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Anaerobic and Unusual Bacterial Pneumonias

Aileen M. Marty
Ronald C. Neafie
Lloyd L. Smrkovski

This chapter is devoted to pleuropulmonary disease caused by anaerobic bacteria, to pulmonary gangrene, and to a group of relatively rare but extremely important bacterial infections of the lung. Among the latter, plague, tularemia, and anthrax are highly infectious, and their recognition should prompt immediate notification of the state health authorities.

ANAEROBIC PLEUROPULMONARY INFECTIONS

The anaerobes include all morphologic forms of bacteria: cocci, coccobacilli, straight rods, curved rods, and spiral rods. They can be gram positive or gram negative. Some of the gram-positive organisms produce spores, and others do not (Fig. 39-1). Although a variety of these organisms have been recovered from pulmonary lesions, we are highlighting two agents of anaerobic pneumonia: *Peptostreptococcus* species and *Bacteroides* species. Treatment of the diseases they produce is difficult because many of these infections are deep seated and polymicrobial.[1]

Anaerobes usually produce an initial suppurative aspiration pneumonia that can progress to a lung abscess or produce a pleural fistula with empyema. Multiple species of aerobic and anaerobic bacteria usually are isolated from these lesions (Display 39-1). The risk factors include conditions that predispose to aspiration, such as alcoholism, drug addiction, seizure disorders, neurologic diseases, anesthesia, and dysphagia. Bronchial obstruction caused by stenosis, enlarged lymph nodes pressing on the airways, foreign bodies, or neoplasms also predispose to anaerobic pulmonary disease.

Anaerobes are common bacteria of the oral cavity. Anaerobic periodontal disease can serve as the source of infection. The bacteria are inhaled by patients in the recumbent position, and the lesions preferentially involve the apical segment of the lower lobe and the posterior segment of the right upper lobe (Fig. 39-2). The basilar segments of the lower lobes are also preferred if aspiration takes place while the person is in the upright position.

Patients with anaerobic aspiration pneumonia present with the typical findings of an acute pneumonia, but the symptoms tend to develop at a slower pace. The patients develop a productive cough, fever, dyspnea, and leukocytosis. Frequently, the sputum is putrid and empyema is present. Rapidly forming large effusions of foul-smelling fluid are characteristic. Chest x-ray films reveal evidence of tissue necrosis with cavity formation.

Cases of pleuropulmonary infections caused by *Peptostreptococcus* sp. are documented.[2,3] *Peptostreptococcus* organisms are gram-positive anaerobic cocci. Four species, *Peptostreptococcus anaerobius*, *Peptostreptococcus magnus, Peptostreptococcus asaccharolyticus*, and *Peptostreptococcus prevotii*, account for most infections in humans.

Bacteroides species can cause severe pneumonia that is often accompanied by empyema. Two mechanisms of pulmonary infection are known. Blood-borne infection is most common in women with pelvic sepsis caused by *Bacteroides* species. In elderly men with chronic lung disease, the route of infection is most likely the tracheobronchial tree from infected tonsillar crypts, carious teeth, or the upper gastrointestinal tract. The lower lobes are often affected with bronchopneumonia, total lobar consolidation, and cavitation. The most common species involved in pleuropulmonary infections is *Bacteroides melaninogenicus*.

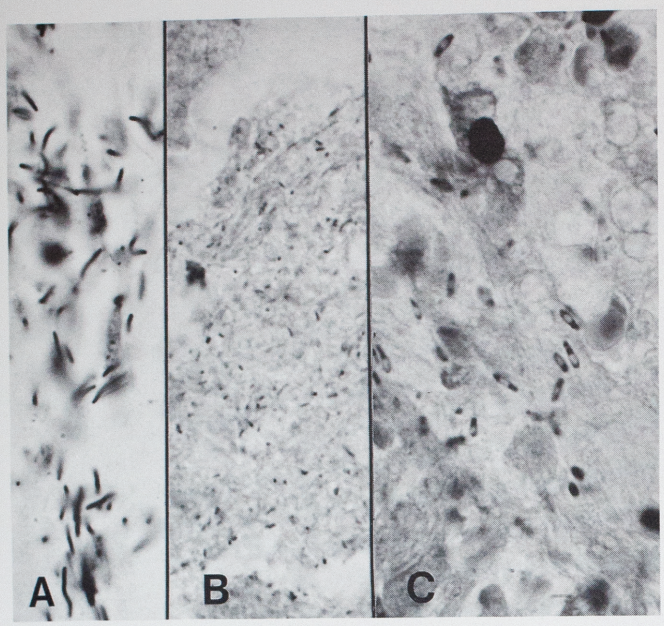

FIGURE 39-1. (**A**) Numerous, long, curved, gram-negative bacilli of *Fusobacterium nucleatum* are present in an inflamed placenta. (Warthin-Starry stain; oil immersion view.) (**B**) Numerous tiny, straight, gram-negative bacilli of *Bacteroides* sp. in necrotic liver. (Brown & Hopps stain; oil immersion view.) (**C**) Gram-positive bacilli of *Clostridium septicum* in a lung, demonstrating subterminal spores. (Brown & Hopps stain; oil immersion view.)

Grossly, the lungs are discolored and soft and have a pronounced foul smell. Microscopic examination reveals extensive necrotizing inflammation with suppuration (Color Fig. 39-1). However, mononuclear cells may predominate over neutrophils in some cases. Tissue Gram stains disclose a mixed bacterial population in the necrotic tissue.

