the median survival was only 10 months in the 14% of patients classified as having “solid carcinoma with mucus formation.” In contrast, the median survival was 31 months in the 57% of patients with “acinar adenocarcinoma” and 32 months in the 12% with “papillary adenocarcinoma.” The most favorable survival was observed in the 18% of patients with “bronchoalveolar cell carcinoma,” in whom median survival was 44 months.

Tumor Differentiation

Conflicting reports exist on the prognostic significance of tumor differentiation. A report from Johns Hopkins indicated that lack of tumor differentiation was a associated with a 24% 5-year survival, compared with 42% in those whose tumors were better differentiated. Similarly, a Japanese study of resected adenocarcinomas of the lung 2 cm in diameter reported that the 5-year survival was 78% for patients with well-differentiated tumors, 54% in those with moderately differentiated tumors, and 28% in those with poorly differentiated tumors ($p = .001$). In another Japanese study of stage I NSCLC, 5-year survival in patients with well-differentiated tumors was

significantly superior to survival in those with moderately or poorly differentiated tumors (83% vs. 72% and 76%, respectively). In contrast, a study from Duke University reported no significant survival differences as a function of degree of tumor differentiation.

Other Pathologic Markers

Lymphatic and Blood Vessel invasion

Lymphatic vessel invasion (LVI) and blood vessel invasion (BVI) have each been reported to be a significant determinant of prognosis, although results of different trials have been somewhat inconsistent. Some of these discrepancies may be explained by variations in pathologic definitions of these features and by the lack of statistical power in some of the trials.

A Veterans Administration study involving 685 resected NSCLCs concluded that LVI was a significant determinant of prognosis, whereas BVI was not. Three-year survival was significantly better among those without LVI than among those with LVI (61% vs. 42%). In a report of 151 stage I NSCLC patients from Japan, the 5-year survival among patients without LVI was 82%; it was 71% in patients with LVI (p = .045). Similarly, the 5-year survival in patients without BVI was 78%, compared with 52% in those with BVI (p = .061). In the Duke University series, only BVI was reported to be a significant determinant of survival in 289 stage I patients. Five-year survival was 68% in patients without BVI, compared with 35% among patients with BVI (p < .001).

Tumor Proliferation

The rate of tumor proliferation can be estimated pathologically by measuring the mitotic index, reported as the number of mitotic figures per 10 high-power fields (HPF) by light microscopy. The 5-year survival of patients with stage I NSCLC was 67% in those with 15 mitoses per HPF and 46% in those with 15 mitoses per 10 HPF (p .02). Similarly, in each of two reports limited to patients with T1N0 adenocarcinomas of the lung, the presence of a high mitotic index was a significant adverse determinant of survival.

Giant Cells

A series from Johns Hopkins reported that the presence of tumor giant cells adversely affected survival in early-stage NSCLC. In contrast, the identification of a brisk plasma cell infiltration within the tumor favorably influenced survival.

Serum Tumor Markers

Serum tumor markers have been extremely useful in evaluating prognosis and/or response to therapy in a number of malignancies, including germ cell tumors, ovarian cancer, colorectal cancer, and breast cancer. The utility of serum markers in NSCLC has been considerably less impressive. Although numerous serum tumor markers have been reported to be elevated in NSCLC, no marker has been shown to have any reasonable degree of specificity for lung cancer. The two serum markers most widely utilized in NSCLC, CEA and CA-125, are more commonly associated with colorectal and ovarian cancer, respectively.

In NSCLC, elevations of serum tumor markers are much more common in stage IV disease than in early-stage disease. Serum markers have not been demonstrated to predict survival in patients with disseminated NSCLC.

Limited data exist on the prognostic significance of serum tumor markers in resectable NSCLC. An LCSG report on resected stage I NSCLC concluded that preoperative CEA levels are prognostically important. Recurrences were observed in 12% of patients with preoperative CEA levels of 2.5 ng/mL, and in 42% of those with CEA levels of 2.5 ng/mL (p = .009). In 152 patients with NSCLC and CEA levels ³10 ng/mL who underwent an attempt at surgical resection, preoperative CEA levels increased as stage increased from I to IIIA (p .05). The preoperative CEA did not predict resectability. Preoperative CEA levels of 30 ng/mL were associated with a significantly shorter survival compared with lower values (p < .05). Nonety-two percent of patients whose preoperative CEA was 50 ng/mL died within 2 years of resection. Patients with resectable NSCLC who had CA-125 levels exceeding 15 U/mL were more than three times more likely to relapse and more than four times more likely to succumb to metastatic disease than those with lower values. Three-year survival was 67% for patients with preoperative CA-125 levels of 15 U/mL, compared with only 20% for those with CA-125 levels of 15 U/mL (p < .001). It appears that very high levels of CEA and/or CA-125 are associated with a poor outcome.

Molecular Markers

A variety of biomarkers expressed by tumor tissue have been reported and may be clinically useful. These can be classified as molecular genetic markers, metastatic propensity markers, differentiation markers, and proliferation markers.

Molecular Genetic Markers

The prognostic importance of mutation and/or protein product overexpression of five distinct oncogenes has been shown to be important in NSCLC. These include the *ras* oncogene, the p53 tumor suppressor gene, the c-*erbB*-2 proto-oncogene, bcl-2 protein, and retinoblastoma (Rb) protein (Table 7).

Author	Total number	T¹ tumor		Y²	T² tumor		Y²	Significance
		No.	%	(OS or DFS)	No.	%	(OS or DFS)	
Mountain	865	439	68%	5 yr OS	426	59%	5 yr OS	$p < 0.01$
Naruke	652	281	72%	5 yr OS	372	52%	5 yr OS	$p < 0.01$
Gail	352	NR	77%	NR	NR	65%	NR	$p = 0.004$
Feinberg	328	170	70%	5 yr DFS	158	58%	5 yr DFS	$p = 0.012$
Martini	598	297	82%	5 yr OS	307	68%	5 yr OS	$p = 0.009$
Ichinose	151	71	85%	5 yr OS	80	67%	5 yr OS	$p = 0.012$
Hoppin	289	173	70%	5 yr OS	116	52%	5 yr OS	$p < 0.001$
Lafitte	204	NR	74%	5 yr OS	NR	38%	5 yr OS	Not reported
Immerman	77	39	64%	5 yr DFS	38	42%	5 yr DFS	Not reported

¹OS, overall survival; DFS, disease-free survival.

TABLE 7. *Prognostic significance of tumor size in surgical–pathologic stage I NSCLC*

K-ras Oncogene and p21 Expression

The *ras* oncogenes are believed to be important to cell growth by regulating signal transduction pathways. They are expressed in virtually all mammalian cells, and mutations in any of three distinct *ras* genes, H-*ras,* N-*ras,* and K-*ras,* can lead to malignant transformation. In lung cancer, almost all mutations affect the K-*ras* gene. Most reports indicate that *ras* mutations are predominantly associated with adenocarcinoma, although a slightly higher proportion of such mutations in squamous cell carcinoma has been reported. The *ras* genes encode for a group of proteins (p21 proteins) associated with the surface of cell membranes.

Activation of the K-*ras* oncogene has been reported to be associated with an adverse prognosis in resectable lung adenocarcinoma. In one series, 63% of patients with the K-*ras* mutation had died, compared with only 32% of those without the mutation, after a median follow-up of 3 years (p = .002). Two other reports have confirmed that K-*ras* mutations adversely affect survival in resectable NSCLC.

Similarly, overexpression of p21, the protein product of K-*ras,* has been reported to affect survival adversely. In one series of 116 resected NSCLC patients, 5-year survival was 64% in patients with negative p21 immunostaining, 38% for those with moderate immunostaining, and 11% in those with strong immunostaining. Multivariate analysis indicated that the association between p21 and survival was independent of stage, histology, and nodal status.

The p53 Tumor Suppressor Gene

The p53 tumor suppressor gene has been more commonly associated with human cancer than any other gene. Although most reports of p53 expression in NSCLC suggest that it carries an adverse prognosis, the opposite has also been found. Abnormalities of p53 in NSCLC have been reported both in terms of gene mutation and protein expression. The relation between survival and p53 gene abnormalities was evaluated in 85 resected NSCLC patients; p53 overexpression was detected in 55%, and mutations were noted in 54%. However, concordance was observed in only 65% of all patients. A significant reduction in survival was noted when p53 was overexpressed, but not when a gene mutation was identified. Similar results were reported in several other studies. It has been stated that p53 oncoprotein expression is “a favorable prognostic factor” in NSCLC. In a group of 156 resected patients, median survival for those with a high level of immunostaining for p53 was 65 months, compared with 26 months for those with low levels of immunostaining and 33 months for those with negative immunostaining.

On the other hand, no significant survival differences could be found in 125 resected NSCLC patients based on p53 immunostaining. Similarly, no significant overall association between p53 expression and survival could be demonstrated in 208 resected NSCLC patients. In another study, of 100 patients with adenocarcinoma, those with p53 expression had a worse survival than those without p53 expression. In contrast, in 88 patients with squamous cell carcinoma, no significant survival differences were observed, although survival trends suggested that p53 might predict for a better outcome.

The prognostic significance of p53 mutations has also been the subject of conflicting reports. No significant associations with gene mutations and survival in NSCLC have been reported; a significantly inferior 3-year survival for patients with p53 mutations compared with patients without mutations has been found (28% vs. 51%; p = .010) in 120 resected patients with NSCLC. Similarly, the presence of a p53 mutation led to a significant shortening of survival in 71 cases of resectable NSCLC (p = .014). The reasons for these conflicting reports are unclear but are likely to be multifactorial. Differences in experimental techniques and specific anti-p53 antibodies likely provide a partial answer.

The c-erbB-2 Oncogene and p185^{neu} Expression

The c-*erbB*-2 oncogene encodes for an epidermal growth factor receptor (erbB-1, EGFr). Three studies have reported that overexpression of its protein product, p185^{neu}, is associated with an adverse outcome in certain patient subsets. Kern reported that patients with adenocarcinoma of the lung who overexpressed p185^{neu} had a significantly worse survival compared with those who did not. In contrast, p185^{neu} expression did not influence survival in squamous cell carcinoma. Tateishi reported on the prognostic importance of p185^{neu} expression in 119 patients with adenocarcinoma and 84 patients with squamous cell carcinoma. Overall, 28% of adenocarcinomas were positive for p185^{neu}, compared with only 2% of the squamous cell cancers. Overexpression of p185^{neu} adversely affected 5-year survival (30%, compared with 52% for patients with tumors that were p185^{neu}-negative; $p < .01$). Finally, Harpole demonstrated p185^{neu} expression in 21% of 271 resected patients with stage I NSCLC. Surivival was significantly worse in those who expressed p185^{neu} than in those who did not ($p < .001$).

The bcl-2 Protein

The *bcl*-2 gene encodes for a protein that inhibits apoptosis. Expression of bcl-2 protein in 122 resected patients with stage I or II NSCLC was evaluated; the protein was detected by immunohistochemical analysis in 25% of patients with squamous cell carcinoma and 12% (5/42) with adenocarcinoma. Patients with tumors positive for bcl-2 protein had a superior survival at 5 years, although the differences reached statistical significance only for those with squamous cell histology (p .02). Similarly, survival was improved in patients with resectable NSCLC who expressed bcl-2 protein.

Retinoblastoma Protein

Loss of expression of the retinoblastoma (Rb) protein has been associated with an adverse prognosis in several human cancers. In lung cancer, no Rb protein expression was identified in 24% of 101 patients with resected NSCLC; median survival was significantly worse for patients with Rb-negative than with Rb-positive tumors (18 vs. 32 months; p = .007). A second study, involving 159 patients with resected NSCLC, reported 18% with Rb-negative tumors; these patients exhibited a trend toward inferior survival, although differences did not reach statistical significance (28 vs. 48 months; p = .37).

Markers of Metastatic Propensity

Although metastatic propensity has traditionally been evaluated by a number of pathologic parameters (lymphovascular invasion, degree of tumor differentiation), a number of markers can provide insights into the likelihood of metastatic spread. These include detection of isolated tumor cells in lymph nodes or bone marrow, cathepsin B expression, intensity of angiogenesis, and basement membrane deposition (Table 8).

Variable	Favorable	Unfavorable
K-ras oncogene activation	No point mutation	Point mutation at codon 12
p21–K-ras protein product expression	Absent p21 staining	Strong p21 staining
p53 tumor suppressor gene	No mutation	Gene mutation present
p53 protein product expression	Normal p53 expression	Overexpression of p53
p185^{neu} expression, the protein product of the C-erbB-2 oncogene	No expression of p185^{neu}	Overexpression of p185^{neu}
bcl-2 protein expression	bcl-2 positive	bcl-2 negative
Retinoblastoma (Rb) protein expression	Rb positive	Rb negative

TABLE 8. *Molecular genetic markers in early-stage NSCLC*

Isolated Tumor Cells in Lymph Nodes

It has been demonstrated that in a substantial percentage of patients with histologically negative lymph nodes, occult nodal metastases are revealed with the use of sensitive immunohistochemical techniques employing tumor-specific monoclonal antibodies. In one report of 60 patients with resected stage I NSCLC, 63% of patients with histologically negative lymph nodes had occult nodal metastases demonstrated by immunostaining with a polyclonal antikeratin antibody using the avidin-biotin complex immunoperoxidase technique. Lymph nodes closest to the primary tumor were most likely to contain occult micrometastases. There was a trend toward decreased median survival among those with occult nodal metastases (5.4 years vs. 6.7 years), although the difference did not reach statistical significance.

In another series, immunostaining with the Ber-Ep4 monoclonal antibody was performed in 72 patients with stage I NSCLC (all of whom had histologically negative nodes). The Ber-Ep4 antibody reacts with two glycoproteins present on the surface and in the cytoplasm of epithelial cancer cells. Individual cells positive for Ber-Ep4 were detected in 15% of patients. Recurrences were observed in 50% of patients with occult lymph nodes metastases and in 14% of those who had negative nodes (p = .005) during a 26-month median follow-up period. Moreover, 30% of patients with nodal micrometastases died of lung cancer during the observation period, compared with 7% without nodal involvement (p = .048).

Isolated Tumor Cells in Bone Marrow

The presence of occult metastases in bone marrow, detected by monoclonal antibody CK2 directed against cytokeratin polypetide 18 (CK18), has been evaluated in a series of 139 patients with resected NSCLC. CK18 was present in only 6 of 215 control patients without epithelial cancer. Overall, isolated bone marrow metastases were detected in 60% of patients. Among 66 node-negative patients, CK18 positivity was a strong predictor for recurrence and survival. During the median follow-up of 39 months, 75% of 12 node-negative, CK18-positive patients relapsed, compared with 35% of 54 patients who were CK18-negative (p = .023). On the other hand, the initial bone marrow status did not predict recurrence in 62 patients with positive regional nodes at the time of primary surgery.

Cathepsin B Expression

Cathepsin B, a lysosomal cysteine proteinase, regulates the catabolism of a variety of intracellular proteins. Cathepsin B is able to degrade extracellular matrix, thereby promoting tumor invasion and metastasis. Fairly extensive literature in breast cancer indicates that a high level of cathepsin B expression is associated with an adverse prognosis. Cathepsin B expression was assessed immunohistochemically using a polyclonal antibody in 108 resected NSCLC patients. A high level of expression was

associated with a statistically significant shortened survival ($p < .01$) in patients with squamous cell carcinoma or adenocarcinoma of the lung.

Intensity of Angiogenesis

An inverse relationship between the intensity of angiogenesis and prognosis has been demonstrated in stage I NSCLC. The intensity of angiogenesis was assessed by counting microvessels and grading their density in a population of 87 patients with resected T1,N0,M0 NSCLC. Microvessels were identified by antibody staining for factor VIII as well as by routine hematoxylin-eosin (H&E) staining. Those in whom recurrence developed had a statistically significantly higher mean number of microvessels and density grade than those in whom metastatic disease did not develop.

Basement Membrane Deposition

The presence of basement membrane deposition, determined by immunohistochemical staining with polyclonal antibodies to human type IV collagen, has been reported to predict for a favorable outcome in stage I and II squamous cell carcinoma of the lung. In 68 patients with early-stage squamous cell carcinoma, those with extensive basement membrane deposition had a significantly longer survival than those with moderate or limited deposition ($p = .02$).

Markers of Differentiation

Expression of certain cell membrane proteins is altered during the process of malignant transformation. Two related cell membrane proteins with reported prognostic significance have been evaluated in NSCLC (Table 9).

Variable	Favorable	Unfavorable
Isolated tumor cells in lymph nodes	Negative immunostaining with polyclonal antikeratin antibody	Positive immunostaining with polyclonal antikeratin antibody
Isolated tumor cells in lymph nodes	Negative immunostaining with the Ber-Ep4 monoclonal antibody	Positive immunostaining with the Ber-Ep4 monoclonal antibody
Isolated tumor cells in bone marrow	Negative immunostaining for cytokeratin polypeptide 18 (CK18)	Positive immunostaining for cytokeratin polypeptide 18 (CK18)
Cathepsin B expression	Low cathepsin B expression	High cathepsin B expression
Intensity of angiogenesis	Low microvessel count and density grade	High microvessel count and density grade
Basement membrane deposition (squamous-cell carcinoma)	Extensive deposition	Limited deposition

TABLE 9. *Markers of metastatic propensity in early-stage NSCLC*

Blood Group Antigens

ABH blood group antigens are present on the surface of most epithelial cells, in addition to being expressed on the surface of erythrocytes. Expression of ABH blood group antigen may be altered on the surface of tumor cells, and such alterations may be associated with prognostic significance. The prognostic significance of blood group antigen A expression in 164 patients with resectable NSCLC has been evaluated. The blood was type A or AB in 71 patients, and 61% of these patients expressed the A antigen on their tumor cells. Median survival of antigen-positive patients was superior to that of antigen-negative patients (71 months vs. 15 months; $p < .001$). In 93 patients whose blood group was O or B, survival was intermediate (39 months; $p = .002$). Expression of blood group antigen B or H on the surface of tumor cells did not correlate with survival.

A second study correlated expression of ABH blood group antigens with survival in 89 patients with resectable NSCLC. Loss of expression of blood group antigens was observed in 54%, whereas the other 46% demonstrated conserved expression. A superior survival was demonstrated in those with conserved expression (p .05). Loss of expression predicted for hematogenous metastases. Loss of expression of blood group antigen B was associated with the most significant decrease in survival (p .05). In contrast, loss of expression of A or H antigen was not associated with a significant survival decrement. A third trial failed to confirm any of these findings, so that the relationship between blood group antigens and prognosis remains unclear.

Expression of Lewis-Related Antigens

Expression of the H/Le^y/Le^b antigen on the surface of the cancer cells occurs only in the context of deletion of A and B blood group antigens, which are precursor antigens. H/Le^y/Le^b expression is detected by immunostaining using migration-inhibiting antibody (MIA) 15-5. In a series of 149 patients with resectable NSCLC, 5-year survival was superior for 58 MIA-negative compared with 91 MIA-positive tumors (59% vs. 21%; $p < .001$). Five-year survival differences were more pronounced in squamous cell carcinoma (62% vs. 11%; $p < .001$) than in adenocarcinoma (61% vs. 37%; $p = .015$). MIA-15-5 status was an important determinant of survival in patients with blood groups A and AB; it was not important for those with blood groups B and O.

In another report, expression of three Lewis-related antigens--Le^y, sialyl Le^x, and sialyl Le^a--was examined in 133 patients with resected stage I NSCLC. Expression of any of the Lewis-related antigens was associated with a significant decrease in survival, although expression of both the Lewis and sialyl Lewis antigens more strongly predicted for an adverse outcome. An association between expression of Lewis antigens and BVI was reported in this population.

Markers of Proliferation

A number of molecular techniques have been used to identify potentially more aggressive, rapidly dividing neoplasms. Biomarkers that correlate with cellular proliferation include DNA ploidy and percent S-phase (measured by flow cytometry), KI-67 proliferation index, and proliferating cell nuclear antigens (Table 10). The mitotic index may also be classified as a proliferation marker.

Variable	Favorable	Unfavorable
Expression of blood group antigens on tumor cells	Conserved expression of blood group antigens on tumor cells	Altered expression of blood group antigens on tumor cells
Expression of H/Le^y/Le^b antigens	Negative staining with MIA-15-5	Positive staining with MIA-15-5

TABLE 10. *Differentiation markers in early-stage NSCLC*

Flow Cytometry

Flow cytometry measures proliferative activity by determining the fraction of cells in the synthetic or S-phase of the cell cycle. Furthermore, it also measures DNA content, or ploidy status. By definition, diploid tumors have a normal DNA content and aneuploid tumors have an abnormal DNA content.

The DNA content of resectable NSCLC has been reported in nine studies. Only two of these trials also reported on cell cycle analysis. Five studies reporting on the

prognostic significance of DNA content in resected NSCLC found that tumor aneuploidy adversely affected survival. Four studies found no significant differences in survival when aneuploid and diploid tumors were compared. Accordingly, despite an extensive literature, the prognostic importance of DNA content in resectable NSCLC is uncertain.

Only two studies have addressed the prognostic significance of percent S-phase in early-stage NSCLC. One study indicated that a high S-phase fraction predicted a poor survival, whereas the other found no survival differences on the basis of cell cycle analysis. Accordingly, the prognostic importance of S-phase fraction in resectable NSCLC remains unknown.

KI-67 Nuclear Antigen

Immunohistochemical analysis for the proliferation-associated nuclear antigen KI-67 can identify rapidly dividing tumors. In a group of 61 patients with resectable NSCLC, the survival of patients with a proliferation index of 5% was significantly inferior to survival of those with a proliferation index of 5% (*p* .04). In a much larger population (271 patients) with resected stage I NSCLC, a continuous effect of the magnitude of KI-67 immunostaining on recurrence and survival was demonstrated. The median proliferation index was 5.3%, and the range varied from 0.1%–71%. Results indicated that the higher the proliferation index, the greater the risk for recurrence and death from lung cancer.

Proliferating Cell Nuclear Antigen

Proliferating cell nuclear antigen (PCNA), a nuclear protein that binds to DNA polymerase, is a marker of cellular proliferation. A highly significant relationship between the magnitude of staining with PCNA and survival has been found; PCNA was defined as positive when 5% of tumor cells stained with the antibody.

CLINICAL PRESENTATION OF LUNG CANCER

As previously discussed, screening for lung cancer is neither recommended nor widely practiced. Accordingly, the vast majority of patients are symptomatic at the time of clinical presentation. In one population-based series of 1539 lung cancer patients from New Hampshire and Vermont, only 2% (28 patients) were asymptomatic. Most asymptomatic patients present incidentally when chest roentgenography is performed for other reasons. The symptoms and signs of lung cancer are often divided into three general categories, according to whether they are related to local manifestations of the tumor, to metastatic disease, or to paraneoplastic syndromes. Many more patients present with signs and symptoms in the first and second categories than in the third.

Symptoms

The most common symptom of lung cancer is cough, which occurs in 45%–75% of all patients. Although cough, often associated with sputum production, is extremely common, it is a nonspecific symptom, because a high proportion of patients with lung cancer have pre-existing emphysema or bronchitis, in which similar symptoms may be found. However, a change in the character of an established chronic cough should raise the suspicion of a superimposed process. The production of large amounts of sputum, termed *bronchorrhea,* occurs in about 15% of patients with bronchoalveolar cell carcinoma. Bronchorrhea is extremely rare in other histologic subtypes.

Dyspnea occurs in about a third to half of all patients. It is also a nonspecific symptom and may be related to underlying COPD. Shortness of breath in the context of lung cancer may be attributable to multiple factors, including airway obstruction, obstructive pneumonitis or atelectasis, lymphangitic spread, pleural or pericardial effusion, or thromboembolic disease.

Hemoptysis has been reported in 27%–57% of patients with lung cancer. It should be noted that bronchitis is still the most common cause of hemoptysis, but lung cancer is diagnosed in 19%–29% of all patients who present with hemoptysis. In such cases, the volume of blood in the sputum tends to be small. In rare cases, tumor erosion into a bronchial artery can produce massive hemoptysis and death from asphyxiation.

Chest pain occurs in about a quarter to half of all patients. Some patients have dull, intermittent pain in the hemithorax in which the tumor is located; this does not necessarily indicate invasion to adjacent structures and does not preclude resection. On the other hand, severe, persistent pain often indicates invasion of the chest wall or mediastinum and portends locally advanced disease. Such pain is often associated with rib erosion.

Unilateral, localized wheezing is uncommon, but when it occurs it should raise suspicion of an underlying bronchogenic carcinoma producing fixed obstruction of a major airway. Tracheal obstruction may produce stridor. These symptoms are usually associated with severe dyspnea.

Weight loss has been reported in 8%–68% of patients with lung cancer. It may reflect symptoms of local or metastatic disease, or symptoms of a paraneoplastic syndrome. Almost all studies demonstrate that weight loss is a negative prognostic factor in lung cancer.

Metastatic Disease

About 70% of patients with lung cancer present with symptoms that reflect intrathoracic or extrathoracic metastasis. Pleural effusions are generally caused by pleural extension of the tumor. Pericardial effusion can occur by direct extension of the tumor to the pericardium and epicardium.

Hoarseness, when caused by lung cancer, is most often caused by compression of the recurrent laryngeal nerve; it has been reported in 2%–18% of cases. It is more common in left-sided tumors, because of the circuitous route of the left recurrent laryngeal nerve around the aortic arch.

Superior vena cava syndrome may result from either compression or direct invasion of the great veins of the thoracic inlet by mediastinal nodes or by the tumor itself. It is most common caused by small-cell carcinoma. Symptoms of superior vena cava syndrome include headache, with a sense of fullness in the head, and dyspnea. Physical signs include swelling of the face or upper extremity, plethora, dilated neck veins, and a prominent venous pattern on the chest. Superior vena cava syndrome was noted in 4% of 2000 patients in one series.

Brachial plexopathy is often caused by tumors in the superior sulcus of the lung. This entity, first described by Pancoast, is characterized by pain in the distribution of the C-7, T-1, and T-2 nerve roots, Horner's syndrome, rib destruction, and atrophy of hand muscles.

The most common organs involved by distant metastases from lung cancer are the brain, bones, liver, adrenal glands, and skin. Lung cancer can metastasize to virtually any bone, although vertebrae are most commonly involved. Ribs and pelvic bones are also very commonly involved. Symptoms include severe pain that may have a pleuritic component when the ribs are involved. Hepatic metastases most commonly produce symptoms of weakness and weight loss and carry a very poor prognosis. Headache, nausea and vomiting, focal neurologic symptoms, seizures, confusion, and personality changes may all be manifestations of brain metastases. The lung is the primary site of approximately 70% of cancers that initially present with symptomatic brain metastases.

Paraneoplastic Syndromes

Symptoms of the third category represent nonmetastatic systemic manifestations of the lung cancer (paraneoplastic syndromes) and are not directly related to tumor dissemination. Such manifestations may be caused by the production of biologically active substances by the tumor or by the body's response to the tumor. Often, the mechanism is poorly understood. Overall, clinically significant paraneoplastic syndromes occur in about 10%–20% of patients with bronchogenic carcinomas.

Some paraneoplastic phenomena are related to specific tumor cell types. Hypercalcemia is most strongly associated with squamous cell carcinoma. Digital clubbing and hypertrophic pulmonary osteoarthropathy (HPO) are most often associated with adenocarcinomas. Small-cell carcinoma is most commonly associated with syndromes related to the production of ectopic hormones, including the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and ectopic Cushing's syndrome resulting from production of corticotropin (ACTH) by the tumor. A variety of poorly understood neurologic syndromes also occur, including Eaton-Lambert syndrome (seen almost exclusively in small-cell lung cancer), peripheral neuropathy, and cortical cerebellar degeneration.

ESTABLISHING THE DIAGNOSIS

The existence of an underlying lung cancer is usually suspected on the basis of abnormal findings on a chest roentgenogram (Fig. 14 and Fig. 15). A definitive diagnosis may be made from an examination of tissue or exfoliated cells obtained from the tumor. Specific diagnostic techniques include sputum cytology, flexible fiberoptic bronchoscopy, pleural biopsy and fluid analysis, fine-needle aspiration (FNA), mediastinoscopy, and open thoracotomy. All patients undergoing a workup for

lung cancer should have a computed tomographic (CT) study of the thorax, with contrast when possible, for staging purposes and evaluation of the mediastinum. Magnetic resonance imaging (MRI) of the chest (with gadolinium) should be performed if there is any question of invasion of blood vessels by the tumor. Proper staging requires that imaging of the head (CT, MRI) and bones (bone scan) be performed to rule out metastatic disease. Appropriate workup also includes full pulmonary function studies and a cardiac evaluation if symptoms or signs warrant.

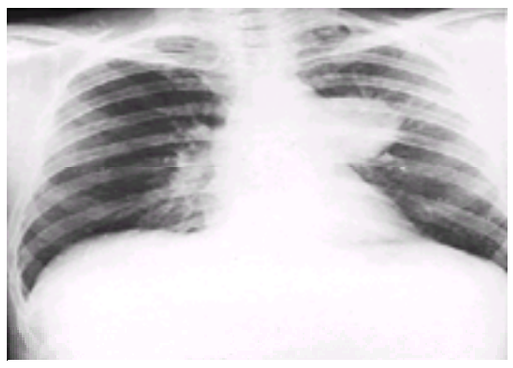


FIG. 14. A large hilar mass caused by carcinoma of the lung. (Reprinted with permission from Morgan WKC, Hales MR. Bronchogenic carcinoma. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* 3rd ed. Boston: Little, Brown; 1983.)

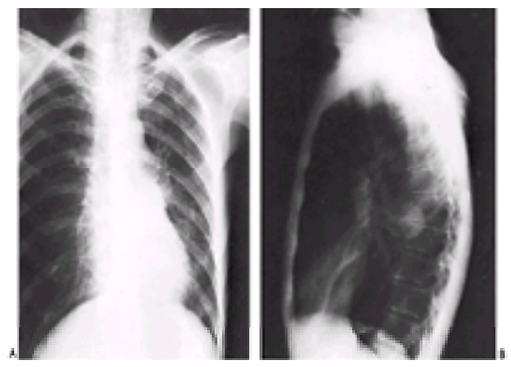


FIG. 15. A: Carcinoma of the lung hidden behind the cardiac silhouette on posteroanterior roentgenogram. **B:** Lateral view of the chest reveals the carcinoma. (Reprinted with permission from Morgan WKC, Hales MR. Bronchogenic carcinoma. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* 3rd ed. Boston: Little, Brown; 1983.)

Computed Tomography of the Chest

The use of CT in the evaluation of hilar or mediastinal lymphadenopathy is controversial. CT is quite sensitive for imaging nodes >1.0 cm; sensitivity ranges from 64%–79%, with a specificity of 62%–66%. The false-negative rate is substantial, with adenocarcinomas having the highest rate of false-negatives. Thoracic CT is usually extended to include the liver, adrenals, kidneys, and upper abdominal lymph nodes, as it is the most effective tool in delineating metastatic disease in these sites.

Sputum Cytology

The diagnosis of central lesions can be made in approximately 80% of cases by the cytologic analysis of freshly expectorated and appropriately prepared sputum (Fig. 16). A specific cell type can be diagnosed 85%–95% of the time if malignant cells are seen.

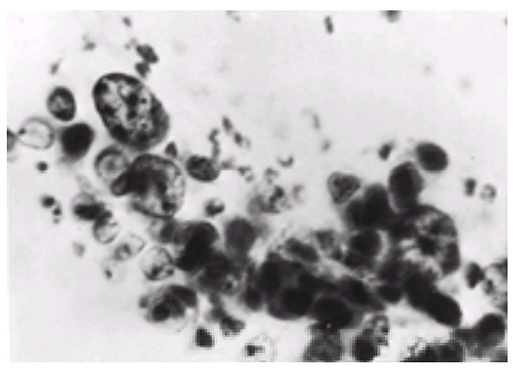


FIG. 16. Photomicrograph of bronchial washings stained by the Papanicolaou technique showing malignant cells. Note the hyperchromatic nuclei with irregularly placed chromatin particles. ×900. (Reprinted with permission from Morgan WKC, Hales MR. Bronchogenic carcinoma. In: Baum GL, Wolinsky E, eds. *Textbook of Pulmonary Diseases.* 3rd ed. Boston: Little, Brown; 1983.)

Flexible Fiberoptic Bronchoscopy

Fiberoptic bronchoscopy is a well-tolerated technique that makes possible visualization of the central tracheobronchial tree and permits brushings, washings, and biopsy specimens to be taken from any visible lesion. Bronchoscopy performed under fluoroscopic guidance permits biopsies of more peripheral lesions. The diagnostic yield is 90% when six to 10 biopsy specimens of endoscopically visible carcinomas are obtained. The diagnostic yield of nonvisualized, peripheral lesions is about 60% if both biopsy specimens and brushings are obtained. In addition, bronchoscopy is a staging procedure that can be used to exclude contralateral endobronchial (M status) lesions and define the proximal extent of an endobronchial lesion in relation to the main bronchi and trachea (T status). Transtracheal and transbronchial thin-needle aspirations (Wang procedure) can be performed to evaluate the involvement of paratracheal, precarinal, and subcarinal nodes (N status).

Analysis of Pleural Fluid and Pleural Biopsy

In a patient with suspected or documented lung cancer and a pleural effusion, analysis of the fluid and also pleural biopsy are required, either to make the initial diagnosis or help define the stage. Cytologic accuracy of pleural fluid examinations in the diagnosis of malignant pleural effusion varies from 40%–87%, depending on the tumor cell type. Accuracy can be increased by examining at least three independently obtained samples. Cytopathologic analysis of both pleural fluid cell blocks and smears should be performed.

Biopsy of the pleura is indicated whenever the cytology of an exudative pleural effusion is nondiagnostic. It will be positive for malignancy 39%–75% of the time. Analysis of pleural fluid will provide the diagnosis of malignancy more often than pleural biopsy.

The presence of a malignant pleural effusion automatically classifies the patient as having an unresectable T4 lesion. Not all malignant effusions are secondary to pleural involvement by tumor. If analysis of multiple pleural fluid and biopsy samples is nondiagnostic and the fluid is exudative, thoracoscopic examination of the

pleural surface should be performed to help make a diagnosis and stage the patient. A transudative, nonbloody effusion should not be considered in the determination of stage if results of the cytopathologic examination are negative.

Fine-Needle Aspiration

FNA is usually performed under CT or fluoroscopic guidance to obtain cells from lesions not accessible by other means. The most common complications of this procedure are pneumothorax (25%–35%) and minor hemoptysis (1%–10%). The diagnostic sensitivity of FNA in lung cancer is 85%. False-negatives result from inadequate sampling or the sampling of necrotic tissue. The false-positive rate of transthoracic needle aspiration is 0.1%–0.5% and is most commonly caused by the presence of an inflammatory process, such as pneumonia, abscess, or active tuberculosis, or fibrosis.

FNA is very useful in determining cell type in patients who are not candidates for surgery, or for staging purposes when either upstaging or downstaging would influence management. The procedure should not be performed in patients who are surgical candidates, because the finding of malignant cells will not affect therapy and because FNA is not a reliable test for diagnosing benign lesions.

Mediastinoscopy/Anterior Mediastinotomy (Chamberlain Procedure)

These invasive surgical procedures are the most accurate methods for staging the mediastinum and identifying patients with unresectable disease: contralateral nodal involvement, extranodal extension of cancer, high paratracheal involvement, or cell type not amenable to surgery (small-cell carcinoma). Many centers use CT as a screening tool to assess the mediastinum, as mentioned above.

Lymph nodes 1.0 cm in the short axis are considered abnormal and require sampling by mediastinoscopy. Patients with an abnormal mediastinum on chest CT should undergo mediastinoscopy or anterior mediastinotomy so that tissue can be obtained to document the presence of malignancy before definitive surgical resection. Cervical mediastinoscopy permits direct imaging and sampling of paratracheal, tracheobronchial, and anterior subcarinal lymph nodes. Anterior mediastinotomy and extended cervical mediastinoscopy allow assessment of the aortic pulmonary window and anterior mediastinal nodes. Mediastinoscopy will exclude from thoracotomy 30%–40% of patients initially thought to have surgically resectable disease.

Direct Lymph Node Biopsy

Palpable cervical or scalene lymph nodes in the setting of suspected lung cancer should be sampled. Evidence of metastasis will usually preclude thoracotomy. In patients with documented lung cancer and palpable scalene nodes, biopsy results have been positive in 83% of cases; only 20% of nonpalpable nodes were positive for malignancy after biopsy.

Thoracotomy

Surgical exploration of the chest is the gold standard for determining the final T and N status of the cancer and permits decisions to be made regarding the surgical procedure required. Thoracotomy should be performed in any patient with a normal mediastinum on CT. All lymph node stations not sampled during mediastinoscopy should be assessed at thoracotomy regardless of appearance on CT. Samples of nodes from the superior mediastinum and subcarinal, subaortic, peribronchial, and intrapulmonary nodes adjacent to the planned site of bronchial resection should be obtained. N status often can be determined only at this time.

STAGING OF LUNG CANCER

Once the diagnosis of lung cancer has been established, a determination of extent of disease, as reflected by surgical pathologic staging, must be made to guide appropriate therapy and determine prognosis. A TNM (tumor, node, metastasis) staging system for lung cancer has been in use for more than two decades, predominantly for NSCLC. The T status (T1-4) describes the size, location, and extent of the primary tumor; the N status (N0-2) delineates lymph node involvement, and the M status (M0-1) represents distant metastases. A three-stage staging system of the American Joint Committee on Cancer (AJCC) was widely utilized until 1986. In this system, stage I included T1,N0,M0 and T2,N0,M0 as well as T1,N1,M0 tumors, whereas stage II consisted exclusively of T2,N1,MO lesions. Patients identified as having regionally advanced disease (consisting of T3 and/or N2 disease) or distant metastatic (M1) disease were grouped together within a single stage III category.

In 1986, the International Staging System (ISS) for lung cancer was introduced and adopted by the AJCC (Table 6 and Fig. 12). This system, like the older AJCC system, is based on the principal of TNM groupings and comprises five stages. In 1997, the ISS was modified, so that stages I and II were divided into IA/IB and IIA/IIB subcategories. This is predominantly related to tumor size, although T3N0M0 lesions were moved from stage IIIA to stage IIB (Table 6).

In stages I, II, and IIIA NSCLC, the stages in which resection plays a therapeutic role, prognosis is better when staging is based on surgical pathologic criteria (pTNM) rather than clinical criteria alone (cTNM) (Fig. 17 and Fig. 18). This is because a significant proportion of patients are found to be understaged at surgery, despite extensive preoperative workup. In a prospective validation of the International Union Against Cancer TNM evaluation involving 3824 patients, concordance between TNM and clinical stages was 61% for stage I disease.

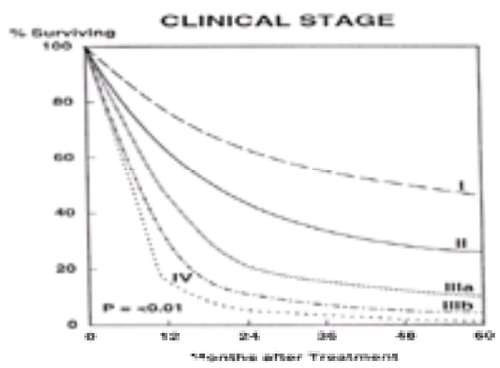


FIG. 17. Cumulative survival according to clinical stage of disease. (Reproduced with permission from Mountain CF. Staging classification for lung cancer. *Clin Chest Med* 1993.)

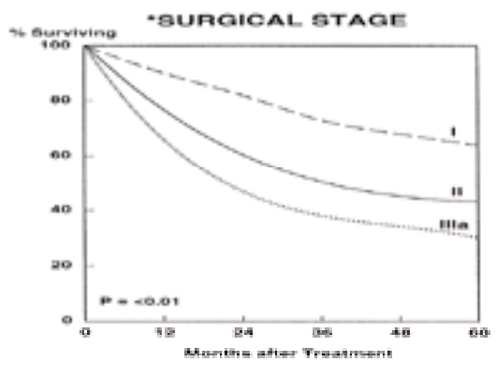


FIG. 18. Cumulative survival according to surgical-pathologic stage of disease. This evaluation of disease extent is based on pathologic examination of resected specimens. (Reproduced with permission from Mountain CF. Staging classification for lung cancer. *Clin Chest Med* 1993;14: 43–51.)

Stage I (T1-2,N0) represents local disease without regional node involvement. Stage II (T1-2,N1) encompasses lymph node involvement that is limited to nodes within

the substance of the lung itself (peribronchial, lobar, and/or hilar nodes). The current standard therapy for stages I and II NSCLC consists of surgical resection. Postoperative radiation may reduce the risk for local recurrence in resected stage II disease.

Stage III comprises regionally advanced disease and is subdivided into stage IIIA and stage IIIB subcategories. Stage IIIA disease consists of regionally advanced disease that is nonetheless technically resectable for cure. It comprises T3,N1 or T1-2-N2 disease. While by definition stage IIIA NSCLC is technically resectable, the efficacy of surgery is controversial. Stage IIIB consists of regionally advanced, technically unresectable (with intent to cure) disease (T4 and/or N3 disease). Modern treatment for both stage III categories is evolving, but most investigative strategies have utilized multimodality approaches consisting of chemotherapy, radiation, and surgery.

Stage IV consists of distant metastatic disease (M1). Treatment generally consists of chemotherapy and palliative radiation, or no treatment is undertaken.

Proportional stage distribution in NSCLC varies enormously among different series and depends very much on the method of detection. Among 3753 patients reported by Mountain, whose staging information was used to formulate the ISS, 1533 (41%) had stage I disease. In this series, stage I was by far the most common stage of disease at presentation and was almost two and a half times as frequent as any other stage grouping. The most accurate data regarding proportional stage distribution at the present time comes from the National Cancer Data Base (NCDB), which contains information on 58,653 lung cancer patients. The anatomic classification of extent of disease employed by the NCDB is neither the AJCC nor ISS classification. Rather, patients are classified into local, regional, or distant categories. After stratification by race and socioeconomic status, the percentages of patients classified with local, regional, and distant disease were 17%–18%, 31%–33% and 35%–39%, respectively (the remainder being not further classified). These data are much more consistent with the current perception that most patients with lung cancer have metastatic disease at presentation. They are also consistent with the current overall 5-year survival of 13% for all lung cancer patients in the United States.

Although the optimal staging system for SCLC remains uncertain, a simple two-stage system dividing patients into those with limited or extensive disease has been widely used. Limited disease refers to disease that is either confined to the hemithorax of origin or is encompassed within a single radiation portal. Extensive disease refers to cancer that has spread beyond the hemithorax of origin.

MANAGEMENT OF STAGE I AND STAGE II NSCLC

Therapeutic management of all stages of NSCLC depends on the stage of disease at clinical presentation. Surgical resection is widely recognized as the most effective therapy for patients with stages I and II NSCLC. By and large, only patients who have undergone complete resection are likely to achieve a cure. The adjunctive role of radiation therapy and chemotherapy is still under investigation.

Surgery

Stage I NSCLC is the only stage of NSCLC in which it is agreed that surgical resection alone constitutes standard treatment, even though its value has never been established by a randomized trial. Nonetheless, the favorable results reported in selected surgical series, and the infrequency of long-term survival among patients treated with nonsurgical means, clearly establishes surgery as the treatment of choice in resectable early-stage NSCLC.

Lobectomy has generally been accepted as the procedure of choice in both stages I and II NSCLC. It is usually possible to remove all known disease with lobectomy, while preserving pulmonary function. Full pneumonectomy may be required with large proximal tumors. Sleeve resection should be considered when the tumor mass is 2 cm from the main carina.

In recent years, advances in video optics have facilitated the development of video-assisted thoracoscopic surgery (VATS). This minimally invasive procedure is associated with a reduction in surgical morbidity, including postoperative pain. VATS has been employed for diagnostic and staging purposes, and for wedge or segmental resections in selected individuals, particularly elderly patients with significant medical comorbidities. Limited resection has been found to be inferior to lobectomy as a definitive cancer operation in patients with small, peripheral, stage I lesions. The efficacy of VATS is therefore not clear.

The reported success of surgical therapy for stages I and II NSCLC varies widely. Success clearly depends on the extent of staging. In Mountain's series, approximately 50% of patients with clinical stage I and 30% of patients with clinical stage II NSCLC survived for 5 years following diagnosis. For patients with pathologic stages I and II NSCLC, 5-year survival was 64% and 45%, respectively. Among patients with pathologic stage I disease, 5-year survival was 69% and 59% for those with T1,N0 and T2,N0 tumors, respectively. In one series of 289 stage I patients treated at Duke University, the 5-year survival was 63%, whereas in a series of 495 patients from the Mayo Clinic, the 5-year survival was 69%.

Probably the most impressive results regarding surgical therapy for stage I NSCLC comes from Memorial Sloan-Kettering, where 598 stage I patients underwent resection. The histologic distribution included 39% with squamous cell carcinoma and 59% with adenocarcinoma (including 16% with bronchoalveolar carcinoma). Interestingly, only 2% of patients had large-cell carcinomas. The overall 5- and 10-year survivals in this series were 75% and 67%, respectively.

Of these patients, 49% were classified as T1 and 51% as T2. As expected, patients who had T1 tumors enjoyed a superior survival compared with those who had T2 tumors (5- and 10-year survivals: T1, 82% and 74%; T2, 68% and 60%; $p < .0004$). Tumor size significantly influenced survival when stratified as <1 cm, >1 to 3 cm, >3 to 5 cm, and >5 cm. For example, 10-year survival for patients with tumors <3 cm, >3-5 cm, and >5 cm was 74%, 62%, and 47%, respectively. Virtually all series confirm the importance of tumor size in pathologic stage I NSCLC.

Surgical therapy consisted of a lobectomy in 85% and pneumonectomy in 4% of patients, whereas 11% underwent wedge resection or segmentectomy. Mediastinal lymph node dissection was performed in 94% and lymph node sampling or no formal dissection in 6%. The 5- and 10-year survivals were 77% and 70%, respectively, among those who underwent lobectomy or pneumonectomy. Patients treated with lesser resection had 5-and 10-year survivals of 59% and 35%, respectively ($p = .026$).

In many series, stage II NSCLC is the least common of any stage of lung cancer. The results of surgical resection among patients with stage II NSCLC are considerably less favorable than the results for patients with stage I disease. The LCSG has reported on 1000 patients with stage II disease and found the histologic subtype to be an important determinant of survival. In patients with T1,N1 disease, the 5-year survival was 75% for squamous cell carcinoma and 52% for adenocarcinoma ($p = .04$). For patients with T2,N1 tumors, the 5-year survival was 53% for squamous cell carcinoma and 25% for adenocarcinoma ($p < .01$).

For patients who undergo complete resection for stage II (T1,N0,M0 or T2,N0,M0) NSCLC, the 5-year survival has been reported to be as high as 47%, based on a study of 214 patients from Memorial Sloan-Kettering Cancer Center. A T2,N1 tumor was present in 84% of all patients in this series. Lobectomy was performed in 68% and pneumonectomy in 31%. The number of involved N1 nodes was a very important determinant of outcome in this series, and patients who had a single nodal site did better than those with multiply involved nodes. Whereas the distinction between T1 and T2 was not significant, there was a significantly better survival in patients with tumors <3 cm than in those with tumors <5 cm.

Radiation Therapy

Radiation treatment has been employed in the management of early-stage NSCLC in nonsurgical candidates, and in the postoperative management of patients with resected stage II disease. Radiation therapy has also been used as a primary alternative to surgery in patients with technically resectable early-stage disease. These individuals usually are elderly, refuse surgical intervention, or have significant medical comorbidities.

The results of 347 patients with clinical stage I NSCLC, treated at the Queensland Radium Institute between 1985 and 1992 with radiation alone, were retrospectively reviewed. All patients received at minimum a 50-Gy tumor dose in 20 fractions during 4 weeks. Overall 5-year survival was 27%, and median survival was 27.9 months. The 5-year survival among the 167 patients with T1,N0 tumors was 32%, and it was 21% for the 180 patients with T2 tumors ($p < .01$).

Another series, of 84 “medically inoperable” patients with early-stage disease, reported a 5-year survival of 31% for clinical stage I and 19% for clinical stage II NSCLC. Most patients received 40 Gy to the primary tumor and mediastinum and a subsequent boost, bringing the dose to 60 to 74 Gy. Tumor size was the most important factor predicting both local-regional failure and survival. Local-regional recurrence occurred in 24% of patients with tumors 5 cm and in 53% of those with larger tumors. Similarly, the 5-year survival was 29% for tumors <5 cm, compared with 14% for those <5 cm. Thus, a substantial minority of patients with early-stage NSCLC may achieve prolonged survival and even cure with radiation alone, but results achieved with this modality are clearly inferior to the results achieved with surgical resection.

With regard to postoperative adjuvant radiation therapy following resection, randomized trials exist both for stage I and stage II disease. The role of postoperative radiation has been studied in a French trial involving 132 patients with T2,N0 lesions. Patients were randomized to surgery alone or to surgery followed by 45 to 60 Gy

of postoperative radiation centered on the hilum and upper mediastinum. The results of the trial demonstrated no advantage for the group undergoing postoperative radiation therapy. In fact, trends in disease-free survival (p = .11) and overall survival (p = .049) favored the nonirradiated group. Overall 5-year survival was 44% in both groups. The proportion of patients who had local recurrence was 15% in the radiation group and 17% in the control group. The proportion with distant metastases was 37% in the irradiated group and 25% in the group with surgery alone.

Similarly, a trial from Belgium studied the role of postoperative radiation in 175 evaluable patients who had completely resected lung cancer without nodal involvement. In this trial, 92 patients were randomized to surgery alone and 83 to surgery and 60 Gy of postoperative radiation delivered to the mediastinum. All histologic subtypes were eligible, and seven patients with SCLC were included in each arm. Like the French trial, this was a negative study, and survival trends at 5 years also favored the nonirradiated group (24% vs. 43%; p = NS). For patients with T2,N0 tumors, there was actually a significant survival detriment associated with postoperative radiation (p < .05). Postoperative radiation did alter the pattern of recurrence. In 25 (of 83) patients in the radiation arm in whom recurrences developed, the percentages of recurrences that were exclusively regional, both regional and distant, and exclusively distant were 4%, 12%, and 84%, respectively. In contrast, among 36 (of 92) patients in the surgery arm who had recurrence, 28% of recurrences were regional only, 25% regional and distant, and 47% distant only. Accordingly, radiation did decrease the risk for regional recurrence in this trial.

In stage II NSCLC, the role of postoperative radiation therapy has been best evaluated by the Lung Cancer Study Group in LCSG protocol 773. In this trial, 230 patients with completely resected squamous cell carcinoma were randomized to no further therapy or to 50 Gy of postoperative radiation. Two thirds of participants had stage II disease, and the remainder had ipsilateral mediastinal nodal involvement (stage IIIA). Overall, recurrences were observed in 37% (38/102) in the radiation group and 47% (51/108) in the group with surgery only (p = .17). Postoperative radiation also led to a striking change in the pattern of recurrence. There was a dramatic reduction in the risk for recurrence to the ipsilateral lung and mediastinum in the radiation group (3% vs. 41%; p < .001) but an increase in distant recurrences (97%). Of recurrences in the group with surgery alone, 59% were at distant sites. Survival analysis demonstrated no difference in overall survival between the groups. Accordingly, the results of this trial demonstrated that postoperative radiation could reduce the risk for local recurrence following resection of squamous cell carcinoma, although overall recurrence rate and survival were not improved. The results underscore the need for effective systemic therapy to control distant metastatic disease.

Adjuvant Chemotherapy

As the most common pattern of failure following curative resection of stages I and II NSCLC is distant metastatic disease, adjuvant chemotherapy represents the most rational therapeutic strategy to diminish this risk. Although numerous adjuvant chemotherapy trials in resectable NSCLC have been conducted during the past several decades, no patient subset has been identified in whom an undisputed benefit from adjuvant chemotherapy has been achieved. Accordingly, adjuvant chemotherapy is not a standard of care for any patients with resected stage I or stage II disease.

A meta-analysis of chemotherapy in NSCLC has been published, with data included from 14 randomized trials comparing surgical resection alone with surgery plus adjuvant chemotherapy. These trials comprised a total of 4357 patients; there were 2574 deaths. Five of the trials evaluated adjuvant chemotherapy based on the use of long-term alkylating agents. In these trials, the hazard ratio favored surgery alone, and this risk for death was 15% *higher* among those randomized to chemotherapy (p = .005).

For studies that utilized a cisplatin-based chemotherapy regimen, the hazard ratio estimates favored adjuvant chemotherapy. Overall, there was a 13% reduction in the risk for death among treated patients in these eight trials, which translated into an absolute 5% improvement in the probability of long-term survival (p = .08).

Although conflicting data exist, a number of studies do support the conclusion that adjuvant chemotherapy in resectable NSCLC is associated with some biologic effect. Nonetheless, adjuvant chemotherapy remains experimental at the present time and is recommended only in the context of a clinical trial.

The availability of newer and potentially more effective agents provides an opportunity to re-evaluate the role of chemotherapy in the adjuvant setting. Newer drugs with encouraging activity include carboplatin, paclitaxel (Taxol), docetaxel (Taxotere), vinorelbine tartrate (Navelbine), gemcitabine (Gemzar), and irinotecan (CPT-11). Adjuvant trials including some of the newer agents have already been initiated. Two ongoing North American adjuvant chemotherapy trials in patients at high risk for recurrence following complete resection of NSCLC deserve mention.

The National Cancer Institute of Canada is conducting a phase III study comparing surgery alone with surgery followed by adjuvant chemotherapy with cisplatin and Navelbine (NCIC BR10). Eligible patients include those with T2,N0 stage I disease and those with stage II (T1,N1 or T2,N1) disease. Tissue is being collected to study molecular markers on a prospective basis. The presence of a *ras* mutation will be utilized as a stratification factor before randomization. Groups in the United States are planning to cooperate in this study, so it will be conducted as an intergroup study.

The Cancer and Leukemia Group B is sponsoring an intergroup study in patients with high-risk stage I NSCLC (CALGB 96-33). Eligible patients must have a T2,N0 primary lesion. A total of 500 patients will be randomized to surgery alone or to surgery followed by adjuvant chemotherapy with carboplatin and Taxol. The rationale for defining “high risk” exclusively on the basis of T status is based on the consistency of individual reports indicating that tumor size is an important predictor of outcome in stage I NSCLC. In this study, it is felt that there is insufficient information to permit treatment decisions to be based on any constellation of molecular and/or pathologic prognostic markers.

Response rates in advanced NSCLC observed with combination chemotherapy regimens employing cisplatin and Navelbine (NCIC adjuvant trial) or carboplatin and Taxol (CALGB trial) exceed the response rates observed with 5-fluorouracil (5-FU) and leucovorin in advanced colorectal cancer or cyclophospamide, methotrexate, and 5-FU (CMF) in advanced breast cancer. Accordingly, there is a strong basis for optimism that the current adjuvant trials in resectable NSCLC will provide definitive evidence that adjuvant chemotherapy contributes to long-term survival in resectable NSCLC. Nonetheless, until such evidence becomes available, adjuvant chemotherapy in resectable early-stage NSCLC remains investigational.

MANAGEMENT OF STAGE IIIA AND STAGE IIIB NSCLC

The management of regionally advanced NSCLC has evolved rapidly during the last decade. The older AJCC staging system had grouped regionally advanced NSCLC along with distant metastatic disease in a single stage III category. However, the ISS subdivides regionally advanced stage III disease into stage IIIA and IIIB categories. Stage IIIA disease is characterized by circumscribed extrapulmonary extension of the primary tumor, implied by the T3 designation or by the presence of N2 nodes. Stage IIIB is characterized by extensive extrapulmonary (although intrathoracic) extension, implied by the T4 designation or nodal disease outside the ipsilateral hemithorax.

Conceptually, stage IIIA was intended to describe regionally advanced yet potentially resectable disease, whereas stage IIIB was intended to described regionally advanced, categorically unresectable disease. Criteria for resectability have changed somewhat, and these distinctions are not absolute. Moreover, in this era of multimodality therapy, surgery may play a cytoreductive role in the management of cancer.

Stage IIIA disease appears to be associated with a better prognosis than stage IIIB disease. According to data presented when the ISS was introduced, stage IIIA is associated with a median survival of 12 months and a 5-year survival of 15%, whereas stage IIIB is associated with a median survival of 8 months and a 5-year survival of <5%.

Radiation Therapy in Stage III NSCLC

Radiation therapy alone has traditionally been considered the “standard” therapy for regionally advanced NSCLC. However, the literature on radiation alone in the treatment of regionally advanced stage III NSCLC consistently demonstrates that the median survival achieved is <1 year in duration, and 5-year survival rates range between 5% and 8%. Radiation is an effective palliative measure in terms of relief of symptoms, but it is not associated with long-term survival in the vast majority of treated patients.

There has been little effort to distinguish stage IIIA from stage IIIB prospectively in patients treated with radiation therapy alone. A designation of stage IIIA or IIIB was retrospectively assigned to 306 patients treated at Fox Chase Cancer Center between 1978 and 1987 with standard radiation alone. No significant differences in outcome were found between the 166 IIIA patients and 140 IIIB patients in median survival time (9.4 vs. 9.8 months) or 2-year survival rates (17% vs. 18%). Although this analysis is limited, because only 28% of patients underwent surgical staging of the mediastinum, the authors concluded that stratification of patients into a stage IIIA or IIIB category has little clinical importance when radiation therapy is used alone.

Local control remains a major problem. A 75% local failure rate at 3 years, even among patients with relatively small tumors treated with >65 Gy of radiation, has been reported. Local control is not enhanced by increasing radiation dose with conventional radiation techniques. Two series have shown that severe radiation pneumonitis increases as the radiation dose is raised.

The ineffectiveness of conventionally fractionated radiation in providing long-term survival for the vast majority of patients raises the question of whether radiation should continue to be considered “standard” therapy of regionally advanced NSCLC. Two randomized trials have suggested that “immediate” radiation therapy delivered at the time of diagnosis provides little if any prolongation of survival compared with “delayed” radiation (given when symptoms supervene) or no radiation at all.

There is some evidence that hyperfractionation radiation, in which multiple daily fractions of radiation are employed, may be superior to conventionally fractionated radiation. The Radiation Therapy Oncology Group (RTOG), in protocol 83-11, performed a randomized trial in which 848 patients with stage III NSCLC were randomized to one of five different hyperfractionated treatment arms in which 60.0 Gy, 64.8 Gy, 69.4 Gy, 74.4 Gy, or 79.2 Gy of radiation was administered. A survival advantage was reported for a retrospectively identified subgroup of “favorable” patients (defined as those with Karnofsky performance status of 70%–100% and <6% weight loss). Such “favorable” patients assigned a dose of 69.4 Gy had a median survival of 13 months and a 2-year survival of 29%, both statistically significantly better than median survival at the lower dose levels. There was no further advantage with the higher dose levels, and no survival advantage was seen in those patients who were not “favorable.” The role of hyperfractionated radiation in stage III disease is still being evaluated.

Surgery in Stage III NSCLC

Because the vast majority of patients with NSCLC who achieve long-term survival have undergone resection, surgery is believed to be the most effective modality in NSCLC. In stage III NSSCLC, most patients with stage IIIA are technically resectable, and even certain subsets of stage IIIB patients are amenable to resection. Considerable data support the conclusion that from a surgical standpoint, stage IIIA NSCLC should be stratified based on the presence of a T3 primary lesion or the presence of N2 regional adenopathy.

Until 1997, T3N0 tumors were classified as stage IIIA disease. Clearly, T3N0 and T3N1 tumors are biologically distinct from those associated with N2 disease. The evidence that surgical resection plays a major role in the treatment of stage IIIA disease is strongest with respect to these categories. Patients with T3N0 tumors have a superior prognosis compared to other stage IIIA subgroup. It is for this reason, the T3N0 tumors were reclassified as stage IIB, according to the 1997 revision of the ISS.

Patients with T3 tumors comprise a heterogeneous group with varying prognoses that depend on the basis for the T3 designation. Patients with T3 tumors based on involvement of the chest wall probably have the most favorable outlook with surgical resection. Reports from the Mayo Clinic and the Brigham and Women's Hospital indicate 5-year survival 50% for resected T3,N0 tumors involving the chest wall.

Similarly, patients who have superior sulcus (Pancoast) tumors without regional nodal involvement enjoy respectable long-term survival rates when surgical resection is employed. In Paulson's series of such patients treated with preoperative radiation followed by resection, the 5-year survival rate was 31%.

In contrast, results of surgical resection for tumors that invade the mediastinum are quite different. In a group of 225 such patients from Memorial Sloan-Kettering Cancer Center who underwent thoracotomy, median survival was 12 months and 5-year survival was 7%. Patients with overt mediastinal invasion would be classified at having T4 primary tumors by the ISS system.

Several series have demonstrated that 5-year survival rates range from 15%–29% among highly selected groups of patients undergoing resection of N2 disease. A number of factors have been identified that adversely affect survival in resected N2 disease. These include the presence of T3 tumors, nonsquamous histology, the presence of high mediastinal nodes, or multiple involved N2 sites.

The largest experience on the role of surgery in N2 disease comes from the Memorial Sloan-Kettering Cancer Center. Of 706 patients judged to have N2 disease by either clinical or pathologic criteria (mediastinoscopy was not routinely performed), 404 underwent thoracotomy, and the disease of 151 of these (37% of thoracotomy patients and 21% of all N2 patients) was completely resectable. The bulk of mediastinal nodal involvement significantly affected the likelihood of complete resection. Of 224 patients who were felt by clinical criteria to have NO or N1 disease but were found to have otherwise inapparent N2 disease encountered at thoracotomy, the disease of 119 (53%) was resectable. In contrast, 179 patients had obvious clinical N2 disease, and the disease of only 32 of them (18%) was resectable. Approximately 90% of all patients who underwent resection also received postoperative radiation to the ipsilateral hilum and mediastinum (40 to 45 Gy). The overall 5-year survival for the entire group of N2 patients who underwent resection was 30%. For those who were clinically NO or N1, the 3- and 5-year survivals were 47% and 34%, respectively. For those with clinically overt N2 disease, the 3- and 5-year survivals were each 9%; the 9% figure is not very different from that achievable with radiation alone.

A report from Toronto General Hospital on the surgical treatment of 141 patients with stage IIIA disease demonstrated that cervical mediastinoscopy is extremely useful in selecting patients for surgical resection. In contrast to the experience cited above from Memorial Sloan-Kettering, all patients in the Toronto report underwent preoperative cervical mediastinoscopy for surgical staging of the mediastinum. In 62 patients, findings at mediastinoscopy were negative, but mediastinal nodal involvement was found at the time of resection. The actuarial 5-year survival in this group was 24%. In contrast, among 79 patients, mediastinoscopy findings were positive. In this group, 67 patients underwent resection, but their 5-year survival was only 9%.

Accordingly, the data support the conclusion that surgical “response rates” (resectability) are impressive in certain N2 subsets. Moreover, long-term survival may be achieved in some patients. It remains uncertain whether surgery is the most effective modality in stage IIIA NSCLC, particularly in patients with clinically overt N2 disease.

Combined Surgery and Radiation in Stage III NSCLC

The rationale for combining radiation and surgery is to improve local-regional control. In theory, an improvement in local control would lead to an improvement in overall survival, although this has not been the case in most solid tumors in adult patients. Studies have been carried out in which radiation was utilized preoperatively as well as postoperatively.

Two large, randomized trials comparing preoperative radiation therapy followed by surgery with surgery alone were conducted in the 1960s and 1970s. The first was the Veterans Administration Study, in which patients were randomized to receive preoperative radiation at 40 to 50 Gy or immediate surgery. The second was a study conducted by the NCI in which patients were randomized to preoperative radiation with a minimum of 40 Gy or to surgery alone. Both trials failed to demonstrate any benefit for preoperative radiation, either in terms of decreased mortality or recurrence. Patients with SCLC were eligible to participate in these trials.

Sherman reported the results of a phase II trial of preoperative radiation followed by surgical resection in stage III NSCLC. Fifty-three patients received 30 to 40 Gy preoperatively followed by resection and postoperative radiation. Forty-six patients underwent thoracotomy; the disease of 38 was resectable. Five-year survival was 18% for the entire cohort of 53 patients and 27% for the 38 patients who underwent successful resection.

The role of postoperative radiation was most definitively evaluated by the Lung Cancer Study Group in LCSG protocol 773. Patients with completely resected stage II or III squamous cell carcinoma were randomized to receive 50 Gy of postoperative radiation or no further therapy. About a third of the patients had stage III NSCLC. As previously discussed, postoperative radiation significantly reduced the incidence of local-regional recurrences to the ipsilateral lung and mediastinum from 41% to 3%. However, this did not translate into a survival advantage, but rather shifted recurrence patterns from local-regional to distant.

Induction Chemotherapy and Radiation Versus Radiation Alone in Stage III NSCLC

The use of systemic chemotherapy before definitive local-regional therapy (radiation and/or surgery) is generally referred to as *induction chemotherapy* or *neoadjuvant chemotherapy.* The term *induction chemotherapy* will be employed here.

The role of induction chemotherapy combined with thoracic radiation has been extensively investigated in stage III NSCLC. Numerous phase II and III studies have been completed. Indeed, the role of induction chemotherapy is perhaps better supported by randomized studies in NSCLC than in any other solid tumor of adults.

There are a number of theoretical advantages for the use of induction chemotherapy. These include stage reduction to facilitate improved local control by radiation and/or surgery. Micrometastases are addressed early in the course of treatment. Finally, some studies suggest that induction chemotherapy is better tolerated than chemotherapy administered later in the course of treatment.

The most influential phase III trial in stage III NSCLC is the trial conducted by the Cancer and Leukemia Group B (CALGB 84-33). Eligibility for this trial was limited to patients with prognostically favorable pretreatment characteristics, including favorable performance status (Eastern Cooperative Oncology Group performance status of

0 or 1) and minimal weight loss (5% of body weight in the preceding 3 months). Patients were randomized to receive 60 Gy of radiation in 6 weeks or two cycles of induction chemotherapy with cisplatin and vinblastine followed by identical radiation treatment.

A recent update of this trial has been published, which includes 7-year follow-up information. A total of 78 patients were randomized to chemotherapy and radiation, whereas 77 were randomized to radiation alone. The objective response rate was 56% to combined treatment and 43% to radiation alone (p = .092). The group randomized to induction chemotherapy achieved a significant improvement in median survival (13.7 vs. 9.6 months; p = .012), and a higher proportion of patients undergoing induction chemotherapy survived 1, 2, 3, 5, and 7 years (54%, 26%, 24%, 17%, and 13% vs. 40%, 13%, 10%, 6%, and 6%, respectively).

The Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) have conducted a three-arm trial involving 452 eligible patients who were randomized to the same two treatment arms employed in CALGB 84-33 and to a third arm that included hyperfractionation radiation to a total dose of 69.6 Gy. The hyperfractionation arm had been shown to produce a survival advantage for favorable patients in RTOG protocol 83-11. Preliminary results of this trial indicate that 1-year and median survivals were superior in the group randomized to induction chemotherapy compared with the other two groups (p = .03). The 1-year and median survivals for the three groups are as follows: induction chemotherapy and radiation therapy, 60% and 13.8 months; hyperfractionation radiation therapy, 51% and 12.3 months; standard radiation therapy, 46% and 11.4 months.

The results of a multicenter French study involving 353 patients who were randomized to 65 Gy of radiation or three cycles of induction chemotherapy with cisplatin, vindesine, cyclophosphamide, and CCNU (chloroethyl-cyclohexyl-nitrosourea) given before radiation followed by three additional cycles of chemotherapy have been reported. The response rate to induction chemotherapy was 27%. For combined chemotherapy and radiation, the 1-, 2-, and 3-year survivals were 50%, 21%, and 11%, respectively; for radiation alone they were 41%, 14%, and 5%, respectively (p = .08). There was a very high rate of local-regional failure in both groups. Local control was 17% in the radiation arm and 15% in the combined modality arm in this trial. However, the distant failure rate was significantly reduced in the combined modality arm (22% vs. 46% failure at 1 year; p < .001); with a mean follow-up of 61 months, there was a statistically significant improvement in survival associated with combined modality treatment (p < .02).

The European Organization for Research and Treatment of Cancer (EORTC) conducted a three-arm study in 331 patients; 50 Gy of thoracic radiation in one arm was compared with two other arms utilizing concurrent cisplatin and radiation on one of two schedules. In one arm, cisplatin was administered daily (6 mg/m^2) along with radiation, whereas in the other arm it was administered weekly (30 mg/m^2). There was a significant improvement (p = .009) in survival for daily cisplatin and radiation compared with radiation alone (2- and 3-year survivals, 26% and 16% vs. 13% and 2%, respectively). For weekly cisplatin and radiation, survival was intermediate (2- and 3-year survivals, 19% and 13%) but was not significantly different from either of the other arms. The survival benefit observed with daily cisplatin and radiation appeared to be result of improved local control (p = .003).

The results of an Italian randomized trial in 95 patients comparing 50.4 Gy of radiation alone with the same radiation given in conjunction with weekly low-dose cisplatin (15 mg/m^2) have been reported. Although there was a trend favoring the combined arm in regard to progression-free interval (9 months vs. 7 months) and median survival (16 months vs. 11 months), neither of these differences was statistically significant. There were 12 intrathoracic relapses in the combined arm, compared with 23 in the radiation alone arm, a difference that was of borderline significance (p = .053). There was no difference between the two groups with regard to distant relapse rates.

The Finnish Lung Cancer Study Group compared split-course radiotherapy (55 Gy) with or without CAP (cyclophosphamide, Adriamycin, cisplatin) chemotherapy in 238 patients with “inoperable” stage III NSCLC. No significant differences in survival were found; the median and 1- and 2-year survivals were 311 days, 41%, and 17%, respectively, for the radiation alone group and 332 days, 42%, and 19%, respectively, for the combination group. In addition, no effect of chemotherapy on local control or relapse patterns was detected.

