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Tuberculosis and Atypical Mycobacterial Infections

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Tuberculosis, a scourge of humankind throughout the ages, has undergone a resurgence in the United States during the past decade. Classically, the term "tuberculosis" refers to disease caused by organisms of the *Mycobacterium tuberculosis* complex, such as *M. tuberculosis* and *Mycobacterium bovis*. The most important disease in humans is produced by *M. tuberculosis*; infection due to *M. bovis* is mainly transmitted through the consumption of contaminated milk from infected cows, and it has been virtually eliminated in developed countries by the pasteurization of milk.

Mycobacterioses are tuberculosislike diseases caused by mycobacteria other than *M. tuberculosis* and *M. bovis*. The nontuberculous mycobacteria (NTM) are an important cause of pulmonary disease, and they have become a major source of morbidity and mortality since the advent of the acquired immunodeficiency syndrome (AIDS). A classification of mycobacteria is presented in Table 41-1.

TUBERCULOSIS

Tuberculosis, called the white plague, has ravaged civilization since antiquity.[1,2] In 1804, Laennec referred to this affliction as *phthisis*, a Greek word meaning "to waste away." The term tuberculosis was coined in 1839 by Schönlein, who recognized the tubercle as the fundamental pathologic lesion.[2] Although tuberculosis was long suspected of being an infectious process, this was not proven until 1882, when Koch announced his discovery of the tubercle bacillus.

In an era of effective antituberculous therapy, it is difficult to comprehend the enormous impact that tuberculosis has had on humanity. In 1801, the annual mortality rate from tuberculosis was 1000 per 100,000 persons in developed countries. At the beginning of the twentieth century, tuberculosis was the leading cause of death in the United States. The mortality rate of tuberculosis is now approximately 1 per 100,000 persons annually.[2] The decreased mortality has paralleled dramatic changes in therapy. In the nineteenth and early twentieth centuries, treatment centered on bed rest and the healthy environment of sanatoria reserved for the care of tuberculosis patients. Once-popular procedures such as iatrogenic pneumothorax, phrenic nerve crush, oleothorax, and thoracoplasty were designed to "put the lung to rest" and halt the progression of the disease.[1] The most important breakthroughs in the control of tuberculosis were the discovery of streptomycin by Waksman in 1945, followed by the introduction of isoniazid in 1952.[2]

The steady annual decline in the national incidence of tuberculosis ended in 1986, when the total number of cases increased for the first time in 33 years of record keeping. Since 1986, the number of reported cases in the United States has continued to rise. Tuberculosis is a disease of the underprivileged, debilitated, and medically underserved. The populations at highest risk include persons with human immunodeficiency virus (HIV) infection, those from areas where tuberculosis is most prevalent (*e.g.*, Asia, Africa, Latin America), alcoholics, intravenous drug abusers, the poor in overcrowded urban ghettos and shelters for the homeless, prisoners, and elderly residents of nursing homes. The escalation of tuberculosis among patients with AIDS and the emergence of multidrug-resistant organisms are disturbing reminders that tuberculosis will continue to be an important pulmonary disease into the twenty-first century.

Pathogenesis

M. tuberculosis is a nonmotile, aerobic, catalase-producing, acid-fast bacillus. The organism can be cultured on specialized egg or agar media, on which it grows slowly, producing rough, cream-colored colonies after at least 2 weeks of incubation. A variety of mycobacterial cytoplasmic and cell wall polysaccharide-protein complexes, lipids, and wax D are antigenic, and cell wall glycolipids (*e.g.*, cord factor, sulfatides) are directly toxic to cells.[3]

TABLE 41-1.
Classification of Pulmonary Mycobacteria

Pathogen	Frequency of Occurrence
MYCOBACTERIA TUBERCULOSIS COMPLEX	
M. tuberculosis	Common
M. bovis	Uncommon
M. africanum	Rare
NONTUBERCULOUS MYCOBACTERIA	
Slow growers	
M. avium-intracellulare	Common
M. kansasii	Common
M. scrofulaceum	Uncommon
M. xenopi	Uncommon
M. szulgai	Uncommon
M. simiae	Uncommon
M. malmoense	Uncommon
M. gordonae	Rare
M. terrae	Rare
Rapid growers	
M. fortuitum	Uncommon
M. chelonae	Uncommon

Pulmonary tuberculosis is spread by interpersonal contact through the aerosolization of droplet nuclei that contain viable bacteria. Organisms are deposited in the alveoli, where they elicit an inflammatory reaction and subsequent cell-mediated immune response.[3,4] In most persons, the initial infection is minimal and focal. The factors that determine progression of disease include the number of bacilli inhaled, the native susceptibility of the host, and the immunologic response of the host to the infection.[4]

After the bacilli are deposited within the alveolus, there is a period of free replication of organisms, followed by a local accumulation of neutrophils and macrophages that signal the initiation of a delayed-type hypersensitivity reaction. Macrophages are the main line of defense against *M. tuberculosis*. They serve as antigen-presenting cells that activate helper T lymphocytes, which are recruited with blood-borne monocytes into the developing lesion. Activation of macrophages through the ingestion of cellular or bacterial debris and by the action of lymphokines is a prerequisite for macrophage destruction of the tubercle bacilli.[4] Once activated, macrophages differentiate into epithelioid cells or fuse to form Langhans giant cells. The local accumulation of lymphocytes, macrophages, epithelioid cells, and Langhans giant cells in the tuberculous lesion imparts the characteristic histologic appearance of granulomatous inflammation.

The course of tuberculosis is determined by the ability of macrophages to contain and kill the mycobacteria compared with the ability of the bacilli to destroy macrophages and spread within or beyond the lung. Granulomatous inflammation eliminates bacilli but simultaneously destroys lung tissue.

After sufficient numbers of organisms have accumulated to produce a sensitizing load, the tuberculin skin test becomes positive and identifies infected persons. The tuberculin reaction and the acquired host immunity are mediated by long-lived memory T cells. These cells have the capacity to proliferate and initiate an immune reaction when presented again with the antigen.[1,4] Comprehensive discussions of the pathogenesis and immunology of tuberculosis are available elsewhere.[3,4]

Morphologic Components of Tuberculous Lesions

Tuberculous lesions are histologically characterized as proliferative or exudative.[5] Proliferative lesions (*i.e.*, hard tubercles) are granulomas composed of compact aggregates of epithelioid cells, lymphocytes, and Langhans giant cells with variable degrees of central necrosis and relatively few acid-fast bacilli. Proliferative lesions are seen in hosts with a high resistance to tuberculosis (Fig. 41-1). Exudative lesions (*i.e.*, soft tubercles) consist of an amorphous exudate of mononuclear cells, neutrophils, fibrin, and usually extensive necrotic debris (Fig. 41-2). Exudative lesions are usually the result of a local accumulation of large numbers of organisms and imply a low resistance to the infection. Exudative and proliferative features often merge within the same lesion.[5] Lesions can be discrete or involve large areas of the lung, depending on the number of bacilli, their mode of spread, and the amount of tuberculoprotein discharged into the developing lesion. Tuberculous pneumonia frequently effaces and destroys lung tissue, but the alveolar architecture may be spared, even though alveolar spaces are filled with acute fibrinonecrotic exudate, loosely cohesive tuberculous granulation tissue, or compact nests of epithelioid cells (Fig. 41-3).[5]

Caseation necrosis is a hallmark of tuberculous lesions. Grossly, caseation necrosis appears as firm, white, consolidated matter resembling Roquefort cheese. Histologically, caseation necrosis is eosinophilic, granular, and amorphous (Fig. 41-4). Areas of caseation are usually devoid of connective tissue elements, although elastic tissue stains occasionally demonstrate residual alveolar remnants.[4,6] Caseation necrosis implies permanent tissue destruction, but it is also a mechanism for the destruction of mycobacteria.[1,4] Within the caseum, low oxygen tension, low *p*H, and the local accumulation of fatty acids inhibit bacillary replication. Caseous lesions can progress in several important ways. The caseum can become inspissated and encapsulated by fibrous tissue (*i.e.*, fibrocaseous granuloma); the caseous area can become completely organized and convert to a fibrous scar that is often calcified or

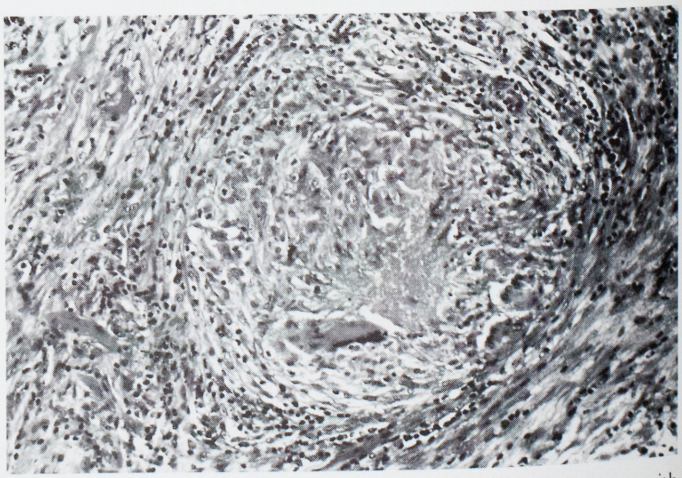


FIGURE 41-1. In a proliferative lesion, the compact granuloma, with central necrosis, is composed of epithelioid cells and a Langhans giant cell. (H & E stain; low magnification.)

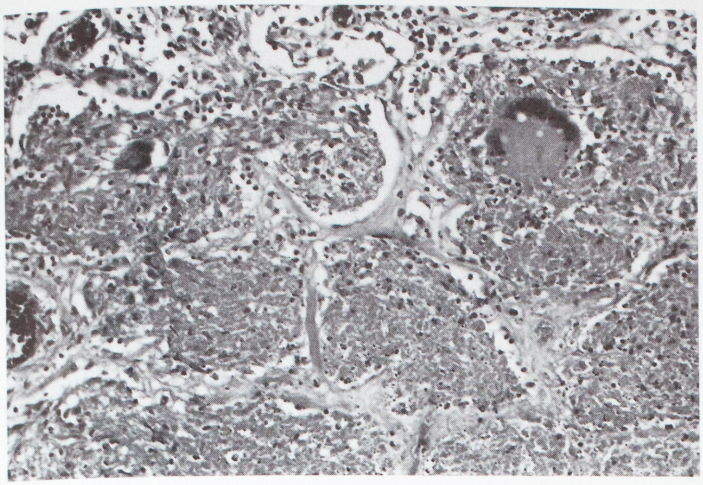


FIGURE 41-2. An exudative lesion consists of an amorphous aggregate of caseonecrotic debris rimmed by loosely cohesive epithelioid cells and Langhans giant cells. (H & E stain; low magnification.)

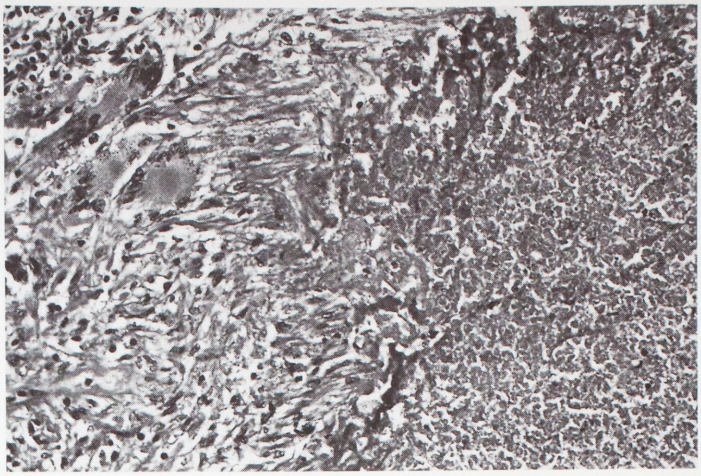


FIGURE 41-4. Caseation necrosis (*right*) is bordered by tuberculous granulation tissue. (H & E stain; low magnification.)

ossified (Fig. 41-5); or the caseous focus can undergo liquefaction and cavitation.

The mechanism of liquefaction probably involves proteolytic enzymes derived from neutrophils and macrophages within or around the caseous focus.[1,4] Unlike caseous debris, liquefied material is usually teeming with bacilli. Cavitation occurs when the liquefied areas rupture into an airway and are evacuated. Dissemination of bacilli in this manner contributes to the development of tuberculous pneumonia within the lung. The oxygen-rich environment of the newly formed cavity stimulates the proliferation of bacilli and renders the host increasingly infective to others.

Tuberculous lesions of all types are frequently surrounded by nonspecific, chronic (*i.e.*, perifocal) inflammation that is considered to represent a hypersensitivity reaction or a response to the by-products (*e.g.*, tuberculoprotein) of destroyed bacilli.[5]

Identification of Organisms

The differential diagnosis of pulmonary tuberculosis includes the spectrum of granulomatous lung disease, especially fungal infections such as histoplasmosis and coccidioidomycosis, pulmonary angiitis and granulomatosis, sarcoidosis, and bronchocentric granulomatosis.

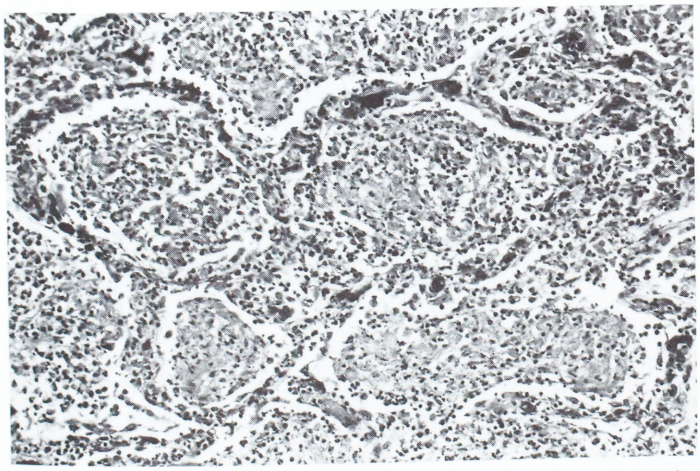


FIGURE 41-3. In tuberculous granulomatous pneumonia, the alveolar spaces are filled by cohesive nests of epithelioid cells. The alveolar septa are preserved. (H & E stain; low magnification.)

Histologic identification of mycobacteria is critical in establishing an early diagnosis of mycobacterial lung disease but does not differentiate the species of mycobacteria. All mycobacteria are acid-fast; they retain certain dyes when washed with acid alcohol. The most widely used staining method is the Ziehl-Neelsen technique, in which bacilli are stained red with carbolfuchsin.[7] Mycobacteria can also be stained by the auramine-rhodamine method in which bacilli are labeled with a fluorescent dye and visualized under ultraviolet light. Immunohistochemical staining of mycobacterial antigen in tissue sections has not been widely applied.[8] Detection of mycobacteria by light microscopy is tedious and best accomplished by systematically searching the slide using a 40× objective and mechanical stage. An oil immersion 100× lens is recommended for confirmation of organisms, but it is not usually necessary for screening purposes.

M. tuberculosis organisms may stain uniformly or in a beaded pattern. They are usually found in necrotic lesions, especially in areas of liquefaction and cavitation. The organisms are much less frequently seen in nonnecrotizing granulomas and rarely identified in nongranulomatous lesions. If initial screening is negative in a patient who is highly suspect for tuberculosis, repeat staining of deeper levels or sections from additional tissue blocks is indicated. The auramine-rhodamine stain allows rapid screening, but it requires an ultraviolet light source and does not permit easy localization of bacilli within specific lesions. Microbiologic culture is mandatory for confirmation, speciation, and drug susceptibility testing.