Gram-negative rods are difficult to differentiate by light microscopy, and when antibiotics have been administered, they can become too scarce to be detectable. The diagnosis depends on bacterial culture under strict anaerobic conditions. It is likely that in the future the diagnosis will be made using molecular techniques. DNA probes for anaerobic bacteria are being introduced into clinical laboratories.[4,5] However, susceptibility testing of a single pathogen from a polymicrobial infection does not necessarily reflect the susceptibility of the pathogen at the site of infection.[6]

DISPLAY 39-1. ANAEROBES FOUND IN PLEUROPULMONARY INFECTIONS

Gram-Positive Cocci

Peptostreptococcus species
Microaerophilic streptococci

Gram-Negative Rods

Bacteroides
- *B. melaninogenicus*
- *B. oralis* group
- *B. buccae*
- *B. ureolyticus* group
- *B. bivius*
- *B. fragilis* group

Fusobacterium
- *F. nucleatum*
- *F. necrophorum*
- *F. naviforme*
- *F. gonidiaformans*

Gram-Positive Spore-Forming Rods

Clostridium

PULMONARY GANGRENE

Gangrene of the lung is a clinicopathologic entity that can be associated with several species of bacteria.[7–10] Other causes include trauma to the lung and torsion of a lobe spontaneously or after surgical ablation of lung tissue or repair of a hiatal hernia. Osler described a diseased lung "converted into a horribly offensive greenish, black mass, torn and ragged in the center."[2] This is probably the first known description of pulmonary gangrene. Pulmonary gangrene usually begins as a lobar pneumonic bacterial

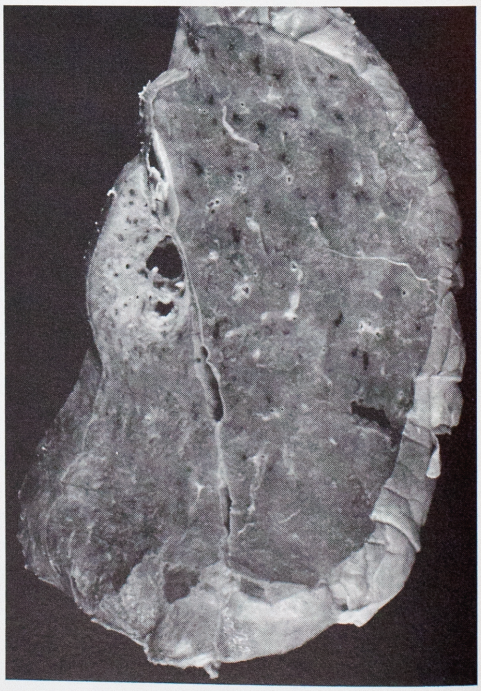

FIGURE 39-2. Aspiration pneumonia characteristically involves the apical segment of the right lower lobe. There is destruction of airways and lung tissue extending to the pleura despite several days of treatment. The patient had a history of neurologic disease and had aspirated in the recumbent position. (Contributed by the editor.)

process. A central mass of lung becomes necrotic, presumably because of arterial and venous vascular occlusion at its periphery. This circumferential devitalization of the lung parenchyma carves out a portion of lung tissue that deflates itself and that may end up floating in a sea of pus. The bacteria cultured from surgical samples with gangrene of the lung are *Klebsiella pneumoniae, Haemophilus influenzae*, *Staphylococcus* species, and *Streptococcus* species.[7] Other bacteria, such as *Pseudomonas aeruginosa*, have been implicated.[8] Why these bacterial infections progress to this more unusual pattern of disease, rather than the more typical pulmonary lesions they produce, is unknown. Preexisting organic lung disease probably plays a role, particularly if accompanied by occlusive disease of the pulmonary vessels. Primary infection or secondary colonization of necrotic lung tissue by anaerobes may explain the pathologic findings in some cases, as in Osler's patient.[2]

Patients with pulmonary gangrene are extremely ill. They present with a high fever, chills, and a cough that produces putrid, brown-green sputum. The sputum may contain chunks of fleshy, necrotic, pulmonary parenchyma. Many patients present with empyema and pleuritic pain. The leukocytosis is usually pronounced. There is a characteristic radiographic pattern of numerous irregular cystic areas interspersed throughout the areas of consolidation.

At surgery or necropsy, the involved lobe is flattened, sloughed, and necrotic (Fig. 39-3). Circumferential adhesions may develop around the lesion, preventing egress of pus to other areas. In the necrotic tissue, the elastic tissue outline of the alveolar structures can still be recognized during histologic examination. Thrombotic occlusion of the terminal vasculature is the hallmark of the lesion. The treatment of choice is lobectomy or pneumonectomy; spontaneous resolution or resolution after medical management with antibiotics is unusual.[10]

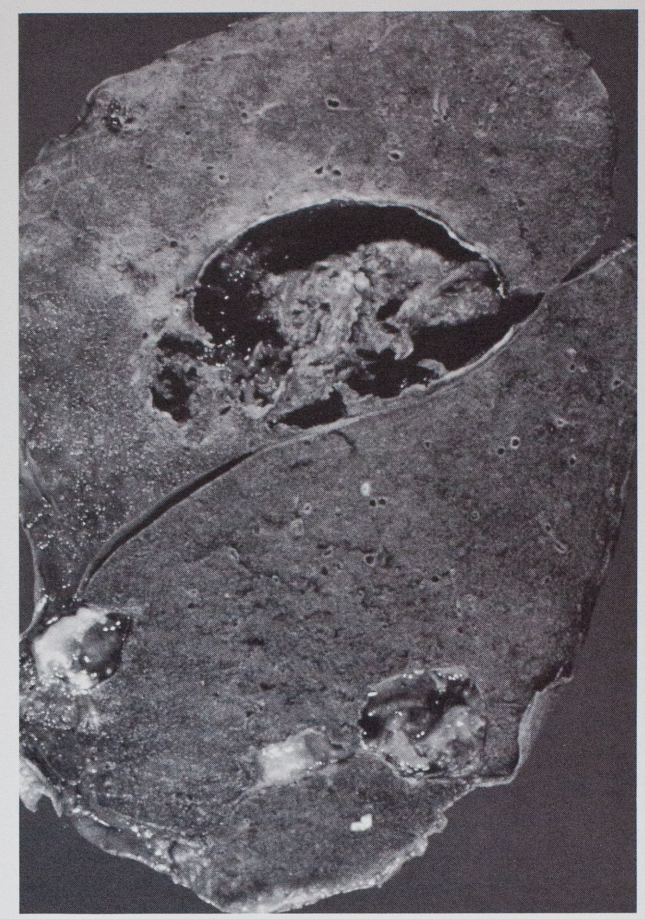

FIGURE 39-3. Sagittal section of the left lung shows several lesions of pulmonary gangrene caused by anaerobic bacterial infection with associated empyema. The larger cavity in the upper lobe contains a necrotic sequestrum. (Contributed by the editor.)