The North Central Cancer Treatment Group compared 60 Gy of radiation alone or two cycles of MACC (methotrexate, Adriamycin, cyclophosphamide, and CCNU) chemotherapy followed by radiation and two additional cycles of MACC in 107 patients with stage III disease. The median and 1- and 2-year survivals for patients treated with radiation alone were 292 days, 43%, and 12%, respectively; for those who received induction therapy, the figures were 317 days, 47%, and 23%, respectively (p = .59). This was the only study in which there was absolutely no suggestion of benefit by the addition of induction chemotherapy. It was also the only trial in which a cisplatin-based regimen was not utilized during induction.

A meta-analysis included data from 14 randomized trials comparing chemotherapy and radiation with radiation alone in regionally advanced stage III NSCLC. A total of 2589 patients participated in these trials. Overall, the meta-analysis revealed that the use of combination chemotherapy and radiation reduced the risk for death by 12% at 1 year, 13% at 2 years, and 17% at 3 years. This corresponds to a mean gain of life expectancy of about 2 months. The magnitude of benefit was similar whether sequential or concurrent chemotherapy and radiation were utilized.

At this time, despite encouraging data of the advantages of combined chemotherapy and radiation, many important questions remain unanswered. The optimal induction chemotherapy regimen has not been established. The optimal sequence of chemotherapy and radiation remains unknown. The role of hyperfractionation radiation has not been firmly established. Most importantly, the vast majority of patients continue to have recurrence and eventually succumb to metastatic disease, despite the use of chemotherapy and radiation for regionally advanced NSCLC. Local-regional recurrence remains a major problem. In CALGB 84-33, the group treated with chemotherapy and radiation had an 80% incidence of local-regional failure, whereas 90% of those randomized to radiation therapy alone had local-regional failure. Green has emphasized that despite the use of induction chemotherapy and radiation, patterns of failure indicate a need for better control of both macroscopic intrathoracic disease and distant micrometastatic disease in the setting of regionally advanced NSCLC.

Phase II Trials of Induction Chemotherapy and Surgery in Stage IIIA NSCLC

In the last decade, many phase II trials have investigated multimodality treatment strategies that include induction chemotherapy and surgical resection in regionally advanced stage III NSCLC. Considerable variability in the design of these trials makes interpretation of results difficult. Some studies incorporated modern surgical staging of the mediastinum, whereas others did not. Some included induction radiation as well as chemotherapy. Of the trials that utilized radiation, some incorporated sequential chemotherapy and radiotherapy, and others employed concurrent administration. The definitions of resectable disease also vary considerably.

Table 11 lists phase II trials that employed induction chemotherapy and surgery with or without radiation in stage IIIA NSCLC (although two trials also included IIIB patients). Perhaps three times as many trials have been conducted as are listed on the table. Each of the trials listed utilized a cisplatin-based regimen in combination with other agents. Seven of the trials used preoperative radiation (given concurrently with chemotherapy in six and sequentially in one), one trial used only postoperative radiation, and two did not employ radiation at all.

Variable	Favorable	Unfavorable
DNA content (flow cytometry)	Diploid	Aneuploid
S-phase fraction (flow cytometry)	Low	High
Proliferation index using Ki-67 nuclear antigen	PI < 3.5	PI > 3.5
Proliferating cell nuclear antigen (PCNA)	<5% of tumor cells stained with PCNA	>5% of tumor cells stained with PCNA
Mitotic index (pathologic marker)	<13 mitoses per 10 high powered fields	≥13 mitoses per 10 high powered fields

TABLE 11. *Proliferation markers in early-stage NSCLC*

Overall, response rates to induction therapy were quite impressive, varying from 39%–77%. Most responses to induction therapy were partial, although complete responses were observed in some trials. Resectability rates exceeded 50% in each of these trials. The highest resectability rate (93%) was noted in a trial that utilized hyperfractionation radiation concurrently with induction chemotherapy. Many trials have noted that a substantial fraction of resected specimens, often in the range of 10%–20%, do not contain viable tumor following induction therapy.

Median survival times have varied considerably, ranging from 13 to 32 months. Long-term survival rates have also varied significantly, from 17%–37%. Nonetheless, all

these trials support the conclusion that a substantial minority of patients treated achieved long-term survival.

Although none of these trials was designed to evaluate the therapeutic role of surgery in the context of regionally advanced disease, several of the trials reported that those who underwent successful resection enjoyed longer survival times than those in whom resection could not be achieved. In the CAP II study from the Dana-Farber Cancer Institute, median survival was 31 months in patients who underwent resection and 13 months in those who did not (p = .001). In the Memorial Sloan-Kettering trial, median and 5-year survivals for patients with complete resection were 27 months and 26%, compared with 12 months and 5% for those with incomplete or no resection (p = .00002). In CALGB 89-35, median and 3-year survivals were 21 months and 46% among those undergoing complete resection, 18 months and 25% for those with incomplete resection, and 8 months and 0% for those with no resection. Similarly, in the Toronto trial, median and 3-year survivals were far superior in the group with complete resection (30 months and 40%).

Surgery improves local control of the tumor. These phase II trials demonstrate a shift in recurrence patterns from local-regional to distant, compared with what is observed in trials utilizing induction chemotherapy and radiation without surgical resection. Local recurrence has generally been observed in 50% of patients in whom recurrence develops after trimodality therapy. This contrasts with an 80%–90% rate of persistent or recurrent local-regional disease in patients with no resection.

Phase II Trials of Induction Chemotherapy and Surgery in Stage IIIB NSCLC

Each of the studies included in Table 12 focused on groups of patients with stage IIIA NSCLC (although stage IIIB patients were included in the Rush study but considered ineligible for surgery). Conceptually, the stage IIIA designation implies regionally advanced yet potentially resectable disease. Such patients have extrapulmonary but intrathoracic disease. As the stage IIIB designation implies extrathoracic disease, the disease of such patients has been considered categorically unresectable for cure. However, the recent report of the results of a Southwestern Oncology Group phase II study, SWOG protocol 88-05, documents a potential role for aggressive local-regional therapy, even in the context of IIIB NSCLC.

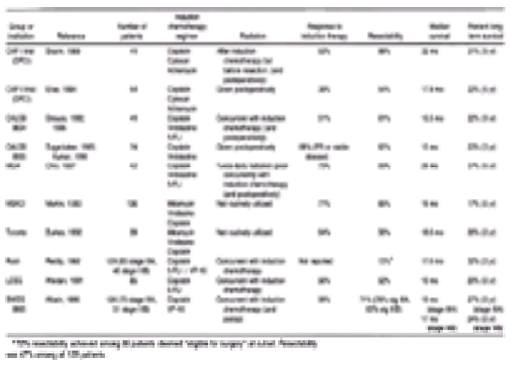


TABLE 12. *Phase II trials on induction chemotherapy and surgery in stage IIIA disease*

In this study, 126 evaluable patients were treated with concurrent induction chemotherapy and radiation, and were then considered for surgical resection. The chemotherapy consisted of cisplatin and etoposide (VP-16). Among evaluable patients, 75 had stage IIIA NSCLC, all with N2 adenopathy. However, 51 patients had stage IIIB NSCLC: 27 with N3 disease, 17 with T4,N0 or N1, and 7 with T4,N2 disease.

Resection was achieved in 85% of patients with stage IIIA disease and 80% of patients with stage IIIB disease. There was no significant survival difference for IIIA and IIIB subsets (p = .81). The median and 2- and 3-year survivals for IIIA patients were 13 months, 37%, and 27%, respectively, whereas for stage IIIB patients the figures were 17 months, 39%, and 24%, respectively.

The strongest predictor of long-term survival in patients with either IIIA or IIIB disease was the absence of mediastinal nodes at the time of surgery. In patients with negative mediastinal nodes at surgery, median survival was 30 months and 3-year survival was 44%, compared with a median survival of 10 months and a 3-year survival of 18% in those with positive nodes (p = .0005).

Moreover, local-regional control was improved in this trial. Only 11% of 65 relapses were local-regional, whereas 61% were distant. The single most common site of disease recurrence was the brain; 26 such relapses were observed, and central nervous system relapse was the sole cause of death in 19 of these cases.

Randomized Trials of Induction Chemotherapy and Surgery Versus Surgery in Stage IIIA NSCLC

Despite encouraging phase II data on the role of induction chemotherapy (with or without radiation) and surgery, randomized trials are believed to be essential to provide definitive proof for the effectiveness of a new treatment strategy. Reports of three randomized trials comparing induction chemotherapy followed by surgical resection with resection without systemic treatment have been influential in modifying the perception of the role of chemotherapy in the management of regionally advanced NSCLC. Indeed, the report by Roth of a randomized trial from M.D. Anderson Hospital declared that induction chemotherapy should now be considered as a standard treatment for this group of patients.

In the M.D. Anderson trial, the group randomized to induction chemotherapy received three cycles of cyclophosphamide, etoposide, and cisplatin followed by resection; the control group received surgical resection alone. The group that received combined therapy achieved an estimated median survival that was almost sixfold greater than that of patients randomized to surgery alone (64 months compared with 11 months; p < .008). Similarly, 2- and 3-year survivals were 60% and 56% for the induction chemotherapy group, compared with 25% and 15% for the surgery alone group.

The report from M.D. Anderson closely followed a similarly designed randomized study reported by Rosell from Barcelona, Spain, which also showed a dramatic threefold survival advantage for patients randomized to induction chemotherapy followed by surgery. In the group randomized to induction chemotherapy, median survival was 26 months; it was 8 months in the surgery alone group (p < .001). In this trial, the chemotherapy regimen consisted of cisplatin, mitomycin C, and ifosfamide.

A third randomized trial from the NCI had preceded the other two. In this trial, the experimental group, treated with induction chemotherapy of cisplatin and etoposide, had a better survival than a control group randomized to primary surgical resection (28.7 vs. 15.6 months).

Although these three prospective randomized studies demonstrate that groups randomized to induction chemotherapy followed by surgical resection achieved an improved survival compared with groups randomized to surgical resection alone in stage IIIA NSCLC, the results should be interpreted with caution. The major problem relates to the fact that each of the trials enrolled small numbers of patients. Only 60 patients were enrolled in both the M.D. Anderson and the Barcelona studies. Because of the huge differences in survival observed in each of these trials, both were discontinued before their projected accrual goals were reached, following accepted rules for early stopping.

The other problem is that the sheer magnitude of the survival differences were far greater than could be reasonably expected from the modestly effective chemotherapy regimens employed in these studies, particularly in the M.D. Anderson trial. The median survival in the experimental group in the M.D. Anderson study, which exceeded 5 years in the 28 patients randomized to induction chemotherapy, has not been approached in any other phase II or phase III study evaluating multimodality therapy in regionally advanced NSCLC. In contrast, the unimpressive response rate associated with induction chemotherapy in this trial is fairly typical of what chemotherapy usually accomplishes in NSCLC. The response rate was 32%, including eight partial responses and one complete response, in the 28 patients in the induction chemotherapy arm of the M.D. Anderson trial. This modest response rate translates into almost a sixfold increase in median survival, and almost a fourfold increase in 3-year survival. Johnson and Piantadosi appropriately caution that “because the outcome of this trial is not entirely consistent with biologic expectations and other evidence, we should be cautious in accepting the results.”

It was shown in the Barcelona study that the group of patients randomized to surgery alone had a higher fraction of tumors associated with more virulent characteristics. For example, many trials have demonstrated that point mutations in the K-*ras* oncogene and aneuploidy are associated with an adverse prognosis in patients with resectable NSCLC. In the Barcelona trial, patients in the surgery alone arm had a higher fraction of tumors with K-*ras* mutations (42% vs. 15%) and DNA aneuploidy (70% vs. 29%). Accordingly, it is possible that an excess of biologically virulent tumors in the group randomized to surgery alone in the Barcelona study contributed significantly to the observed outcome differences, rather than the induction chemotherapy *per se.* In this trial, the response rate to induction chemotherapy

was 60% (16 partial responses and two complete responses among 30 patients).

In addition to the three randomized trials just discussed, a fourth randomized trial, conducted by the CALGB, has been reported by Elias. In this trial (CALGB 91-34), 57 patients with stage IIIA N2 NSCLC were randomized to one of two treatment strategies. One group received two cycles of induction chemotherapy with cisplatin and high-dose VP-16 with granulocyte colony-stimulating factor (G-CSF) support] before surgery, which was followed by two additional cycles of chemotherapy and radiation. The other group received induction radiation (40 Gy) before surgery, which was followed by postoperative radiation. Response to induction chemotherapy was 38% in the induction radiation arm and 47% in the chemotherapy arm. Median disease-free and overall survivals were 9 months and 19 months for the group undergoing induction chemotherapy, compared with 12 months and 23 months in the group receiving preoperative radiation. Although the trend toward reduced survival in the group receiving induction chemotherapy was not statistically significant, the results of CALGB 91-34 conflict with the results of the other three randomized trials, which suggest a dramatic benefit for the use of induction chemotherapy.

Cumulatively, these four phase III studies evaluating the role of induction chemotherapy before surgery have included a total of 204 patients. Although we can learn a great deal from these trials, it is perhaps debatable whether the most important lesson relates to the efficacy of multimodality therapy in stage IIIA NSCLC or to the limitations of small, randomized studies.

Ten phase II studies included 747 patients. Although the results of these trials vary, a greater consistency is seen in the results of the phase II trials than of the randomized trials. The phase II trials provide no hint that the real effect of induction chemotherapy in stage IIIA NSCLC is to produce a 64-month median survival and a 3-year survival of 56%. The implausible and conflicting results of the phase III trials suggest that small, randomized trials may receive greater credibility than they deserve, for the simple reason that they are randomized.

Conclusions Regarding Multimodality Therapy in Stage III NSCLC

Despite the limitations of the randomized surgical trials in stage IIIA NSCLC, they do lend considerable support to the hypothesis that induction chemotherapy followed by surgical resection does improve disease outcome compared with surgical resection alone. Although the magnitude of the survival advantages are very likely to have been exaggerated, particularly in the M.D. Anderson trial, numerous phase II trimodality studies support a similar conclusion, although with a modest degree of effectiveness. Moreover, these results are consistent with numerous phase III studies that have demonstrated that induction chemotherapy and definitive radiation improve outcome when compared with thoracic radiation therapy alone.

Whether induction chemotherapy is now standard therapy for this disease is debatable, and additional clinical trials evaluating such as approach will be difficult to accomplish. CALGB 91-34 was closed because of difficulty in accruing patients following publication of results of the other trials.

The role of resection in stage IIIA and stage IIIB disease remains unproven, but local control appears to be improved in multimodality programs that include resection. A phase III trial designed to evaluate the efficacy of surgical resection in the context of induction chemotherapy and radiation in stage IIIA NSCLC is currently being performed by several cooperative groups under the leadership of SWOG.

The recent results of both phase II and phase III trials have provided a basis for optimism that real therapeutic progress is finally being achieved in regionally advanced NSCLC. Further study of therapeutic strategies that incorporate aggressive systemic therapy and maximal local-regional therapy in both stage IIIA and stage IIIB NSCLC are clearly warranted.

MANAGEMENT OF STAGE IV NSCLC

Stage IV NSCLC is almost invariably a fatal disease. Accordingly, it should generally be approached with strictly palliative intent. No standard therapy exists, but systemic chemotherapy and supportive care are the treatment approaches most often considered.

An exception to such a palliative approach exists for patients who present with a solitary site of metastatic disease. For such patients, consideration of an aggressive local-regional approach to treatment may be appropriate. This approach has been best documented in patients with a solitary brain metastasis, although it has also been used in cases of a solitary adrenal metastasis.

Surgical resection (as well as stereotactic radiosurgery) has been widely utilized in patients with a solitary brain metastasis. The data justify its use in selected patients who present with a solitary brain metastasis that develops after successful therapy for early-stage NSCLC, or who present with a solitary brain metastasis together with an otherwise localized stage I NSCLC. A number of reports have suggested that long-term survival is possible with a combined surgical approach to primary and metastatic sites in approximately 20% of patients with a solitary brain metastasis associated with what is otherwise stage I NSCLC.

However, successful systemic treatment is essential to the effective management of the vast majority of patients with stage IV NSCLC. Unfortunately, NSCLC has proved to be remarkably resistant to chemotherapy. In 1988, in a review of 134 phase II trials of single agents in advanced NSCLC, only five agents (among 48 that had been studied up to that time) could be identified that had a response rate exceeding 15%. These agents included cisplatin, mitomycin C, ifosfamide, vinblastine, and vindesine. The traditional benchmark of success for chemotherapy in advanced NSCLC has been the proportion of patients who survive 1 year from the time of treatment for metastatic disease.

Chemotherapy Versus Best Supportive Care

Because of the limited activity of combination chemotherapy in stage IV NSCLC, many physicians believe that chemotherapy should not necessarily be utilized in the setting of advanced disease. Indeed, stage IV NSCLC is unique in that numerous randomized trials have been conducted comparing combination chemotherapy with best supportive care. Eight such trials have been performed. Five of them have been criticized for using substandard chemotherapy. The two individual trials that are most widely known both employed a similar cisplatin-based chemotherapy regimen. The Canadian study, reported by Rapp, found a statistically significant prolongation of survival from 17 weeks in the control arm to 32.6 weeks in the group receiving cisplatin (100 mg/m^2) and vindesine. An Australian study also reported a 17-week median survival in the best supportive care arm, whereas the group receiving cisplatin and vindesine had a median survival of 27 weeks. However, in this study the survival advantage in the chemotherapy group did not reach statistical significance.

Three meta-analyses have been published comparing chemotherapy with best supportive care. Each of the meta-analyses supports the conclusion that combination chemotherapy is associated with a small but significant improvement in the duration of survival. In one meta-analysis, median survival for patients treated with best supportive therapy was 3.9 months, whereas survival was 6.7 months for those receiving combination chemotherapy.

Prolongation of life is usually the primary objective of chemotherapy, and survival is very simple to quantify. However, there are other important goals in the setting of advanced disease. Improvement in the quality of life is an equally valuable end point as overall survival. One study reported that independently of initial Karnofsky score, 75% of patients treated for advanced NSCLC reported an improved quality of life. Similarly, the meta-analyses suggest that chemotherapy favorably impacts on quality of life.

Nonetheless, the effect of chemotherapy in the setting of advanced disease is modest for most patients. Although chemotherapy may be a reasonable option for many patients, it is not mandatory as the standard of care in all patients. Still, it should be offered to patients with good performance status and minimal weight loss, who are most likely to respond in the setting of advanced disease.

Active Chemotherapeutic Agents in NSCLC

Chemotherapeutic agents that have activity in NSCLC (Table 13) include the platinum compounds (cisplatin and carboplatin), ifosfamide, mitomycin C, etoposide, and vinblastine. During the 1990s, a number of newer chemotherapeutic agents have been identified that are also active in NSCLC. These include Navelbine (a new vinca alkaloid), the taxanes (Taxol and Taxotere), the camptothecins (irinotecan and topotecan), and gemcitabine.

Chemotherapeutic agent	Response rate (%)
Cisplatin	20%
Carboplatin	8–16%
Ifosfamide	21%
Etoposide	5–15%
Mitomycin C	25–30%
Vinblastine	11–28%
Vinorelbine (navelbine)	30%
Taxol	21–24%
Taxotere	20–30%
Irinotecan	32–41%
Topotecan	0–15%
Gemcitabone	20–26%

TABLE 13. *Single agents in advanced NSCLC*

Cisplatin and Carboplatin

Traditionally, cisplatin has been felt by many investigators to be the single most active chemotherapeutic agent in metastatic NSCLC. Its single-agent response rate is about 20%, based on 10 phase II studies of advanced NSCLC including more than 500 patients. Cisplatin-based combination chemotherapy has been associated with higher response rates, up to 40%–50%, and has produced median survivals ranging between 30 and 50 weeks in nonrandomized, predominantly single-institution studies. The vast majority of responses are partial with cisplatin-based chemotherapy, and very few studies have produced more than an occasional complete response.

Cisplatin has a well-established toxicity profile, which can make it a difficult agent to utilize. Toxic effects include severe nausea and vomiting, renal dysfunction, and neurotoxicity. It is not particularly myelosuppressive.

The importance of dose intensity for cisplatin in advanced NSCLC remains uncertain. One randomized trial in which a fixed dose of vindesine was combined with cisplatin at doses of either 60 mg/m^2 or 120 mg/m^2 revealed identical response rates, although there was a significant survival advantage for the responders to the high-dose regimen. Randomized trials by SWOG and EORTC failed to reveal any significant differences in either response rate or survival when low-dose and high-dose cisplatin combination regimens were compared.

Carboplatin is a second-generation derivative of cisplatin; it is believed to form intrastrand and interstrand DNA cross-links, like the parent compound. Single-agent carboplatin has an overall response of 8% in a mixture of previously treated and untreated patients with advanced NSCLC. In a randomized study by ECOG comparing single-agent carboplatin with four other regimens that employed either cisplatin analogues or combinations, carboplatin alone had a 9% response rate but had the lowest frequency of severe or life-threatening toxicity. Furthermore, this agent was associated with the most favorable survival (median, 31 weeks) of the five regimens tested.

The only randomized trial directly comparing carboplatin with cisplatin in NSCLC (in which etoposide was also employed in both treatment arms) demonstrated that response and survival were equivalent and that toxicity was less in the carboplatin arm. It has been recommended that comparative data of platinum analogues justify carboplatin as a replacement for cisplatin in therapy of advanced cancer delivered with noncurative intent.

Carboplatin, in contrast to the parent drug, cisplatin, produces little renal impairment. Its major toxic effect is myelosuppression, particularly thrombocytopenia, and toxicity of carboplatin is closely related to renal function. Approximately 65% of carboplatin is recovered in the urine within 24 hours of intravenous administration, and 32% of the excreted dose is unchanged carboplatin; the plasma half-life is approximately 30 hours. The renal excretion of carboplatin approximates the glomerular filtration rate, with little excretion or reabsorption by the renal tubules. Because of the renal excretion of carboplatin, any impairment in renal function could result in increased toxicity.

Ifosfamide

Ifosfamide is an oxazaphosphorine analogue of cyclophosphamide; it provides more effective DNA crosslinking distance between two independent functional alkylating moieties. Like cyclophosphamide, ifosfamide is activated by liver P_{450} microsomes via hydroxylation of the No. 4 ring carbon to yield 4-hydroxyifosfamide. It is one of the most potent alkylating agents in vitro.

Ifosfamide has considerable single-agent activity in stage IV NSCLC. In 326 patients with advanced NSCLC from multiple series treated with single-agent ifosfamide, the overall response rate was 21% and median survival was 9 months. In the absence of uroprotection, hemorrhagic cystitis is dose-limiting, with an overall incidence of 18%–40%. Cystitis may be exacerbated by the antidiuretic effect of ifosfamide and the resulting fall in urine output. Sodium-2-mercaptoethanesulfonate (mesna), a sulfhydryl compound, prevents hemorrhagic cystitis by inactivating toxic metabolites, thereby allowing administration of larger doses of ifosfamide. The dimeric and inactive form of mesna, dimesna, circulates in the blood and has poor tissue penetration, but it becomes active when reduced to mesna in the kidney. Perhaps for these reasons, mesna does not appear to interfere with the antitumor effect of ifosfamide and protects both upper and lower genitourinary tracts. Because of its short half-life ($t_{1/2}$ of 1.5 hours), mesna should be given for a longer period than ifosfamide ($t_{1/2}$ of 6 to 8 hours). With uroprotection, the predominant toxicity becomes myelosuppression. Thrombocytopenia is much less of a problem.

Etoposide

Etoposide (VP-16) is a semisynthetic, epipodophyllotoxin derivative with significant single-agent activity in NSCLC. By interfering with topoisomerase II activity (the enzyme responsible for creation and repair of breaks in DNA double strands), etoposide prevents DNA repair. Single-agent dose-limiting toxicity is myelosuppression, which develops when etoposide is given at standard daily doses of 75 to 100 mg/m^2 per day as an intravenous bolus for 3 to 5 days.

Because inhibition of topoisomerase II by etoposide is reversible when the drug is no longer present, prolonged exposure may be more effective than short-term infusion. Clinically, the drug has known to be markedly schedule-dependent and is generally given by bolus administration during 3 to 5 consecutive days. Single-agent VP-16 has been shown to produce response rates in the range of 5%–15% when a multiple-day bolus schedule is used in advanced NSCLC.

Mitomycin C

Single-agent mitomycin has long been recognized as having considerable activity in advanced NSCLC. Multiple phase II studies involving 207 patients treated with mitomycin C at doses of 10 to 20 mg/m^2 every 3 to 6 weeks have produced response rates that average 25%. A more recent study reported a 30% response rate in 64 patients with metastatic squamous cell lung cancer treated with single-agent mitomycin C.

Toxicity, including cumulative myelosuppression, can be severe with this agent. Pulmonary toxicity and thrombotic microangiopathy have been well described, although infrequent. Both appear to be related to the cumulative dose of mitomycin C.

Vinblastine and Vinorelbine

Vinblastine, a vinca alkaloid available since the 1960s, has considerable single-agent activity in NSCLC. Vindesine is another vinca alkaloid identified as an active agent in NSCLC, although it has never become commercially available in the United States. Vinca alkaloids inhibit normal microtubule disassembly. Response rates to vinblastine and other vinca alkaloids have ranged from 11%–28% in single-agent trials.

Recently, vinorelbine (Navelbine) has emerged as a new semisynthetic vinca alkaloid with significant activity in NSCLC. It has been approved specifically for use in NSCLC. Its optimal administration schedule appears to be weekly, and response rates have been in the range of 30% in advanced NSCLC. Neutropenia is the dose-limiting toxicity. Although it also causes neurotoxicity, like all vinca alkaloids, it has been shown to spare the axonal microtubules, which translates into less neurotoxicity than occurs with other vinca alkaloids.

Taxol and Taxotere

The taxoids, Taxol and Taxotere, are diterpene plant products derived from the bark of the Western yew (*Taxol brevifolia*). These agents have a unique mechanism of action. Unlike other antimitotic agents, which inhibit microtubule assembly, the taxanes promote microtubule assembly, stabilize microtubules, and inhibit depolymerization to free tubulin.

A number of studies in advanced NSCLC demonstrate that both agents have response rates in excess of 20%. Two initial studies employing Taxol in advanced NSCLC as a 24-hour infusion reported response rates of 21% and 24%. Subsequent studies have demonstrated that Taxol is also active in lung cancer in 3-hour and even 1-hr infusion schedules.

Dose-limiting toxicity of Taxol is reversible myelosuppression. Other toxicities include severe allergic reactions, alopecia, arthralgia/myalgia, and peripheral neuropathy. Severe hypersensitivity reactions are well-known, although they occur in 5% of patients who are premedicated with corticosteroids and H_1 and H_2 blockers. An advantage of shorter infusion schedules is less myelosuppression, although neurotoxicity may be greater.

Taxotere has been employed in four phase II studies in previously untreated advanced NSCLC. At a dose of 100 mg/m^2 given during 1 hour every 3 weeks, the response rate was 30%. Moreover, in two studies in which Taxotere was given to cisplatin-refractory patients, the response rate was 20% and median survival was 9 months. Neutropenia is the dose-limiting toxicity; hypersensitivity reactions and skin rashes may also be seen. A reaction involving fluid retention, which can be associated with pleural effusions, ascites, and weight gain, has been well described and is prevented with prophylactic corticosteroids.

Irinotecan and Topotecan

The camptothecin compounds, derived from the oriental plant *Camptotheca acuminata,* inhibit topoisomerase I and induce DNA strand breaks at the replication fork. Two analogues have been studied in advanced NSCLC.

Irinotecan (CPT-11) has been studied in 161 patients with advanced NSCLC in three trials in Japan. The response rates varied from 32%–41%. Major toxicities include neutropenia and diarrhea, which can be severe. Reversible pulmonary toxicity is also occasionally observed.

A related compound, topotecan, has also been tested in advanced NSCLC, although its activity appears to be less encouraging. In one study, there were no responders among 20 patients. In another trial, the response rate was 15% in 40 patients with advanced NSCLC, with the suggestion of a higher response rate in squamous cell carcinoma. Toxicity has predominantly been reversible myelosuppression.

Gemcitabine

Gemcitabine (22-difluorodeoxycytidine) is a pyrimidine antimetabolite that is closely related to cytosine arabinoside. It possesses considerable single-agent activity in a variety of solid tumors, including advanced NSCLC. It is generally administered on a weekly schedule and has a very attractive toxicity profile. At lower doses, the side effects include influenza-like symptoms, fever, and occasionally hypotension. At higher doses, the major toxicity is myelosupresssion. Peripheral edema, rash, and liver function abnormalities have also been observed.

Seven studies of this drug enrolling a total of 577 evaluable patients with advanced NSCLC have been reported. These studies have consistently reported response rates in the range of 20%–26%. Usual doses are in the range of 800 to 1200 mg/m^2 per week for 3 of every 4 weeks. Higher doses can be given, although it is unclear whether this provides any advantage.

Combination Chemotherapy in Advanced NSCLC

Although combination chemotherapy has been extensively investigated in NSCLC, no single combination has emerged as a standard regimen in advanced NSCLC. Cisplatin has formed the basis of many of the most effective combination regimens, but carboplatin has recently found an increasing role, because of an activity level that is similar to and a toxicity profile that is more attractive than that of the parent compound. Combination cisplatin and etoposide therapy has been widely used; a 38% response was observed in one study of 94 patients with advanced NSCLC, whereas other trials demonstrated a pooled response rate of 28%. The combination of carboplatin with etopside has a reported response rate of 29%–38% (8% complete response).

In recent years, combination regimens incorporating some of the newer chemotherapeutic agents have begun to be reported. Reponse rates in excess of 60% were reported in two studies in advanced NSCLC with the combination of Taxol and carboplatin. A study from Fox Chase Cancer Center reported a response rate of 63% (9% complete response) in 54 patients with stage IIIB and stage IV NSCLC treated with carboplatin and Taxol as a 24-hour infusion. Because myelosuppression was dose-limiting, G-CSF support was used. The 1-year median survival of 51% is superior to that usually reported in advanced NSCLC.

An identical response rate was reported among 40 patients with advanced NSCLC from the University of Southern California. In this study, Taxol was used as a 3-hour infusion along with carboplatin. The overall response rate was 63%, which included two complete responses and 15 partial responses. There was very little significant hematologic toxicity in this study, and G-CSF was not used. The dose-limiting toxicities were myalgias, arthralgias, and cumulative sensory neuropathy.

The combination of cisplatin and gemcitabine was reported to have a 54% response rate in 48 patients with advanced NSCLC. Median survival was an impressive 61.5 weeks for all patients. The main toxicity was thrombocytopenia, which was severe in more than half of patients but was invariably reversible and short-lived. No febrile neutropenia was observed.

Two recent randomized trials in advanced NSCLC have generated considerable interest. The ECOG conducted a three-arm randomized trial comparing cisplatin and etoposide with two other regimens, both utilizing cisplatin and Taxol. Taxol was given by 24-hour continuous infusion, either at a standard dose of 135 mg/m^2 or a higher dose of 250 mg/m^2 (with G-CSF support). A total of 560 patients were enrolled. Response rates and median survival were superior for the two Taxol-containing regimens than for the etoposide arm. There were no differences between the higher- and lower-dose Taxol-containing regimens with respect to response rate (32.1% vs. 26.5%) or median survival time (10.0 months vs. 9.6 months).

A randomized trial has also been reported by SWOG comparing cisplatin alone with cisplatin and Navelbine in advanced NSCLC. A total of 412 eligible patients participated in the trial. There was an advantage for the Navelbine-containing arm with regard to response rate (25% vs. 10%), median survival (7 months vs. 6 months), and 1-year survival (33% vs. 12%). Toxicity was predominantly myelosuppression and was worse for the Navelbine-containing arm.

Conclusions Regarding Systemic Management of Stage IV NSCLC

So what can be recommended regarding chemotherapy in advanced NSCLC? In a situation in which cure is not possible, patient preferences are critical to the development of any appropriate treatment plan. In the author's opinion, patients with poor performance status and those who have had significant weight loss are best managed conservatively. As such patients are unlikely to benefit from chemotherapy, they should be made aware of the fact that best supportive care is an appropriate management option. Palliative radiation for symptomatic sites of metastatic disease should always be considered.

For patients who express a desire to “try something,” single-agent chemotherapy or one of the newer, better-tolerated combination regimens can be offered. Improvements in supportive therapy, which include better antiemetics and prophylactic antibiotics as well as hematologic growth factors, make it more likely that such patients can tolerate chemotherapy than was true in the past, even if they are still unlikely to respond.

For patients with good performance status, chemotherapy should be offered. As an unequivocally best chemotherapy regimen does not exist, patients should ideally be enrolled in a clinical trial. If such a trial is unavailable, or if patients decline participation, one of the newer combination chemotherapy regimens would be reasonable. At the present time, reasonable chemotherapy regimens include carboplatin and Taxol, carboplatin and etoposide, cisplatin and Navelbine, and cisplatin and gemcitabine. However, the field is changing rapidly, and other combinations or single-agent chemotherapy can also be given.

Second-line chemotherapy can also be considered in highly selected patients, preferably with single agents not previously utilized. The best candidates for second-line therapy include patients who previously responded to first-line therapy and those whose performance status remains good at the time of progression.

SMALL-CELL CARCINOMA OF THE LUNG

SCLC represents a clinicopathologic entity that is biologically and clinically distinct from NSCLC. It is distinguished from NSCLC by its characteristic of rapid growth with early development of widespread metastases. It is also extremely sensitive to both chemotherapy and radiotherapy, although relapse usually occurs within 2 years despite treatment. The overall 5-year survival is approximately 3%–8%.

SCLC comprises approximately about one fifth of all lung cancer. It occurs almost exclusively in cigarette smokers, and in one series only 2% of 500 SCLC patients did not have a smoking history. SCLC is also the most common histologic subtype among uranium miners; it is probably caused by exposure to radioactive radon, a byproduct of uranium decay.

Clinical Presentation, Staging, and Prognostic Factors

Because SCLC tends to be a centrally occurring neoplasm, patients typically present with a large hilar mass and bulky mediastinal adenopathy. Typical symptoms tend to be similar to those of other lung neoplasms and include cough, dyspnea, weight loss, and manifestations of postobstructive pneumonia.

Approximately 10% of patients with SCLC present with the superior vena cava syndrome. Indeed, SCLC is the most common malignant cause of superior vena cava syndrome. Survival in SCLC does not appear to be significantly compromised by the presence of superior vena cava syndrome.

Because the tumor tends to arise submucosally, hemoptysis is less common than in squamous cell carcinoma. Cavitation is very uncommon in SCLC. A small cohort of patients with SCLC can present with an apparently solitary pulmonary nodule, although this tends to be uncommon.

SCLC is more commonly associated with certain paraneoplastic syndromes than any other tumors. Syndromes that have been specifically associated with SCLC include SIADH, ectopic Cushing's syndrome, and Eaton-Lambert syndrome (myasthenia-like syndrome). It is much more common to detect polypeptide hormone immunologically, because available immunoassays detect both inactive precursors as well as the active hormones. SCLC is frequently associated with elevated levels of polypeptide hormones, although the clinical syndromes associated with these hormones are much less common. In one series, 11% of patients had laboratory evidence of SIADH at the time of clinical presentation, whereas 27% of patients had symptomatic hyponatremia. The presence of SIADH is not related to the stage of disease or prognosis in SCLC.

About 4% of patients with SCLC present without any obvious primary tumor in the lung or associated hilar or mediastinal adenopathy. The most common primary sites for extrapulmonary small-cell cancers include the uterine cervix, esophagus, larynx, pharynx, colorectum, prostate, and paranasal sinuses. A small fraction of patients present with nodal and visceral metastatases without an evident primary tumor at any site. Histologically, these tumors often resemble SCLC and often contain neurosecretory granules. They behave aggressively and are usually treated with chemotherapy regimens similar to those used for SCLC. There is little question that these neoplasms represent a heterogeneous group of tumors.

The majority of patients with SCLC already have distant metastatic disease at the time of clinical diagnosis. This is underscored by the classic study of Matthews, in which autopsies were performed on patients who had succumbed to a non–cancer-related illness <30 days after apparently curative resection. Among 19 patients with SCLC, 63% had distant metastases, in comparison with 17% of 131 patients with squamous cell carcinoma, 40% of 30 patients with adenocarcinoma, and 14% of 22 patients with large-cell carcinoma.

In the staging system currently utilized in SCLC, patients are simply categorized as having limited disease (LD) or extensive disease (ED). LD is defined as disease confined to the hemithorax of origin or within a single radiation portal. It general, it corresponds to ISS stages I–IIIB. ED refers to overt extrathoracic metastatic disease. Overall, approximately 70% of patients with SCLC present with overt ED. The most common sites of metastastic involvement are the liver, adrenals, bone, bone marrow, and brain.

Adverse determinants of prognosis in SCLC include poor performance status, weight loss, elevated lactate dehydrogenase (LDH), and male sex. However, the worse prognostic feature by far is the presence of clinically apparent distant metastases. In patients with ED, central nervous system or hepatic involvement is particularly unfavorable compared with other sites of metastatic disease. The presence of paraneoplastic syndromes is generally believed to be associated with an adverse outcome.

The diagnosis of SCLC is usually by histologic or cytologic examination of tissue or cells obtained via bronchoscopy, FNA, or mediastinoscopy. Tests for determining the extent of disease include CT of the chest and abdomen (with particular attention directed toward imaging the liver and adrenals), bone scan, CT or MRI of the brain, and unilateral or bilateral bone marrow aspiration and biopsy. Bilateral bone marrow aspiration increases the diagnostic yield by 10% in comparison with unilateral testing. Because SCLC progresses rapidly, staging should proceed quickly; long delays in initiating chemotherapy must be avoided. Although extensive staging procedures are often carried out, it is not at all clear that these are associated with any benefit; there is probably no advantage in conducting more extensive staging than necessary to document the presence of ED.

A possible exception is a CT or MRI of the brain. Approximately 15% of patients with SCLC have central nervous system involvement at the time of diagnosis, and approximately one third of these patients have no symptoms. Early treatment of brain metastases is associated with a reduced rate of chronic neurologic disability.

Chemotherapy in SCLC

The mainstay of treatment for all patients with SCLC is systemic chemotherapy, because SCLC is highly responsive to chemotherapy. Historical data indicate the futility of managing this disease with local-regional modalities alone.

In the 1960s, before the introduction of systemic chemotherapy for SCLC, median survivals for patients with LD was approximately 12 weeks and was 5 weeks for patients with ED. A British Medical Research Council study from the 1960s, in which 144 patients with apparently resectable SCLC were randomized to surgery or radiation therapy, demonstrated that survival was extremely poor in both treatment arms. The median and 1- and 5-year survivals were 6.5 months, 21%, and 1%, respectively, for those randomized to surgery. Among those treated with definitive radiation, the figures were 10 months, 22%, and 4%, respectively.

Martini reported that among patients with SCLC seen at Memorial Sloan-Kettering Cancer Center between 1931 and 1971, only 7% had resectable tumors, and only two patients survived for a minimum of 5 years. Similarly, among 368 surgically treated patients with SCLC reported by Mountain in the 1960s, only a single patient survived 5 years following resection. This contrasted with a 15%–25% 5-year survival for the other three major histologic subtypes. A review of patients felt to have surgically resectable SCLC could find absolutely no advantage for the inclusion of surgery in the treatment regimen.

As SCLC is almost invariably a disseminated disease even in patients with LD clinically, chemotherapy is mandatory for all subsets of patients. Compared with NSCLC, SCLC shows a much higher level of responsiveness to chemotherapy. Moreover, complete responses are quite common in SCLC, as opposed to NSCLC, in which complete responses are distinctly uncommon.

The first report of an improvement in survival in SCLC with the use of chemotherapy was reported by the Veterans Administration Lung Cancer Study Group in 1969, when it reported that three cycles of cyclophosphamide could more than double median survival in comparison with supportive care alone in extensive SCLC. Subsequently, many studies were able to document that chemotherapy improved survival significantly compared with the use of surgery or radiation therapy alone. The results of these trials rapidly established combination chemotherapy as the mainstay of therapy for both limited and extensive SCLC by the early 1970s.

Numerous single agents have been demonstrated to possess activity in SCLC. The most active single agents in SCLC include the alkylating agents (ifosfamide and cyclophosphamide), the epipodophyllotoxins (etoposide and teniposide), the platinum agents (cisplatin and carboplatin), vincristine, and doxorubicin (Adriamycin). Moreover, among the newer chemotherapeutc agents introduced over the last decade, the taxanes (Taxol and Taxotere), the topoisomerase I inhibitors (topotecan, irinotecan), Navelbine, and gemcitabine have all been shown to be possess significant single-agent activity in this disease.

Although few randomized trials have been conducted to address this point, the results with combination chemotherapy are much better than the results that can be achieved with single-agent chemotherapy. A consensus report in the early 1980s concluded that optimal results in the treatment of SCLC could be achieved only with the use of combination chemotherapy. At the present time, the superiority of combination chemotherapy is firmly established for SCLC. Impressive response rates and improved survival have been reported for elderly patients treated with oral etoposide alone. Single-agent chemotherapy is a reasonable option for patients who are elderly or have poor performance status.

The results with multiple combination chemotherapy for SCLC depends on the stage of disease. In patients with LD, modern regimens produce overall response rates of 85%–95%, which include complete response rates of 50%–60%. Median survival times of 12 to 16 months have been regularly observed, and 2-year survival times of 15%–25% are possible.

In ED, response rates and median survival are clearly inferior to those observed in limited disease. The overall response rates of 75%–85% are not substantially inferior to those observed in LD, but complete response rates are considerably lower, in the range of 15%–25% in most trials. Median survival times vary from 7 to 11 months, whereas 2-year survival is seen in 5% of patients with ED. As is discussed below, thoracic radiation improves local control rates from 10% to about 40%–60% in patients with LD and is associated with improved survival.

The optimal combination chemotherapy regimen in SCLC is still not clear. No single regimen is clearly superior to all other regimens at the present time. The combination of cyclophosphamide, Adriamycin (doxorubicin), and vincristine (the CAV regimen) was widely used in the late 1970s and 1980s and was considered to be the “standard regimen,” with which other regimens should be compared.

When etoposide became established as an active agent in SCLC, trials were conducted to determine if the addition of etoposide to CAV (CAVE) or the substitution of etopside for vincristine (CAE) led to improvements in outcome. Some studies have shown modest advantages with the newer regimens, although it remains unclear to what extent these regimens offer real outcome advantages.

In recent years, regimens based on etopside and cisplatin (EP) have become the most widely used combination for the treatment of SCLC. This combination has been shown to be highly synergistic in preclinical studies, and it has been shown to be highly effective in numerous clinical trials, both as first-line therapy and as a salvage regimen. Response rates as high as 95% have been reported. A pooled analysis of 294 previously treated patients with SCLC who were treated with EP produced an overall response rate of 47%. Regimens substituting carboplatin for cisplatin in combination with etoposide in SCLC appear to have similar efficacy.

Although other regimens appear to be comparable with EP in efficacy, none has been proved superior. A number of strategies have been employed in an effort to develop more effective chemotherapy programs. One such strategy has been to use alternating, non–cross-resistant chemotherapy regimens. These have been investigated in SCLC as a method of potentially overcoming drug resistance by exposing the tumor to an increased number of active cytotoxic agents. Some studies have suggested that this strategy may have some merit, but randomized trials have not consistently demonstrated an improvement in response rates or survival. A consensus conference concluded that alternating chemotherapy regimens could not be recommended on the basis of existing results of randomized trials. Accordingly, this approach has not gained wide acceptance in SCLC.

Another approach has been to increase the dose intensity of chemotherapy to enhance response rates and survival. Although a few studies have suggested that this approach may be worthwhile, the preponderance of evidence from randomized comparisons indicates that “high-dose” regimens provide no consistent survival advantages over “standard-dose” regimens employing the same agents, and that toxicity, particularly myelosuppression, is greater with the dose-intense regimens. A meta-analysis of 60 trials showed no demonstrable effect on response rate or survival when dose intensity was increased.

Because SCLC is so highly responsive to chemotherapy, it is an appropriate disease to study in the context of high-dose chemotherapy and autologous bone marrow support. Only a single, small, randomized trial has compared conventional therapy with high-dose therapy and marrow support in SCLC. In this trial, 45 patients who had responded to induction chemotherapy were randomized to conventional or high-dose chemotherapy as intensification. In the dose-intense arm, nine of 12 patients (75%) achieved a complete response, compared with none of eight patients given conventional-dose treatment. Trends toward higher median and long-term survival favored the high-dose arm, but failure of local control remained a major problem. Chest radiation was not employed in this trial.

Elias reported the preliminary results of a phase II study conducted at the Dana-Farber Cancer Institute, in which patients with limited SCLC who had achieved a complete (or nearly complete) response with conventional “induction” chemotherapy were given high-dose chemotherapy and autologous bone marrow transplant. The high-dose therapy, intended to consolidate the remission, consisted of cyclophosphamide, carmustine, and cisplatin with hematopoietic stem cell support. The high-dose therapy was followed by thoracic and prophylactic cranial radiation. Of the first 25 patients treated who had achieved complete (or nearly complete) remission following induction therapy, 57% remained disease-free 2 years after the completion of protocol treatment. These highly encouraging preliminary observations justify the continued study of this approach for highly selected patients with limited SCLC.

In summary, the introduction of combination chemotherapy as standard therapy for SCLC in the 1970s has contributed to significant improvements in survival in both limited and extensive disease. Although a number of chemotherapy regimens may be equivalent to EP or etoposide and carboplatin, alternating regimens or dose-intense regimens have not gained widespread acceptance. Four to six cycles of EP without maintenance therapy appears sufficient. Moreover, high-dose chemotherapy with autologous bone marrow support warrants further study in patients under the age of 60 years who achieve complete remission with conventional combination chemotherapy.

Thoracic Radiation in SCLC

Although disseminated extrathoracic metastasis has traditionally been the most frequent form of failure in SCLC, local and regional failure within the chest occurs in up to 80% of patients with LD treated with chemotherapy alone. This high rate of local failure provides a rationale for the use of thoracic radiation in patients with SCLC. The objective of thoracic radiation is to improve local control and survival. Results from a number of randomized studies have demonstrated that the use of thoracic radiation significantly decreases the rate of local failure in SCLC. It remains unclear whether this improvement is associated with a survival advantage.

The largest individual randomized trial was a study conducted by the CALGB involving 399 patients. They were randomized either to chemotherapy alone or to two concurrent chemotherapy and radiation arms, in which 50 Gy of radiation was either given early, with the first cycle of chemotherapy, or delayed until the fourth cycle of chemotherapy. The chemotherapy consisted of cyclophosphamide, etoposide, and vincristine, with doxorubicin substituted for the etoposide in alternate cycles beginning with the seventh cycle. The rate of local failure was 90% in the chemotherapy alone group and 60% in each of the chemotherapy and radiation groups. Median survival was improved only slightly in the group receiving delayed radiation compared with early or no radiation (14.6 vs. 13.1 vs. 13.6 months). However, 2-year survival was 25% in the delayed radiation group, compared with 15% in the early radiation group and 8% in the chemotherapy alone group.

The role of thoracic radiation in SCLC has best been clarified by two meta-analyses published in 1992. Thirteen randomized trials, including >2100 patients, were evaluated in the larger meta-analysis. Chemotherapy regimens and radiation doses and schedules differed between studies. Both reports demonstrated that the addition of thoracic radiation was associated with a small but significant improvement in 2- and 3-year survival rates, which averaged 5%–7%. Local control rates were improved by 25%. Overall, local control was observed in 23% (172/737) of patients receiving chemotherapy alone, compared with 48% (376/784) of patients who were treated with chemotherapy and radiation. The improvement in long-term survival was greatest for patients who were 55 years of age. The survival benefit was achieved at the cost of increased toxicity. Accordingly, treatment for limited SCLC should include both combination chemotherapy and thoracic radiation for optimal management. Unanswered questions relate to the optimal sequencing of chemotherapy and radiotherapy.

As there is evidence that radiotherapy given after chemotherapy may be associated with inferior local-regional control, radiation should probably be initiated relatively early, although not necessarily at the very beginning of chemotherapy. A randomized trial reported by the National Cancer Institute of Canada showed that early radiation was associated with improved local control and survival and suggested that greater delays may produce significantly inferior results. The CALGB study suggests that administering radiation with the fourth cycle of chemotherapy is reasonable.

An additional questions relates to radiation volume. It is uncertain whether radiation portals should be designed based on the original tumor volume or on the shrinking volume that follows a response to chemotherapy. Available evidence suggests that relatively tight radiation portals appear appropriate, particularly for lesions with substantial postobstructive infiltrates.

Finally, questions about dose and fractionation schedule continue. A number of phase II studies have suggested that hyperfractionation schedules, in which radiation is given two or (or even three) times daily, may have an advantage in terms of local control and survival compared with standard, once-daily fractionation schedules. A randomized trial to prove this point in ongoing.

Prophylactic Cranial Radiation in SCLC

Shortly after the introduction of successful chemotherapy in SCLC, it was recognized that the central nervous system represented an extremely common site of first relapse and was frequently the sole site of failure. This is because most of the commonly used chemotherapeutic agents do not effectively penetrate the blood-brain barrier; accordingly, the brain serves as a sanctuary site.

In a retrospective study of 48 patients achieving a complete response to chemotherapy, central nervous system metastases developed in 38%, none of whom had

received prophylactic cranial irradiation (PCI). In 17% of patients, the brain represented the only site of failure. Others have reported that the brain may be a first or solitary site of failure in 9%–14% of patients with SCLC who achieve complete remission. Moreover, the probability of brain metastases increases with increasing length of survival. Cumulative risk of central nervous system metastases has been estimated to be 58%–80% at 2 years following diagnosis.

Based on these observations, the use of PCI to decrease the rate of central nervous system failure and improve survival has been extensively studied in SCLC in 13 randomized trials. These studies have varied greatly in regard to number of patients entered, dose and schedule of central nervous system radiation, whether PCI was employed only in patients with LD or whether patients with ED were also eligible, and whether only complete responders to chemotherapy were studied.

With reasonable consistency, these studies demonstrate that PCI leads to a definite reduction of the risk of central nervous system metastases. In a pooled analysis including 716 patients in nine randomized studies, it was demonstrated that doses of PCI ranging from 20 to 40 Gy reduced the rate of central nervous system recurrence from 22%–6%.

Two large, multicenter, randomized trials of the value of PCI have been published recently. In a French trial, 300 patients with limited SCLC achieving a complete response to chemotherapy were studied. At 2 years, the rate of central nervous system failure was 67% for those not undergoing PCI, compared with 40% for those who did. The percentage of cases in which the central nervous system was the first site of relapse fell from 45% to 19%. Although survival trends favored the group receiving PCI, there were no significant differences at 2 years (29% vs. 21%; $p = .14$). Similarly, in another multicenter study involving 314 patients, central nervous system failure at 3 years was 55% in those not receiving PCI, compared with 37% in those who did. Although survival trends favored the PCI group in this trial, there were no statistically significant differences in survival. Accordingly, a large body of literature based on randomized comparisons demonstrates that PCI decreases the rate of central nervous system recurrence but has no significant impact on overall survival. All patients in whom central nervous system metastases develop eventually succumb to their disease.

Perhaps the most powerful argument against the routine use of PCI in patients with limited SCLC is related to the toxicity of PCI, particularly the potentially disabling late neurologic and intellectual impairment that occurs. Not all approaches to central nervous system radiation treatment are equally likely to be associated with neurologic sequelae. The probability of significant neurologic problems developing is much more likely when radiation is given concurrently with systemic chemotherapy and/or when a radiation fraction size of 400 Gy is used.

Each of the two recent randomized studies of PCI in SCLC prospectively monitored for the development of central nervous system toxicity by neuropsychologic assessment. The French trial also performed CT. Significant cognitive impairment related to PCI was not documented in either study. It was found that up to 25%–60% of patients had pre-existing cognitive impairments before PCI.

The author believes that because radiation is a local-regional treatment modality, its effectiveness should be judged on the basis of its ability to maintain local control and improve quality of life. This is true unless radiation is being administered with curative intent in the primary management of a particular neoplasm. There are virtually no other examples in oncology in which noncurative radiation has become standard therapy on the basis of survival advantages in randomized trials. In the author's opinion, PCI should be incorporated into the primary management of limited SCLC, because it significantly diminishes the risk for central nervous system recurrence and because recent evidence suggests that it can be safely administered without a substantial risk for significant neurologic disability. There is little question that the development of symptomatic brain metastases has a negative impact on quality of life, particularly if the brain is the sole site of recurrence. Moreover, it is also reasonable to consider PCI for patients with extensive SCLC and good performance status who achieve a complete remission with systemic chemotherapy.

The use of PCI should be limited to complete responders to chemotherapy. It should be given in sequential fashion, after chemotherapy; concurrent chemotherapy and PCI should be avoided. Although the proper dose and schedule of PCI continue to be debated, a relatively low daily fraction size of 2 to 3 Gy and a total dose of 30 to 36 Gy may be optimal

Surgery in the Treatment of SCLC

Surgical resection alone is not a reasonable option for the management of SCLC. SCLC is a highly virulent neoplasm that is presumed to be a systemic disease, even when apparently localized. The question, however, is whether surgery should be considered in the context of combined modality therapy for this disease. A moderate amount of data exist regarding the use of surgery followed by adjuvant chemotherapy, and induction chemotherapy followed by surgery. Most of the data are uncontrolled.

Surgery may be an option for SCLC presenting as a single pulmonary nodule, defined as a single lesion 6 cm in diameter. It has been reported that 4%–12% of lung cancers presenting as a solitary pulmonary nodule turn out to be SCLC. Conversely, a solitary pulmonary nodule was the presentation in 4% (15/408) of patients with SCLC seen at McGill University between 1979 and 1984. About two thirds of SCLC solitary pulmonary nodules are of the “intermediate cell” histologic subtype; in marked contrast, about two thirds of SCLCs presenting in the usual manner are of the classic “oat cell” subtypes.

No controlled data exist, but the long-term survival rates of patients with SCLC solitary pulmonary nodules who have undergone surgical resection are impressive in comparison with those of other groups of patients with SCLC. Kreisman pooled available studies and reported that among patients with stage I SCLC who had solitary pulmonary nodules treated with surgical resection, 40%–53% survived for 5 years.

The role of postoperative therapy in such patients is somewhat unclear. Although most patients undergoing resection receive postoperative chemotherapy, some do not and still enjoy prolonged disease-free survival. Nonetheless, in recognition of the systemic nature of most SCLC, most authorities recommend that patients with resected SCLC solitary pulmonary nodules should receive adjuvant chemotherapy with an established combination regimen. There are no data regarding the efficacy of thoracic radiation or PCI in this setting, although it is reasonable to consider such therapy in the context of potentially curative therapy for these patients.

Other studies have also reported impressive long-term survival rates for patients with SCLC undergoing surgical resection. The data suggest that patients with stage I or stage II SCLC have a 27%–42% chance of 5-year survival after resection. Shepherd reviewed the data and suggested that approximately 50% of patients with stage I SCLC could be cured with surgery followed by adjuvant chemotherapy. Long-term survival was much less common in patients with more advanced SCLC.

Whether the encouraging trends in resectable SCLC reflect a beneficial effect of the surgery itself or a reduced tumor burden in patients in whom resection is possible remains unknown. Nonetheless, such data support continued investigation of the role of surgical resection followed by chemotherapy (and possibly radiation) in early-stage SCLC.

What about surgical resection following induction chemotherapy? Most of the available data come from small phase II trials. Shepherd reviewed the results of nine such trials including 260 patients with limited SCLC treated by induction chemotherapy, after which resection was considered for responders. Overall chemotherapy response rates were at least 88% in eight of the nine trials. Approximately 60% of patients were taken to surgery, and about 80% of these patients underwent complete resections (approximately 50% of those entering the trials). The vast majority of patients undergoing resection had viable residual SCLC in the resected specimens, with pathologic complete response rates averaging about 10%. For patients with pathologic stage I SCLC in whom complete resection was achieved, 5-year survival approached 70%. For patients with stage II or stage IIIA SCLC, survival was less favorable, but there were cohorts who achieved long-term disease-free survival.

These results led to a randomized study by the LCSG to evaluate the role of resection following induction chemotherapy in limited SCLC. All patients with LD were eligible, which translates into ISS stages I, II, IIIA, and IIIB. Patients received five cycles of chemotherapy consisting of cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV). All patients were restaged after induction therapy. Patients judged to be suitable for resection were then randomized to surgery followed by thoracic radiation and PCI, or to an identical regimen of radiation treatment without surgery. A total of 340 patients were registered in the trial. Overall, 66% achieved a response to induction chemotherapy (28% complete and 38% partial responses). A total of 144 (42%) patients were randomized, 68 to the surgery arm and 76 to no surgery. Fifty-eight resections took place, including 54 complete resections (77%). Unfortunately, no significant differences in median or overall survival were observed between the surgery and no surgery groups. Median survival of all patients was 14 months; it was 18 months for those patients who were randomized. Actuarial 2-year survival was 20% in both arms. Accordingly, the study failed to provide any support for the use of surgical resection in limited SCLC.

At the present time, surgery cannot be considered standard for any subgroup of patients with SCLC. However, available evidence from nonrandomized studies does support the conclusion that resection is beneficial in well-staged SCLC patients with ISS stage I, and possibly also in some patients with stage II disease. Among patients with limited SCLC, surgery should not be included in the management of those with ISS stage IIIA or stage IIIB disease. Unfortunately, such patients represent the vast majority of those with limited SCLC.

Conclusions Regarding the Management of SCLC

Combination chemotherapy is the mainstay of standard treatment for virtually all patients with SCLC, including those with LD and ED. Although no consensus for “best” chemotherapy regimen exists, four to six cycles of a standard combination, such as etoposide and cisplatin (EP), is reasonable. However, given the high degree of

sensitivity to chemotherapy of SCLC, consideration of the use of a more intensive combination regimen or an alternating regimen is also reasonable, even outside the context of a clinical trial. An important objective is to maximize the possibility of complete remission.

Thoracic radiation should now be considered to represent standard therapy for patients with LD. Existing data would support that thoracic radiation should be given concurrently with chemotherapy, preferably following two to four cycles of chemotherapy.

PCI should be considered for patients with LD who achieve a complete response to chemotherapy or to chemotherapy and radiation. It can also be considered for patients with ED who achieve a complete remission. PCI should not be given concurrently with chemotherapy.

Both surgical resection and high-dose chemotherapy with autologous bone marrow transplant remain experimental treatment strategies for SCLC at the present time. However, both approaches warrant consideration in specific situations. Surgical resection should be considered for patients with LD who present with stage I SCLC. Experimental protocols employing high-dose chemotherapy and autologous bone marrow transplant warrant consideration for patients 60 years of age who achieve complete remission with conventional chemotherapy and radiation. The objective of both strategies is to enhance the cure rate in a disease in which long-term survival is achieved in only a small minority of patients.

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CHAPTER

69 Tumors of the Lung Other Than Bronchogenic Carcinoma

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INTRODUCTION

Other than bronchial carcinoid and bronchoalveolar carcinoma, the pulmonary tumors discussed in this chapter are exceedingly rare and collectively comprise approximately 2% of all lung tumors. Many of these tumors are benign; some are malignant; and others exhibit locally aggressive behavior.

With the introduction of electron microscopy, immunohistology, and cell culture techniques (and with some ongoing controversy), the commonly accepted World Health Organization classification of these tumors has undergone major changes. One of the more useful classification schemes, devised by Spencer, segregates these tumors according to the cell of origin, as far as possible, as follows:

1. Tumors of APUD cells, neural cells, or of unknown origin:
   a. Bronchial carcinoid tumor
   b. Neurofibroma and neurofibrosarcoma of the lung
   c. Myoblastoma of the bronchus
   d. Malignant melanoma of the bronchus
   e. Pulmonary "chemodectoma"
   f. Benign clear-cell tumor of the lung
2. Tumors derived from bronchial epithelium or bronchial mucous glands:
   a. Bronchial papillomatous tumors
   b. Bronchial cystadenoma, monomorphic and pleomorphic
   c. Pleomorphic bronchial gland adenomas
   d. Oncocytic bronchial gland adenoma
   e. Bronchial mucoepidermoid adenoma
   f. Adenoid cystic carcinoma of the bronchus
   g. Mucinous, multilocular cystcarcinoma of the bronchus
3. Tumors of pulmonary connective tissue origin:
   a. Chondroma of the bronchus
   b. Bronchial and subpleural lipomatous tumors
   c. Fibroma and myxoma of the lung
   d. Pulmonary fibroleiomyoma
   e. Pulmonary sarcoma
   f. Pulmonary rhabdomyosarcoma
   g. Embryonal pulmonary sarcoma
   h. Intravascular and sclerosing bronchoalveolar tumor (IVSBAT)
   i. Tumors of vascular origin:
      i. Angioma
      ii. Lymphangioma
4. Lung tumors of chronic granulomatous or uncertain origin:
   a. Plasma cell granuloma, benign and malignant histiocytoma of the lung
   b. Sclerosing angioma
5. Hamartomas of the lung:
   a. Chondromatous
   b. Fibroleiomyomatous
6. Blastoma and teratoma of the lung
7. Pulmonary reticuloses:
   a. Lymphoid hyperplasia
   b. Hodgkin's disease
   c. Lymphosarcoma and histiocytic sarcoma
   d. Plasmacytoma of the lung
   e. Leukemia
   f. Giant intrathoracic lymph nodes
   g. Histiocytosis X diseasete

The term *bronchial adenoma* has been used for some time to describe fleshy, polypoid tumors of the tracheobronchial tree. Recently, however, in recognition of their malignant potential, the most common types of adenomas have undergone name changes. Cylindromas are now called adenoid cystic carcinoma, mucoepidermoid tumors are now called mucoepidermoid carcinoma, and a suggestion has been made to change the name of bronchial carcinoid tumors to low-grade APUD carcinoma or Kulchitzky cell carcinoma. Bronchoalveolar cell carcinoma is also discussed in this chapter. The illustrative reviews of Dail and Mackay are recommended for further reading.

In general, tumors that originate within a bronchus tend to be discovered earlier because of signs and symptoms of bronchial stenosis and obstruction: wheezing, cough, atelectasis, obstructive pneumonitis, and distal bronchiectasis. Tumors originating in the periphery of the lung, on the other hand, may attain large size before they produce symptoms. They are discovered either incidentally on routine chest x-ray or when they have involved adjacent structures within the chest, at which point

they may be inoperable.

Careful bronchoscopy, fine-needle biopsy, computed tomography, and magnetic resonance imaging (MRI) may provide useful information in the evaluation of these tumors. Positron-emission tomography may be useful in distinguishing benign from malignant lesions. However, in some cases the diagnosis will only be made postoperatively by the pathologist because (lipomas and chondromatous hamartomas excepted) there are no diagnostic roentgenologic signs, and even bronchoscopic biopsy can be misleading. With few exceptions, surgery is the treatment of choice to remove potentially lethal lesions and to relieve symptoms. In general, conservative resection is the rule, employing modern bronchoplastic techniques. Many lesions can now be resected thoracoscopically, without formal thoracotomy.

BRONCHOALVEOLAR CELL CARCINOMA OF THE LUNG

Bronchoalveolar cell carcinoma is a primary tumor of the lung arising within alveoli and terminal bronchioles and spreading along the surface of the airways to involve other parts of the lung. It is also called alveolar cell carcinoma, bronchiolar cell carcinoma, bronchioloalveolar cell carcinoma, and pulmonary adenomatosis because of a controversy concerning the cell of origin. Previously, this tumor comprised approximately 5% of all lung tumors, although recent evidence suggests that the incidence may be much higher. Formerly, the production of mucus by these tumors suggested bronchiolar cell origin, but it has since been shown that alveolar cells also can differentiate into cells capable of mucus secretion. It is now agreed that the tumor arises from type II alveolar pneumocytes and Clara cells. Clinically, two separate entities have been described. Focal bronchoalveolar carcinoma usually presents as a solitary peripheral nodule characterized by slow growth (tumor-doubling time approximately 300 days) and infrequent regional lymph node metastases (Fig. 1). A diffuse form of the disease is less common but more aggressive and is characterized by multiple nodules or consolidation (Fig. 2). Prognosis for focal disease treated by complete resection is excellent; however, if left untreated, some of these cases may progress to the diffuse form, presumably by aerogenous dissemination. A multiclonal theory of cell origin may also play a role.

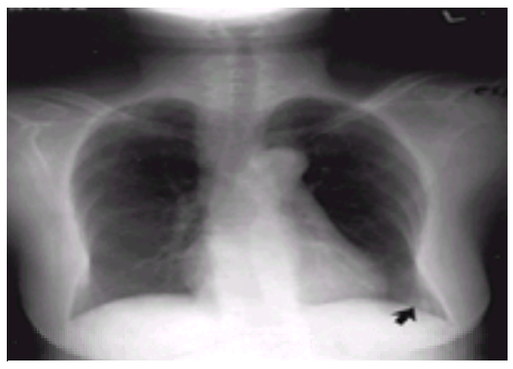

FIG. 1. Asymptomatic focal bronchoalveolar carcinoma of the left lower lobe (*arrow*).

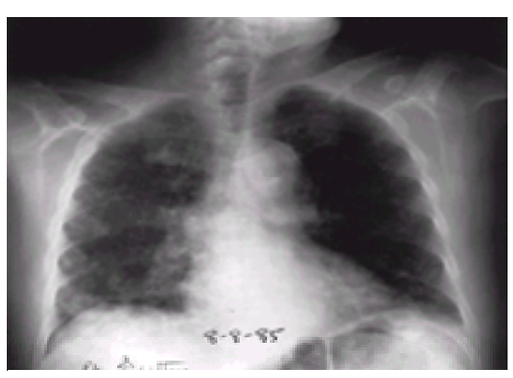

FIG. 2. Diffuse or pneumonic form of bronchoalveolar carcinoma with bilateral patchy tumor infiltrates.

The etiology is unknown, but bronchoalveolar cell carcinoma bears a striking resemblance histologically and in mode of spread to an infectious (presumably viral) disease of animals (primarily sheep) in South Africa called *jaagsiekte.*

The hallmark of the histologic diagnosis is the pattern of growth of flat or columnar malignant cells along alveolar and bronchiolar walls, with frequent intraalveolar projections but with preservation of the general interstitial framework of the lung (Fig. 3). Electron microscopy commonly shows dense cytoplasmic granules and nuclear inclusions (Fig. 4). Immunohistochemical techniques have shown these inclusions to represent a portion of the surfactant molecule.

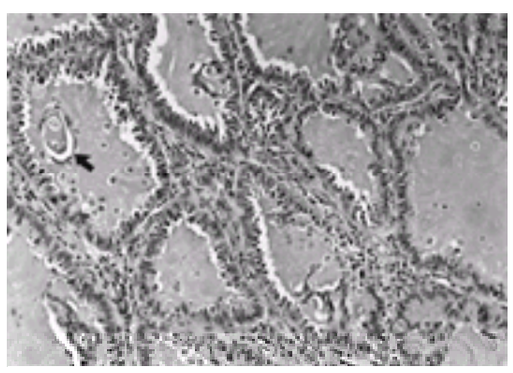

FIG. 3. Bronchoalveolar carcinoma showing tall columnar cells and small nests of tumor floating within mucin (*arrow*) (H&E, ×50). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

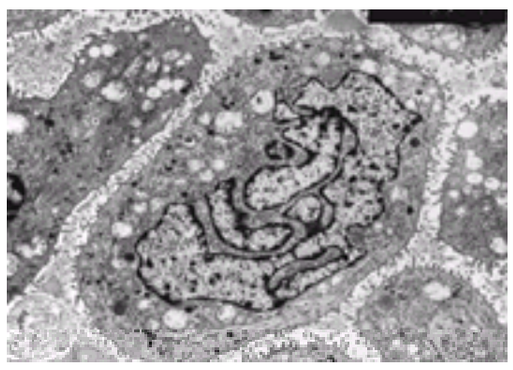

FIG. 4. Electron micrograph of bronchoalveolar cell carcinoma of the Clara-cell type. Note the prominent electron-dense granules, which are characteristic. (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Compared to bronchogenic carcinoma, bronchoalveolar tumors are less likely to be associated with smoking or chronic lung disease. Approximately 40% of patients present with advanced disease (TNM stage III, IV) and are usually symptomatic. Cough, copious watery sputum, dyspnea, and constitutional symptoms and signs such as malaise, fatigue, and clubbing are characteristic of this disease. The diagnosis can occasionally be made by sputum cytology and more often by bronchoscopic brushing and biopsy. Fine-needle biopsy is positive in 75% to 80% of patients.

The treatment of bronchoalveolar cell carcinoma is surgical, and lobectomy is the procedure of choice. Data from the Lung Cancer Study Group have shown a 5-year survival rate of approximately 60% following surgical resection. For tumors more advanced than T_1N_0, the yearly recurrence rate may exceed 20%. Because the disease spreads by local extension, the plane of a segmentectomy or wedge resection is likely to cut across invisible extensions of tumor, making conservative surgery inappropriate. Even for more advanced disease, lobectomy or pneumonectomy should be considered (provided that there is no evidence of spread to the opposite lung), because there is no other suitable treatment. The tumor is not particularly responsive to chemotherapy or radiation therapy. Although the disease tends to spread slowly, untreated bronchoalveolar carcinoma proceeds inexorably to pulmonary insufficiency and death by inanition. Although it is considered experimental, isolated lung perfusion with chemotherapy may be useful.

