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The Pathology of Community-Acquired Pneumonia

CLAUDIA MOLINA AND DAVID H. WALKER

Introduction

The respiratory tract is constantly confronted with numerous noxious agents present in the environment, including a variety of microbial pathogens. Fortunately, it contains a complex host defense system that protects the lung against potentially injurious agents. This system consists of structural, mechanical, secretory, and cellular mechanisms that are designed to eliminate or contain the majority of these pathogenic agents (Canto et al., 1994). Indeed, the lower respiratory tract is normally sterile despite its continuous exchange of gases with the external environment.

Pulmonary infection can result whenever these defense mechanisms are impaired. For example, loss or suppression of the cough and gag reflexes may lead to aspiration of oropharyngeal secretions and gastric contents; smoke, viral infection, or chemical inhalation may alter the mucociliary clearance function of the airways' epithelial cells; exposure to increased oxygen tension, tobacco smoke, or alcohol may impair the phagocytic activity of the alveolar macrophages; accumulation of airways secretions and pulmonary edema may impair clearance and favor bacterial growth (Canto et al., 1994; Kobzik & Schoen, 1994).

Pulmonary defenses are also affected by the overall immunocompetence of the individual. Factors that impair the resistance of the host include immunosuppressive drug therapy, malnutrition, chronic debilitating diseases, and generalized immunodeficiency diseases including AIDS (Linder & Sisson, 1994). Most microorganisms that cause pneumonia are normal inhabitants of the oropharynx and nasopharynx and reach the alveoli by aspiration of secretions. Other routes of infection include inhalation of aerosols containing the microorganisms from the environment, hematogenous dissemination from an infectious focus elsewhere, and rarely, spread of bacteria from an adjacent site (Barnes, 1994).

Traditionally, the pathologic characterization of pneumonia has been by macroscopic distribution. It has been classified as either lobar pneumonia or bronchopneumonia, but these classic categorizations are often difficult to apply, because the patterns overlap.

Lobar Pneumonia

Lobar pneumonia is an infectious process that involves the greater part of a lobe of the lung and classically affects the entire lobe. The consolidation is delimited by the pleura or by a major fissure. Laennec (1781–1826) made a large number of contributions to medicine, but one of the most significant was his accurate description of the basic progression of the consolidative process in lobar pneumonia (Epifano & Brandstetter, 1993; Loosly, 1940). Four stages of the inflammatory response have been described. Two or more stages in the

CLAUDIA MOLINA AND DAVID H. WALKER • University of Texas Medical Branch, Galveston, Texas 77555-0609.

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process of consolidation may coexist in the same lung (Berry, 1920). The first stage, congestion, occurs in the first 24 hours of infection. The lung is heavy, and its parenchyma is red and doughy. Microscopically, there is vascular engorgement, and the alveolar spaces contain edema fluid, scattered neutrophils, desquamated epithelium, and numerous bacteria (Kobzik & Schoen, 1994; Winn & Chandler, 1994).

In the second stage, termed red hepatization, the lung parenchyma is distinctly red, firm, airless, noncrepitant, and heavy with a granular consistency. Microscopically, the alveolar spaces are filled with red blood cells, neutrophils, desquamated epithelial cells, and fibrin. The stage of gray hepatization is characterized by a dense, friable, gray-brown to yellow, and dry pulmonary parenchyma due to progressive disintegration of red cells and the persistence of a fibrinopurulent exudate. Microscopically, there is an extensive alveolar exudate composed of abundant neutrophils and macrophages, and bacteria are generally not identifiable. Cellular outlines are indistinct, and hemosiderin pigment may be evident (Kobzik & Schoen, 1994; Berry, 1920; Winn & Chandler, 1994).

In the final stage of resolution, the consolidated alveolar exudate undergoes progressive enzymatic digestion. The residual debris is resorbed, ingested by macrophages, or coughed up, and the normal pulmonary architecture is restored (Kobzik & Schoen, 1994). When the inflammation extends across the pleura, there is a pleural fibrinous reaction that may similarly resolve or undergo organization, producing a roughened pleural surface with fibrous thickening or permanent fibrous thickening (Kobzik & Schoen, 1994; Winn & Chandler, 1994). The time course for the inflammatory process is variable. The duration of the second and third phases has been estimated to be 2 to 3 days each. The time of maximal consolidation has been estimated to be 2 to 6 days (Winn & Chandler, 1994). Lobar pneumonia rarely progresses through all four stages because they are modified by antimicrobial therapy.

Community-acquired lobar pneumonia is classically associated with *Streptococcus pneumoniae,* but *Klebsiella pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Legionella pneumophila,* and streptococci may also produce a typical lobar configuration (Kobzik & Schoen, 1994; Winn & Chandler, 1994; Winn & Myerowitz, 1981). Individual cases have been ascribed to *Neisseria gonorrhoeae* (Enos et al., 1980), *Mycoplasma pneumoniae* (Macfarlane et al., 1979), adenovirus type 7 (Leers et al., 1981), *Aspergillus* spp. (Young et al., 1969), *Proteus* spp. (Seriff, 1969), *Pseudomonas aeruginosa* (Krafft, 1968), and in patients with HIV infection, *Pneumocystis carinii* (Miller et al., 1994).

Bronchopneumonia

Bronchopneumonia is a patchy consolidation of the lung that involves one or several lobes. It usually involves the dependent and posterior portions of the lung, because of the tendency of secretions to gravitate into the lower lobes. Grossly, the consolidated areas usually have poorly defined margins and appear dry, granular, and gray-red to yellow (Kobzik & Schoen, 1994). In some cases, consolidation affects entire lobules with normal parenchyma on the other side of the interlobular septum. Histologically, there is a suppurative neutrophilic exudate that fills bronchi, bronchioles, and adjacent alveoli. The common causative agents are streptococci, staphylococci, pneumococci, *H. influenzae, P. aeruginosa,* and coliforms (Kobzik & Schoen, 1994).

Lobar pneumonia and bronchopneumonia can undergo complete resolution, but abscess formation may follow with extensive necrosis of the pulmonary parenchyma, particularly with infections caused by type 3 pneumococci, *Klebsiella,* and *Staphylococcus.* Spread of the infection to the pleural cavity can lead to empyema. Some cases may be complicated with bacteremic dissemination and metastatic abscesses in many organs (Kobzik & Schoen, 1994; Winn & Chandler, 1994).

Interstitial Pneumonia

The pneumonic involvement in interstitial pneumonia may be patchy or diffuse. It may involve whole lobes bilaterally or unilaterally. Grossly, the lung parenchyma appears red and congested with no obvious consolidation. The pleura is smooth, and pleuritis or pleural effusions are infrequent (Barnes, 1994).

Microscopically, the inflammatory process is confined to the interstitium, which includes the alveolar walls and the connective tissue around the bronchovascular structures. The alveolar septa are infiltrated with a mononuclear infiltrate composed of lymphocytes, plasma cells, and histiocytes. In the earliest phase, neutrophils may also be present. There is a lack of significant alveolar exudate, but in many cases proteinaceous material is present in the alveolar spaces. Pink hyaline membranes lining the alveolar wall indicate nonspecific alveolar damage similar to that seen diffusely in adult respiratory distress syndrome (ARDS) (Kobzik & Schoen, 1994; Barnes, 1994). Some viruses may be associated with necrosis of bronchial and alveolar epithelium. In some viral pneumonias, the inflammatory exudate undergoes extensive karyorrhexis and karyolysis with abundant cell fragmentation and nuclear dust (Nash, 1972). In most cases, there is complete resolution with restoration of the pulmonary parenchyma. In severe necrotizing infections, fibrosis may occur.

Common etiologic agents include *Mycoplasma pneumoniae,* viruses such as influenza viruses A and B, parainfluenza viruses, respiratory syncytial virus, adenoviruses, rhinoviruses, varicella-zoster virus, *Chlamydia* spp., *Coxiella burnetii,* and *P. carinii* (Kobzik & Schoen, 1994; Winn & Chandler, 1994; Winn & Walker, 1994).

Mixed Patterns

Bacterial infection superimposed on viral pneumonia can modify the histologic picture and can produce a mixed pattern of interstitial and alveolar inflammation, leading to a fibrinopurulent air space inflammatory reaction with mononuclear interstitial inflammation and bronchiolar epithelial necrosis (Kobzik & Schoen, 1994; Barnes, 1994).

Miliary Pattern

Tuberculosis is a disease that goes hand in hand with factors such as poverty, crowding, and undernourishment (Grzybowski, 1982). In 90% of the cases, the primary tuberculous infection heals without progression of the disease. The pulmonary lesions from *Mycobacterium tuberculosis* infection may resolve completely or they can undergo fibrosis and form a fibrotic, scarred nodule, or they may calcify (Pratt, 1979).

In a minority of patients, the disease progresses and is characterized by enlargement of the primary complex or primary focus, with regional lymph node involvement. These lesions can erode into a blood vessel, and bacilli can then embolize in large numbers into the capillaries of the organs supplied by the eroded vessel. The embolization of numerous bacilli produces 2- to 3-mm discrete lesions that resemble millet seeds; thus the disorder is called miliary tuberculosis (Sahn & Neff, 1974). The same pattern of hematogenous dissemination can be seen in patients with overwhelming histoplasmosis (Goodwin et al., 1980) and coccidiodomycosis (Bayer, 1981). The tissue reaction can vary from caseous granulomas to foci of necrosis, fibrinous exudate, and a weak, poorly formed cellular reaction. Hematogenous spread of herpesviruses, varicella-zoster virus, and cytomegalovirus to the lung can occur in severely immunocompromised patients, leading to acute necrotizing hemorrhagic lesions (Winn & Walker, 1994; Ramsey et al., 1982; Beschorner et al., 1980).

The Pathology of Specific Agents

Pneumonia has been classified on the basis of the etiologic agent because the clinical and morphologic features, and the therapeutic implications often vary with the causative organism.

Bacterial Pneumonia

Streptococcus pneumoniae

Streptococcus pneumonia accounts for 30% to 70% of the cases of community acquired-pneumonia (CAP) in general and accounts for 15% to 46% of cases of severe CAP requiring intensive care unit (ICU) management (Coonrod, 1989; Hager et al., 1990; Leeper, 1996). This bacterium is often part of the usual microbial flora of the nasopharynx of healthy individuals but also seems to have a predilection for the airway mucosal surfaces of subjects with chronic lung diseases (Reynolds, 1996).

The pattern of pneumonia is lobar or lobular, and the main pathological features involve the classical evolution of stages of lung consolidation (Winn & Chandler, 1994). The purulent exudate consists of fibrin, polymorphonuclear leukocytes, and macrophages. Bacteria are easily identified in the infiltrate of early infections. Most uncomplicated cases show complete regeneration of the alveolar epithelium without residual scar formation, but massive necrosis of the lung tissue and pneumatocele formation has been reported in children (Anderson & Turner, 1991; Kerem et al., 1994; Asmar et al., 1978). Lung abscess has been reported as a complication of pneumococcal pneumonia with bacteremia (Isaacs, 1986). Alterations of the anatomic, physiologic, and immunologic pulmonary defense mechanisms prior to and during the infection as well as virulence factors of *S. pneumoniae* (i.e., rapid multiplication, presence of capsular polysaccharides, and inhibition of phagocytosis) in concert may result in decreased bacterial clearance from the lung, with consequent necrosis of lung parenchyma (Winn & Chandler, 1994; Yangco & Deresinski, 1980).

Klebsiella pneumoniae

Generally an acute disease of adults, *Klebsiella* pneumonia is most common in alcoholic men in their fifth to seventh decade of life and is strongly associated with poor oral hygiene (Barnes, 1994). It characteristically produces a lobar pattern, but lobular or diffuse patchy infiltrates have been described, having a predilection for dependent sites. Frequently, there is extension across the lobar fissure to involve adjacent parenchyma (Winn & Chandler, 1994). The expectorated sputum and the consolidated lung show a wet mucoid or gelatinous appearance, and gram-negative bacilli can be demonstrated in tissue or respiratory secretions. Extensive necrosis of the lung parenchyma and abscess formation have been reported (Belk, 1926; Majumdar, 1992). More than one half of the cases of pulmonary gangrene or sloughing of a large amount of lung tissue have been ascribed to *K. pneumoniae* in the cases reported by Penner (Penner et al., 1994). Chronic pneumonia has also been attributed to this organism (Winn & Chandler, 1994).