UNUSUAL BACTERIAL PNEUMONIAS

Legionellosis

Legionellosis is caused by bacteria of the genus *Legionella*. Although relatively recently recognized as pathogens, *Legionella* species are among the most common causes of community-acquired pneumonia and are frequently implicated in nosocomial infections.[11,12] Thirty-three species of *Legionella* are recognized, and 50 serogroups are known.[13] About 80% of the documented cases of legionellosis are caused by *Legionella pneumophila*, the first species isolated; the second most common species is *Legionella micdadei*.[14]

The disease occurs in epidemic situations and as a community-acquired disease. Three patterns of epidemics are recognized: explosive point source, ongoing point source, and seasonal upsurges in hyperendemic areas. Legionellae are pervasive contaminants of potable water that reproduce well in the water systems of large buildings such as hospitals. Reproduction is encouraged by water temperatures below 50°C, areas of stagnation, sludge formation, and the presence of amebas.[15] Air-conditioning cooling towers and evaporative condensers are frequently the environmental source of epidemic outbreaks. The incidence of the disease is higher among men and persons older than 50 years of age.[16]

Two clinical presentations of legionellosis are recognized: an acute pneumonia with high mortality and a self-limited flulike illness. The milder form of the illness is called Pontiac fever or Lochgoilhead fever.[17] The acute pneumonia is usually preceded by several days of fever, chills, malaise, and myalgia. The patients manifest a lobar or lobular pneumonia. Chest x-ray films usually reveal a patchy infiltrate that evolves into five-lobe consolidation. Infiltrates are bilateral in about 70% of these patients. Less commonly, patients develop lung abscesses.[18] Some patients have mild to severe extrapulmonary symptoms. Extrapulmonary manifestations include, diarrhea, encephalopathy, and renal failure. Neurologic manifestations tend to appear concurrently with or soon after the onset of fever; rarely, neurologic manifestations precede the development of pneumonia.[19] Dual infection with multiple species, multiple serotypes, or even multiple subtypes can occur.[20]

The legionellae are facultative intracellular pathogens; they multiply within the phagosome of mononuclear phagocytes and are not killed efficiently by neutrophils. Many functional defects of the host and virulence factors of the bacteria permit the intracellular survival of the legionellae, and no single factor appears to be responsible for virulence.[21] *Legionella* species infect specific algae and protozoan hosts in nature.[22,23] *Hartmanella vermiformis* supports several species of *Legionella*. A study of a strain of *Legionella anisa* that was responsible for an outbreak of Pontiac fever revealed that some species of *Legionella* are extremely host specific. The strain of *L. anisa* multiplied only in *H. vermiformis* and not in human phagocytic cells or other protozoans. The inability of this strain to multiply in human phagocytic cells could explain why it produced Pontiac fever rather than pneumonic legionellosis in the exposed persons.[24] The ability of legionellae to infect only certain host cells probably contributes to the differences in human diseases.

The lungs of patients with Legionnaire's disease are heavy

FIGURE 39-4. The involved lung parenchyma is pale and firm in a patient who died of Legionnaire's disease. The patient was a heavy smoker and had extensive centrilobar emphysema. The necrosis with abscess formation in the right lower lobe is a rare but well-known feature of this disease. (Contributed by the editor.)

and have a multifocal lobular pneumonia. The lesions tend to become confluent, producing sublobar or, less commonly, lobar consolidations (Fig. 39-4). There is minimal damage to the pleura. The large amount of fibrin in the exudates generates a granular, white appearance after formalin fixation. The inflammatory material is easily scraped from the cut surface of the lung. Severe cases include marked pulmonary edema.

Microscopic examination reveals an acute fibrinopurulent pneumonia. The architecture of the lung is preserved. The changes are those of a mixed inflammatory infiltrate occurring predominantly within the alveoli and small airways. The proximal bronchioles and bronchi are usually spared. There is minimal interstitial inflammation. The exudate is a mixture of macrophages, neutrophils, and fibrin (Fig. 39-5). Macrophages predominate in most cases, but neutrophils are more abundant in others. Lysis of the exudate is characteristic. Diffuse alveolar damage with hyaline membrane formation occurs frequently. The Warthin-Starry stain at *p*H 4.0 and the Dieterle silver stain coat the bacteria and are useful for demonstrating *Legionella* organisms (Color Fig. 39-2). Gram-negative rods can be seen with the Brown-Hopps Gram stain (Fig. 39-6). Although *L. micdadei* is gram negative, it retains fuchsin against acid decolorization; therefore, it stains with Ziehl-Neelsen, Kinyoun, and Fite-Faraco stains (see Fig. 39-6). A specific immunofluorescence stain can demonstrate the bacteria.

Organs other than the lung usually develop only mild inflammatory changes, but some patients have developed hepatic abscess, skin abscess, pyelonephritis, cerebral microglial reactions, pericarditis, and endocarditis.

Most laboratories arrive at a definitive diagnosis of legionellosis by specialized laboratory testing, especially culture, because the clinical presentation is nonspecific. Sputum cultures are valuable for virtually all species of *Legionella*. *L. pneumophila, L. micdadei*, and *Legionella bozemanii* can be detected in bronchoalveolar lavage fluid specimens by DNA amplification of a specific fragment of the