BRONCHIAL CARCINOID

Although originally classified as bronchial adenomas, bronchial carcinoids should now be categorized as neuroendocrine neoplasms of the lung, which include tumorlets and small-cell carcinoma. Carcinoids comprise approximately 2% of primary lung tumors and usually present in the fifth decade of life as a reddish polypoid mass within view of a bronchoscope, occurring in a main, lobar, segmental, or subsegmental bronchus. Peripheral tumors may occur in 20% of cases, and rare tracheal occurrences have been reported. Because of their location and tendency to expand into the bronchial lumen, carcinoids frequently produce partial or complete bronchial obstruction (see Fig. 5). Wheezing and hemoptysis are common signs, and intermittent lobar or segmental atelectasis is a hallmark of the tumor. Mucopurulent sputum and distal bronchiectasis occur in cases of long-standing obstruction. The majority of patients are symptomatic, but as many as 20% may present with an asymptomatic pulmonary nodule. Smoking, occupation, and environmental factors do not appear to play a role in the genesis of this tumor.

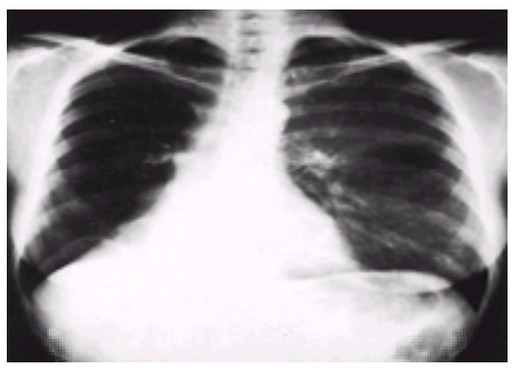

FIG. 5. Bronchial carcinoid tumor causing complete atelectasis of the lower lobe of the right lung.

Cytologic examination of the sputum, bronchial washings, and brushings is not productive, as the tumor is enveloped by normal mucosa. However, fine-needle biopsy may be useful in a small number of cases. Because the tumor is highly vascular, direct biopsy has been avoided in the past for fear of major bleeding. Today, with use of a “microbiopsy” forceps through a fiberoptic bronchoscope, direct biopsy can be performed safely with a diagnostic sensitivity of 60% to 80%.

Many hormones have been reported to be secreted by bronchial carcinoids, including ACTH, ADH, gastrin, somatostatin, calcitonin, and growth hormone. The most common is 5-hydroxytryptamine, or serotonin, but only a very small fraction of patients with bronchial carcinoids exhibit the “carcinoid syndrome,” and only when hepatic metastases have occurred. When present, the syndrome can be controlled effectively with somatostatin analogs.

The tumor usually presents as a polypoid mass, but the base of the “polyp” varies from a pedicle to a broad attachment. In fact, the stalk invariably penetrates through the bronchial wall to the extent that the bulk of the tumor is extrabronchial. Endobronchial resection is, therefore, not a definitive treatment, although in extremely poor-risk patients it may be reasonable to restore airway patency by laser resection.

Microscopically, the typical carcinoid tumor is made up of small, uniform argyrophilic cells with central nuclei and eosinophilic cytoplasm within a vascular stroma (Fig. 6). The cells may form clusters, cords, or tubules or grow in solid sheets. They arise from Kulchitzky cells, which belong to the APUD system. These cells, which are seen under the electron microscope to contain neurosecretory granules, also give rise to small-cell carcinoma of the lung. Previously thought to originate from neural crest cells, Kulchitzky cells are now believed to originate from bronchial germinal epithelium. Immunohistochemical studies may be very useful, as bronchial carcinoids have been shown to express a number of epithelial and endocrine markers such as cytokeratin, neurofilament proteins, neuron-specific enolase, and chromogranins. Of these, chromogranin is the most useful marker, being demonstrated in 86% of specimens.

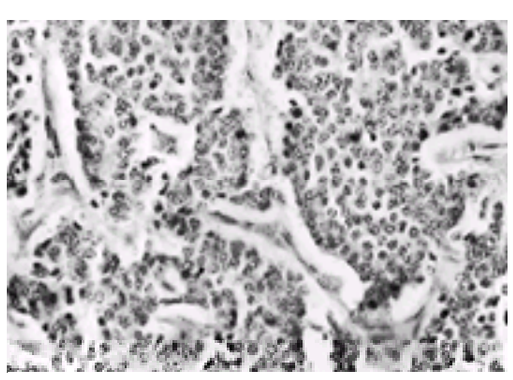

FIG. 6. Bronchial carcinoid tumor. Nests of uniform cells are separated by a delicate connective-tissue stroma. There are round nuclei with evenly dispersed, coarse chromatin and pale cytoplasm (H&, ×400). (Courtesy of Dr. Miriam Lurie, Department of Pathology, Carmel Hospital, Haifa, Israel.)

The typical carcinoid tumor is relatively benign: mitoses are rare in the tissue; regional lymph node metastases are almost never present at the time of thoracotomy; and the 5-year survival rate approaches 100%.

The atypical carcinoid tumor (also termed neuroendocrine carcinoma) is characterized histologically by mitoses, cell necrosis, aneuploid DNA content, and pleomorphism. It is useful to group these tumors into three categories, based on cell size and degree of differentiation: (1) well-differentiated type, (2) intermediate type, and (3) small cell. Types 1 and 2 invariably express neuron-specific enolase and synaptophysin on immunohistologic stains, and a high percentage are in stage II or III at the time of surgery. Type 3 is well known for clinical overproduction of hormones, particularly ADH and ACTH, and for a proclivity for early metastases.

The treatment of typical carcinoids is conservative resection, sparing pulmonary parenchyma where feasible unless the lung has been destroyed by bronchiectasis beyond the point of bronchial obstruction. Bronchoplastic procedures and sleeve resections can be performed even with surgical margins close to the tumor. Atypical carcinoids, on the other hand, should be treated with more aggressive resection (lobectomy or pneumonectomy) to insure adequate margins, and lymph node excision should be performed. A 5-year survival of 60% can be expected; interestingly, both survival and recurrence seem to be dependent more on cell type than on nodal status. The treatment of small-cell carcinoma is in evolution. Because the majority of patients have widely metastatic disease at the time of presentation, chemotherapy is the most appropriate option. However, selected patients with “limited” disease may benefit from surgery before or after multimodality therapy. For further discussion

of small-cell carcinoma of the lung, refer to Chapter 68 and Chapter 71.

NEUROGENIC TUMORS

Primary neurogenic tumors of the lung, which include benign neurofibromas, neurilemmomas, and neurofibrosarcomas, are quite rare, with fewer than 100 cases reported. Intrapulmonary neurofibromas are the most common and are more likely to occur in association with von Recklinghausen's disease. In this situation, the lung tumors may be multiple, causing significant arteriovenous shunting and hypoxemia. Benign neurilemmomas (Schwannomas) are more likely to arise sporadically. These tumors are consistently related to a bronchus, either within the lumen (more commonly) or outside the bronchial wall. Both neurofibroma and neurilemmomas originate from nerve sheath cells; however, their histology may be confused with those of neuroblastomas, leiomyomas, fibromas, and mesotheliomas. Immunostaining for neuron-specific enolase and protein S-100 will help establish nerve sheath origin. Most primary neurogenic tumors of the lung are asymptomatic and therefore may attain a large size over a long period of time. Cough and hemoptysis are caused when a bronchus becomes obstructed or compressed by the mass of a large tumor. Endobronchial lesions may appear as polypoid lesions projecting into the lumen of a bronchus and can be resected successfully with a YAG laser. Parenchymal lesions can be cured by conservative resections, and recurrences are rare.

Malignant Schwannomas (neurosarcomas, neurofibrosarcomas) are often accompanied by the finding of benign neurofibromas in other parts of the tumor. Invasiveness, hemorrhage, and necrosis of the tumor are characteristic. These tumors may grow very large and metastasize late in their natural history. Many patients have been cured by surgical resection, and adjuvant chemotherapy, particularly with Adriamycin, may be useful for extensive tumors.

GRANULAR CELL TUMOR OF THE BRONCHUS

Although granular cell tumors occur in nearly all anatomic sites, they are found predominantly in the tongue and skin and are extremely rare in the lungs. Previously termed myoblastoma, this tumor is now believed to originate from Schwann's cells. The tumor is found in the lung as a benign sessile or polypoid growth within the trachea or a central bronchus and is usually associated with obstructive pneumonitis. Multiple tracheobronchial lesions occur in 20% of patients. Ulceration of pedunculated lesions may produce hemoptysis. The tumor may be multicentric; coexisting lesions outside of the respiratory tract may be frankly malignant. Histologically, the tumor is composed of clusters of polygonal cells with small hyperchromatic nuclei and abundant cytoplasm containing numerous fine, acidophilic granules. These granules appear similar to lysosomes under electron microscopy.

Although benign, these tumors are locally invasive and are associated with squamous metaplasia, simulating malignant tumors of the bronchus. Larger lesions may have extensive submucosal infiltration, making bronchoscopic or laser removal useful only for palliation. Definitive treatment is by surgical resection, with sleeve resection or a bronchoplastic procedure used if feasible.

Oncocytomas and oncocytic carcinoids can be confused with granular cell tumors. Immunohistochemical stains for protein S-100, neuron-specific enolase, and vimentin may be useful in differentiating ambiguous cases. *Mycobacterium avium-intracellulare* should also be considered in the differential diagnosis.

MALIGNANT MELANOMA OF THE BRONCHUS

Cutaneous and ocular malignant melanoma frequently spreads to the lungs, presenting as multiple, bilateral parenchymal nodules. Approximately 2% of malignant melanomas will metastasize to the bronchus, making the diagnosis of primary malignant melanoma of the bronchus a diagnosis of exclusion. Because a complete examination to exclude all other possible primary sites can only be done postmortem, diagnosis before death can only be presumptive (Fig. 7 and Fig. 8). Nevertheless, several authors have suggested the following diagnostic criteria: (1) absence of past or present atypical or malignant pigmented skin lesions from any site, (2) a solitary lung lesion centered on a bronchus with no evidence of other organ involvement, and (3) *in situ* melanocytic change of bronchial mucosa adjacent to or overlying the major tumor mass (the so-called “junctional” or “lentiginous” change). On the basis of these criteria, a small number of reported cases may benefit from surgical resection.

FIG. 7. Lung tomogram showing adenoid cystic carcinoma of the right mainstem bronchus (*arrows*).

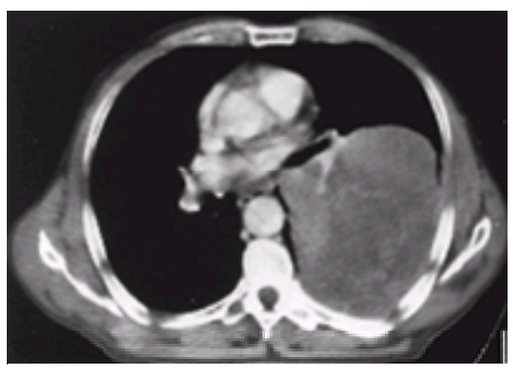

FIG. 8. Primary fibrosarcoma arising from the left mainstem bronchus.

PULMONARY CHEMODECTOMA

Minute, multiple chemodectomas are occasionally found at autopsy in patients who have died from cardiovascular disease, especially pulmonary thromboembolism. Over 80% of cases occur in women. Grossly, these tumors appear as 1-mm to 3-mm nodules on the pleura or within the pulmonary parenchyma. Microscopically, the tumors consist of nests of large cells in the interstitial tissues near or surrounding small pulmonary veins. The tumor cells are large, spindled, or elongated with regular nuclei, eosinophilic cytoplasm, and indistinct cell borders. Immunohistochemical stains for epithelial membrane antigen and vimentin are usually positive. Chemodectomas were formerly thought to have developed from chemoreceptor cells in the lung, but Churg and Warnock failed to find neurosecretory granules ultrastructurally, as would have been expected in paraganglion cells. They suggested that these tumors have characteristics related to meningiomas.

BENIGN “CLEAR-CELL” TUMORS OF THE LUNG

Also known as “sugar” tumors because of their high glycogen content, these tumors present as isolated, asymptomatic, solitary pulmonary nodules on chest x-ray. They are exceedingly rare, occurring mainly in middle-aged adults. Successful diagnosis by fine-needle aspiration has been reported. Grossly, the tumors are not encapsulated. Nevertheless, they remain distinct from surrounding tissue. They are not associated with bronchi. Histologically, these tumors resemble “clear-cell carcinoma” of the kidney, both expressing melanoma antigens, and so are confused with metastatic lesions. However, frequent mitoses should be observed in the

latter. In general, immunohistochemical stains may be helpful. Conservative resection should be considered curative.

BRONCHIAL PAPILLOMATOUS TUMORS

These are benign lesions of the larynx, trachea, and bronchi, usually multiple and only rarely solitary. The tumors are multicentric and are usually caused by human papilloma virus (HPV). These tumors are more common in infants and children, in whom the disease is self-limiting and extends beyond the larynx in only 2% of cases. During the course of cellular proliferation, however, airway obstruction may occur from the florid overgrowth. Disease extending into the bronchopulmonary tree is more virulent, often presenting with symptoms and signs of obstruction and requiring multiple resections for recurrent disease. Endobronchial resection, conventional or laser, is live saving, although many patients will require chronic tracheostomy.

In adults, the prognosis is poorer, especially in the form that spreads to the parenchyma. In most cases, laryngotracheal papillomas always appear first, followed by progressively lower airway involvement. In cases of bronchoalveolar spread, nodules form in the lung and then cavitate to form cysts. Distal bronchiectasis is common, and frank lymphangitic invasion has been described. The lesions tend to increase in number and size with time, and these patients usually die of progressive pulmonary insufficiency. Bronchoscopic and laser resection are the mainstays of therapy; good results have also been reported with photodynamic therapy and interferon-a.

Microscopically, a connective tissue stroma is covered by a cuboidal or squamous epithelium in varying degrees of differentiation and keratinization. Because of cytologic atypia, papillomas may be difficult to distinguish from squamous cell carcinoma. Frank malignancy has been described and is associated with HPV serotypes 16 and 18.

BRONCHIAL MUCOEPIDERMOID ADENOMA

Mucoepidermoid tumors of the bronchus are the third most common type of bronchial adenoma but comprise only 0.1% of all lung tumors as a whole. This is a pedunculated polypoid tumor arising from excretory duct reserve cells of mucous glands. It is usually located in the lobar or mainstem bronchi and, rarely, in the trachea. The tumor is coated with mucus and is capable of producing a large mucocele beyond the point where it causes bronchial obstruction. Histologically, the tumor consists of large cells growing in sheets (“epidermoid,” without keratinization), scattered among which are numerous mucus-containing glands. Tonofibrils and mucin granules are common ultrastructural findings, and tumors are usually immunopositive for epithelial markers. These tumors have been found in virtually all age groups, characteristically producing symptoms of cough, wheezing, hemoptysis, and recurrent pneumonias.

There appear to be a spectrum of mucoepidermoid tumors ranging from benign and completely curable to a malignant and highly lethal variety. The latter are characterized by cytologic atypia, pleomorphic cells, greater mitotic activity, and infiltration into adjacent lung parenchyma. Although exceptions have been reported, in general, the disease is nearly always benign in children. Conservative resection should be employed in this age group. In adults, on the other hand, many of these tumors are highly malignant histologically and very aggressive clinically, with a tendency to local invasiveness and early metastases. Conservative lung resection for low-grade tumors has been suggested, with no evidence of recurrent disease at a mean follow-up of 4.7 years. High-grade lesions, which may be difficult to distinguish from poorly differentiated squamous cell carcinomas, are typically unresectable, and survival is less than 2 years.

BRONCHIAL ONCOCYTOMATOUS ADENOMA

This is a rare benign polypoid tumor that arises from bronchial mucous glands and ducts. Oncocytes are epithelial cells with abundant eosinophilic cytoplasm and small nuclei. Ultrastructurally, they contain abundant mitochondria but no neurosecretory granules, which distinguishes them from carcinoid tumor cells, which they may resemble histologically. Demonstration of chromogranin by immunostaining may be useful. Most cases occur in adults; the tumors rarely exceed 4 cm in size and are benign.

MUCOUS GLAND ADENOMA

These are rare, benign tumors of the bronchial glands that can produce obstructive symptoms or asthma. This tumor, which has also been reported in the trachea, has also been termed *bronchial cystadenoma* and *adenomatous polyp.* The basic histology is that of mucus-filled spaces lined by well-differentiated bronchial gland epithelium. Several subtypes have been proposed (tubular, papillary, mucoepidermoid-type; monomorphic, pleomorphic) based on the predominant cell type. Conservative resection is the treatment of choice.

ADENOID CYSTIC CARCINOMA OF THE BRONCHUS

These tumors originate from mucous glands throughout the body. In the tracheobronchial tree, adenoid cystic carcinoma occurs primarily in the trachea or mainstem bronchus, more central than carcinoid tumors in general (Fig. 7). Although they constitute a small proportion of all primary bronchial neoplasms, they account for approximately 40% of primary tumors of the trachea. Most patients are in their fourth decade.

These are sessile growths, and, like other bronchial tumors, they may present as obstructing lesions, often causing atelectasis of an entire lung.

Histologically, the tumor is composed of duct-lining cells of mucous glands that form into duct-like tubules (hence the older name “cylindroma”) and glands and cysts that contain mucin. The stroma is also myxomatous. This tumor typically immunostains for keratin and vimentin.

These tumors are low-grade adenocarcinomas that spread by local extension through the tracheal wall and metastasize to lymph nodes. Perineural invasion is characteristic.

Treatment is by local wide excision, dictated by anatomic constraints. In some circumstances, sleeve resection of the trachea or of the main bronchus or a bronchoplastic procedure may be feasible. In other instances, tracheal carinal resection or standard lobectomy or pneumonectomy may be required. Local recurrences may occur, usually because of underestimation of intramural spread. Even though adenoid cystic carcinoma is relatively radioresistant, postoperative radiation should be administered when lymph node metastases have occurred or invasion of perineural lymphatics has been demonstrated in the surgical specimen.

CHONDROMA OF THE BRONCHUS

Chondromas grow directly from bronchial or tracheal cartilage into the lumen of the airway as a purely cartilaginous mass unlike hamartomas, which, in addition, contain other elements from the tissues of the bronchial wall. A chondroma has a very smooth, lobulated surface and may grow to be very large. It may be removed by local excision (through a bronchotomy incision) or, preferably, by sleeve resection. Bronchial chondromas may accompany extraadrenal paragangliomas and gastric leiomyosarcomas in Carney's syndrome.

SARCOMAS OF THE LUNG

The most common sarcoma of the lung is metastatic. In general, these tumors are small, multiple lesions that may arise after a long interval after treatment of a primary site. Removal of metastatic lung sarcomas may carry a favorable prognosis, which is discussed in a later section.

In contrast, primary sarcomas of the lung are rare as a group, and some of the varieties are exceedingly rare. These tumors may account for 0.2% to 0.4% of all lung cancer cases and are usually large, solitary, and asymptomatic. The most common primary lesions are malignant fibrous histiocytoma (MFH), fibrosarcoma, and leiomyosarcoma. Kaposi's sarcoma of the lung, associated with acquired immunodeficiency syndrome (AIDS), is now the most common sarcoma affecting the lung. Chondrosarcomas, liposarcomas, myxosarcomas, and rhabdomyosarcomas also occur in the lung. Often the tumor is undifferentiated and referred to simply as a sarcoma or spindle-cell sarcoma of the lung. In general, these tumors do not contain calcium on roentgenograms and do not exfoliate cells into the bronchial tree, making cytologic tests of little value. Grossly, these tumors are not encapsulated and rarely metastasize outside the lung, but local recurrence following resection can be a problem. Differential diagnosis should include plasma cell granuloma, hemangiopericytoma, carcinosarcoma, blastoma, and hypernephroma. Immunohistochemistry (particularly CEA and cytokeratin) may be a useful diagnostic tool.

Pulmonary sarcomas may originate within a mainstem or lobar bronchus (Fig. 8) or peripherally within the pulmonary parenchyma or may arise from major vessels. Fine-needle biopsy and fiberoptic bronchoscopy may be diagnostic for some lesions (e.g., MFH and Kaposi's sarcoma, respectively), and CT or MRI scans may be useful for others. In general, a generous biopsy is needed to secure the diagnosis.

Malignant fibrous histiocytoma of the lung is a particularly aggressive type of sarcoma. It is usually found in middle-aged men and may occur more frequently in patients who have undergone radiation therapy. The tumor is characterized by a mixture of fibroblasts and histiocytes with giant cells and inflammatory cells interspersed. Approximately 50% of patients have local or distant metastases, and the recurrence rate may approach 40%. Not surprisingly, the prognosis is poor; a combination of surgery, radiotherapy, and chemotherapy may improve survival.

Endobronchial fibrosarcomas and leiomyosarcomas have a much better prognosis than their intrapulmonary counterparts, probably because they produce symptomatic bronchial obstruction relatively early in their course and are therefore smaller when resected. Intrapulmonary sarcomas tend to have a highly malignant histologic appearance and metastasize early to hilar and mediastinal lymph nodes. Paradoxically, some fibrosarcomas attain very large size without metastases, but the great majority of these are inoperable because of involvement of adjacent intrathoracic structures.

Chondrosarcomas are rarer. Despite the presence of radiographic calcification, these lesions are not benign. An intrabronchial chondrosarcoma may appear benign on bronchoscopic biopsy only to be found to be invasive at surgery. Intrabronchial chondrosarcomas also have a better prognosis than intraparenchymal tumors. However, the overall prognosis is poor, with most patients surviving only 6 to 12 months from the time of diagnosis.

Pulmonary rhabdomyosarcomas are very rare but may be seen in congenital cystic malformation. Typically, these tumors become extremely large and invasive. They compress the surrounding parenchyma into a fibrous pseudocapsule. Histologically, rhabdomyosarcomas consist of strap-like cells with cross-striations. There are also undifferentiated round and spindle-shaped cells with cross-striations and nonstriated giant cells. The presence of desmin by immunohistochemical staining is diagnostic. The origin of striated muscle cells in the lung is a source of speculation.

Kaposi's sarcoma can be a particularly virulent tumor. Spontaneous occurrence in the lung is rare; however, it has been estimated that 35% of patients with AIDS will develop pulmonary involvement. Many patients present with hemoptysis and may have a bloody pleural effusion. Approximately 50% of patients will have a coexisting opportunistic infection. In contrast to other sarcomas in the lung, Kaposi's follows lymphatic pathways, often resulting in nodal spread. Rapid progression is not uncommon, although chemotherapy may reverse fulminant respiratory failure.

LIPOMAS OF THE BRONCHUS AND LUNG

These are among the least common of benign tumors, consisting of lobules of mature fat cells supported by a delicate fibrous stroma arising from the submucosal or interstitial adipose tissue. They can occur anywhere along the entire tracheobronchial tree. For unknown reasons, these tumors typically occur in middle-aged males.

Many patients present with obstructive symptoms. The diagnosis is difficult to establish by bronchoscopy because the pliable capsule resists the biopsy forceps. A CT scan, however, can accurately make the diagnosis based on the density coefficient of fat; distal bronchiectasis may be seen in long-standing bronchial obstruction.

Removal of the tumor through the bronchoscope may be hazardous because the bronchial wall may be perforated in the process. This technique should be limited to pedunculated lesions. Laser resection may be possible in some cases, but open bronchotomy or sleeve resection is preferable.

Even more rare is the subpleural lipoma, a tumor that may attain great size.

PULMONARY FIBROMA AND MYXOMA

Fibromas of the lung are rare and may occur endobronchially, extrabronchially, or within the lung itself. They are composed of fibrous connective tissue and may become large enough to cause bronchial obstruction, either intraluminally or by extrinsic compression. Sections of gross tumors often show trabeculae. In children, fibromas may be found in the cervical trachea. Recurrences may occur after endoscopic removal. Broad-based, sessile lesions should be removed surgically.

Pulmonary myxomas are extraordinarily rare. They look like fibromas grossly but have a gelatinous and glistening appearance on the cut section. Microscopically, there is abundant extracellular mucin between stellate cells.

PULMONARY LEIOMYOMA

These tumors are some of the most common soft-tissue tumors found in the lungs. In order of frequency, the tumors are found in the peripheral lung, small bronchi, central bronchi, and trachea. Parenchymal tumors are usually asymptomatic and may attain a large size before discovery. Lesions of the airway tend to produce obstructive symptoms and bronchiectasis. In consistency, the peripheral tumor is similar to a hamartoma; it is tough and fibrous and is readily “shelled out” of the parenchyma. Histologically, spindle-shaped cells containing smooth muscle are seen, but immunohistochemical studies and electron microscopy may be necessary to distinguish these tumors from fibromas, neurofibromas, and neurilemmomas. In general, conservative resection using bronchoscopy, laser, or sleeve resection is curative.

There have been many reports of pulmonary leiomyomata occurring in women with similar tumors of the uterus. Whether or not the pulmonary lesions represent “benign metastases” is subject to controversy, as low-grade smooth muscle metastases and primary leiomyomas are difficult to distinguish. Nevertheless, in women with pulmonary leiomyomata, a careful pelvic examination is recommended.

EPITHELIOID HEMANGIOENDOTHELIOMA

Previously known as intravascular bonchioloalveolar tumor (IVBAT), this rare, malignant tumor usually presents as small, asymptomatic, bilateral pulmonary nodules. Over 80% of patients are female, and most are less than 40 years of age. Most patients are asymptomatic, although alveolar and intrapleural hemorrhage may occur (Fig. 9). Sputum cytology is usually negative, although fine-needle biopsy may be suggestive of the diagnosis. Tumor cells typically demonstrate reactivity for factor-VIII-related antigen by immunohistochemistry, and pinocytotic vesicles are present on electron microscopy. Hence, most believe this tumor to be derived from the endothelial cell (Fig. 10).

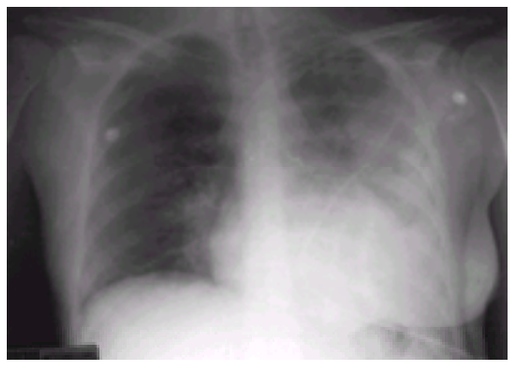

FIG. 9. Epithelioid hemangioendothelioma in a 39-year-old woman presenting with hemoptysis and intrapleural hemorrhage.

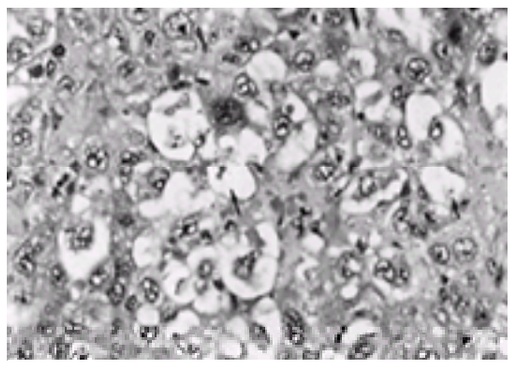

FIG. 10. Epithelioid hemangioendothelioma exhibiting irregular nests of large cells showing hyperchromatic nuclei and frequent mitotic activity. Hemorrhagic, cystic cavities are present (*arrows*); immunostaining for factor VIII was positive (H&E, ×1000). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

These tumors tend to have an indolent but progressive course. Intrapulmonary spread is not uncommon, and extension of tumor to the pleura and pericardium may occur. No effective therapy is available, although radiotherapy may provide some palliation. Hormonal therapy has been suggested, but efforts to substantiate expression of estrogen and progesterone receptors in this tumor have not been successful.

PULMONARY ANGIOMA (ARTERIOVENOUS FISTULA)

These are congenital lesions of mesodermal origin. Developmentally, this tumor may be a vascular type of pulmonary hamartoma. In 30% to 40% of cases, hereditary telangiectasia (Rendu–Osler–Weber syndrome) is present. In a number of cases, the pulmonary lesions are multiple and bilateral. These tumors have a predilection for the lower lobes and are highly variable in size, ranging from minute telangiectasis to cavernous aneurysms with a large right-to-left intrapulmonary shunt (with dyspnea, cyanosis, clubbing, and polycythemia). Diagnostic evaluation should include computed tomography and angiography.

As a result of intrapulmonary shunting, systemic thromboembolism and cerebral abscesses may occur. Furthermore, the lesions tend to increase in size with time; subpleural aneurysm formation may result in free intrapleural rupture. Surgical resection should be conservative (wedge resection or segmentectomy) because other lesions may become manifest later on. Multiple lesions have been successfully treated by angiographic embolization.

There is an acquired form of pulmonary arteriovenous fistula that results from the development of abnormal vessels in chronic liver disease and in AIDS in the form of Kaposi's tumors around the walls of intrapulmonary blood vessels. Arteriovenous malformations may also result from lung trauma.

PULMONARY HEMANGIOPERICYTOMA

Fewer than 100 cases of this tumor have been reported in the literature. They tend to occur in older patients and affect both sexes with equal frequency. Approximately one-third of patients are asymptomatic; radiographic manifestations are nonspecific, although these tumors tend to be found in the left lower lobe and have sharp contours (probably because of the presence of a fibrous capsule in many patients) (Fig. 11).

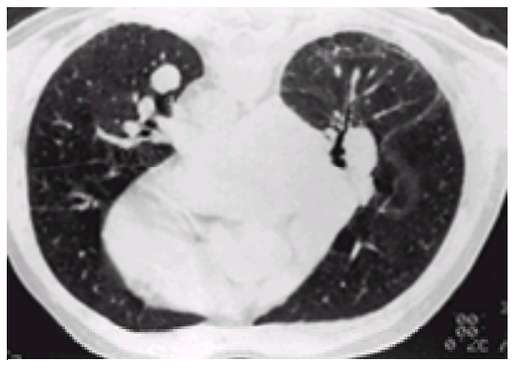

FIG. 11. Asymptomatic hemangiopericytoma of the left lower lung in a 70-year-old man.

This tumor arises from pericytes within the basement membranes of capillaries. Microscopically, “antler-like” vascular spaces are characteristic (Fig. 12). The usual size is less than 5 cm; larger tumors tend to have extensive central necrosis. Necrotic tumors over 5 cm in size, with a mitotic rate over 3 per 10 high-power fields and the presence of pleural, bronchial, or vascular invasion, are predictive of a poor prognosis, and metastases may occur in 21% of patients. Surgical resection is the treatment of choice, as radiation and chemotherapy are ineffective. The differential diagnosis should include pulmonary fibromas, metastatic sarcomas, and bronchial carcinoids.

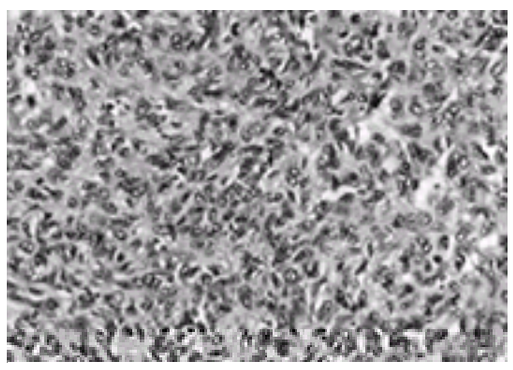

FIG. 12. Hemangiopericytoma exhibiting a fairly uniform population of spindle cells arranged in small whorls and fascicles. Intricate vascular channels that stain positive for factor VIII are present (*arrows*). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

GLOMUS TUMOR

This interesting tumor is usually seen in the extremities (particularly the nail beds) and is thought to be derived from cells of a special arteriovenous shunt, the Sucquet–Hoyer canal, which may be a temperature-sensitive regulator of blood flow. Ectopic tumors from these cells have been described in the lungs and, occasionally, the trachea. Microscopically, the tumor appears similar to carcinoids and hemangiopericytomas. A variable nuclear cytoplasmic border resembling a “chicken-wire” pattern is characteristic. Electron microscopy is helpful, as neurosecretory granules are absent.

PULMONARY PLASMA CELL GRANULOMAS (HISTIOCYTOMAS)

Also known as inflammatory pseudotumor, xanthoma, fibroxanthoma, and mast-cell granuloma, this tumor is known for its controversial nosology. Most authorities

believe this tumor to be reactive; others feel the tumor to be neoplastic, with the originating cell either a myofibroblast or a low-grade B-cell lymphoma. Nearly half of the patients with this disease have a history of prior lung infections. Men and women of all ages tend to be afflicted with equal frequency. The lesions are usually solitary, asymptomatic, and commonly appear either as a circumscribed nodule or an ill-defined mass on chest x-ray. Bronchoscopy and fine-needle biopsy are not useful. Rarely, these lesions may become very large and invade the pleura, mediastinum, diaphragm, chest wall, or vertebral bodies. Metastases do not occur.

Microscopically, plasma cell granulomas contain mature plasma cells and lymphocytes within a framework of granulation tissue. Mast cells may also be present, but true giant cells are rare. Although plasma cell granuloma has been associated with multiple myeloma, immunohistochemical studies show a polyclonal infiltrate.

Treatment is primarily surgical, although some lesions have been known to regress spontaneously. Conservative resection is curative, and recurrences are rare.

SCLEROSING HEMANGIOMA OF THE LUNG

This rare but fascinating tumor has been reviewed extensively by Dail. It is usually a benign lesion presenting as a solitary nodular (less than 5 cm in 90% of cases) density with some predilection for the lower lobes. Over 80% of the patients are female, and the majority are asymptomatic. Hemoptysis is the most common presenting sign. There are no specific radiographic features.

Grossly, these tumors are well circumscribed and can be shelled out from adjacent lung parenchyma. Microscopically, the pattern may be variable but most commonly consists of tumor surrounded by extensive fibrosis and dilated vascular spaces that are filled with blood. Cholesterol clefts and hemosiderin-laden macrophages may also be seen. Originally, this histology led to a theory of endothelial cell origin. However, there have been many immunohistochemical and electron microscopic studies that do not support endothelial differentiation. Instead, many of these studies have demonstrated the presence of surfactant apoprotein in the tumor cells, and most now believe this tumor to be epithelial in nature, originating from type II pneumocytes. In the past, sclerosing angioma has been confused with plasma cell granulomas (histiocytoma), which are also called fibroxanthomas because of fibrosclerotic tissue, cholesterol spaces, and fat-filled macrophages. These degenerative changes occur in both tumors. The difference is the absence of plasma cells in sclerosing angiomas.

Sclerosing hemangiomas may involve adjacent lymph nodes, but they do not metastasize. Malignant variants have been reported and are usually multiple lesions. As a rule, conservative resection is curative, and recurrences are unusual.

PULMONARY RETICULOSES

Lymphoproliferative disorders usually involve the lung secondarily. Primary lesions do occur (Fig. 13), as the lung contains an extensive system of lymphoid tissue. Although generalization is difficult, one concept proposes that the lung contains a specific, bronchial-associated lymphoid tissue (BALT) that has the capacity to form a spectrum of lymphoid proliferations. This spectrum includes follicular hyperplasia of the bronchial wall, nodular hyperplasia (“pseudolymphoma”), and diffuse lymphoid hyperplasia (“lymphoid interstitial pneumonitis”). The latter has been associated with a viral etiology, particularly Epstein–Barr virus and human immunodeficiency virus. Primary lymphomas of the lung are usually low-grade and originate from B-cell lines. Symptoms, signs, and radiographic features are nonspecific. Examination of sputum cytology or fine-needle aspirates for various immunologic markers may be diagnostic. Grossly, primary lung lymphomas usually do not involve the hilar lymph nodes and tend to be surrounded by cytologically benign infiltrates. Large lesions usually exhibit extensive necrosis. Solitary, circumscribed lung lesions may benefit from resection with excellent long-term survival.

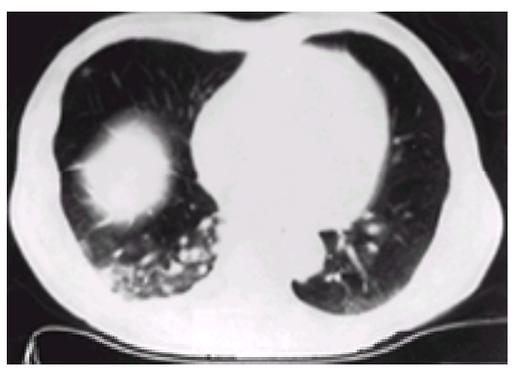

FIG. 13. Primary pulmonary lymphoma presenting as a bilateral nodular infiltrate in the lower lobes.

Pseudolymphomas have true lymphoid germinal centers within a massive infiltrate of well-differentiated lymphocytes and other inflammatory cells. In contrast to malignant lymphomas, the bronchus is spared, leading to characteristic air bronchograms on chest x-ray. Lymphomas, on the other hand, show a uniform cellular infiltrate of poorly differentiated lymphocytes without true germinal centers (Fig. 14).

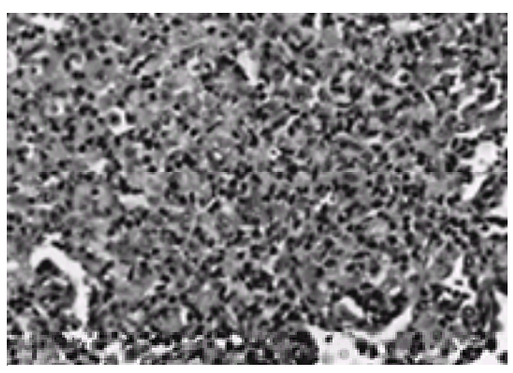

FIG. 14. Open-lung biopsy specimen showing pulmonary lymphoma of a mixed small cleaved and large cell type (material from the patient in Fig. 13). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Subpleural lymph nodes may become enlarged (lymphoid hyperplasia), to be visualized on chest x-ray. The presence of dust-laden histiocytes suggests an environmental etiology. A rare form of diffuse benign intrapulmonary lymphoid hyperplasia also has been described.

Giant intrathoracic lymph nodes occasionally arise at the pulmonary hilum without coexisting pulmonary or mediastinal disease. They may be associated with fever or anemia. In the past, they have been mistaken for thymomas on chest x-ray and histologically.

The lung is also frequently involved with other generalized diseases of the reticuloendothelial system, such as leukemia and histiocytosis X. The latter has a characteristic ring-like appearance on high-resolution chest CT. Lung biopsy may be required to establish the diagnosis in these conditions.

HAMARTOMAS OF THE LUNG

A pulmonary hamartoma is a noninvasive malformation originating from elements normally found in lung tissue. Although the histogenesis is unclear, most investigators feel that hamartomas are not congenital and are true neoplasms. As a group, these tumors are perhaps the most common benign tumors of the lung, accounting for over 60% of benign lesions in one series and estimated to be present in 0.25% of the general population. Men are afflicted more commonly than women, and over 80% are asymptomatic. These tumors are usually found in the periphery of the lung; radiographically, their borders are lobulated and sharp, and speckled calcifications may be seen, giving the appearance of “popcorn.” Some 20% may be endobronchial, resulting in obstructive symptoms (Fig. 15 and Fig. 16). Chest CT scans may be

useful by demonstrating fat within the tumor, and fine-needle aspiration is diagnostic in a high percentage of cases.

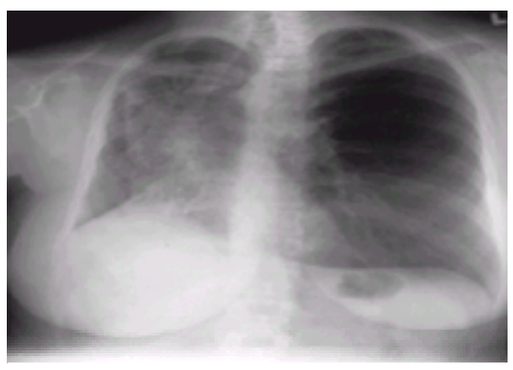

FIG. 15. Endobronchial hamartoma originating in the right middle lobe, resulting in near-complete obstruction of the right mainstem bronchus.

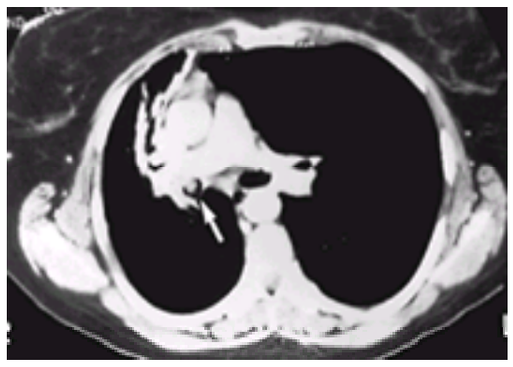

FIG. 16. Endobronchial hamartoma occupying the right mainstem bronchus (*arrow*).

The typical hamartoma contains a mixture of cartilage, fat, smooth muscle, epithelial, and mesenchymal cells (Fig. 17). Growth is slow, with an estimated doubling time of 14 years. Although malignant transformation has been reported, it is exceptional. However, typical bronchial carcinoma may coexist, particularly in high-risk individuals. Excision of hamartomas is recommended if carcinoma cannot be excluded or if growth rates on serial radiographs are excessive. The majority of tumors can be enucleated or removed by conservative resection.

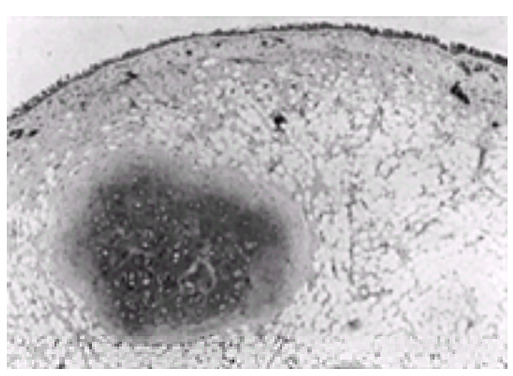

FIG. 17. Section of an endobronchial hamartoma showing typical features of epithelial border and smooth muscle and fat cells. A focus of cartilage is seen centrally (H&E, ×100). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

There is a special instance of a very aggressive tumor, adenomatous hamartoma of infancy, also known as cystic adenomatoid formation, in which an entire lobe or lung is filled with cystic spaces lined with bronchiolar epithelium, with a disorganized arrangement of dilated bronchioles and alveolar spaces. Air trapping within cysts may produce dramatic distention of the opposite lung. Pulmonary resection is urgently indicated in these infants.

PULMONARY BLASTOMA (EMBRYOMA)

Pulmonary blastomas are rare, malignant tumors of mixed epithelial and mesenchymal composition that are believed to recapitulate the fetal lung at 10 to 16 weeks of gestation. A bimodal age distribution is apparent, with an initial peak during the first decade and a later peak in the seventh decade. The tumor may be found in a peripheral or central location, with occasional endobronchial extension. Over 40% of patients are asymptomatic, and radiographic findings are not specific. Diagnosis by fine-needle aspiration has been described.

Grossly, these tumors are usually sharply circumscribed but may contain areas of extensive necrosis. Histologically, the tumor consists of undifferentiated embryonic connective tissue lined by vacuolated columnar epithelium, simulating fetal bronchioles. The epithelial component may form cell balls or “morulae,” which appear similar to squamous metaplasia. Theories of histogenesis must explain how these tumors involve two germ-cell lines. Most pathologists believe that the tumor arises from a single cell type that then differentiates in several directions.

The overall prognosis is poor, with only 50% of patients surviving 5 years. Most patients die of extrathoracic metastases. Combination chemotherapy may be useful in pediatric patients.

INTRAPULMONARY TERATOMAS (DERMOID CYSTS OF THE LUNG)

True, primary intrapulmonary teratomas are exceedingly rare; one must first exclude direct extension from the mediastinum or metastasis from germ-cell tumors in other locations (particularly the testes). Most lesions are found in the left upper lobe, and growth is very slow. They may be solid or cystic and contain tissue derived from all germ layers. They contain hair, sebum, pancreatic, and other tissue. One-third to one-half of these tumors have been classified as malignant on the basis of histologically immature cells. However, pulmonary teratomas rarely behave aggressively.

CARCINOSARCOMA

Carcinosarcoma is a rare tumor, accounting for 0.2% of all pulmonary neoplasms. It is composed of both carcinomatous and sarcomatous elements and is usually found in older men, commonly in the upper lobes. Many patients present with evidence of metastatic disease in patterns similar to traditional lung carcinoma. Endobronchial spread is very common.

Histologically, the epithelial component is usually squamous cell carcinoma, under which there is a cellular, spindle-cell stroma with bone or cartilage. The prognosis is poor, with death occurring within a year of initial diagnosis in the majority of patients.

TUMORS METASTATIC TO THE LUNGS

The lungs are the most frequent site of metastases from nearly all organs, and up to 20% of patients dying of pulmonary metastases have no tumor elsewhere. Carcinoma of the colon, kidney, breast, testis, uterus, head and neck, and ovary, as well as sarcomas and melanomas, are especially prone to metastasize to the lungs. Except for abdominal visceral organs whose venous drainage is directly through the portal system, the lungs are the first organ to filter venous blood. Blood-borne metastases account for the majority of secondary pulmonary malignancies. Tumor also may reach the lungs through lymphatic spread or by direct extension.

Over 80% of patients are asymptomatic; typically, peripheral lung nodules are found on screening chest films obtained during follow-up of the original tumor. The tumors are commonly multiple and bilateral. However, isolated lesions may occur, and it is important to distinguish these from benign lesions and/or primary bronchogenic carcinoma. Fine-needle biopsy can be helpful in these situations, but sputum cytology, bronchoscopy, and mediastinoscopy are usually low-yield. In general, new solitary lesions found in patients with a history of breast or head and neck cancers are most likely primary lung carcinomas. New lung lesions in patients with previous colon cancer are equally likely to represent primary lung carcinoma or metastatic disease, whereas new lung nodules in patients with prior sarcomas or melanomas are almost always metastatic. Rarely, tumors of the breast, colon, or kidney may present as endobronchial metastases, producing obstructive symptoms.

In order to consider resection of metastatic pulmonary nodules, one must first establish that the primary tumor is under control. Second, there must be no evidence of extrapulmonary metastases, and third, resection must not severely compromise lung function. Once these criteria have been satisfied, a chest CT scan should be obtained to investigate the number and laterality of the lesions (Fig. 16 and Fig. 17). Although the number of metastatic lesions, the disease-free interval, tumor histology, and tumor-doubling time have been positively correlated with overall survival, patient selection should not be absolutely dependent on these factors. The overall 5-year survival following resection of pulmonary metastases is approximately 35%.

Because one-third of patients with unilateral disease of chest CT scan are found to have bilateral nodules during surgery, many investigators recommend a median sternotomy approach so that both lungs can be evaluated. Functional disability may be less with this incision, and it may facilitate resection of future recurrences. However, overall survival is not affected by the type of incision. Wedge resection of the metastatic deposits is satisfactory in the majority of patients. More aggressive resections (e.g., pneumonectomy) are sometimes indicated for complete local control of disease. Should recurrent disease develop, some patients, particularly those with metastatic soft-tissue sarcomas, may benefit from repeat resection.

Approximate 5-year survival rates according to tumor histology are presented in Table 1. One particularly interesting metastatic tumor is the so-called benign metastasizing giant-cell tumor. This lesion usually contains a mixture of mono- and multinucleated giant cells and is characteristically found in the distal radius. Although histologically benign, the tumor may spread to the lungs, particularly after a local recurrence of the primary lesion (Fig. 18 and Fig. 19). Spontaneous regression of the pulmonary lesions has been reported; however, surgical resection is indicated for definitive diagnosis and to prevent complications of local growth.

Histology	5-year survival (%)
Teratoma	84
Uterus	54
Kidney	54
Head and neck cancer	47
Osteosarcoma	46
Soft-tissue sarcoma	33
Breast	27
Carcinoma	24
Colon	23
Melanoma	4

TABLE 1. *Actuarial survival according to tumor histology*

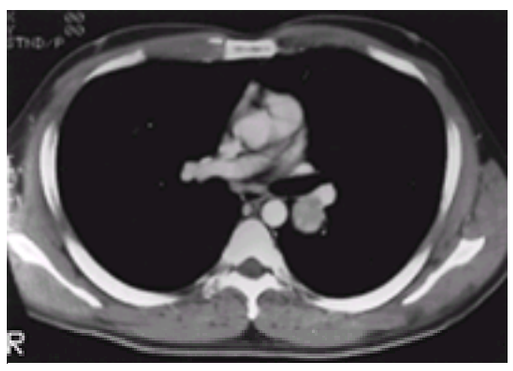

FIG. 18. Well-circumscribed focus of metastatic giant-cell tumor originating from the olecranon process.

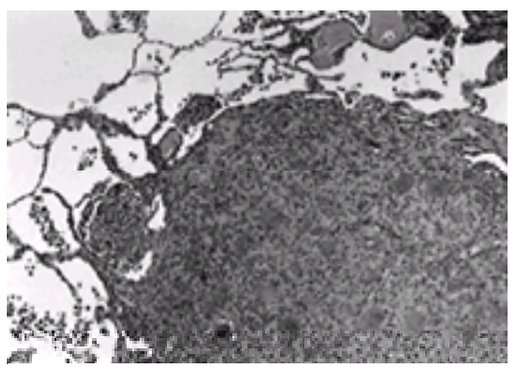

FIG. 19. Metastatic pulmonary giant-cell tumor showing prominent multinucleated cells within a benign architecture. (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Despite optimistic results for several tumors, surgical resection for pulmonary metastases should still be considered palliative. Most patients will die of local recurrence or systemic spread of the primary lesion. The role of adjuvant chemotherapy is not yet clearly defined, but patients with metastatic osteosarcoma may benefit.

ACKNOWLEDGMENTS

Unless otherwise stated, photomicrographs are courtesy of the Department of Pathology, University of California, San Francisco.

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CHAPTER

70 Tumors of the Mediastinum, Pleura, Chest Wall, and Diaphragm

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TUMORS AND CYSTS OF THE MEDIASTINUM

The embryologic development of the mediastinum produces a number of closely opposed structures of different germ layer origins. Mediastinal masses may therefore have distinctly different histologies and predilections for specific locations. There are also major differences in the patterns of occurrence between adults and children. Advances in radiographic imaging techniques, isotope scanning, and tumor markers have made important contributions to the management of mediastinal masses over the past decade.

The mediastinum consists of all structures between the two pleural cavities and is bounded superiorly by the thoracic inlet and inferiorly by the diaphragm. For purposes of discussion, it is customary, by drawing lines on the lateral projection of a chest x-ray, to divide the mediastinum into three compartments (Fig. 1). This compartmentalization is clinically useful because of the predilection of certain tumors to arise within circumscribed areas. The posterior compartment is delineated by a line drawn along the posterior pericardial border and continued upward along the anterior borders of the thoracic vertebral bodies. A second line may be drawn along the anterior pericardial border and continued upward along the anterior surface of the tracheal air shadow in order to create two additional compartments, the anterior mediastinum and the middle mediastinum. In some texts, the anterior mediastinum is further subdivided into superior and inferior subcompartments, but the overlap of tumors such as thymomas between these subdivisions is so great as to limit the usefulness of this refinement.

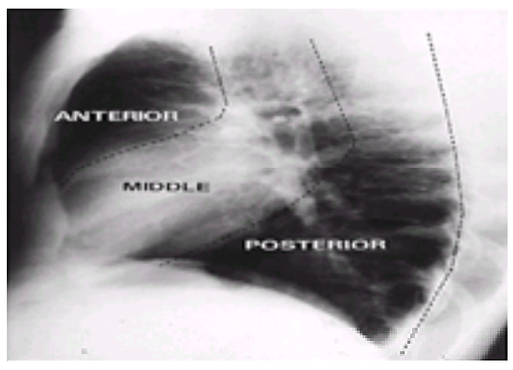

FIG. 1. Lateral chest x-ray film demonstrating the three compartments of the mediastinum. (Reproduced from Sabiston DC Jr, Oldham HN Jr, The mediastinum. In: Sabiston DC Jr, Spencer FC, eds. *Gibbon's Surgery of the Chest,* 4th ed. Philadelphia: WB Saunders, 1983.)

The anterior compartment contains the thymus, ascending aorta, innominate artery and vein, superior vena cava, fat, and lymph nodes. Over 50% of mediastinal masses occur in this compartment. The middle mediastinum contains the heart, pericardium, aortic arch and branches, bronchi, upper esophagus, trachea, and mediastinal lymph nodes. The posterior mediastinum contains the lower esophagus, descending aorta, sympathetic chain, and intercostal nerves and accounts for 25% of all mediastinal masses.

The most common lesions of the anterior mediastinum are thymic neoplasms, lymphomas, and germ-cell tumors, which account for nearly 60% of tumors in this compartment. It is not uncommon for these tumors to enlarge and occupy the middle compartment as well. Masses in the middle mediastinum are primarily cystic; 25% of lesions are metastatic malignancies to lymph nodes (lymphoma, carcinoma). In most reports, 70% of lesions within the posterior compartment are either neurogenic in origin or cystic. In children, neurogenic tumors are more common, and thymomas are rare.

Approximately 30% of mediastinal masses are malignant, with lymphomas, primary carcinomas, malignant thymomas, and malignant germ-cell tumors representing the majority. Malignant lesions are more common in children and between the ages of 20 to 40; several authors have reported increasing numbers of malignant mediastinal lesions coinciding with the increased incidence of lymphomas. The presence of symptoms is also predictive of malignancy.

Approximately 60% of patients with a mediastinal mass will have symptoms. Nevertheless, a large proportion of patients will have benign lesions discovered on routine x-rays. Chest pain, dyspnea, cough, and fever are the most common presenting symptoms. Many tumors will produce systemic syndromes as the result of hormone secretion. For example, excessive ACTH production by mediastinal carcinoids can produce Cushing's disease, and mediastinal pheochromocytoma may produce hypertension. In addition, thymomas have a poorly understood association with myasthenia gravis, red-cell aplasia, and collagen vascular disorders.

In addition to a careful history and physical examination, patients with a suspected mediastinal mass should have a routine chest x-ray and contrast-enhanced computed tomography. These two studies will identify the size, location, and composition of the lesion in the majority of cases. Magnetic resonance imaging (MRI) may help to distinguish vascular from soft-tissue masses in some cases and radiation fibrosis from neoplastic lesions. Several radioisotope scans may accurately localize occult, functional mediastinal tumors. Examples include ^{131}I-*meta*-iodobenzylguanidine (MIBG) to detect pheochromocytomas and technetium–thallium studies for the localization of ectopic parathyroid adenomas. Numerous mediastinal tumor markers have been reported, but only a-fetoprotein (nonseminomatous germ-cell tumors) and human chorionic gonadotropin (teratomas) are clinically useful.

Fine-needle biopsy has been used with accuracy to diagnose mediastinal masses. Occasionally, mediastinoscopy is required to provide sufficient tissue for definitive

diagnosis (e.g., lymphoma). In selected patients, video-assisted thoracoscopy may be diagnostic and therapeutic.

Although they also occur within the boundaries of the mediastinum, tumors and aneurysms of the thoracic aorta, trachea, esophagus, and heart are traditionally discussed as separate topics.

Classification of Mediastinal Tumors

Davis, Oldham, and Sabiston classify mediastinal tumors according to tissues of origin as follows:

1. Neurogenic tumors
    a. Neurofibroma
    b. Neurilemmoma
    c. Neurosarcoma
    d. Ganglioneuroma
    e. Ganglioneuroblastoma
    f. Neuroblastoma
    g. Chemodectoma
    h. Pheochromocytoma
2. Thymomas
    a. Benign
    b. Malignant
3. Lymphomas
    a. Hodgkin's disease
    b. Lymphoblastic lymphoma
    c. Large-cell diffuse growth pattern
        i. T-immunoblastic sarcoma
        ii. B-immunoblastic sarcoma
        iii. Sclerosing follicular cell
4. Germ-cell tumors
    a. Teratodermoid tumors
        i. Benign
        ii. Malignant
    b. Seminoma
    c. Nonseminomas
        i. Embryonal carcinoma
        ii. Choriocarcinoma
        iii. Endodermal
5. Primary carcinomas
6. Mesenchymal tumors
    a. Fibroma/fibrosarcoma
    b. Lipoma/liposarcoma
    c. Myxoma
    d. Mesothelioma
    e. Leiomyoma/leiomyosarcoma
    f. Rhabdomyosarcoma
    g. Xanthogranuloma
    h. Mesenchymoma
    i. Hemangioma
    j. Hemangioendothelioma
    k. Hemangiopericytoma
    l. Lymphangioma
    m. Lymphangiomyoma
    n. Lymphangiopericytoma
7. Endocrine tumors
    a. Intrathoracic thyroid
    b. Parathyroid adenoma
    c. Carcinoid
8. Cysts
    a. Pericardial
    b. Bronchogenic
    c. Enteric
    d. Thymic
    e. Thoracic duct
    f. Nonspecific
9. Giant lymph node hyperplasia
    a. Castleman's disease
10. Chondroma
11. Extramedullary hematopoiesis

A number of nonneoplastic lesions, particularly of the middle and posterior compartments, must be considered in the differential diagnosis of mediastinal masses. These include hiatal hernias, esophageal diverticula, meningoceles, and infections (mediastinitis, paravertebral abscess). An accurate differentiation should be possible in the majority of cases.

Neurogenic Tumors

Tumors that arise from intercostal nerve sheaths (neurilemmoma, neurofibroma), autonomic ganglia (ganglioneuroma, ganglioneuroblastoma), or paraganglionic nervous system (chemodectoma, pheochromocytoma) account for 20% to 25% of all mediastinal tumors in adults and 35% to 50% of mediastinal tumors in children. The etiology of these tumors is unknown, and most are thought to occur spontaneously. However, approximately 25% to 40% of patients with neurofibromas will have von Recklinghausen's disease. Ninety percent of neurogenic tumors arise in the posterior mediastinum, typically along the paravertebral gutter, where the sympathetic chains and the origins of intercostal nerves are located. Seventy-five percent of all posterior mediastinal tumors are neurogenic.

Although the great majority of neurogenic tumors in adults are benign, approximately 1% to 4% are malignant. Neurogenic tumors associated with von Recklinghausen's disease are more likely to be malignant. In contrast, most neurogenic tumors in children are malignant.

Approximately half of all benign and malignant neurogenic tumors are asymptomatic, being discovered incidentally on chest x-rays. The classic appearance is that of a round, smooth, homogeneous mass with sharp margins lying in the posterior mediastinum abutting the vertebral bodies (Fig. 2). The part that reaches the chest wall is flattened, lending a “D” shape to the tumor, a feature that is best appreciated on the lateral or appropriate oblique projection. The benign forms of these tumors usually increase in size slowly over a long period, whereas the malignant tumors tend to enlarge rapidly. Pain and cough are symptoms of local extension and compression. Some tumors enlarge sufficiently to cause dyspnea (Fig. 3). Catecholamine secretion from paraganglionic tumors may produce hypertension, headaches, sweating, and palpitations. Secretion of vasoactive intestinal polypeptide by ganglioneuromas and neuroblastomas may produce profuse, watery diarrhea.

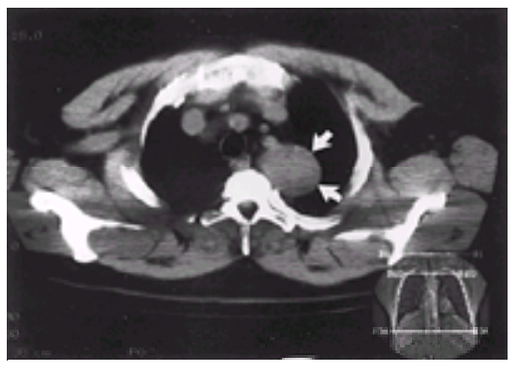

FIG. 2. Chest computed tomographic scan showing a neurilemmoma of the posterior mediastinum *(arrows)* in a 44-year-old man with back pain.

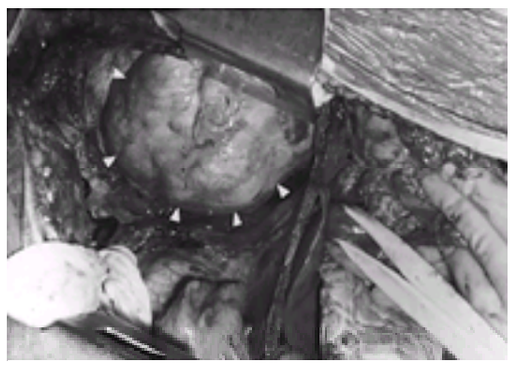

FIG. 3. Operative photograph of a large ganglioneuroma occupying most of the pleural space and producing dyspnea.

Approximately 10% of neurogenic tumors will extend medially through the intervertebral foramen to form “dumbbell” tumors (Fig. 4). These are almost always symptomatic, with back pain, intercostal radicular pain, or signs of spinal compression. Typically, a CT scan will demonstrate erosion of the intervertebral neuroforamen, pedicles, and facets. In this situation, MRI scanning is indicated, as it will more effectively demonstrate intraspinal extension of tumor and spinal cord involvement. If MRI is not available, then myelography should be performed. Current treatment of dumbbell tumors consists of a single-stage combined laminectomy and thoracotomy for complete removal of tumor.

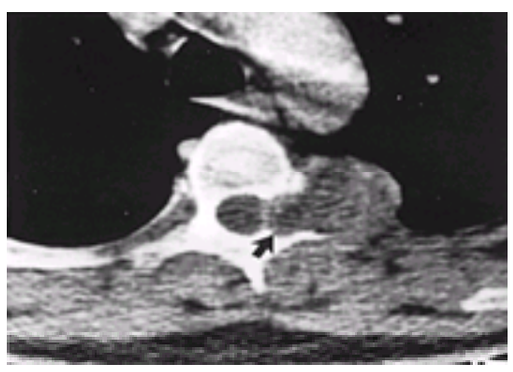

FIG. 4. Chest computed tomography scan showing a neurogenic tumor extending into the intervertebral foramen, forming a “dumbbell” *(arrow)*.

Neurofibromas and *neurilemmomas* account for the great majority of all neurogenic tumors. The former is thought to represent a metaplastic derivative of Schwann cells; it occurs sporadically and in association with phacomatoses (von Recklinghausen's disease, tuberous sclerosis, von Hippel–Lindau disease, etc.) and may arise from any nerve in the thorax. Neurofibromas contain all of the elements of the nerve trunk, including axons and connective tissue. Grossly, a true capsule is usually absent, and on histologic examination, cellular palisading is absent. Immunohistochemical stains will demonstrate S-100 protein, indicating a nerve sheath origin. Because of the propensity for continued slow growth and malignant potential, surgical resection is recommended for all neurofibromas. Complete removal should be considered curative; a plexiform variant may be locally aggressive and difficult to control.

Neurilemmomas are derived from Schwann cells, which encase each axon cylinder of peripheral nerves. In addition to von Recklinhausen's disease, this lesion is also associated with Noonan's syndrome. Histologically, two separate morphologies have been described. Antonio type A is characterized by palisading nuclei within a dense cytoplasmic stroma. Antonio type B typically reveals a loose, myxomatous stroma with areas of hemorrhage (Fig. 5). As with neurofibromas, surgical resection is recommended, and the prognosis is excellent.

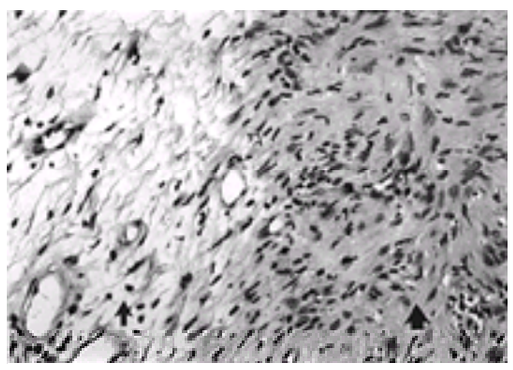

FIG. 5. Neurilemmoma showing Antonio type A *(large arrow)* and type B *(small arrow)* (H&E stain, ×660). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Rarely, malignant degeneration of either neurofibromas or neurilemmomas may occur, giving rise to a neurosarcoma (malignant schwannoma). This lesion may synthesize an insulin analog capable of producing hypoglycemia. Complete resection is possible in only 50% of patients; local recurrence is common, and long-term survival is rare. Radiotherapy may be useful for palliation.

Ganglioneuromas are common benign tumors that arise from peripheral nerve cells of the sympathetic chain (Fig. 6). They occur more frequently in children. Microscopically, they consist of ganglion cells containing three or four nuclei within a stroma of medullated and nonmedullated nerve fibers, connective tissue, and Schwann cells (Fig. 7). Ganglioneuromas may undergo malignant degeneration either into a partially differentiated *ganglioneuroblastoma,* which contains immature sympathetic nerve cells and mature ganglion cells, or into a completely undifferentiated neuroblastoma, which is composed of small lymphocyte-like cells frequently arranged into rosettes. Neurosecretory granules are present on electron microscopy. Although both lesions are seen most often in children, neuroblastomas are much

more common, accounting for 15% of annual pediatric cancer deaths. Only a minority of patients have disease confined to the chest at the time of presentation. In addition to cough, pain, and dyspnea, neuroblastomas can produce catecholamines (which cause hypertension and sweating) or vasoactive intestinal polypeptide (resulting in watery diarrhea) and have been associated with an autoimmune condition known as “opsoclonus-polymyoclonus syndrome.” Serum ferritin levels correlate with the presence of active tumor.

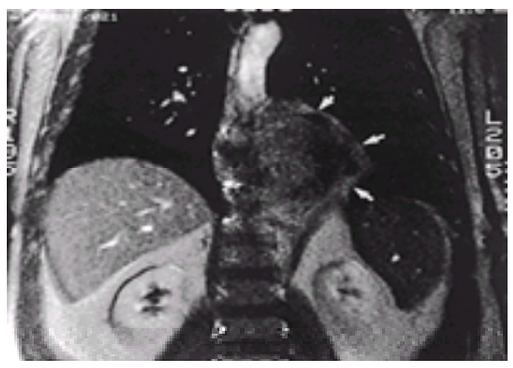

FIG. 6. Magnetic resonance image of a large, smptomatic ganglioneuroma *(arrows)* in a 47-year-old man. Figure 70-3 shows the operative picture.

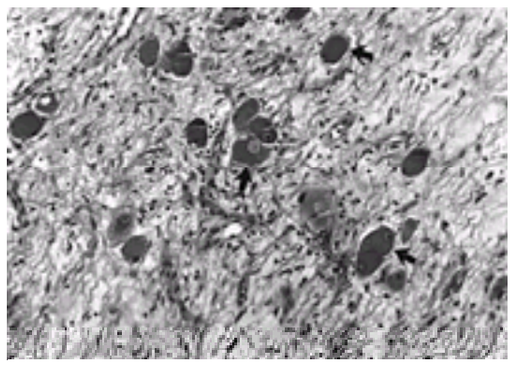

FIG. 7. Ganglioneuroma showing prominent ganglion cells *(arrows)* within a background of loose connective tissue stroma (H&E stain, ×500). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

The treatment of minimally invasive ganglioneuroblastomas is primarily surgical, with an expected 5-year survival of nearly 90%. For neuroblastomas, prognosis is dependent on the age of the patient, the histologic grade of the tumor, tumor location (better prognosis for disease limited to the chest), tumor DNA content, and the presence of certain biological markers (e.g., *N-myc* gene amplification). There is evidence to suggest genetically different subtypes of neuroblastomas, which may explain observed differences in prognosis. For early-stage lesions, resection can effect a cure; only 10% of patients with disseminated neuroblastoma will be disease-free at 2 years. Combination chemotherapy and radiotherapy can achieve good response rates for advanced disease. Autologous bone marrow transplantation has also been used with some success. On rare occasions, neuroblastomas have regressed spontaneously.

Mediastinal paragangliomas are rare lesions, accounting for approximately 1% of all mediastinal tumors. Included in this group are carotid body tumors, chemodectomas, glomus tumors, and pheochromocytomas. All are capable of storing catecholamines intracellularly; pheochromocytomas are best known for their secretory function. Multiple lesions may be present in the 10% of patients with the multiple endocrine neoplasia syndrome (MEA types II, III). Pathologically, these tumors are quite vascular, and immunohistochemical staining will distinguish them from neurogenic tumors. For secretory lesions, symptoms of catecholamine excess are characteristic. Measurement of urinary catecholamines will establish the diagnosis. Chest CT scans and ^{131}I-MIBG scans will localize the majority of pheochromocytomas. Surgical resection is curative for benign paragangliomas; even with benign histology, some lesions will behave aggressively, and 5-year survival approaches 50%.

Thymoma

Several neoplastic conditions may involve the thymus gland, including thymoma, thymic carcinoma, and carcinoid. Of these, thymoma is by far the most common. The normal thymus gland is composed of a mixture of epithelial cells and lymphocytes. Although the great majority of thymomas contain a mixture of these cell types, and though the lymphocytes are predominant, it is the epithelial cells that are neoplastic. It is true that a lymphoma also may occur in the thymus gland as a primary tumor or as a part of systemic disease, but in those cases the lymphocytes and not the epithelial elements are neoplastic. Several schemes have been proposed for the classification of thymomas, based on the degree of invasion (stages I to IV; Table 1) and histology (cortical, medullary, mixed; Table 2). The former is most widely accepted, but both have prognostic utility.

Stage	Descriptor	Proportion of cases	5-year survival (%)
I	Completely encapsulated tumor without evidence of capsular invasion	40	96–93
II	Gross or microscopic extracapsular extension of tumor into adjacent fat or pleura	14	70–85
III	Gross invasion of 3/4 adjacent organs (pericardium, great vessels, etc.)	34	58–72
IVa	Diffuse, metastatic disease involving the pleura or pericardium	9	50–60
IVb	Distant metastases	3	24

TABLE 1.*Staging system for thymoma based on tumor spread*

Histopathology	Proportion of patients (%)	5-year survival (%)
Cortical	41	52
Medullary	12	100
Mixed	46	85

TABLE 2.*Staging of thymoma basedon tumor histopathology*

Thymomas comprise 10% to 20% of all mediastinal tumors. Rare in childhood, thymomas increase in incidence with age. There is an equal sex distribution. Most of these tumors are located centrally in the anterior mediastinum (Fig. 8), but they also may occur laterally in the middle mediastinum when a tumor in the inferior pole of the gland enlarges and descends along the border of the pericardium.