Legionella pneumophila and Other Legionella

There are currently 42 described species of *Legionella* representing 64 serogroups in the family Legionellaceae (Benson & Fields, 1998), but the most important human pathogen is *L. pneumophila,* which accounts for 75% or more of human infections (Winn & Chandler, 1994). *L. pneumophila* has been subdivided into six serogroups on the basis of antigenic structure, and serogroup 1 accounts for more than 70% of the infections, followed by serogroup 6 (Winn & Myerowitz, 1981; Benson & Fields, 1998). Two clinically and epidemiologically distinct respiratory syndromes are caused by *Legionella* spp. Pontiac fever is a self-limiting, influenza-like illness that occurs with extremely high attack rates (>90%) in outbreak settings with a short incubation period and no evidence of pneumonia (Winn & Myerowitz, 1981; Breiman & Butler, 1998). This syndrome has been caused by *L. pneumophila, Legionella feeleii, Legionella micdadei,* and *Legionella anisa* (Winn & Myerowitz, 1981).

The more commonly recognized illness is a systemic infection with acute pneumonia that begins with the abrupt onset of malaise, myalgias, headache, and fever. Cough productive of inflammatory sputum usually occurs later in the course of the infection. *L. pneumophila* occurs in the environment where the causative agent has the capacity to multiply within amoebae in warm water. Person-to-person transmission has not been demonstrated to occur. Outbreak investigations have shown that Legionnaires' disease can be transmitted via contaminated cooling towers and evaporative condensers, whirlpool spas, showers, humidifiers, supermarket vegetable sprayers, decorative fountains, and respiratory therapy equipment. Infection has also resulted from wounds being inoculated with contaminated tap water (Breiman & Butler, 1998; Friedman et al., 1998).

Legionnaires' disease consists of an acute bronchopneumonia that may progress to a lobar pattern. The disease is bilateral in as many as two thirds of the patients (Fig. 1) (Benson & Fields, 1998). *L. micdadei* pneumonia is similar clinically as it occurs in compromised hosts. Other cases have been ascribed to *L. bozemanii* and *L. dumoffii.* All

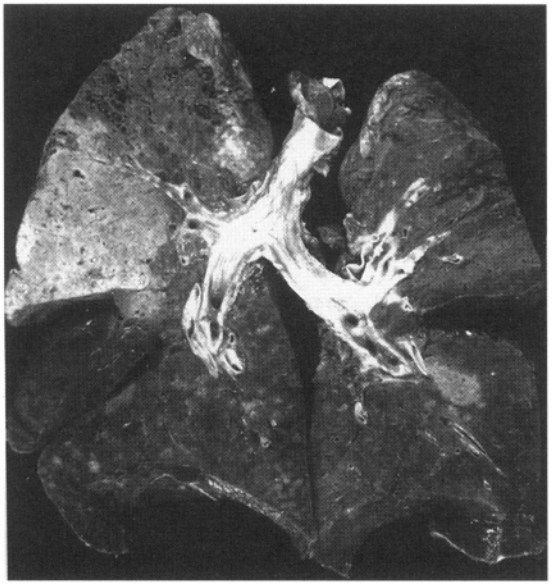

FIGURE 1. *Legionella micdadei* pneumonia. Large area of consolidation in the right upper lobe, primarily in stage of gray hepatization. The right lower lobe contains areas of bronchopneumonia and the left lower lobe a prominent round pneumonic infiltrate.

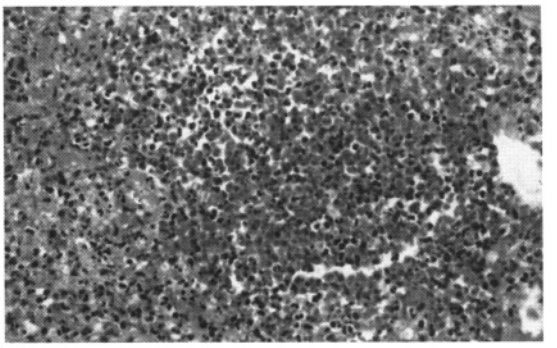

FIGURE 2. *Legionella micdadei* pneumonia. Air spaces are infiltrated with polymorphonuclear leukocytes; cellular exudate is undergoing extensive lysis. Hematoxylin and eosin, ×250.

Legionella species produce a severe confluent lobular or lobar pneumonia, and abscess formation and small pleural effusions are not uncommon. Poorly demarcated, rounded opacities, based in the pleura, may be initially mistaken radiographically for pulmonary embolism or neoplasms (Winn & Chandler, 1994; Muderet al., 1989). Microscopically, a leukocytoclastic inflammatory infiltrate of neutrophils and macrophages is seen, with many nuclear fragments and a dusty appearance, as well as vasculitis of small blood vessels, coagulation necrosis, and focal septal disruption of the parenchyma (Fig. 2). These are characteristic but not pathognomonic features (Winn & Myerowitz, 1981). Fibrin is a prominent part of the exudate, and hemorrhage in the air spaces is common. The periphery of active lesions contains edema and a sparse cellular infiltrate. The interstitium frequently contains a cellular infiltrate, but considerably less than in the adjacent air spaces (Winn & Chandler, 1994). Reaction to damage in the pneumonic areas can be manifested by prominent alveolar lining cells and occasionally hyaline membranes, especially with *L. pneumophila* and *L. micdadei* (Winn & Chandler, 1994; Winn & Myerowitz, 1981; Nusser & Tarkoff, 1978). The bacteria can be demonstrated in tissues by silver impregnation stains, using the Dieterle, Steiner, or Warthin= Starry method or with monoclonal or polyclonal fluorescent antibodies (Winn & Chandler, 1994; Winn & Myerowitz, 1981).

Few cases of chronic organizing pneumonia and pulmonary fibrosis have been attributed to *Legionella* (Winn & Chandler). Factors associated with delayed resolution include altered host defense mechanisms secondary to age or underlying medical conditions (Coletta & Fein, 1998). Other organisms associated with infection in immunosuppressed patients are *L. longbeachae, L. gormanii, L. maceachernii,* and *L. lansingensis* (Schlossberg & Bonoan, 1998).

Staphylococcus aureus

S. aureus is an uncommon cause of CAP but is important because cases are often severe. The incidence of *S. aureus* as a cause of bacterial pneumonia, in the absence of an influenza epidemic, is 1% to 5%; however, the incidence of CAP from *S. aureus* can increase as high as 25% during an influenza epidemic (Leeper, 1996). In the cases reported by Woodhead et al. (1987), 50% of the patients had some underlying disease. The infection occurs at the extremes of life and in patients with cystic fibrosis (Winn & Chandler, 1994; Leeper, 1996).

The lesions may take any pattern, including a lobar configuration. Multiple metastatic lesions may occur when the lungs are seeded hematogenously from distant foci of infection. Histologically, the exudate is rich in polymorphonuclear leukocytes and bacteria. Frequently, there are associated thick-walled abscesses (Winn & Chandler, 1994), pneumatoceles or thin-walled "abscesses," empyema, and spontaneous pneumothorax (MacFarlane & Rose, 1996); Olutola et al., 1984). Methicillin-resistant *S. aureus* (MRSA) strains are a recognized etiology with the majority of community-acquired MRSA infections occurring in intravenous drug users (Johnston, 1994).

Streptococcus pyogenes

S. pyogenes (group A beta-hemolytic *Streptococcus)* is an uncommon cause of pneumonia, and the majority of the pulmonary infections follow influenza. The distribution of the lesions ranges from focal, lobular infiltrates to lobar pneumonia (Winn & Chandler, 1994). Abscess and empyema formation have been described (Mclntyre et al., 1989; Kevy & Lowe, 1961). An important cause of neonatal pneumonia is *Streptococcus agalactiae* (group B beta-hemolytic *Streptococcus),* which can also produce pneumonia in the elderly (Winn & Chandler, 1994; Lerner et al., 1977). Other streptococci which rarely cause pneumonia include *S. anginosus* and enterococci (Winn & Chandler, 1994).

Haemophilus influenzae

H. influenzae, a common cause of lower respiratory tract infections such as purulent bronchitis, accounts for 2% to 8% of CAP. It occurs in the elderly and patients with chronic obstructive pulmonary disease, usually following a viral respiratory infection (MacFarlane, 1994). The viral infection damages the bronchial mucosa, facilitating the bacterial invasion (Wallace et al., 1978). Capsular polysaccharide, lipopolysaccharide, IgA1 proteases, and factors that inhibit ciliary activity are putative virulence determinants of *H. influenzae* (Moxon & Wilson, 1991). Bronchopneumonia and, less frequently, lobar pneumonia have been described. Histologically, there is a purulent exudate containing the gram-negative bacilli. Extensive necrosis can result in abscess, empyema, and pneumatocele formation (Winn & Chandler, 1994; Winn & Myerowitz, 1981; Wallace et al., 1978). Encapsulated strains of types B, C, D, E, and F are associated with pneumonia (Winn & Chandler, 1994). H. *influenzae* is frequently a copathogen with *S. pneumoniae* in severe CAP (Leroy et al., 1995).

Moraxella catarrhalis

Moraxella catarrhalis is a common cause of bronchial infections. It accounts for fewer than 2% of cases of CAP, usually in association with chronic lung disease and lung cancer (MacFarlane, 1994). Radiologically, the infiltrates are described as patchy with focal consolidation or having an interstitial appearance. Bacteremia is rare, and empyema or abscess formation has not been described (Winn & Chandler, 1994).

Rhodococcus equi

Rhodococcus equi, a ubiquitous gram-positive, pleomorphic bacillus, causes respiratory and other infections in domestic animals. Human disease occurs mainly in immunocompromised hosts as in the HIV-infected population (Verville et al., 1994; Prescott, 1991). Usually, a unilobar pulmonary infiltrate progresses to involve several lobes. Acute suppurative bronchopneumonia progresses to necrotizing pneumonia with formation of thick-walled cavities, as those seen in immunocompetent hosts with tuberculosis or nocardiosis. These cavities may contain air-fluid levels and can be associated with empyema (Drancourt et al., 1992; Johnson & Cunha, 1997). Hematogenous dissemination has been reported (Verville et al., 1994). The bacterium can be identified in tissues within macrophages and, less often, polymorphonuclear leukocytes by a modified gram stain such as Brown-Brenn and by Gomori's methenamine-silver stain. Most strains are weakly acid-fast and can be detected by Fite or Fite-Farraco stain (Winn & Chandler, 1994).

Bordetella pertussis

Until recently, whooping cough was considered to have been controlled by immunization. Failure of

vaccination programs, especially in underdeveloped countries, and waning immunity in previously vaccinated people contribute to the current rise in incidence of pertussis. The disease is being recognized increasingly in adolescents and adults. *Bordetella pertussis* has been isolated from patients with AIDS and respiratory infections (Ng et al., 1989). In general, the lesions are in the airways rather than in the alveoli. There is infiltration of the bronchial mucosa with mononuclear cells, and focal or extensive sloughing of the epithelial cells. These features are not pathognomonic of *B. pertussis* and can occur also in infections with respiratory syncytial virus, adenoviruses, and parainfluenza viruses (Winn & Chandler, 1994).

Gram-negative enteric bacilli (GNEB) other than *K. pneumoniae* that are described in some of the studies of CAP include *Escherichia coli, P. aeruginosa, Acinetobacter, Proteus, Serratia,* and other specific organisms. Alcoholics and the elderly, particularly when admitted from nursing homes, are at risk for GNEB infection (MacFarlane, 1994; Elbright & Rytel, 1980; Verghese & Beck, 1983). The reported proportion of GNEB pneumonias is as high as 20% (Lerner, 1983). *E. coli* has been described as causing a patchy and dense consolidation. Bacteremia and empyema have been reported (Winn & Chandler, 1994).