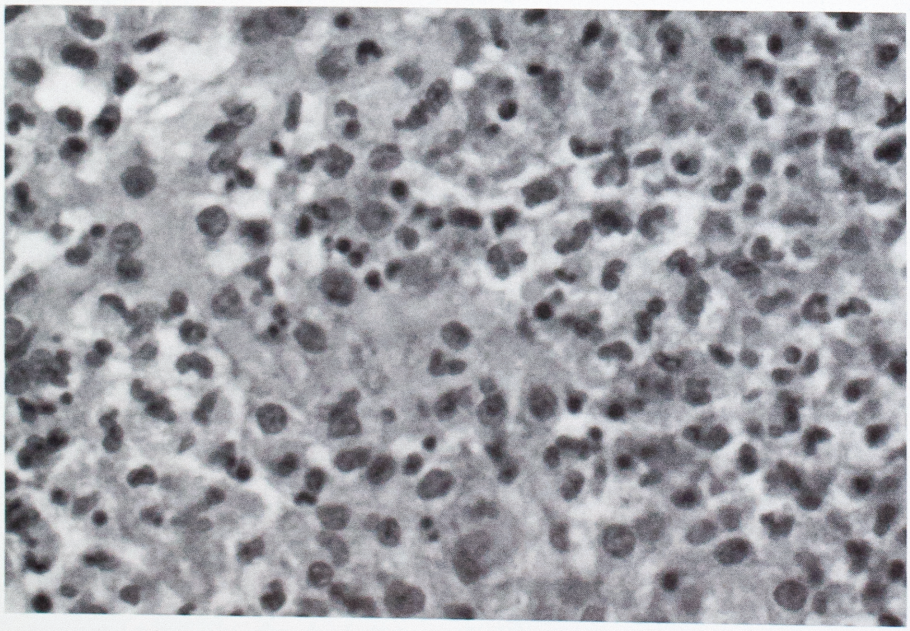

FIGURE 39-5. In this microscopic view of Legionnaire's pneumonia in the same patient as in Figure 39-4, there is a dense infiltrate of macrophages and neutrophils (see Color Figure 39-2). (H & E stain; high magnification; contributed by the editor.)

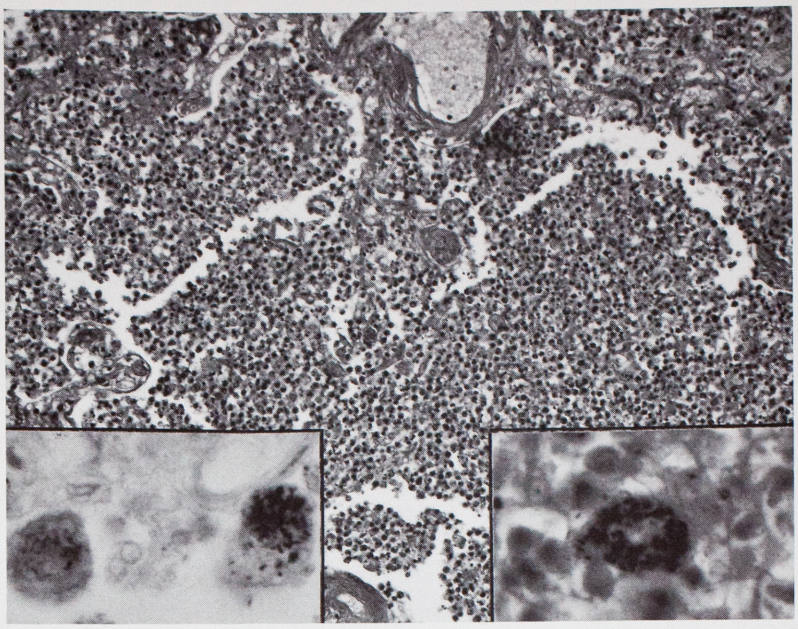

FIGURE 39-6. The alveolar infiltrate is predominantly mononuclear in pneumonia caused by *Legionella micdadei*. (H & E stain, low magnification). The left inset shows gram-negative bacilli delineated with Brown & Hopps stain; the right inset shows a macrophage stuffed with tiny, acid-fast bacilli highlighted by Ziehl-Neelsen stain. (Oil immersion.)

macrophage infectivity potentiator gene from *L. pneumophila*.[25] *In situ* DNA hybridization and detection with an avidin-alkaline phosphatase complex can be used to visualize *Legionella* organisms by light microscopy within the alveoli of lung specimens, but the current technique is not highly sensitive.[26] The urine of patients can be tested for Legionnaire's disease using an enhanced chemoluminescence enzyme-linked immunosorbent assay that detects soluble antigen.[27] Serology is available but can be misleading, because positive anti-*Legionella* antibodies occur with considerable frequency in asymptomatic adults.[28]

Legionella pneumonia can fail to resolve and progress to pulmonary fibrosis with decreased pulmonary function. The treatment of choice is erythromycin.[29] Quinolones have antibacterial activity against intracellular pathogens, and they are useful against *L. pneumophila*.[30]

Plague

The notorious black death of the Middle Ages, plague is caused by a gram-negative bacillus of the Enterobacteriaceae group, *Yersinia pestis*.[31] Plague is primarily a zoonotic infection that predominantly affects rodents, pigs, and birds; humans are accidental hosts. Human plague is typically preceded by an outbreak of plague in the local rodent population, usually rats.[32] In the United States, ground squirrels, rock squirrels, and prairie dogs are the major reservoirs of infection. *Y. pestis* is transmitted from rodent to rodent, from rodent to human, or from human to human by fleas, chiefly *Xenopsylla cheopis* in Asia and *Ceratophyllus fasciatus* in Europe and America. The contaminated flea bite, which usually occurs on the legs, leads to infection of the regional lymph nodes.[33] The lymph nodes enlarge to form the characteristic buboes of bubonic plague. Bubonic plague, an acute febrile lymphadenitis, is the most common clinical form of infection.

Pulmonary infection can occur in two ways. Bubonic plague can progress to septicemic plague with secondary pulmonary involvement, and moribund patients with secondary pneumonic plague expectorate numerous bacilli that are readily inhaled by those nursing the sick. Inhalation of bacilli leads to primary pneumonic plague, and although it occurs toward the end of an epidemic of bubonic plague, it then continues to spread without the need for an insect vector. The pulmonary changes of primary pneumonic plague are identical to those of secondary pneumonic plague. Untreated, pneumonic plague is invariably fatal.

Pneumonic plague begins as a severe bronchitis, bronchiolitis, and alveolitis causing a lobular consolidation that can progress to lobar pneumonia with associated fibrinous pleurisy.

Most often, pneumonic plague is secondary to bubonic plague; it presents in the setting of fever and lymphadenopathy with cough, chest pain, and often hemoptysis. The sputum is usually purulent and contains *Y. pestis*. Patients have marked leukocytosis with neutrophilia. Some patients, especially children, develop leukemoid reactions with leukocyte counts as high as 100,000/mm^3. Radiographically, the lung fields show patchy bronchopneumonia, confluent consolidation or cavities. Without therapy, patients become hypotensive, oliguric, develop altered mental status, and can develop disseminated intravascular coagulation.