Routes of Spread

Tuberculous lesions can spread by direct extension into adjacent tissue or by endobronchial (*i.e.*, intracanalicular), lymphatic, or vascular pathways. Endobronchial spread of liquefied caseous material is a cause of ipsilateral or contralateral acinar pneumonia. Implantation of mycobacteria in the mucosa of the upper airway can result in laryngotracheal, oral, or middle ear tuberculosis. Swallowing infective sputum can also lead to tuberculous ulceration of the intestinal mucosa. Lymphatic spread to ipsilateral hilar

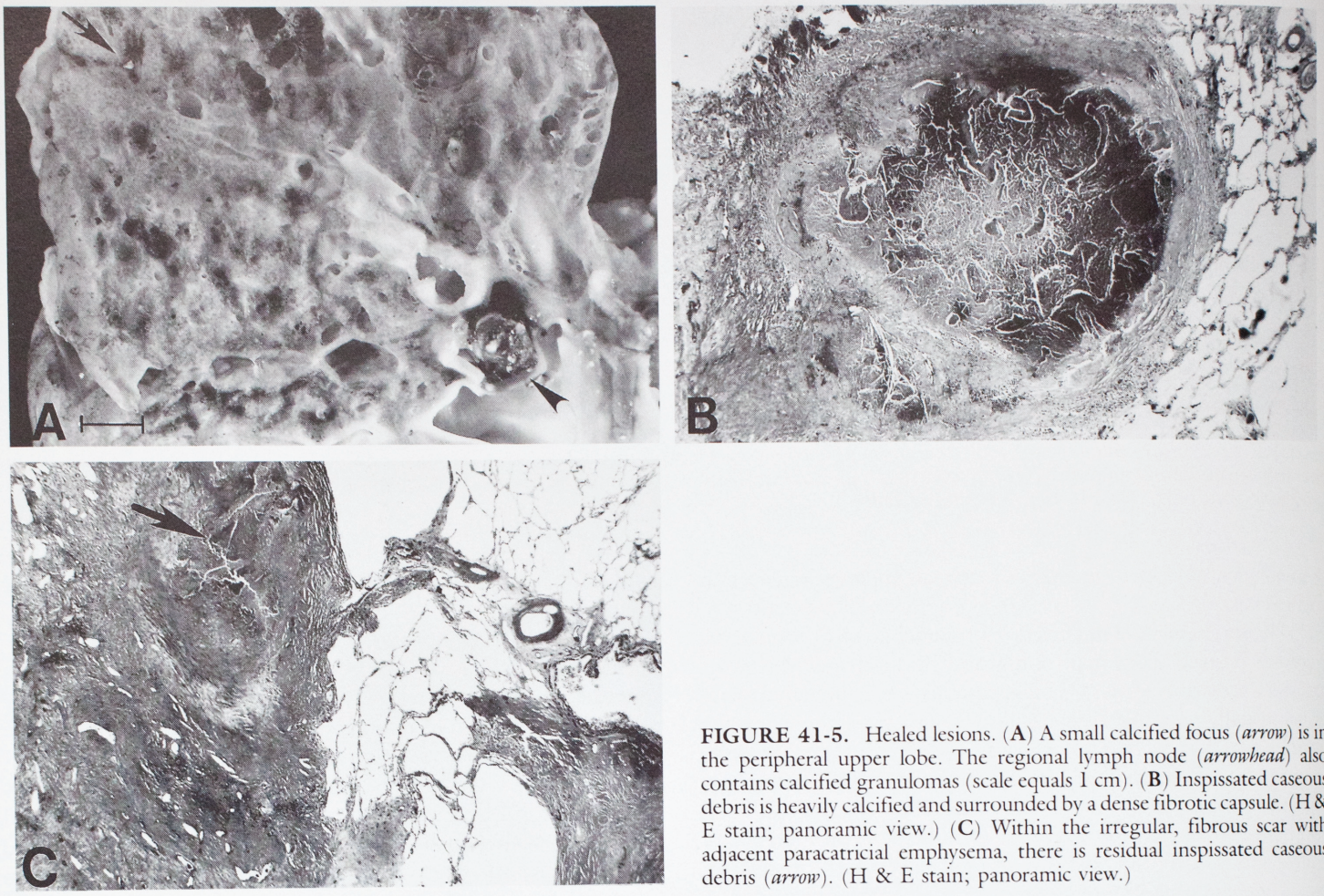


FIGURE 41-5. Healed lesions. (**A**) A small calcified focus (*arrow*) is in the peripheral upper lobe. The regional lymph node (*arrowhead*) also contains calcified granulomas (scale equals 1 cm). (**B**) Inspissated caseous debris is heavily calcified and surrounded by a dense fibrotic capsule. (H & E stain; panoramic view.) (**C**) Within the irregular, fibrous scar with adjacent paracatricial emphysema, there is residual inspissated caseous debris (*arrow*). (H & E stain; panoramic view.)

lymph nodes is especially prominent in primary infections. Perforation of a bronchus by an enlarged caseous lymph node followed by endobronchial spread can result in massive segmental or lobular pneumonia.[5,6] From regional lymph nodes, bacilli can disseminate through lymphatics to the pleura, spine, and other viscera. Hematogenous dissemination can occur after lymph node involvement and spread through the thoracic duct or by direct extension of lesions into branches of the pulmonary vein.

Clinicopathologic Patterns of Disease

PRIMARY TUBERCULOSIS

The sequence of events in the first (*i.e.*, primary) infection by *M. tuberculosis* is depicted in Figure 41-6. The initial site of infection (*i.e.*, primary focus) is usually established in the better ventilated regions of the lung, such as the lower lobe or anterior segment of the upper lobe. A peripheral caseating granulomatous lesion is formed, and the bacilli spread through the lymphatics to the regional lymph nodes. The combination of the primary focus and involved lymph node is called the Ghon complex (Fig. 41-7; see Fig. 41-6).[1,4] Mycobacteria then disseminate by the bloodstream and seed extrathoracic organs. These extrinsic foci are usually well contained and heal completely (*i.e.*, silent bacteremia), but they may persist as a reservoir of viable bacilli with the potential for reactivation.[9] Hematogenous spread to the pulmonary apex can result in a postprimary infective lesion called the Simon focus (see Fig. 41-6).[10] The predilection for the lung apex in postpri-

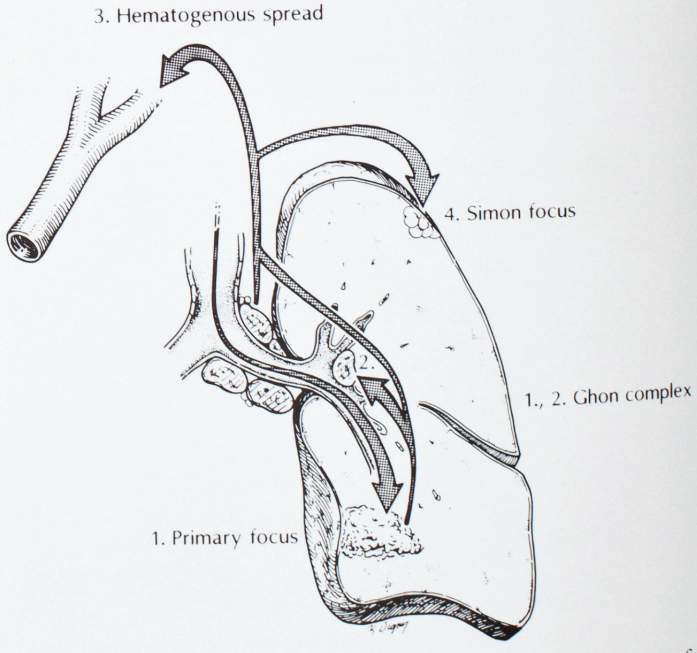


FIGURE 41-6. The spread of tubercle bacilli and associated lesions of the primary infection.

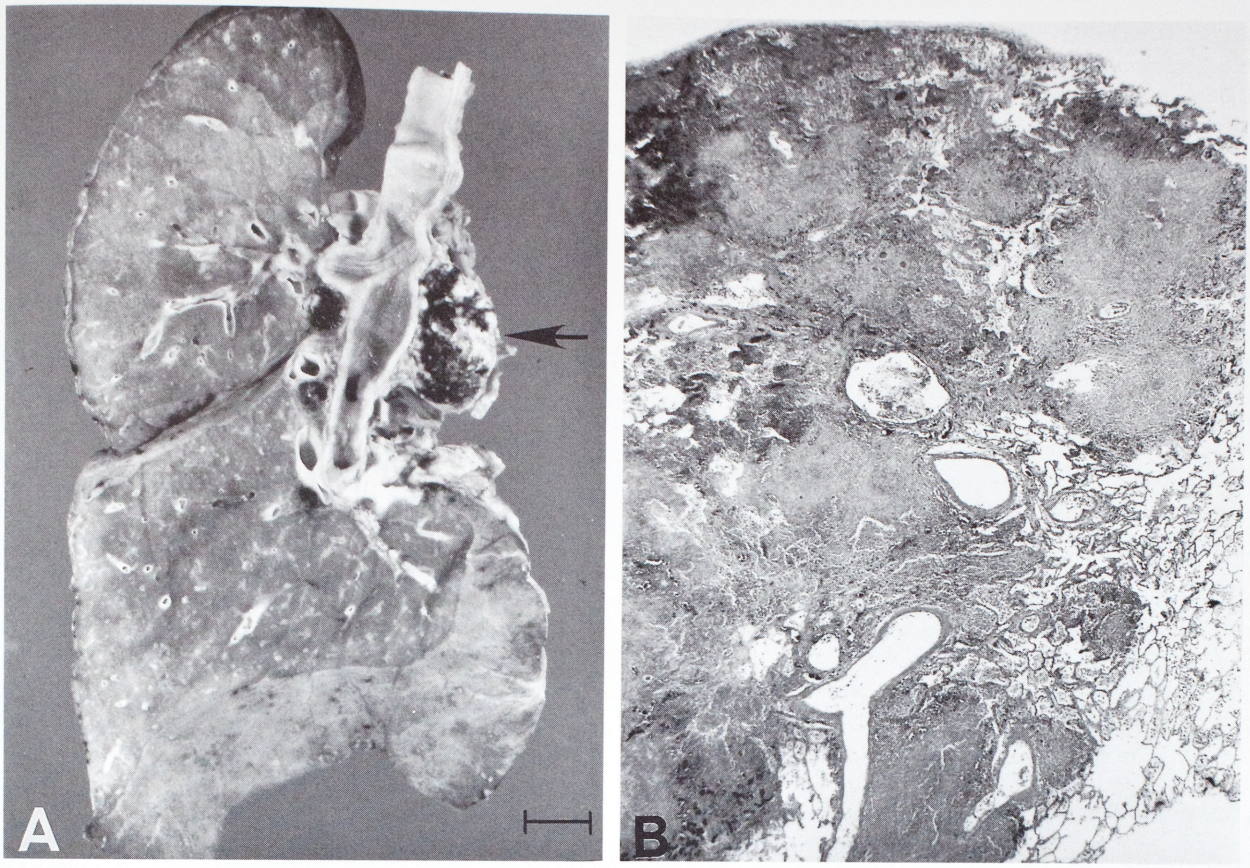


FIGURE 41-7. Primary tuberculosis in a 73-year-old black female nursing home resident was an incidental finding at autopsy. (**A**) The enlarged medial parabronchial lymph node (*arrow*) is focally replaced by pale granulomatous lesions. The primary focus is not shown in this section (scale equals 1.8 cm). (**B**) The primary focus of caseating granulomatous pneumonia is subjacent to the visceral pleura of the lower lobe. (H & E stain; panoramic view.)

mary seeding is probably because of the higher apical oxygen tension, which favors bacillary growth.

In most patients, the primary infection is innocuous or undergoes rapid resolution or healing. The morphology of the healed lesion is similar in the lung and lymph node and may take the form of a calcified fibrous scar, an inspissated encapsulated caseous focus with or without calcification, or an ossified nodule. The healed primary lesion is often minuscule and readily missed on gross examination. A large, encapsulated caseous focus (*i.e.*, tuberculoma) may present on a chest radiograph as a solitary nodule simulating a neoplasm.

Symptomatic primary tuberculosis in children produces the typical radiographic picture of a parenchymal infiltrate coupled with prominent regional node enlargement and a tendency toward rapid calcification.[1] Extrinsic compression or perforation of a bronchus by the enlarged lymph nodes may result, respectively, in segmental parenchymal collapse or tuberculous pneumonia (*i.e.*, epituberculosis).[5,11] Hematogenous spread is rarely symptomatic, but in a host with low resistance, disseminated (*i.e.*, miliary) tuberculosis sometimes occurs on the heels of the primary infection. Primary childhood tuberculosis infrequently progresses to chronic fibrocavitary disease.

Compared with childhood disease, primary tuberculosis in adults more frequently results in radiographically apparent upper lobe infiltrates, less pronounced enlargement of hilar lymph nodes, and less of a tendency for rapid calcification of lesions. According to Stead, apical infiltrates in adult primary tuberculosis represent hematogenous seeding of the upper lobe.[12] There is a tendency for adult primary tuberculosis to progress directly to chronic pulmonary tuberculosis, and primary tuberculosis in the adult can often be differentiated from reactivation tuberculosis only by the documentation of a recent tuberculin conversion.[10]

REACTIVATION AND REINFECTION TUBERCULOSIS

Pulmonary tuberculosis may recur in adults long after the primary lesion has healed (*i.e.*, adult-type or postprimary tuberculosis). Most instances of adult-type tuberculosis in developed countries are probably due to reactivation of dormant lesions resulting from an incompletely healed apical focus (*i.e.*, Simon focus).[12,13] This mechanism of recrudescent disease is also referred to as endogenous reinfection tuberculosis. Tubercle bacilli have been cultured from chronic, encapsulated, fibrocaseous lesions, although fully calcified or ossified lesions are usually sterile.[13,14] Another mechanism of adult-type tuberculosis is exogenous reinfection, in which a newly acquired infection occurs after the inhalation of mycobacteria by a previously infected host.[1] Exogenous reinfection assumes great importance if the prevalence of tuberculosis is high and acquired immunity within the population is impaired because of poor hygiene, debilitation, or starvation. Exogenous reinfection has been documented in a shelter for the homeless in the United States.[15] It is almost impossible to make

the histologic distinction between exogenous reinfection and reactivation tuberculosis unless a recent breakdown and acute extension of a chronic, encapsulated lesion is fortuitously observed, indicating reactivation disease.[5]

PROGRESSIVE FIBROCAVITARY DISEASE

Reactivation or reinfection tuberculosis usually presents in the apical and posterior segments of the upper lobe. Hilar node involvement is minimal. The lung parenchyma is replaced and destroyed by slowly progressive, fibrocaseous pneumonia with cavitation (Fig. 41-8). Histologically, conglomerate, caseating granulomas are associated with extensive fibrosis. The age of the lesions varies within the lung because new foci of acinar pneumonia follow endobronchial spread. Healing of progressive fibrocaseous disease results in extensive scarring, inspissated caseous foci, calcification, and paracicatricial emphysema (Fig. 41-9). In patients with lowered host resistance, large portions of lung may be involved by an exudative, cavitary tuberculous pneumonia, also called galloping consumption (Fig. 41-10).

Tuberculous cavities are typically lined by a layer of necrotic debris, degenerated neutrophils, and abundant acid-fast bacilli. Focally, the inner membrane may be fibrinous with numerous neutrophils and erythrocytes (*i.e.*, pyogenic membrane). An exuberant layer of tuberculous granulation tissue is interposed between the inner lining and the outer rim of fibrous tissue.[16] The bronchial mucosa is ulcerated at the bronchocavitary junction, and ulceration extends for a short distance along the proximal airway.

