

BACERAL/INFECTIOUS DISEASE

Diphtheria

Diphtheria is caused by Corynebacterium diphtheriae, a slender gram-positive rod with clubbed ends, that is passed from person to person through aerosols or skin exudate. C. diphtheriae may be carried asymptotically or cause illnesses ranging from skin lesions in neglected wounds of combat troops in the tropics, and a life-threatening syndrome that includes formation of a tough pharyngeal membrane and toxin-mediated damage to the heart, nerves, and other organs. C. diphtheriae produces only one toxin, which is a phage-encoded A-B toxin that blocks host cell protein synthesis.[68] The A fragment does this by catalyzing the covalent transfer of adenosine diphosphate (ADP)-ribose to elongation factor-2 (EF-2). This inhibits EF-2 function, which is essential for the translation of mRNA into protein. A single molecule of diphtheria toxin can kill a cell by ADP-ribosylating, and thus inactivating, more than a million EF-2 molecules. Immunization with diphtheria toxoid (formalin-fixed toxin) does not prevent colonization with C. diphtheriae but protects immunized people from the lethal effects of the toxin.

Morphology. Inhaled C. diphtheriae proliferate at the site of attachment on the mucosa of the nasopharynx, oropharynx, larynx, or trachea but also form satellite lesions in the esophagus or lower airways. Release of exotoxin causes necrosis of the epithelium, accompanied by an outpouring of a dense fibrinosuppurative exudate. The coagulation of this exudate on the ulcerated necrotic surface creates a tough, dirty gray to black, superficial membrane (Fig. 8-21). Neutrophilic infiltration in the underlying tissues is intense and is accompanied by marked vascular congestion, interstitial edema, and fibrin exudation. When the membrane sloughs off its inflamed and vascularized bed, bleeding and asphyxiation may occur. With control of the infection, the membrane is coughed up or removed by enzymatic digestion, and the inflammatory reaction subsides.

Although the bacterial invasion remains localized, generalized hyperplasia of the spleen and lymph nodes ensues as a result of the entry of soluble exotoxin into the blood. The exotoxin may cause fatty change in the myocardium with isolated myofiber necrosis, polyneuritis with degeneration of the myelin sheaths and axis cylinders, and (less commonly) fatty change and focal necroses of parenchymal cells in the liver, kidneys, and adrenals.

Anthrax

Bacillus anthracis is a large, spore-forming gram-positive rod-shaped bacterium. These bacteria are common pathogens in farm and wild animals that have contact with soil contaminated with B. anthracis spores. Anthrax spores can be ground to a fine powder, making a potent biologic weapon. There are between 20,000 and 100,000 cases of anthrax each year, and recent use of the microbe as an agent of bioterrorism has heightened concern about this organism. In 1979, accidental release of B. anthracis spores at a military research institute in Russia killed 66 people. In 2001, 22 people in the United States were infected with B. anthracis, mostly through spores delivered in the mail.

B. anthracis is typically acquired through exposure to animals or animal products such as wool or hides.[70] There are three major anthrax syndromes.

- **Cutaneous anthrax**, which makes up 95% of naturally occurring infections, begins as a painless, pruritic papule that develops into a vesicle within 2 days. As the vesicle enlarges, striking edema may form around it, and regional lymphadenopathy develops. After the vesicle ruptures, the remaining ulcer becomes covered with a characteristic black eschar, which dries and falls off as the person recovers. Bacteremia is rare with cutaneous anthrax.

- **Inhalational anthrax** occurs when spores are inhaled. The organism is carried by phagocytes to lymph
nodes where the spores germinate, and the release of toxins causes hemorrhagic mediastinitis. After a prodromal illness of 1 to 6 days characterized by fever, cough, and chest or abdominal pain, there is abrupt onset of increased fever, hypoxia, and sweating. Frequently, anthrax meningitis develops from bacteremia. Inhalational anthrax rapidly leads to shock and frequently death within 1 to 2 days.