Primary pneumonic plague can be fatal so rapidly that death occurs on the day of exposure, and it is invariably fatal if antibiotic therapy is delayed for more than 1 day after the onset of illness.

Y. pestis is highly pathogenic. It is encapsulated; thrives on hemic iron; produces abundant endotoxin, coagulases, and fibrinolysins; and is capable of rapid proliferation. *Y. pestis* resists destruction within mononuclear phagocytes. Bacteria released from monocytes are relatively resistant to further phagocytosis.

The lungs of patients with plague reveal widespread hemorrhagic lobular pneumonia. The consolidated zones are gray-red in the center. The remaining lung is congested, hemorrhagic, and edematous. Fluid is readily expressed from the cut surface. Mediastinal and peribronchial lymph nodes are enlarged, edematous, and congested.

Histologic sections display extensive hemorrhage, hyaline membrane formation, proteinaceous edema, and a mixed inflammatory cellular infiltrate. Extensive necrosis is evident, with neutrophils and macrophages filling alveoli and invading bronchioles and bronchi. Many bacilli are found among the inflammatory cells in the small bronchi, bronchioles, and adjacent alveoli; the abun-

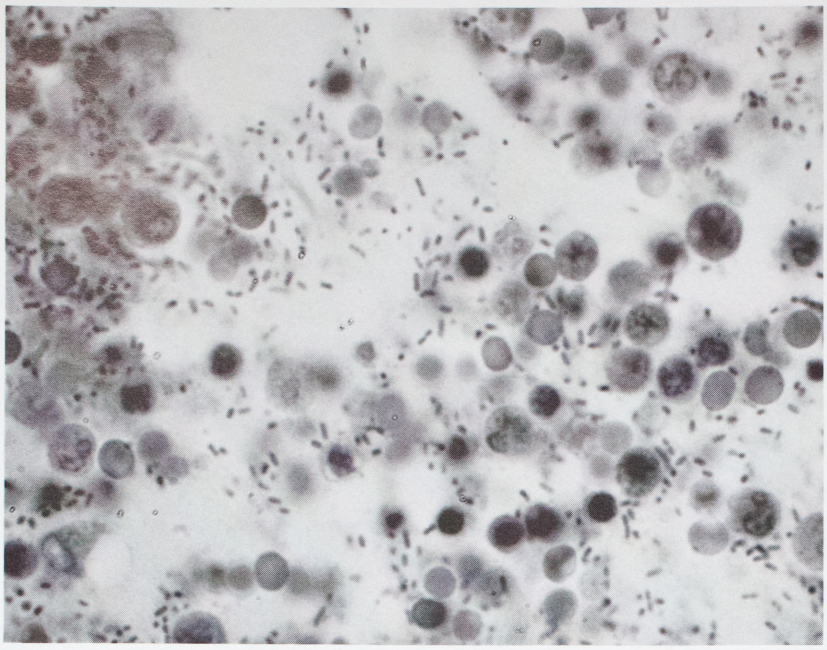

FIGURE 39-7. The numerous, pleomorphic, gram-negative bacilli of *Yersinia pestis* have a safety-pin configuration in the exudate of a primate lymph node. (Giemsa stain; oil immersion.)

dance of bacteria produces a bluish haze on slides stained with hematoxylin and eosin. *Y. pestis* is a 0.5- to 1.5-μm-long, gram-negative bacillus with prominent bipolar staining that produces a safety-pin configuration (Fig. 39-7).

Plague, because of its high morbidity, is one of the three internationally quarantinable diseases, along with cholera and yellow fever. Care must be taken by laboratory personnel handling material suspected of harboring this bacillus. A vaccine is available for persons traveling to epidemic or hyperendemic areas, for rodent handlers, and for laboratory workers exposed to *Y. pestis*.

Tularemia

Tularemia is a systemic disease caused by *Francisella tularensis* (*i.e., Pasteurella tularensis*). Tularemia is endemic in ground animals, especially rabbits, hares, and muskrats, and it can be transmitted to humans through the handling or consumption of improperly cooked meat of these animals. In the United States, most infections are acquired through tick bites.[34,35] Transmission by mosquito also occurs.[36] Less commonly, the disease is transmitted by animal bites (*e.g.*, cat, squirrel, coyote), inhalation of infectious aerosols, or ingestion of contaminated water.[37] Men are infected three to four times more often than women.[38]

Most patients have an abrupt onset of fever, chills, malaise, and fatigue, and they develop one of five clinical syndromes. The most common syndrome is ulceroglandular disease, characterized by an ulcerated skin lesion and painful regional lymphadenopathy; the remaining four syndromes are glandular, typhoidal, oculoglandular, and oropharyngeal tularemia. Pleuropulmonary complications are seen in a large percentage of typhoidal tularemia and in 10% to 15% of the ulceroglandular cases.

Tularemia pneumonia usually occurs in bacteremic patients who have acquired the infection parenterally. Inhalation of *F. tularensis* causes fever, headache, malaise, and a nonproductive cough with or without radiologic evidence of pneumonia. Some patients have abnormal roentgenograms without respiratory symptoms. Some develop lobar pneumonia, and rarely, patients present with a lung abscess or an isolated pleural effusion.[39] Ingestion of the bacteria can cause inflammation of the pharyngeal mucosa with cervical lymphadenopathy. A rash occurs in about 20% of patients. *F. tularensis* is a facultative intracellular gram-negative coccobacillus, and serum antibodies alone do not confer significant protection against infection, but cell-mediated immunity does.[40,41]

At autopsy, the lungs exhibit multifocal pneumonia. Multiple microabscess or lobar consolidation can be seen. Histologic sections reveal extensive acute inflammation (Fig. 39-8). Vascular thrombosis of medium and small arteries and veins can produce extensive necrosis. Epithelioid cell aggregates forming small granulomas without giant cells are sometimes found. The granulomas are well circumscribed and rarely cavitated. *F. tularensis* is difficult to visualize in tissue with conventional special stains. Immunohistochemistry using monoclonal antibodies against *F. tularensis* can be used if the diagnosis is suspected.[42]

The diagnosis depends on culturing the organism, serologic data, or detection by immunohistochemistry. Streptomycin is considered the drug of choice for all forms of tularemia. Mortality in treated patients is 1% to 2% and is highest in typhoidal tularemia.