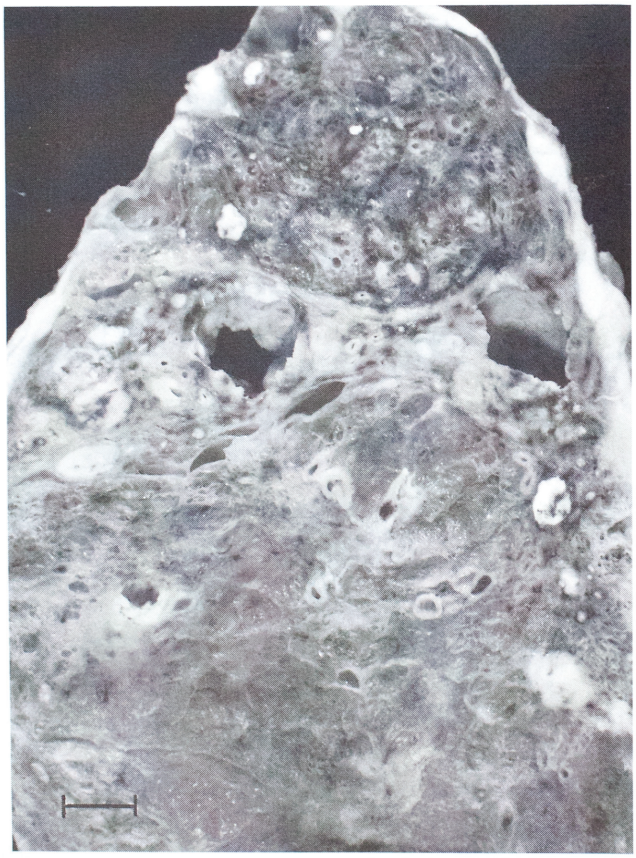


FIGURE 41-8. Chronic progressive fibrocavitary tuberculosis is illustrated by the two large cavities in the superior segment of the lower lobe. Pale foci of tuberculous pneumonia and inspissated fibrocaseous lesions are scattered in the upper and lower lobes. The visceral pleura is thickened (scale equals 1.2 cm).

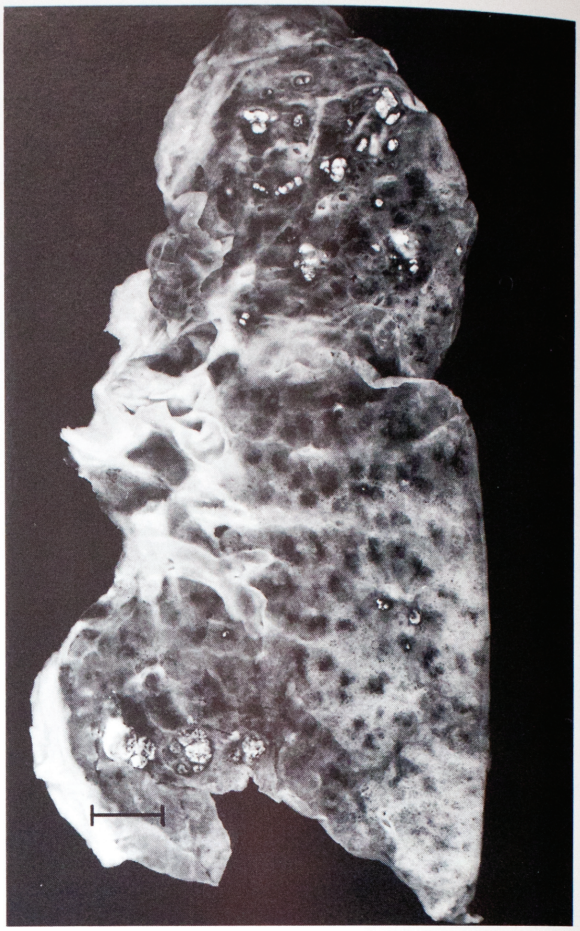


FIGURE 41-9. Healed fibrocaseous pneumonia in a 54-year-old black man who was previously treated with a triple-drug regimen is indicated by the inspissated fibrocaseous lesions scattered throughout the upper lobe and the medial basal segment of the lower lobe (scale equals 1.6 cm).

Airways adjacent to cavities are usually chronically inflamed and contain noncaseating mural granulomas. Rarely, a branch of the pulmonary artery is eroded by the fibrinous reaction on the cavity surface, forming a Rasmussen aneurysm. Rupture of the aneurysm into the cavity can cause massive hemoptysis and death.[17]

Before the use of chemotherapy, tuberculous cavities usually healed by gradual inspissation of the cavity contents and fibrous encapsulation. Less frequently, cavities were completely replaced by fibrous scar.[18] Treatment with antituberculous chemotherapy has enabled a greater proportion of cavities to undergo open healing, in which a noninfectious cavity with a bronchocavitary junction persists (Fig. 41-11). The open-healed cavity is composed of a fibrous wall devoid of granulomas. Metaplastic squamous epithelium may extend for a short distance from the draining bronchus over the fibrous inner wall.[19]

PLEURITIS AND PLEURAL EFFUSION

Pleural involvement in tuberculosis occurs by direct extension from an underlying parenchymal lesion or by lymphohematogenous seeding.[20,21] Pleural involvement by direct extension results in granulomatous pleuritis and pleural thickening by caseous debris, fibrin, and tuberculous granulation tissue. The serosal surface may be extensively destroyed. Severe pleuritis may lead to fibrothorax and massive calcification, although this complication is rarely seen in patients treated with antituberculous chemotherapy (Fig. 41-12). Hematogenous seeding of the pleura pro-

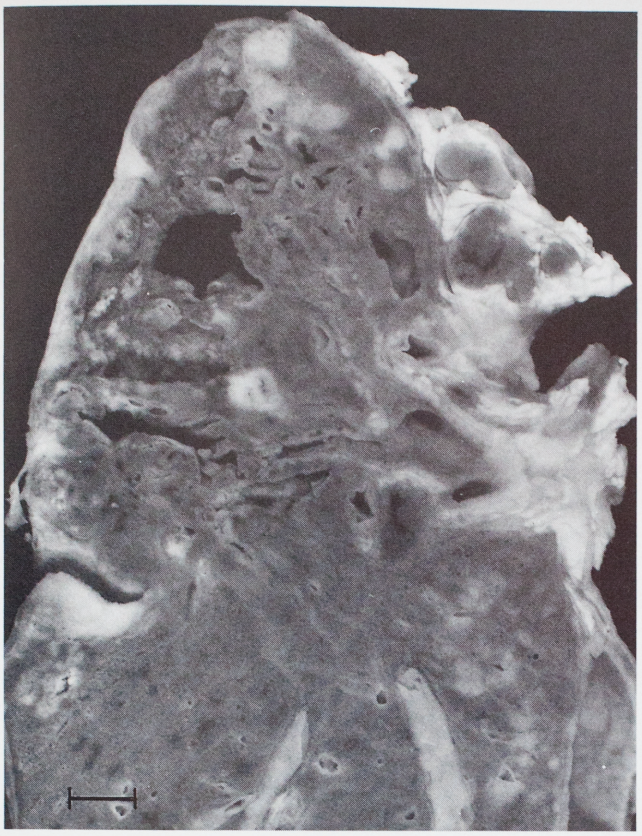


FIGURE 41-10. An acute fulminant tuberculous pneumonia caused extensive cavitation and pleuritis in a 31-year-old alcoholic Caucasian man. The pale foci in the medial aspect of the lower lobe represent acinar pneumonia. The patient developed a bronchopleural fistula shortly before his death (scale equals 1 cm).

duces discrete, 1- to 3-mm granulomatous foci beneath the serosal surface. Healing of the subserosal granulomas is associated with minimal residual scarring.[22]

Tuberculous pleuritis is a cause of exudative pleural effusion that may be a presenting manifestation of primary pulmonary tuberculosis, particularly in young adults. Effusion may precede a radiographically apparent parenchymal infiltrate by 3 to 6 months. Cytologic study of tuberculous pleural effusions usually indicates lymphocytosis (*i.e.*, >50% of cells are small lymphocytes) and a paucity of mesothelial cells (*i.e.*, <5% of cells).[20] The lack of mesothelial cells is ascribed to serosal destruction by tuberculous granulation tissue. Chemical analysis of pleural fluid yields few distinctive features, although the protein level may exceed 5 g/dL. Pleural fluid cultures are positive for mycobacteria in fewer than 25% of these patients.[20]

Transthoracic pleural biopsy is useful in establishing the diagnosis of tuberculous pleurisy. Pleural biopsy demonstrated granulomas in 63% and nonspecific inflammation in 37% of a series of patients with tuberculous pleuritis.[23] Although granulomas disclosed by biopsy are not specific for pleural tuberculosis, more than 90% of patients with this finding prove to have tuberculosis. Acid-fast bacilli can be demonstrated in the pleural biopsies from only about 20% of patients, but acid-fast stains are indicated in all patients suspected of having tuberculous pleurisy, even if granulomas are not seen.[20,23] Culture of the biopsied tissue is important, because mycobacteria can be isolated from about 55% of the patients with this method. Using a combination of histologic examination and culture of pleural tissue, a diagnosis of tuberculous pleurisy can be established for about 80% of patients.[23]

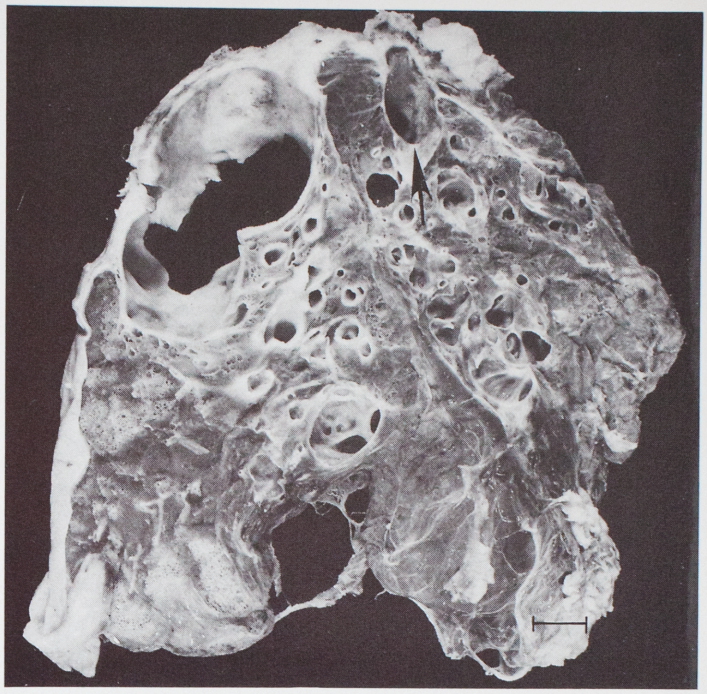


FIGURE 41-11. Open healed cavities persist in a 62-year-old black man after his tuberculosis was treated with a triple-drug regimen. There is a large, smooth-walled cavity in the superior segment of the lower lobe and a smaller cavity in the upper lobe apex (*arrow*). The lung is extensively involved by bronchiectasis and emphysema (scale equals 1.7 cm).

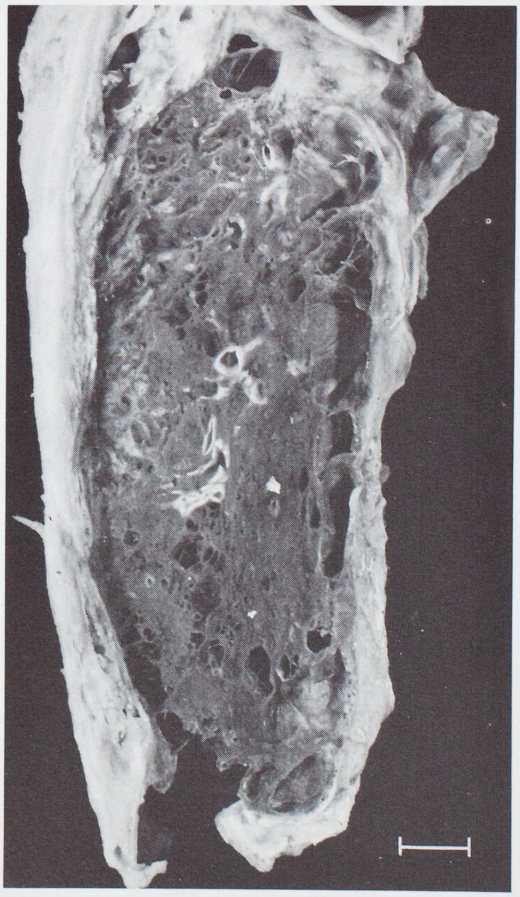


FIGURE 41-12. In the healed tuberculous pleurisy of a 72-year-old Caucasian man diagnosed with tuberculosis in 1939 (45 years before death), the visceral pleura is more than 1 cm thick and heavily calcified. Notice the apical scarring and extensive paraseptal and irregular emphysema (scale equals 2 cm).

Delayed hypersensitivity to tuberculoprotein plays a major role in the pathogenesis of pleural effusion. The tuberculoprotein in the pleural space initiates a lymphocytic reaction. Mycobacteria are few within the pleural fluid, accounting for the low yield of positive cultures. Pleural effusions usually resolve spontaneously, but they may be followed by progressive parenchymal tuberculosis.

Bronchopleural fistula is a rare complication caused by the rupture of a cavity into the pleural space.[20,24] The predisposing factors in the development of bronchopleural fistula are inadequate medical treatment for tuberculosis, acute fulminant tuberculous pneumonia, or prior collapse therapy. Tuberculous bronchopleural fistulas are frequently superinfected by bacteria, resulting in a mixed tuberculous and pyogenic empyema. Surgical decortication and thoracoplasty are usually required to treat patients with bronchopleural fistula.

MILIARY TUBERCULOSIS

Miliary tuberculosis occurs when massive numbers of bacilli are spread hematogenously in a patient with lowered host resistance. The risk for developing miliary tuberculosis is increased for children, the elderly, and the immunosuppressed, especially patients with AIDS. Disseminated lesions, 1 to 3 mm in diameter, involve the lungs or extrapulmonic sites, including, in order of frequency, the spleen, liver, bone marrow, kidneys, and adrenals.[25] Spread to the brain and meninges occurs in approximately 20% of fatal cases. Miliary tuberculosis occasionally complicates primary tuberculosis, especially in young children. More frequently, dissemination is initiated from a pulmonic or extrapulmonic dormant focus. Rarely, miliary tuberculosis occurs during the course of chronic, fibrocaseous tuberculous pneumonia.[26]

Miliary tuberculosis can present as an acute fulminant process with fever, chills, sweats, and prostration. The chest radiograph reveals diffuse, small, nodular densities. A subacute form of miliary tuberculosis produces a protracted illness in which the miliary nodulation seen on chest radiographs occurs late in the course of the disease. Miliary tuberculosis may be difficult to diagnose clinically. Cryptic miliary tuberculosis, in which a reticulonodular infiltrate is not evident on chest radiographs, occurred in 40% of the patients in one series and was more likely to affect persons older than 60 years of age.[27] Macroscopically, small, discrete lesions are scattered throughout the lung (Fig. 41-13). The number and size of the nodules tend to be greater in the upper lobe. With chronicity, larger, confluent lesions may extend into bronchioles and produce acinar pneumonic lesions (*i.e.*, progressive miliary tuberculosis).[26] Microscopically, lesions are exudative or proliferative, depending on the resistance of the host. Acid-fast bacilli are usually numerous and readily identified. In acute miliary tuberculosis, lesions are more frequently exudative and may be associated with diffuse alveolar damage, causing adult respiratory distress syndrome.[28]

The lesion fostering dissemination may be a caseous focus that perforated a pulmonary vein (*i.e.*, Weigert tubercle). In most instances, lymph node involvement followed by drainage into systemic veins or vascular invasion from an extrapulmonic caseous lesion is the most likely mechanism of dissemination.[26]

Tuberculosis in Patients With Acquired Immunodeficiency Syndrome

The incidence of tuberculosis is higher among patients with depressed cell-mediated immunity, including those with renal failure, cancer treated with chemotherapy, and organ transplants treated with high-dose steroids and other immunosuppressants. Tuberculosis has become an important HIV-related infection, particularly in groups already at risk for tuberculosis: intravenous drug abusers, persons from places with a high prevalence of tuberculosis (*e.g.*, Haiti, Africa), and hospitalized patients.[29] Tuberculosis in the AIDS population is the most important factor accounting for the overall increased incidence of tuberculosis in the United States.[2]

In AIDS patients and other immunocompromised hosts, tuberculosis usually represents reactivation of a latent focus. In these patients, tuberculosis is usually more severe than in immunocompetent patients, mortality rates are higher, and extrapulmonary involvement occurs more frequently. Because *M. tuberculosis* is a relatively virulent organism, tuberculosis tends to occur earlier than other opportunistic infections in patients with AIDS.[29] In HIV-infected patients, the disease of reactivation often resembles a primary infection with hilar adenopathy, frequent lower lobe involvement, and absence of cavitation and scar formation.[30] In the late stages of AIDS, when CD4 cell counts are markedly depressed, tuberculosis presents with diffuse lung involvement and extrapulmonary dissemination (see Fig. 41-13).[31]

The lesions of tuberculosis in AIDS patients reflect poor host resistance. Histologically, extensive caseation is generally associated with poorly formed or absent granulomas and no encapsulation. In those who die with fulminant disseminated tuberculosis, the morphology is frequently that of "nonreactive" tuberculosis, in which intraalveolar necrosis, devoid of giant cells and epithelioid cells, is surrounded by normal lung parenchyma.[31] Large numbers of bacilli are usually present with lesions.