Pseudomonas aeruginosa

P. aeruginosa produces proteases, including elastases that are responsible for the characteristically extensive necrosis. Macroscopically, pneumonia occurs as a terminal bronchiolitis with firm, yellow-brown, elevated, necrotic nodules with sharp delimitation from the surrounding lung tissue in the shape of 2- to 5-mm shamrocks *or fleur de lis* that may progress to an extensive confluent bronchopneumonia with abscess formation (Tillotson & Lerner, 1968). Focal nodular and poorly delimited hemorrhagic lesions have also been reported, often in a subpleural location. Abscesses with liquefactive necrosis occur frequently. The lesions are hemorrhagic, with necrosis of the alveolar septa, scattered inflammation, and numerous gram-negative bacteria. These nodules may show an intense inflammatory infiltrate that consists of neutrophils, macrophages, and lymphocytes. Grossly, similar necrotic nodules or lesions resembling pulmonary infarcts reveal extensive coagulative necrosis and large numbers of gram-negative bacilli and leukocytes infiltrating the blood vessels and concentrated in the adventitia where they appear as a bluish haze in hematoxylin and eosin-stained sections (Fig. 3) (Fetzer et al., 1967).

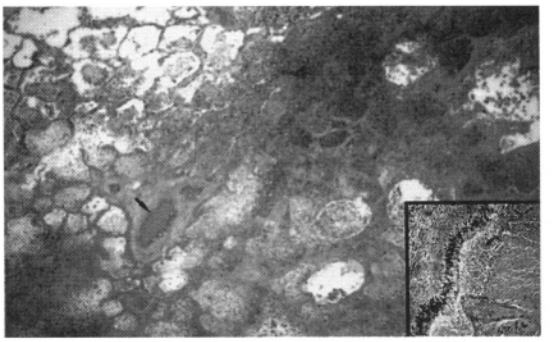

FIGURE 3. *Pseudomonas aeruginosa* pneumonia. An intense acute inflammatory exudate and fibrin fill the air spaces with areas of alveolar septal necrosis; small arteries show perivascular necrosis (*arrow*) and early infiltration by leukocytes. Hematoxylin and eosin, ×100. **Inset**: Note the large number of bacilli densely packed in the medial and adventitial layers of a pulmonary vessel. Steiner stain, ×250.

Burkholderia pseudomallei

Primary pulmonary infections follow the inhalation of aerosolized water droplets or dust contaminated with *Burkholderia* (formerly *Pseudomonas) pseudomallei,* a small, motile, gram-negative, aerobic bacillus that is found frequently in tropical regions such as Southeast Asia (Winn & Chandler, 1994). Grossly, the lungs reveal consolidation or small nodular densities in the upper lobes. The disease can mimic tuberculosis due to the frequent formation of cavities (Everett & Nelson, 1975). Microscopically, the acute infection is characterized by multiple discrete abscesses rich in neutrophils, macrophages, multinucleated giant cells, and fibrin. The stellate abscesses become surrounded by epithelioid histiocytes, lymphocytes, and Langhans and foreign-body-type multinucleated giant cells that may also be observed in lymph nodes. The granulomata may contain a central area of caseous necrosis later in the course. The bacteria can be

demonstrated within macrophages in the tissue sections of acute lesions using Steiner, Dieterle, Brown–Hopps, and Giemsa stains (Everett & Nelson, 1975; Piggott & Hochholzer, 1970).

Francisella tularensis

Approximately 10% to 20% of cases of tularemia either present with pneumonia as a primary event from inhalation of aerosolized droplets or develop pneumonia as a hematogeneous complication of ulceroglandular or typhoidal tularemia (Gill & Cunha, 1997). The bacterium is a small, pleomorphic, nonmotile, intracellular, gram-negative coccobacillus. The bacteria can enter the body by tick or deer-fly bite, skin cut, inoculation of the conjunctiva, ingestion, or inhalation (Gill & Cunha, 1997; Cunha, 1990; Spach et al., 1993). Six classic clinical forms correlate with the portal of entry: ulceroglandular (which accounts for 70% to 80% of cases), glandular, oculoglandular, oropharyngeal, typhoidal, and pleuropulmonary. The pleuropulmonary form, which more often results from hematogenous spread to the lungs, usually portends a poor prognosis (Stuart & Pullen, 1945). A case of tularemia presenting as CAP without classic epidemiological risks has been reported in the literature (Fredericks & Remington, 1996). The lungs show multifocal areas of pneumonia or lobar consolidation. Multiple abscesses can be present. Histologically, abundant fibrin and macrophages fill the alveoli and bronchioles (Fig. 4). Extensive thrombosis of small and medium-sized arteries and veins may lead to necrosis of pulmonary parenchyma resembling caseation or infarction. Giant cells are seldom observed in foci of granulomatous inflammation (Stuart & Pullen, 1945; Miller & Bates, 1969; Avery & Barnett, 1967). In tissue sections, the bacteria are generally difficult to detect.

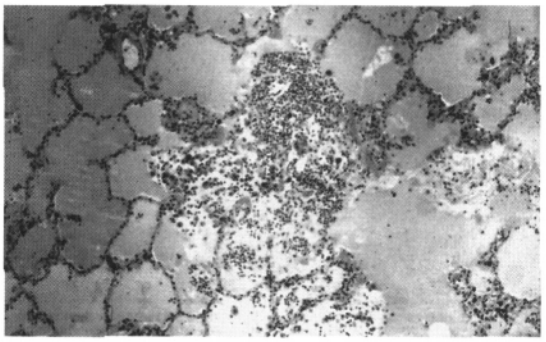

FIGURE 4. Tularemic pneumonia. Edema fluid fills alveolar spaces. Note focal acute inflammation, fibrin, and macrophages. Hematoxylin and eosin, ×250 (Contributed by L. W. Lamps, M.D., Little Rock, Arkansas).

Yersinia pestis

Yersinia pestis, a pleomorphic, gram-negative coccobacillus, is transmited to humans by flea bite or inhalation of contaminated aerosol (Butler, 1995). Clinical syndromes include bubonic, septicemic, and pneumonic plague. The bubonic form is most common, accounting for 75% of cases worldwide. After inoculation of the organism, the regional lymph nodes become infected and develop the typical fluctuating buboes. Septicemia occurs frequently (Butler, 1995; Cleri et al., 1997; Morris & McAllister, 1992). Plague pneumonia may occur after bacteremic spread during bubonic or septicemic plague, or after inhalation of bacteria from a person or animal (most often a domestic cat) with plague pneumonia (Doll et al., 1994; Werner et al., 1984). The gross appearance of the lungs includes hemorrhagic lesions in a lobular, lobar, or multilobar pattern. Peribronchial and mediastinal lymph nodes are enlarged and may be hemorrhagic (Burmeister et al., 1962). Microscopically, a mild inflammatory infiltrate consists of scant neutrophils and macrophages with hemorrhage, edema, and extensive parenchymal necrosis. Massive numbers of gram-negative coccobacilli are present in alveolar spaces, bronchi, and bronchioles. In impression smears, the bacteria display bipolar staining with methylene blue and gram stain. In tissue sections, the bacteria can be demonstrated with Brown–Hopps and silver impregnation stains, such as the Steiner, Warthin-Starry, or Dieterle procedures (Burmeister et al., 1962; Smith, 1976).

Bacillus anthracis

Inhalational anthrax is a highly lethal form of infection with toxemia. Humans are infected through exposure to animal products contaminated by spores of this nonmotile aerobic gram-positive rod, most often from animal hair and wool used in the textile

industry (Van Ness, 1971; Smith, 1973). Inhalational anthrax is rare in comparison with cutaneous disease, which accounts for over 90% of cases (Penn & Klotz, 1997). In the United States, the most recent fatal case of inhalation anthrax was documented in 1976 (LaForce, 1994). After inhalation of the spores, the alveolar macrophages transport them to the mediastinal lymph nodes where they germinate and multiply, followed by secretion of lethal toxin and edema toxin and hematogenous dissemination (Dalldorf et al., 1971). Radiologically, chest radiographs are characterized by a widened mediastinum (Vessal et al., 1975). In most cases, there is no pneumonia, but rather a severe hemorrhagic necrotizing mediastinal lymphadenitis and mediastinitis and death due to the effects of the toxins (Fig. 5). The lungs are heavy and may show extensive hemorrhagic pulmonary edema and a serofibrinous exudate. In a recently reported outbreak associated with release of aerosols from a military facility in Russia in 1979, there were a few cases that showed round areas of necrotizing pneumonia. In either situation, numerous large and elongated bacilli can be demonstrated in impression smears or tissue sections by Brown–Brenn stain or direct immunofluorescence (Ross, 1957; Cowdery, 1947; Cherry & Moody, 1965; Abramova et al., 1993). The majority of bacteria are observed within capillaries. The disease is often accompanied by hemorrhagic meningitis, and cerebrospinal fluid analysis yields evidence of hemorrhagic fluid with easily identified gram-positive bacilli (Abramova et al., 1993).

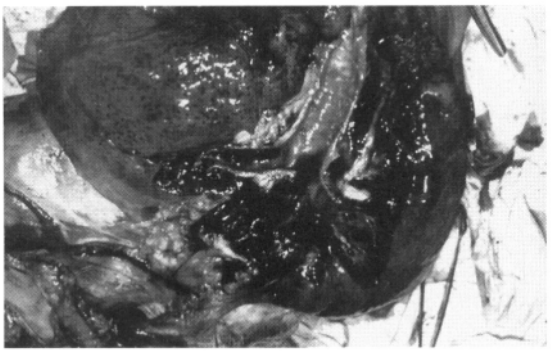

FIGURE 5. Inhalational anthrax. Note necrotizing and hemorrhagic mediastinitis and lymphadenitis (Provided by Lev Grinberg, M.D., and Faina Abramova, M.D.).

Brucella Species

In contrast with the Middle East and some Mediterranean countries where brucellosis remains a major health problem, only 95 cases were reported in the United States in 1994 (Sanford, 1997). The disease is acquired by ingestion, inoculation through abraded skin or the conjunctiva, or inhalation of infectious droplets from tissues or body fluids of chronically infected animals, particularly cattle with *Brucella abortus,* goats and sheep with *B. melitensis,* and swine with *B. suis* (Buchanan et al., 1974). Following entry into the body, the organisms spread to the regional lymph nodes, and subsequently through the blood to the liver, spleen, and lungs (Sanford, 1997). In the subacute stage of infection, patients may develop noncaseating epithelioid cell granulomata and lymphocytic infiltrates in the reticuloendothelial system, meninges, genitourinary tract, and lungs. The organisms can be demonstrated within macrophages in the acute and subacute lesions using Brown–Hopps tissue gram stain and the Steiner, Dieterle, or Warthin–Starry silver impregnation procedures (Hunt & Bothwell, 1967; Weed et al., 1956). In the chronic stage, there are caseous or suppurative granulomas that may resemble tuberculosis. Residual fibrocaseous granulomas or coin nodular lesions can resemble tuberculosis, histoplasmosis, or coccidioidomycosis (Weed et al., 1956).

Nocardia Species

Among the nine species of *Nocardia, N. asteroides* accounts for 80% to 90% of all infections; 3% to 9% are caused by *N. brasiliensis,* and 0.5% to 3% are caused by *N. ottidiscaviarum* (previously known as *N. caviae)* (Rolfe et al., 1992). This gram-positive, weakly acid-fast, filamentous, branching bacillus occurs in soil and decaying organic material worldwide (Filice, 1993). Approximately half of the patients with nocardiosis are immunocompetent, but immunosuppressive therapy, organ transplantation, diabetes mellitus, and pulmonary alveolar proteinosis increase the risk of contracting the infection (Palmer et al., 1974). *Nocardia* is a rare cause of CAP. In a prospective study of more than 1100 cases of CAP, no cases of nocardiosis were reported by Marrie (1994). The infection causes a lobular,

lobar, or diffuse consolidation, and in the acute stage suppurative and necrotizing inflammation leads to formation of sinus tracts and walled-off abscesses. In chronic infections, the latter are filled with thick exudate composed of neutrophils and macrophages. Epithelioid histiocytes and multinucleated giant cells are present at the periphery of the abscesses. The bacteria appear as beaded, branching filaments that can be demonstrated in tissue sections by Brown–Brenn, Brown–Hopps, modified Ziehl–Neelsen, or Gomori's methenamine-silver stain. Empyema and cavitation are frequent (Winn & Chandler, 1994; Marrie, 1994; Frazier et al., 1975).

