receptor that is highly expressed on endothelial cells. Then a host protease removes a fragment of the B subunit, and the remaining fragment self-associates to form a heptamer. The B unit is not toxic, but serves to deliver the toxic A units into cells. Anthrax toxin has two alternate A subunits: *edema factor* (EF) and *lethal factor* (LF), each named for the effect of the toxin in experimental animals. One to three molecules of the EF or LF bind to a B subunit heptamer, and this complex is endocytosed into the host cell. Each B heptamer binds either EF or LF. The low pH of the endosome causes a conformational change in the B heptamer, which then forms a channel in the endosome membrane through which the EF or LF moves into the cytoplasm. In the cytoplasm, EF binds to calcium and calmodulin to form an adenylate cyclase. The active enzyme converts ATP to intracellular cyclic adenosine monophosphate (cAMP), altering cell function. LF has a different mechanism of action. LF is a protease that destroys mitogen-activated protein kinase kinases (MAPKKs). These kinases regulate the activity of MAPKs, which are important regulators of cell growth and differentiation (Chapter 1). The mechanism of cell death caused by dysregulation of MAPKs is not understood.

MORPHOLOGY

Anthrax lesions at any site are typified by necrosis and exudative inflammation rich in neutrophils and macrophages. The presence of large, boxcar-shaped gram-positive extracellular bacteria in chains, seen histopathologically or grown in culture, suggests the diagnosis.

Inhalational anthrax causes numerous foci of hemorrhage in the mediastinum and hemorrhagic lymphadenitis of hilar and peribronchial lymph nodes. The lungs typically show a perihilar interstitial pneumonia with infiltration of macrophages and neutrophils and pulmonary vasculitis. Hemorrhagic lung lesions associated with vasculitis are also present in about half of cases. Mediastinal lymph nodes are expanded by edema and by macrophages containing phagocytosed apoptotic lymphocytes. *B. anthracis* is most likely to be seen in the alveolar capillaries and venules and, to a lesser degree, within the alveolar space and draining hilar lymph nodes (Fig. 8-20). In fatal cases, however, the organism may be found in multiple organs (spleen, liver, intestines, kidneys, adrenal glands, and meninges).

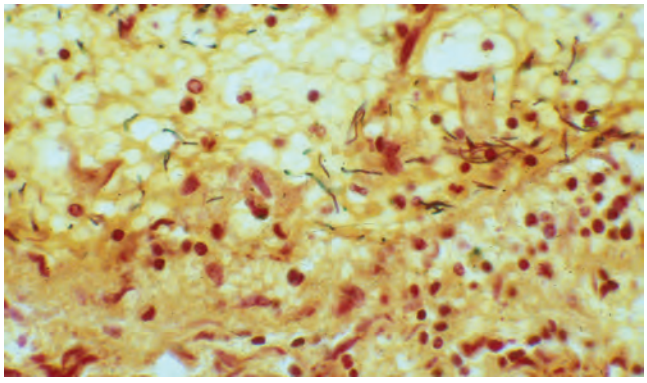

Figure 8-20 *Bacillus anthracis* in the subcapsular sinus of a hilar lymph node of a patient who died of inhalational anthrax. (Courtesy Dr. Lev Grinberg, Department of Pathology, Hospital 40, Ekaterinburg, Russia, and Dr. David Walker, UTMB Center for Biodefense and Emerging Infectious Diseases, Galveston, Texas.)

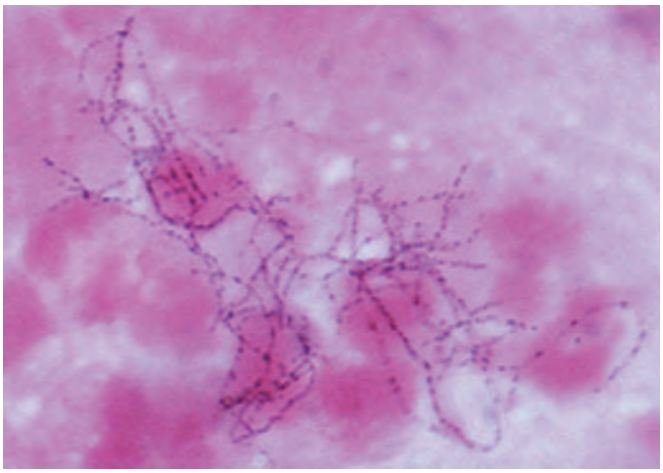

Figure 8-21 *Nocardia asteroides* in a Gram-stained sputum sample. Note the beaded, branched gram-positive organisms and leukocytes. (Courtesy Dr. Ellen Jo Baron, Stanford University Medical Center, Stanford, Calif.)

Nocardia

***Nocardia* are aerobic gram-positive bacteria found in soil that cause opportunistic infections.** The organism grows in distinctive branched chains. In culture, *Nocardia* form thin aerial filaments resembling hyphae. Despite this morphologic similarity to molds, *Nocardia* are true bacteria.

Nocardia asteroides causes respiratory infections, most often in patients with defects in immunity due to prolonged steroid use, HIV infection, or diabetes mellitus. Respiratory infection with *N. asteroides* causes an indolent illness with fever, weight loss, and cough, which may be mistaken for tuberculosis or malignancy. In some cases *N. asteroides* infections disseminate from the lungs to the CNS. Infections of the CNS are also indolent and cause varying neurologic deficits depending on the site of the lesions. *Nocardia brasiliensis* causes skin infections following injuries contaminated with soil. Manifestations include cellulitis, lymphocutaneous disease, and actinomycetoma with formation of nodules that progress to form chronic draining fistulae.

MORPHOLOGY

Nocardia appear in tissue as slender gram-positive organisms arranged in branching filaments (Fig. 8-21). Irregular staining gives the filaments a beaded appearance. *Nocardia* stain with modified acid-fast stains (Fite-Faraco stain), unlike *Actinomyces*, which may appear similar on Gram stain of tissue. *Nocardia* elicit a suppurative response with central liquefaction and surrounding granulation and fibrosis. Granulomas do not form.

Gram-Negative Bacterial Infections

Only a few gram-negative bacteria are discussed in this section. A number of important gram-negative pathogens are discussed in the appropriate chapters of organ systems, including bacterial causes of gastrointestinal infections and urinary tract infections. Anaerobic gram-negative organisms are considered later in this chapter. Gram-negative bacterial infections are usually diagnosed by culture.