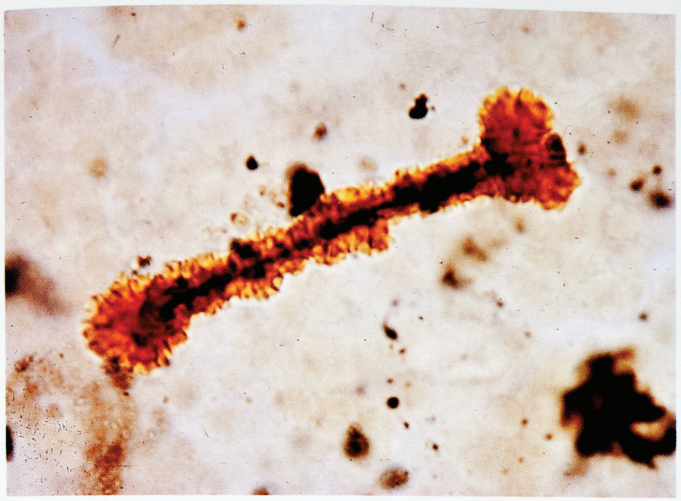
Drug-Resistant Tuberculosis

Multidrug-resistant mycobacteria are emerging as a serious problem in the control of tuberculosis and pose an added threat to health care workers, including pathologists, who handle infected specimens. In New York City, approximately 20% of tuberculosis cases are caused by bacilli resistant to at least two antituberculosis drugs. Resistant organisms may emerge during the course of chemotherapy, especially if patient compliance is poor or inadequate drug regimens are used.[1] Primary infection by resistant strains, including strains resistant to all commonly used antituberculous agents, has become a particular problem among immigrants from highly endemic areas (*e.g.*, Asia, Latin America, Africa) and in the AIDS population.[32,33]

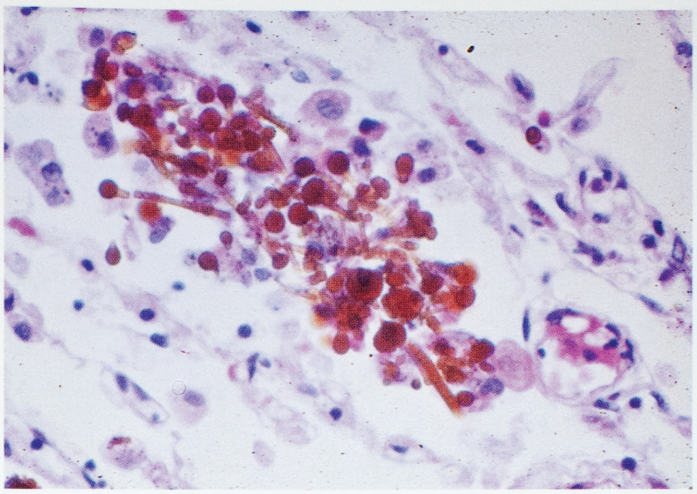
Surgical resection is likely to assume increased importance in the management of infection due to drug-resistant strains.[34] The histopathology of lesions due to resistant strains is similar to those caused by sensitive organisms, although the disease may be relatively more advanced. In the absence of antimicrobial therapy for tuberculosis, perifocal inflammation is generally more intense, tuberculous bronchitis more frequent, and caseonecrotic cavities show little evidence of healing.[35]

MYCOBACTERIOSES

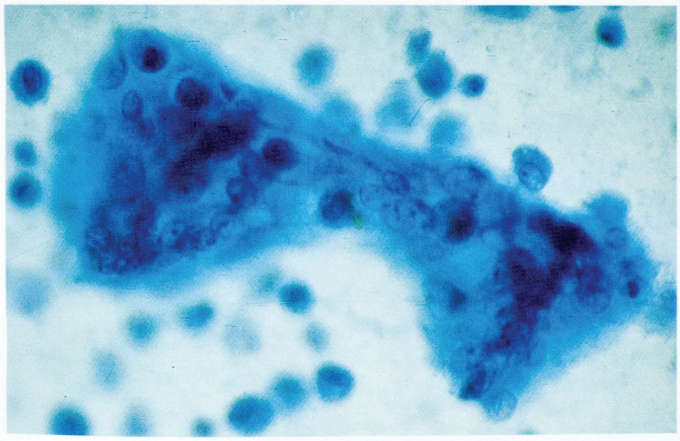
NTM are an increasingly important cause of pulmonary disease. NTM are ubiquitous inhabitants of the natural environment and exist in a variety of animal hosts and nonbiologic reservoirs, including soil and water. Potential pulmonary pathogens among the



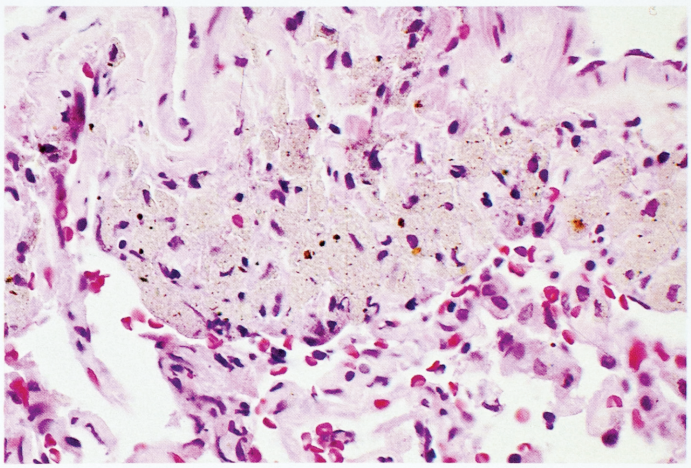
COLOR FIGURE 36-1. A pseudoasbestos body with a black core fiber was recovered from the lungs of a gray-iron foundry worker (see Fig. 36-3 and Color Fig. 37-4). (H & E stain; high magnification; contributed by the editor.)



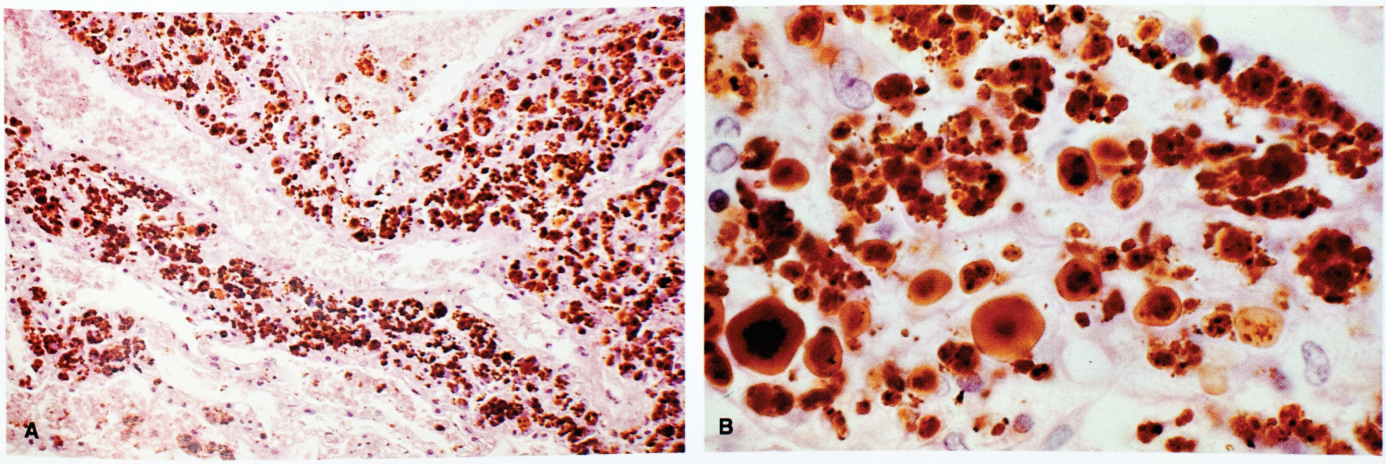
COLOR FIGURE 36-2. Numerous asbestos bodies are present in the lung tissue of a patient with asbestosis (see Fig. 36-6). (H & E stain; low magnification; contributed by the editor).



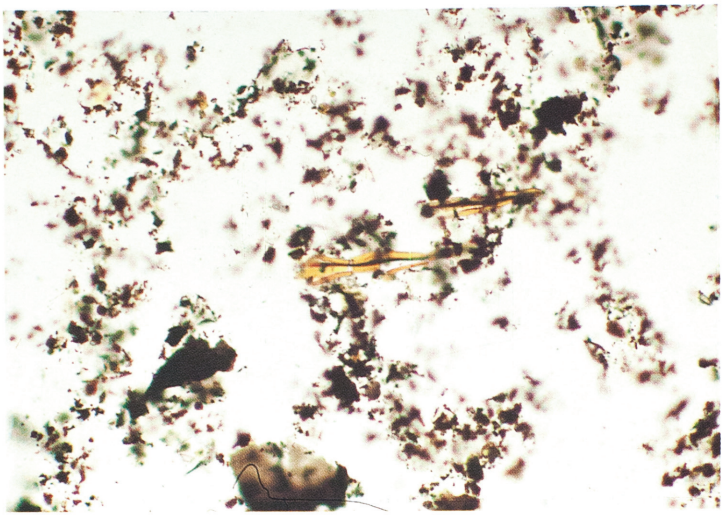
COLOR FIGURE 37-1. A multinucleate giant cell is found in a bronchial washing from a patient with hard metal lung disease (see Figs. 37-4 and 37-5). (Papanicolaou stain; high magnification; from Sprince NL, Oliver LC, Eisen EA, Greene RE, Chamberlin RI. Cobalt exposure and lung disease in tungsten carbide production: a cross-sectional study of current workers, Am Rev-Respir Dis 1988;138:1220.)



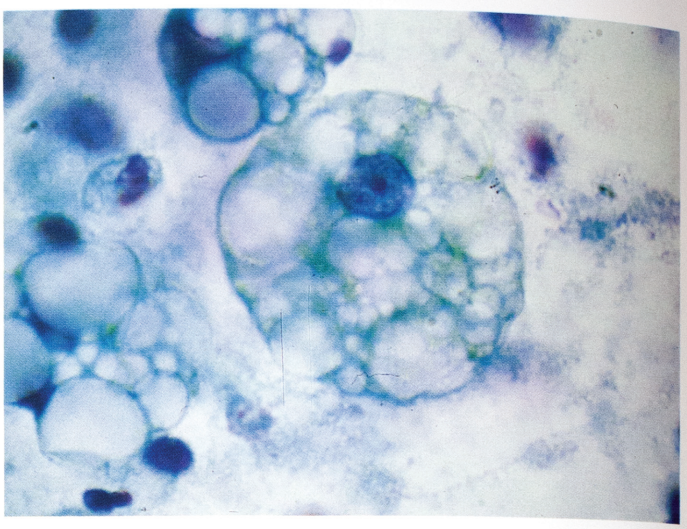
COLOR FIGURE 37-2. Dust-laden macrophages are seen in an open lung biopsy specimen from an aluminum arc welder. The cytoplasm has a gray-tan appearance. (H & E stain; low magnification.)



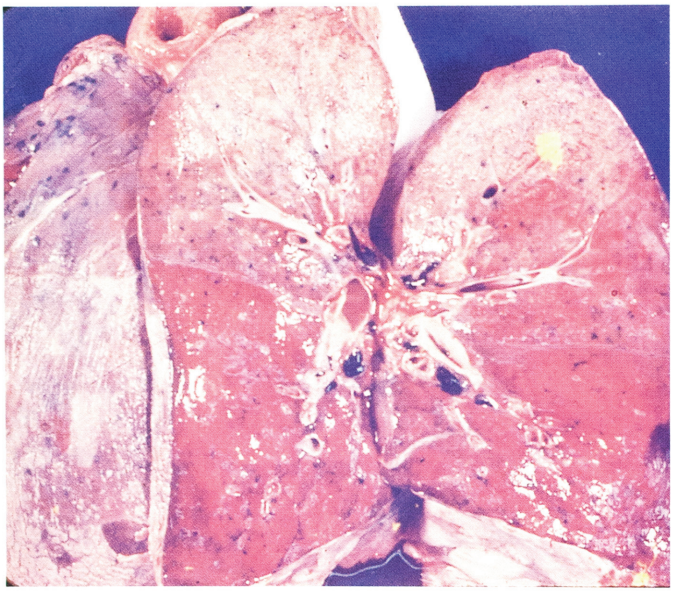
COLOR FIGURE 37-3. Arc welder's lung. (**A**) Intraalveolar and interstitial accumulation of iron oxide particles is seen in the lung of an arc welder. (**B**) The black center and golden brown outer rim of many of the particles is characteristic of iron oxides. (H & E stain; low magnification; courtesy of George T. Hensley, M.D., Miami, FL.)



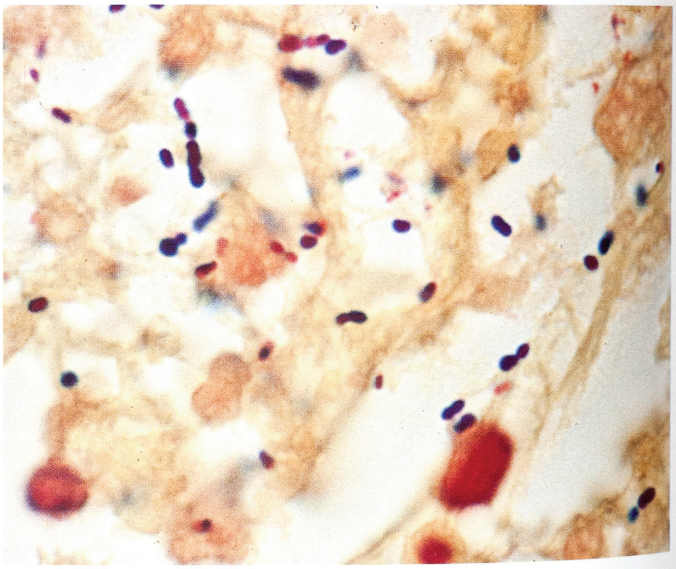
COLOR FIGURE 37-4. Nuclepore filter preparation of a lung tissue digest from a gray-iron foundry worker reveals two ferruginous bodies with black central cores composed of iron oxide. (Low magnification.)



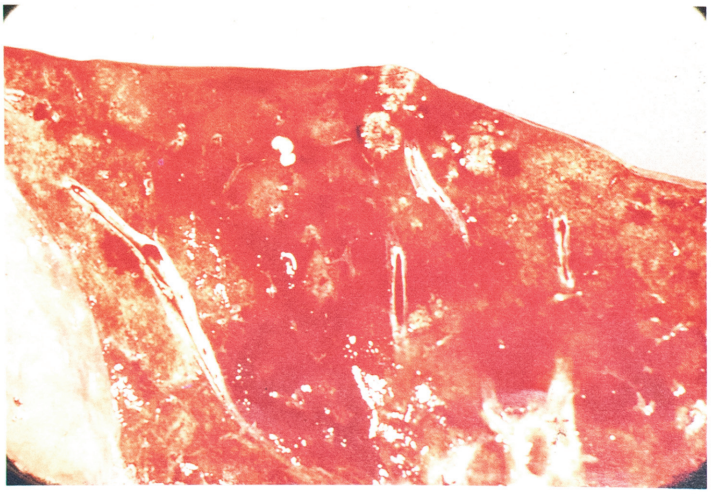
COLOR FIGURE 37-5. A sputum cytology specimen from the same patient as in Fig. 37-10 shows numerous, variably sized vacuoles within the cytoplasm of macrophages. The vacuoles are considerably larger than those present in the foamy macrophages typical of endogenous lipoid pneumonia. (Papanicolaou stain; high magnification; courtesy of W. Johnston, M.D., Durham, NC.)