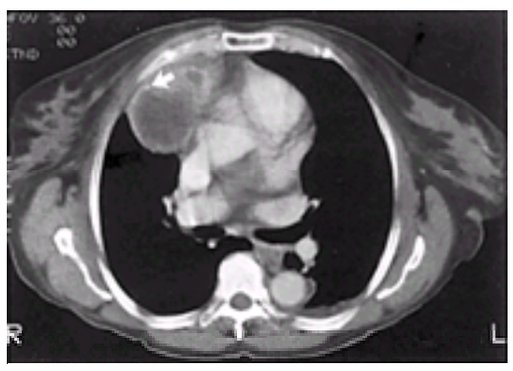

FIG. 8. Invasive thymoma in a patient with chest pain and arthralgias. Calcium is present within the mass *(arrows).*

Fifty percent of patients are asymptomatic. Approximately 25% have cough, dyspnea, or chest pain. Superior vena caval obstruction is usually a sign of malignancy. Approximately 25% to 35% have an associated paraneoplastic syndrome, and myasthenia gravis is the most frequent.

From 10% to 50% of thymomas are associated with myasthenia gravis, whereas approximately 10% to 15% of patients with myasthenia will be found to have a thymoma at surgery. In the past, the occurrence of myasthenia in patients with a thymoma was thought to have a negative impact on survival. With improvement in drug therapy and plasmapheresis, this is no longer true. Myasthenia has been observed more frequently with certain histologic types of thymoma. A number of other autoimmune or immune phenomena have been associated with thymomas. Among the most common are red cell hypoplasia (virtual absence of erythroblasts and reticulocytes in the bone marrow), hypogammaglobulinemia, systemic lupus erythematosus, and Cushing's syndrome. Red cell hypoplasia occurs in 5% of thymomas. However, 50% of all cases of red cell hypoplasia are associated with thymoma. Hypogammaglobulinemia occurs in a smaller percentage of thymomas, but approximately 10% of patients with this condition also have a thymoma. Cushing's syndrome is associated with carcinoid tumors of the thymus.

Standard chest radiographs in patients with thymomas typically show a smooth, lobulated mass located in the anterior mediastinum. Calcification within the mass may be present. Retrospective examination of serial roentgenograms suggests that thymomas usually enlarge slowly over a long period. Thymomas associated with myasthenia gravis are usually smaller than average. In fact, many are discovered incidentally during thymectomy intended for the relief of myasthenic symptoms. Magnetic resonance imaging is useful in determining the relationship of large tumor to the great vessels; a lobulated internal architecture may be associated with malignancy. One must always be aware of the “thymic rebound” phenomenon, which typically occurs after chemotherapy for lymphoma. The chest CT scan reveals symmetric thymic enlargement, consistent with hyperplasia. Biopsy may be necessary in these situations.

Grossly, thymomas are encapsulated, lobulated tumors. Degenerative changes are often found, including focal hemorrhage, calcification, and cyst formation. On cut section, the grayish-tan tumor is frequently compartmentalized by fibrous septa. Although thymomas are commonly adherent to adjacent structures, frank invasion occurs in only 20% to 40% of patients.

Microscopically, a mixture of epithelial cells and lymphocytes may be found. The epithelial cells are either round, oval, or elongated, with vesicular nuclei and indistinct cell margins (Fig. 9), whereas the lymphocytes are normal in appearance. Rosettes are formed in 20% of cases, and Hassal's corpuscles (keratinized epithelial cells) are frequently present. With a predominance of epithelial cells, the lesion is called an epithelial thymoma; when the epithelial cells assume a fusiform shape, the lesion is termed a spindle-cell thymoma; a predominance of lymphocytes is termed a lymphocytic thymoma. These groups occur with equal frequency; however, myasthenia is more commonly seen in association with lymphocytic thymomas, and red cell hypoplasia is more common in association with spindle lesions.

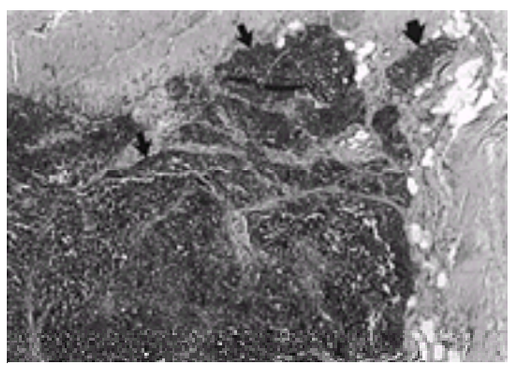

FIG. 9. Invasive lymphocytic thymoma showing characteristic tumor lobules *(small arrows).* A focus of invasive tumor is seen *(large arrow)* (H&E stain, ×132). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Surgical resection is recommended for most thymomas. *En bloc* removal of the tumor and surrounding tissue through a sternotomy incision is the most common practice, although thoracoscopic approaches have been used. Often, the distinction between a benign and malignant lesion is made at operation, with the finding of tumor invasion. Even without gross evidence, microscopic invasion is seen in 20% of tumors. The 5-year survival for stage I disease is approximately 90% (Table 1). Several studies have shown that oncogene protein expression or tumor DNA content may predict outcome. However, the most accurate indicator of long-term prognosis is the degree of tumor invasion. For advanced lesions or recurrences, radiotherapy and/or cisplatin-based chemotherapy can extend survival. Thymectomy improves the symptoms of myasthenia in a approximately 25% of patients with thymomas; nearly twice as many myasthenic patients without thymomas will improve with thymectomy. Red cell hypoplasia is rarely helped by thymectomy, and hypogammaglobulinemia never is.

Lymphomas

As a group, the lymphomas represent approximately 20% of all adult mediastinal malignancies; this number doubles in children. The incidence of malignant mediastinal lesions has increased, primarily as a result of an increase in the number of lymphomas. The majority of mediastinal lymphomas are found in the anterior and middle compartments, arising from nodal tissue in association with systemic disease. Occasionally, the primary tissue of origin is the thymus, thyroid, or heart. The classification of lymphomas is based on the cell of origin (B cell, T cell), cellular histology, degree of maturation, and cell surface antigen marker. Hodgkin's lymphoma, lymphoblastic lymphoma, and diffuse large-cell non-Hodgkin's lymphoma account for 90% of primary mediastinal lymphomas. The tumor biology, clinical presentation, and response to therapy varies according to the type of lymphoma.

The mediastinum is usually involved as part of generalized systemic lymphoma. These patients suffer from fever, fatigue, weight loss, lymphadenopathy, hepatosplenomegaly, etc. The diagnosis can be made by biopsy of lymph nodes or bone marrow and by study of the peripheral blood.

However, approximately 10% of lymphomas present with disease apparently confined to the mediastinum (Fig. 10 and Fig. 11). In addition to systemic symptoms, mediastinal lymphomas may cause pain, cough, and dyspnea. In advanced stages, involvement of adjacent structures may result in pleural and pericardial effusions, tracheal obstruction, and superior vena caval obstruction.

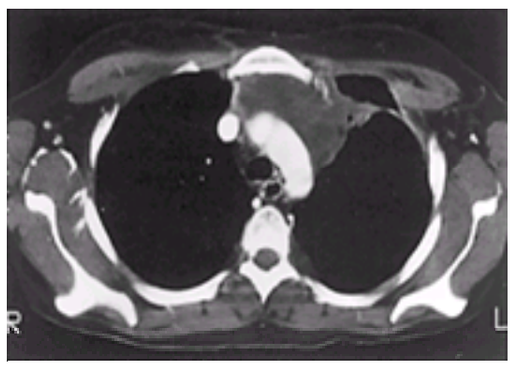

FIG. 10. Anterior mediastinal Hodgkin's lymphoma in a 24-year-old woman.

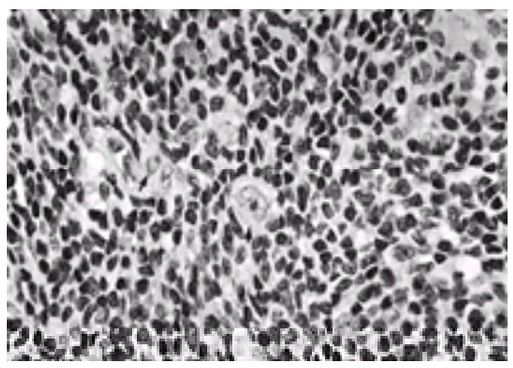

FIG. 11. Typical Hodgkin's lymphoma showing a background of benign lymphocytes and prominent Reed–Sternberg cells *(arrows)* (H&E stain, ×600). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

There are no specific radiographic features that define mediastinal lymphomas. However, CT and MRI scans are essential to determine the extent of disease, invasion into contiguous structures, and to establish a baseline for therapeutic response. Thymomas, germ-cell tumors, and Castleman's disease (a benign lymph node hyperplasia seen in the mediastinum) should be considered in the differential diagnosis.

Because many lymphomas require electron microscopy and immunohistochemical stains for definitive diagnosis, open biopsy techniques are frequently required to provide sufficient tissue for examination. Anterior mediastinal masses can be accessed by mediastinoscopy. Middle and posterior lesions can be biopsied during thoracoscopy. There are no serum markers specific for lymphomas, although serum lactate dehydrogenase is elevated in many patients.

The treatment of patients with mediastinal lymphomas is based on primary radiotherapy (stage I, II Hodgkin's disease) or radiation with combination chemotherapy (non-Hodgkin's lymphomas). Early-stage Hodgkin's disease has a 10-year survival of over 90%. Modern cure rates for non-Hodgkin's lymphomas are approximately 50%. Recurrences are more frequent with “bulky” mediastinal disease. Although surgical resection of isolated lesions and tumor “debulking” have been reported with good results, this approach has limited application.

Germ-Cell Tumors of the Mediastinum

These tumors can be divided into benign teratodermoid tumors and malignant tumors, which include seminomas, embryonal carcinomas, choriocarcinomas, and endodermal sinus (yolk sac) tumors. Germ-cell tumors are thought to originate during abnormal migration of germ cells during embryogenesis. Fewer than 1% represent metastases from a gonadal primary. Approximately 50% to 70% of all extragonadal germ-cell tumors occur in the anterior mediastinum; other locations include the pineal gland, retroperitoneum, and sacrococcygeal areas. Germ-cell tumors are more common in men with Klinefelter's syndrome.

Teratodermoid Tumors

The term teratoma indicates that a tumor is composed of tissues derived from all three germ layers and that all those tissues are foreign to the organ in which they are found. Dermoid cysts, the name applied to the simplest form of teratoma, is a misnomer because tissue elements other than skin are also present in the cyst lining.

Approximately 10% of mediastinal tumors are teratomas; which is the most common germ-cell neoplasm of the mediastinum. Essentially all mediastinal teratomas develop within the anterior compartment in connection with the thymus gland and sometimes within it.

Mostly asymptomatic, they are usually discovered on routine chest x-ray as a mass in the anterior mediastinum projecting into either hemithorax. Symptoms of pain and dyspnea are related to compressive effects. In infants and children, compressive symptoms occur earlier because there is less space for tumor enlargement. Occasionally, these tumors erode, by pressure necrosis or infection, into adjacent organs such as the lung, pericardium, pleura, or superior vena cava, into which the cyst's contents may be discharged. A patient may, for example, cough up hair from a cyst that has eroded into the lung. Typically, chest CT scans show a cystic structure that may contain calcium, bone, and fat (Fig. 12).

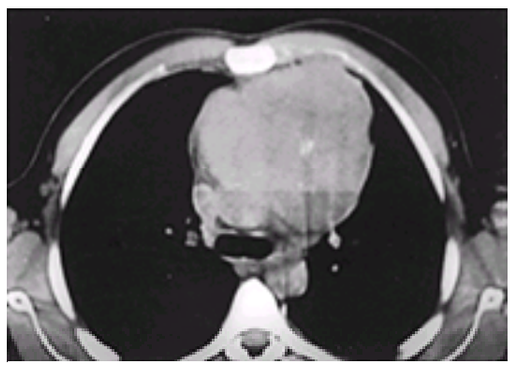

FIG. 12. Teratoma of the anterior mediastinum with central calcium deposits.

Benign teratomas tend to be smooth and rounded, whereas their malignant counterparts are usually lobulated. Grossly, most benign mediastinal teratomas are multicystic, whereas the malignant forms tend to be solid. Microscopically, benign teratomas contain cystic structures lined by tall mucus-secreting cells and a large number of different types of tissue attempting to form organs. Teratomas may be extremely complex and contain a great variety of tissues, including skin, hair, teeth, sebum, muscle, bone, cartilage, fat, respiratory epithelium, pancreas, nerve tissue, and others in various stages of embryologic development. Eighty percent of teratomas are composed of mature tissue elements and are therefore considered benign. Immature tissue elements in a teratoma constitute a sign of malignancy, especially in an adult.

Except for areas of inflammatory reaction or malignant invasion, teratomas have no real tissue attachment and can practically be shelled out of the mediastinum once the overlying pleura has been incised. Because the diagnosis is usually not known beforehand, it is probably good practice to approach the tumor through a median sternotomy, regardless of whether it projects more to one side than the other, and to remove the contiguous thymus *en bloc* with the tumor. All fistulous connections to

other organs (e.g., bronchocystic fistulas) must be interrupted and properly sealed. Care must be exercised to avoid damaging the phrenic nerve, which is frequently stretched over the tumor. Resection of benign teratomas should be considered curative. For malignant lesions, chemotherapy may prolong survival.

Seminoma

Seminoma, also known as *dysgerminoma,* is a rare primary malignant tumor that almost invariably arises in the anterior mediastinum. It occurs almost exclusively in men, between the ages of 20 to 40 years, and accounts for half of all mediastinal germ-cell tumors. Chest pain, cough, dyspnea, and hoarseness are the most common symptoms. The superior vena cava syndrome may be present in 10% to 20% of patients. Typically, a large, homogeneous anterior mediastinal mass is seen on chest CT, but there are no specific radiographic signs; metastatic spread tends to be local into the adjacent lung and/or great vessels. A small number of patients will have elevations of b-human chorionic gonadotropin (b-HCG). This tumor is histologically identical to seminoma of the testis, but the testicular tumor rarely metastasizes to the anterior mediastinum. In the absence of testicular enlargement and retroperitoneal adenopathy on CT scan, a seminoma in the mediastinum may be considered to be a primary extragonadal germ-cell tumor.

Seminomas are solid, nonencapsulated tumors adjacent to the thymus and sometimes enclosed within the gland. On cut section, they are homogeneous, pale tan to yellow, and firm in consistency. On microscopic examination, the tumor is typically divided into numerous islands by fine reticulum fibers. The cells have large, dense nuclei, and the abundant cytoplasm contains glycogen (in contrast to thymomas, which they may resemble). Noncaseating granulomas are also frequently found in the tumor.

Surgery, radiotherapy, chemotherapy (usually cisplatin, bleomycin, and etoposide), and combinations of these have been used as the primary treatment for seminomas. Operative resection is indicated only for small, localized lesions because the recurrence rate for larger lesions is high. Because the tumor is usually very radiosensitive, radiotherapy (4500 to 5000 cGy) has been used extensively, and approximately 60% of patients will be cured with this approach. For large, bulky lesions and in patients with extrathoracic spread or recurrence, the addition of cisplatin-based combination chemotherapy can produce complete remission rates of 80% to 90%.

Nonseminomatous Germ-Cell Tumors of the Mediastinum

Embryonal carcinoma, choriocarcinoma, and teratocarcinoma of the mediastinum are quite rare, and endodermal sinus (yolk sac) tumor of the mediastinum is extremely rare. As a group, they comprise approximately 3% to 10% of all mediastinal tumors. Nonseminomatous germ-cell tumors of the mediastinum almost always occur in men between the ages of 20 and 50. Rapid growth and invasive behavior are the rule. Symptoms include pain, cough, hemoptysis, dyspnea, fever, and weight loss. Approximately 20% of patients develop signs of superior vena caval obstruction. Gynecomastia develops in a significant percentage of nonseminomatous germ-cell tumors and is associated with high levels of b-HCG; b-HCG and/or a-fetoprotein (AFP) is produced by the majority of these tumors. Assays of these biomarkers are an extremely useful way to assess the efficacy of chemotherapy.

Almost all patients with nonseminomatous germ-cell tumors have one or more foci of metastatic disease at the time of diagnosis. Tumors tend to be large, with invasion into local structures, and, in contrast to seminomas, the response to radiotherapy is poor. Multiagent cisplatin-based chemotherapy is the treatment of choice. With this approach, approximately 50% to 70% of patients will achieve complete remission, and half may be long-term survivors. A significant number of patients will have normalization of tumor markers, but residual disease is visible on x-ray studies. Although 70% of these residua contain scar or mature teratoma, active tumor persists in the remainder. In this situation, surgical resection of the remaining tumor may be of benefit.

Mesenchymal Tumors of the Mediastinum

Mesenchymal tumors may arise from connective tissue, muscle, blood vessels, fat, and lymphatic tissue. As a group, they account for approximately 6% of all mediastinal tumors, and about half are benign. These tumors include fibroma (benign mesothelioma), lipoma, and liposarcoma. Myxoma, leiomyoma, leiomyosarcoma, rhabdomyosarcoma, xanthogranuloma, and mesenchymoma occur so rarely that there are few recent reports. In addition, there are tumors of vascular and lymphatic origin, including hemangiopericytoma, lymphangioma, cystic hygroma, and lymphangiomyoma (lymphangiopericytoma). All these are relatively more common in other parts of the body than in the mediastinum. Some of these tumors are of mixed cell type. Swanson has provided a comprehensive review of these tumors.

Fibromas occur more frequently in the pleura (benign pleural mesothelioma) than in the mediastinum. Some cases of mediastinal fibromas have been associated with hypoglycemia and may degenerate into fibrosarcomas. Lipomas account for 2% of all primary mediastinal tumors and are found predominantly in the anterior mediastinum. They must be differentiated from mediastinal lipomatosis, the excessive fat accumulation caused by excessive corticosteroid stimulation, herniated omentum, and thymolipoma (a histologically normal hyperplasia of thymus and fat cells). The diagnosis of a lipoma can be made on CT scan by the low specific coefficient of attenuation (-30 to -100 Hounsfield units) of fat. Lipomas in the lower mediastinum are usually asymptomatic, but large cervicomediastinal lipomas can produce tracheal obstruction. Over 50 cases of liposarcoma of the mediastinum have been reported. Typically, this lobulated tumor may become quite large and infiltrate soft tissues and organs, producing symptoms of airway compression and chest pain. Most of these tumors are “low grade” but have a propensity to recur following resection.

Lesions of vascular origin, hemangiomas, hemangioendotheliomas, and angiosarcomas may arise anywhere in the mediastinum and are extremely rare. Hemangiomas may be quite vascular and may rupture into a pleural space. Complete resection may be difficult but is usually curative. Hemangioendotheliomas and angiosarcomas behave more aggressively. Thirty percent are malignant. Direct extension of tumor into adjacent bone may occur, and local recurrence is common.

Mediastinal lymphangiomyoma (lymphangiopericytoma) is a noninvasive benign tumor closely associated with the thoracic duct, derived from perilymphatic smooth muscle of the lung. The tumor oozes chyle and produces chylothorax. Many mediastinal lymphangiomas begin in the neck (“cystic hygroma”) and descend into the mediastinum. They are composed of multilocular thin-walled cysts lined by endothelium and filled with clear fluid. These tumors are surrounded by a vascular and fibrous reaction and grow in a budding fashion, making surgical resection difficult. Nevertheless, recurrence is rare following removal. Radiotherapy is not recommended, as malignant transformation has been described.

Intrathoracic Thyroid

This is a common lesion, estimated to occur in 0.02% of the general population. More frequent in women, intrathoracic goiter frequently arises as an extension from the isthmus or inferior pole of the cervical thyroid gland and descends into the mediastinum between the trachea and prevertebral fascia. The mass may present either anterior to the trachea or in the posterior mediastinum, partially overlying the trachea. Approximately half of patients complain of respiratory distress. Typically, inspiratory stridor or a choking sensation is aggravated by leaning forward. Venous engorgement of the neck and arm may result from compression of the innominate vein. Hyperthyroidism may be present in 13% of patients. On the chest x-ray, the trachea is usually displaced laterally, and the lumen is reduced. Esophageal compression can be appreciated on barium swallow. Findings of chest CT scan are characteristic, consisting of a nonhomogeneous mass with distinct borders containing course calcifications (Fig. 13). Prolonged enhancement of the mass after injection of iodinated contrast is typical. Radioactive iodine scans (^{131}I) are invariably positive.

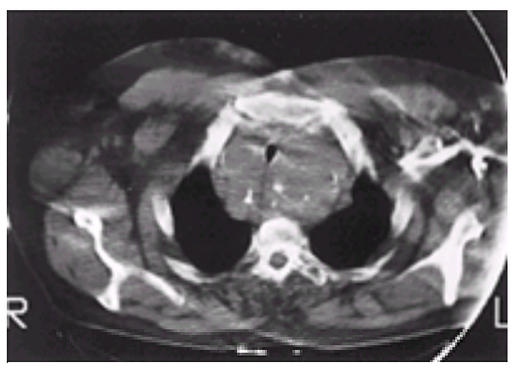

FIG. 13. Computed tomographic scan of a large intrathoracic thyroid causing severe airway compression and stridor.

Histologically, intrathoracic thyroid tumors are usually multinodular goiters. Follicular adenoma may be present on occasion, and approximately 3% to 5% will contain

occult carcinoma.

True ectopic thyroid tissue is a very uncommon condition. The tissue is usually found in the anterior mediastinum adjacent to the thymus. The blood supply is from the mediastinum rather than from the neck. Symptoms are infrequent. Rarely does this tissue represent the only functioning thyroid tissue in the body.

The use of L-thyroxine to suppress an intrathoracic goiter will do little to change the size of the mass. Because of the propensity for airway compromise, either acutely or from tracheomalacia, and the possibility of occult carcinoma, most clinicians recommend surgical resection. This can be accomplished through a cervical incision in most cases.

Intrathoracic Parathyroid Adenoma

Approximately 10% of parathyroid adenomas are found in the anterior mediastinum, where they produce symptoms only by parathormone secretion. These adenomas are often embedded within the thymic tissue because they share a common embryologic origin (third branchial cleft). They are rarely visible on a chest x-ray and are usually the subject of an intensive search in a patient with persistent or recurrent hyperparathyroidism. High-resolution CT scanning, MRI, ultrasonography, thallium–technetium scintigraphy, and selective venous sampling in combination will localize the lesion in 80% to 90% of cases. Angiographic ablation may provide long-term control in 60% of patients; surgical removal is curative.

Thymic Cysts

Cysts develop as a result of a persistent thymopharyngeal duct and therefore may be found anywhere from the mandible to the lower anterior mediastinum, often in the lateral neck. An acquired inflammatory process may be required to produce cyst formation in ductal epithelium. They are usually discovered incidentally, although they occasionally produce tracheal compression.

Cysts are round in the mediastinum and tubular in the neck. They have a thin, fibrous wall, a smooth inner lining, and are filled with straw-colored fluid. They are prone to hemorrhage and hence may contain old blood and cholesterol crystals.

Microscopically, they are lined by columnar, cuboidal, or stratified squamous epithelium. In order to make the diagnosis of thymic cysts, it is necessary to identify thymic tissue in the wall of the cyst, which may be difficult in an atretic thymus gland. The differential diagnosis includes cystic thymoma or lymphoma, making resection of all thymic cysts advisable.

Thoracic Duct Cysts

These cysts are very uncommon. Although thay are usually asymptomatic, the larger cysts may compress the esophagus or adjacent structures. A fatty meal may exacerbate symptoms. The principal diagnostic feature is the observation that the thoracic duct enters and leaves the cystic mass. This can be demonstrated by lymphangiogram. Symptomatic lesions are usually excised, but chylothorax may result.

Enteric Cysts

Also known as *enterogenous cysts, reduplication cysts, inclusion cysts,* or *gastric cysts,* these cysts originate from the dorsal foregut that develops into the gastrointestinal tract. Approximately 15% of all mediastinal cysts are enteric in origin and are more frequent in children. They may be found at any level in the posterior mediastinum (Fig. 14).

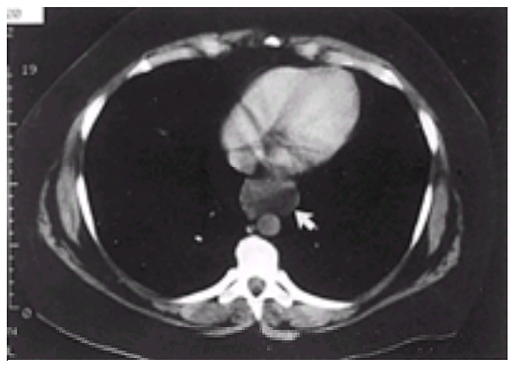

FIG. 14. Enteric cyst of the posterior mediastinum *(arrow)* causing dyspnea and chronic cough in a 32-year-old woman.

Although most patients are asymptomatic, children frequently present with cough, dyspnea, and recurrent pulmonary infections. In adults, dysphagia from esophageal compression is the most common symptom.

Grossly, enteric cysts are smooth-walled structures attached to the wall of the esophagus or completely embedded within the muscle (Fig. 15). Characteristically, a two-layer muscularis is present (Fig. 16). The mucosa may resemble that of esophagus, stomach, or small intestine. Gastric mucosa is capable of acid secretion and may result in peptic ulceration with perforation into adjacent esophagus or bronchus. Rarely, adenocarcinoma may arise from chronic cysts.

FIG. 15. Operative photograph of the woman shown in Fig. 70-14, showing the cyst originating from the esophageal wall.

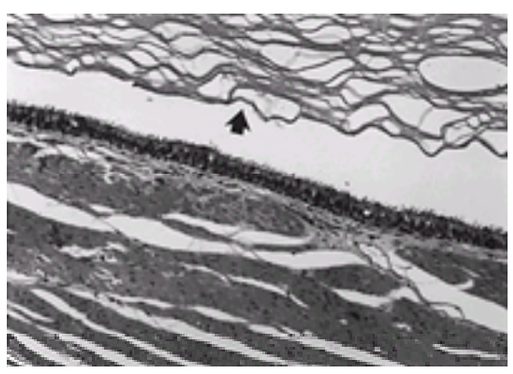

FIG. 16. Enteric cyst with ciliated columnar epithelium, bands of smooth muscle, and mucous debris *(arrow)* (H&E stain, ×500). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

There are no specific radiographic findings, although technetium-pertechnetate scans may localize gastric mucosa. Chest CT scans typically show a low-attenuation mass with smooth borders. Endoscopic and thoracoscopic decompression of these cysts has been described, but recurrence is likely if the cyst wall remains intact. Complete excision is the treatment of choice in symptomatic patients and to prevent the complications of infection and hemorrhage.

Bronchogenic Cysts

Originating as duplication cysts of the ventral foregut that forms the respiratory system, these cysts are usually located in the lung parenchyma (most common) or in the mediastinum (immediately posterior to the carina) (Fig. 17). They account for approximately 10% of mediastinal tumors and represent the most frequent mediastinal cyst. They are round, frequently multilocular, and are lined by pseudostratified ciliated columnar epithelium. The cyst wall may contain cartilage, smooth muscle, fibrous tissue, and mucous glands. Communication with the tracheobronchial tree is uncommon, but they are nearly always attached either intimately or by a cartilaginous band to the trachea.

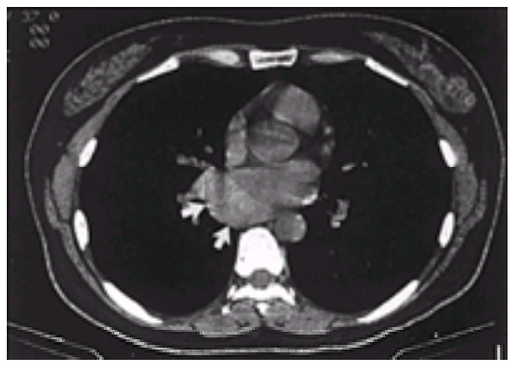

FIG. 17. Chest computed tomographic scan showing mediastinal bronchogenic cyst *(arrows)* posterior and inferior to the carina.

The majority of patients are symptomatic from bronchial or tracheal compression or cyst infection. In infants and children, these symptoms may be life-threatening. Hemorrhage, rupture, and malignant degeneration of bronchogenic cysts have been reported. Therefore, excision of these lesions is recommended.

Pericardial Cysts

These are round, usually unilocular, fluid-filled cysts that sit on the diaphragm in contact with the pericardium and anterior chest wall. Embryologically, they represent a failure of fusion of the mesodermal elements that form the pericardium. The majority of pericardial cysts are located in the right cardiophrenic angle and are asymptomatic. Occasionally, cysts have been observed to change in size with respiration. This correlates with the finding at surgery in approximately 5% of cases of a communicating tunnel between the cyst and the pericardium through which the cyst contents are reducible. On CT scans, pericardial cysts classically have smooth borders and water density (Fig. 18). The differential diagnosis includes hydatid cyst, localized anterior exenteration of the diaphragm, pleural tumors, peripheral right middle lobe or lingular tumors, foramen of Morgagni hernias, and extraperitoneal fat hernias. Large cysts have been managed successfully with needle aspiration.

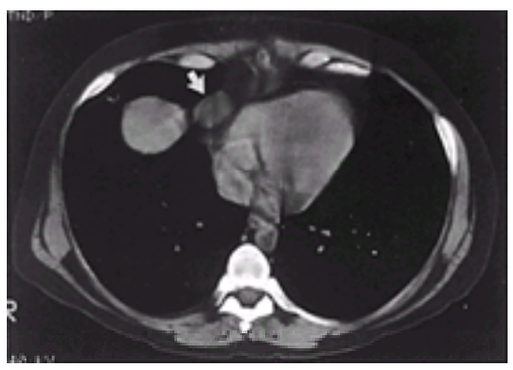

FIG. 18. Pericardial cyst located in the right cardiophrenic angle *(arrow).*

TUMORS OF THE PLEURA

The majority of pleural tumors are metastatic, with carcinoma of the lung or breast and lymphoma accounting for 75% of cases. Benign primary tumors such as lipomas, endotheliomas, and cysts do occur but are very rare. The most common and clinically important primary pleural neoplasms are mesotheliomas. Chest films, chest CT scans, cytologic analysis of pleural fluid, and pleural biopsy should lead to a diagnosis in most patients with pleural tumors.

Mesothelioma

Pleural mesotheliomas are tumors derived from the serosal surface of the lung. They may be classified as benign or malignant; malignant forms can be further classified as localized or diffuse. Benign lesions, also known as pleural fibromas, tend to be pedunculated tumors attached by a narrow stalk to the visceral or parietal pleural surface of the lung (Fig. 19 and Fig. 20). They represent approximately 10% of all mesotheliomas and may become very large before producing symptoms. Grossly, these tumors consist of fibrous tissue and are well encapsulated. Patients may present with pulmonary osteoarthropathy or hypoglycemia. These symptoms resolve after resection of the tumor.

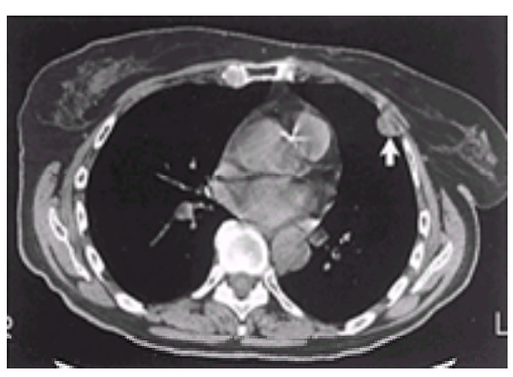

FIG. 19. Chest computed tomographic scan of an asymptomatic fibrous mesothelioma *(arrow)* arising from the visceral pleura.

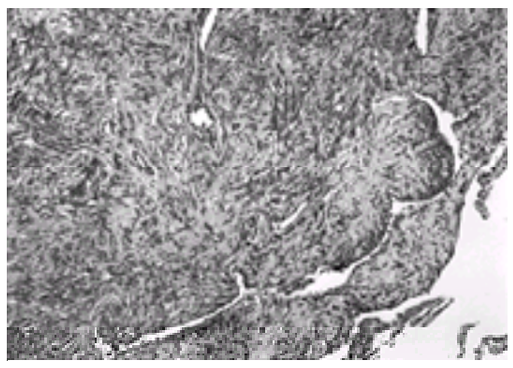

FIG. 20. Fibrous mesothelioma, characterized by bland spindle cells without mitoses (H&E stain, ×250). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Malignant mesothelioma is a rare tumor, accounting for 1% of cancer deaths. The majority of cases are of the diffuse form and are unilateral. This disease usually presents between the ages of 50 to 70 years and is seen more frequently in men. Shortness of breath and nonpleuritic chest pain are the most common complaints, and a pleural effusion is often present, which may cause significant compression of the lung.

Malignant mesothelioma may develop at the site of pleural injury from a number of causes. The inhalation of asbestos fibers, especially crocidolite, is carcinogenic and is associated with the development of mesothelioma in 5% to 7% of exposed workers. A latent period of 20 to 40 years between the time of exposure and the development of disease is not uncommon. Inhalation of other mineral fibers, such as zeolites, is also associated with the development of mesothelioma.

Grossly, the entire lung often becomes encased within a mass of fibrous tissue, which also invades the chest wall, diaphragm, and mediastinum (Fig. 21). Some areas of the tumor are hard, like scar tissue, and other areas may be soft and gelatinous or necrotic. Histologically, mesotheliomas are classified with soft-tissue sarcomas, although a number of types are described (epithelial, sarcomatoid, transitional). The distinction between the epithelial type (most common) and metastatic adenocarcinoma is often difficult and requires electron microscopy and immunohistochemical stains (particularly cytokeratin and CEA).

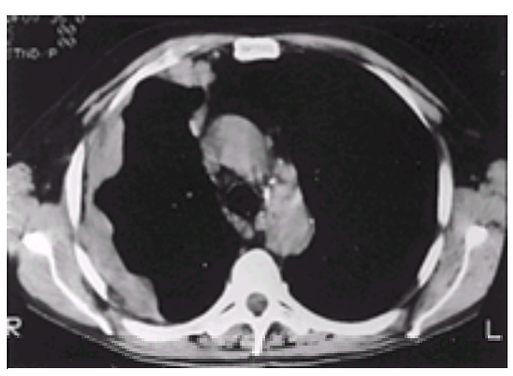

FIG. 21. Diffuse malignant mesothelioma showing the characteristic lobulated pleural mass.

Cytologic diagnosis from pleural fluid is frequently inadequate; usually only hyperplastic mesothelial cells are retrieved. Needle biopsy of the pleura is equally unrewarding due to insufficient cellular material; seeding of the biopsy tract with tumor is a recognized problem. Thoracoscopy or thoracotomy is often required to obtain sufficient material for analysis.(Fig. 22).

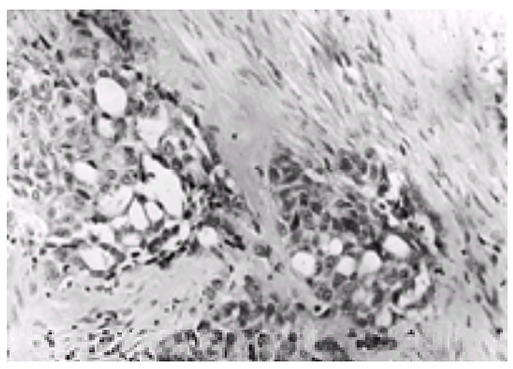

FIG. 22. Malignant pleural mesothelioma, mixed type, showing mesothelial and spindle cells (H&E stain, ×400). (Photomicrograph courtesy of Dr. Miriam Lurie, Department of Pathology, Carmel Hospital, Haifa, Israel.)

At the present time, the treatment of malignant pleural mesothelioma is palliative. Conservative strategies include chemical pleurodesis for control of pleural effusions. Aggressive radiation and/or chemotherapy or photodynamic therapy may control symptoms, but no survival benefit has been documented. Similarly, radical pleurectomy and extrapleural pneumonectomy have not been shown to significantly alter survival, which averages 8 to 12 months.

Endometriosis of the Lung and Pleura

This is a very rare condition characterized by extragenital deposits of endometrial tissue on the visceral or parietal pleural surfaces. Symptoms of hemoptysis and pleuritic chest pain tend to be cyclical and more pronounced during menses. Some cases have been associated with recurrent pneumothorax and hemorrhagic pleural effusions, with endometrial cells in the pleural fluid samples. One theory proposes that hormonally active endometrial implants obstruct small bronchioles, resulting in bulla formation. Treatment with synthetic androgens or gonadotropin-releasing hormone agonists may be useful.

TUMORS OF THE CHEST WALL

Tumors may originate in the soft tissue (skin, subcutaneous tissue, muscles, nerves, and blood vessels) or in the bony skeleton of the thoracic cage. Signs and symptoms depend on the location, size, and degree of malignancy of the neoplasm. In general, chest wall tumors usually present as a slowly enlarging mass causing localized, dull pain. Radicular pain indicates intercostal nerve involvement. Occasionally, an asymptomatic mass is palpated by the patient or seen incidentally on a routine chest x-ray. A chest wall tumor also may project inward and involve the lung as it expands. Approximately 60% of chest wall tumors are malignant.

Benign tumors include chondroma, fibrous dysplasia, osteoblastoma, eosinophilic granuloma, lipoma, giant-cell tumor, fibroma, neurofibroma, osteochondroma, desmoid tumor, hemangioma, cystic hygroma, lymphangioma, and pigmented nevus. Aneurysmal bone cysts are benign lesions found in the ribs but are generally thought to represent a nonneoplastic response to injury. Malignant tumors include fibrosarcoma, chondrosarcoma, solitary plasmacytoma, Ewing's sarcoma,

liposarcoma, osteogenic sarcoma, reticulum cell sarcoma, rhabdomyosarcoma, hemangiopericytoma, and melanoma.

It should be noted that 40% to 50% of chest wall tumors are metastatic in origin. Tumors of the genitourinary tract, thyroid, colon and soft tissue sarcomas are particularly likely to spread to the chest wall. Also, the chest wall may be invaded by direct extension from intra- and extrathoracic tumors such as a superior sulcus tumor, bronchogenic carcinoma, breast carcinomas, and pleural mesotheliomas.

The evaluation of patients with a chest wall tumor should include conventional chest radiographs as well as computed tomography. The latter is particularly important in delineating the pleural, mediastinal, and pulmonary involvement of the lesion. Bone scans should be performed if metastatic disease is suspected. There is little utility in fine-needle or incisional biopsy for primary chest wall lesions, as the tissue is usually insufficient for diagnosis. Exceptions include Ewing's sarcoma and plasmacytoma, where chemotherapy and/or radiation may be the primary therapy.

Benign Tumors

Chondromas, also known as enchondromas, are the most common benign lesions of the chest wall, occurring at the costochondral or sternochondral junctions. They usually present between the ages of 35 and 55. These tumors are rubbery and multicystic, with a gelatinous center. On x-ray, the medullary mass thins but does not penetrate the cortex. These tumors may undergo malignant degeneration into chondrosarcomas. Hence, radical excision is warranted.

Fibrous dysplasia (osteitis fibrosa) accounts for approximately 15% of benign chest wall tumors. They are usually situated in the posterior or lateral rib. The rib appears locally expanded and filled with small cysts (Fig. 23). This tumor can become very large and may be locally aggressive. Histologically, the lesions consists of fibrous tissue and incompletely mineralized bone lacking a rim of osteoblasts (Fig. 24). Pathologic fractures are common. Osteochondroma is a small, hard, painless tumor. In the rib it appears as an excrescence of cartilage with a cap projecting out of the rib. Lipomas are usually found superficially in the chest wall. Neurofibromas occur as isolated sessile or pedunculated skin tumors or as part of generalized neurofibromatosis (von Recklinghausen's disease).

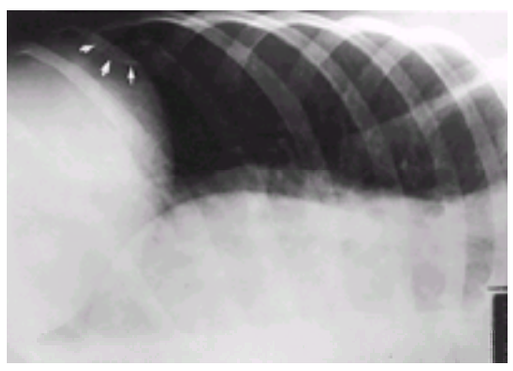

FIG. 23. Standard x-ray film of the rib showing fibrous dysplasia *(arrows).* The cortex is expanded, and a lytic core is prominent.

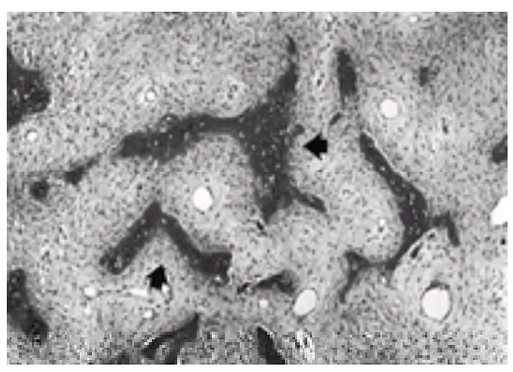

FIG. 24. Fibrous dysplasia showing the characteristic “Chinese characters” pattern *(arrows)* of bone formation. A background of bland fibrous reaction has replaced the marrow tissue (H&E stain, ×250). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Osteoblastoma is a benign lytic lesion originating in the medulla of bones, affecting the ribs in 4% of cases. The great majority occur in patients less than 30 years of age. Characteristically, CT scans show a lytic lesion with a thin bony shell that concentrates technetium on bone scans (Fig. 25). Abundant osteoblasts and giant cells may be present on light microscopy (Fig. 26). Surgical removal is the treatment of choice.

FIG. 25. Technetium bone scan of osteoblastoma involving the right ninth rib.

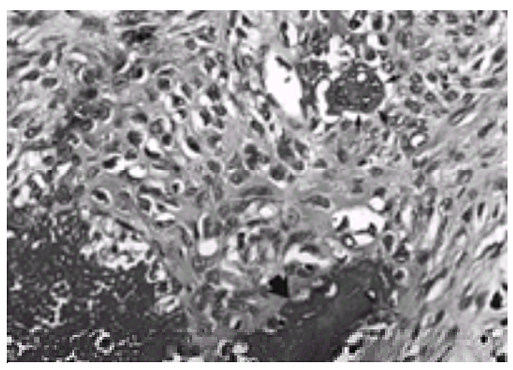

FIG. 26. Osteoblastoma, characterized by osteoblasts, prominent giant cells *(small arrows),* and oteoid formation *(large arrow)* (H&E stain, ×500). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Eosinophilic granulomas are well-defined lytic lesions that can occur in the ribs. They represent 10% of benign chest wall lesions. These tumors are composed of histiocytes and eosinophils with occasional giant cells, fibroblasts, and plasma cells. Surgical resection is curative, although radiation therapy can be effective in poor-risk patients.

Desmoid tumors are slow-growing hard masses occurring most often in the soft tissues of the abdomen and extremities; approximately 20% to 50% have been reported on the chest wall. Women are affected more frequently than men. These tumors are low-grade fibrosarcomas but lack cellular pleomorphism and mitotic activity. Because tumor cells tend to infiltrate along muscle bundles, recurrence after surgical resection is a significant problem, averaging 30%. Low-dose radiotherapy can control local recurrences.

Cystic hygromas originate in the neck but may extend into the axilla. *Lymphangiomas* are more extensive, growing through the muscles of the chest wall into the mediastinum and lung. They cause pleural effusions and, occasionally, chylothorax (for which thoracic duct ligation may be required). *Hemangiomas* are seen in infancy and early childhood and spontaneously regress after the first 2 years of life.

Malignant Tumors

Fibrosarcomas usually occur in young adults, frequently near the scapula. It is the most common soft-tissue sarcoma of the chest wall and may account for 20% to 50% of all malignant chest wall neoplasms. These tumors are slow growing and metastasize to regional lymph nodes and to the lungs. Wide local resection is the treatment of choice, although local recurrence may develop in a significant number of patients. Prognosis depends on the grade of the tumor; in general, a 5-year survival rate of 50% to 60% can be expected for low-grade lesions. For high-grade lesions, large tumors, and for incomplete resection, the addition of adjuvant chemotherapy and/or radiotherapy may be beneficial.

Chondrosarcoma is the most common chest wall neoplasm. In order of frequency, these tumors are found in the ribs, scapula, and sternum. Most patients are over 40 years of age. A presumptive diagnosis can often be made radiographically, with the finding of a large, lobulated mass with poorly defined margins and cortical bone destruction. Mottled calcification of the mass is commonly seen. These are indolent lesions characterized by slow growth and local recurrence (Fig. 27). Patients with recurrent tumors often have metastatic disease involving local lymph nodes and the lung. Prognosis depends on tumor size, location, and grade as well as the extent of primary resection. Complete resection should achieve a 60% to 70% 5-year survival rate. Incomplete resection and/or recurrence is ominous, as there is no effective role for chemotherapy or radiation.

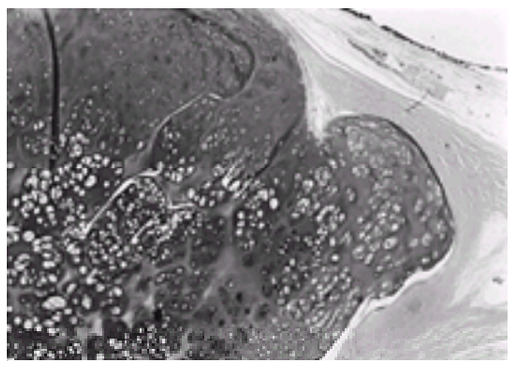

FIG. 27. Chondrosarcoma showing a lobular tumor with a hypercellular matrix (H&E stain, ×250). (Courtesy of Dr. Gordon Honda, Department of Pathology, University of California, San Francisco.)

Solitary *plasmacytomas* are uncommon in general but account for approximately 30% of malignant chest wall neoplasms. Most patients complain of a mass or pain in the ribs, and the characteristic radiographic finding is that of a punched-out, lytic lesion. Grossly and microscopically, this disease is indistinguishable from multiple myeloma. Local control of solitary plasmacytoma can be achieved with radiotherapy or chemotherapy in the majority of patients, with an expected 5-year survival of 40%. However, most patients will eventually develop multiple myeloma, which is usually fatal despite chemotherapy.

Ewing's sarcoma occurs during the first three decades of life and involves ribs, scapula, clavicle, or vertebrae. Approximately 7% will involve the ribs primarily. The disease usually presents as a painful mass and is associated with fever and leukocytosis. X-rays typically show evidence of rib destruction or bone lysis. Occasionally, there is widening and sclerosis of the bony cortex with multiple layers of new bone formation, producing an “onion peel” appearance. Histologically, Ewing's sarcoma requires electron microscopy to distinguish it from other round-cell tumors such as neuroblastoma and lymphoma. Disease located primarily in the chest wall is more aggressive than primary tumors of the extremities, probably because of a higher incidence of metastatic disease at presentation. Treatment for isolated rib lesions is surgical resection; combination chemotherapy and radiation has been used successfully for more advanced lesions. Five-year survival rates of 50% have been recently reported.

Osteogenic sarcoma is one of the rarest tumors of the ribs or sternum. Patients usually complain of a painful mass, and a significant number have received previous radiation for treatment of other diseases. The x-ray typically shows dense cortical sclerosis with radiating calcified subperiosteal spicules, producing a “sunburst” effect (Fig. 28). Thirty percent of patients will have synchronous metastases, usually to the lung. The overall 5-year survival following surgical resection for primary chest wall lesions is 15%. Adjuvant chemotherapy may improve survival.

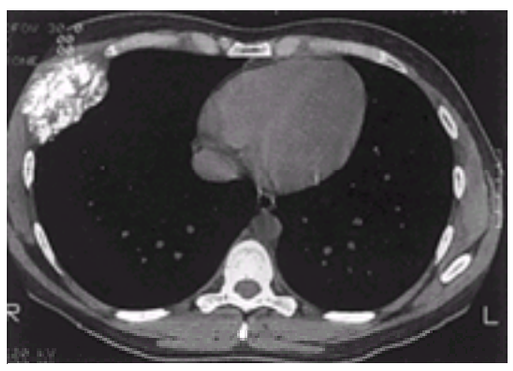

FIG. 28. Osteosarcoma of the rib showing the classic “sunburst” pattern.

Rhabdomyosarcomas are rare and highly malignant. The tumor spreads along fascial planes and metastasizes early by hematogenous spread. It is resistant to irradiation; surgical resection should be combined with adjuvant chemotherapy to achieve the best survival. *Liposarcomas,* in contrast to benign lipomas, which are superficial, tend to develop in deep fascial planes. Resection of low-grade lesions is followed by excellent survival. *Reticulum cell sarcoma* and *hemangiopericytoma* occur extremely rarely in the chest wall.

The mainstay of treatment of malignant tumors of the chest wall, especially fibrosarcomas and chondrosarcomas, is wide local excision. Maintaining 4-cm margins around the tumor will provide the lowest recurrence rates and best survival. Tumors of the sternum should all be regarded as malignant. In lesions involving the manubrium, the head of the clavicle and costal cartilages also should be removed. Reconstruction of large chest wall may be accomplished by the use of muscle flaps, myocutaneous flaps, rib grafts, Marlex mesh, and molded acrylic plates. Operative mortality is less than 5% in most series, and there is little effect on pulmonary function.

TUMORS OF THE DIAPHRAGM

Although the diaphragm is frequently invaded by tumors arising from adjacent stomach, esophagus, liver, colon, ribs, and vertebrae, primary tumors of the diaphragm are extremely rare. Fewer than 100 cases have been reported; of those, approximately 60% are malignant.

Benign tumors include lipoma, fibroma, mesothelioma, angiofibroma, neurofibroma, and neurilemmoma. Congenital and acquired cysts also have been found in the diaphragm.

Malignant tumors are primarily of mesenchymal origin: fibrosarcoma (most common), liposarcoma, rhabdomyosarcoma, and neurogenic sarcomas. A few leiomyosarcomas have also been reported.

Benign lesions are usually asymptomatic. Malignant lesions give rise to pain in the lower chest and flank. Phrenic nerve involvement causes cough, hiccups, and shoulder pain. Large tumors may produce dyspnea. Clubbing has occasionally been noted.

The differential diagnosis includes peripheral pulmonary parenchymal tumors, an elevated portion of hemidiaphragm, loculated subpulmonic pleural effusions, and hiatal hernia. A subdiaphragmatic mass may indent a portion of the diaphragm, which consequently protrudes superiorly simulating a tumor of the diaphragm itself.

Diagnostic tests to differentiate among these entities include CT scan and artificially induced pneumothorax and pneumoperitoneum. Computed tomographic scanning is particularly useful in diagnosing lipomas, which have a very low specific coefficient of attenuation.

Diaphragmatic tumors should be excised. The resulting diaphragmatic defect can be repaired either directly with sutures or with a prosthetic patch, if necessary.

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CHAPTER

71 Extrapulmonary Syndromes Associated with Tumors of the Lung

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INTRODUCTION

In 1928, Brown described unexpected adrenal hyperactivity in a bearded woman with diabetes who had an oat-cell carcinoma of the lung. Clearly, she had a tumor producing adrenocorticotropin (ACTH). More case reports of hormone activity associated with lung cancer followed, but it was not until 1941 that Albright and Reifenstein suggested a possible mechanism for the association. They proposed that tumors secrete hormone-like substances producing clinical syndromes. This was confirmed 20 years later when high ACTH concentrations were discovered in the plasma of patients with adrenal hyperactivity and bronchogenic carcinoma. Syndromes resulting from production of unexpected or “inappropriate” substances by tissues not normally associated with hormone production were termed ectopic hormonal syndromes.

Initially, ectopic hormone secretion was thought to be a rare event, but now we know that peptide hormone production is characteristic of all cancers and that these peptides are produced by the normal tissues from which the tumors are derived. Increased peptide hormone production by lung neoplasms is quantitatively abnormal but not truly ectopic. Many of the hormones are secreted as inactive large-molecular-weight polypeptide precursors because of either abnormal posttranslational modification or an alternative process of secretion. Recognizable clinical syndromes result only if neoplastic tissue is able to metabolize the precursor to a bioactive hormone.

Lung cancers, particularly small-cell carcinomas and bronchial carcinoid tumors, have the highest reported incidence of tumor expression of neuroendocrine peptides. However, evidence that a circulating hormone is actually produced by the tumor often is not available. Criteria for establishing tumor hormone production are (1) the presence of both the tumor and a hormonal syndrome or elevated blood or urine concentration of the hormone; (2) failure of normal feedback mechanisms to suppress hormone levels in plasma or urine; (3) demonstration of the polypeptide in tumor tissue or tissue extracts; (4) increasing hormone concentrations across the tumor capillary bed; (5) decreased hormone concentrations if therapy directed toward the tumor is successful; (6) demonstration of hormone synthesis and release by the tumor *in vitro;* (7) cell-free translation of tumor peptide messenger RNA; and (8) exclusion of other sites of significant hormone production. An invasive procedure and a research laboratory are required to obtain tissue and perform the analyses to fulfill these criteria.

It is unlikely that hormone production by tumors occurs as a result of random activation of areas of the genome that normally are repressed. This concept does not account for the strong association of some hormonal syndromes with specific lung and other carcinomas. Baylin and co-workers developed an elegant model suggesting that the different types of bronchogenic carcinoma arise through a continuum of differentiation events occurring in cells of common cellular origin. The less differentiated cells secrete many peptide hormones and growth factors, whereas more differentiated cells, which are more rigorously regulated, secrete only a few.

The true incidence of hormone production associated with lung carcinomas is difficult to determine for many reasons. Surveys probably reflect the minimum incidence. Tumors secrete peptides sporadically. Changes in tumor metabolism and peptide production occur with time, but tumor markers frequently are measured only once. Metastases may produce peptides that are different from those in the primary neoplasm. Excess hormone secretion frequently occurs only in response to a stimulus, and provocative tests for hormone responsiveness usually are not done. Finally, the presence of a hormone usually is assessed by radioimmunoassay, and the antibodies used vary from laboratory to laboratory.

Many tumors produce an array of peptide hormones, and no peptide is specific for a given bronchogenic carcinoma. This is as expected if different neoplasms arise from common precursors. Fluctuations in the concentration of peptides elaborated by bronchogenic carcinomas sometimes reflect the clinical course of these tumors, but not always. Peptide production may be better correlated with the state of tumor differentiation than with tumor mass, but changes in tumor peptide concentrations can signal changes in tumor metabolism or malignant potential. It is important to recognize hormone-induced extrapulmonary syndromes to avoid unnecessary procedures and to provide appropriate treatment.

HORMONAL AND METABOLIC SYNDROMES

Adrenocorticotropin and Cortocotropin-Releasing Hormone

Gewirtz and Yalow were the first to show that tissue extracts from lung carcinomas of all types contain a large-molecular-weight, biologically inactive form of ACTH (pro-ACTH) that can be converted to bioactive ACTH. Normal lung and all lung carcinomas also contain the precursor peptide proopiomelanocortin (POMC) and its component peptides: pro-ACTH and b-lipotropin, a hormone with weak lipotrophic and melanocyte-stimulating activity. In normal lung the concentration of POMC mRNA is only 0.008% to 0.08% of that in the pituitary gland, and smaller forms of POMC mRNA predominate. These do not code for a signal sequence, so the POMC peptides cannot be secreted. The ACTH concentration in normal lung is only 0.000003% to 0.00005% of that in the pituitary gland. However, lung carcinomas contain larger amounts of full-length POMC mRNA and can secrete enough POMC-derived peptides to produce clinical syndromes. The POMC also is cleaved to melanocyte-stimulating peptide fragments, b-endorphin, and corticotropin-like intermediate-lobe peptide (CLIP), which has no known function.

Why so many tumors, especially lung carcinomas, produce excess pro-ACTH, ACTH, and other POMC-derived peptides remains an enigma. Luster and co-workers found that the ACTH produced by a small-cell carcinoma induced an increased rate of growth of the tumor *in vitro* and suggested that ACTH might play an autocrine role. If so, it might be important to suppress tumor ACTH as early as possible.

Some patients with high plasma ACTH concentrations have no clinical manifestations, even though morning cortisol concentrations are high and the normal diurnal variation of cortisol is absent. Plasma 11-deoxycorticosterone and dehydroepiandrostenedione sulfate concentrations and urinary free cortisol, 17-hydroxysteroids, and 17-ketosteroids are increased as well. Either the circulating cortisol concentrations are not high enough to produce symptoms or death ensues before there is sufficient time for symptoms and signs of hypercortisolism to develop.

Other patients with ectopic ACTH production are markedly symptomatic. Most of these patients have small-cell carcinoma or bronchial carcinoid tumors. The classic signs of Cushing's seldom occur in patients with small-cell carcinoma because progression of the disease is so rapid. Because the effects of high ACTH on electrolyte flux develop more rapidly than the effects on lipid and carbohydrate metabolism, these patients present with weight loss, severe proximal muscle weakness, pretibial and ankle pitting edema, polyuria, and hypokalemic alkalosis (serum bicarbonate usually $^{3}30$ mmol/liter and pH ^{3} 7.45), which may be very resistant to treatment. Hyperpigmentation (Fig. 1) is the result of the excess lipotropin or the melanocyte-stimulating fragments of POMC. Cortisol excess fosters opportunistic infections, which frequently are fatal, and also is responsible for the poor response to chemotherapy, even in patients who are not neutropenic. In patients with small-cell carcinoma, the prognosis is terrible.

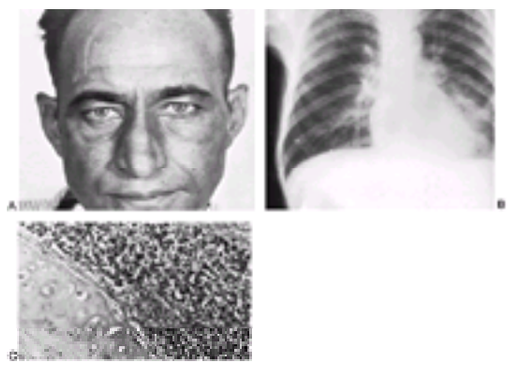

FIG. 1. (A) This patient with carcinoma of the lung complained of darkening of the skin. Note the hyperpigmentation under his eyes and around his mouth. **(B)** His chest film revealed an area of infiltration along the left cardiac border. Scalene node biopsy was positive for anaplastic carcinoma. The patient had increased 17-ketosteroids, total 17-ketogenic steroids, and 17-hydroxycorticosteroids but no clinical Cushing's syndrome. **(C)** Small-cell anaplastic carcinoma arising in the left lower lobe bronchus was found at postmortem examination. Note the marked variation in the size and shape of the deeply staining nuclei (×450).

Patients with more slowly progressive bronchial carcinoid tumors do develop classic features of Cushing's syndrome, including moon facies, truncal obesity, purple abdominal striae, hirsutism, psychosis, hypertension, edema, osteoporosis, and hyperglycemia (Fig. 2). Differentiating pulmonary tumor ACTH production from pituitary tumor ACTH production in these patients can be difficult. Plasma ACTH and cortisol concentrations usually are not suppressed by high-dose dexamethasone administration in patients with lung cancers, but partial suppression can occur with carcinoid tumors. Ectopic ACTH-producing tumors usually do not respond to corticotropin-releasing hormone (CRH), and serum 11-deoxycortisol levels usually do not rise after metyrapone administration, but there are exceptions. Because excess CLIP is produced by lung carcinomas but not by pituitary tumors, the CLIP/(CLIP + ACTH) ratio could be used to confirm ectopic origin of the ACTH if the CLIP assay were readily available.

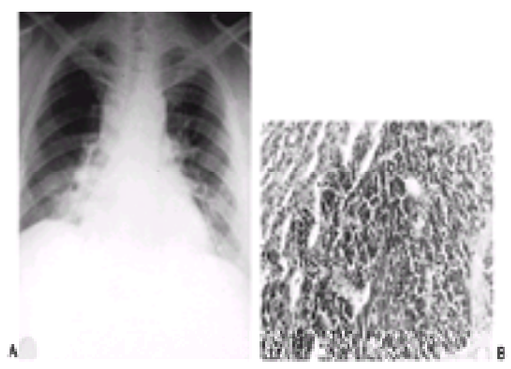

FIG. 2. (A) Chest roentgenogram showing an area of increased density along the right cardiac border. The patient was a 34-year-old man with truncal obesity, edema, hypertension, hypokalemic alkalosis, polycythemia, and the typical urinary steroid values of Cushing's syndrome. **(B)** A liver biopsy was obtained at abdominal exploration. A large nest of anaplastic carcinoma cells metastatic from the lung is seen adjacent to cords of liver cells (×450).

Occasional patients with bronchial carcinoid tumors develop Cushing's syndrome because of tumor CRH, which induces pituitary hyperstimulation and bilateral adrenal hyperplasia. These tumors are even more difficult to differentiate from pituitary adenomas by biochemical testing than are carcinoids producing ACTH.

In several series of patients with Cushing's syndrome secondary to small-cell carcinoma, the only ones who achieved a remission were those in whom cortisol levels were controlled before chemotherapy was begun. Inhibitors of steroid biosynthesis such as ketoconazole, metyrapone, and aminoglutethimide can be used to treat Cushing's, but all have serious side effects. Patients with small-cell carcinoma usually require high doses of these drugs, sometimes in combination. RU-486, a drug that blocks steroid action at the receptor level, has been used successfully. The adrenocorticolytic drug *o',p'*-DDD is not useful because its onset of action is slow, and several weeks is required to control cortisol secretion. Potassium and spironolactone can be given to control hypokalemia.

The same drugs can be used for patients with Cushing's syndrome caused by the more indolent carcinoid tumors; smaller doses or drug combinations are required in those individuals. The somatostatin analog octreotide also has been used for these patients, although paradoxic increases in ACTH following octreotide and lanreotide, the slow-release somatostatin analog, have been reported. There is one report of carcinoid tumor ACTH suppression by bromocriptine. Bilateral adrenalectomy is effective if medical therapy fails.

Antidiuretic Hormone (Arginine Vasopressin) and Atrial Natriuretic Factor

Winkler and Cranshaw described a patient with the combination of lung cancer, hyponatremia, and excessive urinary sodium loss in 1938. Twenty-two years later, Schwartz and colleagues observed that despite an increased extracellular fluid volume and hypotonic plasma, the urine of similar patients was hypertonic. They proposed that the fluid and electrolyte imbalance seen in these patients was a consequence of inappropriate secretion of antidiuretic hormone (ADH; also arginine vasopressin, AVP). Since then, inappropriately elevated ADH concentrations have been found in 50% to 68% of patients with small-cell carcinoma and somewhat less

often with other types of lung cancer. Inappropriate ADH secretion may precede evidence of the tumor mass by several months. The highest and most persistent ADH concentrations occur in patients with extensive or rapidly progressing tumors. Pituitary ADH is stored attached to another polypeptide, a neurophysin, and the two peptides are secreted together. Tumor neurophysin is detectable in only 70% of patients with small-cell lung cancer. Radioactive neurophysin antibodies are being tested to see if they can be used for localizing tumors or to follow the response to therapy.

The clinical response to tumor-produced ADH depends on the degree of water loading and other therapies. Hyponatremia is also exacerbated by chemotherapy, particularly cyclophosphamide, radiation therapy, or prostaglandin inhibitors (prostaglandins of the E_2 series are inhibitors of ADH action). Most patients are asymptomatic if the serum sodium is at least 120 mmol/L, and no treatment is necessary. If the serum sodium falls below 120 mmol/L, patients are likely to develop headache, lethargy, generalized weakness, confusion, and somnolence. If severe hyponatremia develops rapidly, patients may present with nausea and vomiting. When the serum sodium falls below 110 mmol/L, the risk of seizures, hypothermia, coma, and death increases markedly.

Fluid restriction to an intake less than insensible water loss often restores the sodium concentration. If the hyponatremia is severe, hypertonic saline infusion can be coupled with furosemide administration and replacement of urinary electrolyte losses until the serum sodium concentration increases. Demeclocycline, which produces reversible ADH resistance, can be added if fluid restriction alone is not sufficient. Lithium also produces nephrogenic ADH resistance, but the side effects of lithium are greater, and the effects, which may be permanent, are unpredictable.

Lung cancer patients with hyponatremia also have abundant atrial natriuretic factor (ANF). It is usually impossible to determine whether tumor production of ANF is the primary cause of the hyponatremia or whether ANF is increased in response to an expanded plasma volume caused by inappropriate ADH.

Calcium Metabolism and Bronchogenic Carcinoma: Humoral Hypercalcemia of Malignancy

Hypercalcemia without evidence of bony metastases is associated with solid tumors of many kinds. The syndrome is known as “humoral hypercalcemia of malignancy” (HHM). In the lung, HHM is associated most often with squamous cell tumors and sometimes with adenocarcinomas and bronchial carcinoid tumors. Most hypercalcemia associated with small-cell carcinoma probably reflects unidentified bone metastases or concomitant parathyroid hyperplasia or adenoma.

The hypercalcemia results primarily from increased bone resorption relative to bone formation, and increased renal tubular resorption of calcium contributes also. In patients with lung cancer, these usually are caused by tumor production of parathyroid hormone-related protein (PTHrP). Eight of the 13 amino acids of the N-terminal region of PTHrP and parathyroid hormone (PTH) are identical, and the two hormones bind to the same receptors; the remaining structure of each is unique. The function of PTHrP in normal tissues is unknown. Concentrations are especially high in epidermis, breast milk, and amniotic fluid, so PTHrP might be an important regulator of fetal calcium homeostasis. PTHrP increases osteoclast activity, bone resorption, nephrogenous cyclic AMP, and renal phosphate wasting just as PTH does but has less effect on renal calcium retention. PTHrP does not activate the renal hydroxylase that converts 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D, so intestinal calcium absorption is decreased in HHM.

Most patients with mild hypercalcemia are asymptomatic. Even serum calcium concentrations of 3.0 to 3.25 mmol/L (12 to 13 mg/dl) or more often are associated with surprisingly mild anorexia, constipation, myalgias, or lethargy. Patients with decreased mobility and patients receiving chemotherapeutic drugs toxic to bone cells have increased bone resorption and are at high risk for worsening hypercalcemia, as are patients with fever, anorexia, or vomiting who become dehydrated. If hypercalcemia is severe, patients develop nausea and vomiting, abdominal pain, polyuria, dehydration, and weakness and become confused or obtunded. Patients with bronchogenic carcinoma who have a serum calcium ³2.63 mmol/L (³10.5 mg/dl) are likely to have large tumor masses and a poor outcome. Symptoms improve with treatment, but median survival is only 4 to 6 weeks. Patients do not live long enough to develop band keratitis, uremia, and renal calculi.

Patients with HHM have high ionized serum calcium levels, hypercalciuria, low serum phosphorus, and low or low-normal PTH levels because PTH is suppressed when plasma calcium is high. It is usually unnecessary to order a PTHrP level because the malignancy is obvious, and a good history and the low PTH level eliminate most other causes of hypercalcemia. Plasma levels of 1,25-dihydroxyvitamin D are low or low normal.

If rapid treatment is required, intravenous saline and furosemide lower serum calcium acutely. Dietary calcium restriction, oral phosphate, glucocorticoids, and indomethacin are effective only transiently, if at all. This is not surprising because calcium absorption from the gastrointestinal tract is decreased in HHM, and prostaglandins are not responsible for the hypercalcemia. The effect of calcitonin is short-lived (24 to 48 hr), perhaps because of down-regulation of receptors. Mithramycin (plicamycin) inhibits osteoclastic bone resorption, but its use is limited by renal and hepatic toxicity and bone marrow suppression.

Bisphosphonates are potent inhibitors of osteoclast activity by mechanisms that are still uncertain. When they are given intravenously to patients with HHM, the plasma calcium concentration begins to fall within 48 hr; the calcium nadir is reached at 5 to 7 days. In good responders, normocalcemia can persist for 14 to 30 days. Two bisphosphonates that are available at the present time are etidronate disodium and pamidronate. Pamidronate is more effective than etidronate disodium (normocalcemia in 70% versus 41% and longer duration of action). Slight fever (1°C), asymptomatic hypocalcemia, hypophosphatemia, hypomagnesemia, and small increases in creatinine occur transiently in some patients.

Gallium nitrate also inhibits bone resorption and has been shown to lower serum calcium when administered as a continuous infusion with concomitant hydration and diuresis. Gallium nitrate also is more effective than etidronate disodium (normocalcemia in 82% versus 43%, median duration 8 days versus 0 days).

Oncogenic Osteomalacia: Renal Phosphate Wasting

The association of renal phosphate wasting, osteomalacia with bone pain, muscle cramps and weakness, and cancer has been known for many years. Patients with oncogenic osteomalacia also have a 1,25-dihydroxyvitamin D deficiency. Usually oncogenic osteomalacia occurs with small mesenchymal tumors, which are notoriously difficult to locate, but it has been found in several patients with small-cell carcinoma of the lung. All of these patients had marked hypophosphatemia with renal phosphate wasting (low tubular resorption of phosphorus and TmP/GFR), inappropriately low or low-normal 1,25-dihydroxyvitamin D concentrations, elevated alkaline phosphatase, and osteomalacia or increased osteoid on bone biopsy.

The biochemical picture is very similar to that of X-linked hypophosphatemic rickets. Tumor production of a substance that causes proximal renal tubule phosphate wasting and inhibition of renal 25-hydroxyvitamin D 1a-hydroxylase is thought to be responsible. A substance with these properties that is heat labile, lipid insoluble, and presumed to be a peptide has been found in tumor extracts. The substance is not PTH or a PTH-related protein, even though tumor extracts stimulate PTH-responsive renal adenylate cyclase. Serum calcium is normal or only slightly decreased; this substance may not react with bone receptors. Serum 25-hydroxyvitamin D and calcitonin levels are normal too.