Brucellosis

Brucellosis is a systemic infection, a zoonosis that produces abortions and other reproductive problems in domesticated animals. In humans, it is manifested by fever, profound fatigue, and other symptoms that recur for weeks, months, or years. There are six recognized species of *Brucella*, and four are known to infect humans; these are, in decreasing order of severity, *Brucella melitensis* from goats, *Brucella suis* from swine, *Brucella abortus* from cattle, and *Brucella canis* from dogs. Brucellosis is transmitted from animals to humans in three ways: direct contact of broken skin, mucous membranes, or conjunctiva with infected tissues or body fluids; ingestion of contaminated meat or dairy products; and inhalation of infectious aerosols. It is an occupational hazard for cattle and pig farmers, meat processing workers, and to a lesser

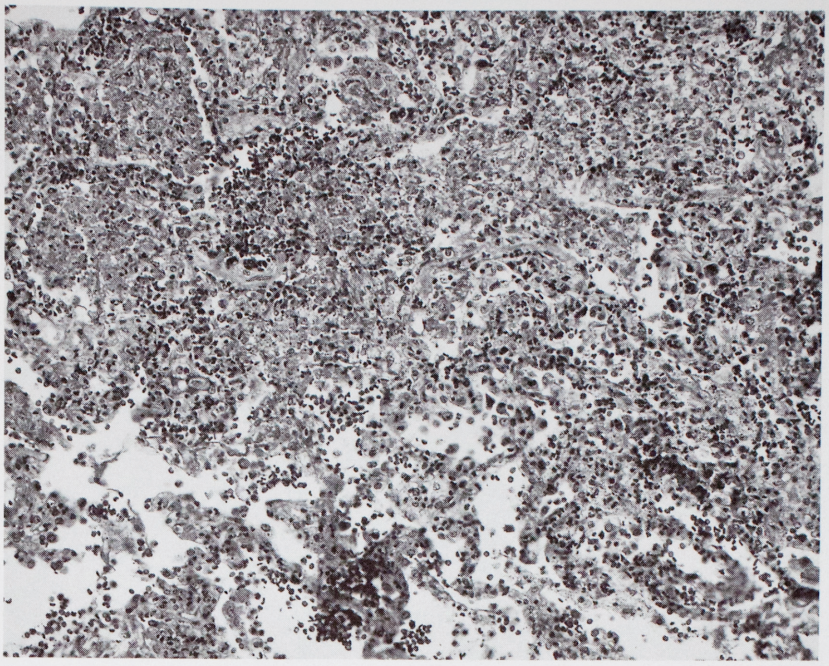

FIGURE 39-8. The lung of a patient with tularemia demonstrates nondescript acute and chronic inflammation with fibrinous debris. (H & E stain; low magnification.)

extent, veterinarians. *Brucella* organisms are found in the milk of domesticated animals, and a probable case of breast-milk transmission to a human infant has been reported.[43]

The incubation period varies from 5 days to several months, but it is usually 3 to 4 weeks. It can be an asymptomatic infection, an acute malignant illness, an acute recurrent undulant fever, or a chronic disease.[44] Complications occur in 10% to 15% of patients, especially in those infected with *B. melitensis* or *B. suis*. Osteomyelitis and other bone and joint lesions are the most common complication,[45–48] followed by neurologic complications, hepatobiliary changes, cardiovascular abnormalities, genitourinary changes, thrombophlebitis, hypersplenism, ocular changes, and colitis.[49–57] Current evidence indicates that *Brucella* infection causes only a slight increased risk of spontaneous abortions in pregnant humans, unlike the situation in domestic animals, but neonatal brucellosis has been reported.[58–60]

Some persons have subclinical illness or mild flulike disease, and others develop an acute illness. Acutely ill patients complain of sweats, chills, fever, weakness, malaise, headache, and anorexia. Pulmonary symptoms occur in about 15% to 25% of the patients. Cough and other signs of bronchitis are common. Patients can also manifest pneumonitis, bronchitis, pleurisy, lung abscess, a coin lesion, or pulmonary edema.[61–64]

Neutrophils are the first line of defense against *Brucella* species. They are capable of killing *B. abortus* but are less effective against the more virulent *B. melitensis*. The bacteria are carried through lymphatics to nearby regional lymph nodes, where they multiply. Hematogenous dissemination to other reticuloendothelial tissues can give rise to acute symptoms. The bacteria multiply within macrophages, where they can survive for prolonged periods. This causes a generalized lymphadenopathy and hepatosplenomegaly, detectable in about one half of the infected patients.

B. melitensis and *B. suis* often cause necrotizing granulomas or stellate abscesses, and *B. abortus* generally causes nonnecrotizing granulomas. The lesions can become confluent, producing soft, well-demarcated, yellow foci. Old lesions may contain flecks of calcification. Rarely, the small, gram-negative, nonencapsulated, coccobacilli are visible in tissue sections stained with Brown-Hopps Gram stain. The most difficult aspect of diagnosing brucellosis is in considering it in the differential diagnosis of a patient with nonspecific signs and symptoms.[65] It is important to document a history of recent travel, a likely occupation, or exposure to unpasteurized dairy products. The microbiology laboratory personnel should be alerted to use appropriate media and take special precautions. Blood and bone marrow cultures of patients with *B. melitensis* usually reveal the microorganism. The diagnosis of *B. suis* and *B. abortus* is made serologically; serologic tests can also detect *B. melitensis*.[66–68] Newer serologic techniques permit differentiation between active and inactive human brucellosis.[69,70]