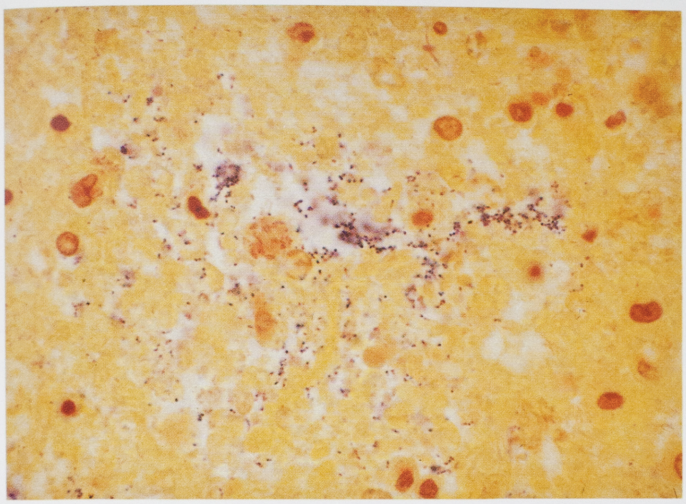
COLOR FIGURE 38-1. Gross features of pneumococcal pneumonia involving the left lung include red hepatization preferentially involving the lower lobe, in contrast with gray hepatization in the left upper lobe. Extensive fibrinous pleuritis is also present. (Contributed by the editor.)



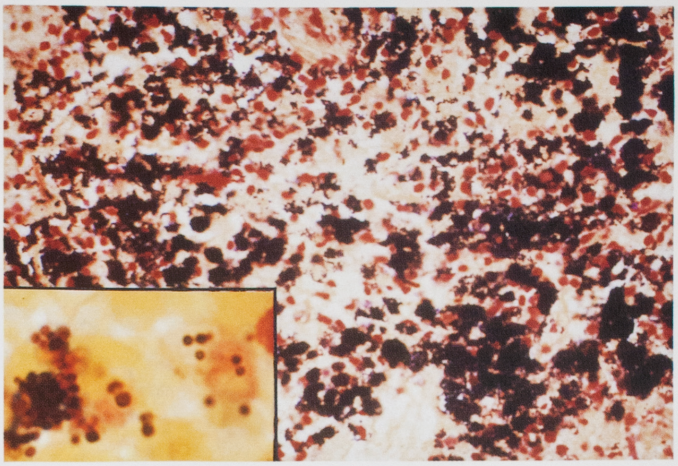
COLOR FIGURE 38-2. Gram-positive cocci in pairs and short chains are seen in the fibrinoleukocytic exudate of a patient with pneumococcal pneumonia. (Brown & Brenn stain; oil immersion; contributed by the editor.)



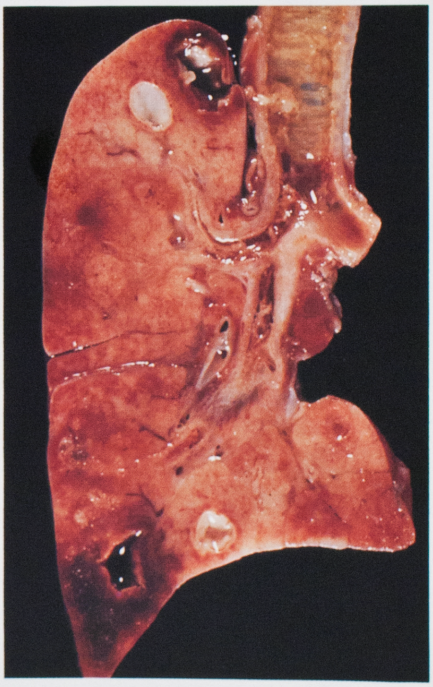
COLOR FIGURE 38-3. Gross features of the lung of a patient with culture-proven β-hemolytic streptococcal pneumonia include red patches of confluent bronchopneumonia with microabscesses. (Contributed by the editor.)



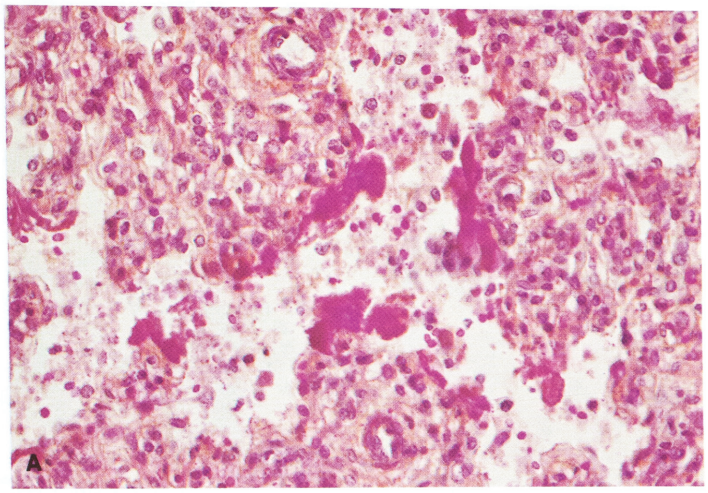
COLOR FIGURE 38-4. A necrotizing lesion of streptococcal pneumonia contains collections of gram-positive cocci. (Brown-Hopps stain; high magnification; contributed by P. Angritt, M.D., Washington, DC.)

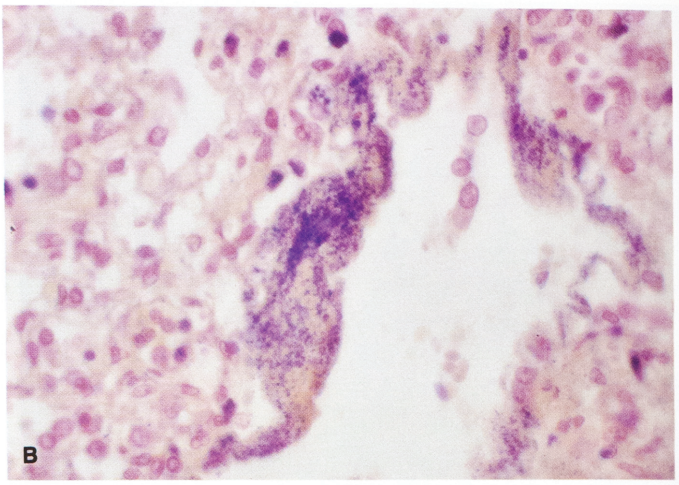


COLOR FIGURE 38-5. Innumerable clusters of gram-positive staphylococci are seen in a patient with pneumonia. (Brown-Hopps stain; intermediate magnification; courtesy of P. Angritt, M.D., Washington, DC.) Intracellular and extracellular organisms may be present (*inset*). (Brown-Hopps stain; oil immersion.)

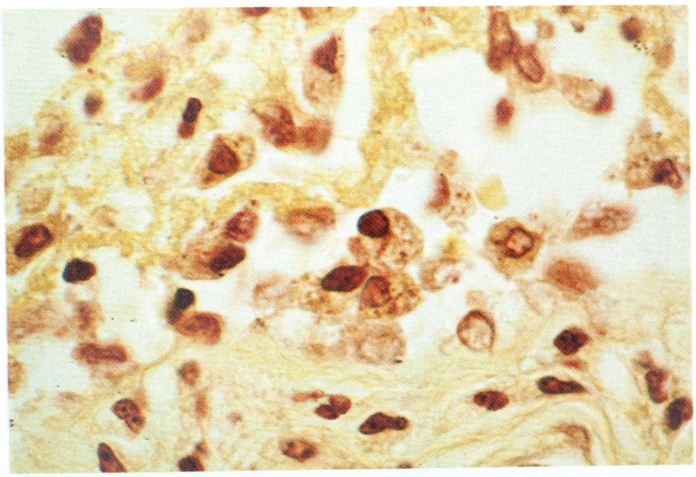


COLOR FIGURE 38-6. A gross specimen of lung from a child with staphylococcal pneumonia shows patchy pneumonic consolidations and cystic abscesses, some of which are hemorrhagic. The subpleural location of the cystic abscesses is characteristic. (Contributed by the editor.)



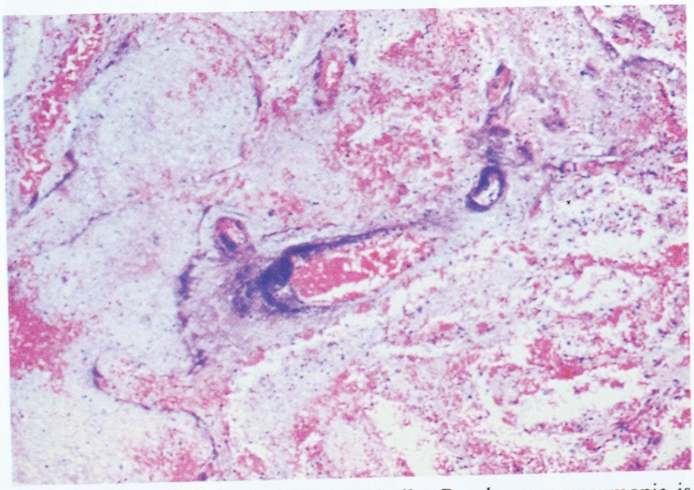


COLOR FIGURE 38-7. A newborn infant with fatal staphylococcal pneumonia died following premature rupture of placental membranes. (**A**) The lungs exhibit the appearance of hyaline membrane disease. (H & E stain; intermediate magnification.) (**B**) The bluish discoloration of the hyaline membranes is produced by colonies of staphylococci. (Brown & Brenn stain; high magnification; contributed by the editor.)

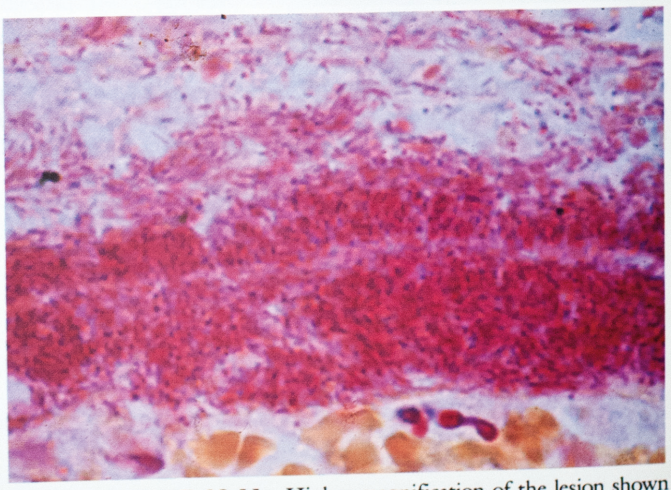


COLOR FIGURE 38-8. Sparse intracellular coccobacillary forms are seen in alveolar macrophages in a patient with a well-documented case of *Haemophilus influenzae* pneumonia. (Brown-Hopps stain; oil immersion; courtesy of P. Angritt, M.D., Washington, DC.)

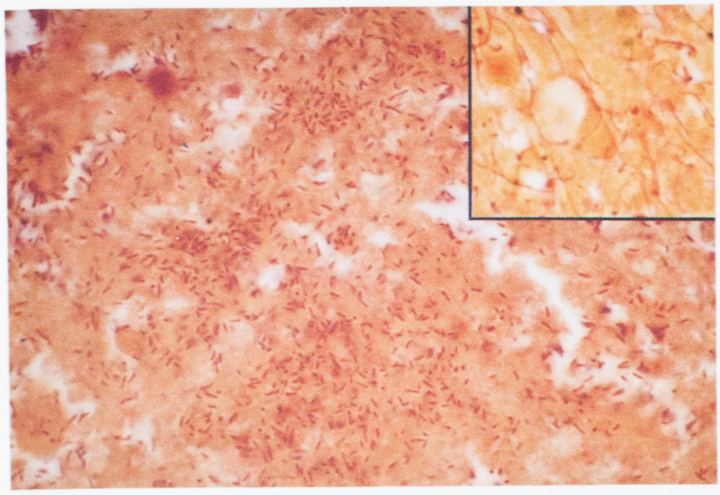
COLOR FIGURE 38-9. Gross appearance of *Pseudomonas* pneumonia shows patchy, confluent hemorrhages surrounding the punctate foci of necrosis. (Contributed by the editor.)



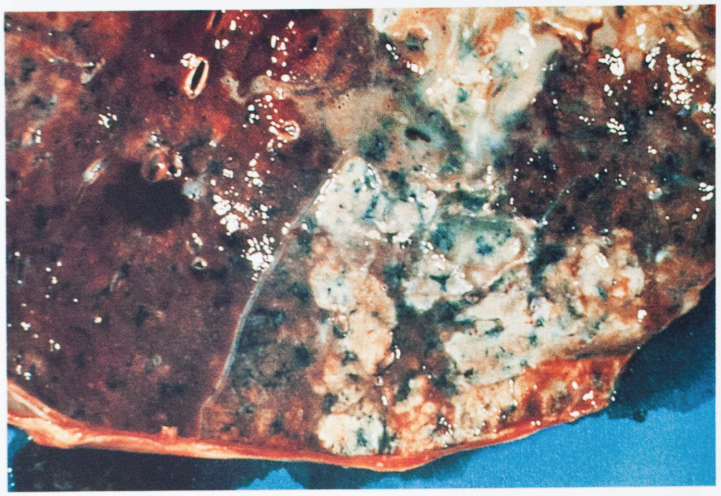
COLOR FIGURE 38-10. Histologically, *Pseudomonas* pneumonia is characterized by hemorrhage and scant numbers of recognizable leukocytes as a result of karyolysis. The contour of the blood vessels is deeply basophilic as a result of proliferating bacteria. (H & E stain; low magnification; contributed by the editor.)



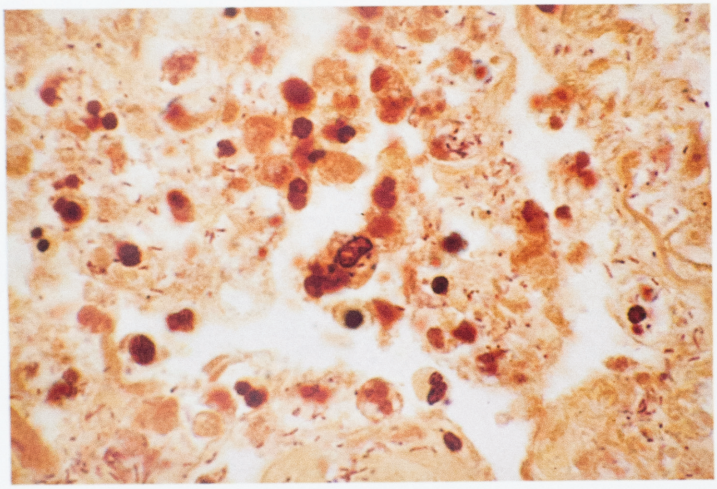
COLOR FIGURE 38-11. Higher magnification of the lesion shown in Color Figure 38-10 demonstrates heavy colonization of the arterial wall by *Pseudomonas aeruginosa*. (Brown & Brenn stain; high magnification; contributed by the editor.)