Renal phosphate handling improves only if chemotherapy induces a remission. Patients may have a partial response to calcium, phosphate salts, and 1,25-dihydroxyvitamin D.

Calcitonin and Calcitonin Gene-Related Peptide

Calcitonin inhibits bone resorption and decreases renal tubular resorption of calcium and phosphorus, but the precise role of calcitonin in normal human physiology is unknown. The highest concentration of calcitonin is found in the parafollicular cells of the thyroid gland, but calcitonin is produced by neuroendocrine cells in many tissues. Indeed, the lungs contain more calcitonin than the thyroid gland. Serum and urine calcitonin levels are increased in smokers and in chronic COPD, and calcitonin has been found in extracts of neoplasms of all types, particularly small-cell carcinoma of the lung. An increased serum calcitonin response to pentagastrin has been described in lung cancer patients whose basal calcitonin concentrations were normal. Both serum and urine calcitonin concentrations correlate positively with lack of tumor differentiation and increased disease activity. Calcitonin concentrations are decreased in patients who respond to therapy and are increased in association with relapse or tumor progression.

Alternative intranuclear splicing of calcitonin mRNA yields either calcitonin or calcitonin gene-related peptide (CGRP), which is a potent vasodilator and is found in pulmonary neuroendocrine cells. The CGRP messenger RNA has been detected in lung tumor cell lines by several groups but may not be produced by lung tumor cells *in vivo.*

No adverse clinical consequences of calcitonin or GCRP production by bronchogenic carcinoma are known. Patients do not develop diarrhea, and serum calcium, inorganic phosphate, and vitamin D concentrations remain normal.

Gonadotropins

Human chorionic gonadotropin (HCG) was once thought to be a specific marker for tumors derived from trophoblast tissue. However, HCG has been found in extracts

from a wide range of normal tissues, including the lung, and in extracts of all types of carcinomas. At least three different HCG-related molecules can be measured in lung cancer patients who have high immunoreactive serum HCG: intact HCG, free HCG b subunit, or HCG b core fragment (b-CF). Only 12% to 30% of lung cancer patients have high serum HCG, and the HCG concentration does not reflect the extent of disease. Because tumor HCG is poorly glycosylated, secreted HCG may be degraded too rapidly to be measured in most patients. Approximately 50% of patients with lung cancers of all types have elevated levels of b-CF in their urine whether or not serum values are high. The more advanced cases are more likely to have high urine b-CF, but even with stage IV cancers, urine b-CF was elevated only 72% of the time.

In one series of patients with lung cancer and high serum HCG, testosterone levels actually were lower in the cancer patients than in the control group. Estrogen concentrations were not measured in that study, although increased estradiol concentrations, which correlated with tumor mass and HCG concentration, were reported by another group. None of the male patients in the series had gynecomastia, although gynecomastia has been found in other patients with lung cancers producing HCG. Gynecomastia is very common in men over 50 years of age and is correlated with body weight. Because gynecomastia usually is not measured as part of the routine physical examination, it is difficult to determine whether the gynecomastia reported in lung cancer patients is of recent onset and whether its absence reflects weight loss secondary to disease. Tumor HCG is not suppressed by administration of androgens, estrogens, or progestins.

There is one case report of a step up in the arteriovenous gradient of FSH but not LH across a bronchogenic carcinoma capillary bed. Serum concentrations of both FSH and LH were elevated before tumor resection and decreased postoperatively. In all other cases in which lung tumors have been associated with gonadotropin production, either the gonadotropin proved to be HCG or the immunoassay was not sufficiently specific that cross-reactivity with HCG could be excluded.

Human Placental Lactogen and Prolactin

Increased serum levels of human placental lactogen (HPL) and prolactin have been found in a few patients with bronchogenic carcinoma, but no clinical concensequences of either HPL or prolactin have been reported.

Hormones Regulating Growth

Small amounts of human growth hormone (HGH) are found in all normal human tissues and in extracts of lung carcinomas of all histologic types. Growth hormone-releasing hormone (GHRH)-producing bronchial carcinoid tumors can produce classic acromegaly. The clinical features and the pattern of HGH secretion are the same whether the GHRH comes from the hypothalamus or the lung. Many patients with carcinoid tumor secretion of GHRH have an intrasellar mass. Clinical improvement of acromegalic features in soft tissues occurs after carcinoid tumor resection. Treatment with chemotherapy (CCNU and 5-fluorouracil), bromocriptine, or the somatostatin analog octreotide have been reported to decrease circulating GHRH, HGH, and somatomedin-C concentrations and to reduce symptoms and signs of acromegaly. These treatments may not affect the size of the tumor mass.

Somatostatin is a tetradecapeptide that inhibits release of many hormones, including growth hormone. Somatostatin is found in all bronchial carcinoid tumors and in 25% to 40% of small-cell carcinomas. Paracrine and autocrine effects of tumor somatostatin such as inhibition of local growth factors or bombesin-like peptides have been proposed. No clinical sequelae of tumor somatostatin production are known.

Initially somatostatin receptors were thought to be expressed only in bronchial carcinoid tumors and small-cell carcinomas, but non-small-cell carcinomas and their metastases also express somatostatin receptors, albeit fewer of them. Scintographic labeling of the somatostatin receptor by ^{111}In-pentetreotide cannot be used clinically to identify lung tumor type but has been used to locate small tumor masses.

Gastrointestinal Hormones

Bombesin-Like Peptides

Gastrin-releasing peptide (GRP) has considerable homology with bombesin (BN), a tetradecapeptide first found in amphibians, and also with the slightly smaller peptide neuromedin C. GRP does considerably more than regulate gastrin secretion, and all of these bombesin-like peptides have similar actions. They are modulators of CNS activity, especially in the hypothalamus, and also have a wide range of peripheral actions. They lower body temperature, increase the pain threshold, increase plasma glucose, cause satiety, increase GI motility, and affect respiration in addition to stimulating release of gastrin and glucagon. Peak levels in pulmonary neuroendocrine cells occur shortly after birth, indicating a role for bombesin-like peptides in fetal lung development.

Most small-cell carcinomas produce BN/GRP, although only 5% of patients with small-cell carcinoma have elevated serum levels; BN/GRP also is found in carcinoid tumors and adenocarcinomas. A role for BN/GRP as an autocrine stimulator of small-cell carcinoma growth has been proposed because BN/GRP stimulates clonal growth and DNA synthesis in small-cell carcinoma cell lines. An antibody directed against the BN/GRP binding site prevents growth of tumor cells. No clinical manifestations of BN/GRP produced by a bronchogenic carcinoma are known, but BN/GRP might contribute to cancer patients' anorexia. Gastrin is found in small-cell carcinomas and in bronchial carcinoid tumors, but no clinical consequences are known.

Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP) is another intestinal peptide that actually is a neuropeptide with a wide central and peripheral distribution, structural similarity to a many-peptide family, and multiple actions including regulation of blood flow, relaxation of smooth muscle, and stimulation of electrolyte and water secretion. Patients with small-cell carcinomas with VIP hypersecretion have developed the watery diarrhea–hypokalemia–achlorhydria syndrome usually associated with VIPomas. Stools do not contain blood, mucus, or excess fat. The hypokalemia can produce profound weakness. Acidosis results from loss of bicarbonate in the stool, and hyperglycemia results from the hypokalemia and from VIP-induced liver glycogenolysis. Treatment includes fluid and electrolyte replacement. Prednisone may reduce the volume of diarrhea. Octreotide inhibits VIP secretion and improves symptoms in most cases.

Renin

Most renin-secreting tumors are of renal origin. The renin usually is secreted in the form of a large, inactive precursor, which suggests that the tumor is unable to carry out normal posttranslational processing. However, occasional bronchial carcinoid and small-cell carcinomas of the lung secrete enough active renin to produce hypertension and hypokalemia. The hypertension may be severe, resulting in retinal hemorrhage, and is poorly responsive to treatment, including treatment with b blockers and angiotensin-converting enzyme inhibitors.

Hypoglycemic Factors

Most tumor-associated hypoglycemia occurs in patients with large retroperitoneal tumors, but hypoglycemia has been reported with intrathoracic tumors including bronchogenic carcinoma. Increased glucose utilization by the tumor mass cannot account for the hypoglycemia. In most cases circulating insulin concentrations are low. Insulin-like growth factors (IGF-I and IGF-II) and other peptides with insulin-like bioactivity not suppressible by antibodies directed against insulin are almost never associated with bronchogenic carcinoma. The mechanism responsible for most hypoglycemia associated with bronchogenic carcinoma is unknown. Hypoglycemia usually develops when patients are fasting. Food ingestion may not be sufficient to relieve symptoms in patients with very severe disease.

HORMONAL SYNDROMES ASSOCIATED WITH BRONCHIAL CARCINOID TUMORS

Carcinoid tumors are neuroendocrine tumors that arise from a heterogeneous population of enterochromaffin cells found mostly in the submucosa of the intestine and the bronchi. Carcinoids have been classified according to the part of the primitive gut from which they are derived and by whether or not they reduce silver salts and produce 5-hydroxytryptamine (5-HT). Carcinoid tumors arising in tissues derived from the primitive foregut usually produce 5-HT. They may produce a wide array of peptides and amines and have receptors for numerous peptide hormones and neurotransmitters. Both bronchial carcinoids and small-cell carcinomas contain secretory granules that are typical of polypeptide-secreting endocrine tissues. Carcinoid tumors arising from primitive midgut usually produce 5-hydroxytryptophan (5-HTP), which is converted to 5-HT in other tissues. Tumors arising from the hindgut secrete neither 5-HT nor 5-HTP.

The carcinoid syndrome refers to the clinical manifestations that occur if sufficient quantities of vasoactive substances from the carcinoid tumor reach the systemic circulation.The syndrome is characterized by episodic flushing, diarrhea, paroxysmal bronchospasm, and valvular disease of the right side of the heart. These are attributed to overproduction of serotonin and its metabolites and possibly to prostaglandins and substance P, an undecapeptide distributed in gut and brain. Severe tryptophan depletion may result from excessive diversion of tryptophan into 5-HT synthesis. The carcinoid syndrome occurs in £10% of bronchial carcinoid tumors even though most of them contain 5-HT.

Bronchial carcinoids are remarkable for the number of clinical syndromes resulting from the peptide hormones they secrete. Production of ACTH or corticotropin-releasing hormone or both results in Cushing's syndrome. ACTH and/or melanocyte-stimulating hormone can produce hyperpigmentation (Nelson's syndrome). Secretion of growth hormone or growth hormone-releasing hormone results in acromegaly. Bronchial carcinoid tumors can produce enough parathyroid hormone to cause hypercalcemia, enough ADH to cause hyponatremia, or enough insulin to cause hypoglycemia. Immunoperoxidase staining reveals additional hormones that are not accompanied by clinical syndromes: calcitonin, HCG and its a subunit, gonadotropin-releasing hormone, somatostatin, gastrin, VIP, and bombesin. As many as eight to ten hormones may be found within a single bronchial carcinoid tumor.

Bronchial carcinoid tumors have been classified either as typical carcinoids, which are centrally located, have classic morphologic features, numerous secretory granules, little pleomorphism, and have a benign course, or as atypical carcinoids, which may be peripherally located, are more pleomorphic, have fewer, smaller secretory granules, and are more likely to metastasize. Clinical syndromes resulting from hormone secretion are reported almost exclusively with the atypical tumors.

If the carcinoid tumor cannot be removed, treatment must be directed toward the systemic manifestations. Nicotinamide supplementation may be necessary to counteract tryptophan depletion. The somatostatin analog octreotide is the treatment of choice. It does not reduce tumor size but inhibits flushing, diarrhea, and bronchoconstriction. Flushing occasionally responds temporarily to phenoxybenzamine, and diarrhea may be ameliorated by serotonin antagonists such as cyproheptadine. Response rates are <25% for either single chemotherapeutic agents or combinations; remissions usually last only a few months. Anesthetics, surgery, and chemotherapy can precipitate a carcinoid crisis—severe flushing with hypotension. This can be treated with octreotide or methoxamine or angiotensin. Other pressors should be avoided.

ADDITIONAL PEPTIDE/PROTEIN PRODUCTS OF BRONCHOGENIC CARCINOMAS

Oncofetal Antigens

Several glycoproteins normally are found in high concentrations in the developing fetus but in low concentrations in tissues in adults. Increased carcinoembryonic antigen (CEA) has been found in patients with all types of lung tumors as well as in smokers and in patients with nonneoplastic pulmonary disease. Attempts to use scintographic localization of CEA for tumor location, to use serum CEA concentrations to follow tumor progression, to differentiate benign from malignant pleural effusions, and to differentiate adenocarcinomas from mesotheliomas have usually not been successful in individual patients.

a-Fetoprotein is seldom produced by lung tumors. Immunoreactivity against this antigen is found in less than 3%.

Neuron-Specific Enolase

Neuron-specific enolase (NSE) is found in normal neurons and in neuroendocrine cells, all of which contain secretory granules and store and secrete peptides and biogenic amines. Carcinoid tumors and small-cell carcinomas, which are derived from these cells, contain secretory granules and express NSE. Neuron-specific enolase is elevated in fewer than 15% of patients with other types of lung carcinoma. Trump and co-workers have proposed that NSE might be a useful marker for detection and monitoring of small-cell carcinoma and for separating atypical carcinoid tumors from epidermoid tumors, large-cell tumors, and adenocarcinomas. Levels of NSE have been reported to be correlated with the tumor burden in patients with small-cell carcinoma, and the transient rise in serum NSE following initial chemotherapy is thought to reflect tumor cell destruction.

Additional Proteins

High levels of creatine kinase BB are found in the serum of 25% to 62% of patients with small-cell cancer and correlate with patient survival. Alkaline phosphatase, amylase, thymidine kinase, ferritin, pancreatic oncofetal antigen, calmodulin, b-microglobulin, keratin and other cytoskeletal markers, and calmodulin all have been reported to be elevated in association with bronchogenic carcinoma. However, their presence and levels are too erratic and too nonspecific to allow their use as tumor markers.

NEUROLOGIC SYNDROMES

Denny-Brown first described a sensory neuropathy associated with bronchogenic carcinoma in 1948. Since then, neurologic syndromes accompanying lung cancer, primarily small-cell cancer, have been shown to be more common than previously thought and can involve any part of the central or peripheral nervous system. These disorders often are discovered before the tumor becomes evident, but, unfortunately, unlike the hormonal syndromes, most neurologic syndromes do not remit if the malignancy is removed. There is little correlation between the size of the tumor burden or the rate of progression of the tumor and the severity of the neurologic disease.

Some role for the immune system seems well established, based on a strong association between a neurologic syndrome and a specific antibody in cancer patients but not the controls. Kornguth has proposed that the immunologic response to the tumor initially protects the patient by slowing tumor growth. Paraneoplastic syndromes occur when antibodies to tumor tissue cross-react with neuronal antigens. It is not clear how the antibodies gain access to neuronal cells.

Most paraneoplastic neurologic syndromes do not respond to immunosuppression, plasmapheresis, cancer chemotherapy, or radiotherapy. Even if serum antibody titers are reduced, CSF titers remain elevated, and there is no clinical improvement. Occasional cases with milder syndromes remain stable for months.

Central Nervous System

Paraneoplastic Encephalomyelitis

The umbrella term paraneoplastic encephalomyelitis (PEM) covers limbic encephalitis, brainstem encephalitis, myoclonus-opsoclonus, and cerebellar degeneration. These disorders are characterized by perivascular inflammation as well as neuronal degeneration. Patients present with a variety of psychiatric disorders, memory loss, dementia, and seizures. Brainstem encephalitis may result in ophthalmoplegia, bulbar palsy, involuntary movements, evidence of bilateral pyramidal tract lesions, etc., depending on the location involved. Opsoclonus is characterized by involuntary, chaotic eye movements. Cerebellar disease presents with ataxia and may be mild or severe, localized or diffuse.

Paraneoplastic encephalomyelitis is one of the paraneoplastic syndromes that is associated with antineuronal nuclear antibodies, known as anti-ANNA-1 or anti-Hu antibodies, which bind selectively to neuronal tissue. These antibodies can be found in serum and cerebrospinal fluid in patients with small-cell carcinoma as well as in tumor extracts and tumor cell lines. Whether these are responsible for the development of the neuronal syndromes or are an epiphenomenon is not certain. Paraneoplastic encephalomyelitis is frequently associated with paraneoplastic subacute sensory neuropathy, which is described below.

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) occurs far more often in association with breast cancer than with small-cell lung cancer. It is associated with specific serum and CSF immunoglobulins that bind to Purkinje cell cytoplasm and proximal dendrites in a characteristic pattern. A group of cerebellar proteins that react with the anticerebellar antibodies has been identified. Neither the proteins or the antibodies have been found in patients with cerebellar degeneration who do not have a malignancy. The gene coding for one of the PCD target antigens has been cloned, and its mRNA identified in cerebellar and tumor tissue. These experiments support the concept that paraneoplastic neurologic syndromes are the end result of cross-reactivity of antibody with shared brain-tumor antigens.

The clinical presentation usually begins with ataxia, and nystagmus, dysmetria, tremor, or dysarthria may develop later. Degeneration of Purkinje cells is diffuse and is coupled with thinning of other molecular layers. In contrast to the cerebellar degeneration associated with anti-Hu antibodies and paraneoplastic encephalitis, in PCD few inflammatory lesions are found.

Cancer-Associated Retinopathy

Cancer associated retinopathy (CAR) is a syndrome characterized by the triad of scotomatous visual field loss, photosensitivity, and retinal arteriolar narrowing, all of which may precede discovery of the small-cell carcinoma. Patients produce circulating antibodies to components of retinal cells and optic nerve. Circulating antibodies primarily recognize the photoreceptor cell protein recoverin. Histologic examination reveals loss of the photoreceptor cell layer. Patients present with rapid visual loss,

color loss, and night blindness. Unlike the other paraneoplastic neurologic syndromes, CAR responds to immunosuppressive therapy, particularly with prednisone.

Necrotizing Myelopathy

Necrotizing myelopathy is a rare paraneoplastic syndrome associated with anti-ANNA-1 or anti-Hu antibodies. The syndrome presents with bilateral loss of motor, sensory, and sphincter function but little pain. Most patients deteriorate rapidly, with ascending paraplegia resulting in death.

Peripheral Nervous System

Subacute Sensory Neuropathy

Subacute sensory neuropathy (SSN), like paraneoplastic encephalitis, is associated with the anti-ANNA-1 or anti-Hu antibodies, and the two syndromes often occur together. Patients develop symmetric numbness and parasthesias, especially in the lower limbs. Painful dysesthesias develop later. Vibration and position sense are most often impaired, but all sensory modalities are involved. Later in the course, patients frequently are unable to walk because of pain and loss of proprioception. Pathologic findings include loss of sensory neurons of the dorsal root ganglia and degenerative changes in the remaining cells. Some investigators suggest serologic testing for anti-ANNA-1 in elderly smokers with a peripheral sensory neuropathy of unknown cause and screening for occult cancer if the antibody is present. However, there is no treatment advantage accompanying early diagnosis.

Peripheral Sensorimotor Neuropathy

A heterogeneous group of sensorimotor peripheral neuropathies may occur alone or in combination with other paraneoplastic neuropathies and may antedate the diagnosis of malignancy. An axonal form is seen most often in patients with small-cell carcinoma. Lower neuron symptoms and signs predominate and are symmetric; symptoms progress at a variable rate. The etiology is unknown.

Autonomic Neuropathy: Chronic Intestinal Pseudoobstruction

Pseudoobstruction is characterized by weight loss, early satiety, nausea and vomiting, gastroparesis, abdominal pain, small and large bowel dilation, and constipation. Some patients have other signs of abnormal autonomic nervous system function. This paraneoplastic syndrome may be present for months to years before the small-cell lung carcinoma is diagnosed. Pseudoobstruction results from degeneration of neurons in the myenteric plexus. Autopsy studies of the gut reveal axonal degeneration, infiltration of plasma cells and lymphocytes, and proliferation of Schwann cells of the myenteric plexus—findings similar to those in other paraneoplastic neurologic syndromes.

Pseudoobstruction is associated with high serum titers of the same antineuronal nuclear antibodies (anti-ANNA-1 or anti-Hu) that are associated with paraneoplastic encephalitis and paraneoplastic subacute sensory neuropathy. In one series very high titers of anti-ANNA-1 were found in four of five patients with small-cell lung cancer with chronic pseudoobstruction but were not found in 29 patients with small-cell cancer without pseudoobstruction or in patients with chronic idiopathic intestinal pseudoobstruction or in other control patients.

Because teatment of the tumor can halt progression of neuronal degeneration or at least its symptoms, the serum anti-ANNA-1 antibody titer seems to be a useful diagnostic tool in cases of unexplained chronic pseudoobstruction. Pharmacologic approaches to increase bowel motility usually fail, so total parenteral nutrition and supportive therapy are the primary treatments. A few patients regain bowel motility, but most do not, and their symptoms do not improve.

Paraneoplastic Vasculitic Neuropathy

Paraneoplastic vasculitic neuropathy (PVN) occurs with both small-cell carcinoma and adenocarcinoma. The syndrome is characterized by an asymmetric sensorimotor peripheral neuropathy. Nerve conduction studies reveal either no response or slowed conduction, indicating axonal disease. In most cases the sedimentation rate is high. In contrast to the other paraneoplastic neurologic syndromes, with which it often occurs, spinal fluid protein is high. The diagnosis is confirmed by nerve biopsy, which reveals microvasculitis and axonal degeneration. Improvement following cyclophosphamide treatment directed against the vasculitis has been reported in only one case.

Neuromuscular Junction Syndromes: Lambert–Eaton Syndrome

The Lambert–Eaton syndrome (LES) is the best understood of all of the paraneoplastic neurologic syndromes. It occurs in 2% to 5% of patients with small-cell lung carcinoma but also occurs with other cancers and is associated with many autoimmune disorders. Patients complain of easy fatigability and weakness, which affect the pelvic girdle and shoulder girdle muscles more than distal strength and bulbar function. Lambert–Eaton syndrome differs from myasthenia gravis because muscle strength improves with exercise, and the response to edrophonium chloride is poor.

A presynaptic defect in the calcium-dependent release of acetylcholine from nerve terminal storage vesicles is the underlying cause of LES. Acetylcholine release requires influx of calcium through voltage-gated channels. In patients with LES, these channels are the targets of IgG autoantibodies. The best evidence that antibodies are the actual cause of LES comes from passive transfer experiments in which the syndrome was transferred to mice by administration of purified IgG from the sera of LES patients with and without a malignancy. Investigators are exploring whether antibodies to specific calcium channel subtypes are the ones most involved.

Patients improve with corticosteroid or other immunosuppressive drug treatment or plasmapheresis.

CONNECTIVE TISSUE AND OSSEOUS SYNDROMES: HYPERTROPHIC OSTEOARTHROPATHY AND CLUBBING

Hypertrophic osteoarthropathy (HOA, Bamberg– Marie syndrome) is a combination of (1) proliferative subperiostitis, primarily along the shafts of long bones; (2) symmetric arthropathy; and (3) increased blood flow in the long bones, digits, nose, and, occasionally, periauricular tissues that is frequently associated with lung malignancies, especially squamous cell carcinoma. Patients develop bone pain and joint pain with swelling and effusions in the elbows, wrists, knees, and ankles. Bone scans show increased uptake in cortices of the affected bones. Radiographic changes occur most often in the tibia and fibula, femur, ulna, and the phalanges (Fig. 3).

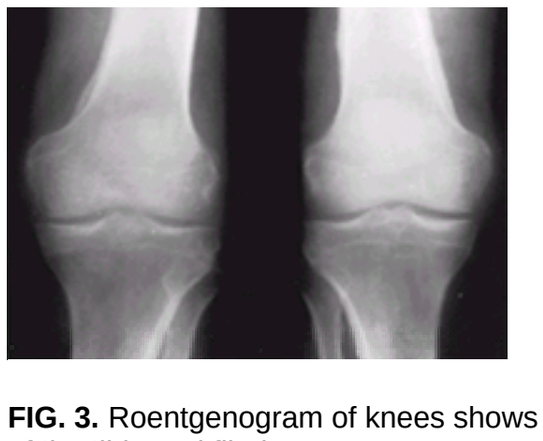

FIG. 3. Roentgenogram of knees shows pulmonary hypertrophic osteoarthropathy. Note the periosteal thickening along the distal shaft of the femur and proximal shaft of the tibia and fibula.

This form of HOA often is referred to as secondary hypertrophic pulmonary osteoarthropathy to differentiate it from pachydermoperiostosis or primary HOA. The primary form, a rare familial disorder with the bone features of HOA but not the lung disease or pain, is accompanied by oily, thickened, deeply furrowed facial skin, broadening of the nose, and prominent nasolabial folds; this form is not associated with cancer.

Clubbing of the fingers and toes, which was described by Hippocrates, is a painless, symmetric uniform swelling of the soft tissues at the ends of the digits (Fig. 4). The

earliest changes occur at the base of the nail, where the skin becomes shiny and tense, and the nail rocks more easily on its bed. Later the nail becomes curved, and the angle between the nail and the soft tissues at the base increases to over 180°. At a more advanced stage, soft-tissue hypertrophy develops. The transverse diameter of the distal phalanx is increased (referred to as acropachy), and the digit resembles a drumstick. Histologic examination of the clubbed digits reveals dilated, engorged vessels in the nail bed, edema, and deposition of new collagen.

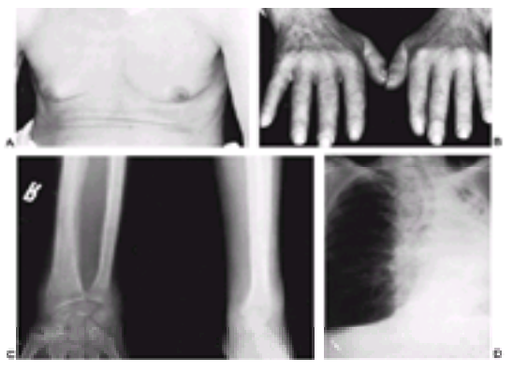

FIG. 4. A 64-year-old man presented with dyspnea, **(A)** gynecomastia, **(B)** clubbing of the fingers, and tender wrists. **(C)** Roentgenogram of the forearm and wrist shows hypertrophic osteoarthropathy. Note the periosteal thickening of the long bones. **(D)** Chest roentgenogram shows complete atelectasis of the left lung. A scalene node biopsy was positive for anaplastic carcinoma.

Both HOA and clubbing may develop long before the underlying tumor is apparent. Although clubbing almost always accompanies HOA, the reverse is not true. When clubbing does occur with HOA, the time of onset may be quite different, and the severity may not be proportional to the bone and joint changes. It is likely that clubbing results from a different process but one that usually occurs when HOA develops. Both HOA and clubbing respond to removal of the underlying tumor or to radiation or chemotherapy.

The mechanisms causing HOA and clubbing are uncertain. Tumor production of a vasodilator is considered unlikely because studies in dogs and humans have shown that vagotomy alone decreases peripheral blood flow and abolishes HOA. The increased blood flow is thought to be mediated through a reflex arc with afferents traveling via the vagus nerve, but the site and type of receptors mediating this pathway do not appear to involve any of the known chemoreceptor reflexes in the lung. The efferent pathway for the development of HOA is unknown. Vasodilators (i.e., nitric oxide) produced by vascular endothelium in response to nonadrenergic, noncholinergic neurotransmitters may be involved.

Increased estrogen, gonadotropin, and growth hormone secretion have been reported in some but not all patients, and the digital changes of acromegaly are different from those associated with clubbing and HOA.

The inflammatory changes resulting in damage to the microvasculature that have been seen with electron microscopy may be important and may explain the response of HOA symptoms to prostaglandin synthetase inhibitors such as indomethacin and aspirin and to glucocorticoid therapy.

VASCULAR SYNDROMES

Venous Thrombosis

The association of venous thrombosis and malignancy has been reported repeatedly since it was first described by Trousseau in 1868. Thrombosis is associated particularly with mucin-producing adenocarcinomas including those of the lung. Pulmonary embolism is a frequent complication of deep venous thrombosis (DVT); large thrombi also may cause gangrene or priapism. Possible mechanisms for thrombosis include release of procoagulants from tumor cells or monocytes and macrophages, hypercalcemia, dysfibrinogenemia, and decreased antithrombin III in addition to mechanical obstruction by the tumor, thrombocytosis, and increased platelet adhesiveness.

Pulmonary embolism with or without overt deep vein thrombosis may precede appearance of the neoplasm by months or years. One prospective study followed 153 acute DVT patients with no history of previous DVT, obvious risk factors, or cancer. Sixteen percent developed cancer within 2 years. Most of the cancers were detected in those who had a second DVT. Another study that screened patients with a first DVT more aggressively using tumor markers, CT scans, etc., found a 23% incidence of underlying malignancy. The positive predictive value of DVT for cancers of all types is approximately 20%, but only one patient in each series had unsuspected lung cancer. It is not clear what the impact of more aggressive screening and earlier diagnosis would be on survival.

Evaluation for an underlying malignancy probably is most useful if the location of the thrombosis is unusual (i.e., thrombosis migricans, Budd–Chiari syndrome) or recurrent. Treatment is difficult if the tumor cannot be removed. Anticoagulants may be effective in acute situations and can be used to prevent pulmonary emboli, but thromboses often recur despite apparently adequate anticoagulation.

Nonbacterial Endocarditis

Nonbacterial endocarditis is characterized by formation of sterile vegetations as a result of accumulation of fibrin on the mitral and aortic valves in patients with a variety of wasting illnesses, including bronchogenic carcinoma.

Fibrinogen Deficiency

Fibrinogen deficiency has been reported in patients with bronchogenic carcinoma, although this is seen more commonly with carcinoma of the prostate. Fibrinogen deficiency may be caused by widespread intravascular clotting, but elaboration of a circulating fibrinolysin by the tumor also has been suggested.

HEMATOLOGIC SYNDROMES

Anemia

Anemia in the absense of blood loss is common in malignancy. Most anemias result from nonparaneoplastic causes such as iron deficiency, impaired iron utilization and erythrocyte formation, chemotherapy and hemolysis, and bone marrow infiltration. However, hemolytic anemia does occur in response to tumor production of hemolysins.

Leukemoid and Leukoerythroblastic Reactions

Leukemoid and leukoerythroblastic reactions also are associated with bronchogenic carcinoma. Profound eosinophilia may occur, especially with tumor necrosis. Blood eosinophilia is not always associated with tumor eosinophilia. Several eosinophilopoietic and eosiniophil chemotactic peptides have been described.

CUTANEOUS SYNDROMES

Acanthosis Nigricans

Adult acanthosis is characterized by bilateral, soft, symmetric, darkly pigmented, verrucous lesions situated in the axillae, in flexural areas, in body folds, around the neck, around the umbilicus, and in the perianal region. Mucous membranes also may be involved. Histologic examination reveals thickened layers of the epidermis with an increase in the pigmented basal layers. If acanthosis nigricans is associated with malignancy, the tumor is usually intraabdominal, but about 5% of patients have adenocarcinoma of the lung. Although detection of acanthosis nigricans may precede detection of the underlying tumor, both the tumor and the skin disorder tend to

progress together. Removal of the tumor may lead to regression of the cutaneous changes.

Dermatomyositis

Approximately 15% of persons with dermatomyositis have an underlying malignancy. The percentage is higher in persons over 50, especially in men. Cutaneous manifestations often precede overt appearance of the tumor. Classical findings include a violaceous rash on the face, heliotrope eyelids, and proximal muscle weakness and atrophy. The mechanism underlying the development of this disorder is unknown. The skin changes may or may not resolve after the malignancy is treated.

Erythema Gyratum Repens

This is a rare condition usually found in association with cancer, especially lung cancers. Erythema gyratum repens is a slowly moving, erythematous, gyrate macular eruption that gives the skin a knotty-pine appearance. This condition is thought to develop in response to altered organ proteins produced by tumor necrosis. Immunoglobulin deposits are found at the basement membrane zone of the skin and in the lung tumor, and antibodies to basement membrane also appear in the circulation. The mechanism of the migration is unknown but has been compared to the movement of amebae in agar. Resection of the tumor results in disappearance of the cutaneous stigmata.

Additional Cutaneous Conditions Associated with Lung Cancers

A number of nonspecific dermatitides have been associated with lung cancers, including hyperpigmentation, erythema, bullous and eczematous rashes, ichthyosis, hypertrichosis, and pruritus. Tripe palms are thickened palms with hyperkeratosis and acanthosis and exaggerated skin markings that are associated with lung and gastric malignancies. The palm contours supposedly resemble the surface of tripe.

GASTROINTESTINAL SYNDROMES

Chronic Intestinal Pseudoobstruction

This condition has been discussed above; see the section on autonomic neuropathy under neurologic syndromes.

Biliary Tract Dilation

Three cases of biliary tract dilation associated with adenocarcinoma of the lung have been described. None of these patients had biliary symptoms, but they had high levels of alkaline phosphatase, modestly increased total and direct bilirubin, and increased g-glutamyltransferase. All had dilation of the entire biliary tree confirmed by CT scan and ERCP (endoscopic retrograde cholangiopancreatography). None of these patients had any other explanation for biliary tree dilation. There was no anatomic obstruction, no evidence of metastases to the liver, bile ducts, or bone, and no evidence of any other infiltrative process or gallstones. These patients had no evidence of hepatitis, no use of drugs or medications associated with liver disease, and no history of surgery or other systemic disease to explain the biliary tract dilation. Biliary mannometry and liver biopsies were not done.

RENAL SYNDROMES: NEPHROTIC SYNDROME

Nephrotic syndrome presenting in adult patients, especially older adult patients, is associated with bronchogenic carcinoma approximately 3% of the time. In most cases involving bronchogenic carcinoma, nephrotic syndrome is caused by membranous glomerulonephritis, with deposition of immune complexes including tumor antigen and IgG or IgA on the glomerular basement membrane. Nephrotic syndrome regresses in 75% of cases if the tumor responds to surgery or chemotherapy.

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CHAPTER

72 Developmental Anomalies of the Respiratory System

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INTRODUCTION

The larynx and trachea begin as a lengthwise groove in the floor of the embryonic gut. Furrows appear at the lateral edges of this groove and then fuse, separating the developing larynx and trachea from the esophagus. This structure is ridge-like, and its rounded caudal end forms the lung bud. The larynx develops from endoderm lining the cranial end of this laryngotracheal ridge. Supporting structures derive from the mesoderm of the fourth and fifth branchial arches. Arytenoid swellings then form laterally to the opening in the trachea or glottis. These swellings move cranially and forward to fuse into the primitive epiglottis. Proliferating epithelium obliterates the larynx before 10 weeks. After continuity is restored, the vocal folds appear below the lateral recesses of the ventricles. Innervation is provided by the vagus nerve, which supplies the structures derived from the fourth and fifth branchial arches.

The trachea develops from the midportion of the laryngotracheal tube and then elongates and descends into the thoracic cavity, as do the lungs. The muscles and cartilage-supporting structures derive from splanchnic mesoderm. Tracheal glands develop from the epithelial lining. The lung buds divide into right and left bronchopulmonary buds that later become the mainstem bronchi. These buds extend into the primitive pleural cavities. Secondary bronchi then form: two on the right, one on the left, which will develop into the three-lobed right lung and two-lobed left lung. By 7 weeks' gestation, third-order bronchi appear and then further develop into 18 bronchopulmonary segments, ten on the right and eight on the left. Twenty-four generations of bronchi and bronchioles develop by 16 weeks' gestation.

The following classification of the intrauterine development of the fetal lung is based on Boyden's description:

1. Pseudoglandular period (5 to 17 weeks). The lung appears as acinous glands, and elaborate branching of the airways and pulmonary vasculature dominates. Epithelium is cuboidal toward the periphery and pseudostratified near the hilum. By the end of this period, all prealveolar structures have developed.
2. Canalicular period (13 to 25 weeks). The bronchi and bronchiolar lumina enlarge during this period. At 24 to 25 weeks, each terminal bronchiole elongates and divides into two respiratory bronchioles. Vascularization rapidly proceeds, and proliferating vessels thin the cuboidal lining of these respiratory bronchioles. This process is necessary for subsequent terminal sac and alveolar development.
3. Terminal sac period (24 weeks to birth). During the final trimester, new respiratory bronchioles continue to develop within a thinned epithelium. Two types of epithelial lining pneumocytes can now be recognized. Surfactant, produced by type II pneumocytes, is first detected at this time. The developing pulmonary vasculature and thinned epithelial lining allow for extrauterine survival of increasing numbers of infants born preterm (38 weeks of gestation).
4. Alveolar period (late fetal period to 8 years). The number of alveoli reach adult levels by the age of 8 years. The newborn has one-sixth to one-eighth as many alveoli as does the adult.

DEVELOPMENTAL ANOMALIES INVOLVING THE LARYNX AND TRACHEA

Embryology of the Larynx and Trachea

The epiglottis develops anteriorly from the upper portion of the larynx, then broadens and grows upward toward the posterior pharynx. The arytenoid swellings form the lateral boundaries of the glottal opening. Proliferation of this epithelium temporarily occludes the larynx, which lengthens and reopens at 10 weeks of gestation. The laryngeal ventricles are lateral outpouchings found below the glottis opening. The vocal folds, which will eventually be lined with stratified squamous epithelium, are just caudal. From this point down, the lining will be pseudostratified columnar respiratory epithelium. The trachea lengthens considerably during development as the primary lung buds differentiate and move approximately eight segments downward into the pleural cavities. Developmental anomalies of the larynx and trachea result from aberrations in the pattern of normal differentiation.

Laryngomalacia

Sometimes called congenital stridor, laryngomalacia is caused by the flaccidity of a long epiglottis, short arytenoepiglottic folds, or bulky arytenoid swellings. These abnormal structures prolapse upward on inspiration, causing stridor. A soft expiratory stridorous component may be present as well. Stridor may present at birth or during an upper respiratory tract infection and may subsequently recur unrelated to any infectious episode. Stridor usually increases with quiet breathing and thus may be noted only during sleep. It can also be exacerbated by agitation or the supine position. Approximately half the affected infants have associated feeding difficulties, with vomiting or prolonged feeding time. The diagnosis is usually suspected clinically and must be confirmed by direct laryngoscopy, which is the procedure of choice. Severely affected infants manifest obstructive apneas and can develop cor pulmonale. The problem tends not to persist, with most symptoms resolving by the age of 1 to 2 years. Findings on indirect laryngoscopy in 19 children performed 7 to 12 years after the initial diagnosis were reported as normal. However, some children have persistent symptoms that occur during stress in later childhood. Current surgical therapy utilizes endoscopic CO_2 laser removal of redundant tissue performed unilaterally. Some individuals will require subsequent removal of tissue on the other side. There is a higher incidence of pectus excavatum in individuals with laryngomalacia.

Subglottic Stenosis

Congenital narrowing of the subglottic area may be caused by cricoid cartilage anomalies or by increased amount of soft tissue surrounding the subglottis. It is thought to result from external compression by the sixth branchial arches before 10 weeks of gestation. Affected infants present with stridor at birth, and the stridor is persistent.

Differentiation from laryngotracheobronchitis (croup) may be aided by roentgenographic findings. In both entities, the subglottic air column is narrowed on inspiration, and the hypopharynx is distended with air. On expiration, however, the narrowing associated with subglottic stenosis appears fixed, whereas it often widens in croup. Minimal findings of anterior or posterior indentations of the air column are unlikely to be related to croup. Infants with mild symptoms of subglottic stenosis may require no treatment; others require tracheostomy or other surgical interventions.

The extreme form of subglottic stenosis is subglottic atresia. Prolonged endotracheal intubation for respiratory support has caused an increase in acquired laryngotracheal stenosis. Laryngotracheal reconstruction has been performed in some patients.

Laryngotracheoesophageal Cleft

Laryngotracheoesophageal (LTE) cleft is a rare disorder associated with significant morbidity and mortality. The disorder may be separated into a mild form involving the posterior larynx but not extending through the cricoid cartilage, a form that extends through the cartilage into the cervical tracheal rings, and into a complete LTE cleft involving the thoracic trachea. A LTE cleft is usually caused by a lack of rostral extension or failure in formation of the tracheoesophageal septum. Failure in fusion of the dorsal portion of the developing cricoid cartilage plays a contributory role. These infants have increased oral secretions, cyanosis, and choking with all feedings. The presentation may simulate esophageal atresia (EA) or tracheoesophageal fistula (TEF). The LTE cleft and EA or TEF coexist in 20% of patients with LTE. The diagnosis may be suspected from the anterior position of a nasogastric tube on a lateral chest radiograph. On occasion, the diagnosis may be missed because of a physiological apposition of the edges of the cleft with inspiration. Cineesophagram reveals spillover of liquid into the larynx and trachea on swallowing. Laryngoscopy is the preferred method for diagnosis and repair of supraglottic clefts. Those LTE clefts extending to the carina or beyond to the mainstem bronchi present major challenges to successful surgical and postoperative management. Postoperative management may require prolonged nasotracheal intubation or tracheostomy.

Tracheal Agenesis

Floyd and associates divided tracheal agenesis into three types: type 1 (10%) consists of agenesis of the upper trachea with communication between the esophagus and the distal patent trachea; type 2 (59%) is agenesis of the entire trachea with a small fistulous connection between the esophagus and the carina where normal bronchi are fused; and type 3 (31%) is complete agenesis of the trachea with the bronchi arising from the esophagus. Polyhydramnios during pregnancy and prematurity are risk factors. There is very high incidence (70%) of major associated malformations in other organ systems, particularly in the cardiac, renal, and gastrointestinal systems. Of the embryologic explanations offered, Bremer's theory of a marked ventral location of the developing LTE system appears most tenable. Infants will present with respiratory distress and an inability to vocalize, and intubation will be impossible. The diagnosis can be made by immediate laryngoscopy, which will reveal a blind pouch, and esophagoscopy to look for a fistula. A temporary airway can be surgically created, and a tracheostomy can be done for type I agenesis if the pouch is long enough, but definitive therapy of the other types is not possible.

Complete Tracheal Rings

The posterior membranous portion of the tracheal rings may rarely be replaced by cartilage. The trachea is then poorly distensible, which causes respiratory distress that worsens markedly with infection. When the defect is limited, segmental resection may be attempted. However, the most common anomaly has not been successfully repaired thus far.

Laryngeal Web

This is a rare anomaly of the larynx, with an estimated incidence of one in 10,000 births. The web is caused by partial or complete failure of the larynx to reopen at 10 weeks of gestation. Seventy-five percent of laryngeal webs result from membranes extending across the anterior one-half to two-thirds of the true vocal cords. The remainder occur in supraglottic (1.5%), subglottic (7.5%), or combined locations. An absent or hoarse cry is usually present at birth. Respiratory distress may be a presenting sign. The diagnosis is made by direct laryngoscopy. The membrane may be quite dense, with muscle, fat, and/or cartilage present. Insertion of a Silastic or tantalum keel can prevent the incised edges from rejoining in such cases. Simple incision is insufficient for well-differentiated webs.

Laryngocele

This rare anomaly presents as an air-filled cystic outpouching of the laryngeal wall. It is most often palpated in the anterior triangle of the neck at the level of the thyrohyoid membrane. The cyst increases in size during a Valsalva maneuver and decreases in size with palpation. These lesions may become infected, increase in size, and obstruct the airway. Surgical intervention is necessary; an external approach is preferred.

Vascular Rings

Extrinsic compression of the trachea by anomalous vessels may cause respiratory difficulty during infancy. The anomalous vessels represent persistent branchial arch vessel(s), as in double aortic arch, the most common of the vascular compression syndromes. A lateral chest film may show tracheal compression. The diagnosis can be confirmed on esophagram, which will reveal narrowing of the esophagus.

ESOPHAGEAL ATRESIA AND TRACHEOSOPHAGEAL FISTULA

The anomalous development of the esophagus was first described by Gibson in 1696 in a report of a proximal EA with a distal TEF. The first feeding gastrostomy was done in 1888 by Steele, and the length of the blind distal segment was measured. In 1913, Richter first attempted transpleural ligation of the distal fistula with establishment of a feeding gastrostomy. In the late 1930s, adoption of an extrapleural approach plus establishment of cervical esophagostomy foreshadowed the subsequent primary repair independently developed by Leven and Ladd in 1939. Both patients underwent gastrostomy, ligation of the distal fistula, cervical esophagostomy, and eventual anastomotic repair of the proximal and distal esophagus.

Several different categorizations have been proposed for these anomalies. Esophageal atresia with distal TEF is by far the most common type (86.6%). Atresia without fistula (7.7%), TEF without EA or H-type TEF (4.2%), EA with proximal fistula (0.8%), and EA with proximal and distal fistulas (0.7%) are much rarer in occurrence. All these entities occur sporadically, with an incidence of one in 3000 live births. Only a few examples of more than one case in a family have been reported.

The prognosis is dependent on the severity of the esophageal pathology and the overall condition of the infant. Measurement of the length of the atresia (gap length) may be a useful predictor of outcome. Longer gaps have a worse prognosis. When the proximal esophagus ends in a blind pouch, aspiration pneumonitis is common. A proximal TEF results in direct flow of proximal esophageal contents into the tracheobronchial structures. A distal TEF results in regurgitation of stomach contents in a retrograde manner into the trachea. Crying causes acute gastric dilation followed by flow of gastric acid into the lungs. Attempts at feeding produce crying with resultant choking, regurgitation, and cyanosis. The capacity of the proximal segment may be limited to only a few milliliters.

Findings on anteroposterior and lateral chest radiographs may confirm the diagnosis (Fig. 1). Absence of air in the gastrointestinal system suggests no associated distal fistula, and a technically more difficult surgical repair can be anticipated. The morbidity and mortality associated with surgical repair depend on the presence of other anomalies, which are common (50%) in these patients (Table 1). Esophageal atresia also has been associated with pulmonary agenesis.

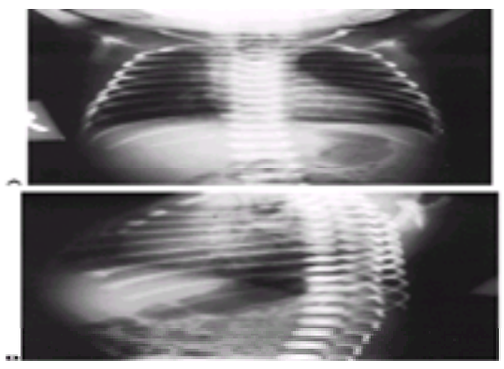

FIG. 1. Tracheoesophageal fistula. Note the curving nasogastric tube in the proximal esophagus. Presence of air throughout the remainder of the gastrointestinal tract results from the fistulous connection.

Patients with no associated anomalies (52%)	553
Patients with associated anomalies (48%)	505
Congenital heart disease	201
Gastrointestinal anomalies	134
Genitourinary anomalies	109
Imperforate anus	99
Musculoskeletal anomalies	91
Central nervous system anomalies	63
Facial anomalies	53
Other	99
Total number of anomalies	849

TABLE 1. *Incidence of additional anomalies in patients with respiratory anomalies*

Division of the TEF and primary anastomotic reconstruction of the esophagus are the procedures of choice in term infants. With sick, preterm, or small-for-gestational-age infants, a staged repair has been advocated to decrease morbidity and mortality. A gastrostomy is done, followed in a few days by retropleural division of the distal TEF. After aspiration pneumonitis has been controlled and nutrition provided via gastrostomy, an end-to-end anastomosis may be performed. Esophageal atresia without TEF (»7.7% of cases) and EA with proximal TEF (1% of cases) are associated with the widest gaps between the proximal and distal segments. When primary repair is not possible, colonic interposition using an isoperistaltic segment of transverse colon has been the procedure of choice. Postoperative complications have included stricture, leak at the anastomotic site, and pneumonia.

Long-term follow-up has shown an increased incidence of respiratory infection secondary to aspiration from reverse peristalsis and mild restrictive pulmonary deficits. Feeding should continue, and patients should sleep in a 60° upright position indefinitely.

CONGENITAL DIAPHRAGMATIC HERNIA

The diaphragm results from the embryonic fusion of four structures; the largest of these, the septum transversus, arises from the same cervical somites (C3 to C5) as the phrenic nerve. This septum extends inward from the ventral surface to separate the pericardial and peritoneal cavities. The bilateral pleuropericardial and pleuroperitoneal folds then arise from the body wall to surround and separate the embryonic lungs from the heart and abdominal viscera. The mediodorsal portion of the diaphragm is formed from the dorsal mesentery. The pleuroperitoneal folds join the septum transversus to form the diaphragm. Failure of this fusion allows herniation of abdominal contents to occur through the patent pleuroperitoneal canals and accounts for the posterolateral herniation through the foramen of Bochdalek in 80% of all cases of congenital diaphragmatic hernia (CDH). This usually occurs at gestational age of 10 to 12 weeks, when bronchi and bronchiolar differentiation is taking place. Retrosternal herniation through the foramen of Morgagni accounts for most of the remaining cases.

The incidence of congenital diaphragmatic hernia (CDH) is thought to be about one in 2200 births, based on the British Perinatal Mortality Survey. There is no significant correlation with increased parity, advanced maternal age, or socioeconomic status. Boys are affected twice as often as girls. Although CDH is almost always sporadic in occurrence, some families with near-total unilateral agenesis of the diaphragm inherited as an autosomal recessive trait have been described. Associated anomalies (cardiac, genitourinary, extralobar sequestration, neural tube defects, other chromosomal abnormalities) are commonly associated with CDH.

Infants with CDH through the foramen of Bochdalek present in the first day(s) of life with dyspnea, tachypnea, and cyanosis. There may be dullness to percussion and decreased breath sounds on the affected side, prominence of the affected hemithorax, and a scaphoid abdomen as a result of displacement of abdominal contents into the thorax. Herniated contents consist of stomach, small intestine, and the descending colon (Fig. 2), and the herniation occurs through the left hemidiaphragm approximately five times as often as through the right. Herniation of some but not all bowel would fail to produce a scaphoid abdomen. Accurate prenatal diagnosis can be made with ultrasonography: polyhydramnios, mediastinal shift, bowel herniation and malrotation, and absence of an intraabdominal stomach bubble suggest the diagnosis. The diagnosis can be confirmed at the time of birth by conventional chest radiography showing the herniated contents and mediastinal shift toward the opposite side. Contrast studies are rarely needed.

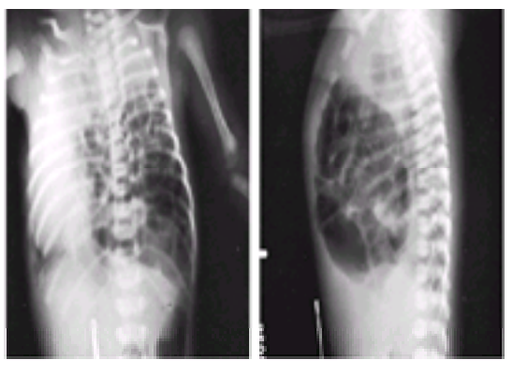

FIG. 2. Congenital diaphragmatic hernia. There is herniation of small intestine, large intestine, and stomach (or parts thereof) into the left hemithorax. Note the air in the descending colon.

Congenital herniation of abdominal contents into the thoracic cavity was rarely recognized during life before roentgenography became available. Successful surgical correction began in the 1930s, and the techniques were well described by Ladd and Gross in 1940. Survival rates have not improved since that time despite improved newborn care, anesthesia, and surgical management. Advances in care have allowed patients with more severe abnormalities to survive until operation. Mortality rates range from 30% to 80% and depend on (1) the severity of the defect, (2) persistent fetal circulation with associated pulmonary hypertension, and (3) associated pulmonary hypoplasia (ipsilateral, contralateral, and bilateral).

Antenatal correction is still experimental but has been successful in selected cases (22 to 30 weeks of gestation). It is now felt that neonatal surgical intervention should be delayed until the respiratory status has been stablized by mechanical ventilation. Several authors advocate an abdominal approach because of easier reduction by traction and the high incidence of associated malrotation (30%). A transthoracic approach also has been used, with comparable survival rates. Bowel reduction does not ensure survival. The associated pulmonary hypoplasia affects the ipsilateral and, in some cases, contralateral lung. The total number of airways and airway generation number are decreased. Even when herniation is unilateral, there are associated elevated pulmonary arterial pressure and vascular resistance. No abnormality in the nitric oxide system or in thromboxane levels has been found. There is an increase in endothelin-1. Increased pulmonary arterial muscle mass has been observed in children dying with CDH. In addition to pharmacologic management and instillation of artificial surfactants at the time of birth, partial liquid ventilation and extracorporeal membrane oxygenation (ECMO) have been employed; these modalities may be associated with improved survival rates. Comparisons in outcome among institutions are difficult to make but may be facilitated by using predictors of severity such as the best postductal PO_2. Values higher than 100 mm Hg were associated with survival in 41 (91%) of 45 patients, and only one (7%) of 14 patients with a best postductal PO_2 less than 100 mm Hg survived. At the present time, mortality rates for patients with CDH diagnosed in early gestation are still high despite optimal postnatal therapy including ECMO.

CONGENITAL CYSTIC DISEASES OF THE LUNG

This group of entities is characterized by cystic pulmonary tissue. Although the exact embryogenesis of various forms is disputed, all result in aberrant differentiation of bronchi, bronchioles, alveoli, and pulmonary vasculature. The major forms of congenital cystic lung disease include bronchogenic cyst, pulmonary sequestration, congenital cystic adenomatoid malformation, and congenital lobar emphysema.

Bronchogenic Cyst

Bronchogenic cysts originate in abnormal diverticuli of the lung bud in the third to sixth week of fetal life. They are usually located adherent to the left mainstem bronchus or carina and are extrapulmonary in location within the middle mediastinum. Abnormal budding in the distal tracheobronchial tree causes intraparenchymal cysts. The cyst wall contains all elements of the normal bronchus: columnar and mucus-secreting epithelium, smooth muscle, elastic tissue, and cartilage.

Most children with obstructing cysts who present in early infancy have moderate to severe respiratory distress and clinical signs of airway obstruction such as stridor, wheezing, and cyanosis. Cysts may be air filled, fluid filled, or exhibit air–fluid levels. Chest radiographs may not show a mass but may reveal signs consistent with obstruction by a cyst: postobstructive hyperlucencies or severe obstructive atelectasis with mediastinal shift; a lucent cystic area containing curvilinear shadows consistent with lobar hyperaeration may also be seen (Fig. 3). Subcarinal bronchogenic cysts have been demonstrated using real-time ultrasonography and a parasternal approach. The optimal modality for imaging cysts is computed tomography (CT). Cysts may also be visualized by magnetic resonance imaging and generate high signal intensities on T_2-weighted scans. T_1-weighted scans are of variable intensities depending on the contents of the cyst.

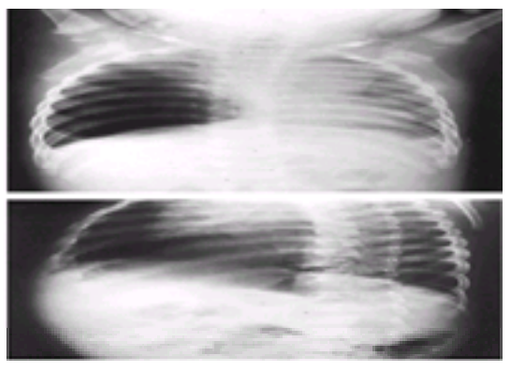

FIG. 3. Bronchogenic cyst. Hyperaeration with definable boundary within a lobe.

The diagnosis can usually be made by barium swallow, which reveals an esophagus typically deviating backward and to the right, with the trachea pushed forward and narrowed. A communication between the cyst and the tracheobronchial tree cannot always be demonstrated at operation. Bronchoscopy is generally not helpful, and bronchography is dangerous and not recommended.

Bronchogenic cysts generally range in size from 1.5 to 4.0 cm. All identified bronchogenic cysts should be surgically removed because they have a high likelihood of eventually becoming infected. After removal, prognosis is excellent; however, cysts have recurred. Imaged thoracoscopic surgery has been successful in removing mediastinal cysts without a thoracotomy. Two cases of embryonal rhabdomyosarcoma have been found within lung cysts.

Pulmonary Sequestration

Sequestrations are cysts that are not connected with the tracheobronchial tree. They are generally divided into intralobar sequestration, which is located within lobar tissue, and extralobar sequestration or accessory lobe, which has its own pleural covering. About two-thirds are located within the left lower lobe, and the remainder in the right lower lobe. Sequestrations arise from accessory bronchial buds located either inside (intralobar) or outside (extralobar) the developing lung, along with persistence of a pulmonary branch of the dorsal aorta secondary to failure of the pulmonary artery to vascularize the periphery of the lower lobe. Exposure of the pulmonary aortic branch to systemic pressure then causes cystic degeneration of the sequestered lobe. About 75% of sequestrations receive blood via a feeding artery from the thoracic/abdominal aorta. The remainder receive blood from many sources, including the subclavian, intercostal, pulmonary, pericardiophrenic, innominate, internal mammary, celiac, gastric, splenic, and renal arteries. Feeder vessels are usually solitary, but between 15% and 25% of sequestrations may be fed by multiple vessels. Venous drainage is most commonly via the pulmonary veins (intralobar) or bronchial or other (extralobar) vessels. One review of 42,000 pediatric autopsies questions the designation of intralobar sequestration as a congenital malformation.

The clinical presentation is variable (Table 2). Extralobar sequestration is associated with diaphragmatic hernia on the left in almost 60% of cases. Intralobar sequestration usually presents as an inflammatory mass in the posterobasal segments of the lower lobes (Fig. 4). There are several reports of pulmonary sequestration presenting with congestive heart failure rather than the far more common respiratory symptoms.

Distinguishing feature	Extralobar	Intralobar
Bronchopulmonary tissue	Found above or below the diaphragm	Confined to posterior basilar segments of lower lobe
Pleural covering	Separate from the rest of the lung	No pleural separation
Side affected	Left > 90%	Left 65%
Foregut communication present	Occasionally	Rarely
Associated anomalies	Frequent	Uncommon
Found in neonates	Often	Never
Age at diagnosis	<1 year in 60%	>20 years in 50%
Sex distribution	M:F = 4:1	M = F
Venous drainage	Systemic or portal	Pulmonary

[a] From Hutchin P. Congenital cystic diseases of the lung. Ann Surg 1971;28:652.

TABLE 2. *Pulmonary sequestration*[a]

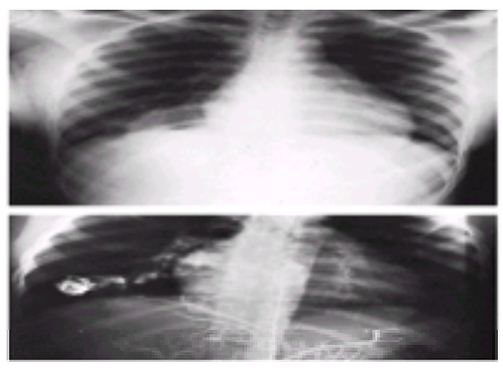

FIG. 4. Intralobar sequestration in the right lower lobe. Retrograde arteriogram shows that the blood supply is from the aorta below the level of the diaphragm. Opaque material remains from the previous bronchogram.

The diagnosis is generally made by CT imaging. Barium contrast studies may demonstrate the occasional extralobar sequestration that is associated with a fistulous connection to the esophagus. Magnetic resonance angiography and ultrasonography have been useful in demonstrating the aberrant systemic blood supply, but angiography remains the gold standard, as these other modalities do not detect small vessels. Surgical removal is curative.

Congenital Cystic Adenomatoid Malformation

Congenital cystic adenomatoid malformation (CCAM) is a rare form of congenital cystic disease of the lung, with fewer than 100 cases reported before 1978. The lesion is caused by an arrested alveolar development associated with a proliferation of terminal bronchioles in the affected lobe. These bronchioles are lined by columnar or cuboidal epithelium and have soft walls. Air enters and then is trapped, causing cystic dilation of the bronchioles. The entire malformation may cause a mediastinal shift to the opposite side and compressive atelectasis of otherwise normal adjacent lung tissue.

Three morphologic types have been described. Type I is characterized by large cysts 3 to 10 cm in diameter. Type II is characterized by numerous cysts, each between 0.5 and 3.0 cm in diameter. Type III is characterized by many small cysts, each less than 0.5 cm in diameter. The CCAM specimen shown in Fig. 5 demonstrates radiolucent areas with curvilinear densities associated with scattered coalescent soft-tissue density infiltrates, representing areas of atelectasis, that may also be seen with bronchogenic cysts.

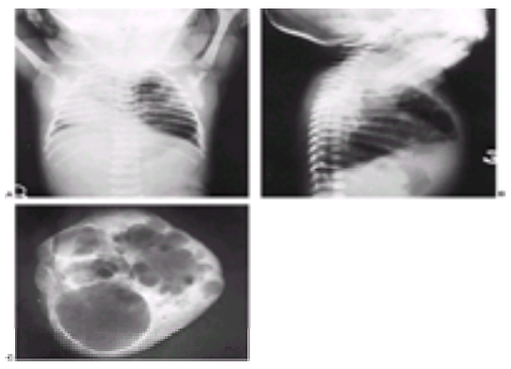

FIG. 5. (A and B) Congenital cystic adenomatoid malformation of the lung. **(C)** A roentgenogram of the surgically resected specimen.

CCAM has three distinct clinical presentations. About a third of patients present as stillborns with anasarca with or without a history of maternal polyhydramnios. Early detection of these patients by ultrasonography is possible, and an early clinical clue to the presence of CCAM is polyhydramnios. The CCAM in these cases is severe in that the involved lobe hampers cardiac function and obstructs venous return, causing anasarca. In type I lesions, intervention *in utero* with placement of a thoracoamniotic catheter may be done and allows resolution of hydrops and mediastinal shift. Resection of the CCAM may be done after delivery. The CCAM may also be removed during fetal life in selected cases.

The newborn infant may present with tachypnea, dyspnea, and cyanosis. Roentgenographic diagnosis of the mass may be difficult; it may be confused with congenital lobar emphysema (CLE). Lobectomy is the procedure of choice; on occasion, an anomalous vessel may be found. Preoperative bronchography or aortography is generally not necessary. Resected patients have a good prognosis. Less commonly, patients with CCAM present in childhood with a history of recurrent pulmonary infection or when the mass ruptures into the pleural space.

Congenital Lobar Emphysema

Congenital lobar emphysema is a surgically correctable cause of severe respiratory distress in infancy. Affected infants may present with respiratory distress that is mild or severe, precipitated by crying, feeding, or, on occasion, respiratory infection. Boys are somewhat more often affected than girls. The left upper lobe is most frequently involved, followed by the right middle lobe. Disease of the lower lobes and bilateral disease are rare (Fig. 6). Congenital lobar emphysema is almost always not of genetic origin, but two affected sisters and an affected mother and daughter have been reported.

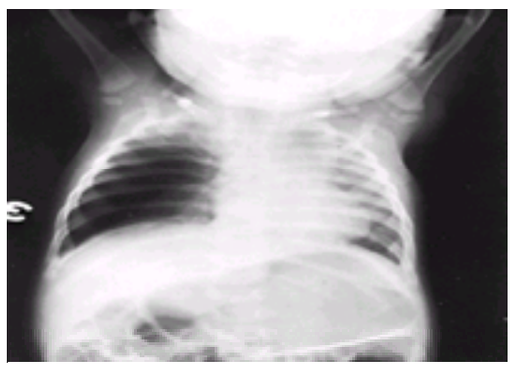

FIG. 6. Congenital lobar emphysema with hyperexpansion of the right middle lobe. The compressed lower lobe is visible as a triangular shadow in the cardiophrenic angle.

The pathology of CLE has been attributed to deficient bronchial cartilage in the affected main bronchus, which causes endobronchial proliferation of mucous membranes and subsequent obstruction. Deficient cartilage (25% of cases), endobronchial obstruction (13%), extrinsic compression of the bronchus by an anomalous vessel (1%), and diffuse lobar bronchial abnormalities (4%) have all been demonstrated; no cause has been found in 50% of cases. An alveolar wall defect in the quantity, quality, or distribution of collagen or elastin has been postulated to explain CLE of unknown cause.

Affected neonates or infants present with respiratory distress. Half the cases present in neonates, and three-fourths in infants under the age of 6 months. The thoracic wall may be prominent over the involved lung, with hyperresonance on percussion and decreased breath sounds over the involved lobe. The apical cardiac impulse may be shifted away from the involved side, and the diaphragm may be depressed on the affected side. Chest radiographs reveal a hyperinflated lobe with the mediastinum shifted away from the affected lobe. The emphysematous lobe may be herniated into the contralateral hemithorax. Retained fetal fluid may cause the cyst to have a more solid appearance. With clearing, the more typical radiolucent lobe is revealed. The differential diagnosis of CLE includes pneumothorax, pneumatocele, and congenital cyst of the lung. Congenital lobar emphysema may be distinguished from these entities by the persistence of lung markings in the affected lobe on chest radiographs. The other lesions cited have absent lung markings in involved areas. In CLE, the vessels may be attenuated and abnormally separated within the emphysematous lobe. Lung scanning has provided helpful information regarding ventilation and perfusion in the cystic areas. Pneumothorax is rarely associated with CLE. There are associated cardiac defects (ventricular septal defect, patent ductus arteriosus) in a much higher percentage of patients with CLE than with other congenital cystic diseases of the lungs. Some authors have speculated that dilation of the pulmonary artery is pathogenetically related to the evolution of CLE in some patients.

Congenital lobar emphysema may be treated surgically with excellent results. Lobectomy is generally advocated. High-frequency jet ventilation has been used intraoperatively to maintain oxygenation and provide a near-motionless lung. Segmental resection may be curative in some instances. Nonoperative management is almost never indicated. There have been some reports of nonsurgical treatment in individuals presenting with concurrent viral infection during infancy or when patients were older (7 and 10 years) at initial diagnosis.

DEVELOPMENTAL ANOMALIES OF MEDIASTINAL STRUCTURES

The mediastinum contains all the viscera of the thorax with the exception of the lungs and their surrounding pleura. Embryologically, pleuropericardial folds appear longitudinally against the lateral body wall in the fourth week of gestation. These grow together in the midline and separate the developing heart from the lungs as they grow downward into the pleural canals. When the primary lung buds appear in the fifth week, the heart is a large structure. Over the next 2 weeks, the lungs undergo two subsequent divisions, and the bronchopulmonary segments are established. The lung enlarges relative to the heart, and the pleural membranes form the lateral

boundaries of the mediastinum.

The mediastinum may be anatomically divided into superior and inferior compartments, with the inferior further subdivided into anterior, middle, and posterior portions. Alternatively, the entire mediastinum may be divided into anterior, middle, and posterior divisions.

The anterior mediastinum contains the thymus, the anterior portion of the pericardium, and the heart. A few anterior mediastinal lymph nodes and, rarely, a substernal extension of the thyroid may be present. The most common anterior mediastinal mass in infancy is a hyperplastic thymus gland (Fig. 7). Regardless of the size of the thymus, it does not cause tracheal compression or displacement. If compression of the anterior tracheal wall is noted, an esophagram is indicated. Findings positive for a mass exclude enlarged thymus from the differential diagnosis. Surgical intervention should not be required because the thymus undergoes involution with age. Thymomas rarely occur and are frequently associated with immunodeficiency. Thymomas presenting in adult life may be associated with myasthenia gravis, diabetes, chronic hepatitis, or arthritis.

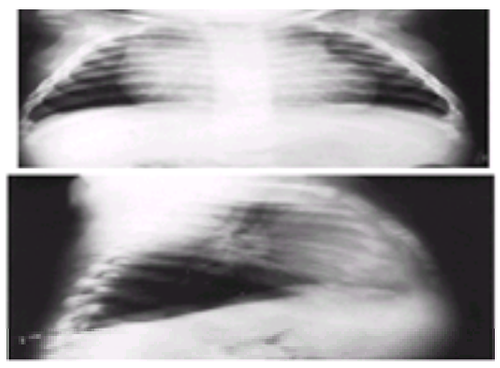

FIG. 7. Normal thymus. Note the absence of the retrosternal clear space and of tracheal compression.

Teratomas also occur in the anterior mediastinum. These lesions contain cells from all three germ layers (Fig. 8). Teratomas also may be intrapericardial in origin (Fig. 9). When symptomatic, mediastinal teratomas produce respiratory compromise, and newborns may present with signs of cardiac tamponade or hydrops fetalis. Teratomas may be benign or malignant. Pericardial cysts may also be found in the anterior mediastinum at the right cardiophrenic angle. They are neither symptomatic nor premalignant.

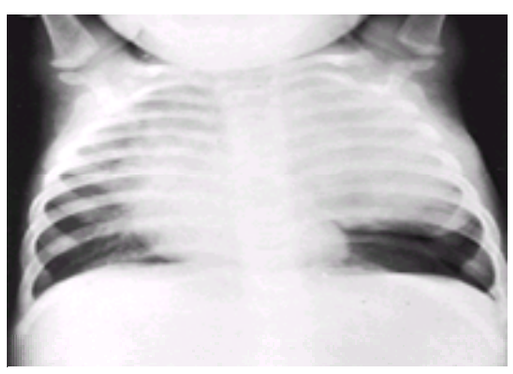

FIG. 8. Mediastinal teratoma. Air in the pleural space outlines the inferior margin of the teratoma. This particular lesion had no distinguishing characteristics such as teeth or bone. Obliteration of the upper portion of the heart border is a positive silhouette sign indicating anterior location of the mass.

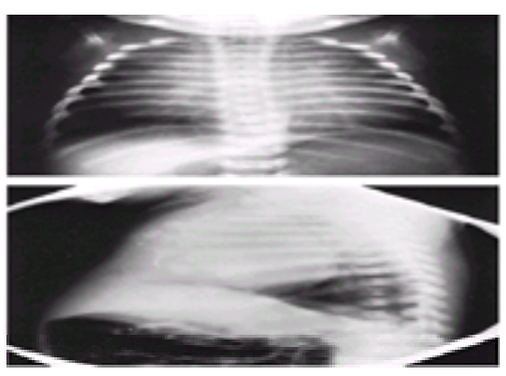

FIG. 9. Pericardial teratoma. Note the calcification within the pericardium on the lateral view.