Anthrax

Also known as woolsorter's or ragpicker's disease, anthrax is caused by *Bacillus anthracis*. It usually presents as a cutaneous lesion, but *B. anthracis* can produce a highly lethal pneumonia and septicemia. Pulmonary anthrax results from septicemic spread of vegetative *B. anthracis*. The initial source can be the cutaneous lesion or inhalation of spores of *B. anthracis*. Anthrax is rare in the United States, where strict control of the disease in animals is maintained. Anthrax still poses a threat to the world, particularly in countries where sanitation is poor, especially in Turkey, Iran, Pakistan, Sudan, and many countries in Latin America and Southeast Asia.[71,72] The spores of *B. anthracis* can remain viable for more than 30 years, and these spores can be imported within products from infected regions of the world. Animal feed supplemented with ground bones, hides, wool, and other materials from animals infected with anthrax spores can pose a threat of spread to nonendemic areas.[73]

Inhaled spores are taken up by alveolar macrophages and transported to hilar lymph nodes. Vegetative bacilli develop, destroy their host macrophages in lymph node sinuses, and enter the bloodstream. Pulmonary anthrax arises as a result of the septicemic infection or from the germination of the inhaled spores within the lung parenchyma. The pathologic changes of anthrax

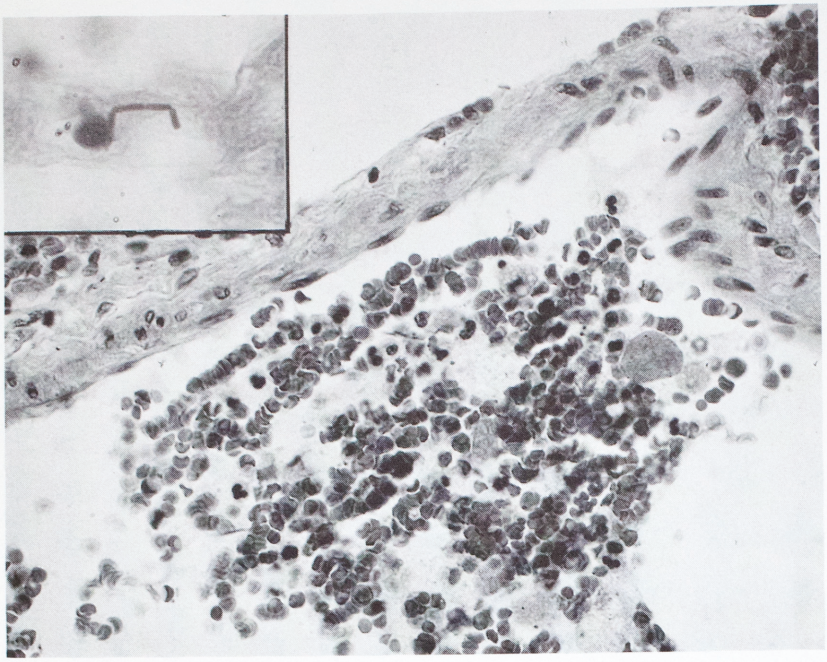

FIGURE 39-9. The pneumonic infiltrate has several bacilli of *Bacillus anthracis* among the reactive neutrophils. (H & E stain; high magnification.) The inset shows a chain of four gram-positive bacilli of *B. anthracis*. (Brown & Brenn stain; oil immersion.)

arising from inhalation of spores or from an initial cutaneous lesion (*i.e.*, primary and secondary pulmonary anthrax) are indistinguishable.

Pulmonary anthrax presents as a rapidly evolving pneumonitis with extreme weakness, a cough producing blood-tinged sputum, marked dyspnea, cyanosis, and symptoms of shock.[74] Less commonly, fulminating disease produces sudden death. The infection can spread to the brain and cause meningitis.

The virulence of *B. anthracis* is caused by production of a three-component exotoxin and an antiphagocytic poly-D-glutamic acid capsule. The genes that produce the toxins and capsule, are encoded by plasmids, pX01 and pX02, respectively. *B. anthracis* organisms that lack these plasmids are less virulent.[75,76]

At autopsy, there are prominent, severe hemorrhagic mediastinal adenitis and serosanguineous pleural effusion. The pleural surfaces are smooth, but the lungs are heavy and lack crepitation. The cut surface releases a bloody fluid, and consolidation is not observed.

The lungs are markedly hemorrhagic, and there is edema within alveolar sacs. There is little inflammatory reaction. The bacteria are readily apparent on sections stained with hematoxylin and eosin. Tissue Gram stains demonstrate the large, 1.0- × 3.5-μm, gram-positive rods (Fig. 39-9).

The diagnosis of anthrax is established by culturing the organism from any tissue or body fluid infected. Every precaution must be taken when handling live *B. anthracis*. It grows well on ordinary blood agar, forming characteristic, although not pathognomonic, medusa-head colonies. Anthrax can also be detected serologically or by the use of molecular biologic technology.[71,77]

MISCELLANEOUS LUNG INFECTIONS

Melioidosis

Melioidosis is a pseudomonal infection that is endemic to a zone 20 degrees above and below the equator, from Madagascar in the west to Guam in the east, including Southeast Asia, parts of Australia, New Guinea, and the Phillipines. The disease became familiar to French physicians during the Indochine War and to American physicians during the Vietnam War.

Melioidosis is caused by *Pseudomonas pseudomallei*, and unencapsulated, gram-negative rod. The organism readily grows in moist soil and stagnant water (*e.g.*, rice paddies), and the infection is acquired through skin abrasions.

Three types of melioidosis infection are recognized.[78,79] An asymptomatic infection exists, which explains the presence of positive hemagglutinins and complement-fixing antibodies in up to 15% of the population in endemic areas. A second type consists of an acute infection characterized by fulminant septicemia and pneumonia, resulting in the death of the patient within 24 hours to a few weeks of infection. The third type of melioidosis is a chronic infection involving several organs, including the lungs. The patients with chronic disease have unilateral upper lobe lesions of a nodular and cavitary character, which therefore resemble tuberculosis.

Histologically, the acute form of the disease is characterized by disseminated abscesses in many organs. The lung parenchyma is diffusely consolidated and shows microabscesses with hemorrhages. Neutrophils and monocytes are abundant, and giant cells resembling megakaryocytes are also noted. The lesions grow and coalesce to form larger abscesses as the disease progresses and the lesions consist entirely of neutrophils.