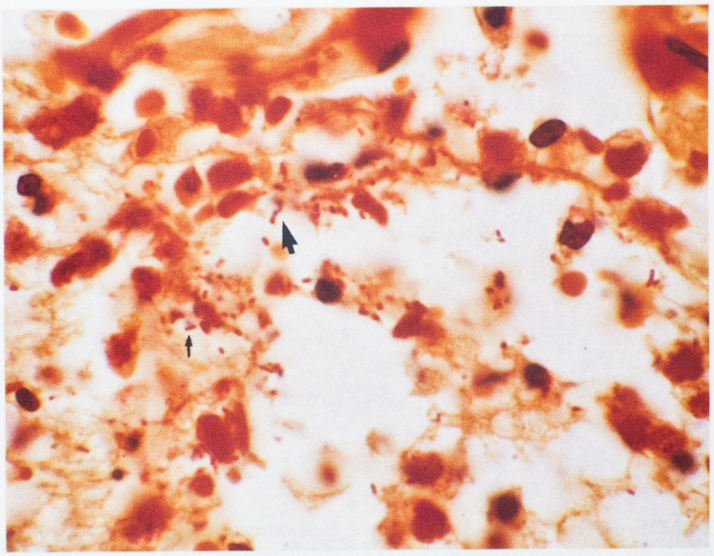
COLOR FIGURE 38-12. Numerous gram-negative rods are present in a patient with *Pseudomonas aeruginosa* pneumonia. There is a paucity of leukocytes. (Brown-Hopps stain; high magnification.) *Pseudomonas aeruginosa* can appear as a filamentous bacteria (*inset*). (Brown-Hopps stain; oil immersion; contributed by P. Angritt, M.D., Washington, DC.)



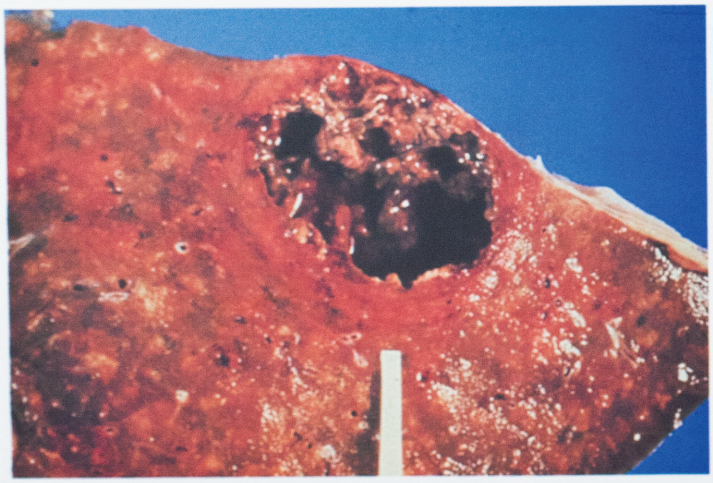
COLOR FIGURE 38-13. A gross specimen from a man who died of *Klebsiella* pneumonia shows consolidation of lung tissue and many confluent abscesses that contain a creamy, mucoid pus. (Courtesy of Luis Alvarez, M.D., Miami, FL.)



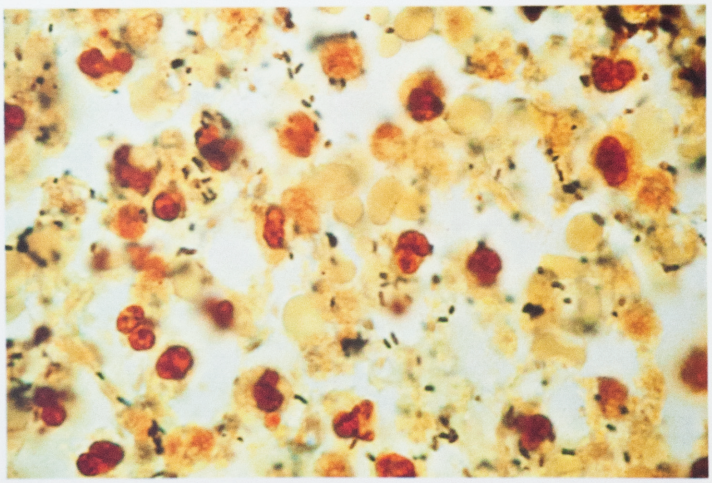
COLOR FIGURE 38-14. Myriads of gram-negative bacilli are present in the center of an abscess in a patient with *Klebsiella* pneumonia. (Brown-Hopps stain; oil immersion; courtesy of P. Angritt, M.D., Washington, DC.)



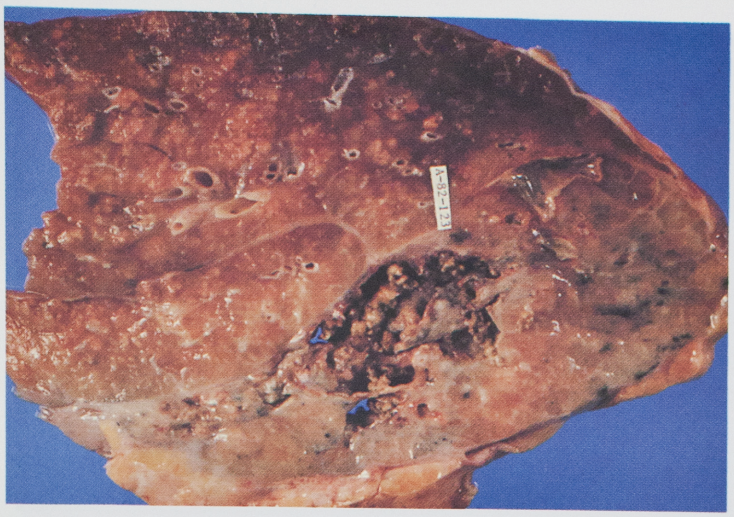
COLOR FIGURE 38-15. Intraalveolar neutrophilic exudate with organisms is seen (*arrows*) in a patient with a documented case of *Escherichia coli* pneumonia. (Brown-Hopps stain; oil immersion.)



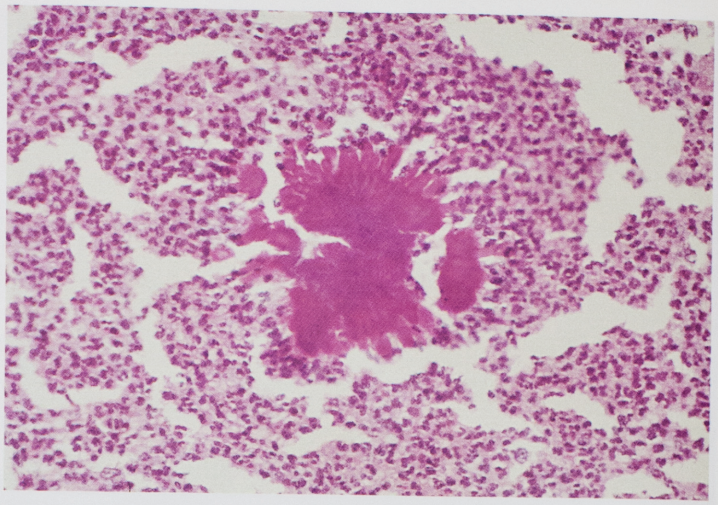
COLOR FIGURE 39-1. Pneumonia with abscess of the right lower lobe occurred in a man with carious teeth and extensive periodontal disease. The abscess was darkly hemorrhagic and exuded a rancid odor. Cultures under strict anaerobic conditions grew *Bacteroids melaninogenicus*. (Courtesy of Luis Alvarez, M.D., Miami, FL.)



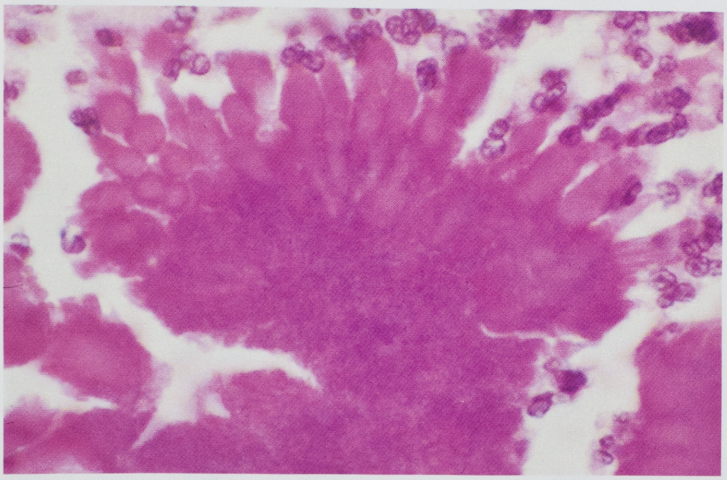
COLOR FIGURE 39-2. Microscopic view of the lung in the same patient with *Legionella* pneumonia as in Figure 39-4 and 39-5. Numerous coccobacillary organisms are present both within and outside the leukocytes. (Dieterle silver stain; oil immersion; contributed by the editor.)



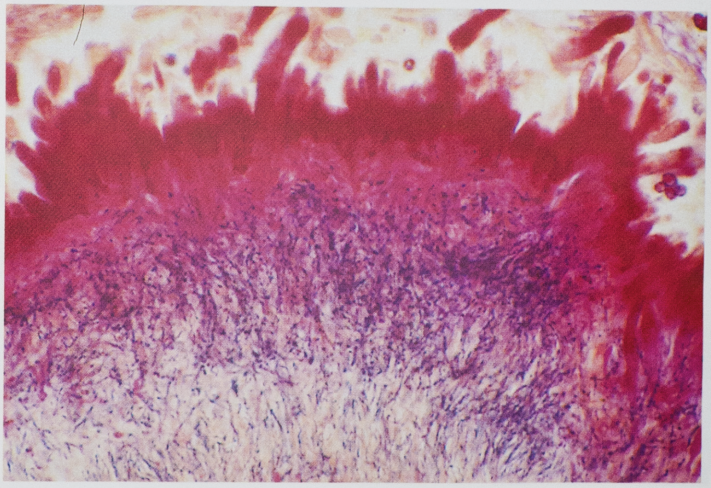
COLOR FIGURE 40-1. A gross view of the lung in a patient with actinomycosis shows a large cavitary lesion of the right upper lobe, extensive pneumonic consolidation, and marked pleural fibrosis. (Courtesy of Bolivar Kunhardt, M.D., Miami, FL.)



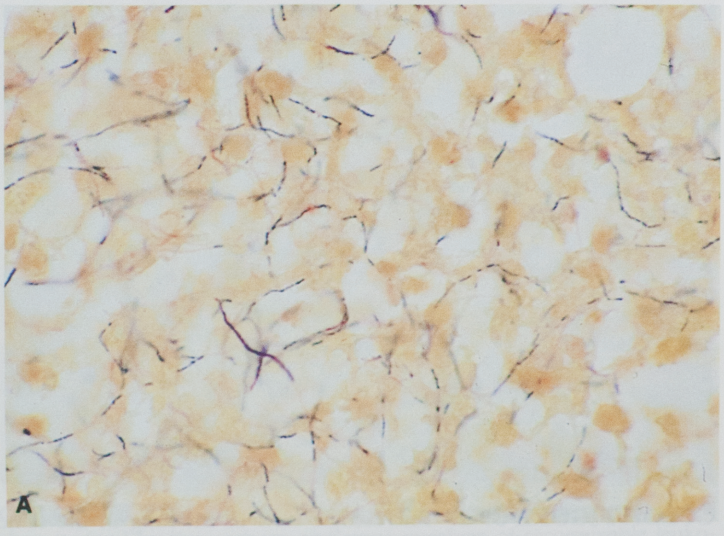
COLOR FIGURE 40-2. Actinomycotic granule with associated suppurative inflammation in lung parenchyma. (H & E stain; low magnification.)

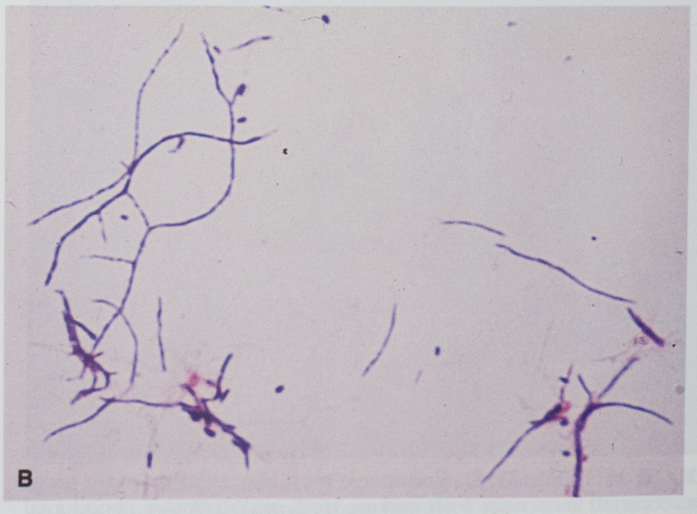


COLOR FIGURE 40-3. The same actinomycotic granule as in Color Figure 40-2 demonstrates prominent club-shaped endings at its periphery. (H & E stain; high magnification.)

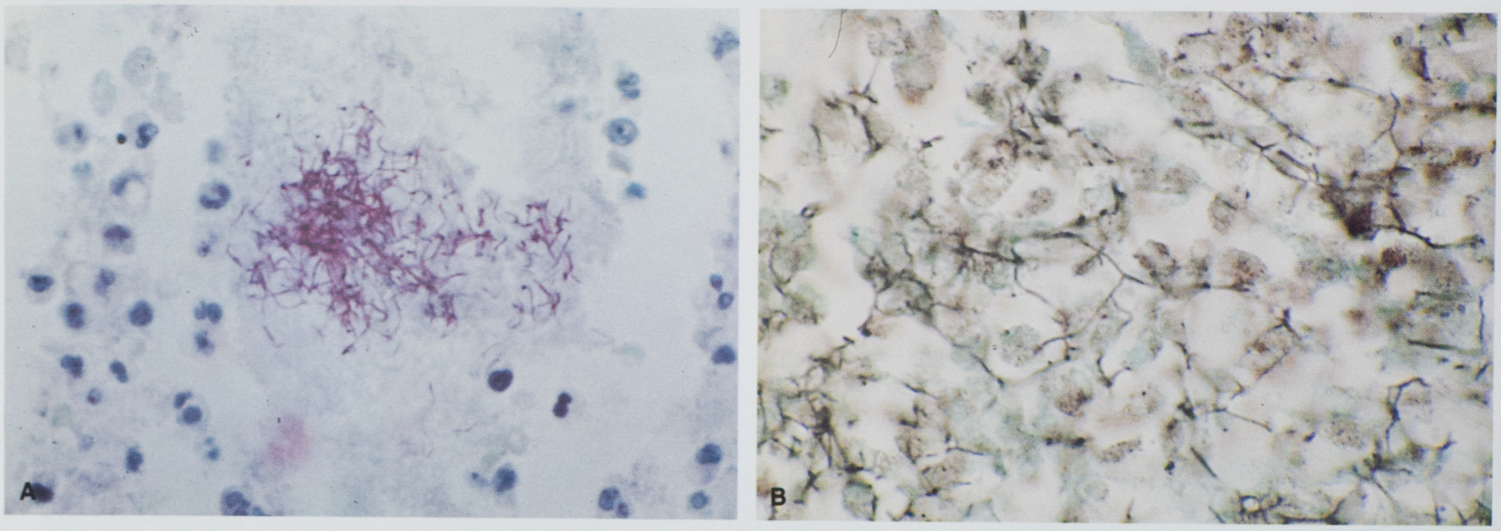


COLOR FIGURE 40-4. An actinomycotic granule with numerous, radially oriented, gram-positive filamentous bacteria and peripheral clubs at its edge. (Brown-Hopps stain; high magnification.)