Actinomyces Species

Pulmonary actinomycosis may occur as part of a mixed anaerobic infection in an immunocompetent host as a result of aspiration of infectious material or a direct extension of cervicofacial infection (Winn & Chandler, 1994). Pulmonary consolidation may be accompanied by numerous small abscesses and cavitation. Sinus tracts into soft tissues can be seen with the characteristic sulfur granules (Oddo & Gonzalez, 1986). Microscopically, these delicate, branched, gram-positive and often beaded filaments arranged in tangled aggregates or radially oriented at the periphery of the granule are frequently surrounded by eosinophilic material, an example of the Splendore–Hoeppli phenomenon. Fragmented coccobacillary forms may be present. Brown–Brenn and Gomori's methenamine-silver stain may be used to demonstrate actinomycetes in tissue sections (Oddo & Gonzalez, 1986; Hotchi & Schwarz, 1972).

Anaerobes

Anaerobic bacteria are rarely identified as a cause of CAP. Perhaps because the diagnosis of anaerobic pneumonia depends on obtaining pulmonary samples anaerobically, these infections may go unrecognized. Conditions that predispose to aspiration and poor oral hygiene increase the likelihood of anaerobic infections (Meeker & Longworth, 1996). Sixty percent to 90% of patients with anaerobic infections have conditions associated with stasis of secretions or necrosis of tissue such as pulmonary infarction, tumors causing endobronchial obstruction, or bronchiectasis (Bartlett, 1991). The two main overlapping patterns of pulmonary infection are lung abscess and necrotizing pneumonia. Histologically, there is extensive necrosis, and often foreign material including cell walls of plant substances with foreign body giant cells are present. Aspiration of gastric contents may induce a chemical pneumonitis with intense neutrophilic interstitial reaction and diffuse alveolar damage. In this context, extensive necrosis of the right middle and lower lobes is common. Pleural fibrosis, empyema, and bronchiectasis may develop (Barnes, 1994; Anderson & Turner, 1991). The etiologic anaerobic organisms include *Peptostreptococcus, Peptococcus, Fusobacterium,* and *Bacteroides* species (Bartlett, 1991). Superinfection in aspiration pneumonia often involves mixed anaerobic and/or aerobic microorganisms including Enterobacteriaceae, *P. aeruginosa,* and others (Anderson & Turner, 1991).

Mixed Infections

Mixed viral and bacterial pneumonia is more frequent than pneumonia due to virus alone. The incidence is approximately 9% (MacFarlane, 1994). Viral infections promote epithelial cell desquamation and destruction of mucociliary defenses, which decreases bacterial clearance. Superinfection with *S. pneumoniae, S. aureus, A. fumigatus,* or *H. influenzae* may follow influenza or measles. Infection with respiratory syncytial virus may be followed by *S. pneumoniae* or *H. influenzae* pneumonia (Anderson & Turner, 1991; Fischer & Walker, 1979). The histological features are those of bacterial and viral pneumonia.

Mycobacterial Pneumonia

Mycobacterium tuberculosis

From 6 to 8 million new cases of tuberculosis occur worldwide each year, with 2 to 3 million fatalities, making *M. tuberculosis* the most common identifiable cause of death of any infectious agent. In the developing world, tuberculosis accounts for 6.7% of all deaths (Wallis & Ellner, 1994). Although the incidence of *M. tuberculosis*

as a cause of CAP varies, it must be considered as a potential pathogen. It is transmitted by airborne droplet nuclei that usually implant in the middle or lower lung fields. The bacilli stimulate an acute inflammatory reaction which is replaced by alveolar macrophages. These macrophages enter the lymphatics and transport some of the bacilli to the regional lymph nodes, from which they may be carried lymphohematogenously throughout the body and lodge and multiply in the posterior half of the upper lobes of the lungs due to the high oxygen tension and relative lymphostasis (Hruban & Hutchins, 1994). In more than 90% of cases, the primary tuberculous lesions heal without progression of disease. These lesions undergo fibrosis and/or calcification (Pratt, 1979). In susceptible individuals, the primary infection progresses. The primary complex enlarges, eroding into a blood vessel embolizing large numbers of bacilli. This spread results in many 2- to 3-mm lesions that resemble millet seeds (Fig. 6). If the lesion erodes into a bronchus, the bacilli are spread to other areas of the lung resulting in tuberculous bronchopneumonia, fibronodular lesions (Pratt, 1979; Sahn & Neff, 1974), cavitation, and/or tuberculous empyema (Hruban & Hutchins, 1994). In tissue sections, stains used most commonly for detection of acid-fast bacilli (AFB) are Ziehl–Neelsen (Fig. 7), Kinyoun, and auramine O (with or without rhodamine) (Woods & Walker, 1996).

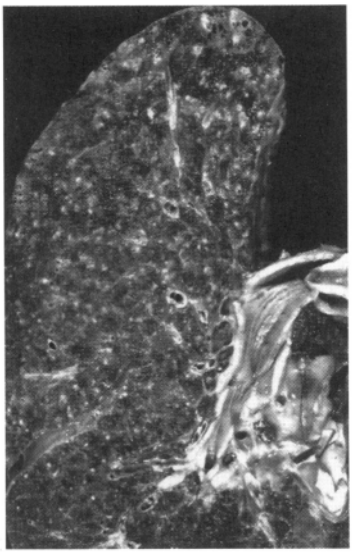

FIGURE 6. Miliary tuberculosis as a result of hematogenous dissemination of numerous bacilli.

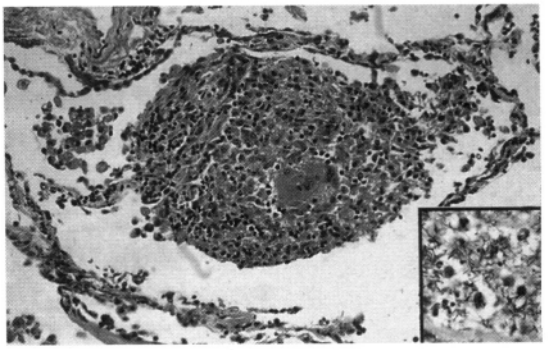

FIGURE 7. Miliary granuloma with abundant epithelioid histiocytes and occasional giant cells. Hematoxylin and eosin, ×250. **Inset**: Multiple acid-fast organisms. Ziehl-Neelsen stain, ×1000.

Nontuberculous Mycobacteria

Infection with nontuberculous mycobacteria (NTM) is acquired directly from the environment, and patients with decreased immunity and underlying lung diseases are particularly susceptible (Hruban & Hutchins, 1994). Four clinical syndromes can be identified: pulmonary disease, lymphadenitis, skin or soft tissue lesions, and disseminated disease in AIDS (Horsburgh, 1996). Before AIDS, pulmonary disease was the most frequent clinical presentation of NTM infection, in the United States most commonly caused by *M. avium* complex (MAC). In immunocompetent individuals, the classic picture resembles chronic tuberculosis. Involvement of the upper lobes predominates, frequently with thin-walled cavities. Pleural thickening may be present, but pleural effusion is rare. Noncaseating granulomas are characteristic. Primary pulmonary MAC infection, analogous to primary tuberculosis, is difficult to identify (Rosenzweig, 1996). *M. kansasii* infections closely resemble pulmonary disease caused by MAC but are less frequent, accounting for 10% to 15% of NTM cases (O'Brien et al., 1987). These bacteria are slightly larger and more coarsely beaded than most of the other mycobacteria (Hruban & Hutchins, 1994). Thin-walled cavities also are characteristically present in the upper lobes (O'Brien et al.,

1987). Rapidly growing mycobacteria, including *M. abscessus, M. fortuitum,* and *M. chelonae,* account for fewer than 5% of cases. Cavity formation is uncommon, and nodular infiltrates are the rule (Ahn et al., 1982). Other NTM that cause lung disease in humans include *M. simiae, M. szulgai, M. xenopi,* and *M. malmonense* (Gangadharam, 1996). In addition to stains specific for the detection of AFB, MAC bacilli stain positively with periodic acid-Schiff (PAS), a unique feature among the mycobacteria and, therefore, a useful diagnostic criterion (Woods & Walker, 1996).

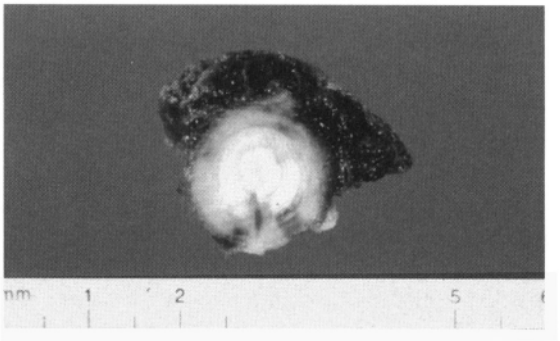

FIGURE 9. Residual pulmonary nodule (histoplasmoma) contains concentric layers of dense calcifications.

Fungal Pneumonia

Histoplasma capsulatum

Among the causes of acute fungal pneumonia acquired in communities in the United States, histoplasma is the most common. Infection occurs after inhalation of spores from aerosols of contaminated soil. Once infection is established, polymorphonuclear leucocytes infiltrate the tissues, followed by macrophages which engulf the yeasts. Lymphatic spread occurs with subsequent access to the circulation (Johnson & Sarosi, 1989). The majority of infections are asymptomatic, and the presence of calcified granulomata in the lung and spleen are usually incidental findings. In susceptible individuals, there is progressive disseminated histoplasmosis in the classical miliary pattern (Fig. 8) (Goodwin et al., 1980). Rarely, the infection leads to the development of thin-walled cavities with extensive destruction of the parenchyma. Chronic pulmonary infection is associated with extensive fibrosis, emphysema, bronchiectasis, and the residual solitary nodule or histoplasmoma (Fig. 9). The latter varies from 0.5 to several centimeters in diameter, is usually subpleural, and consists of a large central zone of caseous necrosis surrounded by lymphoid aggregates, epithelioid and multinucleated giant cells, and a thick fibrous capsule in the periphery. The necrotic zone may contain stippled or concentric calcifications (Goodwin et al., 1976; Goodwin et al., 1969; Baker, 1964). Pleural effusions are uncommon. In tissue sections, the intracellular yeast cells are spherical and oval, often in clusters, and are readily stained with Gomori's methenamine-silver method.

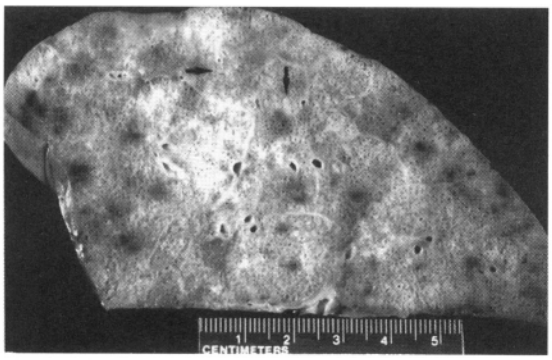

FIGURE 8. Disseminated histoplasmosis capsulati. Cut surface shows numerous miliary nodules (*arrows*) resembling "millet seeds."

Coccidioides immitis

Pulmonary infections with *C. immitis* are usually asymptomatic. Single or patchy infiltrates occur in a segmental or lobar distribution. Necrosis of lung tissue is accompanied by the development of both thick- and thin- walled cavitary lesions. Pleural effusions are observed, and pneumohydrothorax results when a peripheral cavity erodes into the pleural space (Rosenzweig, 1996; O'Brien et al., 1987). Single pulmonary nodules may cavitate or appear as coin lesions in chest radiographs. Miliary spread of *C. immitis* occurs in 4% of the patients, most commonly immunosuppressed individuals, with a suppurative reaction rather than a well-developed granulomatous response to the infection. Histologically, the spherules are generally abun-

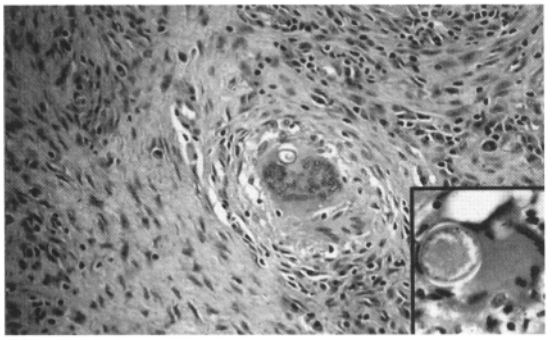

FIGURE 10. Coccidioidal pneumonia. Granuloma with multinucleated giant cell surrounded by epithelioid histiocytes and other mononuclear cells. Hematoxylin and eosin, ×250. **Inset**: Spherule within a multinucleated giant cell. Hematoxylin and eosin, ×400.

dant in active pulmonary and disseminated lesions (Fig. 10). They are visualized with hematoxylin and eosin stain and may be surrounded by a radiating corona of eosinophilic Splendore–Hoeppli material. Septate hyphae and arthroconidia are seldom produced in tissue (Bayer, 1981; Drutz & Catanzaro, 1978a,b; Chandler & Watts, 1994).