Computed tomography of the chest is the imaging procedure of choice in the evaluation of suspected mediastinal masses. The CT differentiates cystic, solid, vascular, and fatty lesions. Diagnostic thoracotomy or mediastinoscopy may not be necessary in patients with benign fat deposition or asymptomatic cysts.

Enterogenous Cysts (Duplications)

Foregut duplications may present in the mediastinum. Occasionally, the presence of cervical vertebral anomalies such as hemivertebrae may suggest a foregut duplication. The endoderm of the foregut develops in close proximity to the notochord. A portion of endoderm may adhere to notochord as the latter is surrounded by paraxial mesoderm to form the vertebral bodies. Defects in these bodies are then formed. There may or may not be a fistulous connection to an enterogenous cyst, which forms at the cervical level and is then pulled into the thorax with the developing fetal lung. More commonly, duplications result from accessory foregut budding in early fetal life.

Enterogenous cysts present as rounded densities in a retropleural, paraesophageal position adherent to the esophageal wall (Fig. 10). They are lined by the columnar epithelium of the primitive esophagus. Other duplications may present in the mediastinum but are lined by gastric mucosa or other distal endodermal lining. In the latter cases, erosion with perforation into the right lower lobe may occur. These patients present with respiratory distress and hemoptysis from massive hemorrhage. Treatment is surgical when vertebral anomalies accompany the mediastinal cyst; a spinal cyst may be present as well. Computed tomographic scanning with myelography should be done even when the patient is asymptomatic.

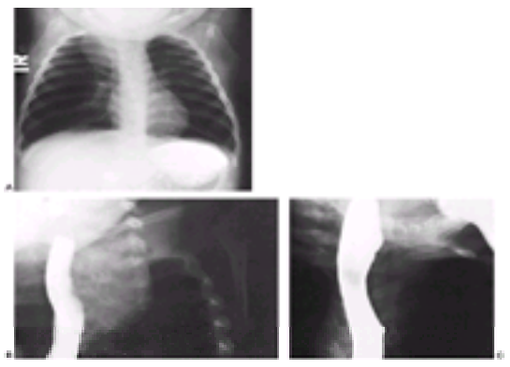

FIG. 10. Esophageal duplication. **(A)** Anteroposterior chest x-ray film shows a rounded soft-tissue density of mediastinal origin. **(B** and **C)** Spot films from esophagram show pressure on the esophageal wall from an extrinsic mass. The obtuse angle of the barium above and below the mass shows it to be submucosal in origin.

ANOMALIES OF THE PLEURAL FISSURES

The visceral pleura constitutes the most distal layer of the visceral mesothelial tissues enveloping the lung, and the fissures may be regarded as inward plications of the pleura, separating the pulmonary lobes. There are some anomalies of these fissures or pleural extensions that, though seldom of clinical importance, deserve brief mention.

Absence or Incomplete Development of Fissures

One or more of the major interlobar fissures may be absent or incomplete. Such a defect may be suspected when an expected fissure marking is not visible in the posteroanterior or lateral roentgenogram. Absence or incomplete fissure formation can be proved only at thoracotomy. These defects are significant because absence of a fissure may permit direct extension of lesions, notably tuberculous lesions, from one lobe to another and also because such defects may complicate operative procedures such as lobectomy.

Complete or Incomplete Accessory Fissures

Complete or incomplete accessory fissures are responsible for the formation of the following accessory lobes: (1) a dorsal lobe, set apart from the superior segment of one of the lower lobes; (2) a cardiac lobe, lung tissue cut off from the medial basal segment of one of the lower lobes; (3) an anterior basal lobe, a fragment separated from one of the anterior basal segments; and, at times, (4) a true left middle or lingula lobe, the lingula fully separated from the rest of the left upper lobe by an accessory fissure.

These accessory fissures may be recognized in roentgenograms as linear densities at the locations indicated. They are generally of no clinical significance.

AZYGOS LOBE

The azygos lobe is actually a portion of the right upper lobe. It is separated from the rest of that lobe by an abnormally laterally placed azygos vein, which is invaginated into the pleural covering of the lobe, producing a linear roentgenographic density that courses upward and outward from the upper pole of the right hilum to midclavicle or apex. This anomaly, of no practical significance, is said to occur in about 1% of individuals.

SUBCARDIAC LOBE

The so-called subcardiac lobe (lobus caval) is created when a part of the right lower lobe herniates into a pocket formed by the parietal pleura, in close relationship to the inferior vena cava. Like the azygos lobe, it has no clinical importance.

ANOMALIES OF THE THORACIC CAGE (PECTUS DEFORMITIES)

Pectus excavatum and pectus carinatum are congenital abnormalities of the anterior chest wall. They are probably caused by abnormal growth rates in costal cartilages causing retrusion (excavatum) or protrusion (carinatum) of the sternum. Excavatum is seen eight to 12 times as frequently as carinatum and occurs three times more often in boys than girls. Most cases are sporadic, although genetic transmission occurs.

The functional consequences of these deformities have been difficult to document. Some children complain of chest pain and reduced exercise tolerance. Studies of pulmonary function have shown mild restrictive deficits compared with normal controls, with decreases in vital capacity, total lung capacity, and maximal breathing capacity. These deformities may be corrected using a number of different techniques. Reviews of surgical series report good cosmetic and psychological results. Some patients have improved exercise tolerance after surgery. Cardiac function has been studied in some patients; results of complete right-sided heart catheterization were normal, as was the response to supine exercise. Upright treadmill exercise showed decreased cardiac output compared with that of normal controls. Cardiac output was improved after surgery, although neither value was in the abnormal range.

Many patients with pectus deformities require no surgical intervention. There is generally no progression of the deformity. Indications for correction include young age (4 to 6 years) to prevent compressive thoracic deformity and pulmonary and cardiac dysfunction and to improve cosmetic appearance. The current surgical technique for excavatum, described by Haller and colleagues, includes subperichondrial removal of all abnormal cartilages preserving the perichondrium. A sternal osteotomy is then done, and the sternum is elevated and fixed in place with nonabsorbable sutures. In older children and adults, the correction is supported by a metal strut placed anterior to the rib cage and beneath the sternum in a perpendicular position. In patients with carinatum deformity, the lateral depression on either side of the deformity is surgically corrected.

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CHAPTER

73 Genetic Diseases of the Lung

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INTRODUCTION

Many pulmonary diseases may be viewed as having both genetic and nongenetic components in their causation. In some conditions, inherited as Mendelian traits, the disease is primarily caused by the effects of a single mutant gene but is influenced to different degrees by environmental factors. These entities are relatively few and usually present as systemic diseases in which pulmonary manifestations are prominent. Cystic fibrosis is the prime example. At the opposite end of the spectrum are many common pulmonary disorders in which environmental factors predominate, but in which genetic factors may play some modulating role. The genetic component in this latter group may fit the model for polygenic or multifactorial inheritance, in which several genes, each with a small additive effect, place the individual at increased risk of developing disease when exposed to inciting environmental factors. The multifactorial inheritance model fits when applied to some congenital malformations, exemplified by spina bifida and cleft palate. Disorders with a significant polygenic component would be expected to show familial aggregation and perhaps exhibit differences among ethnic groups or races. The identification of the polygenic components of pulmonary disease would provide clinically useful data because individuals at increased risk could be counseled and the patients' environment modified to prevent the disease or ameliorate its course.

In the following sections, several diseases are described in which a genetic cause is either proved or implied. For some of these entities, detailed information is lacking on the mode of inheritance, the frequency of the mutant gene in populations, or on the basic biochemical defect producing the disease.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is the most common lethal genetic disease in Caucasian populations and is the cause of much of the chronic progressive pulmonary disease encountered in children. With improving prognosis over the past several decades (the median survival age is now approximately 30 years), CF has also become a disease of young adults.

Cystic fibrosis is characterized by the clinical triad of excessive concentrations of sodium and chloride in exocrine sweat, chronic obstructive pulmonary disease (typically associated with chronic bacterial infection with *Staphylococcus aureus* and/or *Pseudomonas aeruginosa*), and exocrine pancreatic insufficiency. However, the severity of expression is variable, especially with regard to pancreatic function. Approximately 7% of patients have clinically sufficient pancreatic function; many of these have specific mutations in the CF gene that are associated with relatively mild pulmonary disease. Other patients have mutations in the gene associated with CF but do not exhibit typical clinical manifestations of disease; whether these individuals should be diagnosed as having CF is problematic. Congenital bilateral absence of the vas deferens (CBAVD) is the primary example of this phenomenon.

Genetics

It has long been known that CF is an autosomal recessive disorder involving approximately one in 2500 to one in 3500 newborns in North America. CF results from a mutation in a gene located on the long arm of chromosome 7 (7q31.3). The most common mutation involves a three-base pair deletion, which results in the absence of a phenylalanine residue at amino acid position 508 of the gene product. This mutation is referred to as the DF508 mutation. About two-thirds of all CF chromosomes examined to date carry this mutation. Several hundred other mutations, some of which are associated with relatively mild clinical disease, have been documented in this same gene.

Cystic fibrosis heterozygotes are clinically normal. It is estimated that approximately one in 25 to one in 35 white individuals in North America is a heterozygote. Various theories have been proposed to explain a putative heterozygote survival advantage given the high gene frequency. In view of the current understanding of the gene and its function, the most attractive such hypothesis is that heterozygotes are relatively protected against the effects of chloride-secreting diarrhea, especially infantile or epidemic diarrhea such as cholera.

The gene product, known as the cystic fibrosis transmembrane regulator (CFTR), is a large, glycosylated, 1480-amino-acid protein. CFTR functions as a chloride-selective ion channel located in the apical membrane of epithelial cells in the airways, sweat glands, and intestine or may be the entire channel. The function of CFTR is regulated in part by changes in intracellular cyclic adenosine monophosphate (cAMP). Different mutations lead to loss of chloride channel functions by a variety of mechanisms.

Incidence and Prevalence

The incidence of CF varies widely in different populations; it is most common in southern Europe and least common in Asian and black populations. Likewise, the incidence of specific mutations varies. The DF508 mutation is more common in northern than in southern European populations. Reported incidence figures range from 1:620 live births in individuals of Dutch descent in Southwest Africa to 1:90,000 live births in Orientals. The incidence in U.S. blacks has been estimated to be about 1:17,000. Cystic fibrosis is predominately a disease of Caucasians, in which the incidence of heterozygotes is estimated to be approximately 3% to 4%.

The total number of patients with CF is unknown. The Patient Registry of the Cystic Fibrosis Foundation (Bethesda, MD) records data on each patient followed by care centers in the United States. At the end of 1995, approximately 20,000 patients have reported to the Registry; of these, 24.6% were age 21 years or older; 96.2% were white, and 3.3% were black; 53.6% were male, and 46.4% were female. The total number of individuals with CF has been estimated to be twice as high as the number recorded in the Registry data base; but 25,000 may be a more reasonable estimate.

Pathophysiology

The most important clinical feature of CF is chronic obstructive pulmonary disease, which is characterized by accumulation of thick secretions in airways and chronic bacterial infection. Although ciliary structure and beat are apparently normal, mucociliary clearance is impaired, and mucous plugging of small airways can be detected in infants with no discernible pulmonary infection. The current (though incomplete) understanding of this phenomenon relates to the function of CFTR (and chloride permeability of respiratory epithelial cells) in the regulation of mucociliary transport and the composition and volume of the fluid lining the airway surfaces.

Because of the dysfunctional gene product, the apical membrane of the respiratory epithelial cells is impermeable to chloride, and the normal flux of chloride across the luminal surface is reduced. At the same time, there is excessive active sodium reabsorption. These phenomena are reflected in the bioelectric properties of the airway epithelium. The resting transepithelial electrical potential is elevated in CF individuals, from the normal range of 25 to 35 mV to 55 to 90 mV. Selective inhibition of the sodium pump (i.e., by a drug such as amiloride) reduces the transepithelial potential to nearly 0 mV. Amiloride does not reduce the potential nearly as much in normal subjects, as continued flux of chloride maintains a potential of 10 to 15 mV (lumen-negative). Furthermore, chloride flux is normally increased by b agonists such as isoproterenol, but this response is absent in CF individuals. These electrophysiological phenomena have been utilized to facilitate the diagnosis in patients with equivocal sweat test results or atypical clinical manifestations.

Although a full understanding of the mechanisms is lacking, it is widely assumed that failure of normal regulation of the volume and/or electrolyte composition of the periciliary fluid results in impaired clearance of pulmonary secretions, thus leading to obstructive pulmonary disease. Infants and young children may have evidence of airway obstruction such as bronchial casts recovered in bronchoalveolar lavage fluid. Infection may or may not be present. Failure of mucociliary function alone does not account for the entire pathogenesis, as patients with congenitally absent ciliary function (primary ciliary dyskinesia) do not have the same degree of viscous changes in their pulmonary secretions, nor are they characteristically infected with *Ps. aeruginosa.* The role of CFTR in other cellular membranes (such as the Golgi apparatus) is not yet understood, but it is possible that alterations in the function of such membranes could play a role in other CF-specific phenomena such as the marked susceptibility to infection with *Ps. aeruginosa* and the increased sulfation of mucus glycoproteins.

The hypothesis that the primary event in causing clinical disease is mucus hypersecretion or mucociliary clearance failure has been challenged. There is apparently a dysregulation of inflammation in the lungs of CF patients, with increased levels of proinflammatory mediators and decreased levels of antiinflammatory mediators such as IL-10. The relationship of this phenomenon to dysfunctional CFTR is unclear, but the two may be linked. Autopsy studies of young infants with CF suggested that in at least some patients, evidence of infection begins before there is evidence of airway obstruction. Other investigators have reported elevated levels of inflammatory mediators (IL-8) in BAL fluid from very young infants with CF even in the absence of a neutrophil response. Destruction of the bronchial epithelium by infection or impairment of mucociliary transport by abnormally viscous secretions also contributes to widespread airway obstruction. High concentrations of neutrophil elastase are found in the purulent airway secretions, which may overwhelm the indigenous antiprotease activity and destroy airway walls. Chronic inflammation and proteolysis may therefore contribute substantially to the progressive bronchiolectasis and bronchiectasis that are characteristic of CF. For this reason, there has been interest in the use of antiinflammatory and protease inhibitor therapy as part of the comprehensive management of CF patients.

Abnormalities of chloride permeability are also found in nonrespiratory epithelia, including the pancreatic and sweat ducts. In the pancreas, obstruction of small ducts as a result of decreased fluid secretion with subsequent release of pancreatic enzymes into the tissue leads to autodigestion of the exocrine pancreas. In the majority of patients, this process has progressed to the point of clinical pancreatic insufficiency by the time of birth and can be detected by elevations in circulating trypsinogen or pancreatic isoamylases. Ultimately, at least 90% of such patients require enzyme replacement therapy. Deficiency of pancreatic enzyme secretion and the consequent maldigestion in turn lead to a myriad of secondary problems, including protein–calorie malnutrition and fat-soluble vitamin deficiencies.

The primary secretory product of sweat glands is isotonic with plasma, and the composition of sweat at the skin surface is controlled by the relative reabsorption of water and electrolytes by the sweat duct. The volume of sweat is regulated by blood flow into the gland and thus by the total volume of ultrafiltrate in the primary secretory coil. Normally, sodium and chloride are actively reabsorbed, leaving a hypotonic fluid at the surface. The concentration of chloride in normal sweat is on the order of 10 to 20 mEq/liter; in CF, the ductal epithelial cells are relatively impermeable to chloride, so that the concentration of chloride in the sweat at the skin exceeds 60 mEq/liter. If the rate of sweat formation is very low, there may be enough reabsorption of chloride so that the concentration at the skin is in the normal range (<60 mEq/liter). Thus, for diagnostic purposes it is important to measure sweat chloride concentrations in secretions from maximally stimulated sweat glands (see below).

Diagnosis

The traditional diagnostic criteria for CF include a sweat chloride concentration exceeding 60 mEq/liter and at least one of the following: (1) chronic obstructive pulmonary disease (especially if associated with *Ps. aeruginosa* infection), (2) exocrine pancreatic insufficiency, and (3) confirmed family history of classic CF in a sibling, parent, child, or first cousin. DNA analysis, with demonstration of two mutations known to be associated with CF, is another diagnostic criterion. However, because of the possibility that yet another mutation could modify the effects of the CF mutation, some authorities do not accept a diagnosis of CF made solely on the basis of DNA analysis. At least one patient has been reported with typical pulmonary and gastrointestinal manifestations of CF but with a normal sweat chloride; this individual was homozygous for the DF508 mutation but also had the R553Q mutation. It is not practical to assay for every known mutation in the CF gene (several hundred have been reported), and therefore, a “negative” DNA analysis does not totally exclude the diagnosis of CF.

In practice, the most important diagnostic tool is the sweat test. This test, although simple in concept, is difficult to perform accurately. As mentioned, sweat must be collected from glands maximally stimulated by iontophoresis of pilocarpine. At least 100 mg of sweat should be collected to ensure an adequate sweat volume. The sweat should be collected with great care to avoid evaporation and analyzed titrimetrically for chloride. Alternative methods for sweat analysis involve quantification of chloride by ion-specific electrodes or by conductivity. These methods are unreliable, even for screening purposes. Sweat osmolality has been used instead of electrolyte measurements but may be less specific. The use of nonstandard sweat test methods is partly responsible for the high rate of false-negative and false-positive results commonly seen in patients referred to major CF centers after diagnostic studies elsewhere.

The normal value for sweat chloride is less than 60 mEq/liter and, in the majority of normal subjects, less than 40 mEq/liter. There may be a slight increase in normal values with age, with an occasional normal adult having a sweat chloride concentration as high as 70 mEq/liter. In patients with suggestive clinical presentations who consistently have sweat chloride values in the range of 50 to 60 mEq/liter, additional testing, including DNA studies, may be helpful. Physiological studies may help with the diagnosis if the genetics are uncertain. Studies would include measurement of the transepithelial bioelectric potential in the nasal epithelium and its response to amiloride and isoproterenol (the abnormal response is an elevated basal potential, with marked response to amiloride but none to isoproterenol), and the response of sweat glands to intracutaneous injection of atropine and isoproterenol (the abnormal response is a lack of secretion).

The most important and practical aspects of DNA-based diagnostic tests for CF involve prenatal diagnosis and the identification of family members who are heterozygous for the gene. Within families, even though the affected individuals may have an unusual or as-yet-undefined mutation, it may be possible to identify heterozygotes with reasonable accuracy. DNA-based population screening (i.e., universal newborn screening), however, is impractical with present technology.

Other methods have been advocated for population screening. Sweat testing would be extremely expensive and is therefore impractical. Screening for pancreatic insufficiency in newborns has been done by detecting increased amounts of albumin in the meconium or finding evidence of active pancreatic destruction (elevated serum levels of immunoreactive trypsin). These tests do not necessarily detect those patients with normal pancreatic function and are, therefore, of somewhat limited value. A positive result from any screening test must be confirmed by definitive testing.

Diagnosis in Adults

The majority of patients are diagnosed in the first year of life, but many will escape recognition until adolescence or even adulthood. Thirteen percent of patients reported to the Patient Registry of the Cystic Fibrosis Foundation in 1995 were diagnosed after the age of 10 years (and 5% after age 20 years). These patients may

have milder or atypical forms of the disease and thus escape clinical suspicion. It is a mistake to think that a patient looks too good to have CF or is too old. Well-characterized patients have been diagnosed in the sixth decade of life. Cystic fibrosis should be suspected in patients with early onset of chronic bronchitis, especially if accompanied by chronic gastrointestinal symptoms of nearly any kind. Chronic sinusitis, male (or female) infertility, nasal polyps, a history of rectal prolapse or heat prostration, and pulmonary colonization with *Pseudomonas* species (especially if a mucoid strain) are all potential indications for further investigation. Many adult patients will successfully deny their gastrointestinal problems (malabsorption) and may attempt to hide their chronic cough behind a cloud of tobacco smoke.

Pathology

Lung

The earliest manifestations of CF in the lung are dilation and hypertrophy of bronchial glands and goblet cell metaplasia. As obstruction proceeds, infection develops, and a vicious cycle is established, the result of which is bronchiectasis and decreased lung function. Early in the course of disease, the bronchioles are the principal location of obstruction and inflammation, and peribronchial abscess formation and fibrosis develop late. The alveolar spaces are relatively spared, although interstitial disease has been reported. Cystic bronchiectasis is common in end-stage disease.

Gastrointestinal Tract

Exocrine pancreatic insufficiency, which occurs in more than 90% of patients, results from inspissation of secretions in the pancreatic ducts. The consequent autolytic destruction of the exocrine portions of the organ gives the disorder its original name, cystic fibrosis of the pancreas. The islet tissue is relatively spared despite near-total fibrofatty replacement of the remainder of the organ.

Intestinal mucous glands are hypertrophied, with extensive ductal obstruction, and goblet cells are prominent. Similar changes in mucus-secreting elements may be seen in salivary glands. Fatty changes occur in the liver of as many as 30% of patients, and biliary cirrhosis, caused by inspissation of bile, may be found in 20% to 30% of older patients. Portal hypertension with esophageal varices occurs in 2% to 3% of patients.

Genitourinary Tract

Male infertility is almost universal and results from absence or atresia (perhaps from *in utero* obstruction) of the vas deferens. Testicular function and spermatogenesis are normal. There are no specific abnormalities of the female reproductive tract, although evidence of mucus hypersecretion and inspissation of gland ducts may be seen.

Sweat Glands

The sweat glands are anatomically normal despite their failure to reabsorb sodium and chloride.

Clinical Manifestations

The clinical manifestations of CF are variable and are influenced by treatment and by genetic and environmental variables. In the majority of patients, the pulmonary component predominates, but some patients have virtually no lung symptoms until the second or third decade of life. Patients with clinically normal pancreatic function tend to have milder pulmonary involvement.

Pulmonary

Cough is the earliest and most prominent clinical manifestation of pulmonary disease. It may begin as an infrequent and nonproductive cough but progresses inexorably (usually over years) to become productive of thick sputum. The chest often remains clear to auscultation until the airways disease is relatively advanced (the thick secretions do not generate noise). Radiographic and physiological (i.e., spirometric) evaluation is helpful in following the course of disease. Wheezing may be prominent during acute exacerbations in infants, but coarse crackles and rhonchi are more likely, especially in older patients. There is a distinct predilection for involvement of the right upper lobe, and many patients have worse disease in the right lung than the left. With progression, digital clubbing develops, the lungs become hyperinflated, physical findings become persistent, and the patient grows more symptomatic. Usually, however, patients do not exhibit cyanosis or marked decreases in exercise tolerance until relatively late in the course. In contrast with chronic obstructive lung disease in adults, the clinical course of CF is usually precipitous once overt respiratory failure develops.

The upper airway may also be involved. Pansinusitis is almost universal, and nasal polyps are present in 10% to 15% of patients. In 1995, 2.8% of patients reported to the CF Patient Registry required surgery for nasal polyps.

Chronic pulmonary infection is an almost constant finding in CF patients. Early in the course, *S. aureus, H. influenzae,* and a variety of other organisms may be found. Eventually, *Ps. aeruginosa* becomes the predominant or only organism in the majority of patients (two-thirds to three-quarters of patients between ages 11 and 24). Other gram-negative organisms such as *Stenotrophomonas maltophilia* may also be pathogens in CF patients. Viral agents are often responsible for symptomatic exacerbations and may be implicated in the initiation of lung damage early in life. Fungi, especially *Aspergillus* species, also may be isolated from sputum, although their clinical significance may be difficult to discern. Allergic bronchopulmonary aspergillosis is not rare in CF patients; a 1.8% incidence was reported in 1995. Recently, *Burkholderia cepacia* (formerly known as *Ps. cepacia*) has became a major pulmonary pathogen and was reported in 7.2% of patients aged 18 to 34 years. In about 20% of patients who become colonized with *B. cepacia,* a catastrophic downhill course ensues. For this reason, patients known to be colonized with *B. cepacia* should be isolated from other CF patients when hospitalized. Strains of atypical mycobacteria are also found in some patients and may be pathogenic.

Other pulmonary manifestations of CF include hemoptysis (which may be massive), atelectasis, pneumothorax, and cor pulmonale.

Gastrointestinal

Meconium ileus (neonatal intestinal obstruction) occurs in 15% to 20% of patients with CF. In addition to the usual clinical findings of obstruction, there may be radiographic evidence of *in utero* perforation, with sterile peritonitis resulting in peritoneal calcifications. Malrotation or volvulus may also occur in association with meconium ileus.

More than 90% of patients have clinically significant exocrine pancreatic insufficiency. In some, secretion of bicarbonate and enzymes may be reduced, but sufficient function may remain to prevent steatorrhea. Episodes of acute pancreatitis may occur in these patients. The effects of pancreatic insufficiency include fat and protein maldigestion with consequent malabsorption and production of bulky, greasy, foul-smelling stools. Secondary caloric, protein, and fat-soluble vitamin deficiencies may develop in untreated or inadequately treated patients. Rectal prolapse is common in younger, untreated patients and may be a presenting symptom.

Late intestinal obstruction (“meconium ileus equivalent”) may develop as a result of inspissation of bowel contents in the cecum or terminal ileum and occurs in 2% to 4% of patients annually. The colon tends to be distended because of the malabsorption, and intussusception (often relatively painless and sometimes without obstipation) is not uncommon. Patients taking very high doses of pancreatic enzyme supplements may develop a syndrome of fibrosing colonopathy with colonic strictures.

Genitourinary

Almost all men with CF are sterile, but a semen analysis is required to be certain, as some patients have normal sperm counts. Female fertility is reduced, both by chronic illness and by thick cervical mucus. However, a significant number of women with CF have conceived (151 pregnancies were reported in 1995). Those with moderate to advanced disease who become pregnant are at risk of worsening their clinical condition. Infants born to these women are obligate heterozygotes.

Sweat Glands

Failure to reabsorb salt from the sweat ducts is almost universal in patients with CF, with sweat electrolyte concentrations above 60 mEq/liter. With adequate replacement of salt in the diet, there are usually no significant clinical manifestations of the sweat defect. Excessive loss of salt can lead to heat prostration, and, in infants, metabolic alkalosis can develop, even in cold weather. Patients presenting with metabolic alkalosis unexplained by loss of gastric or intestinal fluid should be

carefully evaluated for CF.

Metabolic

Many patients develop glucose intolerance in the late second or third decade of life, with an incidence reaching 16% by age 35 to 44. This is presumably related to gradual loss of functioning pancreatic islet tissue. Although ketoacidosis is unusual, many patients require insulin to control their glucosuria.

Treatment

Recent advances in the understanding of the molecular basis of CF have been impressive. Improvements in therapy have been somewhat slower to evolve but are the subject of intensive development. Unfortunately, because the rate of progression of disease is slow, it is very difficult to discern meaningful benefit in clinical trials. Another difficulty of developing new therapy is compounded by the fact that the most benefit can be expected in infants and young children, in whom clinical research is more difficult. Definitive evidence of successful therapy may be difficult to obtain in a short-term study, and it is often necessary to utilize surrogate indicators for success.

New and Developing Therapy for CF

Pharmacologic manipulation of epithelial ion transport is an obvious target for therapy aimed at reversing defective CFTR function. Amiloride blocks the increased absorption of sodium from the airway lumen, thus (presumably) maintaining better hydration of the periciliary fluid and secretions. Results of pilot studies in adult patients were encouraging, but larger-scale clinical trials have not borne out the early enthusiasm. Nucleotide triphosphates (ATP, UTP) appear to open an alternative chloride channel in airway epithelial cells; clinical trials of UTP and amiloride in combination are under way.

Pharmacologic manipulation to reduce the viscoelastic properties of tracheobronchial secretions has long been a goal of therapy. The presence of high concentrations of DNA in purulent secretions may contribute substantially to viscosity. Human recombinant DNase has been reported to reduce the viscosity of airway secretions and, in clinical trials, has led to modest improvement in pulmonary function in some patients.

Modification of the inflammatory processes in the airways has been attempted by several approaches. Administration of alternate-day prednisone (1 mg/kg) resulted in improved pulmonary function in a multicenter trial, but there were unacceptable side effects. Aerosolized steroids are currently under investigation. Nonsteroidal antiinflammatory agents such as ibuprofen have also been shown to have moderating effects on the progression of pulmonary disease, at least in young patients, by reducing neutrophil migration into the airways. Ibuprofen must be given at very high doses, and there is evidence that low doses may actually enhance inflammation. Clinical trials of aerosolized protease inhibitors are under way.

Modification of the function of the defective gene product and modification of posttranslational processing of the gene product are additional potential therapeutic approaches under development.

Ultimately, CFTR gene transfer seems the best hope for a cure. Successful experiments with *in vitro* gene transfer have been reported from many laboratories. *In vivo* studies have also begun to show promise, and a number of different approaches are being developed. Transduction of the CFTR gene into epithelial cells via modified viral vectors, by encapsulation within cationic liposomes, and by receptor-mediated transfer are some strategies that have been used. At present, it can be said that gene therapy is exciting and promising but unlikely to be totally successful in the near term. It is clear that gene therapy will not be curative in patients with extensive bronchiectasis, so it is imperative that patients be treated aggressively today in hopes of preserving their lungs in preparation for curative therapy in the future.

Conventional Treatment

The empirical, conventional therapy for CF has not changed dramatically in the past two decades. There is considerable disagreement as to the most effective therapeutic regimen, and objective data in support of one or another method are scant. In general, however, it may be said that CF is a complex disorder that involves multiple organ systems, and treatment is best handled in specialized centers where concentrated expertise and experience are available. Continuity of care and a strong patient–physician relationship are important components of successful therapy.

Pulmonary Therapy

The main goal of pulmonary therapy is to prevent or reverse the progression of pulmonary disease. This is approached in two ways: by efforts to improve airway clearance and by efforts to reduce infection.

Physical measures to enhance clearance of pulmonary secretions include chest percussion, forced expiratory maneuvers, vigorous exercise, and cough. The flutter device is a useful adjunct to mobilization of secretions and can be used by patients without dependence on parents or other caregivers. Airway obstruction begins at a very early age, and chest physiotherapy should be initiated at the time of diagnosis, even in patients who are asymptomatic. At times of symptomatic exacerbation, the frequency or the intensity, or both, of such therapy should be increased. Dehydration should be avoided.

Various forms of aerosol therapy, including mucolytic agents, bronchodilators, and antibiotics, have been used. There is little evidence to support the use of mucolytic aerosols. b-Adrenergic agents have been shown to increase mucociliary transport in patients with CF, but the clinical efficacy of such therapy is unknown. Some patients exhibit increased airway obstruction following bronchodilator therapy, and the response is not necessarily consistent over time. Therefore, such treatment must be individualized. Aminoglycoside (or other antibiotic) aerosols may be effective, either alone or in combination with parenteral therapy. In general, aerosolized agents may be expected to be more effective in the earlier stages of the pulmonary disease because obstruction with thick secretions limits the penetration of aerosols.

Antibiotic therapy is important in reducing the pulmonary bacterial burden. The presence of large numbers of bacteria in the airways induces secondary inflammatory responses that may in themselves be harmful; reducing bacterial numbers is usually helpful. Early in the course of disease, patients may produce little or no sputum, and it may be difficult to define the bacterial flora of the lower respiratory tract. In young children, infection with organisms such as *H. influenzae* or *S. aureus* is more common than with *Ps. aeruginosa,* although this organism may also be seen in infants. Oral antibiotics may be efficacious for younger patients, but with *Ps. aeruginosa* infection, or in those with significant disease, parenteral therapy is usually necessary. The choice of antibiotics should be guided by cultures of respiratory secretions. If sputum is not available, swabs of the posterior pharynx (taken after vigorous coughing) or cultures of bronchoscopic specimens may be used; the latter are much more sensitive and specific but should be used selectively because of the associated cost and other factors. Bronchoscopic investigation at the time of initial diagnosis may be important, as the initial therapy may help determine the future course of disease.

Patients with CF require higher doses of virtually all antibiotics than do other patients because of the larger volume of distribution, more rapid renal clearance of most drugs, and more rapid metabolism of others. When drugs such as aminoglycosides are used, care must be taken to ensure that the doses are sufficient to produce effective levels while avoiding toxicity.

All reasonable measures should be taken to prevent infection. Children (and parents) should be taught good hygiene practices to reduce the incidence of viral respiratory infections, especially in infants. On the other hand, isolation of young patients with CF is not necessarily a good thing, even though it may reduce the frequency of viral infections. Immunization against respiratory infections such as influenza is important.

When the disease cannot be controlled by oral or aerosolized antibiotic therapy, or when only parenteral drugs can be effectively used, hospitalization may be required. Indications for intensified therapy or hospitalization include weight loss, increased cough and sputum production lasting more than 2 weeks, worsening pulmonary function, and the development of complications such as pneumothorax, significant hemoptysis, or cor pulmonale. In selected patients, parenteral therapy can be continued at home. In the hospital, intensive chest physiotherapy, nutritional support, psychosocial support, and other therapeutic modalities may be employed. In the majority of patients, clinical improvement will be evident after 5 to 7 days, but courses of therapy shorter than 2 weeks rarely result in a satisfactory clinical response. In many patients, longer (or even continuous) therapy is necessary. Monitoring of the patient for drug toxicity and for the development of resistant organisms is essential.

End-stage lung disease in CF patients is increasingly being managed by lung transplantation (135 transplants were reported in the United States in 1995). This procedure is expensive, is difficult for patient, family, and physician alike, and is not appropriate for all patients. Indications for transplantation are not yet clearly defined. The long-term prognosis of patients who have undergone lung transplantation is uncertain. Although many patients exhibit amazing improvement, others die within weeks or months from complications of the transplant or rejection. In 1995, 10% of deaths in CF patients in the United States were related to transplant complications.

Gastrointestinal Therapy

Nutrition plays a major role in the global well-being of CF patients. Because of inefficient digestion and absorption, as well as other factors, CF patients require 125% to 150% of the usual daily requirement of calories and other nutrients. High-fat diets are important to provide sufficient calories. In addition, fat-soluble vitamins should be given in water-miscible form.

Pancreatic insufficiency should be treated with pancreatic enzyme replacement. Enteric-coated preparations are most effective, and the dosage should be spread throughout the meal to achieve optimal mixing. The dosage is empirical and is adjusted according to the quantity and nature of the food ingested as well as by the patterns of growth and stool character. Steatorrhea is almost never totally eliminated despite adequate enzyme replacement.

Meconium ileus can sometimes be relieved nonoperatively by an enema of hygroscopic radiographic contrast material, but more often, surgery is necessary. Late intestinal obstruction can usually be relieved by enemas, as can intussusception, and such methods should be tried before surgery is resorted to. Cleansing of the bowel with oral electrolyte solutions can also be effective if the obstruction is not complete.

Liver disease with symptomatic portal hypertension develops in a small percentage of patients. Endoscopic sclerotherapy, vascular shunting, and even liver transplantation have been utilized for management. Somewhat surprisingly, despite the presence of chronic bacterial infection in the lungs, many CF patients do well after liver transplantation and the immunosuppressive regimens necessary to maintain the transplant. Hepatocellular damage short of portal hypertension may respond to treatment with ursodeoxycholic acid.

Treatment of the Sweat Defect

Patients should be encouraged to maintain a high salt intake, especially in hot weather. No other treatment is necessary unless salt depletion has occurred. Some years ago, when low-sodium infant foods and formulas were introduced, the incidence of hypochloremic alkalosis in infants with CF increased significantly.

Metabolic Therapy

Patients who develop glucose intolerance may require treatment with oral hypoglycemic agents or insulin. Ketoacidosis is rare, and the primary goal of therapy is symptomatic relief rather than tight control of blood sugar. Treatment is otherwise similar to that of adult-onset diabetes.

Psychosocial Therapy

Cystic fibrosis is a chronic, progressive, and ultimately fatal disease. Virtually no form of therapy yields dramatic, immediate results, and it is therefore difficult for patients and other caregivers to discern the benefit of day-to-day therapy. Compliance with therapy may thus be compromised, even in the most motivated and intelligent patients and families. The importance of a positive attitude on the part of the patient, family, and the physician and other caretakers cannot be overemphasized. A fatalistic attitude can literally be fatal. As more and more patients reach adulthood, problems with education, career planning, marriage and family, sterility, dependence–independence, fear of impending death or disability, and the cost of medical care assume major proportions and can be overwhelming. It is therefore important to pay as much attention to mental health as to physical health.

Prognosis

The outlook for patients with CF has improved dramatically over the past several decades. In 1966, the median survival age of patients reported to the Patient Registry of the Cystic Fibrosis Foundation was just over 10 years. By 1995, the median survival age had increased to 30.1 years, although the prognosis is slightly worse for female than male patients. The prognosis for any individual is difficult to predict.

The reasons for the improving prognosis are not fully understood. The mean age at diagnosis has not changed substantially over the past several decades, suggesting that neither earlier diagnosis nor diagnosis of older, more mildly affected patients is what has changed. Significant differences in survival patterns have been reported by various centers, suggesting that differences in treatment may be of importance. Centers in Europe and Australia have reported survival experiences similar to that of major North American centers.

What is clear is that further improvements in prognosis will depend on advances in therapy. Several large centers that have traditionally had very high survival rates have not seen increases in survival rates over the past two decades, while survival rates in other centers have been “catching up.” The rapid progress in the molecular biology of CF over the past several years promises dramatic changes in our approach to therapy and, we hope, improvements in prognosis. In anticipation of potentially curative therapy in the relatively near future, it is important to treat patients aggressively today.

PRIMARY CILIARY DYSKINESIA (IMMOTILE CILIA SYNDROME, KARTAGENER'S SYNDROME)

The clinical triad of situs inversus, bronchiectasis, and pansinusitis was recognized as a distinct entity in 1936 by Kartagener, who also noted the occurrence of the triad in siblings. Kartagener's syndrome remained a clinical oddity until Afzelius and colleagues reported that sperm from these patients were immotile and that their ciliary ultrastructure was abnormal. Subsequently, the generalized nature of the ciliary abnormality was recognized. Several kindreds have since been reported to have a variety of ultrastructural abnormalities and a common clinical picture of chronic sinus and bronchial disease, with or without situs inversus. Because many patients with similar clinical syndromes have abnormal cilia with disordered but not absent movement, the preferred term today is *primary ciliary dyskinesia* (PCD) rather than *immotile cilia syndrome.*

Genetics

The familial pattern of Kartagener's syndrome is consistent with an autosomal recessive mode of inheritance. The syndrome has been documented in siblings of both sexes but has rarely been seen in two consecutive generations. Other variants of PCD have been observed in siblings. At least one family has been reported with an X-linked inheritance pattern. From the estimated incidence figures above, it may be calculated that approximately one in 70 persons is heterozygous for one form or another of the disorder.

Incidence and Prevalence

Situs inversus occurs with an incidence of one in 8000 to one in 24,000 live births, and of these, only 12% to 25% have the complete triad of Kartagener's syndrome. It is not clear whether situs inversus occurs with a 50% (i.e., random) incidence in all patients with immotile cilia. However, with a few assumptions, it may be estimated that the incidence of PCD may be as high as one in 20,000 live births.

Pathophysiology

Mucociliary function depends on a number of factors, including the number, orientation, and beat frequency of cilia and the dimensions and viscoelastic properties of the mucus and the aqueous periciliary fluid layers. Virtually any structural abnormality of cilia that results in an abnormal ciliary beat can result in clinical abnormalities. The ultrastructure of cilia is quite constant, with two central microtubules surrounded by nine outer microtubule doublets. The microtubules are composed of tubulin, a protein with no intrinsic contractile activity. Radial spokes extending from the central doublet to the outer tubules and nexin links help maintain the structure. Other structures projecting from the outer doublets (dynein arms) have ATPase activity. Motion of the cilia is thought to occur by interaction of the dynein arms with adjacent microtubules via a sliding mechanism similar to that of muscle contraction.

Electron microscopy of cilia from sperm tails and from nasal and bronchial epithelium of patients with Kartagener's syndrome reveals the partial or complete absence of dynein arms. Other kindreds with absent radial spokes or with other ultrastructural patterns have also been reported. Familial clusters of patients with ciliary aplasia have also been reported; these patients have similar clinical manifestations to those with classical PCD.

Not all patients with chronic sinopulmonary disease have immotile cilia, yet many of these patients do demonstrate abnormal ciliary ultrastructure. Chronic infection or inflammation may itself produce abnormalities. Clinical and ultrastructural data must be interpreted with caution, and it is difficult to assign a genetic basis to a particular patient's problem unless the ultrastructure is classic (i.e., absence of dynein arms) or there is familial clustering. It also should be pointed out that fixation and staining

techniques may have a great impact on the ultrastructure visualized, and artifacts are common.

It has been postulated that ciliary beat is necessary for the normal embryonic rotation of the primitive foregut and that the situs inversus commonly associated with immotile cilia results from an essentially random rotation. Although this hypothesis is unproven, it is clear that siblings of patients with Kartagener's syndrome often have pansinusitis and bronchiectasis without situs inversus. Many other patients with immotile cilia who do not have situs inversus have been reported. In 65 patients with Polynesian bronchiectatic disease, there were none with situs inversus. These patients have been reported to have deficient dynein arms on their ciliary microtubules, but the relationship between the two syndromes remains unclear.

Patients with PCD develop bronchial disease much more slowly than do those with CF and do not usually have the extensive mucous hypersecretion and airway plugging so characteristic of CF. Also in striking contrast to CF, they do not have a high frequency of infection with *Ps. aeruginosa.* The very existence of the clinical syndrome emphasizes the physiological importance of cilia in the respiratory tract, but it is clear that other factors are of importance in the pathogenesis of severe bronchopulmonary disease.

Diagnosis

The diagnosis of PCD may be suspected on the basis of the clinical picture, and it must be emphasized that situs inversus is not a necessary finding. A simple screening test may be performed by microscopic examination of scrapings of nasal epithelium (obtained from the middle to posterior third of the nose and placed into tissue culture medium). If adequate specimens are obtained, and the patient does not have an acute infection, the absence of ciliary beat on repeated testing is presumptive evidence of immotile cilia. In adult men, sperm also may be examined. It is important to obtain sheets of ciliated epithelium rather than isolated cells for examination and to compare the ciliary motility of the specimen with that of control material. Most isolated cells will not be viable, and their cilia will not beat. Confirmation of the diagnosis depends on the demonstration of characteristic ciliary ultrastructural abnormalities. No other laboratory findings are diagnostic. Specimens for ultrastructural study may be obtained from the nose or a bronchus.

Patients may have defective mucociliary transport for reasons other than immotile cilia, and the demonstration of normal ciliary beat or normal ciliary ultrastructure does not mean that mucociliary function is normal.

Pathology

Primary ciliary dyskinesia affects all ciliated epithelia, including those of the middle ear, Eustachian tube, nose, paranasal sinuses, tracheobronchial tree, and perhaps other locations. However, there is no distinctive histologic picture, and these patients cannot be distinguished from those with other forms of bronchiectasis or sinusitis on the basis of light microscopy. Electron microscopy reveals characteristic ultrastructural abnormalities, including disorientation of the ciliary basal bodies. The classic finding is absence of inner or outer dynein arms (or both), but microtubular transposition, absence of radial spokes, and other abnormalities have been reported as well.

Clinical Manifestations

The clinical manifestations of PCD may begin early in life, or they may not become apparent until the second or third decades. In infants and children, cough and recurrent otitis media may be the primary signs. Patients are often suspected of having CF, but sweat testing will exclude this possibility. The usual signs and symptoms of sinusitis, bronchitis, and bronchiectasis are present in most patients; cough and sputum production, recurrent fevers, hemoptysis, digital clubbing, and eventually cyanosis may be present. Recurrent otitis media and conductive hearing loss are common. Although sperm counts may be normal, most men are infertile; some patients with well-documented PCD have fathered children.

Treatment

There is no specific treatment that will alter ciliary function in patients with PCD. The bronchopulmonary disease is treated by chest physiotherapy, antibiotics, and bronchodilators as needed. Sinusitis should be treated with antibiotics and surgical drainage if necessary. Attention to the management of upper respiratory tract infections and otitis media should help reduce the complications of conductive hearing loss. When bronchiectasis is localized and severe, excision of involved areas of the lung may be indicated if medical management is insufficient.

The ultimate therapy for PCD is correction of the genetic defect. Techniques being developed for gene transfer therapy of other diseases such as cystic fibrosis will have direct and immediate application to PCD once the defective gene has been identified. The Human Genome Project can be expected to result in the identification of the gene or genes involved in PCD, so that it is not unreasonable to anticipate successful gene transfer therapy in the foreseeable future.

Prognosis

The complete spectrum of PCD is not yet defined. What is clear is that the involvement and severity are quite variable. The classical patient develops severe bronchiectasis in the third to fourth decade and may succumb to pulmonary complications. Patients can reach advanced age, and many live a comparatively normal life. The majority of patients appear to develop bronchitis in childhood and to demonstrate findings of airway obstruction after two to three decades. Infections may be most severe in childhood and adolescence, with a partial clinical remission in adult life. Effective gene therapy would be expected to substantially impove prognosis.

ASTHMA

The familial disposition toward asthma has long been a part of conventional clinical wisdom, but no studies have succeeded in defining the precise role of genetic factors in its pathogenesis. The imprecise nature of the definition of asthma emphasizes the diversity of predisposing factors and the difficulty of defining a genetic role. A study of 7000 Swedish twin pairs found that although 4.8% of the dizygotic twin pairs were concordant for asthma, 19% of the monozygotic twin pairs were concordant. This is strong evidence for genetic factors in the causation of the asthmatic syndrome. In recent years, a number candidate genes for roles in asthma have been investigated, but no single gene has emerged as being responsible for even a small percentage of clinical cases of asthma. The genetic basis of asthma is almost certainly polygenic and involves a number of different, though related, mechanisms. Mutations in genes involving adrenergic receptors, inflammatory mediators, and immune responses are most likely involved. The role of environmental factors in the pathogenesis of asthma cannot be underestimated; identification of genetic factors that increase susceptibility to environmental stimuli could be helpful in patient counseling and possible prevention.

CYSTIC LUNG DISEASE (LOCALIZED SACCULAR BRONCHIECTASIS)

Cystic lung disease is a name given to a wide variety of conditions in which bronchiectasis is associated with fluid- or air-filled, sharply defined, round structures that have a definite wall. The cysts are usually discovered on chest roentgenograms or in anatomic specimens. In most patients, cysts found with the cylindrical variety of bronchiectasis have been related to the syndrome of infectious chronic bronchitis. Localized saccular bronchiectasis, which appears to be a distinct entity, has been described in Sephardic Jews emigrating to Israel and in the Maoris, Polynesian natives of New Zealand. Whether these are examples of genetic lung disease remains a somewhat open question. A recent report suggests that the Polynesian patients with bronchiectatic disease have deficient dynein arms on their ciliary microtubules. Thus, the disease in the Maoris may have the same basis as PCD. This observation lends further credence to the hypothesis that it is a genetic disorder. In the Jewish patients, the striking findings were cylindric dilations of the medium-sized and small bronchi with cyst-like cavities that were usually connected to the bronchi. The cylindric nature of the bronchiectatic changes suggests that these cases were not the classic, acquired forms of bronchiectasis. Perhaps the most compelling evidence to support a genetic component in this form of bronchiectasis was the ethnic clustering. In Israel, 92% of the patients were found among immigrants from Yemen, Iraq, and Morocco, groups that have been isolated and highly inbred for 2000 years. Jews who emigrated from central and western Europe made up only 8% of the patient population. Similar clustering was observed in the Maoris as compared with the Anglo-Saxon immigrant populations of New Zealand. Higher frequencies of a disease in specific population groups suggests a genetic component in its cause if environmental conditions are held constant. Thus far, multiple cases in a family or transmission in two consecutive generations has not been reported. The hypothesis that saccular bronchiectasis has a genetic basis needs to be confirmed by additional studies.

YELLOW NAIL SYNDROME

The association of primary lymphedema with yellow discoloration of the nails has been termed the yellow nail syndrome. A third manifestation is unexplained recurrent pleural effusion. Patients studied by lymphangiography show lymphatic abnormalities consisting mostly of lymphatic hypoplasia. Bronchiectasis is common (five of 12 patients in one report and four of four in another). Sinusitis has been reported in a high percentage of patients but is not felt to be caused by primary ciliary dyskinesia, as ciliary beat frequency is normal. The recurrent pleural effusions are most likely secondary to hypoplastic lymphatics. Chronic cough is present in all patients. Dyspnea may be present and is related to the extent of pleural effusion or to bronchiectasis. Lymphedema, pleural effusion, or bronchiectasis may not become evident for years after the nails become yellow. Lymphedema usually occurs before pleural effusions become manifest. The disorder has been reported in a mother and child

as well as in cousins, suggesting a genetic basis.

TRACHEOBRONCHOMEGALY

Mounier-Kuhn presented the first clinical description of tracheobronchomegaly, a unique syndrome characterized by striking dilation of the trachea and bronchi. The occurrence of two documented cases in a single family suggests a familial cause, but the genetic basis has not yet been firmly established. The incidence of tracheobronchomegaly in the general population is unknown but is undoubtedly low. Six cases were discovered in a series of 1200 adults undergoing bronchography for chronic pulmonary disease. Affected individuals show a distinctive clinical and roentgenographic picture consisting of marked dilation of the trachea and major bronchi associated with chronic respiratory infection. The symptoms of chronic respiratory disease in this condition do not differ from those of a great variety of other respiratory diseases. Patients may have cough, dyspnea, hoarseness, and copious production of purulent sputum. The course is often of long duration, with onset of symptoms in infancy or childhood.

The diagnosis is based on roentgenographic findings. Plain films of the chest may reveal the width of the tracheal air column to be equal to that of the vertebra. The major bronchi are also markedly enlarged, and there are large outpouchings between cartilage rings in which secretions may pool. Occasionally, cystic changes in the peripheral bronchi are noted. Computed tomography is a convenient method to confirm the diagnosis. The size of the trachea and bronchi in affected adults deviates by more than 3 standard deviations from that in normal adults. Normative data are now available for infants and young children. The dynamics of the trachea and bronchi are abnormal, with diffuse tracheobronchomalacia.

The pathogenesis of tracheobronchomegaly is not known, but it has been speculated that it is caused by a sparsity of elastic and muscular fibers in the airway walls. It is of interest that the syndrome has been reported in patients with connective tissue disorders, including the Ehlers–Danlos syndrome, Marfan's syndrome, and cutis laxa. Acquired forms of tracheobronchomegaly may be related to prolonged respiratory support with positive-pressure ventilation, especially in premature infants.

Treatment measures include chest physiotherapy to improve clearance of secretions and prompt treatment of infections. If pulmonary clearance of secretions can be maintained, the prognosis is relatively good, but if there are recurrent infections, the prognosis is poor. In selected patients, tracheobronchial stenting may be helpful.

OTHER FORMS OF AIRWAYS DISEASE WITH POSSIBLE GENETIC BASES

Williams and Campbell described a group of patients with bronchiectasis caused by a generalized deficiency of bronchial cartilage. The clinical picture is characterized by persistent cough and wheezing, digital clubbing, chest deformities, and short stature. In the original reports, no familial pattern was seen, but later, two siblings with this syndrome were reported. Recurrent respiratory infections are the rule in these patients, and pulmonary function studies reveal marked air trapping and airway obstruction on expiration. Bronchographic studies demonstrate ballooning of the bronchi during inspiration and collapse during exhalation. Approximately 25% of the reported patients died before age 5, and most of the remainder have chronic pulmonary disease with persistent symptoms. Treatment is the same as for other forms of bronchiectasis.

At least one sibship has been reported in which four or five siblings had symptomatic bronchiectasis of the right middle lobe.

Generalized bronchomalacia without bronchiectasis has been reported on a familial basis. Laryngomalacia also has been reported to have a familial pattern. One family has been reported in which two siblings had severe tracheal obstruction caused by an anomalous innominate artery, requiring emergency surgery. Two sets of siblings with nasal polyps in infancy, aplasia of the nasal sinuses, and bronchiectasis have been described. This condition has been termed Woake's syndrome.

There are a number of familial immunologic disorders that lead to sinopulmonary infection and bronchiectasis, including X-linked agammaglobulinemia, common variable immunodeficiency, and selective immune globulin deficiencies. Esophageal atresia with associated tracheoesophageal fistula has been reported to occur in families. Infants with bronchopulmonary dysplasia may have a higher proportion of first-degree relatives with asthma than infants with normal lungs. It is possible that infants with a genetic predisposition toward reactive airways may respond adversely to neonatal insults, with consequent development of permanent airways disease.

a_1-ANTITRYPSIN DEFICIENCY

a_1-Antitrypsin deficiency is an inherited disorder associated with emphysema, bronchiectasis, and hepatic cirrhosis. a_1-Protease inhibitor (a_1-antitrypsin, AAT) is the major protease inhibitor in human plasma. Its primary role is to neutralize neutrophil-derived elastase by tightly binding to it, forming a stable complex that can be catabolically metabolized. Any mutation that reduces the ability of AAT to tightly bind neutrophil elastase will reduce its activity and functionality.

Mechanisms causing functional a_1-antitrypsin deficiency include abnormalities in the transcription, translation, and intracellular processing of AAT. The resulting mutant proteins are characterized by their electrophoretic mobility and are referred to by their PI (“protease inhibitor”) types. Because each allele is codominant, both alleles must be identified in order to characterize the individual. The most common (normal) phenotype is PIMM; the most common abnormal variants are the S and Z alleles.

Genetics

a_1-Antitrypsin deficiency results from inheritance of two abnormal AAT alleles on chromosomal segment 14q32.1 in the AAT gene locus. This locus (PI) is situated in a cluster of genes that code for related proteins of the serpin superfamily including cortisol-binding globulin, a_1-antichymotrypsin, a_1-antitrypsin, a_1-antitrypsin pseudogene/protease inhibitor-like gene (AATP), and the protein C inhibitor. With the exception of the AAT pseudogene, all of these proteins have substantial amino acid and structural homologies. a_1-Antitrypsin is synthesized primarily by liver but also may be made by mononuclear cells, polymorphonuclear leukocytes, intestinal epithelium, and the kidney parenchyma. a_1-Antitrypsin is an acute-phase reactant, and concentrations in plasma may vary by as much as fourfold in response to acute infection or inflammation.

The AAT gene is composed of seven exons and six introns spanning more than 12 kb. The first three exons contain the promoters responsible for macrophage and hepatocyte transcription. The remaining four exons encompass 1434 bp. The start codon ATG and the 24-amino-acid signal peptide sequence are located on the fourth exon. The fifth exon contains the most common polymorphic site within the coding region, and the sixth exon contains the site of the most common mutation associated with a_1-antitrypsin deficiency. This exon also contains the stop codon and the polyadenylation site.

The AAT mRNA synthesized by hepatocytes is 1.6 kb in length, and three macrophage-derived a_1-antitrypsin mRNAs of 1.8, 1.8, and 2.0 kb have been identified. These differences result from alternative splicing of the first three exons. The promoter region is a 557-bp fragment that starts 20 nucleotides upstream from the transcription start site. This region contains a conventional TATA box and three additional elements (X, Y, and P elements) that are necessary for efficient transcription. The X and P elements are required for transcription in hepatocytes. Transcriptional factors that have been identified to play an important role include LFB-1/HNF-1, C/EBP, HNF-3, and HNF-1/LFA-1. Interleukin-6, the major cytokine associated with development of the acute-phase reaction, up-regulates AAT transcription.

Translation of AAT mRNA results in a 418-amino-acid protein with a 24-amino-acid leader signal peptide that directs the protein to the rough endoplasmic reticulum. Here, the signal peptide is cleaved, and glycosylation of the protein takes place. The glycosylated protein is then transported to the Golgi, where further processing occurs. After this, the completed 52-kDa globular glycoprotein is secreted into the serum. This entire process takes about 90 min.

Molecular Epidemiology, Incidence, and Prevalence

DNA sequencing has revealed the presence of at least 49 AAT allelic variations, and about 100 phenotypic (PI) variants of AAT may be detected by the isoelectric focusing technique. PI*M (with its several subtypes) is the most common allele associated with normal levels of activity. Evidence suggests that all PI*Z alleles have a single geographic origin.

Most mutations occur in the coding sequence for the AAT protein and are generally spread evenly throughout the sequence, with two exceptions. A higher concentration of mutations may be found in codons 51 to 53 and in codons 361 and 362. These areas may be sites of excessive deletions or insertions of one or more bases because they contain highly repetitive sequences on which the DNA polymerase may make mistakes.

The majority (95%) of individuals with severe AAT deficiency are homozygous with a PI type of ZZ. These individuals are most commonly white and of European extraction. The condition is not found in Asian and black populations. The frequency of this defect in Europe and North America is about 0.0122, which corresponds to

an incidence of about one in 5000 to 7000. Because of this frequency, it is thought that only a very small proportion of those with AAT deficiency have been diagnosed.

The remaining 5% of AAT-deficient persons who are not PI*ZZ exhibit about 20 other variants that are not identifiable by PI typing. These variants may be associated with substantially reduced levels of functional protein or with normal or reduced levels of nonfunctional AAT or with undetectable levels of the protein. Homozygous individuals with null alleles (PI*Q_0Q_0) have either zero or less than 1% of the normal amount of AAT. The frequency of this mutation is estimated to be about 1.7×10^{-4}, which is approximately 1/100th of the frequency of the PI*ZZ genotype.

Population studies suggest that the known number of AAT-deficient persons is much less than the actual number of those present in the population: 4.5% in the United Kingdom, 6% in Sweden, and about 5% in the United States. The reason for this is that physicians often do not diagnose the disease in young smokers. An average delay of 7.2 years between the first onset of symptoms and the initial diagnosis of AAT deficiency was found in 304 AAT-deficient individuals. Many of these patients had been seen by multiple physicians before the diagnosis was made. It is important to consider this diagnosis in all patients who present with emphysema at a young age, whether they smoke or not.

About one in 25 individuals of Northern European descent carry the Z mutation of AAT, which is the most common form of genetic abnormality. This particular mutation does not allow AAT to fold properly during synthesis so that it is more susceptible to intracellular breakdown. Individuals homozygous for the ZZ genotype synthesize normal amounts of the protein in the liver but secrete only 15% into the blood. The remaining 85% remains in the hepatocyte and is either degraded or accumulates as large intracellular inclusions. Two other mutations are associated with the deletion of most of the coding region of a_1-antitrypsin. Other mutants are associated with abnormalities in mRNA splicing or stability or abnormal retention in the rough endoplasmic reticulum or Golgi with subsequent degradation.

Clinical Manifestations

The clinical manifestations of AAT deficiency involve primarily the lung, although some young patients have hepatic involvement.

Chronic Obstructive Pulmonary Disease

The most common syndrome associated with AAT deficiency is chronic obstructive pulmonary disease (COPD), usually of the emphysematous type, and is usually panacinar and basilar in location. Clinical findings are similar to those of patients with other forms of COPD (see Chapter 43). The primary symptom is dyspnea, but many patients also have chronic cough and sputum production. Physical findings include an increased anteroposterior diameter of the chest, hyperresonance, and decreased breath sounds. Digital clubbing is not usually present unless there is also bronchiectasis. Radiographic abnormalities include marked hyperinflation with bilateral hyperlucency, predominantly in the lower lobes. Physiological studies reveal marked increases in lung volumes and decreases in expiratory flows (reflecting air trapping as a result of loss of tissue elastic recoil with airway collapse on expiration) as well as decreased diffusing capacity (reflecting loss of alveolar tissue). Hypoxemia is common in patients with advanced disease, who may also have signs of congestive heart failure. Chronic bronchitis is seen in 20% to 35% of patients, and as many as 45% of patients may develop bronchiectasis.

Liver Disease

Hepatic disease is the second most frequent clinical manifestation of AAT deficiency and usually presents in the postnatal period as cholestatic jaundice. Only patients with the PI*ZZ variant develop hepatic disease, which is caused by intracellular accumulation of AAT in the hepatocytes. Liver disease in most AAT-deficient children is mild, with only 10% having clinically significant disease. Abnormal liver chemistries often disappear as the child develops. AAT-deficient children with severe hepatic disease may require liver transplantation.

Dermatologic Manifestations

Panniculitis is the least common manifestation of AAT deficiency and is found in individuals with a variety of phenotypes, including PI*ZZ, PI*MZ, PI*SS, and PI*MS. It is characterized by inflammatory and necrotizing lesions of the skin.

Pathophysiology

The panacinar emphysema in AAT-deficient individuals is produced by elastolysis of lung elastin, which occurs by several mechanisms. Generally, these individuals have a relative deficiency of anti-neutrophil-elastase activity in lung tissue at all times, resulting in a relative imbalance between elastase and antielastase activity. In addition, smoking causes a large influx of neutrophils and macrophages to the lung, thus increasing the elastase burden in lung tissue. Oxidant components of cigarette smoke also inactivate any AAT that is present in lung by oxidizing a crucial methionine (position 358) at the center of the active site of the molecule and thus potentiate the effects of neutrophil elastase. Thus, individuals with reduced levels of AAT are at greatly increased risk of elastolysis with loss of normal alveolar structure, especially if they smoke. Macrophages also secrete an elastase; cells in contact with elastic fibers have the potential of degrading elastin. Bronchiolar pathology (cellular infiltration, goblet-cell metaplasia, fibrosis, luminal secretion, increased airway smooth muscle) is not always present with the emphysema.

Smoking is clearly the most important associated risk factor for the development of chronic obstructive pulmonary disease. Individuals who do not smoke do not necessarily develop disease, and if they do, it usually begins by the third decade and becomes evident in the fifth or sixth decade of life, when reductions in expiratory flow may be noted. However, the emphysema may be very severe, even in individuals who have never smoked. Usually, ZZ homozygous patients will develop moderate airflow reduction between the ages of 45 and 55.

Little is known about the deleterious effects of environmental air pollution on the development or severity of lung disease in individuals with AAT deficiency. It is likely that breathing ozone, sulfur dioxide (SO_2), oxides of nitrogen, and other such pollutants will increase the rate of worsening of lung disease occurring in the AAT-deficient setting. Individuals with AAT deficiency should make every attempt to limit their exposures to these materials.

Respiratory infections in early childhood seem to be a risk factor for the early development of emphysema in individuals with severe AAT deficiency. Chronic bronchitis with repeated acute bacterial exacerbations by the usual offending organisms in AAT-deficient adults also seems to be a risk factor. Other genetic factors may promote the early development of COPD because the risk of an AAT-deficient individual developing COPD is increased if a parent has emphysema, bronchitis, or asthma.

Chronic liver disease is not a sequela of AAT deficiency, although cirrhosis and carcinoma of the liver are found in about 5% to 15% of AAT-deficient adults older than 50. The presence of hepatitis B is an additional risk factor for disease. The development of hepatocellular carcinoma in these individuals is not related to alcohol abuse. The relation to previous viral hepatitis, especially hepatitis C, is unclear.

Diagnosis

When a diagnosis of AAT deficiency has been established by low serum levels, the PI phenotype should be determined. It may be necessary to determine the genotype in the case of patients with unusual clinical phenotypes. Genotyping can give a more precise diagnosis and enable prognostic statements to be made with more confidence.

Screening

The overwhelming majority of patients with emphysema are not AAT deficient, so that screening for this condition is both costly and not generally effective. About 3% of this population will have AAT levels below the normal range. Screening of siblings of known AAT-deficient individuals is useful because the positive yield will be 25%. These individuals can be counseled to stop smoking and can be evaluated for therapy, although it is unclear whether currently available therapy alters the course of the disease.

Historically, screening for AAT deficiency has been done in three ways. The first is general screening of adults, usually done in the blood donor population. This has been useful for estimating the prevalence of undiagnosed AAT deficiency in the community, but it is not cost effective because of its low yield.

Directed screening of adults who have a higher-than-average risk of having AAT deficiency is useful. Such screening has been offered by the AAT Deficiency Detection Center in Salt Lake City since 1991 to individuals with chronic bronchitis, emphysema, and asthma, who have a family history of AAT deficiency. In the five years ending February 29, 1996, 16,748 samples were received for testing; 514 PI*ZZ individuals were found with levels of immunoreactive AAT <11 M. It is estimated that the center has diagnosed ~15% of the known individuals with AAT deficiency in the U.S.A. during its 5 years of operation.

Last, several neonatal screening programs have provided knowledge about the prevalence of the disease and eventually will provide information about the natural history of the disease in children and adults. Over 300,000 neonates have been screened in past years.

Therapy

Treatment of AAT deficiency may be divided into measures directed at the primary defect (low levels of AAT) and those directed at the secondary effects of the disease (i.e., emphysema, bronchitis, bronchiectasis). The latter measures are similar to those in other patients with COPD (Chapter 43). Smoking cessation should play a prominent role in any therapy program for AAT deficiency, as smoking is the most important single risk factor for development of lung disease in AAT-deficient individuals.

Intravenous AAT Augmentation

A serum AAT level exceeding 80 mg/dl (11 µM) is thought to protect against the development of emphysema. Repeated weekly infusions of partially purified, plasma-derived AAT at a dose of 60 mg/kg body weight was found to result in a mean nadir AAT level of 126 mg/dl in 21 patients whose pretreatment level was 30 mg/dl. Antibodies were not produced in response to the AAT, and the infusion was shown to result in increases in serum and bronchoalveolar lavage fluid anti-neutrophil elastase activity, suggesting that the infused AAT was active in the lung and might afford some protection against continued elastolysis and alveolar wall destruction and reduce the progression of emphysema. The half life of the infused AAT was between 4–5 days. At this time, about 2000 individuals with AAT deficiency are being treated worldwide with pooled plasma concentrate (Prolastin) on a weekly basis.

In a few patients given Prolastin at a dose of 250 mg/kg once every 28 days for 1 year, serum AAT levels of 70 to 80 mg/dl were maintained for 20 days. Even at 28 days, the BAL AAT levels and anti-neutrophil-elastase capacities were above threshold, suggesting that alveoli were protected over the whole cycle. These results are controversial at this time, and a once-a-month dosing regimen is not currently recommended.

Recombinant AAT is a 45,000-kDa nonglycosylated protein produced by yeast. This protein does not contain the terminal methionine and three carbohydrate chains of the native molecule. Recombinant AAT has a half-life of hours because of rapid renal clearance, and its clinical use is not appropriate.

Studies evaluating whether augmentation therapy prevents worsening of emphysema are not feasible because of the long intervals needed for study, the lack of a noninvasive, objective marker of emphysema, the large numbers of patients needed, and expense. A random, double-blinded study would require at least 250 patients in each arm of a placebo-versus-AAT augmentation trial followed for 3 years. Although preliminary data have suggested that the annual change in FEV_1 in 235 patients treated for 2 to 6 years with Prolastin was less than for 161 untreated patients, the difference was small and not statistically significant.

Side effects of Prolastin are few and include headache, myalgias, arthralgias, and low back pain. Some patients with pulmonary hypertension related to their disease develop worsening dyspnea during or shortly after the infusion. This may be secondary to the protein load and water retention. All patients slated to receive Prolastin should be vaccinated against hepatitis B, although no cases have been reported. Acute allergic or anaphylactic reactions have been few. Rare patients with severe AAT deficiency may also be IgA deficient; because they may receive some IgA with the Prolastin infusion, acute anaphylactic reactions have been noted in these individuals.

Patient selection for i.v. AAT augmentation therapy is somewhat controversial. The American Thoracic Society has published guidelines for therapy, but they are not universally accepted, given the uncertainty of therapeutic efficacy and the cost involved. In general, only patients with clearly deficient AAT levels (PI*ZZ, PI*Null-Null, PI*Z-Null, PI*S-Null, and a few PI*SZ) should be treated. The age at which therapy should be begun is unclear; although *a priori* reasoning would suggest initiation of therapy at a young age, there are no data on which to base judgment on this issue. The ATS recommends that patients who continue to smoke not be treated, as they are unlikely to benefit from the treatment.

Aerosol delivery of AAT is currently under investigation. This could potentially offer effective enhancement of AAT levels in the airway surface liquid while utilizing much less protein (and thus be more cost effective).

Lung Transplantation

More than 4300 patients, about 30% with COPD, have undergone lung transplantation (LT) worldwide. Approximately 12% of these transplants were performed for emphysema caused by AAT deficiency. Although the 6-year actuarial survival for all LT recipients is approximately 40%, patients with emphysema have a 4-year survival rate of 54%, the best survival among all groups. Recipients who are AAT-deficient have an actuarial survival of 45% at 5 years. Most LT survivors have reported functional improvement. Because of the shortage of suitable lung donors, most patients now receive single lung transplantation.

Liver Transplantation

Liver transplantation is associated with normal circulating levels of AAT and, thus, presumably with a normal pulmonary prognosis. Liver transplantation is not a viable form of therapy for lung disease, but in those few (mostly pediatric) patients with end-stage liver disease, liver transplantation is also an effective form of pulmonary therapy.

Lung Volume Reduction Surgery

Lung volume reduction (LVR) is a surgical technique that attempts to reduce hyperinflation and improve lung function by removing multiple emphysematous areas of lung identified by computed tomography. Physiological function has been shown to improve in selected individuals through partial restoration of the normal domed shape of the diaphragm and its mechanical advantage. In addition, elastic recoil of the lung may increase after reduction pneumoplasty, thereby increasing compliance and improving function.

Patients with end-stage emphysema, i.e., those with generalized severe disease associated with pulmonary hypertension (mean pulmonary artery pressure > 35 mm Hg), severe hypercapnia (P_aCO_2 > 55 mmHg), low FEV_1 (<20% of predicted), and barrel chests, are not good candidates for resection. Persistent air leaks and inability to wean from mechanical ventilation are major problems in these individuals.

Inclusion and exclusion criteria for this procedure are not yet well defined. Reported mortality is about 5%. Functional improvement with increased FEV_1 is variable, although many patients report lessened dyspnea and an increase in exercise tolerance. Long-term benefits more than 1 year after surgery have not yet been reported. Very few patients with AAT deficiency have had LVR, and results are not clear.