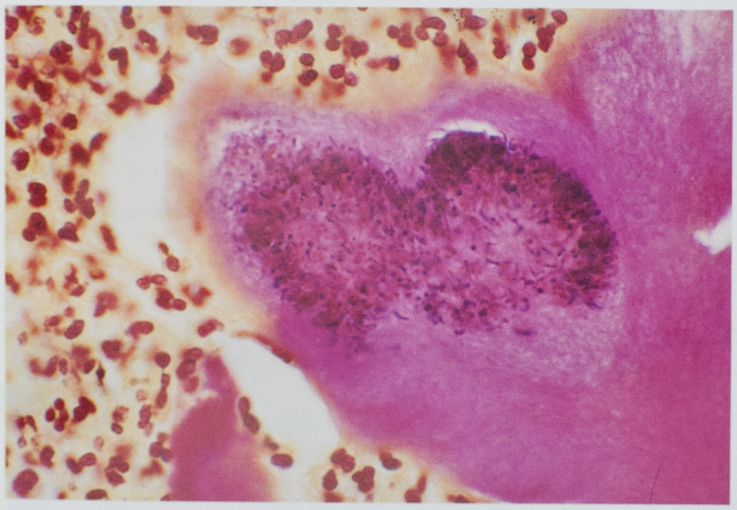




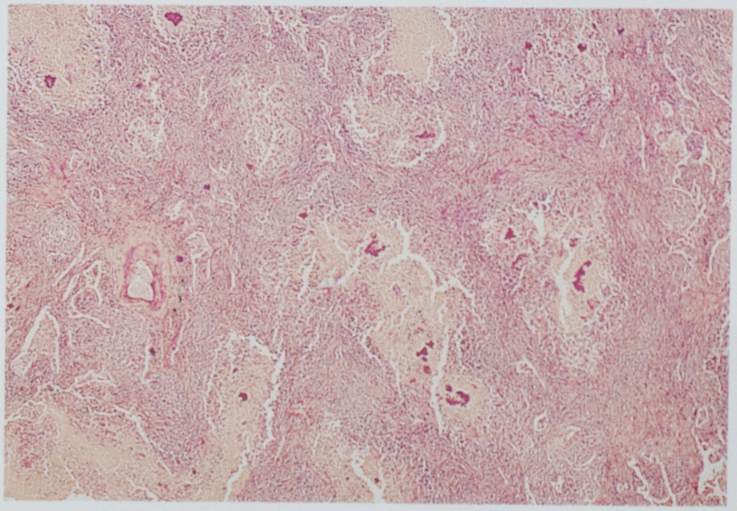
COLOR FIGURE 40-5. (**A**) A lesion of pulmonary nocardiosis has gram-positive filamentous and branching bacteria in alveolar exudate. (Brown & Brenn stain, oil immersion. (**B**) Touch preparation of a nocardial lesion shows the same features. (Gram stain; oil immersion; contributed by the editor.)



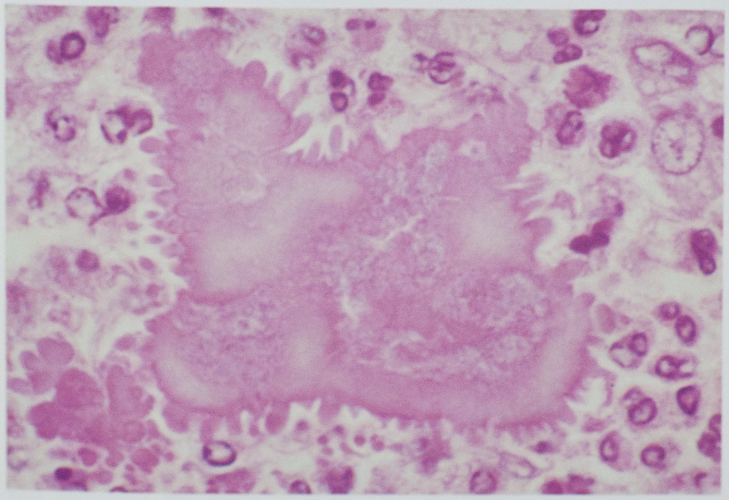
COLOR FIGURE 40-6. (**A**) At high magnification, the filamentous bacteria *Nocordia asteroides* demonstrate their acid-fast nature (Coates modified Fite stain; oil immersion.) (**B**) *N. asteroides* can be demonstrated by silver impregnation. (GMS stain; oil immersion.)



COLOR FIGURE 40-7. A granule of *Streptomyces* is in the center of a suppurative abscess of the subcutis. The center is amorphous, and the blunted edges are light purple with pink patches. (Brown-Hopps stain; intermediate magnification.)

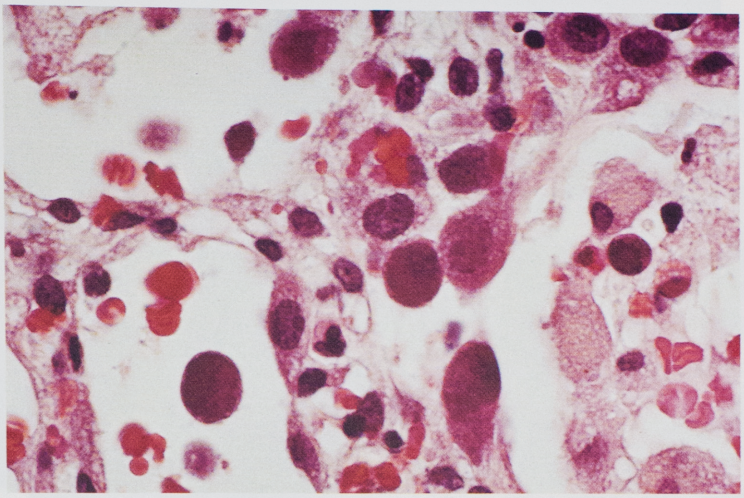


COLOR FIGURE 40-8. In suppurative lung lesions caused by botryomycosis, granules are present within microabcesses. (Brown-Hopps stain; low magnification.)

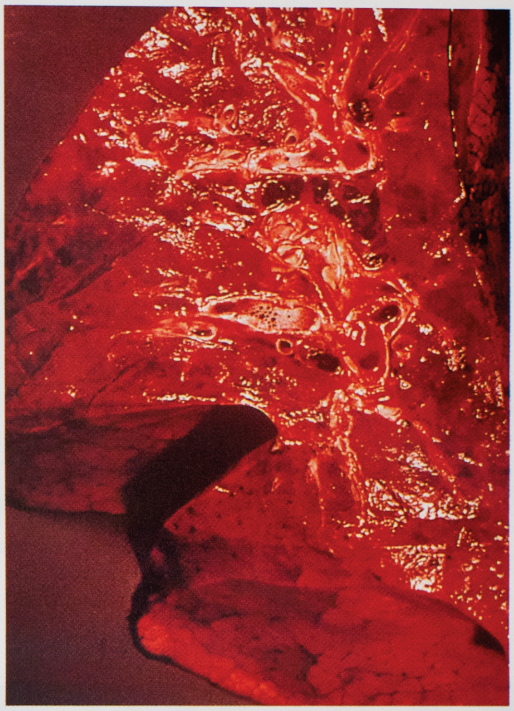


COLOR FIGURE 40-9. Clumps of bacteria are surrounded by an amorphous eosinophilic coating (*i.e.*, Splendore-Hoeppli phenomenon) in the lung of a patient with botryomycosis. (H & E stain; high magnification.)

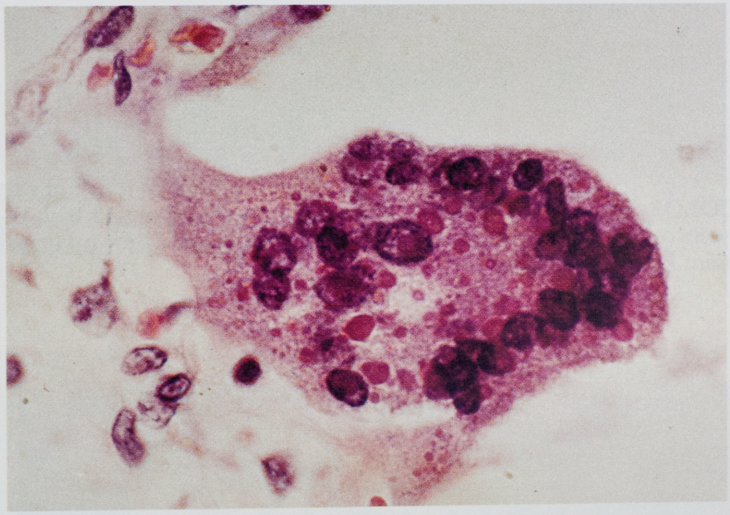
COLOR FIGURE 42-1. Gross appearance of the lung of a child who died of disseminated varicella infection. Hemorrhagic foci and blisters are present in the parenchyma and pleura. (Courtesy of George T. Hensley, M.D., Miami, FL.)



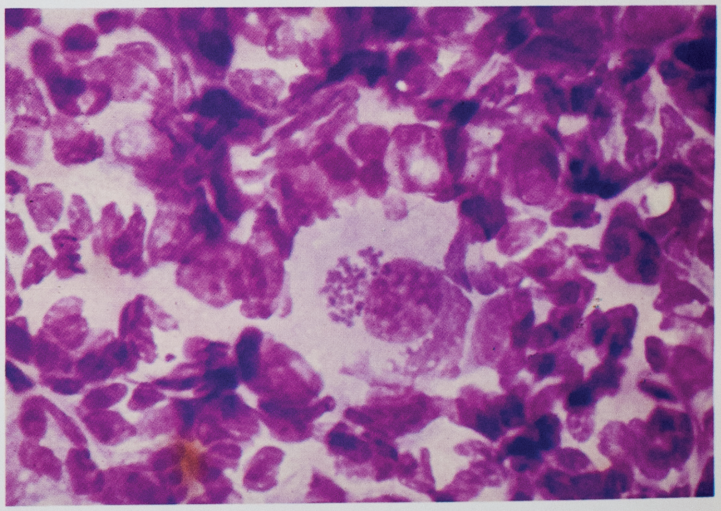
COLOR FIGURE 42-2. In adenovirus pneumonia, several enlarged smudge cells contain a single intranuclear basophilic inclusion. (H & E stain; high magnification; courtesy of D. Schwartz, M.D., Grady Memorial Hospital, Atlanta, GA.)



COLOR FIGURE 42-3. Gross appearance of the lung at postmortem from a patient with well-documented influenzae pneumonia. The lungs are heavy, hemorrhagic, and meaty in consistency. Foamy edema fluid exudes from the bronchi. Microscopically, there was a picture of diffuse alveolar damage with extensive hyaline membrane formation. (Contributed by the editor.)



COLOR FIGURE 42-4. In measles virus pneumonia, a multinucleated cell demonstrates numerous eosinophilic intranuclear and intracytoplasmic inclusions. (H & E stain; high magnification; courtesy of D. Schwartz, M.D., Atlanta, GA.)



COLOR FIGURE 42-5. Intracytoplasmic inclusions of *Chlamydia trachomatis* are seen in a conjunctival scraping of a newborn infant. (Giemsa stain; high magnification; contributed by the editor.)

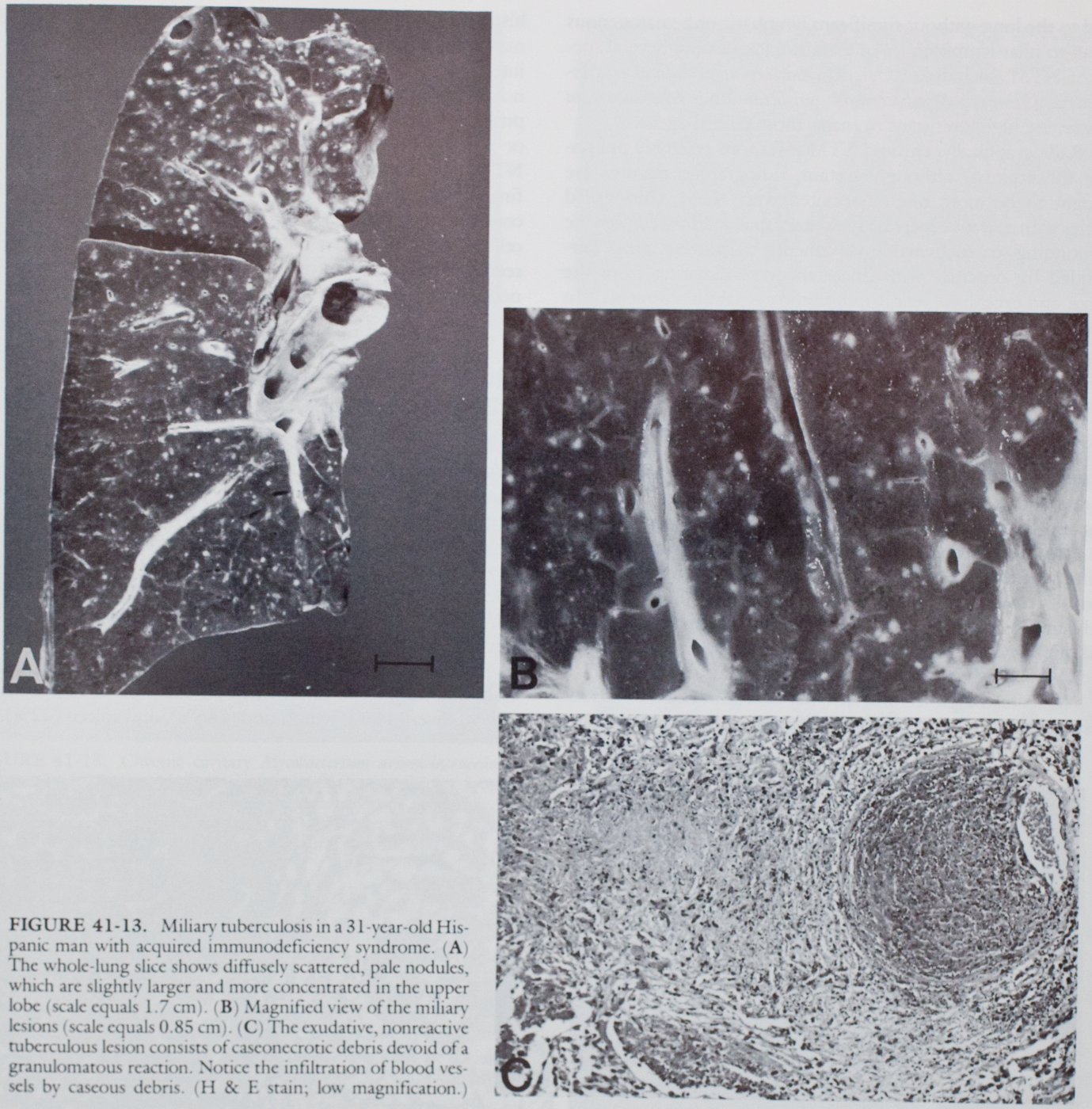


FIGURE 41-13. Miliary tuberculosis in a 31-year-old Hispanic man with acquired immunodeficiency syndrome. (**A**) The whole-lung slice shows diffusely scattered, pale nodules, which are slightly larger and more concentrated in the upper lobe (scale equals 1.7 cm). (**B**) Magnified view of the miliary lesions (scale equals 0.85 cm). (**C**) The exudative, nonreactive tuberculous lesion consists of caseonecrotic debris devoid of a granulomatous reaction. Notice the infiltration of blood vessels by caseous debris. (H & E stain; low magnification.)

NTM are shown in Table 41-1. *Mycobacterium avium-intracellulare* (MAI) has emerged as the predominant pathogen of this group.[36,37]

Pulmonary disease may be the result of airborne infection from the environment, or the lung may be secondarily infected as part of a disseminated process from an extrapulmonary primary site, such as the gastrointestinal tract. Because NTM are organisms of relatively low pathogenicity, saprophytic colonization of the lung must be differentiated from overt pulmonary disease. The repeated recovery of large numbers of MAI or *Mycobacterium kansasii* from the sputum is usually associated with lung disease, but repeated recovery of other less pathogenic NTM, such as *Mycobacterium fortuitum* or *Mycobacterium gordonae*, may represent colonization with no invasive lung disease. Granulomas confirmed by transbronchial biopsy combined with recovery of NTM in sputum is regarded as *prima facie* evidence of NTM pulmonary disease. Detailed diagnostic criteria for pulmonary disease caused by NTM have been published.[37]

Chronic Progressive Pulmonary Disease

Pulmonary infection with NTM clinically resembles chronic progressive infection with *Mycobacterium tuberculosis* and usually affects persons with underlying pulmonary disorders such as silicosis or another of the pneumoconioses, chronic obstructive pulmonary disease, prior tuberculosis, bronchiectasis, and esophageal disease with chronic aspiration.[36] An increasing number of patients, particularly elderly Caucasian women, with pulmonary NTM infection have no obvious predisposing chronic pulmonary disease.[38] After inhalation of the organisms, the primary infection is con-

fined to the lung without significant lymphatic or hematogenous spread to hilar lymph nodes or extrathoracic viscera. Several species of NTM, including MAI, *Mycobacterium scrofulaceum*, *Mycobacterium simiae*, *Mycobacterium fortuitum* and *Mycobacterium chelonae*, are highly resistant to many antimicrobial agents.