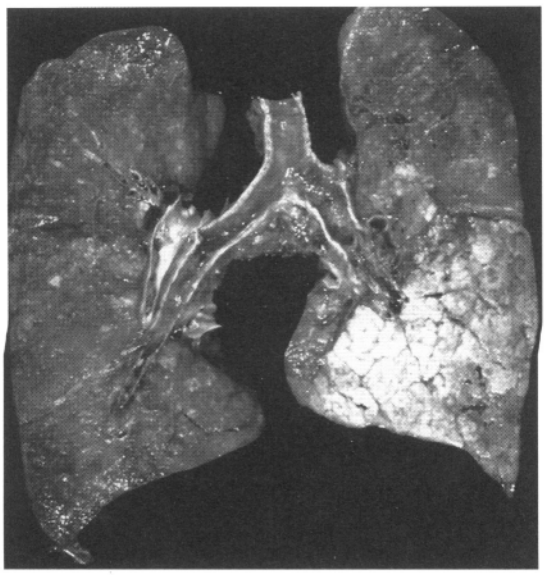

FIGURE 11. Acute pulmonary blastomycosis with dense area of consolidation in left lower lobe.

Blastomyces dermatitidis

Blastomyces, a soil-dwelling organism, can cause an asymptomatic infection similar to histoplasmosis and coccidioidomycosis. In overt disease, pleura-based infiltrates or lobar consolidation infrequently lead to cavitation or pleural involvement (Fig. 11) (Klein et al., 1986). Hematogenous dissemination is not frequent and occurs most commonly in immunocompromised individuals. Histologically, there is an intense neutrophilic infiltrate. *B. dermatitidis* is found in both suppurative and granulomatous foci as intracellular and extracellular, round to oval, multinucleated yeast cells with thick, refractile, doubly contoured walls and broad-based budding. Organisms are as readily identified in hematoxylin and eosin-stained sections as with the PAS method or Gomori's methenamine-silver technique (Sarosi & Davies, 1979).

Aspergillus Species

Ubiquitous within the environment, *A. fumigatus, A. flavus,* and *A. niger* are the most commonly isolated species in compromised patients, and less often acute pulmonary aspergillosis has been reported to cause CAP in immunocompetent hosts. The classic presentation is colonization of preexisting cavities, which waxes and wanes insidiously over months to years (Clancy & Nguyen, 1998). Underlying conditions include cavitary tuberculosis or sarcoidosis, chronic obstructive pulmonary disease, and neoplasia (Young et al., 1969; Clancy & Nguyen, 1998; Aslam et al., 1971). Microscopically, septate hyphae with uniform diameter and 45° angle dichotomous branching are seen on Gomori's methenamine-silver or PAS stain. The hyphae may be seen surrounded by eosinophilic Splendore–Hoeppli material or may appear with bizarre, globose, thick walls. Fungus ball consists of convoluted layers of radially arranged mycelia containing both typical viable and distorted, necrotic hyphae in a prominent inflammatory exudate and, particularly with *A. niger,* calcium oxalate crystal deposition in the surrounding tissue (Chandler & Watts, 1994; Clancy & Nguyen, 1998).

In patients with alcoholism or previous influenza A infection, invasive pulmonary aspergillosis can occur as a CAP. Hyphae invade through the

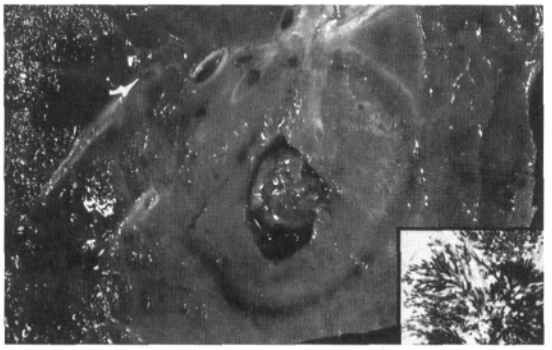

FIGURE 12. Cavitation in nodular infarct in a case of *Aspergillus fumigatus* pneumonia. Cavity contains necrotic lung with invasive hyphae. **Inset**: Hyphae are septate with dichotomous branching. Gomori's methenamine-silver stain, ×1000.

walls of the bronchi and into the adjacent pulmonary and bronchial arteries causing thrombosis, obstruction, and pale anemic infarction, owing to obstruction of both the pulmonary and bronchial arteries. The necrotic tissue frequently undergoes cavitation; in contrast to the preexisting cavities, these cavities contain necrotic lung tissue with invasive hyphae (Fig. 12) (Seriff, 1969; Fischer & Walker, 1979; Chandler & Watts, 1994).

Mycoplasmal, Chlamydial, and Rickettsial Pneumonias

Mycoplasma pneumoniae

Transmitted from person to person, *M. pneumoniae* is responsible for about one fifth of all cases of CAP, is more common in children and young adults, but is not uncommon in the elderly (Johnson & Cunha, 1993). The organism appears to contain adhesion proteins for attachment to host cells and damages the respiratory tract epithelium by liberating hydrogen peroxide and superoxide radicals (Murray & Tuazon, 1980). Tracheobronchitis occurs more often than pneumonia. The pattern of pneumonia ranges from unilateral lobar or lobular consolidation to a diffuse interstitial pneumonitis (Barnes, 1994; Johnston & Cunha, 1993). Microscopically, there is interstitial infiltration by macrophages, lymphocytes, and plasma cells. The lumens of bronchi and bronchioles contain polymorphonuclear leukocytes, mucus, fibrin, and desquamated epithelial cells (Maisel et al., 1967).

Chlamydiae

Chlamydial pneumonia may be caused by all three species that are pathogenic for humans. *C. trachomatis* can produce pneumonia in children aged 1 to 18 months, but infection has also been reported in adults as CAP (Andersen, 1998). Most of the pathologic features have been described in children, with a mixed picture of interstitial and alveolar pneumonitis and bronchiolitis with lymphocytes, plasma cells, eosinophils, neutrophils, and macrophages (Harrison et al., 1979). *C. psittaci* is transmitted to humans from infected birds, either by direct contact or by inhalation of aerosols of infectious excreta or dust (Leigh & Clyde, 1987). Tracheobronchitis and interstitial and alveolar pneumonitis with hilar lymphadenopathy are common pathological features. Pulmonary inflammation consists mainly of mononuclear cells. There is proliferation and desquamation of alveolar lining cells (Gregory & Schaffner, 1997). *C. pneumoniae* is the third or fourth most frequent cause of CAP (Reynolds, 1996). Ninety percent of the infections are mild or asymptomatic, but severe pneumonia has been reported in the elderly and persons with underlying disease, where small pleural effusions have been described (Johnson & Cunha, 1993; Grayston & Thom, 1991).

Rickettsia rickettsii, R. typhi, R. prowazekii

The etiologic agents of Rocky Mountain spotted fever, murine typhus, and epidemic typhus are transmitted by tick bite, infected flea feces, and louse feces, respectively, and reach the endothelial cells of blood vessels of many organs and the pulmonary microcirculation via the bloodstream (Donohue, 1980). As a consequence, the lungs show edema, congestion, focal hemorrhage, interstitial pneumonia, and diffuse alveolar damage. Microscopically, there is endothelial damage and interstitial and alveolar edema with diffuse interstitial mononuclear inflammatory infiltrate and perivascular lymphohistiocytic infiltration. Intra-alveolar hemorrhage and small-vessel vasculitis may be

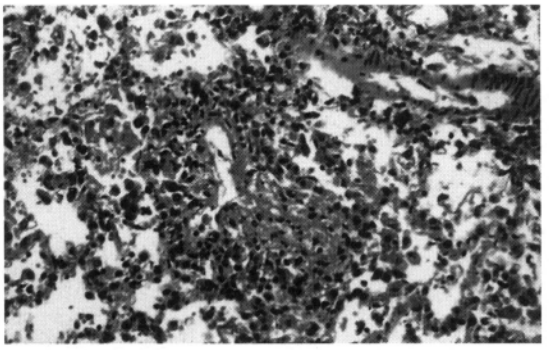

FIGURE 13. Interstitial pneumonia associated with Rocky Mountain spotted fever. Note the dramatic perivascular infiltration by lymphocytes and macrophages. Hematoxylin and eosin, ×250.

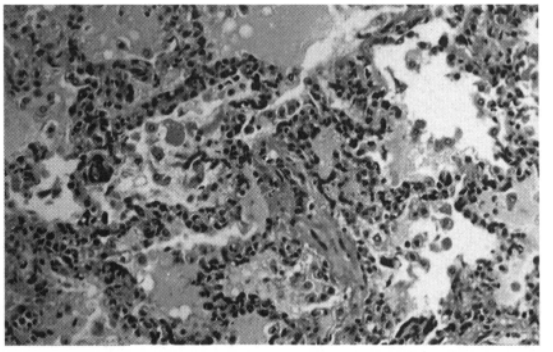

FIGURE 14. Scrub typhus interstitial pneumonia with edema filling the alveolar spaces. Hematoxylin and eosin, ×250.

present (Fig. 13). Intracellular organisms may be demonstrated within endothelial cells using immunohistochemistry (Walker et al., 1980; Roggli et al., 1985).

Orientia tsutsugamushi

Scrub typhus is a zoonosis transmitted to humans by the larval mite (chigger) of *Leptotrombidium* spp. (Traub & Wisseman, 1974). Infected patients can develop encephalitis and pneumonitis. Grossly, the lungs show hemorrhage and congestion. Histologically, there is intra-alveolar and interstitial infiltration by lymphocytes and plasma cells, alveolar and interlobular septal edema, and diffuse alveolar damage with hyaline membranes lining the alveolar spaces (Fig. 14) (Traub & Wisseman, 1974; Levine, 1946; Settle et al., 1945). Superinfection with bacterial bronchopneumonia may coexist in 30% of the cases (Chayakul et al. 1988).

Coxiella burnetii

This organism is a small obligately intracellular gram-negative pleomorphic coccobacillus that infects humans who inhale the aerosol of products of conception of sheep, cattle, goats, cats, rabbits, and dogs (Antony & Schaffner, 1997). Radiologically, lesions are patchy infiltrates or round opacities that tend to be more frequent in the lower lung fields. Pleural infiltrates may occur, some with small pleural effusions (Millar, 1978). Focal or lobar consolidation may be present. The organisms can be demonstrated within alveolar macrophages by immunohistochemistry. Granulomas, plasma cells, and lymphocytes characterize the inflammatory response; polymorphonuclear leukocytes are rarely present (Pierce et al., 1979).

Viral Pneumonia

Influenza Viruses

Influenza viruses are orthomyxoviruses that infect a wide range of avian and mammalian hosts, including humans. Influenza viruses, particularly type A, produce pandemic disease, are the leading viral etiology of pneumonia in adults, and account for 10,000 to 40,000 excess deaths each winter. Influenza virus B produces epidemic disease and is rarely associated with mortality (Ruben, 1993). Both viruses contain hemagglutinin and neuraminidase, which are important for the attachment of the virus to the cells and their subsequent entry. Viral infection impairs the function of the mucociliary escalator, allowing bacteria to invade the lower respiratory tree and predisposing to the development of secondary bacterial pneumonia, frequently caused by *S. aureus, H. influenzue,* or *S. pneumoniae.* Functional impairment of the phagocytes by the deterrent action of the virus has also been described (Spera & Shepp, 1994). There are many reports of

the pathology of fatal influenza pneumonia, and those from Hers et al. (1958) dealing with the Asian influenza epidemic in the 1950s are particularly noteworthy. They described focal lesions sometimes in a lobular distribution. Characteristically, there were cytopathic changes of the respiratory and alveolar epithelium; capillary thrombosis and necrosis with focal leukocytic exudate; capillary aneurysms and hemorrhage (Fig. 15); presence of a plasma–rich exudate after 3 to 4 days with hyaline membranes lining the alveolar spaces (Fig. 16); and metaplastic regeneration of the respiratory and alveolar epithelium after 5 to 7 days. Similar findings were observed by Winternitz et al. (1920) in 1918 (Fig. 17). Changes in the upper respiratory tract have been well described by Walsh et al. (1961) who performed tracheal and bronchial biopsies in patients with clinically uncomplicated influenza. Histologically, there was desquamation of the respiratory epithelium with loss of cilia, edema, hyperemia, areas of necrosis, ulceration of the mucosa, vacuolation of columnar epithelium with nuclear hyperchromasia, and a mononuclear cell infiltrate in the submucosa (Walsh et al., 1961). Viral antigen can be found in type 1 and 2 pneumocytes and in alveolar macrophages. No viral inclusions have been described (Walsh et al., 1961; Oseasohn et al., 1959). Interstitial fibrosis has been observed with residual inflammation. Obliterative bronchiolitis and metaplasia may persist for weeks or months after the infection (Winn & Walker, 1994).