Gene Therapy

Although AAT deficiency may be treated with weekly infusions of AAT, this treatment is expensive and inconvenient. Investigations are currently ongoing regarding transfection of the complete a_1-antitrypsin cDNA to the respiratory tract of deficient individuals. Expression of the protein in the airway and alveolar space would theoretically provide levels of AAT sufficient to prevent reductions in pulmonary function.

Similar to what has been used for genetic therapy of cystic fibrosis, modified nonreplicating retroviruses and adenoviruses and nonviral vectors have been used to deliver AAT cDNA to the lung or other tissues. Retroviral delivery systems are effective in placing the AAT cDNA into cells, and AAT protein has been produced by cells not normally synthesizing the protein. However, serum therapeutic levels are not achieved. Transfection efficiency is low, and the transfections are not always stable. The modified viruses are incapable of replication. One study administered modified transfected fibroblasts intraperitoneally to mice and demonstrated AAT production. Another study utilized transfected hepatocytes that were returned to animals and demonstrated effective AAT production and systemic levels for more than 6 months. Exogenously transfected T lymphocytes have also been used.

Unlike retroviruses, adenoviruses function in the cytoplasm of the cell. They have also been shown to be effective in transfecting respiratory epithelium of rats with human AAT cDNA and producing AAT protein that can be detected in cells and bronchoalveolar lavage fluid. Administration of the modified vector must be repeated on a periodic basis because the transfection is not stable. This form of therapy is undergoing active investigation at this time; clinical application of this approach may be limited by the recipient's immune response to the viral vector.

Plasmids containing AAT cDNA and a cytomegalovirus promoter contained within cationic liposomes have been given to rabbits by the aerosol or intravenous route.

Respiratory tract epithelial cells take up the liposomes and express and release AAT protein into bronchoalveolar lavage fluid.

Prognosis

The natural history of lung dysfunction in AAT deficiency is one of progressive decline. Although lung function is relatively normal during the first two decades of life, it declines thereafter at a variable rate ranging from about 40 to 300 ml of FEV_1 lost per year. Death among homozygotes is usually from respiratory failure, although some may be ascribed to complications of hepatic disease. Only about 16% of ZZ homozygotes survive to age 60 as compared to 85% of normal age-matched individuals, so that severe AAT deficiency leads to reduced survival.

AAT Deficiency Registries

The natural history and the efficacy of intravenous augmentation therapy with human AAT in patients with severe AAT deficiency and pulmonary emphysema is currently being studied in three large multicenter registries including a U.S. NHLBI Registry, a Danish–Dutch registry (European Randomized Placebo-Controlled Trial of a_1-Protease Inhibitor Replacement Therapy), and a German registry (the Westdeutsche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen, WATL; Multicenter Trial of a_1-PI Augmentation Therapy in Patients with a_1-PI Deficiency). These studies are all of different designs. Because of limited patient numbers and slow disease progression, it is unlikely that results will demonstrate statistically significant reductions in the rate of decline of pulmonary function.

Patients with AAT deficiency are often severely depressed. The a_1 National Association (A1NA) is the main source of information for AAT-deficient patients regarding new developments and support groups. Free screenings, an informational CD-ROM for patients and health professionals (AlphaMedia), and information about patient infusion services (AlphaNet) are available. The a_1 *News* is produced by the association, as is an information hotline (*AlphaLine,* 1-800-4ALPHA1).

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CHAPTER

74 Vascular and Other Genetic Diseases Affecting the Lungs

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PULMONARY ARTERIOVENOUS MALFORMATIONS

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular connections that cause intrapulmonary right-to-left shunting of unoxygenated blood. They can be congenital or (rarely) acquired and occur as single or multiple lesions. A PAVM is frequently a manifestation of hereditary hemorrhagic telangiectasia (HHT; Osler–Weber–Rendu syndrome). The latter is characterized by multiple arteriovenous communications in any organ system of the body, such as telangiectasia of the skin, mucous membranes, and viscera and AVMs of the brain and lung. Hereditary hemorrhagic telangiectasia is an autosomal dominant disorder with an estimated incidence of one in 50,000. Genetic linkage for some HHT families has been found on chromosome 9 (gene locus at 9q3.41), but the syndrome is genetically heterogeneous. The gene may code for endoglin, a binding glycoprotein of vascular endothelium. Pulmonary AVMs occur in approximately 30% of patients with HHT and tend to be multiple, whereas single pulmonary lesions are more common in sporadic, nonfamilial cases. Hereditary hemorrhagic telangiectasia is often unrecognized in patients with PAVM; examination of family members for telangiectasias can be helpful. In most large series, 60% or more of all patients with PAVMs have HHT.

Over 500 cases of PAVM have been described in patients of all ages. Although there are reports of symptomatic infants and children, most patients present in the second decade of life or later. Typical symptoms include dyspnea on exertion, palpitations, cough, and chest pain. Hemoptysis is not uncommon, and pulmonary hemorrhage is a major cause of mortality. Mortality or morbidity may also result from stroke or brain abscess from emboli arising from PAVMs. In HHT, epistaxis, gastrointestinal bleeding, and neurologic symptoms may occur. Physical and laboratory signs of PAVM include digital clubbing, cyanosis and polycythemia as a result of right-to-left intrapulmonary shunting of blood, with hypoxemia refractory to supplemental oxygen therapy. The chest radiograph often shows a smooth, noncalcified pulmonary nodule or mass in the lower lobes (Fig. 1 and Fig. 2). Diagnostic sensitivity can be improved by the use of contrast-enhanced chest computed tomography (CT); helical CT with three-dimensional surface reconstruction; chest fluoroscopy; magnetic resonance imaging; contrast echocardiography; and/or pulmonary angiography/cardiac catheterization (the latter being the “gold standard”).

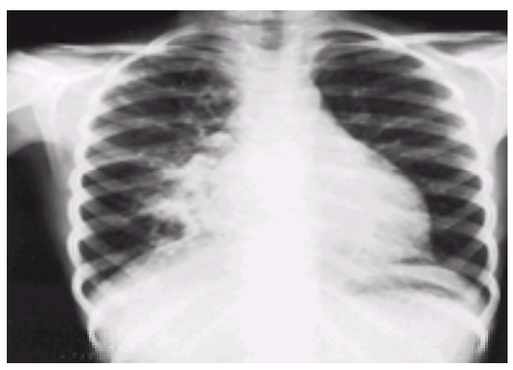

FIG. 1. An irregular density in the right lower lobe of a patient with arterial hypoxemia, a continuous murmur, dyspnea, and palpitations.

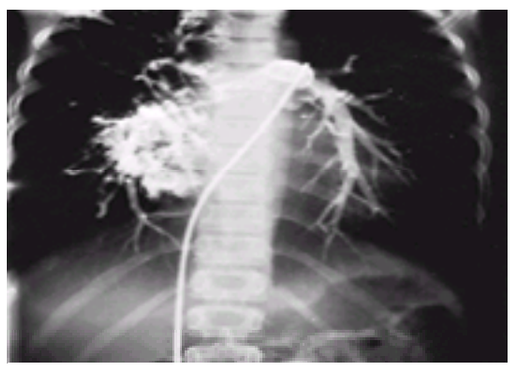

FIG. 2. Angiographic demonstration of a single pulmonary arteriovenous fistula in the patient shown in Fig. 1.

Treatment options for PAVMs include embolotherapy and operative resection. Transcatheter embolization using detachable balloons and/or stainless steel coils has been successful. These procedures are especially effective in patients with multiple PAVMs (e.g., in association with HHT) or patients who are poor surgical candidates. Occluding all arteries supplying a PAVM that are 3 mm or larger in diameter has been reported to optimize results. Surgical resection of PAVMs can be curative and is generally associated with minimal postoperative morbidity or mortality. Lung-conserving resection (such as segmentectomy or local excision) should be performed when possible to preserve lung function. In cases of multiple PAVMs or recanalization of PAVMs, combined staged surgical/embolization therapy has been successful. The role of observation alone for PAVMs is unclear. Further study is necessary to better define the optimal timing of PAVM therapy, especially for asymptomatic cases. Stricter therapeutic guidelines will be difficult as long as the natural history of PAVMs remains unknown.

FAMILIAL PRIMARY PULMONARY HYPERTENSION

Primary pulmonary hypertension (PPH) is characterized by elevated mean pulmonary artery pressure (>25 mm Hg at rest or >30 mm Hg during exercise) in the

absence of secondary causes such as chronic cardiopulmonary diseases or chronic pulmonary venous hypertension. The condition is rare (194 patients in the 1981 NIH registry). The familial form of PPH is thought to account for only 7% of cases. Primary pulmonary hypertension affects women more often than men with typical onset in the 20- to 50-year age range.

Familial PPH has been documented in at least 19 families. Inheritance varies: in some families, more than one generation is affected, suggesting autosomal dominant inheritance. In other families, only members of the same generation are affected, suggesting autosomal recessive inheritance. There is some evidence that PPH demonstrates “genetic anticipation”; i.e., the severity worsens and age of onset decreases with successive generations. In any event, for both sporadic and familial PPH, the prognosis is almost always poor. The median life expectancy after diagnosis is approximately 2 to 5 years but varies with clinical status and is inversely related to the degree of elevation of mean pulmonary artery pressure.

All PPH is characterized by obliteration of the small pulmonary arteries. Diagnosis is made on the basis of clinical symptoms, laboratory/imaging studies and, if available, tissue pathology. Pathologic subtypes include “isolated” medial hypertrophy (IMH), plexogenic pulmonary arteriopathy (PPA), thrombotic pulmonary arteriopathy (TPA), and pulmonary venoocclusive disease. As in sporadic PPH, pathologic heterogeneity is evident in familial PPH, and pathologic subtypes may coexist among individuals in the same family and within blood vessels from the same individual. The clinical symptoms of PPH include dyspnea, fatigue, chest pain, syncope, and palpitations. Physical findings include a loud pulmonic component of the second heart sound, a murmur of tricuspid regurgitation, and a right-sided third or fourth heart sound. The typical chest roentgenogram shows dilation of the main and/or hilar pulmonary arteries, occasionally with pruning of the peripheral vessels. The ECG shows right axis deviation and right ventricular hypertrophy. Pulmonary function testing may show a mild restrictive pulmonary defect with decreased D_LCO.

The cause of PPH is unknown. Recent theories have focused on inflammatory or immunologic abnormalities associated with endothelial dysfunction. There is likely an imbalance of vasodilator and vasoconstrictor factors and abnormal platelet aggregation and thrombosis. No treatment strategy has proven very effective. Some patients have better survival when treated with chronic anticoagulation. Digoxin, diuretics, and oxygen therapy are used in some clinical trials but are usually of limited benefit. Vasodilators benefit some patients, especially those who demonstrate “pulmonary vascular reactivity” (i.e., >20% reduction in pulmonary vascular resistance with the study drug). A trial of calcium channel blockers, especially in high doses, may reduce pulmonary artery pressure. Prostacyclin or epoprostenol has recently been approved by the FDA for continuous intravenous administration for PPH. It has a very short half-life (about 6 min) and is theoretically a more selective, safer pulmonary vasodilator when delivered through a central venous catheter. Patients can be treated long-term with a portable pump; a recent study showed improved survival. Recently, inhaled nitric oxide has been used with short-term success. The limitations of vasodilators include negative inotropic effects and systemic hypotension. Nitric oxide may circumvent these potential side effects by providing selective pulmonary vasodilation; however, long-term studies are lacking. Heart-lung or single lung transplantation is another possible treatment. Four-year survival of approximately 49% has been reported, with serious complications outside the perioperative period most often related to bronchiolitis obliterans or infection. Although transplantation appears to be the current treatment of choice, the supply of transplant organs is limited, and mean waiting time for lung transplantation is 1 to 2 years.

Because the genetics of familial PPH are not well defined, and clinical symptoms are not apparent until the disease is advanced, patients with PPH require a thorough family investigation. Whenever possible, autopsy reports and death records should be examined for clues to familial PPH. In established familial PPH, serial examinations and laboratory testing (such as estimation of pulmonary artery pressure by echocardiography) are recommended for early diagnosis of family members.

SCIMITAR SYNDROME

Over 95 cases of the scimitar syndrome have been described. It is a rare disorder of partial anomalous pulmonary venous connection (PAPVC), accounting for approximately 3% to 5% of all PAPVC. The basic features of the disorder include hypoplasia of the right lung associated with dextroposition of the heart, systemic arterial supply to the right lung, and anomalous right pulmonary venous drainage to the inferior vena cava. The most constant feature is the anomalous venous drainage. The entire right lung is usually drained by a single vein that runs parallel to the right border of the heart to join the inferior vena cava between the right atrium and the hepatic veins. The site of junction is usually below the diaphragm. The arterial supply to the right lung is variable and can arise from the pulmonary, bronchial, or systemic arterial systems. Typically, arteries arise from the aorta, often below the diaphragm. Hypoplasia or absence of the right upper lung segment is frequent; cardiac malformations (especially atrial septal defects) are common. Extracardiac malformations may include vertebral anomalies, scoliosis, or an abnormal right hemidiaphragm.

The cause of the syndrome is undefined, but it probably arises early in right lung bud development secondary to the persistence of embryonic connections of the pulmonary plexus with the cardinal veins. The syndrome can show familial clustering. An affected father and daughter have been reported, which suggests autosomal dominant inheritance. The majority of cases appear to be sporadic; however, the fact that affected individuals may be asymptomatic and are discovered accidentally by routine chest roentgenogram complicates genetic assessment. A systematic study of first- and second-degree relatives of affected individuals could clarify the genetic component of this syndrome.

In the infantile form of the disorder, symptoms are severe and occur in the first year of life. Congestive heart failure, pulmonary artery hypertension, substantial left-to-right shunts, and respiratory failure are common. Older children and adults may present with milder symptoms, including recurrent pneumonia, mild exertional dyspnea, or, rarely, hemoptysis. Not uncommonly, the disorder is diagnosed in asymptomatic individuals.

The chest roentgenogram may suggest the diagnosis when the anomalous vein that courses downward parallel to the right atrium to the inferior vena cava produces an arc-like shadow that resembles the blade of a Turkish sword or scimitar (Fig. 3). Hypoplasia of the right lung and dextrocardia are common radiographic findings. Contrast-enhanced CT of the chest may be helpful. Definitive diagnosis and anatomic characterization of the arterial and venous supply to the right lung require angiocardiography. In addition, cardiac catheterization is useful to evaluate pulmonary artery pressure and left-to-right shunt.

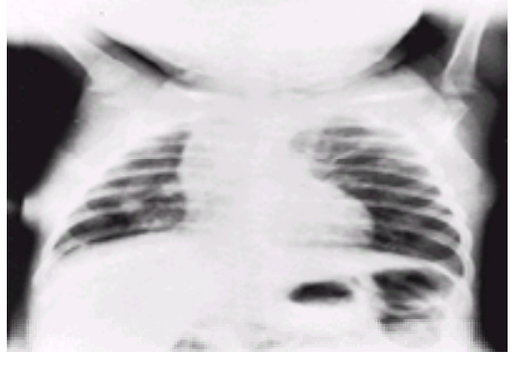

FIG. 3. Scimitar syndrome in a child. The pulmonary vein on the right runs parallel to the right atrium to its connection with the inferior vena cava below the diaphragm.

The optimal therapeutic strategy is not known. For infants and older patients who present with severe symptoms associated with pulmonary artery hypertension and large left-to-right shunts, surgical repair is indicated. In some patients with large shunts, redirection of the anomalous pulmonary venous return has been successful. However, thrombosis of the anastomosis of the anomalous vein to the left atrium has been reported and is a severe potential complication. Pneumonectomy may improve hemodynamic abnormalities; more often, it is reserved for cases of severe recurrent lung infection. The prognosis of older children and adults without pulmonary hypertension is very good. For these patients, medical therapy with aggressive management of pulmonary infections appears to be at least as effective as surgical management. Long-term complications, however, may include bronchiectasis. Conservative management is also indicated if infradiaphragmatic drainage is diagnosed, as surgical risk in these cases is substantial.

DEFECTS IN IMMUNITY

Inherited defects in immunity are very rare. Most inherited defects can be conveniently divided into antibody (B-cell) immunodeficiencies, cellular (T-cell) immunodeficiency, combined antibody and cellular deficiencies, phagocytic dysfunction, and complement deficiency. Recurrent pulmonary infections characterize most of these disorders. A complete review of immunodeficiency is outside the scope of this chapter. We focus on selected immunodeficiency states that affect the lungs.

Antibody Deficiency

Antibody deficiency disorders include X-linked agammaglobulinemia, selective IgA deficiency, common variable immunodeficiency, IgG subclass deficiency, and

immunodeficiency with elevated serum IgM. These diseases are caused by a disorder in B cells resulting in a functional deficiency in antibody. Screening for antibody deficiency can be accomplished with immunoglobulin quantification, from isoagglutinin titers (anti-A, anti-B), and by assaying functional immunity with antibody titers before and after immunization to pneumococcus, *H. influenzae,* and tetanus. The frequency of primary inherited antibody deficiencies varies from about one in 50,000 for X-linked agammaglobulinemia to approximately one in 500 people for selective IgA deficiency. It has been estimated that antibody deficiencies account for 46% of all primary immunodeficiencies.

In X-linked agammaglobulinemia, symptoms generally occur after loss of maternal antibody (after 6 months of age). There is susceptibility to infection with pyogenic organisms, such as pneumococcus and *H. influenzae,* and to enterovirus. In contrast, infection with viral, fungal, and parasitic pathogens is more common with combined cellular and antibody deficiencies or isolated cellular deficiencies.

The level of cellular defect in X-linked agammaglobulinemia is at the pre-B-cell stage of lymphocyte maturation. T-cell number and function are usually normal; serum concentrations of IgG, IgA, IgM, and IgE are markedly decreased or absent. The current therapy of choice is intravenous replacement g-globulin (IVIG). Potential for anaphylaxis from anti-IgA antibodies is a risk when IVIG that contains IgA is used. Transmission of hepatitis B and, more recently, hepatitis C by IVIG has also been described. Despite IVIG, chronic bronchiectasis is common, and the prognosis is guarded.

In contrast to X-linked agammaglobulinemia, common variable immunodeficiency (CVID) is characterized by a later age of onset, approximately equal sex distribution, and generally milder severity of immunoglobulin deficiency and clinical symptoms. It is associated with an arrest of B-cell maturation into plasma cells. T-cell function is usually intact, but some patients have moderate helper T-cell depletion. The disorder is clinically and genetically diverse; a recessive mode of inheritance is present in some families. The diagnosis is associated with a high incidence of autoimmune disease and malignancies (e.g., lymphomas, especially in female patients).

Isolated IgG subclass deficiency is a somewhat controversial clinical entity. Most investigators agree that some IgG subclass deficiencies (especially of IgG_2) are associated with an absence of functional immunity. Reduced antibody response to vaccines (e.g., *H. influenzae, S. pneumoniae* polysaccharides) may aid in the diagnosis of functional immunodeficiency. Patients without IgG subclass deficiency but who lack functional immunity may also be susceptible to recurrent infections. There is also literature associating IgG subclass deficiency with clinical asthma, and a few studies suggest clinical improvement in asthmatics treated with replacement immunoglobulin. This therapeutic approach remains extremely controversial, however, and there are several reports of individuals lacking various IgG subclasses who are entirely asymptomatic.

Cellular and Combined Immunodeficiency

Severe primary T-cell immunodeficiency is rare, with an estimated incidence of one in 100,000 births in Europe. Individuals with T-cell immunodeficiency are susceptible to opportunistic infections, including *Pneumocystis carinii,* fungi, and parasites. Infection with herpes viruses is especially common, including herpes simplex, cytomegalovirus (CMV), varicella-zoster, and enteroviruses. Severe combined immunodeficiency (SCID) affects both B- and T-cell function; most affected individuals become ill in the first few months of life. Clinical findings include profound lymphopenia and cutaneous anergy. Failure to thrive, thrush, anemia, and chronic diarrhea (e.g., from adenovirus or rotavirus) are common. Interstitial pneumonia caused by *Pneumocystis carinii* or CMV infection can be fatal, and many affected individuals die in the first year of life. Vaccination with live, attenuated viruses (e.g., polio, measles) can cause severe, even fatal infection. Blood transfusions are often necessary because of anemia of chronic illness; care should be taken to obtain CMV-negative, irradiated blood products. Without irradiation, blood transfusions include donor white cells that can induce fatal graft-versus-host disease in individuals with SCID. Most patients with SCID are treated with replacement immunoglobulin, which may help protect against vaccine complications. Bone marrow transplantation has been successful in a limited number of patients with SCID.

Severe combined immunodeficiency can be inherited in an X-linked or autosomal recessive manner. In approximately 40% of patients with autosomal recessive SCID, absence of the enzyme adenosine deaminase (ADA) is observed. Gene therapy is especially promising in ADA-SCID.

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is a rare inherited disorder of immunity, affecting one in 500,000 to 1,000,000 persons. Both X-linked and autosomal recessive inheritance has been described. This is a genetically diverse disease; approximately 60% of affected individuals have X-linked CGD. It is characterized by recurrent pyogenic infections caused by bacteria and fungi. Pulmonary involvement may include bronchopneumonia, empyema, or lung abscess. Serious infections of the gastrointestinal tract, skin, and draining lymph nodes are common. The liver, bone, or kidney can be infected by contiguous or hematogenous spread. Most patients are symptomatic by the first year of life. Clinical findings include lymphadenopathy, hepatosplenomegaly, anemia, failure to thrive, short stature, hypergammaglobulinemia, and granulomatous obstruction of the gastrointestinal tract.

Phagocytes from people with CGD ingest but cannot kill pathogenic microorganisms because of an inability to generate a “respiratory burst.” This functional deficiency, the result of an inherited defect in the enzyme NADPH oxidase, leads to prolonged retention of material in leukocytes and to a chronic granulomatous inflammatory response. The major components of the NADPH oxidase system are a membrane-bound cytochrome b and at least two cytosolic factors. X-linked CGD is most commonly caused by a defect in the gp^{91}-phox subunit of the cytochrome b system (designation $X91^0$, i.e., complete deficiency of the 91-kDa glyprotein subunit). Defects in the other cytochrome subunit (p^{22}-phox) or one of the cytosolic factors (especially p^{47}-phox) are found in most cases of autosomal recessive inheritance.

When the NADPH oxidase system malfunctions, superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl) are lacking, resulting in severe impairment of microbial killing. Patients with CGD are especially susceptible to organisms that contain catalase because catalase prevents the CGD phagocyte from using the H_2O_2 generated by microbials. Common pathogens in CGD include *Staphylococcus aureus, Aspergillus* and *Nocardia* species, and gram-negative bacilli including *Pseudomonas cepacia.*

The prognosis of CGD is poor. Although the clinical course is variable, death in young adulthood is common. Approximately 50% of patients have been reported to survive to age 20 years because of improvements in antibiotic therapy. It has been reported that more than 80% of CGD patients present with life-threatening infections of the lung and that 50% of childhood CGD mortality is attributed to lung infections. The use of prophylactic antibiotics (e.g., trimethoprim–sulfamethoxazole) appears to be effective in reducing the frequency of serious infections. Recombinant human interferon-g also appears to reduce the frequency of serious infections and is generally well tolerated. Potentially curative therapies for CGD include bone marrow transplantation (BMT) and somatic gene therapy. Thus far, however, BMT has been successful in only a limited number of patients, and gene therapy remains in the preclinical stages of development.

CHROMOSOME ABNORMALITIES

The chromosome disorders discussed in this section were selected because they have been associated with defects in immunologic function. In none of these disorders is the pulmonary lesion diagnostic. Problems related to the lung reflect primary systemic defects in host resistance.

Down's Syndrome

Trisomy of chromosome 21 was the first chromosomal abnormality described in humans and is the most frequent autosomal anomaly. The clinical phenotype is well known and is usually recognized at birth. Early diagnosis is important because mental retardation is a consistent feature. The dysmorphoses observed include a small, round head with a flat occiput, palpebral fissures that slant upward and outward with the inner angle marked by epicanthal folds, and irises that show a ring of small, round, irregular whitish spots (Brushfield's spots). The ears are usually small. The nape of the neck is short, flat, and broad with redundant skin folds. Infants always show marked muscle hypotonia. The fifth finger is short and incurved, and the hands may show a single palmar crease (simian crease). Associated structural defects are found in the heart in 40% of patients. Malformations of the gastrointestinal tract include duodenal stenosis or atresia, annular pancreas, and anal atresia. Infection, leukemia, other cancers, and thyroid disease occur with increased frequency.

These clinical observations may be related to the qualitative and quantitative defects in the immune response described in affected individuals. Abnormalities of T-cell and B-cell function and numbers have been described in Down's syndrome, but the observations are not consistent. The lung in Down's syndrome may show pulmonary hypoplasia because of a diminished number of alveoli in relation to acini. The resultant decrease in alveolar surface area may account for the severe pulmonary hypertension observed in some Down's syndrome patients. The obstructive sleep apnea (OSA) syndrome is another factor that produces pulmonary hypertension unassociated with, and out of proportion to, the presence of congenital heart disease. Oropharyngeal muscle hypotonia, small airways, large tongue (relative to mouth size), and adenotonsillar hypertrophy may contribute to OSA. Adenoidectomy and/or tonsillectomy may be helpful but is rarely curative. There are reports of tracheal stenosis and segmental “ring” tracheal cartilages (absence of the pars membranacea) in Down's syndrome. In addition to OSA and pulmonary infections, cystic pulmonary disease has been associated with Down's syndrome. There is a high frequency of wheezing and gastroesophageal reflux disease in young patients. There is also an association with tracheoesophageal fistula and recurrent aspirations. Thus, the causes of wheezing/recurrent pulmonary infiltrates in an infant or child with Down's syndrome are likely multifactorial, and their respiratory management can be challenging and complex.

The clinical diagnosis of Down's syndrome should be confirmed by cytogenetic analysis, which is indispensable for genetic counseling. The majority of cases (90%) show trisomy of chromosome 21 resulting from nondisjunction at the time of the first (73%) or second (23%) meiotic division. The patients have 47 chromosomes instead of the normal number of 46. Trisomy 21 can be considered an isolated accident, with the risk of recurrence related to parental age. In women at age 20, the frequency of trisomy 21 is on the order of one in 2000 births, but the frequency increases exponentially to one in 50 births after 45 years of age. Approximately 5% of Down's syndrome patients show a chromosome number of 46, with the extra 21 chromosome attached to another autosome, usually one of the D group. This translocation is a sporadic event in half the cases. In the remaining translocation patients, a balanced translocation is demonstrated in one of the parents, who is phenotypically normal. In these families, the risk of recurrence is high, ranging from 1% or 2% if the father is the carrier to 10% to 15% if the mother is the carrier. Down's syndrome can be diagnosed before birth by amniocentesis and chromosome analysis of fetal cells. This option may be considered by families with the translocation form of Down's syndrome or in women over age 35 because of the statistical increase of nondisjunction.

CHROMOSOME INSTABILITY

Ataxia-Telangiectasia

Ataxia-telangiectasia is a recessively inherited disease characterized by ataxia, telangiectasia of the bulbar conjunctiva, and sinopulmonary infections as the result of variable cellular and/or humoral immunodeficiency. Susceptibility to both bacterial and viral infections is increased, and there is an increased risk of malignancy. Cerebellar ataxia becomes evident when the child begins to walk. Oculocutaneous telangiectasia may be delayed until 2 to 6 years. Neurologic dysfunction is often progressive, with complete incapacitation by 12 years of age. However, the prognosis is variable, with death commonly occurring from pulmonary infection or lymphoreticular malignancy. The most frequent immunologic abnormality is IgA deficiency. However, IgG/IgG subclass levels may also be low; specific antibody titers may be depressed; and lymphopenia is often present, with moderately decreased T-cell function and absent responses to delayed hypersensitivity skin tests. Cell-mediated immune deficiency is also evidenced by delayed skin allograft rejection and inhibition of *in vitro* lymphocyte responses to mitogens. Pathologically, there is depletion of lymphocytes in lymphoid tissues with a predominance of reticular epithelial cells. Between 10% and 30% of patients develop lymphoreticular malignancies or other neoplasms. The syndrome appears to be causally related to a basic repair defect in the DNA of ataxia-telangiectasia cells. Cultured cells from patients show increased numbers of breaks, gaps, and rearrangements, especially involving chromosomes 7 and 14. There is an increased susceptibility to radiation with defective DNA repair. Chromosomal breaks are clustered at chromosome 14q12 with translocations to chromosomes 6, 7, and X. Ring formation of chromosome 14 also has been noted. There are no definitive tests to detect carriers of the mutant gene, although family members may show some degree of anergy, delayed hypersensitivity responses, or IgE deficiency. The abnormal gene has been mapped to the long arm of chromosome 11 (11q22.3) and was recently identified by positional cloning.

Treatment is supportive and consists of antibiotics to control respiratory infections, aggressive pulmonary toilet, immunization with killed vaccines only, and physical therapy for the neurologic dysfunction. Replacement of immunoglobulins may be considered if IgG and other specific antibody levels are significantly depressed, but care must be taken to minimize the risk of anaphylaxis in IgA-absent individuals.

Bloom's Syndrome

The major clinical features of Bloom's syndrome are dwarfism with normal body proportions, a narrow face with nasal prominence, dolichocephaly, and sun-sensitive telangiectatic erythema of the face, usually in a butterfly distribution. Affected children are small at birth, and body size remains small. This disorder is inherited as an autosomal recessive trait, predominantly among Ashkenazic Jews. During the first decade of life, infections of the upper and lower respiratory tracts are frequent. The increased incidence of infection is associated with immune dysfunction, which may include a poor lymphoproliferative response to pokeweed mitogen and variable changes in serum immunoglobulin levels (especially IgM deficiency). The significant predisposition to cancer shown by these patients is probably related to the tendency to excessive spontaneous mutations. The characteristic cytogenetic abnormality consists of a marked increase of sister chromatid exchange in cultured cells. This finding is consistent and is of diagnostic value. Chromosome-transfer studies have shown the locus for Bloom's syndrome mapping to chromosome 15q26.1. The diagnosis is suggested in dwarfed children with normal body proportions who show facial dysmorphism and sun-sensitive telangiectatic skin lesions of the face. The prognosis is poor, with death occurring from cancer or infection. Treatment of pulmonary complications consists of aggressive use of antibiotics and possibly replacement immunoglobulin.

HERITABLE DISORDERS OF CONNECTIVE TISSUE

Connective-tissue proteins are complex and interdependent in their anatomic arrangement and physical properties. The major proteins of connective tissue are collagen, elastin, and proteoglycans. A large number of enzymes participate in the biosynthesis and degradation of these proteins. Genetic mutations affecting biosynthetic enzymes at the level of transcription or translation may alter the primary structure of the protein. Mutations also could alter the function of enzymes involved in the posttranslational modification of the protein, thereby affecting its secondary or tertiary structure. A change in protein structure could be expected to alter the normal organization and function of connective tissue and produce disease. Genetic mutations affecting enzymes involved in the degradation of connective tissue proteins are well documented, as they produce diseases through the accumulation of material in lysosomes.

Several reviews relate the biochemistry of collagen, elastin, and proteoglycans to connective-tissue disease. The disorders selected for discussion in this section illustrate the progress made in defining the biochemical basis for certain connective-tissue disorders that affect the lungs. The heritable disorders of connective tissue provide models that define the functions of specific connective-tissue proteins in normal pulmonary function.

Marfan's Syndrome

Marfan's syndrome (MFS) is an inherited multisystem disorder of connective tissue—specifically, fibrillin, a component of elastic fibers, one of the components of extracellular matrix. Marfan's syndrome affects the eyes, skeletal system, heart, skin, and blood vessels. The Marfinoid habitus is a result of overgrowth of arms and legs, resulting in an unusually tall, thin body with long extremities (dolichostenomelia) and long fingers and toes (arachnodactyly). Spontaneous pneumothorax, bullous emphysema, sleep-disordered breathing (obstructions), airways defects or hyperreactive airways, scoliosis, and pectus excavatum can all contribute to pulmonary morbidity. Inheritance is autosomal dominant. As in all autosomal dominant genetic diseases, spontaneous mutations are common. There is a broad range of clinical expression of the gene, and genetic testing is not perfected.

The salient criteria to diagnose MFS include a family history, ocular findings, cardiovascular abnormalities, and the skeletal features described previously. At least two features should be present to make the diagnosis. In the absence of positive family history, there must be skeletal and either cardiovascular or ocular defects present. In classic cases, three or four features are usually evident. Because each of the clinical features of the syndrome occurs with variable frequency in the general population, it is to be expected that several can occur by chance alone in some individuals. For example, individuals with isolated pectus excavatum may also have mitral regurgitation and/or mitral valve prolapse. Determining whether such individuals are affected with Marfan's syndrome will tax the acumen of the best clinician.

The basic genetic defect that produced Marfan's syndrome has now been identified. The syndrome is caused by mutations in the gene encoding fibrillin-1 (FBN-1), localized to the long arm of chromosome 15. The fibrillin monomer is a 350-kDa glycoprotein that is associated with microfibrillar fibers. These fibers are integral components of elastic elements and are also present in a variety of other cells and tissues. A decreased content of fibrillin has been documented in the microfibrils of tissues from patients with Marfan's syndrome and in cultured Marfan's fibroblasts using monoclonal antibodies to fibrillin. In addition, there appears to be a direct relationship between the decreased content of fibrillin and the presence of symptoms.

Life expectancy in MFS has improved substantially with aggressive medical and surgical management of the cardiovascular complications. Specific surgical interventions include aortic root replacement and aortic aneurysm repair. Medical therapy includes use of b-adrenergic receptor blocking agents, which may decrease the rate of aortic dilation in MFS. A recent study of 417 MFS patients showed a 25% increase in mean age at death, from 32 years in 1972 to 41 years in 1993.

Ehlers–Danlos Syndrome

The classic clinical features of the Ehlers–Danlos syndrome include hyperelastic skin, hyperextensible joints, fragile tissues, and bleeding diatheses; however, the clinical phenotype is variable. At least nine variants are recognized on the basis of clinical, genetic, and biochemical criteria. The biochemical defect is not known for several types. Types I, II, and III are almost always inherited as dominant traits. They are classified by the severity of the clinical features described above. Type I patients have gross skin extensibility, severe joint hypermobility, fragile skin, poor wound healing, and moderate bleeding diatheses. They are frequently born prematurely with rupture of fetal membranes before the mother goes into labor, because these tissues are derived from the fetus and share the same connective-tissue defect. Musculoskeletal deformities are common. Patients with the type II variants are less severely affected, whereas type III patients may show only hypermobile joints.

The ecchymotic form or type IV variant is characterized by bleeding diatheses, arterial rupture, and intestinal perforation. Autosomal dominant and recessively inherited

kindreds have been described. In all type IV patients studied, the unifying biochemical abnormality is a defect in the synthesis, structure, or secretion of type III collagen with a resultant deficiency in mature type III collagen. The gene for type III collagen (COL3A1) has been localized to chromosome 2q31-32. Analyses of lung tissue from a patient with type IV Ehlers–Danlos who developed recurrent pneumothoraces and whose apical bullae were resected, showed that the relative proportion of type III collagen in the lungs was markedly decreased. These data suggested that the structural abnormalities in the lung that led to pneumothorax were consequences of a deficiency of type III collagen.

A case of fatal hemoptysis has been described in an individual with type IV Ehlers–Danlos, most likely because of vascular fragility with recurrent pulmonary hemorrhage. Respiratory pathology may occur from kyphoscoliosis, rupture of the lung, mediastinal emphysema, and pneumothorax. In patients who died from rupture of an artery, large emphysematous subpleural bullae have been described. Pulmonary function has not been extensively studied in affected individuals; no consistent spirometric or lung volume abnormalities have been detected.

THE LUNG IN LYSOSOMAL STORAGE DISEASE

Lysosomes are pleomorphic cellular organelles that contain a variety of hydrolytic enzymes with an acid pH optimum. These acid hydrolases are synthesized in the endoplasmic reticulum, transported through the Golgi apparatus, and finally packaged in lysosomes, where they degrade biological macromolecules. The sequence by which macromolecules are degraded is complex, involving several enzymes acting in a coordinated sequential fashion. The deficiency of a single degradative enzyme leads to the accumulation of the macromolecule or its partially degraded metabolite within the lysosome; such accumulation produces disease. The best-characterized groups of lysosomal storage disorders are the mucopolysaccharidoses and the glycosphingolipidoses. Almost all lysomal storage diseases show phenotypic heterogeneity ranging from severe infantile to mild adult forms.

In the mucopolysaccharidoses (MPS), glycosaminoglycans are abnormally accumulated in lysosomes. Hurler's syndrome is the prototype MPS in which at least 13 variants are known. This disorder is inherited as a recessive trait. The gene has been isolated and mapped to cytogenetic band 4p16.3. The biochemical basis for the disease is a deficiency of the enzyme a-L-iduronidase. As a result of the enzyme deficiency, dermatan sulfate and heparin sulfate are stored in cells throughout the body, which produces multiple organ dysfunction and mental retardation.

Pulmonary problems develop secondary to kyphoscoliosis and deformities of the ribs. Storage of mucopolysaccharides in bone decreases the size of the chest cavity and limits chest excursions. Hepatosplenomegaly compresses the diaphragm from below. Upper airway obstruction is frequent as a result of storage of polysaccharides in lymphoid tissue and deformity of respiratory cartilage. The tongue is large and thick, and the mandible is small and immobile. Chronic rhinorrhea is common. Tracheal and bronchial airways may be abnormally shaped and collapsible. Airway problems dominate the clinical course of many severely affected individuals. Obstructive sleep apnea is common, and endotracheal intubation is very difficult. Perioperative mortality has been reported to be as high as 20% in patients with MPS. As the disease progresses, recurrent respiratory infections, upper airway obstruction, and aspirations may lead to chronic hypoxemia and cor pulmonale. Intercurrent infections can produce respiratory decompensation. Bronchopneumonia is a frequent cause of death.

The pulmonary problems in the mucopolysaccharidoses are but one component of a systemic metabolic disorder. The clinical appearance of the patient with Hurler's syndrome suggests the diagnosis, which can be confirmed by appropriate biochemical studies. The other variants may show similar pulmonary problems to those described for Hurler's syndrome, especially as the patients enter the second decade of life. All variants are inherited as autosomal recessive traits except for type II (Hunter's syndrome), which shows X-linked inheritance. The clinical phenotype, biochemical defects, and genetics of the other established disorders of mucopolysaccharide metabolism are detailed in various reviews. The disease phenotypes are secondary to gene mutations that result in the synthesis of dysfunctional degradation enzymes. All mutant genes have been mapped to specific chromosomes, and many have been defined. Bone marrow transplantation has partially reversed upper airway and CNS symptoms in some patients but is available only in specialized centers.

Two disorders of glycosphingolipid metabolism may present with pulmonary symptoms. The chronic nonneuronopathic form of Gaucher's disease (type 1) may produce respiratory difficulties because of diffuse interstitial pulmonary involvement (Fig. 4) or because of capillary plugging with Gaucher cells. The primary clinical findings are bone abnormalities, hematologic abnormalities (including anemia and thrombocytopenia), hepatosplenomegaly, and metabolic dysfunction with variable pulmonary and kidney involvement. In some patients, the pulmonary process is severe enough to produce cor pulmonale. Gaucher's disease is inherited as a recessive trait. The biochemical basis for the storage of glucosylceramide in lysosomes is a deficiency of the enzyme glucocerebrosidase, which is required for the hydrolysis of glucocerebroside to ceramide and glucose. Enzyme replacement therapy improves the clinical course of type 1 Gaucher's disease and may improve oxygenation and diffusing capacity of the lung in some patients. Potential disadvantages include the high cost of the replacement enzyme and the production of antienzyme IgG antibodies. Gene therapy holds promise: the defect has been localized to chromosome 1q21, and its nucleotide sequence has been ascertained.

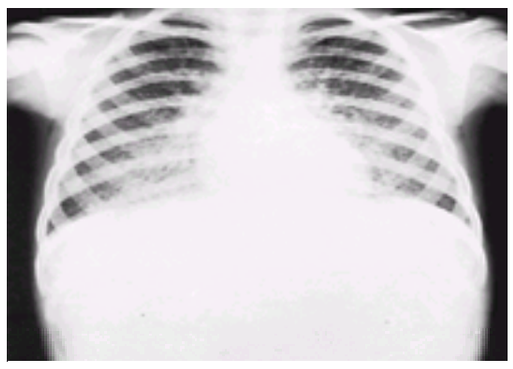

FIG. 4. Chronic nonneuropathic Gaucher's disease in a child showing diffuse pulmonary infiltrates.

The second group of lysosomal storage diseases involving glycosphingolipids that may present with pulmonary symptoms comprises the nonneuronopathic forms of Niemann–Pick disease. Radiographically, the lungs show diffuse reticular infiltrates. Histologic examination at autopsy frequently shows foam cells in the alveoli, lymphatic vessels, and branches of the pulmonary artery. This disorder is also inherited as an autosomal recessive trait. The biochemical basis for the lysosomal storage of sphingomyelin is a deficiency of the enzyme sphingomyelinase, which is required for the hydrolysis of sphingomyelin to ceramide and phosphocholine. The gene has been defined and mapped to chromosome 11p15.1.

In both Gaucher's and Niemann–Pick disease, patients usually show hepatosplenomegaly in addition to pulmonary infiltrates, which should suggest these diagnostic possibilities. Aspiration pneumonia may cause death in these and the other glycosphingolipidoses; the pulmonary problems in neuronopathic glycosphingolipidoses are secondary to involvement of the central nervous system with attendant difficulties in handling secretions and swallowing.

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CHAPTER

75 Diseases of the Pleura and Pleural Space

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PLEURAL EFFUSIONS

The clinical recognition of a pleural effusion signifies that an abnormal physiological state exists whereby there is a dysequilibrium between the formation and removal of pleural fluid. The pleural fluid usually is the sequela of primary pulmonary disease but can also result from disease in an extrapulmonic focus such as the heart (congestive heart failure), kidneys (nephrotic syndrome), liver (cirrhosis), and pancreas (acute pancreatitis). Pleural fluid can also result from systemic diseases, such as systemic lupus erythematosus, metastatic malignancy, and iatrogenic causes such as drug therapy (nitrofurantoin) and extravascular migration of central venous catheters. Thus, patients with pleural effusions may present not only to the pulmonologist but to the internist, family physician, medical specialist, and surgeon.

The clinical presentation, chest radiographic findings, pleural fluid analysis, treatment, and outcome of the most common causes of transudates and exudates are discussed (see Chapter 12).

Transudates

Congestive Heart Failure

Congestive heart failure is the most common cause of a transudative effusion and probably is the most common cause of all pleural effusions, certainly in those over the age of 60 years. The precise incidence of pleural effusion with congestive heart failure is difficult to ascertain, as there is variance in the study populations, the techniques of detecting the effusions, and the stage and degree of heart failure at the time of evaluation. Clinically, about 40% of patients with congestive heart failure have pleural effusions; however, if a more sensitive technique such as ultrasonography is used to evaluate such patients, the incidence would be substantially higher. Pleural effusions in the presence of congestive heart failure are related to elevated pulmonary venous pressures, and most patients with congestive heart failure effusions have pulmonary capillary wedge pressures ^{3}24 mmHg. Interestingly, this is the pulmonary venous pressure associated with visualization of Kerley B-lines on a chest radiograph. It appears that pleural effusions result when high pulmonary venous pressures cause increased filtration of fluid from the microvessels into the lung interstitium, and this interstitial fluid moves along a pressure gradient between mesothelial cells into the pleural space.

If pleural fluid formation exceeds pleural space lymphatic drainage, then fluid will accumulate in the pleural space. Patients with an isolated increase in right atrial pressures or patients with primary pulmonary hypertension do not develop pleural effusions, thus supporting the association of elevated pulmonary venous pressures and the development of pleural effusions. For example, patients with COPD and cor pulmonale rarely have pleural effusions. Patients with pleural effusions from congestive heart failure always have left ventricular failure and frequently associated right ventricular failure.

Most patients with pleural effusions secondary to congestive heart failure have the classic symptoms and signs. The chest radiograph shows cardiomegaly and bilateral small to moderate-size pleural effusions of relatively equal size, with the right being slightly greater than the left. There is usually evidence of pulmonary congestion on chest radiograph, and the severity of pulmonary edema appears to correlate with the presence of pleural effusions.

The pleural fluid is a transudate with mesothelial cells and lymphocytes accounting for the majority of the cells; it is unusual for the neutrophil count to exceed 10%. Acute diuresis over several days can transform the congestive heart failure transudate into a pseudoexudate.

In the patient with clinical congestive heart failure, bilateral pleural effusions, and an enlarged cardiac silhouette, finding a transudative effusion makes a presumptive diagnosis. Treatment consists of decreasing pulmonary venous hypertension and improving cardiac output with diuretics, digitalis, and afterload reduction. When heart failure is managed successfully, the effusions resolve over days to weeks. In patients with refractory heart failure and symptomatic pleural effusions, unilateral chemical pleurodesis should be considered.

Hepatic Hydrothorax

Pleural effusions occur in approximately 6% of patients with cirrhosis of the liver and clinical ascites. However, in rare cases, hepatic hydrothorax can occur without clinical ascites. Pleural fluid results from movement of ascitic fluid through diaphragmatic defects. When enough ascitic fluid is present, peritoneal pressure exceeds pleural pressure, and fluid moves through the diaphragmatic defects into the pleural space.

The patient usually has the physical stigmata of cirrhosis and clinically apparent ascites. With a large to massive pleural effusion, the patient may present with acute dyspnea, but with a smaller effusion, dyspnea may be present only with exertion, or the effusion may be detected on a routine chest radiograph.

The typical chest radiograph shows a normal cardiac silhouette and a right-sided pleural effusion (70%) that can vary from small to massive (<10%); effusions are sometimes isolated to the left pleural space (15%) or are bilateral (15%). Thoracentesis shows a serous transudate with a low nucleated cell count and a predominance of mononuclear cells, a pH > 7.40, a glucose similar to that in serum, and a low amylase concentration. Fluid can be hemorrhagic in the presence of an underlying coagulopathy.

A transudative right pleural effusion in the setting of cirrhosis with ascites provides a presumptive diagnosis. To be more certain, the clinician can compare pleural and ascitic fluid protein and LDH values, which should be similar. On occasion, the protein and LDH may be slightly higher in the pleural fluid than in ascitic fluid; this occurs when the increased portal pressure prevents reabsorption of non-protein-containing fluid by the peritoneum. To absolutely confirm the diagnosis, injection of a radiolabeled tracer into the ascitic fluid with detection on chest imaging within 1 to 2 hrs supports pleural–peritoneal communication through a diaphragmatic defect. Spontaneous bacterial empyema has been noted and occurs by hematogenous seeding or transfer of infected ascites through a diaphragmatic defect.

The treatment of hepatic hydrothorax is directed at the ascites with sodium restriction and diuresis. A pleural effusion frequently persists unchanged until all the ascites have been mobilized clinically. Patients refractory to therapy who remain symptomatic from a large pleural effusion can best be treated by thoracoscopy with repair of the diaphragmatic defect and pleural abrasion/talc pondrase. These patients should not undergo chest tube drainage because it can lead to hypovolemia, protein depletion, and immunosuppression. Patients with spontaneous bacterial empyema usually can be treated with antibiotics without chest tube drainage.

Nephrotic Syndrome

Pleural effusions are frequent in nephrotic syndrome (21% in one series), with the incidence varying with the degree of hypoalbuminemia. The mechanism responsible for pleural fluid accumulation is decreased oncotic pressure in the pleural microvascular circulation as a result of hypoalbuminemia; increased hydrostatic pressure from salt and water overload may also be contributory.

Patients with pleural effusions from nephrotic syndrome usually have anasarca by the time pleural effusions develop. In the evaluation of a pleural effusion in a patient

with nephrotic syndrome, pulmonary thromboembolism needs to be considered, as this complication occurs in approximately a third of patients. The chest radiograph in patients with nephrotic syndrome usually shows small to moderate bilateral pleural effusions without evidence of pulmonary edema.

Thoracentesis reveals a serous transudate with a small number of mononuclear cells, a normal glucose concentration, and a pH > 7.40. The presence of hemorrhagic fluid, an increased protein concentration, or neutrophil predominance suggests thromboembolic disease or another diagnosis. Treatment should be directed at arresting the protein-losing nephropathy. A therapeutic thoracentesis should be done only for increasing dyspnea. If medical therapy is ineffective for the symptomatic pleural effusion, chemical pleurodesis should be considered.

Hypoalbuminemia from any cause is associated with bilateral pleural effusions. When the albumin concentration is £1.8 g/dl, pleural effusions may develop. It is unusual for patients with hypoalbuminemia to have edema fluid isolated only to the pleural space, as the pleural lymphatics are effective in clearance of a moderate amount of increased pleural fluid formation. Therefore, by the time patients with hypoalbuminemia develop pleural effusions, they have anasarca. Other causes of hypoalbuminemia that result in pleural effusions include severe malnutrition, which is commonly seen in patients admitted to the ICU and in end-stage AIDS, and in patients with protein-losing enteropathy.

Atelectasis

Atelectasis is a common cause of small pleural effusions in the postoperative patient, especially following upper abdominal surgery, and in patients in medical intensive care units. Atelectasis was the cause of pleural effusions in 23% of patients admitted to a medical intensive care unit. Atelectatic effusions also occur with major bronchial occlusion from lung cancer, a mucus plug, or foreign body. The mechanism producing atelectatic effusions is decreased pleural pressure. With alveolar collapse, the lung and chest wall separate further, creating local areas of increased negative pressure. This decrease in pleural pressure favors the movement of fluid into the pleural space, presumably from the parietal pleural surface. Fluid accumulates until the parietal pleural interstitium/pleural space pressure gradient returns to normal. The chest radiograph typically shows small unilateral or bilateral pleural effusions with normal heart size and absence of parenchymal infiltrates. Pleural fluid in acute atelectasis has not been studied in detail; however, in patients with mainstem bronchial obstruction and a chronic effusion, the fluid is a serous transudate with a small number of mononuclear cells, a normal glucose concentration, and a pH > 7.40. It is not known whether effusions from atelectasis remain transudates or transform into exudates over time. If the stoma remain patent and there is no preferential removal of liquid over protein, the fluid should remain a transudate. The diagnosis is presumptive in the proper clinical setting. Treatment should be directed at reversing the cause of the atelectasis. If it is successful, the pleural effusion resolves over several days.

Peritoneal Dialysis

Although peritoneal dialysis frequently is associated with small, transient pleural effusions, massive right pleural effusions are occasionally seen. These large effusions usually occur within 48 hr after the initiation of peritoneal dialysis and presumably result from opening of a congenital diaphragmatic defect from the increased peritoneal pressure, causing a rapid transfer of fluid from the peritoneal to the pleural cavity. Patients generally present with the acute onset of dyspnea. The chest radiograph shows a large to massive right pleural effusion with contralateral mediastinal shift. Thoracentesis shows pleural fluid resembling the dialysate. The total protein is usually <1 g/dl with a nucleated cell count of <100/ml and a glucose concentration in the 300 to 400 mg/dl range. The combination of a protein concentration <1 g/dl and a markedly elevated glucose concentration virtually confirms the diagnosis. Rapid movement of a radiolabeled tracer from the peritoneal to the pleural cavity confirms the diaphragmatic defect if there is doubt about the diagnosis. Continued drainage from the peritoneal catheter should be allowed to occur and will result in pleural space drainage as well. If the patient has severe dyspnea or cardiovascular instability, a therapeutic thoracentesis should be performed promptly. The most effective long-term treatment is to change to hemodialysis. The effusion will resolve completely with discontinuation of peritoneal dialysis, but success also has been reported after switching from continuous ambulatory peritoneal dialysis to intermittent dialysis in the semierect position.

Urinothorax

Urinothorax, a pleural effusion secondary to obstructive uropathy, has been associated with carcinoma of the genitourinary system, nephrolithiasis, trauma, surgical stent manipulation, and following renal transplantation. With urinary tract obstruction and hydronephrosis, perirenal and retroperitoneal fluid collections can occur. Pleural fluid moves from the retroperitoneal space through diaphragmatic defects into the pleural space. Patients present with evidence of urinary tract obstruction; the pleural effusion is suspected because of acute dyspnea or is discovered on a routine chest radiograph. The pleural effusion is always ipsilateral to the obstructed kidney; the chest radiograph shows a small to moderate pleural effusion without other abnormalities. Thoracentesis shows a straw-colored transudate with the odor of urine. The nucleated cell count is low, with a predominance of mononuclear cells. Pleural fluid glucose is similar to blood glucose; pleural fluid pH has been reported from 7.00 to 8.00. The pleural fluid pH depends on the urinary pH and on how rapidly the fluid moves from the perirenal area into the pleural space. The pH of a urinothorax is probably determined by the rate of hydrogen ion back-diffusion into the blood from extravasated acidic urine during passage from the retroperitoneal to the pleural space. As the hydrogen ion gradient is dissipated during the movement of fluid, the fluid pH approaches blood pH. Thus, the pH of urinothorax should lie intermediate between that of urine and blood, generally acidic, but can be alkaline if the urine pH is high. Urinothorax is the only cause of pleural fluid acidosis in the setting of a transudative effusion.

The diagnosis of urinothorax can be established by finding a pleural fluid/serum creatinine ratio >1.0. Early thoracentesis may be an important factor for diagnostic sensitivity, as the longer the fluid remains in the pleural space, the more likely equilibration between pleural fluid and serum will occur. In a patient with urinary tract obstruction, a low-pH transudate with a pleural fluid/serum creatinine ratio >1.0 establishes the diagnosis of urinothorax. Relief of the urinary tract obstruction results in prompt resolution of the effusion.

Trapped Lung

A trapped lung is the result of pleural inflammation that causes a pleural peel to develop over a portion of the lung surface. It is most commonly observed after empyema but can be seen with rheumatoid pleurisy, uremic pleuritis, benign asbestos pleural effusion (BAPE), malignancy and any other inflammatory pleural process. The trapped lung cannot expand to the chest wall, creating increased negative pleural pressure and increasing the parietal pleura/pleural space pressure gradient, leading to increased formation of pleural fluid. The formation of pleural fluid continues until a new steady state is reached. The patient may be asymptomatic if the effusion is small or complain of dyspnea if the area of trapped lung is large. The chest radiograph generally will show a small to moderate unilateral pleural effusion without other chest radiographic abnormalities. Thoracentesis usually shows fluid that is borderline between a transudate and exudate and has a small number of mononuclear cells with a normal pH and glucose. Diagnosis can be confirmed by finding a pleural liquid pressure of more negative than –7 cm H_2O at the initial entry of the needle into the pleural space and a rapid decrement in pleural liquid pressure when a small volume of fluid is removed. Therapeutic thoracentesis usually results in rapid reaccumulation of a similar volume of pleural fluid. In the asymptomatic patient with a small effusion, no treatment is indicated; if the patient has a large symptomatic effusion, decortication is the treatment of choice. Decortication can be done years after the initial event with an excellent result as long as the underlying lung parenchyma is normal.

Constrictive Pericarditis

It is common knowledge that pleural effusions are associated with constrictive pericarditis, but it is not generally appreciated that a pleural effusion may be the presenting manifestation of constrictive pericarditis. Pleural effusion was the presenting feature in 60% of patients in one series of 30 patients, with some presenting as a pleural effusion of unknown origin. The most common cause of constrictive pericarditis today is cardiac surgery. Other causes include uremia, radiation therapy, tuberculous pericarditis, bacterial pericarditis, connective tissue diseases, malignancy, or fibrosing mediastinitis.

Constrictive pericarditis is an uncommon disorder with a varied presentation. It is misdiagnosed frequently as chronic liver disease, abdominal carcinomatosis, malignant pleural effusions, tuberculous pleurisy, and restrictive cardiomyopathy. The presenting symptoms include exertional dyspnea, peripheral edema, and increased abdominal girth. Jugular venous distention is the cardinal physical finding, with pleural effusions occurring in 50% to 60% of cases. Pedal edema and ascites are commonly present. The pleural effusions are caused by a combination of pulmonary and systemic venous hypertension, low oncotic pressure, and possibly inflammatory pericardial disease. The chest radiograph is abnormal in most patients, with the majority showing nonspecific findings such as pleural effusion and increased cardiac silhouette. Pericardial calcification, if present, is a specific finding in association with a typical presentation. The pleural fluid is serous and may be an exudate or a transudate, with the total protein concentration being <4 g/dl. Nucleated cell count is modest, usually being <5000/ml with a lymphocyte predominance. The pleural fluid glucose is equal to the serum glucose, and the pH is >7.30. When the diagnosis is suspected clinically, it can be confirmed by echocardiography, CT scan, or cardiac catheterization. Treatment is pericardiectomy.

Exudates

Parapneumonic Effusions

Parapneumonic effusion, pleural fluid associated with bacterial pneumonia, is the most common cause of an exudative effusion. Parapneumonic effusions occur in 36%

to 57% of patients with pneumonia, resulting in an estimated 1,000,000 people per year in the United States developing these effusions. Parapneumonic effusions may be uncomplicated (free-flowing effusions that resolve spontaneously with antibiotic therapy) or complicated (effusions that require pleural space drainage for resolution of pleural sepsis). The natural course of a complicated parapneumonic effusion is to develop a single loculus or multiple loculations and to progress to an empyema cavity. Empyema, from the Greek meaning accumulation of pus in a body cavity, represents the end stage of a complicated parapneumonic effusion.

After the aspiration of microorganisms into subpleural alveoli, neutrophils migrate and adhere to the adjacent endothelium. Oxygen metabolites, granule constituents, and products of membrane phospholipases released by activated neutrophils result in endothelial injury of the pulmonary, subpleural, and pleural vessels, causing increased capillary permeability. The resultant extravascular fluid increases the interstitial–pleural pressure gradient and drives more fluid from the interstitium between mesothelial cells into the pleural space if the rate of fluid production exceeds lung lymphatic clearance. Pleural fluid accumulation occurs only when fluid entering into the pleural space exceeds the absorptive capacity of the parietal pleural lymphatics.

The parapneumonic effusion that occurs in the first 48 to 72 hr is a small, sterile, neutrophil-predominant exudate (capillary leak/exudative stage). The pleural fluid pH is >7.30, the glucose is >60 mg/dl, and the LDH is <500 IU/liter. If the pneumonia remains untreated, after several days there is further endothelial injury with increased permeability edema and the formation of a greater volume of pleural fluid. Bacterial multiplication in the lung continues, and bacteria invade the pleural space and become persistent. The pleural fluid in the bacterial invasion/fibrinopurulent stage is characterized by an increased number of neutrophils, a fall in pleural fluid pH and glucose, and an increase in pleural fluid LDH. Interleukin-8 is a major chemotactic factor from neutrophils in empyema, and TNF-a may play a role in the local production of IL-8. The absolute glucose concentration is usually <40 mg/dl because of increased glycolysis from neutrophil phagocytosis and bacterial metabolism. As the end products of glucose metabolism, CO_2 and lactic acid, accumulate in the pleural space, the pH falls, usually to <7.10. The LDH increases to >1000 IU/liter because of cell lysis. Also during this stage, pleural fluid becomes clottable because of the movement of large concentrations of plasma proteins into the pleural space in conjunction with a loss of pleural space fibrinolytic activity by the inflammatory injury. These processes result in a deposition of a dense layer of fibrin on both pleural surfaces, and metabolically active fibroblasts move into the pleural space unimpeded by the injured mesothelium to begin to secrete glycosaminoglycans and collagen into clottable pleural fluid. Both fibrin and collagen compartmentalize the pleural fluid into loculations by bridging the two pleural surfaces in addition to limiting lung expansion. Pleural fluid volume may increase further because of blockage of the parietal pleura stoma by fibrin, collagen, and mesothelial swelling.

Without treatment, the organization/empyema stage ensues over the next few weeks, resulting in a single cavity or multiple loculations that are formed as fibroblast migration and growth continue in the fibrin–pleural fluid matrix. This process results in an inelastic pleural peel that inhibits pleural fluid drainage as well as lung expansion. Empyema fluid (pus) is a thick purulent coagulum not adequately drained by tube thoracostomy, assuming its specific character because of the coagulability of pleural fluid, the abundance of cellular debris, and increased fibrin and collagen deposition. Untreated empyema rarely resolves spontaneously. It may drain through the chest wall (empyema necessitatis) or into the lung (bronchopleural fistula).

The rapid identification of patients who are likely to develop complicated parapneumonic effusions would improve clinical outcome by allowing early pleural space drainage (Fig. 1). Unfortunately, it is not possible to differentiate clinically those patients with complicated parapneumonic effusions from those with uncomplicated parapneumonic effusions. Pleural fluid analysis remains the most useful diagnostic test in identifying the stage of a parapneumonic effusion and guiding therapy. If pus is aspirated at thoracentesis, diagnosing an empyema, pleural space drainage should be accomplished without delay. Empyema fluid is usually diagnostic for specific pathogens if the specimen is handled expeditiously, appropriate microbiological technique is applied, the patient has not received antimicrobial therapy, and the pleural space is not multiloculated. The pleural fluid protein concentration, nucleated cell count, or percentage of neutrophils cannot differentiate a complicated from an uncomplicated effusion; however, pleural fluid biochemistry can help do so. If the pleural fluid pH is <7.10, the glucose <40 mg/dl, and the LDH >1000 IU/liter, the fluid is a complicated parapneumonic effusion that requires pleural space drainage. If, however, the pH is >7.30, the glucose >60 mg/dl, and the LDH <1000 IU/liter, the fluid is almost always an uncomplicated effusion and will resolve spontaneously on appropriate antibiotic therapy directed at the pneumonia.

FIG. 1. Algorithm for management of parapneumonic effusions. Management of these patients has not been subjected to randomized clinical trials and, therefore, represents a rational approach based on current data.

Complicated parapneumonic effusions should be assessed by CT scan to determine the number and position of pleural fluid loculations. A single loculus with minimal pleural enhancement can be drained by a chest tube or radiologically guided catheter. Multiple locules will require either empyemectomy and decortication or tube drainage with the use of fibrinolytic agents, either urokinase or streptokinase. Many thoracic surgeons today are using thoracoscopy in the initial management of complicated parapneumonic effusions with debridement, pleural irrigation, and decortication. Open drainage should be reserved for the debilitated patient who is too ill to tolerate a major thoracotomy.

Malignant Pleural Effusions

Malignant pleural effusions are the most common cause of exudative effusions in patients over the age of 60. They are frequently the first manifestation and diagnostic source of malignancy, signal incurability, and often represent the first manifestation of recurrent disease. The diagnosis is established by finding malignant cells in pleural fluid or pleural tissue. Some patients, however, will have a pleural effusion associated with malignancy, but malignant cells cannot be demonstrated in pleural fluid or pleural tissue and actually are not present at the time of the diagnostic procedure. These effusions are termed paramalignant effusions and are caused by the malignancy but do not result from direct pleural involvement. Causes of paramalignant effusions include (1) direct local effect of the tumor (lymphatic obstruction, bronchial obstruction with pneumonia or atelectasis), (2) systemic effects of the tumor (pulmonary embolism, hypoalbuminemia), and (3) results of therapy (radiation pleuritis and fibrosis and drug reactions). Lymphatic obstruction, the predominant mechanism of pleural fluid formation in malignancy, can occur with blockage of the lymphatic system at any point from the stoma of the parietal pleura to the mediastinal lymph nodes.

In lung cancer, pleural metastasis occurs when cancer invades the pulmonary vasculature and embolizes to the visceral pleural surface. Once the visceral pleural surface is seeded with tumor, malignant cells migrate across the pleural space along preformed or tumor-induced adhesions. Alternatively, free tumor cells shed from the visceral pleura may adhere to the parietal pleura and multiply. Adenocarcinoma is the most common cell type to involve the pleura because of its peripheral location and propensity for contiguous spread.

Carcinoma from any organ can metastasize to the pleura; however, lung cancer is the most common tumor to result in malignant and paramalignant effusions. Carcinoma of the breast is second in incidence and, in some series, exceeds lung cancer as the cause of malignant effusions, depending on the study population. Ovarian and gastric carcinoma represent about 5% of malignant effusions. Approximately 7% to 10% of patients with malignant pleural effusions have an unknown primary site at the time of the initial diagnosis.

The most common presentation of patients with carcinomatous pleural effusion is dyspnea on exertion. The mechanism of dyspnea from a large pleural effusion is multifactorial and is related to decreased chest wall compliance, contralateral mediastinal shift, loss of ipsilateral lung volume, and neurogenic factors of the lung parenchyma.

The chest radiograph in lung cancer most commonly shows a pleural effusion ipsilateral to the primary lesion. If the primary site is other than lung, with the possible exception of breast cancer, there appears to be no ipsilateral predilection, and bilateral effusions are common. Most patients with carcinoma of the pleura will have a moderate to large pleural effusion, usually 500 to 2000 ml. Ten percent will have an effusion less than 500 ml, and a similar number will show a massive pleural effusion. Seventy percent of patients who present with a massive pleural effusion (occupying the entire hemithorax) will have a malignancy.

Malignant pleural effusions may be serous, serosanguinous, or grossly bloody. A grossly bloody effusion suggests direct pleural involvement with tumor; a serous effusion can result from either lymphatic obstruction or an endobronchial lesion with atelectasis. A majority of the nucleated cells are lymphocytes, macrophages, and

mesothelial cells, with lymphocytes representing more than 50% of the cell population half the time. The percentage of neutrophils is usually <25%. Pleural fluid eosinophilia is inexplicably rare, approximately 5%, in malignant effusions.

The pleural fluid associated with carcinoma of the pleura usually is exudative, but approximately 5% of patients have transudates. Transudative malignant effusions result from early stages of lymphatic obstruction, atelectasis from bronchial obstruction, or congestive heart failure with concomitant shedding of malignant cells into the pleural fluid.

A third of patients with malignant effusions on presentation will have pH < 7.30, which usually is associated with a glucose < 60 mg/dl. Low-pH/low-glucose malignant effusions usually have been present for several months and are associated with a large tumor burden and fibrosis of the pleura. These patients have a poor prognosis (average survival from time of thoracentesis of 2 months), a high yield (95%) of positive cytology on initial evaluation, and a poor (25% to 40%) response to chemical pleurodesis.

The most effective and minimally invasive treatment for patients with recurrent, symptomatic malignant pleural effusions is chest tube drainage with instillation of a chemical agent. Talc, either by poudrage or slurry, results in the best success rate (93%).

Malignant Mesothelioma

Malignant pleural mesothelioma is the signal neoplasm of asbestos exposure. Pleural mesotheliomas are more common in men in the sixth to seventh decade of life. The age occurrence is related to the long latency period of 20 to 40 years following initial exposure. The onset is usually insidious, with localized chest pain being the most common manifestation. A unilateral pleural effusion, more frequently on the right, is the most common radiographic finding. Early in the course, the effusion may be large or massive and cause contralateral mediastinal shift. As the tumor progresses, it encases the lung, grows along the mediastinum, and inhibits mediastinal shift, a radiographic sign suggestive of mesothelioma in the absence of an endobronchial lesion. The pleura may show marked thickening or nodularity, which is first noted near the diaphragm. Other signs of asbestos pleuropulmonary disease may be noted in the contralateral hemithorax.

At thoracentesis, there is marked resistance to the needle entering the pleural space. The pleural fluid may be serous, serosanguinous, or frankly bloody. The fluid is an exudate with nucleated cell counts <5000/ml. At diagnosis, 60% of patients with malignant mesothelioma have a low pleural fluid pH (<7.30) because of the large tumor bulk covering the pleural surface.

The diagnosis is suggested by the chest radiograph or chest CT scan and can be confirmed when a large amount of tissue can be obtained by thoracoscopy or thoracotomy for examination by special stains, electron microscopy, and immunologic studies.

Some patients with large pleural effusions may obtain relief with chest tube drainage and chemical pleurodesis. Chemotherapy, radiation therapy, and debulking surgery have not been shown to improve survival. Gene transfer therapy has shown promise in experimental animals.

Tuberculous Pleurisy

Tuberculous pleurisy is common in both the AIDS and non-AIDS population. Pleural effusion in tuberculosis occurs on an immunologic basis when a subpleural focus of *Mycobacterium tuberculosis* grows and ruptures into the pleural space. Tuberculin protein or the live bacillus interacts with sensitized T lymphocytes with liberation of lymphokines, which may alter the permeability of the pulmonary vasculature and affect activity of the mononuclear phagocyte and pleural fibroblast. Pleural effusions may also result from hematogenous dissemination of mycobacteria. Tuberculous pleurisy commonly occurs 3 to 7 months following the primary infection but can result from reactivation at any time.

The clinical presentation covers the spectrum from an acute illness simulating bacterial pneumonia to an indolent disease first suspected on a chest radiograph in a patient with minor constitutional symptoms. A nonproductive cough and chest pain, usually pleuritic, are the two most common symptoms at presentation. The patient is usually febrile, but peripheral leukocytosis is unusual.

The chest radiograph shows a unilateral, small to moderate pleural effusion, although massive effusions have been noted. Parenchymal disease can be detected radiographically in about a third of patients and can be seen on CT scan in most patients. The effusion is almost always ipsilateral to the infiltrate and is a marker of active parenchymal disease. The PPD will be negative in 30% of patients at presentation; most will convert their skin tests to positive in 6 to 8 weeks. A negative skin test with tuberculous pleurisy in the acute phase of the disease probably results from circulating mononuclear cells that suppress the sensitized T lymphocyte in the peripheral blood and skin but not in the pleural space.

The pleural fluid is a serous (serosanguinous in <10%) exudate with a total protein concentration almost always >4.0 g/dl. The nucleated cell count is generally <5000/ml with a predominance of lymphocytes (usually 90% to 95%). Neutrophil predominance occurs in the first few days following entry of the tubercle bacillus into the pleural space; neutrophils are rapidly replaced by mononuclear phagocytes and then by lymphocytes. A paucity of mesothelial cells is characteristic of tuberculous pleurisy, and pleural fluid eosinophilia is rarely observed. Low pleural fluid pH and glucose are found in 20% of patients. A pleural fluid pH >7.40 is rarely found in tuberculous pleurisy.