Radiographically, chronic NTM infections resemble pulmonary tuberculosis, although certain radiographic features are thought to be more often associated with NTM: thin-walled cavities with a relative increase in cavitary space compared with the surrounding parenchymal involvement; translucent areas surrounded by opacities with linear shadows radiating from the lesion; and excessive pleural and peribronchial involvement.[36] In patients with no underlying lung disease, the chest radiograph frequently indicates slowly progressive, discrete pulmonary nodules involving the upper lobe.[38] None of these radiographic features is specific for NTM infection.

Chronic lung disease caused by NTM cannot reliably be differentiated grossly or histopathologically from that caused by *M. tuberculosis*.[39] The predominant lesions include caseating granulomas and cavities associated with various degrees of fibrosis (Figs. 41-14 and 41-15). Acid-fast bacilli are usually sparse within the caseum of chronic NTM infections. On the basis of acid-fast stains, species of NTM cannot be differentiated from each other or from *M. tuberculosis*, except that *M. kansasii* often appears large and banded. In patients with lipoid pneumonia and *M. fortuitum* and *M. chelonae* infection, lipid droplets may be impregnated with acid-fast bacilli in the absence of significant inflammation.[40]

Other histologic features that may be seen in NTM infections, possibly more frequently than in tuberculosis, are abundant foamy histiocytes, granulomatous endobronchitis, epithelioid granulomas without caseation, nonspecific organizing pneumonia, and interstitial fibrosis without granulomas.[39,41] Most patients with nongranulomatous lesions are immunocompromised, and it is probable that these atypical lesions are merely colonized by NTM or represent a biopsy sampling error. Approximately 20% of NTM infections are associated with dimorphic granuloma, defined by Reid and Wolinsky as a focus of central suppuration containing numerous neutrophils and surrounded by epithelioid cells and macrophages (Fig. 41-16).[4,42] Similar granulomas are seen in tuberculosis, especially during the early stages of caseation necrosis and if the necrosis contains numerous tubercle bacilli or is undergoing liquefaction.

Disseminated Nontuberculous Mycobacterial Disease

Before the AIDS epidemic, NTM were an infrequent cause of disseminated disease in immunocompromised hosts.[36,43] The organisms most likely to produce disseminated disease in this population were, in order of decreasing frequency, MAI, *M. kansasii*, *M. scrofulaceum* or another of the scotochromogens, and the rapid growers (*e.g.*, *M. fortuitum* and *M. chelonae*). Disseminated MAI infection is seen at autopsy in approximately 50% of patients with AIDS.[44] Almost every other recognized species of NTM infrequently infects AIDS patients.

Among non-AIDS patients with disseminated NTM infection, the lung is involved in 65%, followed by bone marrow (46%), liver (46%), lymph node (46%), and spleen (22%).[43] In

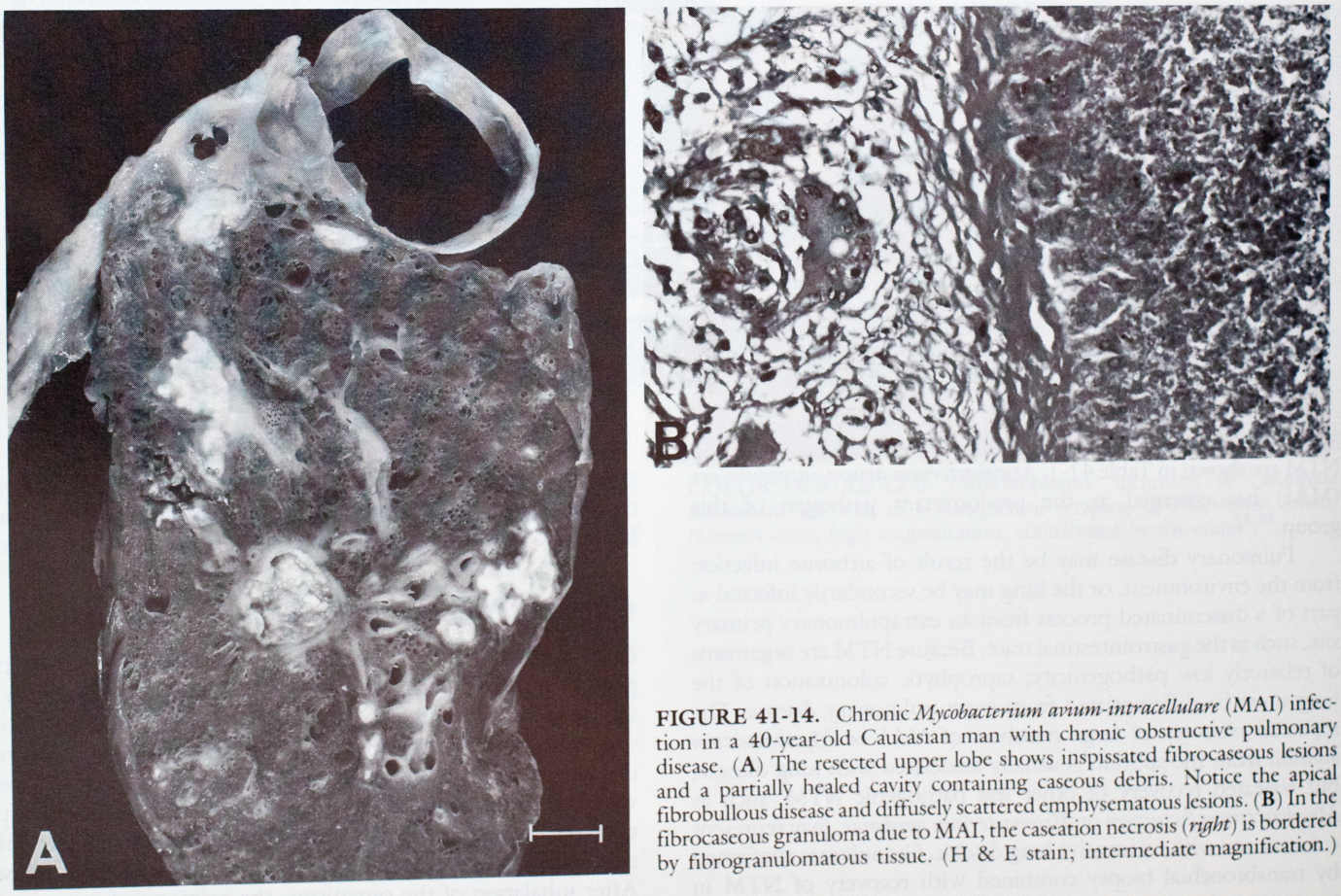


FIGURE 41-14. Chronic *Mycobacterium avium-intracellulare* (MAI) infection in a 40-year-old Caucasian man with chronic obstructive pulmonary disease. (**A**) The resected upper lobe shows inspissated fibrocaseous lesions and a partially healed cavity containing caseous debris. Notice the apical fibrobullous disease and diffusely scattered emphysematous lesions. (**B**) In the fibrocaseous granuloma due to MAI, the caseation necrosis (*right*) is bordered by fibrogranulomatous tissue. (H & E stain; intermediate magnification.)

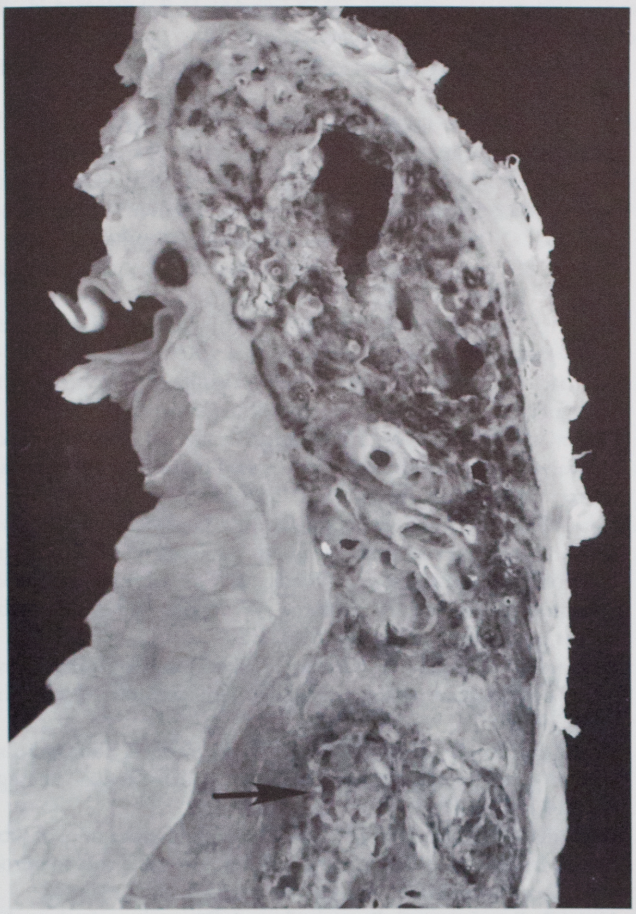


FIGURE 41-15. Chronic cavitary *Mycobacterium avium-intracellulare* infection in a 77-year-old Caucasian man who was a former foundry worker with simple silicosis. A large, irregular cavity is surrounded by diffuse granulomatous pneumonia in the left upper lobe. Notice the scattered, black, silicotic nodules, severe pleural fibrosis, and lower lobe bronchiectasis (*arrow*).

the non-AIDS population, the morphology of pulmonary lesions has been infrequently described. Lesions in extrapulmonary sites are composed of poorly formed granulomas containing loose aggregates of mononuclear cells, infrequent epithelioid cells, significant numbers of neutrophils, and focal necrosis.[45] In most cases, acid-fast bacilli are scarce, but in one large series, 20% of patients, who were mainly younger than 3 years of age, demonstrated tremendous numbers of bacilli within macrophages, just as in lepromatous leprosy.[43]

Disseminated MAI disease in AIDS patients predominantly involves the reticuloendothelial system, especially the spleen.[44] The portal of entry of MAI is thought to be the gastrointestinal tract, and stool smears and cultures for acid-fast bacilli are often positive. Disseminated MAI infection causes a chronic, wasting illness with persistent fever, diarrhea, abdominal pain, weight loss, and anemia.[44] Blood cultures are frequently positive for MAI. Disseminated MAI infection tends to occur late in the course of AIDS, when CD4 lymphocyte counts are most depressed and the patient has been debilitated by other complications and opportunistic infections. MAI has been isolated at autopsy from the lungs of 34% of AIDS patients with disseminated infection, but clinically important pulmonary involvement is unusual.[46] Rarely is disseminated MAI infection the immediate cause of death of the AIDS patient.

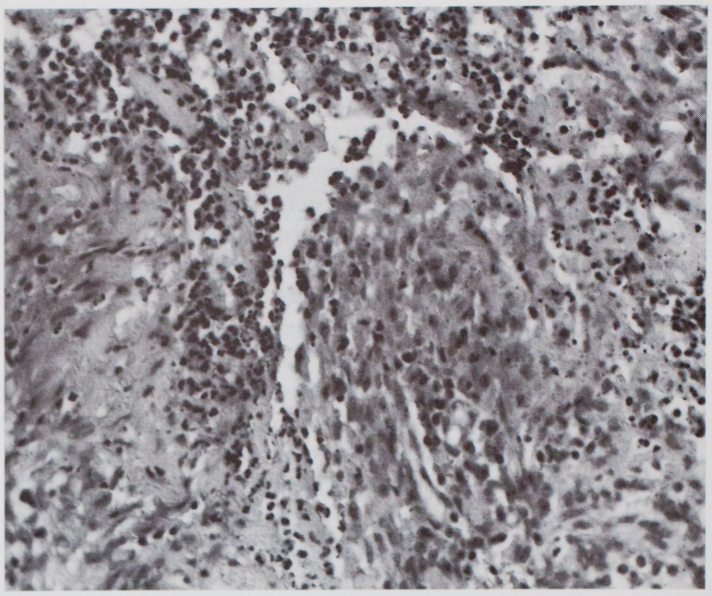


FIGURE 41-16. In dimorphic granuloma caused by *Mycobacterium chelonae*, a peripheral rim of epithelioid cells encompasses a central area of suppurative necrosis, in which neutrophils are numerous. (H & E stain; intermediate magnification.)

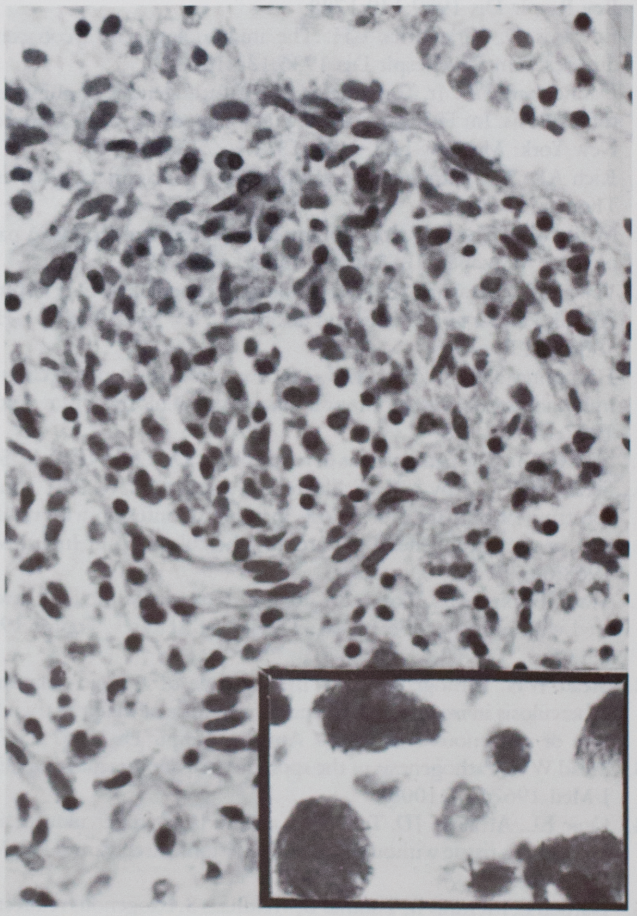


FIGURE 41-17. In disseminated *Mycobacterium avium-intracellulare* infection in a patient with acquired immunodeficiency syndrome, the poorly formed granulomas, composed of loosely cohesive histiocytes, efface the lymph node architecture. (H & E stain; high magnification.) Innumerable acid-fast bacilli are present within the cytoplasm of histiocytes and in the extracellular space (*inset*). (Ziehl-Neelsen stain; oil immersion view.)

Discrete or confluent, yellow, miliary granulomas are concentrated in the lymph nodes, spleen, and liver, and they infrequently invade the lung.[47] Histologically, lesions at all sites consist of poorly formed granulomas or loose aggregates of gray-to-blue striated histiocytes, which usually contain innumerable acid-fast bacilli (Fig 41-17). In the small bowel, periodic acid-Schiff–positive macrophages laden with mycobacteria histologically resemble Whipple disease. Within the lung, acid-fast bacilli can be identified histologically in approximately 13% of patients with disseminated infection. Pulmonary lesions attributable to MAI are rarely found histologically, and even then, they are usually overshadowed by coexistent opportunistic infections.[46] Histiocytes laden with mycobacteria occasionally colonize preexistent cavities, and extension of granulomatous infection into the lung from adjacent infected lymph nodes can occur. If disease extends into the central bronchi, the tumorlike masses of granulomatous tissue can obstruct the airways.[48] Necrotizing pulmonary parenchymal granulomas, such as those in patients without AIDS, are rarely identified.

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