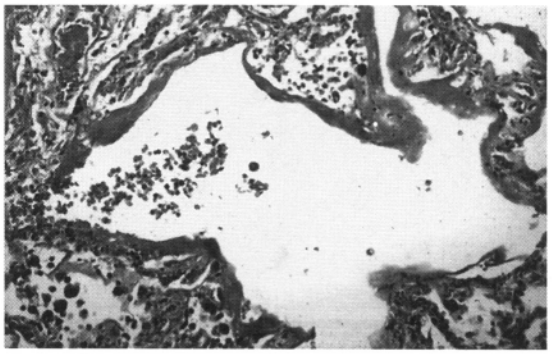

FIGURE 16. Influenza virus A pneumonia. Thick hyaline membranes line the alveolar spaces. The interstitium is congested, edematous, and contains mononuclear leukocytes. Hematoxylin and eosin, ×250.

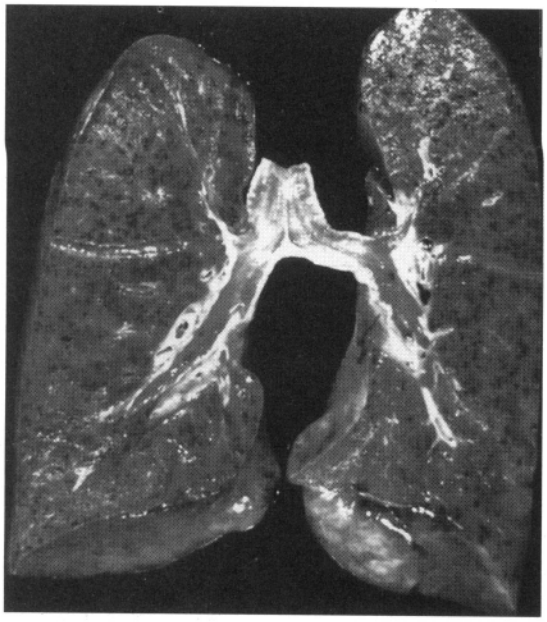

FIGURE 15. Influenza virus A pneumonia. The cut surface of the pulmonary parenchyma is markedly congested and hemorrhagic.

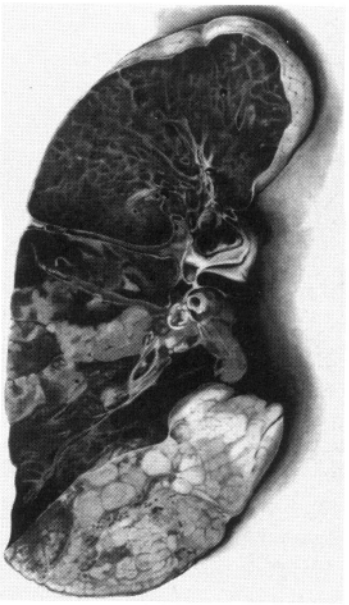

FIGURE 17. A case of influenza virus A pneumonia from the epidemic of influenza in New Haven, Connecticut, 1918. Watercolor representing a cross section of the lung with a diffuse hemorrhagic appearance. The lower lobe shows areas which may represent bacterial superinfection (From Winternitz et al., 1920).

Parainfluenza Viruses

These paramyxoviridae are an important cause of respiratory disease in infants and young children, ranging from croup and bronchiolitis to pneumonia. Human infection with types 1, 2, 3, 4A, and 4B rarely results in the patient's death (Clover, 1994). The lung pathology includes bronchitis with regenerative epithelial hyperplasia, hyperplasia of alveolar lining cells, and interstitial pneumonia. Immunocompromised patients may show an alveolar exudate, alveolar cell hyperplasia, interstitial fibrosis, and alveoli lined by multinucleated giant cells with large cytoplasmic inclusions (Little et al., 1981).

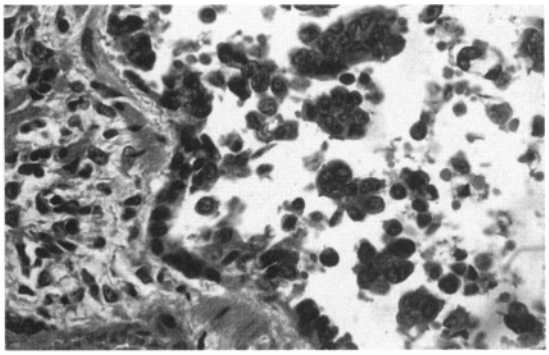

FIGURE 18. Respiratory syncytial virus bronchiolitis. Damage of the epithelium is evident with formation of small papillary projections and multinucleated giant cells. There is a mononuclear peribronchiolitis, and mononuclear cells are present in the lumen. Hematoxylin and eosin, ×250.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) pneumonia occurs in early childhood, particularly in children aged 1 to 3 years, and is most severe in children less than 1 year of age (Ruben, 1993). It has been reported to cause pneumonia in healthy adults and death in immunocompromised hosts (Vikerfors et al., 1987; Englund et al., 1988). Lung infections are characterized by the scanty fusion of RSV-infected cells and occasional multinucleated syncytial giant cells, hyperplasia of alveolar epithelial cells, epithelial necrosis of bronchioles and bronchi, papillary epithelial hyperplasia, and an inflammatory infiltrate composed of lymphocytes and macrophages in the peribronchial space and interstitium (Fig. 18). Alveolar edema and hyaline membranes have been reported. Bacterial superinfection by *H. influenzae* has been described (Winn & Walker, 1994).

Measles Virus

Among a small portion or unvaccinated children and young adults, cases of fatal measles pneumonitis have shown diffuse, patchy, or nodular lesions with areas of hemorrhage in a peribronchial and peribronchiolar distribution. Histologically, the classic giant-cell pneumonitis contains readily demonstrable intranuclear inclusions that may resemble those of herpes simplex virus, as well as eosinophilic cytoplasmic inclusions and mononuclear interstitial infiltration (Fig. 19) (Radoycich et al., 1991). Hyaline membranes and pulmonary thromboemboli have been described (Winn & Walker, 1994). Necrotizing bronchiolitis may be present (Radoycich et al., 1991).

Adenoviruses

Adenoviral respiratory infections affect young children, military recruits, and immunocompromised hosts. The types 1–7, 7a, 11, 21, 31, and 35 have been associated with pneumonia (Winn & Walker, 1994). Extensive necrotizing bronchiolitis

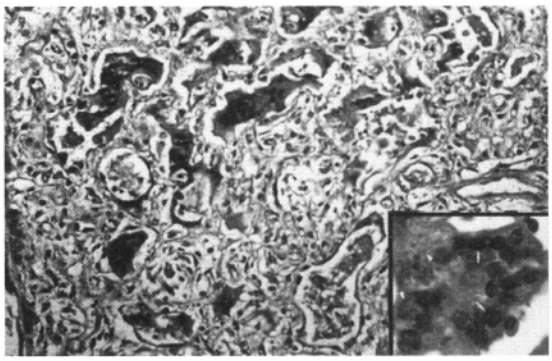

FIGURE 19. Measles pneumonia. The air spaces are obliterated by a mixed inflammatory infiltrate, proliferation of alveolar epithelial cells, and formation of multinucleated epithelial cells. Hematoxylin and eosin, ×250. **Inset**: Eosinophilic intranuclear (*arrows*) and cytoplasmic (*arrowheads*) inclusions are easily seen in multinucleated giant cells. The nuclear inclusions resemble those of herpes simplex virus. Hematoxylin and eosin, ×400.

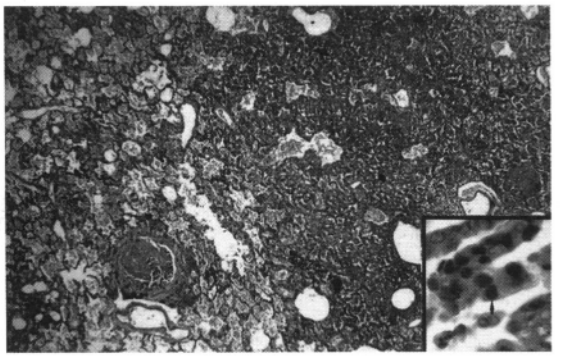

FIGURE 20. Adenovirus pneumonia. Alveolar spaces are lined with hyaline membranes. Interstitial pneumonia is present. Hematoxylin and eosin, ×100. **Inset**: Dense adenoviral (herpes-like) intranuclear inclusions (*arrow*) and smudge cells can be seen. Hematoxylin and eosin, ×1000.

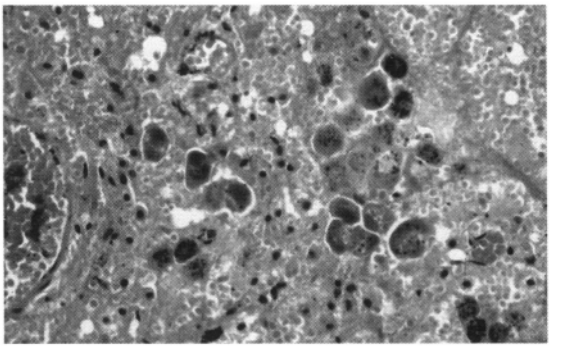

FIGURE 21. Cytomegalovirus pneumonia. Necrosis of the pulmonary parenchyma with sparse mononuclear cells. Numerous enlarged cells contain both intranuclear and cytoplasmic inclusions. Hematoxylin and eosin, ×250.

and alveolitis with basophilic to amphophilic nuclear change (smudge cells) or eosinophilic herpes-like nuclear inclusions, alveolar edema, and hyaline membranes have been reported (Fig. 20) (Pinto et al., 1992). Electron microscopy of lung tissue may show the characteristic intranuclear crystalline arrays of typical icosahedral virions (Green & Williams, 1989).

Cytomegalovirus

Human cytomegalovirus (CMV) pneumonitis is a major problem with a high mortality rate in bone marrow and organ transplant recipients, patients with malignant neoplasms receiving intensive chemotherapy, and patients with AIDS. In immunocompetent hosts, the infection is usually asymptomatic (Oda et al., 1994). Histologically, enlarged cells contain viral inclusions in both the nucleus and the cytoplasm (Fig. 21). The intracellular inclusions are larger and more rounded than the inclusions of herpes simplex and varicella-zoster viruses. The amphophilic inclusions are usually surrounded by an artefactual halo in formalin-fixed tissue. The basophilic cytoplasmic inclusions are round or granular and can be stained by PAS and Gomori's methenamine-silver methods (Winn & Walker, 1994). In the lungs, especially in immunocompromised hosts, the cytomegalic cells may be found in the alveolar epithelium with minimal evidence of inflammation. A second pattern of multifocal miliary lesions that contain cytomegalic inclusion cells has also been described. In these focal lesions the pulmonary architecture shows an exudative inflammatory response in the interstitium and air spaces, sometimes with central necrosis, hemorrhage, and accumulation of fibrin, mononuclear cells, and neutrophils (Winn & Walker, 1994; Norhfelt et al., 1993). A diffuse interstitial pneumonia with lymphocytes, macrophages, and plasma cells may also be seen. In this pattern, there is edema in the interstitium, serofibrinous exudates in the alveolar spaces, and hyperplasia of the alveolar lining cells, and hyaline membranes may be also present. The infection may resolve completely or undergo organization (Winn & Walker, 1994; Craighead, 1971).