AFB (Acid-fast bacillus) smear of pleural fluid is positive in fewer than 10% of patients, whereas pleural fluid culture is positive in 25% to 70%. Pleural biopsy is the best single test for establishing the diagnosis. A granuloma can be demonstrated in the parietal pleura in 50% to 80% of patients and provides a presumptive diagnosis. Culture of the pleural biopsy specimen will grow *M. tuberculosis* 55% to 80% of the time. If pleural fluid and pleural tissue studies and sputum analysis are combined, the diagnosis can be confirmed in 90% to 95% of cases. Clinical presentation, pleural fluid findings, and diagnostic yield are similar with both AIDS and non-AIDS patients with tuberculous pleurisy.

Patients with tuberculous pleurisy can be treated with the same regimen used for pulmonary tuberculosis (three or four drugs for 2 months and INH and rifampin for 4 months). Some investigators have shown that because of the low organism load, INH and rifampin for 6 months is adequate therapy.

With treatment, the patient usually becomes afebrile within 2 weeks; however, fever may persist for as long as 6 to 8 weeks. The pleural effusion usually resolves by 6 weeks but can persist for 3 to 4 months.

Rheumatoid Pleurisy

Pleural involvement is the most common thoracic manifestation of rheumatoid disease and occurs in approximately 5% of patients. The typical patient is a man in the sixth decade who develops a pleural effusion within 5 years after the onset of rheumatoid disease. Effusions, however, can develop before or 20 years after the onset of articular disease. These patients usually have moderate to severe arthritis and subcutaneous nodules. The patient can present with pleuritic chest pain or dyspnea, or the disease may be discovered on a routine chest radiograph. Fever is not a frequent manifestation, in contrast to lupus pleuritis.

The chest radiograph shows a small to moderate unilateral effusion without other manifestations of rheumatoid lung disease. The effusion may appear turbid with a yellow-green tint. Occasionally it is milky (because of cholesterol) or appears to contain debris. These exudative effusions have high protein values and have the characteristic triad of glucose < 30 mg/dl, pH 7.00, and LDH > 1000 IU/liter. Pleural fluid nucleated cell counts vary from a few hundred up to 15,000/ml, with the cellular predominance depending on the timing of thoracentesis in relation to the active pleural process.

Rheumatoid pleural effusions have low total hemolytic complement and complement components and a rheumatoid factor usually ^{3}1:320 along with high levels of immune complexes. A characteristic cytologic picture consisting of a background of orange or red granular material, large elongated cells, and giant round or oval multinucleated cells is specific for rheumatoid pleurisy. The exudate appears to be derived from palisading histiocytes and their breakdown products, which occur in the inflamed rheumatoid pleura. Pleural biopsy generally shows nonspecific pleuritis and fibrosis. Because the majority of the rheumatoid nodules are found on the visceral pleural surface, the yield from pleural biopsy is low.

The course of rheumatoid pleurisy is variable. It is uncommon, however, for resolution to occur in less than 3 to 4 weeks; in the usual case, the effusion will resolve over several months. Some patients, however, have a prolonged course that lasts years and occasionally progresses to marked pleural thickening requiring decortication. The efficacy of corticosteroids in the long-term outcome of patients with rheumatoid pleurisy is unknown.

Lupus Pleuritis

Involvement of the pleura occurs during the course of systemic lupus erythematosus (SLE) in 50% to 75% of patients and can be the presenting manifestation in 5%.

Chest pain, the most common presenting symptom, is found in 90% of patients. Cough, dyspnea, pleural friction rub, and fever are also frequent findings. An episode of lupus pleuritis usually is associated with an exacerbation of SLE. The most common radiographic presentation of lupus pleuritis is small to moderate bilateral pleural effusions. Other abnormalities include alveolar infiltrates, atelectasis, and enlarged cardiac silhouette, which may result from pericardial effusion or congestive heart failure.

The pleural fluid may be serous, turbid, or bloody. Nucleated cell counts range from several hundred to 20,000/ml. Cellular predominance can be either neutrophil or mononuclear, depending on the time of thoracentesis in relation to the acute injury. In 20% of patients, the pH can be <7.30 and the glucose <60 mg/dl. Finding LE cells in pleural fluid is diagnostic of lupus pleuritis. These patients also frequently have low pleural fluid total hemolytic complement or complement components and can have immune complexes in the pleural fluid. If the pleural fluid ANA exceeds the serum ANA, the diagnosis of lupus pleuritis is suggested.

Patients with active lupus pleuritis usually have a dramatic response to corticosteroids with abatement of symptoms over several days and disappearance of the pleural effusion within 2 weeks.

Post-Cardiac-Injury Syndrome

Post-cardiac-injury syndrome (PCIS) is characterized by the onset of fever, pleuropericarditis, and parenchymal infiltrates 3 weeks (range 2 to 86 days) following injury to the myocardium or pericardium. The incidence following myocardial infarction has been reported from <1% to 15% and, following cardiac surgery, up to 30%.

The pathogenesis has not been clearly elucidated, but the syndrome appears to be an immunologic reaction in the lung, pleura, and pericardium associated with antimyocardial antibodies. It has recently been shown that a patient with PCIS had higher levels of antimyocardial antibodies in pleural fluid than in serum. However, at present the diagnosis remains one of exclusion.

The most common presenting symptom is pleuritic chest pain, which occurs in over 90% of patients. Fever, pericardial rub, dyspnea, and rales occur in approximately half the patients. Fifty percent of patients will have a leukocytosis, and almost all will have an elevated erythrocyte sedimentation rate in the range of 60 mm/hr.

The chest radiograph is usually abnormal, with the most common finding being a pleural effusion. In most instances the effusion is left-sided or bilateral. Pulmonary infiltrates are usually present, most commonly in the left lower lobe. A large cardiac silhouette has been noted in half of the patients.

The pleural fluid is a serosanguinous or bloody exudate with grossly bloody effusions occurring early in the course of the illness. The nucleated cell count ranges from 500 to 40,000/ml with a neutrophil predominance early and a mononuclear predominance late. Pleural fluid glucose and pH are normal.

Post-cardiac-injury syndrome is usually self-limited and may not require therapy if symptoms are trivial. The patient usually responds to aspirin or nonsteroidal antiinflammatory agents, but some patients require corticosteroid therapy for resolution. Recurrences may be related to withdrawal of corticosteroid therapy or reduction of the dose to below a critical level. In responders, the pleural effusion resolves within 1 to 3 weeks.

Pulmonary Embolism

Pleural effusions occur in up to 50% of patients with pulmonary embolism. Pleural effusions result from (1) increased pleural capillary permeability, (2) an imbalance in microvascular and pleural space hydrostatic pressures, and (3) pleuropulmonary hemorrhage. Ischemia from pulmonary vascular obstruction, in addition to evoking release of inflammatory mediators from platelet-rich thrombi, can cause capillary leak into the lung and subsequent pleural space, explaining the usual finding of an exudative pleural effusion. Transudates have been described in approximately 20% of patients and result from atelectasis.

With pulmonary infarction, necrosis and hemorrhage into the lung and pleural space may result. If infarction is present, more than 80% of the patients have bloody pleural effusions, but over 35% of patients with pulmonary embolism without radiographic infarction will also have hemorrhagic fluid.

Chest pain, usually pleuritic, occurs in almost all patients with pleural effusions complicating pulmonary embolism and is invariably ipsilateral despite the fact that lung scans or angiograms indicate that the emboli are bilateral. This suggests that pleural effusions from pulmonary embolism are unusual in the absence of ipsilateral chest pain.

The chest radiograph typically shows a small (less than a third of the hemithorax), unilateral pleural effusion. An associated pulmonary infiltrate is seen in 50% of patients. With radiographic infiltrates, effusions tend to be larger and resolution time longer, presumably because the infiltrate represents a pulmonary infarction.

Pleural fluid analysis is variable and nondiagnostic; however, the fluid is bloody in two-thirds of patients, and the number of red blood cells exceeds 100,000/ml in fewer than 20% of patients. Nucleated cell counts range from <100/ml in atelectatic transudates to >50,000/ml with pulmonary infarction. Neutrophil predominance occurs when thoracentesis is performed near the time of the acute embolus; a lymphocyte predominance occurs later. Pleural fluid eosinophilia may be a feature of the bloody pleural effusion. The pleural effusion usually is apparent on the admission chest radiograph and reaches maximum volume during the first 72 hrs. Patients with pleural effusion that progress with therapy should be evaluated for recurrent embolism, hemothorax secondary to anticoagulation, an infected infarction, or an alternate diagnosis. When consolidation is absent on chest radiograph, effusions resolve in less than a week. With consolidation, there is a longer resolution time.

The association of pleural effusion with pulmonary embolism does not alter therapy. The presence of a bloody effusion is not a contraindication to full-dose anticoagulation because hemothorax is a rare complication of heparin therapy. An enlarging pleural effusion on therapy necessitates thoracentesis to exclude hemothorax, empyema, or another etiology. Active pleural space hemorrhage necessitates discontinuation of anticoagulation, tube thoracostomy, and consideration of vena caval interruption.

Pancreatic Pleural Effusions

Pleural effusion has been described in 3% to 17% of patients with pancreatitis. Effusions can occur with either acute or chronic pancreatitis, with different clinical presentations, management, and prognosis. Several mechanisms are involved in the pathogenesis of pancreatic pleural effusion. These include direct contact of pancreatic enzymes with the diaphragm, transfer of ascitic fluid via a diaphragmatic defect, communication of a fistulous tract between a pseudocyst and the pleural space, and retroperitoneal movement of fluid into the mediastinum with mediastinitis or rupture into the pleural space. A probable explanation for the pleural fluid amylase being higher than the concomitant serum amylase is impaired lymphatic drainage from the pleural space and increased amylase clearance by the kidneys.

The pleural effusion associated with acute pancreatitis is usually small and left-sided; however, an effusion may be right-sided or bilateral. The patient usually presents with abdominal symptoms of acute pancreatitis. The diagnosis is confirmed by finding a pleural fluid amylase concentration that is greater than the serum amylase. Pleural fluid amylase has been found initially normal in acute pancreatitis but increases on serial measurement. The fluid is a neutrophil-predominant exudate with glucose values approximating those of serum. Nucleated cell counts may reach 50,000 cells/ml. The pleural fluid pH is usually between 7.30 and 7.35.

Patients with effusions from chronic pancreatitis usually present with dyspnea, chest pain, or cough from a large or massive pleural effusion. Effusions tend to recur rapidly following thoracentesis. Pleural effusions are slightly more common on the left, and bilateral effusions can occur. Patients with massive pancreatic pleural effusions frequently do not relate a history of pancreatic disease, although the majority are alcoholics. In contrast to acute pancreatitis, the amylase concentration in chronic effusions is always elevated and may reach levels >100,000 U/liter. Serum amylase may be elevated as a result of back-effusion or may be normal. The diagnosis of chronic pancreatic pleural effusion is suggested by an amylase-rich exudate that rapidly reaccumulates following thoracentesis in a patient with respiratory symptoms only. Ultrasound and CT scan are useful in confirming the diagnosis by demonstrating the pseudocyst and fistulous tract.

No specific treatment is necessary for the pleural effusion of acute pancreatitis—the effusion resolves as the pancreatic inflammation subsides. Approximately 50% of patients with chronic pancreatic pleural effusion respond to conservative management while the other half require surgery for resolution.

Benign Asbestos Pleural Effusion

Pleural effusion resulting from asbestos exposure is the most common manifestation of asbestos pleuropulmonary disease in the first 20 years following asbestos exposure. The latency period from time of initial asbestos exposure until the development of pleural effusions can be very short, occurring in the first year, or can be lengthy, occurring after 50 years.

The majority of patients are asymptomatic at the time the pleural effusion is discovered, usually by routine chest radiograph. The most common symptom is chest pain, which is noted in about a third of cases. The chest radiograph typically shows a small, unilateral pleural effusion. Pleural plaques may be seen in 20% of patients, and

moderate to severe asbestosis in fewer than 10% of patients.

The pleural fluid is usually a serosanguinous exudate, although the fluid may be serous or bloody on occasion. The cell count is usually <6000/ml with either mononuclear or neutrophil predominance. Pleural fluid eosinophilia (up to 50% eosinophils) occurs frequently. These effusions do not have high levels of hyaluronic acid, as seen in some patients with mesothelioma, and pleural plaques are usually not seen.

The diagnosis of benign asbestos pleural effusion (BAPE) is presumptive in a patient with known asbestos exposure. The effusion can remain from under a month to a year or more, with an average duration of 3 to 4 months. Resolution usually results in a blunted costophrenic angle (>90%) and diffuse pleural thickening in about 50% of patients. Recurrence is common, either ipsilateral, bilateral, or contralateral. Diffuse pleural thickening, with or without progression, may occur years after the initial asbestos effusion. A short latency period and absence of symptoms suggests BAPE, whereas a long latency period and symptoms suggest mesothelioma.

Chylothorax

Chylothorax is a pleural effusion that contains chyle. Chyle, the lymph found in the thoracic duct, is characterized by the presence of chylomicrons. When the thoracic duct ruptures, its contents can spill into the pleural space. Chylothorax can also result from movement of chylous ascites into the pleural space. The thoracic duct has its origin in the cisterna chyli, which are midline structures just anterior to the first or second lumbar vertebrae. The course moves cephalad through the aortic hiatus into the posterior mediastinum to the right of the midline between the aorta and azygous vein. The thoracic duct ascends between the T_{12} and T_8 thoracic vertebrae, crosses the midline between T_6 and T_4 posterior to the esophagus, and enters the left posterior mediastinum. It courses behind the aortic arch and left subclavian artery into the superior mediastinum and then descends and enters near the junction of the left internal jugular and subclavian veins. This anatomic course explains why thoracic duct injury below T_5 to T_6 produces a right chylothorax and injury above this level a left chylothorax. However, there is marked variability in thoracic duct anatomy. Because of the elaborate collateral lymphatic network, with distal obstruction, collaterals and anastomoses become functional, permitting ligation at any point of the thoracic duct. Within the lymphatic system, numerous valves insure unidirectional flow of 1500 to 2400 ml of lymph per day into the venous system.

Approximately 30% of chylothoraces are the result of trauma, mostly related to thoracic surgery. Seventy percent of chylothoraces are nontraumatic, with lymphoma representing 50%. Metastatic cancer from any organ of the body can result in a chylothorax. Idiopathic chylothoraces represent about 15% of all cases. Other nonmalignant, nontraumatic chylothoraces include lymphangiomyomatosis, cirrhosis, and lupus.

Several misconceptions concerning chylothorax have been perpetuated and often confuse the clinician in establishing the diagnosis. First, not all milky pleural fluid represents chylothorax; it also could be a cholesterol effusion or an effusion with a large number of leukocytes. Second, a milky effusion can stain negative for fat and still be chylous; the total fat content of chyle can be low, particularly in the malnourished patient. Third, chylous effusions can be bloody, turbid, or serous. Chyle is composed largely of proteins such as albumin and globulins, lymphocytes, electrolytes, and lymph from the lower extremities. Chylomicrons and lipoproteins compose only a small percentage of thoracic duct lymph.

The presentation of a patient with chylothorax will depend on the underlying cause. The most common presenting symptom is dyspnea on exertion as a result of a large pleural effusion. The chest radiograph characteristically shows a unilateral pleural effusion without parenchymal disease; mediastinal adenopathy may be present. The pleural fluid typically is milky in appearance but can be bloody, turbid, or serous. A chylothorax is an odorless exudate with a predominance of lymphocytes. Pleural fluid glucose is similar to serum glucose, and the pH is >7.40. Although chylous effusions tend to have a cholesterol/triglyceride ratio of <1.0, and nonchylous effusions have ratios >1.0, overlap exists. Cholesterol concentrations are not different in chylous and nonchylous pleural effusions; however, there is a striking difference in the triglyceride concentrations. If the pleural effusion has a triglyceride concentration >110 mg/dl, it has less than a 1% chance of not being chylous. Pleural fluid with a triglyceride concentration of <50 mg/dl has less than a 5% chance of being chylous. Values between 50 and 110 mg/dl require lipoprotein electrophoresis to diagnose or exclude a chylous effusion, which would contain chylomicrons. Patients with chylous effusions with triglyceride concentrations between 50 and 110 mg/dl are either severely malnourished or have concomitant bleeding into the pleural space causing a dilutional effect.

The major complications of chylothorax are malnutrition and immunologic compromises as protein, fat, and lymphocytes are depleted from the body with repeated thoracenteses or prolonged chest tube drainage. Initial treatment consists of pleural space drainage to relieve dyspnea, diminution in the rate of chyle formation, and maintenance of adequate nutrition. Tube thoracostomy is the most efficient method for pleural space drainage; because chyle is relatively bacteriostatic, the incidence of chest-tube-related empyema is low. Chyle formation is minimized by intravenous hyperalimentation, discontinuation of oral feedings, the use of gastric suction, and bed rest. Medium-chain triglycerides, which are absorbed into the portal vein and into the circulation directly, may be used as an oral source of fats. Most traumatic chylothoraces respond with either cessation or slowing of chyle flow within 7 to 10 days. If chylous drainage persists or is progressive, pleurodesis or thoracic duct ligation should be considered.

The basic management of nontraumatic chylothorax is similar to that of traumatic chylothorax, but a cause needs to be established in the former. If lymphoma is diagnosed, mediastinal radiation should be given because it controls the chylothorax in the majority of patients. If this is unsuccessful, chemical pleurodesis or pleuroperitoneal shunt should be considered for palliation.

Esophageal Perforation

Endoscopy or dilation is the most common cause of esophageal perforation today. Spontaneous esophageal rupture, Boerhaave's syndrome, is a potential life-threatening event requiring immediate diagnosis and therapy.

Patient presentation, radiologic evaluation, and outcome vary depending on the cause, location, and extent of the perforation. Most patients eventually have chest pain, which is universally present in those with cervical perforation. Dyspnea and dysphagia appear to be more frequent following mid- and distal esophageal perforation. Almost all patients will have a febrile response to perforation, and about half will demonstrate subcutaneous emphysema.

The history in spontaneous rupture usually is severe retching or vomiting or a conscious effort to resist vomiting. Early recognition of spontaneous rupture depends on interpretation of the chest radiograph. Several factors can influence chest radiographic findings: (1) the time between perforation and the chest radiograph; (2) the site of perforation; and (3) mediastinal pleural integrity. Mediastinal emphysema probably takes at least 1 to 2 hr to be demonstrated radiographically and is present in fewer than half of patients. Mediastinal emphysema tends to occur early with perforations of the intrathoracic esophagus. Pneumothorax, present in 75% of patients with spontaneous esophageal rupture, indicates violation of the mediastinal pleura and occurs with a 70% incidence on the left, 20% on the right, and is bilateral in 10%. Mediastinal air is seen early if pleural integrity is maintained, and pleural effusion secondary to mediastinitis tends to occur later. Pleural fluid, with or without associated pneumothorax, occurs in 75% of perforations.

The diagnosis is usually more obvious in iatrogenic than spontaneous rupture, as the symptoms are easily related to the recently performed procedure. With minor perforations, the mediastinal pleura usually remains intact, and the pleural fluid produces a sterile, neutrophil-predominant exudate with normal pH and amylase levels.

In spontaneous esophageal rupture, the acuteness of the pressure rise, rather than the absolute pressure, is critical in causing perforation. The tear almost always occurs in the distal half of the esophagus because that portion of the esophagus is devoid of striated muscle and is deficient in extramural support.

Radiographic confirmation of a presumptive diagnosis needs to be accomplished immediately. Esophagrams are positive in about 90% of patients. The contrast study should be done with the patient in the appropriate lateral decubitus position.

The pleural fluid findings in spontaneous esophageal rupture will depend on the degree of perforation and the timing of thoracentesis from the acute injury. Early thoracentesis without mediastinal perforation will show a serous, sterile exudate with a predominance of neutrophils and normal pleural fluid amylase and pH. Once the mediastinal pleura tears, amylase of salivary origin will appear in the fluid in high concentration. As the pleural space is seeded with anaerobic organisms from the mouth, the pH will rapidly fall to approach 6.00. Experimentally, it has been shown that pleural fluid leukocyte metabolism, not gastric acid reflux, is the major contributor to the low pH of esophageal rupture effusions. Other findings in pleural fluid suggestive of esophageal rupture include the presence of squamous epithelial cells and food particles.

The diagnosis of spontaneous esophageal rupture dictates immediate operative intervention. If it is diagnosed and treated with primary closure within the first 24 hr, survival exceeds 90%. In addition to primary closure, antibiotics covering mouth anaerobes, parenteral nutrition, and mediastinal and pleural space drainage constitute the therapeutic regimen. For iatrogenic rupture in patients with minimal symptoms and without signs of clinical sepsis, antibiotics, gastrointestinal tract drainage, and hyperalimentation usually are effective.

Uremic Pleural Effusions

At autopsy, approximately 20% of patients with uremia have a fibrinous pleuritis. Clinically, the incidence of uremic pleural effusions varies from 3% to 16%. Patients who develop uremic pleural effusions have usually been on chronic hemodialysis for more than 1 year. Half of the patients present with fever and chest pain, and cough is seen in about a third. Most patients do not complain of dyspnea. A friction rub is heard in one of three patients and usually lasts 2 to 3 days.

The chest radiograph typically shows a unilateral, moderate pleural effusion, although massive and bilateral effusions have been described. The pleural fluid can be serous, serosanguinous, or bloody. This exudate usually has fewer than 1500 nucleated cells per microliter, with a predominance of lymphocytes. Neutrophil predominance and pleural fluid eosinophilia have not been noted. The creatinine concentration is high, reflecting the blood creatinine, but the ratio of pleural fluid to serum creatinine is less than 1.0.

The differential diagnosis of the patient developing a pleural effusion on hemodialysis includes, most commonly, congestive heart failure, uremic pleural effusion, tuberculous pleurisy, and parapneumonic effusion. Pleural effusions usually resolve with continued dialysis over several weeks but may recur. Reports of fibrothorax following uremic pleurisy have been described with a successful result following decortication. Despite the coagulopathy that these patients have, this procedure has been carried out successfully.

Hemothorax

Hemothorax is defined as blood in the pleural space and connotes substantial pleural space bleeding. However, it is often problematic clinically to assess the degree of pleural space hemorrhage from visualization of the pleural fluid. Therefore, a hematocrit should be measured on all grossly bloody effusions. A hemothorax is arbitrarily diagnosed when the hematocrit of the pleural fluid is at least 50% of the peripheral blood hematocrit. Establishing the diagnosis of a hemothorax directs a more aggressive course of treatment that is different from that used for the patient with a hemorrhagic effusion.

Bleeding into the pleural space can originate in the chest wall, diaphragm, lung, or mediastinum. When blood enters the pleural space, it coagulates rapidly, although there is the potential of the mesothelial cell, through its fibrinolytic activity, to convert the clot to liquid hemothorax. However, transient clotting or lack of fibrinolysis may occur because of mesothelial cell injury. The clotted blood cannot be drained by tube thoracostomy.

Blunt or penetrating chest trauma is the major cause of hemothorax. Virtually every vessel within the chest can bleed into the pleural space following injury. Bleeding most commonly arises from laceration of the pulmonary vessels or intercostal veins. Blunt chest trauma often causes hemothorax from rib fracture, the risk increasing with the number of ribs fractured; delayed hemothorax following rib fracture has been noted. Life-threatening pleural-space hemorrhage can occur from the pulmonary, internal mammary, or subclavian artery as well as from cardiac lacerations. Bleeding from organs below the diaphragm, such as the liver, spleen, and kidneys, can also present as a hemothorax. A traumatic hemothorax is usually suspected when a unilateral pleural effusion is found on the initial chest radiograph. However, the diagnosis may be delayed, as the subtle, unilateral haziness is not noted on the supine radiograph. Pneumothorax is a frequent accompaniment of both blunt and penetrating chest injury.

Iatrogenic hemothoraces are common, seen mostly with laceration of the large arteries or veins of the thorax after central venous catheterization.

Other causes of iatrogenic hemothorax include leaking from the aorta after translumbar aortography and as a complication of thoracentesis or pleural biopsy.

Nontraumatic or spontaneous hemothoraces are uncommon. The two most common causes of nontraumatic hemothorax are metastatic pleural malignancy and anticoagulation for pulmonary embolism. Sarcomas of the lung and pleura are the most common malignancy to result in hemothorax. There have been only a few reports of lung cancer causing hemothorax despite the large number of patients and the high incidence of hemorrhagic effusions. Spontaneous hemothorax in patients receiving anticoagulant therapy (either heparin, warfarin, or both) has been described within the first week of treatment and after several months of therapy. The coagulation parameters are usually within the therapeutic range, and the hemothorax is usually on the side of the pulmonary embolus.

Other causes of spontaneous hemothorax include arteriovenous malformations, bleeding diathesis, dissecting aortic aneurysm, pneumothorax, neurofibromatosis, pulmonary sequestration, splenic artery rupture, thoracic endometriosis, and the blue rubber bleb nevus syndrome.

In the management of traumatic hemothorax, a large-bore chest tube (36 to 40 French) should be inserted to drain the pleural space, reexpand the lung, and monitor the rate of bleeding. Lung reexpansion often stops the bleeding by a tamponade effect. Although no study has quantified the amount of chest tube bleeding as an absolute indication for thoracotomy, if bleeding persists at 200 to 300 ml/hr or is not decreasing, exploratory thoracotomy should be performed to locate the bleeding site and achieve hemostasis.

The complications of hemothorax include retention of clotted blood in the pleural space, empyema, pleural effusion, and fibrothorax. Controversy exists whether residual clotted blood should routinely be removed from the pleural space. However, recent studies have shown that there is no difference in the incidence of empyema or residual pleural abnormalities in patients with or without residual hemothorax. Therefore, not all patients with residual hemothorax need a thoracotomy; thoracotomy should be reserved for patients who have >30% of the hemothorax occupied by clotted blood. There are no controlled studies evaluating the use of thrombolytic agents in management of clotted hemothorax.

Empyema occurs following hemothorax in 1% to 4% of patients. Risk factors for development of empyema include shock, gross contamination of the pleural space at the time of the original injury, associated abdominal injuries, and prolonged chest tube drainage. Treatment of hemothorax-related empyema is similar to that for pneumonic empyema. Empyemectomy and decortication should be accomplished without delay if tube thoracostomy drainage is unsuccessful in resolving pleural sepsis.

Pleural effusions are common following removal of the chest tube for hemothorax. A diagnostic thoracentesis should be done to exclude empyema. If thoracentesis is negative, observation is warranted as the effusion resolves over several weeks without pleural space sequela.

In fewer than 1% of patients following hemothorax, a fibrothorax develops. The risk of fibrothorax is increased when there is concomitant empyema or pneumothorax. If the patient has a persistent restrictive ventilatory defect several months following the hemothorax, decortication should be considered.

Pleural Effusions in AIDS

Pleural effusions are common in hospitalized AIDS patients, having been found in 27% of a large series. The cause was infectious in two-thirds of patients. Pleural effusions were most commonly caused by bacterial pneumonia and represented a third of all patients with pleural effusions. Half of the patients with parapneumonic effusions had pneumococcal pneumonia. Other infectious causes of pleural effusions in AIDS patients included, *Pneumocystis carinii* pneumonia, *Mycobacterium tuberculosis,* septic embolism, *Nocardia asteroides, Cryptococcus neoformans,* and *Mycobacterium avium intracellulare.* Among the noninfectious causes, hypoalbuminemia was the most common, occurring in 19% of all patients with effusions. Other noninfectious causes included congestive heart failure, atelectasis, Kaposi's sarcoma, uremic pleurisy, and the acute respiratory distress syndrome. Patients with AIDS who had pleural effusions had lower serum albumin levels and lower CD4 counts than those AIDS patients without pleural effusions. Most pleural effusions in hospitalized AIDS patients are small and asymptomatic and do not require pleural space drainage. Large pleural effusions in AIDS patients are most commonly caused by lymphoma, Kaposi's sarcoma, and tuberculosis.

PNEUMOTHORAX

Classification

Pneumothorax (air in the pleural space) can be classified as spontaneous, traumatic, or iatrogenic. Primary spontaneous pneumothorax (PSP) occurs in individuals without clinical lung disease, whereas secondary spontaneous pneumothorax (SSP) results as a complication of preexisting lung disease. A traumatic pneumothorax occurs from either direct or indirect chest trauma and iatrogenic pneumothorax results as a complication of a diagnostic or therapeutic procedure.

Primary Spontaneous Pneumothorax

Primary spontaneous pneumothorax is most commonly seen in tall, thin men when an apical subpleural bleb ruptures. Subpleural blebs can result from congenital abnormalities, small airway inflammation, and disturbances of collateral ventilation. Over 90% of patients with PSP are smokers or ex-smokers. Chest pain and dyspnea are the two prominent symptoms and usually occur while the patient is at rest. Physical examination may be unremarkable with a small pneumothorax. With a large pneumothorax, there may be decreased chest movement, decreased fremitus, hyperresonance to percussion, and diminished or absent breath sounds on the

ipsilateral side. A marked tachycardia (>135 beats/min) should alert the clinician to the possibility of a tension pneumothorax.

The physiological consequences of pneumothorax are a decrease in vital capacity and a fall in arterial oxygen tension; hypocapnia is usually present as a consequence of hyperventilation in response to hypoxemia and to chest pain. Hypercapnia is unusual with normal underlying lungs. The increased alveolar–arterial oxygen difference results from low-*V/Q* areas and shunts.

The diagnosis depends on demonstration of the visceral pleural line on an upright chest radiograph. In problematic cases, an expiratory or lateral decubitus radiograph with the suspected side up should be obtained. An expiratory film results in the pneumothorax gas occupying a larger portion of the hemithorax, and, therefore, the visceral pleural line may be more easily visualized.

The major treatment decision in PSP is whether or not to remove the air from the pleural space. Because these patients do not have clinical lung disease, a more conservative approach can be taken if the pneumothorax is small and the air leak has ceased. In general, if the patient's symptoms have resolved, and the pneumothorax is thought to be <15%, observation is warranted, as the pneumothorax gas would be resorbed in about 2 weeks; it is estimated that about 1.25% of the volume of the pneumothorax is absorbed daily.

Treatment options for PSP >15% include supplemental oxygen, catheter aspiration, tube thoracostomy, or tube thoracotomy with instillation of a chemical pleurodesis agent. Pleural air is absorbed more rapidly when patients are given oxygen supplementation, as the net gradient for gas absorption from the pleural space to blood will increase. Catheter aspiration will be successful if the air leak has stopped; its only advantage is in decreasing the resolution time of the pneumothorax. Standard chest tube drainage results in rapid resolution of the pneumothorax; small catheters may be equally successful if the air leak is not large. The chest tube or catheter can be removed 24 to 48 hr after the lung is fully expanded and the air leak has ceased. Chest tube drainage does not appear to decrease the rate of recurrence. Because approximately half of the patients with PSP will have a recurrence, chemical agents have been instilled intrapleurally through a chest tube, and talc has been administered as a poudrage through a thoracoscope in an attempt to diminish the recurrence rate. A recent VA cooperative study showed a decreased rate of recurrence of both PSP and SSP in patients receiving 1500 mg of intrapleural tetracycline compared to placebo. However, many clinicians are cautious concerning the use of chemical pleurodesis in young individuals with PSP because of the possibility of developing significant pleural fibrosis. Some prefer thoracoscopy with pleural abrasion and partial pleurectomy instead of the use of chemical agents. Laser therapy at thoracoscopy has also been advocated in the initial treatment of recurrence of PSP.

Secondary Spontaneous Pneumothorax

In contrast to the benign nature of PSP, SSP may be life-threatening, as these patients have significant underlying lung disease. There are multiple causes of SSP; however, the most common cause is chronic obstructive pulmonary disease (COPD). Other common causes include cystic fibrosis and interstitial lung disease, especially pulmonary histiocytosis and stage IV sarcoidosis. Malignancies, necrotizing pneumonias, tuberculosis, *Pneumocystis carinii,* and lymphangiomyomatosis are also causes of SSP (Table 1).

Diseases	Comments
Disease of the airways	
Chronic obstructive pulmonary disease	Most common cause of secondary spontaneous pneumothorax (SSP)
Cystic fibrosis	Usually in adolescents and adults
Asthma	Associated with status asthmaticus
Interstitial Lung disease	
Pulmonary histiocytosis X	Pneumothorax may be presenting problem; often recurrent
Sarcoidosis	Usually stage IV sarcoidosis
Idiopathic pulmonary fibrosis	Pneumothorax less common than in pulmonary histiocytosis
Tuberous sclerosis	Usually found in women
Other types	Risk of pneumothorax increases with advanced stage of disease
Infection	
Necrotizing pneumonia	Gram-negative aerobes, anaerobes
Tuberculosis	Usually active
Atypical mycobacteria	Usually active
Pneumocystis pneumonia	Pneumothorax associated with aerosolized pentamidine when *Pneumocystis carinii* infection develops
Malignancy	
Sarcomas	The most common tumors presenting as pneumothorax; incidence of pneumothorax from metastatic malignancy <1% of all SSPs
Lung cancer	
Others	
Lymphangiomyomatosis	Pneumothorax occurs in 66% of patients during course of disease
Endometriosis	Catamenial pneumothorax most common form of thoracic endometriosis
Marfan's syndrome	Incidence of pneumothorax 4% to 17%; with recurrence common
Pulmonary infarction	Rare complication of infected infarction

TABLE 1. *Diseases associated with secondary spontaneous pneumothorax*

Secondary spontaneous pneumothorax occurs when there is hyperexpansion of the distal air spaces because of inflammation or obstruction of the airways. When alveolar pressure exceeds interstitial pressure, air enters the interstitium and dissects retrogradely along the bronchovascular sheath to the hilum, causing pneumomediastinum. If the visceral pleura ruptures, then pneumothorax will occur. Necrotizing pneumonia causes pneumothorax from a distal visceral pleural tear.

The two major symptoms of SSP, dyspnea and chest pain, are the same as with PSP; however, the presentation may be more dramatic. Shortness of breath is universal, and some patients may have cardiovascular compromise. The finding of hypercapnia with pneumothorax signifies underlying lung disease, usually COPD. Occasionally it is difficult to differentiate between a pneumothorax and a bullous lesion. The visceral pleural line with pneumothorax usually follows the configuration of the chest wall, whereas a bullous lesion may have a concave relationship to the chest wall. Chest CT scan may help to differentiate problematic cases.

Because recurrence rates with SSP are similar to that of PSP, and, in the setting of lung disease, pneumothorax may be life-threatening, preventing recurrence is the primary concern. Virtually all patients with SSP should be treated with chest tube drainage. Even with tube thoracostomy, lung expansion takes longer, and the air leak persists longer, than in PSP. Options to prevent recurrence include instillation of chemical agents (talc slurry, doxycycline, or minocycline) through a chest tube, talc poudrage through a thoracoscope, laser therapy, and pleural abrasion/pleurectomy with thoracoscopy or thoracotomy.

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CHAPTER

76 Surgery and Pleural Space: Fibrothorax, Thoracoscopy, and Pleurectomy

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INTRODUCTION

The pleura is a thin membrane made up of mesothelial cells and connective tissue that envelopes the lung (visceral pleura) and reflects back over the mediastinum, diaphragm, and chest wall (parietal pleura) to create a potential space. It allows smooth movement of the lung during respiration and recirculates the pleural fluid via the lymphatics situated within both of the pleural leaves.

Surgery for disorders of the pleural space has a long and storied history dating back to the early therapy for tuberculosis and involves the first use of thoracoscopy. Tuberculosis helped define the field of thoracic surgery. Anesthetic techniques matured at a time when tuberculosis became widespread. Treatment strategies, before the development of antituberculous medication, centered around therapeutic pneumothoraces. The first use of thoracoscopy was carried out by Jacobaeus, a Scandinavian internist, in 1910 using a cystoscope to examine the pleural space and divide adhesions with a primitive cautery device to allow lung collapse in the treatment of tuberculosis.

PRESENTATION AND DIAGNOSTIC WORKUP

Many disease processes affect the pleura, the most common and notable being empyema and various malignancies such as lung cancer. Because of the intimate association with the underlying lung, diaphragm, and mediastinum and overlying chest wall, these problems lead to severe symptoms and physiological impairment requiring aggressive treatment. Manifestations typically include dyspnea and localized pain that worsens with respiration. Therapeutic interventions require a precise understanding of the etiology of the disorder. The diagnostic workup inevitably involves a chest x-ray, which typically displays thickening of the pleura or fluid within the pleural space. The differentiation between these possibilities traditionally requires positional x-rays (decubitus views) or, more commonly in the current era, a chest computed tomographic (CT) scan.

Once the abnormality is identified, a sample of the fluid or a biopsy of the abnormal pleura will make the diagnosis and direct treatment. Usually this is accomplished by thoracentesis, with or without radiologic guidance, depending on whether the fluid is loculated, or by a closed pleural biopsy. If the needle drainage or biopsy is deemed too dangerous or proves to be inadequate, then a surgical procedure can provide a diagnosis and often treatment. In particular, to differentiate an adenocarcinoma from a mesothelioma, a surgical biopsy is critical in providing enough tissue to make this sometimes subtle distinction. With the recent advent in fiberoptic and instrumentation technology, this can be accomplished using minimally invasive techniques, which, with respect to the chest, are referred to as thoracoscopy (see below). Thoracoscopic surgical biopsy is associated with minimal morbidity and close to 100% sensitivity and specificity. In many cases a simultaneous therapeutic procedure can be carried out (for example, drainage and decortication of an empyema).

FIBROTHORAX

Fibrothorax occurs when the lung becomes “trapped” in an incompletely expanded position because of the presence of fibrous tissue in the pleural space as the result of a prior infection (empyema) or hemothorax. The same mechanical problem can occur with a neoplastic process such as a malignant mesothelioma or pleural dissemination of a lung or other cancer. Both situations lead to physiological impairment of gas exchange and alterations in the mechanics of breathing secondary to shunting and restriction.

The treatment of fibrothorax depends on the magnitude of the functional impairment, the underlying etiology (malignant versus nonmalignant, including infection), and the presence of any medical comorbidities. The goal is to provide symptomatic relief and salvage lung function by removing the pleural peel (decortication) that is responsible for the collapsed lung. Achieving complete reexpansion of the lung will not only relieve the symptoms of the associated dyspnea but also, in the case of an empyema, eliminate a space in which a recurrent infection could develop. In the case of a malignant process, the goals are similar except for certain cases, such as malignant mesothelioma, in which complete eradication is the aim.

The goal of surgery, then, where there is a symptomatic pleural process, is the eradication of this process by completely removing the parietal pleura (pleurectomy) and associated fibrinous peel (inflammatory or neoplastic) to allow the lung to regain its full capacity and therefore function. Exceptions to this include mesothelioma with no other signs of dissemination, where radical surgery with a more curative intent may be warranted. At our institution, the treatment of malignant mesothelioma would entail an extrapleural pneumonectomy, which removes the parietal pleura, the underlying lung with its intimately associated visceral pleura, and the diaphragm and pericardium (Fig. 1).

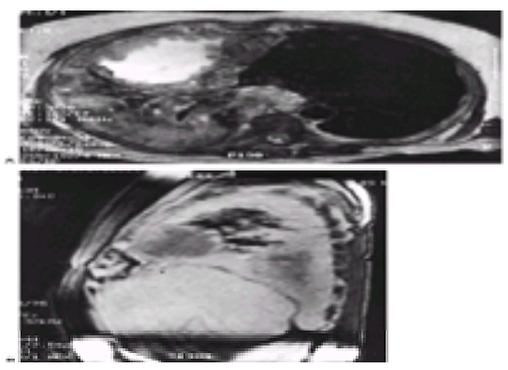

FIG. 1. Magnetic resonance imaging scan of the chest of a patient with malignant mesothelioma. **(A)** A cross-sectional image just above the diaphragm demonstrates the bulky pleural tumor compressing the lung. **(B)** A sagittal view of the same patient illustrates that even with bulky disease, the diaphragm is rarely transgressed.

In most situations where there is malignant involvement of the pleura leading to a fibrothorax, the cause is related to either disseminated (small-cell or non-small-cell) lung cancer or to metastases from another primary site, such as the breast. In these cases, palliation is clearly the goal, and the patient's life expectancy and ability to undergo an operation would determine the possible treatment. Ideally, a decortication would be performed.

SURGERY FOR PLEURAL DISEASE

In surgically treating pleural lesions, the aim of the surgery (palliative or curative) and the extent of the process determine the approach, either thoracoscopic or via a

thoracotomy.

Thoracoscopic surgery, as alluded to above, is surgery that involves a fiberoptic camera to provide visualization for the manipulations that are to be carried out using videoscopic surgical instruments. Typically, a true thoracoscopic procedure utilizes two to four small (2-cm) incisions in the thorax, which are made large enough to allow placement of the ports through which the camera or instruments will be placed. These ports are generally between 10 and 12 mm in diameter. They are positioned to triangulate the lesion that lies within the chest and, in the cases discussed here, are associated with the pleura (Fig. 2). The lung on the side of the surgery is collapsed by the anesthesiologist, who disconnects or clamps the lumen of the double-lumen endotracheal tube providing airflow to the lung of interest. Therefore, to undergo this type of surgery, the patient must be able to tolerate one-lung ventilation. Alternatively, under certain special circumstances, the procedures can be carried out using intermittent apnea and its associated passive atelectasis.

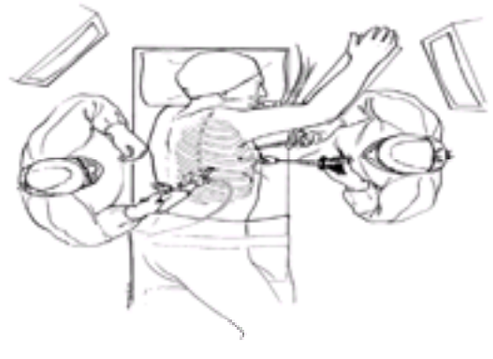

FIG. 2. Typical operating room setup for thoracoscopic surgery. (Reprinted with permission from Axford TC, Clair DG, Bertagnoli MM, Mentzer SJ, Sugarbaker DJ. Staged antrectomy and thoracoscopic truncal vagotomy for perforated peptic ulcer disease. *Ann Thorac Surg* 1993;55:1571–1573.)

Once the lung is collapsed, a videoscopic camera is placed through one of the ports and connected to the VCR monitor. Using the access provided by the other one to three ports, instruments for retracting the lung and sampling the pleural lesion or fluid are placed into the thorax under videoscopic visualization. Once an adequate sample has been obtained, it can be analyzed immediately by pathologic examination (“frozen section”) to assure that tissue from the lesion has in fact been isolated. Also, this may allow the surgeon to carry out simultaneous therapeutic intervention based on the pathologic information obtained. In addition, the remainder of the hemithorax, including the diaphragm, lung, and mediastinum, can be inspected carefully to look for and sample any other associated pathology. When the surgery is completed, hemostasis is obtained, usually with electrocautery or surgical clips, and a chest drain is typically placed through one of the ports and optimally positioned with the help of videoscopic visualization. It is secured to the skin with a suture. The pleural space is gently irrigated with saline, and then the other port incisions are closed with absorbable subcuticular sutures. A local anesthetic such as 0.5% bupivacaine with epinephrine is used to carry out a rib block to the five ribs surrounding the region of the incisions as well as a local field block to the area of the incisions themselves. This will provide 6 to 8 hr of excellent analgesia following the surgery. Where the thoracoscopic surgical procedure requires one of the port incisions to be enlarged to create a utility incision (of approximately 6 cm) to allow a larger portion of tissue to be removed or to provide direct visualization of some areas within the hemithorax where there are difficulties with videoscopic visualization—for example, areas of adhesions—then this is referred to as video-assisted thoracic surgery (VATS). In either case, limiting the incisions used for thoracic surgery appears to lead to less pain, earlier discharge from the hospital, and, in general, a shorter recovery period.

When drainage of fluid is the most important aspect of the procedure, and the pleural lesion is less extensive, a thoracoscopic technique utilizing two or three thoracoscopic ports will be sufficient to remove the fluid and strip the limited pleural disease. In most cases, however, the pleura is quite thickened, and the hemithorax is frozen by the tumor or the fibrotic process to some degree, necessitating a limited thoracotomy with guidance from the videoscopic camera (VATS) (Fig. 3). The procedure begins with the placement of the camera port in a position that will afford visibility of the involved area. Typically this is in the seventh interspace in the posterior axillary line because this gives the broadest view of the hemithorax and usually is also close to the most commonly involved area, which is in the base of the chest. After the lesion is identified via the camera, the next two ports are placed directly over the involved area. The goal is to set up the placement of the ports so that the area of interest is centered by the ports and at least one of the ports affords the possibility of direct digital palpation as part of the assessment. After any associated fluid has been removed, thoracoscopic scissors and forceps are employed to completely strip the peel from the lung using both sharp and blunt dissection. Typically, this requires the complete removal of the parietal and visceral pleura in the area of interest. Depending on the amount of inflammation that is present, this is quite often a bloody process, and an expeditious operation is important. Direct, gentle compression with a sponge mounted on a forceps or packing the area will control the bleeding until the lung is reinflated, at which time the majority of the bleeding ceases.

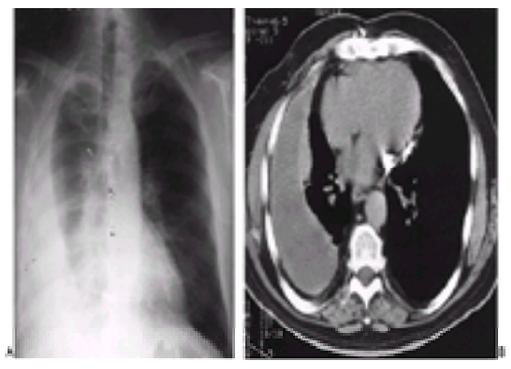

FIG. 3. Images of the radiologic examination of a patient with a fibrothorax on the basis of chronic empyema. **(A)** Posteroanterior view of the chest radiograph demonstrating the extensive nature of the pleural involvement. Linear calcification can be seen on the right at the base of the pericardium. **(B)** The chest CT scan at the level of the heart again demonstrates the extensive pleural disease, and pericardial calcification can be seen.

Because a visceral pleurectomy is often part of the procedure, a moderate air leak will occur when the lung is reinflated. As it is quite peripheral in its location, the leak will always stop over time if the lung completely reexpands. If there appears to be a deeper rent in the parenchyma, the edges can be reopposed with an endoscopic stapler or with an interlocking suture. This must be done very carefully because the lung is usually quite friable and will not hold either sutures or staples well. If the air leak is deemed sizable, it may be prudent to leave the patient on positive-pressure ventilation for 12 to 24 hr to allow the lung to adhere to the chest wall without excessively fatiguing the patient. If the lung will not reexpand to fill the space despite a maximal decortication, then recurrence of an empyema in the setting of infection or a prolonged air leak and probable secondary infection in other cases is likely to result. The ideal solution is to fill the resulting space with vascularized tissue such as an intercostal muscle pedicle or pericardial fat pad when the space is small or with a transposed muscle or omentum if the space is sizable.

Where the pleural process involves the majority of the hemithorax, the peel is quite thickened, or the adhesions are too great, then a standard posterolateral thoracotomy is required. Often in these cases, the chest is frozen as a result of the extent of the process, and thus the removal of a rib is helpful to obtain adequate exposure. The goal remains to remove the entire abnormal pleura and associated inflammatory or neoplastic rind. This, too, is accomplished in an open technique using sharp and blunt dissection. In the case where the process is extensive, it may be helpful to perform the dissection on an inflated lung because inflation makes the demarcation of the underlying normal lung more obvious. In the open technique, the failure of complete reexpansion of the lung is even more critical because the resulting space is potentially larger.

RESULTS

The results of surgical intervention for pleural space disease are variable and depend on the etiology. A recent study by Martella and colleagues revealed a 96% success rate for decortication for chronic postpneumonic empyema. They reported a 4% mortality. Pothula and colleagues reported a series of 90 patients in which 71 (79%) had a formal thoracotomy and 19 (21%) a limited operative approach. There was a 10% mortality in the former group and no deaths in the latter group. However, 10% of the patients in the limited group required a second operation for prolonged drainage or nonhealing. In a more acute or fibrinopurulent phase of empyema, surgical management can be accomplished using a thoracoscopic approach. Results for the surgical treatment of malignant pleural processes are more variable and depend to a large extent on the stage and type of the cancer and the overall health of the patient. In a recent series from the Brigham and Women's Hospital, certain

groups of patients with mesothelioma enjoyed a significant long-term survival (39% at 5 years) when treated with an extrapleural pneumonectomy in conjunction with adjuvant radiotherapy and chemotherapy. Last, the results of surgery for metastatic malignant pleural processes are dependent on the status of the underlying primary.

SUMMARY

In the current era, thoracoscopic techniques provide diagnosis of pleural diseases with a high degree of sensitivity and specificity and minimal morbidity. In early or limited diseases such as early empyema, or for palliation of malignant processes, the minimally invasive technique is an excellent therapeutic strategy. For more extensive or chronic fibrotic processes or for curative purposes for malignant disease, a traditional thoracotomy is the best approach.

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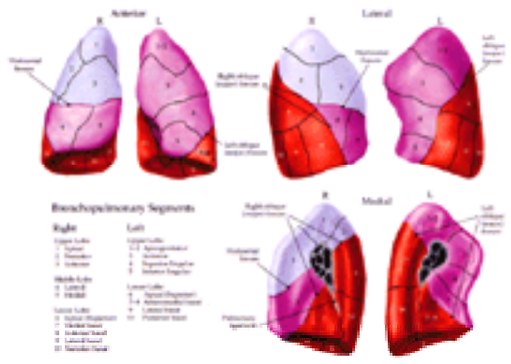
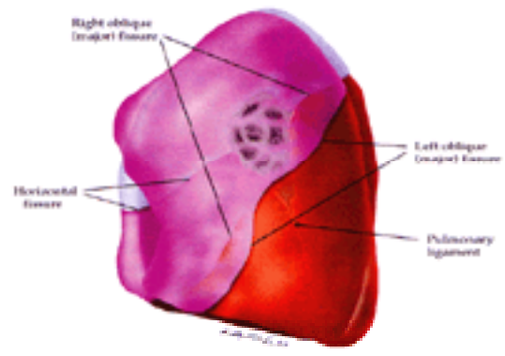
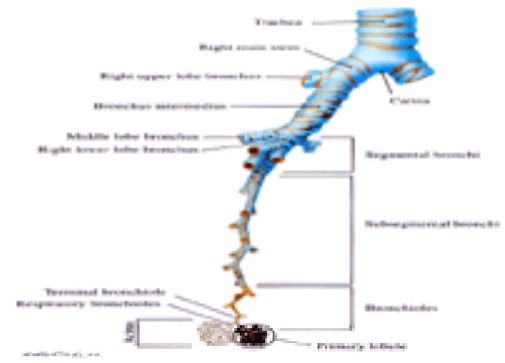
Color Plates for Volume 1



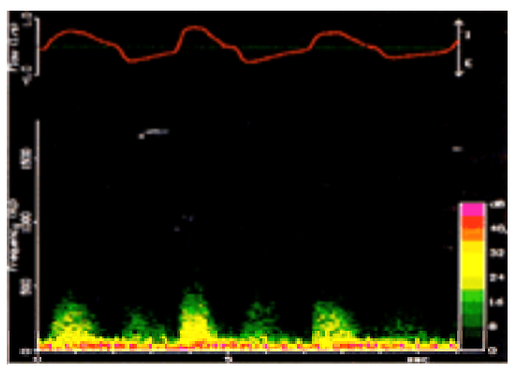
COLOR PLATE 1. Location of bronchopulmonary segments from anterior, lateral, and medial views. (See Fig. 1 in Chapter 1)



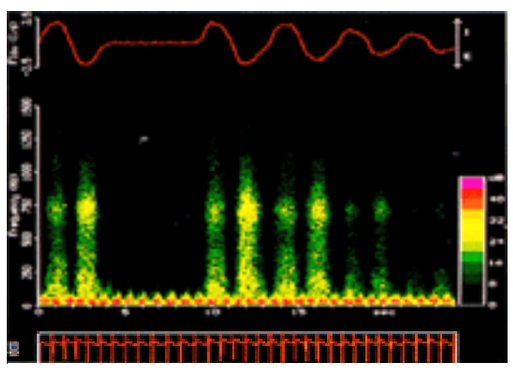
COLOR PLATE 2. Left lateral view of the lungs. Partially translucent image of the left lung allows the right lung to be seen. The location of the major fissures and the horizontal fissure of the right lung are illustrated in the positions in which they would appear on a left lateral chest radiograph. Note that the major fissure on the right side lies slightly anterior and apical to the major fissure on the left side. (See Fig. 2 in Chapter 1)



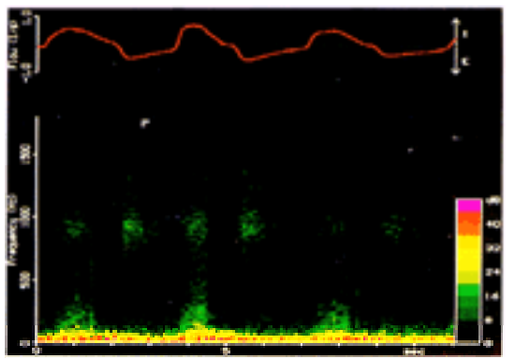
COLOR PLATE 3. Airway anatomy of the human tracheobronchial tree. This figure illustrates typical branching along one of the longer paths to a right lower lobe segment. In the normal human lung, there are approximately five to 15 branch points from a segmental bronchus to a terminal bronchiole. In a completely binary, symmetric branching system, 14 to 15 branch points from the trachea would be required to create the 43,000 terminal bronchioles in a human lung. Because many paths are shorter, there are also path lengths with >15 branch points from the trachea. Segmental bronchi are characterized by the presence of cartilaginous plates in their walls, whereas bronchioles contain smooth muscle in their walls but no cartilage. (See Fig. 8 in Chapter 1)



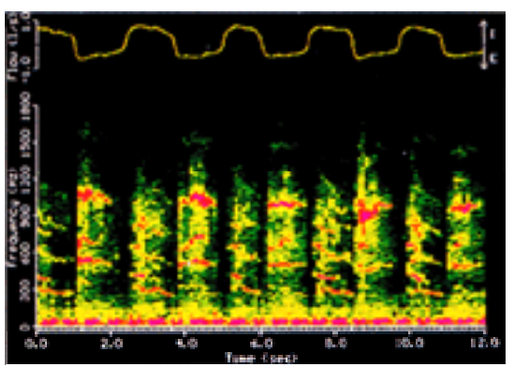
COLOR PLATE 4. Normal vesicular breath sounds. Sound spectrogram with simultaneous pneumotachogram (*top*); sound frequency in hertz (Hz) is represented on the ordinate, time (s) on the abscissa; colors designate sound intensity in decibels (dB) on the scale (*lower right*). Recorded over the left posterior lung base in a 13-year-old boy with cystic fibrosis. Note that inspiratory breath sounds are louder than expiratory sounds and that there is no pause between the respiratory phases. The frequencies are virtually all below 500 Hz and are most intense below 250 Hz. Contributions of low-frequency muscle and cardiovascular sound are visible. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) (See Fig. 17 in Chapter 14)



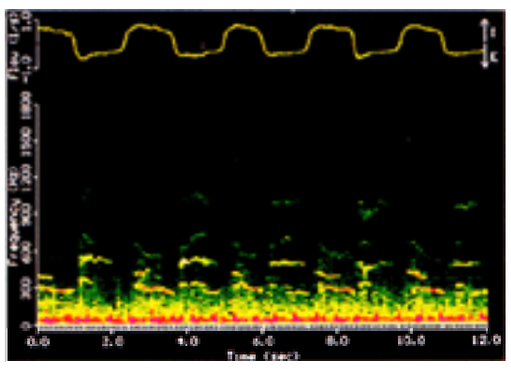
COLOR PLATE 5. Bronchial breath sounds. Sound spectrogram as described in Color Plate 4, simultaneously recorded over the corresponding site on the right posterior lung base in the same patient as in Color Plate 4. Pneumonia and consolidation of the right lower lobe were present, and bronchial breathing is evident. In comparison with the left side (Color Plate 4), there is a decrease in intensity of breath sounds but an increase in high-frequency components extending above 1000 Hz. This is most evident during expiration; in contrast to the normal left side (Color Plate 4), expiratory breath sounds are louder than inspiratory breath sounds. Contributions of low-frequency muscle and cardiovascular sound are visible. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) (See Fig. 19 in Chapter 14)



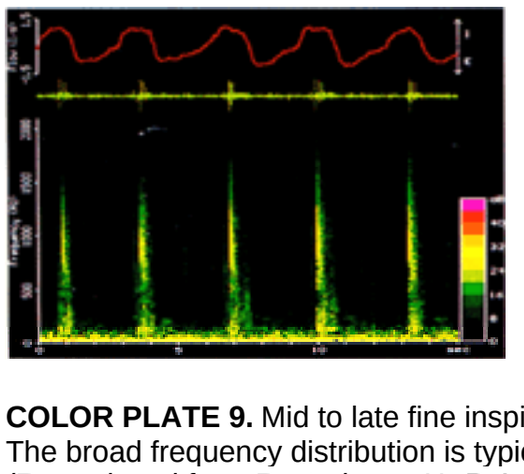
COLOR PLATE 6. Normal tracheal breath sounds. Sound spectrogram as described in Color Plate 4, but with simultaneously recorded electrocardiogram (*bottom*). Recorded over the trachea at the suprasternal notch in a healthy, 26-year-old, male nonsmoker. The typical features of normal tracheal sounds are evident, with a broad frequency distribution, extending close to 1500 Hz during both inspiration and expiration, a slightly louder expiration, and a clear break (absence of respiratory sound) between the respiratory phases. During 5 seconds of breath holding and zero air flow, the contribution of low-frequency cardiovascular sounds becomes evident. The electrocardiogram helps to identify the high-intensity, low-frequency heart sounds. The dependence of sound intensity on air flow is obvious during the latter parts of this observation, when the subject was breathing more shallowly. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) (See Fig. 18 in Chapter 14)



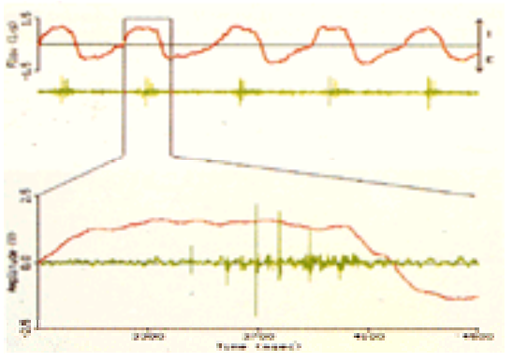
COLOR PLATE 7. Tracheal breath sounds in a patient with exercise-induced asthma. Sound spectrogram as described in Color Plate 4. Polyphonic wheezing is present during both inspiration and expiration, seen as broad bands of intense sound with a narrow distribution of frequencies. Contributions of low-frequency muscle and cardiovascular sound are visible. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) (See Fig. 20 in Chapter 14)



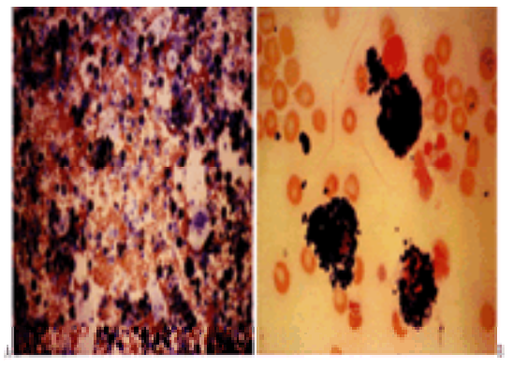
COLOR PLATE 8. Pulmonary breath sounds with wheezes. Sound spectrogram as described in Color Plate 4. Sounds recorded over the right infraclavicular region in the same patient as in Color Plate 7. Inspiratory and expiratory wheezes are seen as broad bands of intense sound with a narrow distribution of frequencies. The intensity of sound is less than in Color Plate 7. No sounds have frequencies higher than 900 Hz. (Reproduced from Pasterkamp H, et al. Digital respirosonography. *Chest* 1989;96:1405.) (See Fig. 21 in Chapter 14)



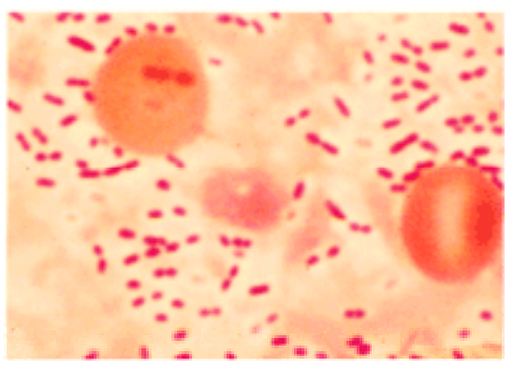
COLOR PLATE 9. Mid to late fine inspiratory crackles in a 60-year-old man with interstitial pulmonary fibrosis. These were recorded over the right posterior lung base. The broad frequency distribution is typical for fine crackles (coarse crackles would be contained largely below 1000 Hz). There are a few expiratory crackles as well. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) (See Fig. 22 in Chapter 14)



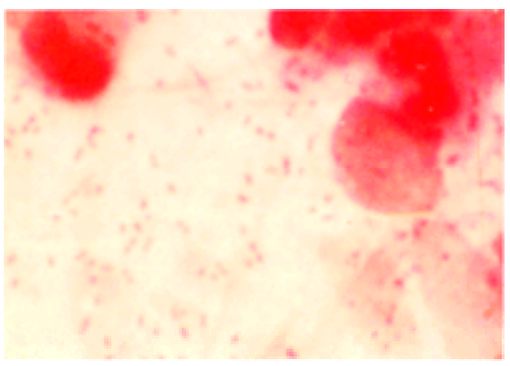
COLOR PLATE 10. The upper two records are the same as in Color Plate 9. One expiration and a small part of the adjacent inspiration are shown on an expanded time-based display. The mid to late crackles are well shown. (Reproduced from Pasterkamp H. *R.A.L.E. Computer-Aided Instruction in Chest Auscultation with Digital Audio Presentation of Lung Sounds.* Winnipeg, Manitoba, Canada: PixSoft; 1990.) (See Fig. 23 in Chapter 14)



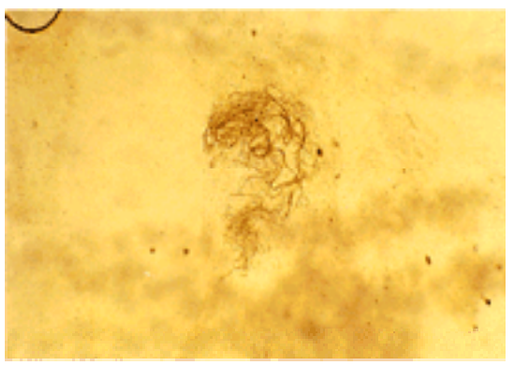
COLOR PLATE 11. A: Hemosiderin-laden macrophages. Photomicrograph of BAL fluid demonstrating numerous hemosiderin-laden macrophages with adjacent red blood cells indicating alveolar hemorrhage. Wright stain, low power. **B:** Photomicrograph of BAL fluid showing hemosiderin-laden alveolar macrophages stained blue by iron stain. Prussian blue stain, high power. (See Fig. 10 in Chapter 21)



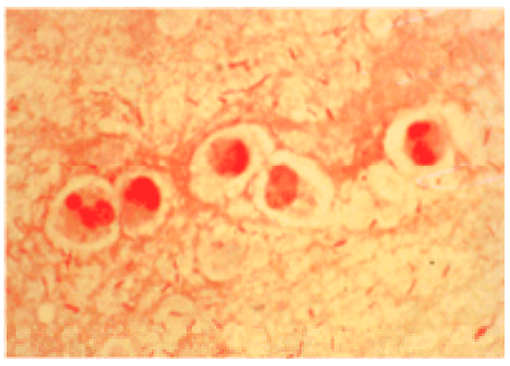
COLOR PLATE 12. *Streptococcus pneumoniae* in Gram's stain of sputum. x900. (See Plate 1 in Chapter 24)



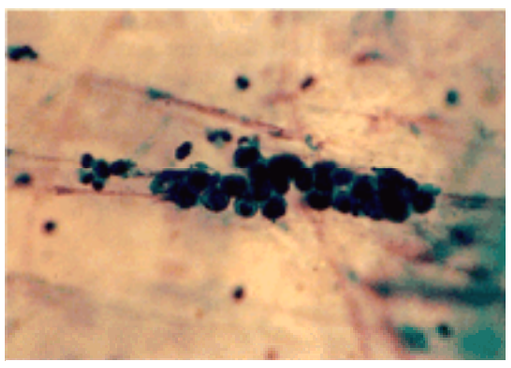
COLOR PLATE 13. *Haemophilus influenzae* in Gram's stain of sputum. X900. (See Plate 2 in Chapter 24)



COLOR PLATE 14. Elastin fibers in a potassium hydroxide preparation of sputum. (See Plate 1 in Chapter 25)

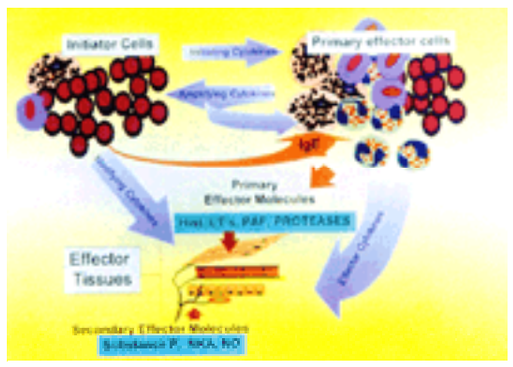


COLOR PLATE 15. *Pseudomonas* in sputum of a neutropenic patient. ×900. (See Plate 2 in Chapter 25)

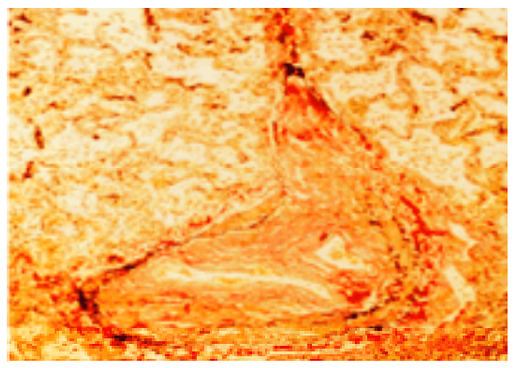


COLOR PLATE 16. Giemsa stain of endotracheal secretions showing intranuclear inclusions of HSV. Fever and diffuse interstitial pneumonia developed in this patient after coronary bypass surgery. (See Plate 3 in Chapter 25)

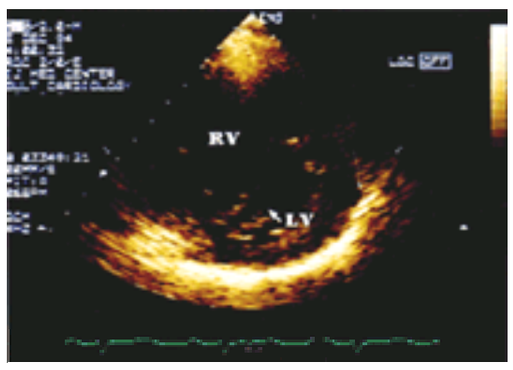
Color Plates for Volume 2



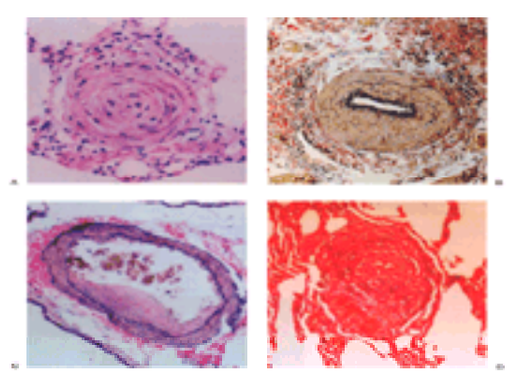
COLOR PLATE 17. Schema relating airway inflammation, shown in the top half of the figure, to airway obstruction, shown in the bottom half of the figure. See text for details. (See Fig. 1 in Chapter 40)



COLOR PLATE 18. Medium-sized pulmonary vein in a case of venoocclusive disease demonstrating intraluminal fibrosis and variably sized intravascular channels, suggesting recanalization of prior thrombosis. (Courtesy of Dr. D. Dantzker.) (See Plate 2 in Chapter 65)



COLOR PLATE 19. Ventricular pressure–volume diagram. EDP, end-diastolic pressure; PADP, pulmonary arterial end-diastolic pressure; ESP, end-systolic pressure; SV, stroke volume. See text for explanation. (See Fig. 5 in Chapter 67)



COLOR PLATE 20. (A) Small muscular pulmonary artery showing almost complete occlusion by myointimal hyperplasia and fibrosis. This is also termed concentric laminar intimal fibrosis or an onionskin lesion (H&E). (Courtesy of Dr. G. Pietra.) **(B)** Medium-sized pulmonary artery showing medial muscular hypertrophy between the external muscular coat and the internal elastic lamina (elastic stain). (Courtesy of Dr. D. Dantzker.) **(C)** Muscular pulmonary artery demonstrating eccentric intimal fibrosis, which is suggestive of remote thromboembolism (H&E). (Courtesy of Dr. G. Pietra.) **(D)** Plexiform lesion. (See Plate 1 in Chapter 65)

Image available in print only.

COLOR PLATE 21. Standard nasal CPAP mask connected to a “bilevel” type of portable pressure-limited ventilator (BiPAP S/T, Respironics, Inc., Murrysville, PA). (See Fig. 1 in Chapter 50)