Chronic melioidosis fundamentally is a granulomatous disease, and the differential diagnosis includes tuberculosis, cat-scratch disease, and lymphogranuloma venereum. The organisms can be recognized with Giemsa and Brown-Hopps stains, particularly in the acute lesions.[80]

Listeriosis

Listeriosis is a worldwide infection caused by *Listeria monocytogenes*, a gram-positive bacillus. There is a reservoir of infection in both domestic and wild animals, and animal-to-human transmission is well documented. However, in the majority of cases, the

source of infection, the vehicle of transmission, and the portal of entry remain unknown. Listeriosis affects women during pregnancy and can result in abortions or infections in liveborn babies. In neonatal listeriosis, respiratory distress and pulmonary manifestations predominate. Multiple organs are involved, including the lungs, liver, lymph nodes, adrenals, and tonsils. The lesions consist of grayish white or yellowish nodules that are 1 mm to several millimeters in diameter. Histologically, the lesions are characterized by necrosis of tissue and large numbers of degenerating neutrophils containing the short, gram-positive bacilli.[81] Central nervous system involvement is most common in adult patients with listeriosis; pneumonia also can occur.[82]

Diphtheria

Diphtheria pneumonia caused by the JK group of *Corynebacterium* is discussed in Chapter 38. This section focuses on classical diphtheria involving the respiratory tree.[83] The causative organism, *Corynebacterium diphtheria* (*i.e.*, Klebs-Loeffler bacillus), is a pleomorphic gram-positive bacillus related to *Nocardia* and *Micobacterium* species. *C. diphtheria* cannot be reliably distinguished by morphology from the diphtheroids, or nonpathogenic *Corynebacteria*, which are common inhabitants of the upper airways; the distinction is made by culture characteristics and biochemical reactions.

Since the introduction of massive vaccination, diphtheria has become uncommon in the United States; however, it remains prevalent in many areas of the world and affects children older than 6 months of age, when passive immunity disappears, and younger than 15 years of age.

The inhaled organisms are deposited on the epithelium of the upper and lower airways, where they reproduce and cause necrosis of the tissue. Transudation of fibrin becomes mixed with the necrotic epithelium, neutrophils, and the causative organisms, resulting in the characteristic diphtheria pseudomembranes. Lesions usually begin on the posterior pharynx, where they can remain localized or spread to the uvula, nasopharynx, nose, larynx, trachea, and bronchi. Sometimes, a complete cast of the tracheobronchial tree is formed, which may lead to obstruction of the airways.[84] Respiration also is impaired by paralysis of the palate and accessory respiratory muscles as a result of neuropathy. Myocarditis develops in 50% of patients and can cause arrhythmias, cardiac failure, or cardiogenic shock.

Proteus Pneumonia

Proteus mirabilis is a gram-negative rod that uncommonly causes pneumonia. It shares many features with *Kleibsiella pneumoniae*, in that it preferentially affects people who are middle-aged or older, alcoholic, diabetics, and patients with chronic pulmonray disease.[85] Characteristically, the pneumonia begins with an episode of chills, fever, and dyspnea following an episode of alcoholic stupor or delirium tremens.

Pathologically, *Proteus* pneumonia shows consolidation of the dependent portions of the lung, with production of multiple abscesses. In patients recovering from treatment, repair of the abscesses results in mild foci of fibrosis. Histologically, the abscesses consist of a mixed neutrophilic and mononuclear cell exudate with necrosis of alveolar walls and secondary hemorrhage.[85]

Syphilis

In secondary syphilis, the characteristic mucosal patches of the infection can involve the bronchial mucosa and be recognized by bronchoscopy. As tertiary syphilis has become a rarity, pulmonary disease in this late stage is practically nonexistent. Active lesions of syphilis involving the lung fall into three main categories: tracheobronchial syphilis, syphilitic pneumonia, and gummas of the lung.[86,87]

In tracheobronchial syphilis, the submucosa of airways is densely infiltrated by lymphocytes and plasma cells; the respiratory epithelium shows hyperplastic changes. Ulceration of the respiratory mucosa with subsequent healing can result in bronchiectasis formation and bronchial stenosis.

Syphilitic gummas can be single or multiple. They vary in size from a few millimeters to several centimeters and tend to be rounded, like granulomas. They show a preference for the peripheral portions of the lungs. Their centers consist of yellow-to-gray necrosis resembling caseation. However, the underlying alveolar structure remains intact, as demonstrated by elastic tissue stains. Gummas are surrounded by a fibrous capsule, which extends as irregular bands of scar into the surrounding pulmonary tissue. Gummas can cavitate if they erode into a bronchus. Arteries and arterioles may show syphilitic arteritis.

Congenital syphilis, also designated pneumonia alba, mostly has been seen in stillborn infants as pale, heavy lungs that sink in water. The air spaces contain macrophages and fat admixed with lymphocytes, plasma cells, and extensive fibrosis. Pulmonary immaturity, extramedullary hematopoiesis, and interstitial fibrosis have been noted.

The interesting association of multiple saccular aneurysms of the ascending aorta and arch in a patient with syphilis and tuberculosis has been noted.[88] In a patient reported by Preston and colleagues, multiple syphilitic aneurysms of the aorta were associated with compression of the left main pulmonary artery and hypoperfusion of the left lung.[89]

Leptospirosis

Leptospirosis is a spirochetal infection of zoonotic origin that produces a variety of clinical symptoms, characteristically, the hepatorenal syndrome (*i.e.*, Weil disease). Petechiae and subconjunctival hemorrhages associated with visceral bleeding are characteristic. There are no specific pulmonary lesions except for the presence of alveolar hemorrhages, and in that sense, the disease enters in the differential diagnosis of diffuse alveolar hemorrhage syndrome (see Chap. 62).[90]

Whipple Disease

Whipple disease involving the lung has been carefully described in one case by Winberg and colleagues and by others before them.[91] The lesion consists of nodular infiltrates in the submucosa of bronchi and adjacent alveolar tissue. Histologically, the lesions consist of dense accumulations of large, pale-to-pink histiocytes that may be mistaken for tumor. With the periodic acid-Schiff—diastase stain, the cytoplasm of these histiocytes is seen to be loaded with granular structures. Silver stains (*e.g.*, Gomori methenamine silver stain) also show short, positive-staining bacillary forms.

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