Herpes Simplex Virus

Herpes simplex viruses (HSV) types I and II, are spread from person to person by contaminated secretions. Viral pneumonia occurs most often in immunocompromised hosts (Oda et al., 1994). Focal and diffuse interstitial pneumonia and miliary hemorrhagic, necrotic lesions have been described, but most often necrotizing pneumonia with ulcerations of trachea and bronchi and peribronchial alveolar spaces obliterated by nuclear debris, fibrin, necrotic cells, and inflammatory cells mimic bacterial bronchopneumonia. A careful search will di-

vulge multinucleated giant cells containing angulated, eosinophilic, intranuclear inclusions that are surrounded by a clear halo with margination of chromatin (Winn & Walker, 1994).

Varicella-Zoster Virus

Varicella-zoster virus (VZV) infection occurs primarily as chickenpox or herpes zoster. Viral pneumonia is the most serious manifestation of disseminated VZV infection, especially in newborns, pregnant women, and patients with compromised immunity. The incidence of varicella pneumonia in healthy adults with primary chickenpox has been estimated to range from 10% to 50% (Feldman, 1994) and, if untreated, is fatal in approximately 10% of pneumonia cases (Triebwaser et al., 1967). The lungs are firm, heavy, and plum-colored. Necrotic, hemorrhagic, miliary lesions are evident. Histologically, these lesions involve the alveolar walls, blood vessels, and small bronchioles. Eosinophilic intranuclear inclusions and multinucleated giant cells are identified, sometimes only after a prolonged search (Fig. 22). Other findings include interstitial pneumonia, mononuclear cell infiltrates with intra-alveolar fibrinous exudates, hemorrhage, and hyaline membranes. Occasionally there are necrotizing bronchitis and bronchiolitis. Secondary bacterial pneumonia and pulmonary fibrosis with diffuse nodular pulmonary calcifications are common complications (Winn & Walker, 1994; Feldman, 1994).

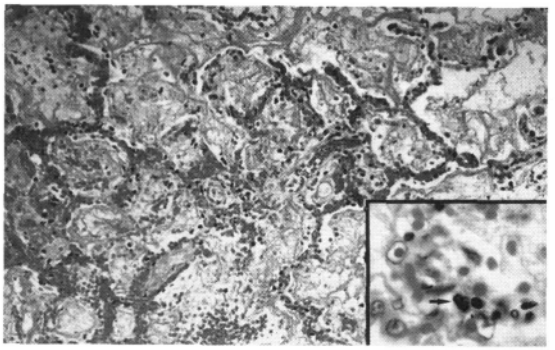

FIGURE 22. Varicella-zoster pneumonia. Extensive necrosis of the parenchyma with intra-alveolar edema and few mononuclear cells in the interstitium. Hematoxylin and eosin, ×100. **Inset**: Intranuclear inclusions (*arrow*) in a focus of necrosis. Hematoxylin and eosin, ×1000.

Hantavirus Pulmonary Syndrome (HPS)

The Hantavirus genus, within the *Bunyaviridae* family, includes a group of single-stranded RNA viruses responsible for Hantavirus pulmonary syndrome. The virus shed in saliva, urine, and feces of the deer mouse, *Peromyscus maniculatus,* infects humans through inhalation of aerosols (Kahl et al., 1997). The hallmark of HPS is respiratory insufficiency owing to noncardiogenic pulmonary edema. Most cases progress to severe disease. Radiographic findings include rapid progression to bilateral interstitial and alveolar edema, and pleural effusions (Moolenaar et al., 1997). Gross examination reveals heavy, edematous, airless lungs, usually with bilateral serous pleural effusions. Histologically, there is intra-alveolar and septal edema, patchy fibrinous alveolar exudate and hyaline membranes, interstitial infiltration with mononuclear cells, and an absence of neutrophils, cellular debris, and evidence of vasculitis or thrombosis. Although the disease resembles ARDS histologically, there are no neutrophilic infiltrates or type II pneumocyte hyperplasia unless there is a prolonged course or history of prolonged mechanical ventilation (Kahl et al., 1997; Moolenaar et al., 1997). Immunohistochemical analysis shows the widespread presence of hantaviral antigens in endothelial cells of the microvasculature. Hantaviral inclusions are usually present in endothelial cells of the lungs in association with pulmonary capillary leak (Zaki et al., 1995).

Human Herpesvirus 6

Human herpesvirus 6 (HHV-6) infects more than 90% of the U.S. population early in life, causing fever and rash in some children, a disease called roseola or exanthem subitum (Yamanishi et al., 1988). In immunocompetent adults, DNA of HHV-6 is commonly found in peripheral blood mononuclear cells and saliva, suggesting that the infection is lifelong (Cone et al., 1993). Over the past several years it has been demonstrated that HHV-6 is an important opportunistic pathogen in immunocompromised patients and causes fatal pneumonitis

in adult bone marrow transplant recipients and in adult patients with AIDS (Cone et al., 1993; Knox et al., 1995). Pathological findings include interstitial pneumonitis, diffuse alveolar damage, extensive atelectasis, diffuse mononuclear inflammatory infiltrates, and hyperplasia of type II pneumocytes (Knox et al., 1995).

Epstein-Barr Virus

Pulmonary involvement during acute infectious mononucleosis is rare (Dunnet, 1963). Epstein-Barr virus-infected lymphocytes can infiltrate the lung, especially in AIDS patients, and this condition is characterized pathologically by interstitial pneumonitis with marked mononuclear inflammatory infiltrate (Sriskandan et al., 1996).

Protozoal Infections

Toxoplasma gondii infection is a major cause of morbidity and mortality in HIV-infected patients (St. Georgiev, 1993). The overall prevalence of pulmonary toxoplasmosis in AIDS is approximately 0.5%. Reactivation of latent disease is the most common cause of pulmonary toxoplasmosis in the immunocompromised host. Rare cases have been reported in immunocompetent individuals. It usually accompanies cerebral or disseminated infection. Radiologically, diffuse bilateral pneumonia, multiple miliary nodules, and interstitial and lobar infiltrates have been described. Pleural effusion and pneumothorax have also been reported. Histologically, there may be necrotizing pneumonia, diffuse alveolar damage, and interstitial pneumonitis (Campagna, 1997). Organisms may be found in the alveolar spaces, alveolar macrophages, and capillary endothelial cells. Giemsa, hematoxylin-eosin, and eosin-methylene blue stains may show crescent-shaped tachyzoites (Campagna, 1997; Baird et al.. 1994).

Amebiasis is the third leading parasitic cause of death in the world. Pleuropulmonary complications of *Entamoeba hixtolytica* infection occur almost exclusively in individuals with liver abscess. Common pleuropulmonary complications of rupture of hepatic amebic abscess into the pleural space include right-sided pleural effusions, empyema, basilar atelectasis, and lung abscess (Lyche & Jensen, 1997). The core of an amebic abscess contains necrotic debris with occasional inflammatory cells and trophozoites. The latter are concentrated in the periphery of viable tissue around the abscess (Baird et al., 1994; Lyche & Jensen, 1997).

Protozoa such as *Plasmodium, Babesia,* and *Cryptosporidium* seldom cause pulmonary disease. Infection with *P. falciparum* produces acute pulmonary insufficiency in 7% of nonimmune hosts via the development of pulmonary edema (Kemper, 1997). Pleural effusions, interstitial edema, and lobar consolidations have also been reported (Baird et al., 1994). *Babesia microti* can also produce respiratory failure and ARDS similar to *P. falciparum.* Many cases of *Cryptosporidium parvum* infection have been complicated by the presence of concurrent pulmonary infections, but the contribution of the cryptosporidial infection to significant pulmonary disease in these cases is not clear. Virtually all the cases reported with evidence of the organism in respiratory specimens also had intestinal disease. The organism was found along the ciliated border of the bronchial and tracheal mucosa and in the bronchial submucosal glands (Baird et al., 1994; Kemper, 1997). Microsporidium has been reported in AIDS patients who developed pleuritis and a lobar infiltrate with edema, vascular congestion, and a mixed inflammatory infiltrate. Microsporidian spores of *Encephalitozoon helium* can be found within the cytoplasm of bronchiolar and alveolar duct epithelial cells (Kemper, 1997).

P. carinii pneumonia is caused by an organism more closely related to fungi than protozoa. This organism is a common cause of pneumonia in immunocompromised patients (Kroe et al., 1997). Grossly, the pulmonary parenchyma appears pale-gray and firm. The infiltrate may be patchy or progress to lobar or whole lung involvement. Atypical bronchopneumonic patterns are not uncommon (Miller et al., 1994; Sobonya, 1994). When associated with the histologic pattern of diffuse alveolar damage, the process involves a large portion of the pulmonary parenchyma, and the lungs are pink-gray (Sobonya, 1994). The most characteristic histologic feature is the presence of intra-alveolar foamy eosinophilic exudates on hematoxylin and eosin stain. Basophilic dots may be seen within the exudates. The alveolar septa are lined by hyperplastic type II pneumocytes. The interstitium in some

cases contains an infiltrate composed of plasma cells, lymphocytes, and histiocytes (Weber et al., 1977). Cavitary lesions, pneumothoraces, granulomas, and pleural effusions are less common (Sobonya, 1994; Travis et al., 1990).

Helminthic Infections

Unlike most pulmonary pathogens, many helminthic parasites migrate to the lung from distant portals of entry. Many respiratory syndromes are a direct result of parasite migration through the lung as part of its natural life cycle. Although the role of parasites as etiologic agents of CAP is unclear, some parasitic infections deserve consideration.

Strongyloides stercoralis is endemic in tropical and subtropical areas worldwide. The parasitic females live buried in the crypts of the duodenum and upper jejunum producing eggs that develop rapidly into larvae that pass in the feces (rhabditoid larvae) and continue maturation to the infective form in the fecal mass or soil. Infective (filariform) larvae penetrate the skin and travel via the bloodstream to the lungs, break into the alveoli, migrate to the epiglottis, are swallowed, and once in the duodenum, mature to adult females (Gutierrez, 1990). Migration of the larvae through the lungs is obligatory. In the pulmonary capillaries, the larval penetration of the alveoli causes petechial hemorrhages and infiltrates of polymorphonuclear leukocytes and monocytes. Sensitized patients may experience discomfort, but usually there are no symptoms (Baird et al., 1994; Haque et al., 1994). However, in patients with compromised immunity, autoinfection leads to life-threatening hyperinfection. Large numbers of larvae migrate to the lungs. Grossly, there is uniform consolidation of all lobes, hemorrhagic cut surfaces, and bronchi filled with inspissated mucus. Microscopically, there is hemorrhage, a variable inflammatory reaction, and presence of *S. stercoralis* infective larvae in alveolar spaces, in the bronchi, and within mucous plugs (Fig. 23) (Baird et al., 1994; Gutierrez, 1990). Chronic strongyloidiasis, especially in immunocompromised hosts, may cause cavities and abscesses in the lungs. ARDS may be present. The lung may also show changes secondary to superimposed bacterial infection (Baird et al., 1994; Haque et al., 1994; Wehner & Kirsh, 1997).

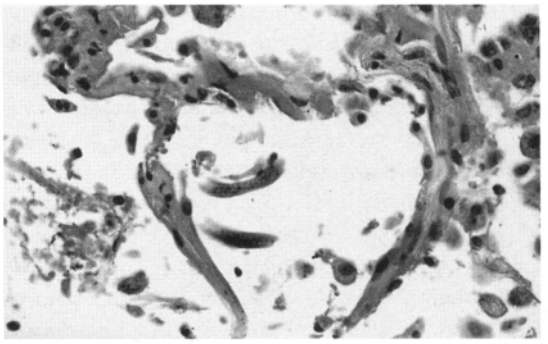

FIGURE 23. *Strongyloides stercoralis* in alveolar spaces (filariform larvae) in an immunosuppressed patient (Contributed by A. K. Haque, M.D., Galveston, Texas).

Pulmonary manifestations *of Ascaris lumbricoides* occur during the stage of larval migration through the lungs and are rarely a complication of the intestinal phase. This is the most common worldwide cause of transient eosinophilic pulmonary infiltrates (Löffler's syndrome) (Sarinas & Chitkara, 1997). Pathologically, the lungs show consolidated gray patches most often in the lower lobes. Bronchioles contain eosinophils and fibrin. Interstitial pneumonitis with thickened alveolar walls may be present. *A. lumbricoides* may be found within alveolar walls, bronchioles, and bronchi. Granulomata may develop and consist of larvae surrounded by clusters of eosinophils, histiocytes, and epithelioid cells (Baird et al., 1994; Sarinas & Chitkara, 1997). Lung pathology in hookworm infection *(Ancylostoma duodenale* and *Necator americanus)* may show intra-alveolar hemorrhage caused by the larval migration through capillary walls and interstitial pneumonitis (Sarinas & Chitkara, 1997).

Dirofilaria, Toxocara, and the filarial parasites, *Wuchereria* and *Brugia,* produce an array of pulmonary manifestations in humans. Infections are common in temperate, tropical, and subtropical regions of the world. Human pulmonary dirofilariasis is caused by a ubiquitous canine parasite, *Dirofilaria immitis,* the dog heartworm (Chitkara & Sarinas, 1997). Larvae are transmitted by mosquito bite to another dog or human being. Most larvae die in the subcutaneous tissue. Some develop further and reach the right ventricle before dying and em-

bolizing to the pulmonary arteries, producing thrombosis, infarction, and subsequently a granulomatous reaction. Most commonly, radiologic studies show a spherical, peripherally located solitary pulmonary nodule that ranges from 1 to 4.5 cm in diameter (Asimacopoulos et al., 1992). The nodule is a localized infarct that shows a narrow zone of granulomatous reaction surrounded by a well-formed fibrous wall and in some cases eosinophilic inflammation. *Dirofilaria* is identified as a smooth multilayered organism with a thick cuticle, transverse striations, broad lateral cords, and a thick band of somatic muscles projecting far into the body cavity (Fig. 24) (Baird et al., 1994; Chitkara & Sarinas, 1997). If the parasite has degenerated, it can easily be missed in hematoxylin and eosin-stained tissue. Nonspecific fluorescent whitening stain aids in distinguishing the organisms or its fragments within granulomas (Green et al., 1994). Visceral larva migrans (VLM) or systemic toxocariasis is a zoonotic disease with human viscera involved by the migrating larvae of *T. canis* or *T. cati.* Pulmonary involvement, both in children and adults, occurs in 20% to 85% of cases of VLM. Asthma, acute bronchiolitis, and acute pneumonia can develop (Taylor et al., 1988), frequently with bilateral segmental, or diffuse alveolar infiltrates. Eosinophils predominate in the early response. Histiocytes and granulomata are present (Baird et al., 1994; Chitkara & Sarinas, 1997).

Wuchereria bancrofti and *Brugia malayi* usually cause tropical pulmonary eosinophilia with functional alterations in the lungs characterized by wheezing, dyspnea, and pain or tightness in the chest. Extreme eosinophilia persists for weeks (Baird et al., 1994). Histologically, there are eosinophilic abscesses and granulomata with foreign-body giant cells and palisading epithelioid cells (Baird et al., 1994; Chitkara & Sarinas, 1997). Interstitial fibrosis may develop with a residual mixed inflammatory infiltrate. Cavitation, bronchiectasis, and pleural effusions are uncommon.

Paragonimiasis (caused by *Paragonimus westermani)* is a parasitic disease of carnivorous animals including humans. The clinical symptoms are often the cause for an erroneous diagnosis of tuberculosis (Kagawa, 1997). When the larvae penetrate the visceral pleura, they may cause a small to massive exudative effusion. They can also cause bronchiectasis, interstitial pneumonitis. or bronchopneumonia with transitory hemorrhage. An exudate of eosinophils and neutrophils surrounds the worms. A fibrous wall may rupture into a bronchiole, and the patient may expectorate blood-streaked sputum containing parasite eggs, inflammatory cells, Charcot–Leyden crystals, and necrotic tissue (Baird et al., 1994; Kagawa, 1997).

Echinococcosis (hydatid disease) is caused by the postlarval metacestode stage of the dog tapeworms *Echinococcus granulosus* and *E. multilocularis* (Bhatia, 1997). Pulmonary disease is a complication of liver involvement (Baird et al., 1994). Cysts in the lung are not life-threatening. Histologically, cysts of *E. granulosus* and *E. vogeli* are surrounded by a thick wall of the host fibrous tissue. Cysts of *E. multilocularis* are surrounded by necrotic debris and occasionally cavitate. Those that rupture into the bronchi may cause chronic suppuration and abscess. Necrotizing granulomas have been reported (Baird et al., 1994; Bhatia, 1997).

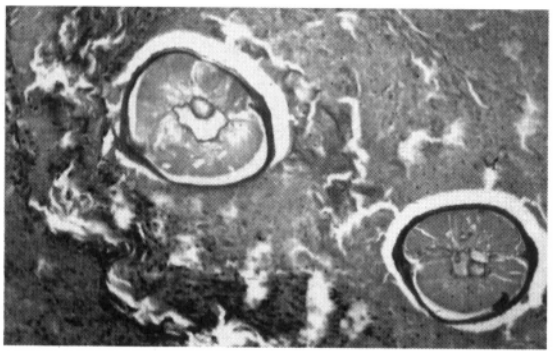

FIGURE 24. Transverse section of immature *Dirofilaria immitis* in a pulmonary vessel surrounded by necrotic tissue. Hematoxylin and eosin, ×250.

Chemical Pneumonia

There are noninfectious conditions that can produce a clinical syndrome similar to pneumonia which may result in lung injury and consequent impairment of pulmonary function following acute or chronic exposure. If the clinical picture does not fall in line with the more common causes of CAP, consideration of these "unusual" causes of pneumonia may be essential. Two mechanisms account for the lung toxicity encountered in most patients

with chemical pneumonia: (1) inhalation of the toxic agent, causing direct irritation and inflammation of the tracheobronchial tree resulting in pulmonary edema (e.g., ammonia, nitrogen dioxide) and (2) absorption of noxious substances that can affect the lung directly or through their metabolites (White & Templeton, 1992).

Organic Chemical Agents

Mineral Oils

The aspiration of mineral oils used as laxatives or nose drops by the elderly patients is well known. However, occupational exposure occurs in industries in which large amounts of lubricants are used. Pulmonary disease may be caused by acute or chronic inhalation of oil mists or aspiration (White & Templeton, 1992). Radiologically, there are multiple small opacities and more focal, often basal, consolidations (Weill, et al., 1964). The lungs are gray to yellow and solid. The air spaces are filled with vacuolated or foamy macrophages. There are foreign–body multinucleated giant cells, an inflammatory exudate, and fibrous obliteration and reduction of the lung parenchyma (Pinkerton, 1928).

Organophosphates

The organophosphates are a group of anticholinesterase-inhibiting compounds that have attained global usage as agricultural pesticides. Farmers and crop sprayers are at risk for occupational exposure, especially from parathion and malathion (Namba et al., 1971). They are absorbed through the gastrointestinal tract, the lungs, and the mucous membranes. The depletion of synaptic acetylcholinesterase results in a prolongation of the effects of acetylcholine and systemic parasympathetic symptoms. In the lungs, organophosphate toxicity is characterized by bronchial hypersecretion, bronchoconstriction, and depression of the respiratory center and musculature, leading to hypoxia and death. The lungs show diffuse pulmonary edema (Bledsoe & Seymour, 1972).

Paraquat

Paraquat is an herbicide that is used in agriculture in more than 130 countries. Poisonings may be occupational but are often intentional. Paraquat accumulates in the lungs and is thought to be responsible for the production of superoxide radicals, which indirectly damage the pulmonary alveoli (Bismuth et al., 1990). The lungs show diffuse pulmonary consolidation due to pulmonary edema followed by alveolar fibrosing alveolitis (Im et al., 1991; Davidson & MacPherson, 1972).

Polyvinyl Chloride

Polyvinyl chloride (PVC) is a polymer used in the plastics industry. Workers sustain ill effects from fumes or dust caused by PVC or vinyl chloride. Inhalation of PVC fumes has been associated with acute bronchospasm. Lengthy exposure leads to a pneumoconiosis characterized histologically by pulmonary fibrosis with a granulomatous reaction (Cordasco et al., 1980; Lilis, 1980).

Thesaurosis

The term thesaurosis has been applied to lung disease associated with the use of hair sprays. Hairdressers are at occupational risk, and significant accidental exposure may occur at home. The most important chemical in hair sprays, polyvinylpyrrolidone, is responsible for inciting a sarcoid-like illness. Interstitial pneumonitis, fibrosing alveolitis, and granulomata are the histological findings (Bergmann et al., 1958).

Other organic chemicals that produce pulmonary edema after exposure include tetrafluoroethylene (Teflon®) fumes and trimellitic anhydride (TMA). The latter is used in the manufacture of paint, epoxy resins, and plasticizers (White & Templeton, 1992). Inhalation of kerosene may produce pulmonary edema and interstitial pneumonitis (Nussinovitch et al., 1992). Similar findings may be seen after furniture polish and lighter fluid ingestion, frequently seen in small children. Pneumatoceles are a late complication of hydrocarbon ingestion after the consolidation has cleared. These are often large, septate, and irregular, and sometimes contain fluid (Akisu et al., 1996). Chronic intoxication due to abuse of solvents, including thinner, by workers who inhale the solvent vapor is frequently encountered, but acute intoxication may lead to severe complications such as rhabdomyolysis, polyneuropathy, and chemical pneumonia (Harris & Brown, 1975).

Inorganic Chemicals

Gases

Ammonia is a corrosive gas used in the production of explosives, petroleum, agricultural fertilizers, and plastics. The chemical is also used in refrigeration. Prolonged exposure produces pulmonary edema. Patients who survive may develop bronchiectasis or bronchiolitis obliterans (Caplin, 1941). Chlorine is an irritant gas used in the manufacture of plastics and bleaches and in water purification. Its irritant properties made it a desirable agent for chemical warfare in World War I (Jones et al., 1986). Toxicity results from its reaction with water, which produces unstable oxidizing agents. The reaction of the oxidizing agents to form hydrates of organic chloride causes tissue damage, with ulceration and swelling of mucosal surfaces. Chest radiographs usually demonstrate bilateral opacities typical of pulmonary edema. A complicating pneumonia may occur within several days (Beach et al., 1969). The toxic effects of nitrogen oxides are best described in workers exposed to forage silo gas (silo–filler's disease), but occupational hazard is well recognized in mining, acetylene welding, and in the manufacture of explosives. In forage silos, nitrogen oxides are produced by the fermentation of corn or hay. When inhaled, they combine with water to form nitric acid, which causes severe tissue damage (Morrissey et al., 1975). Histopathologic examination of the lungs during the acute phase demonstrates mucosal edema and inflammatory cell exudation. Alveolar capillaries are dilated and congested with edema fluid and blood filling the alveolar space. Bronchiolitis obliterans may also develop (Casey, 1991). Phosgene ($COCl_2$) is best known as a lethal chemical warfare agent used in World War I. It is also used as a chlorinator in the production of organic dyes and in the separation of metals (Everett & Overholt, 1968). The gas produces pulmonary edema, which may be fulminant. In animals, it can produce ulcerative bronchitis and obliterative bronchiolitis (Casey, 1991).

Metals

Occupational exposure to cadmium fumes occurs in ore smelting, alloying, and welding. After inhalation, it is absorbed into the bloodstream and produces tracheobronchitis and pulmonary edema. Long-term exposure has been implicated in the development of emphysema, both panacinar and centrilobular (White & Templeton, 1992). Exposure to mercury vapor occurs in the manufacture of thermometers and in the cleaning of boilers. Severe tracheobronchitis and pulmonary edema may develop. Interstitial fibrosis occurs in some patients (Seaton & Bishop, 1978; Hallee, 1969). Pneumonitis, bronchitis, and pulmonary edema have also been described in association with exposure to compounds of osmium, manganese, nickel, and vanadium (White & Templeton, 1992; Casey, 1991).

The variety of CAP cases that occur throughout the world are influenced by epidemiologic and host factors that require careful evaluation of the past medical history, travel, and occupation as well as microbiologic, histopathologic, and in some cases, toxicologic investigation.

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