- **Gastrointestinal anthrax** is an uncommon form of this infection that is usually contracted by eating undercooked meat contaminated with *B. anthracis*. Initially, the person has nausea, abdominal pain, and vomiting, followed by severe, bloody diarrhea. Mortality is over 50%.

**Pathogenesis.**

*Bacillus anthracis* produces potent toxins and a polyglutamyl capsule that is antiphagocytic. The mode of action of anthrax toxin is well understood\(^{[85]}\) (Fig. 8-22). It has A and B subunits. The B subunit is also referred to as the **protective antigen**, because antibodies against this protein protect animals against the toxin. The protective antigen binds to a cell-surface protein, and then a host protease clips off a 20-kD fragment of the B subunit. The remaining 63-kD fragment self-associates to form a heptamer. 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. Three A subunits bind to the B heptamer, and this complex is endocytosed into the host cell. The low pH of the endosome causes a conformational change in the B heptamer, which then forms a selective channel in the endosome membrane through which EF and LF move into the cytoplasm. In the cytoplasm, EF binds to calcium and calmodulin to form an adenylate cyclase. The active EF converts ATP to cyclic adenosine monophosphate (cAMP), an important signaling molecule that stimulates efflux of water from the cell, leading to interstitial edema. 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 3). The mechanism of cell death due to dysregulation of MAPKs is not understood.

**Morphology.** Anthrax lesions at any site are typified by necrosis and exudative inflammation with infiltration of neutrophils and macrophages. The presence of large, boxcar-shaped gram-positive extracellular bacteria in chains, seen histopathologically or recovered in culture, should suggest the diagnosis.

Inhalational anthrax causes numerous foci of hemorrhage in the mediastinum with hemorrhagic, enlarged hilar and peribronchial lymph nodes.\(^{[72]}\) Microscopic examination of the lungs typically shows a perihilar interstitial pneumonia with infiltration of macrophages and neutrophils and pulmonary vasculitis. Hemorrhagic lesions associated with vasculitis are also present in about half of cases. Mediastinal lymph nodes show lymphocytosis, macrophages with phagocytosed apoptotic lymphocytes, and a fibrin-rich edema (Fig. 8-23). *B. anthracis* is present predominantly in the alveolar capillaries and venules and, to a lesser degree, within the alveolar space. In fatal cases, *B. anthracis* is evident in multiple organs (spleen, liver, intestines, kidneys, adrenal glands, and meninges).

**MYCOBACTERIA**

Bacteria in the genus *Mycobacterium* are slender, aerobic rods that grow in straight or branching chains. Mycobacteria have a unique waxy cell wall composed of mycolic acid, which makes them **acid fast**, meaning they will retain stains even on treatment with a mixture of acid and alcohol. Mycobacteria are weakly Gram positive.

**Tuberculosis**

*Mycobacterium tuberculosis* is responsible for most cases of tuberculosis; the reservoir of infection is humans with active tuberculosis. Oropharyngeal and intestinal tuberculosis contracted by drinking milk contaminated
with *M. bovis* is rare in countries where milk is routinely pasteurized, but it is still seen in countries that have tuberculous dairy cows and unpasteurized milk.

Epidemiology.

Tuberculosis is estimated to affect 1.7 billion individuals worldwide, with 8 to 10 million new cases and 1.6 million deaths each year, a toll second only to HIV disease. Infection with HIV makes people susceptible to rapidly progressive tuberculosis; over 10 million people are infected with both HIV and *M. tuberculosis*. From 1985 to 1992, the number of tuberculosis cases in the United States rose by 20% because of increase in the disease in people with HIV, immigrants, and those in jail or homeless shelters. Because of public health efforts, the number of cases of tuberculosis has declined since 1993. Currently, there are about 14,000 new cases of active tuberculosis in the United States annually, about half of which occur in foreign-born people.

Tuberculosis flourishes wherever there is poverty, crowding, and chronic debilitating illness. In the United States tuberculosis is mainly a disease of the elderly, the urban poor, and people with AIDS. *Certain disease states also increase the risk*: diabetes mellitus, Hodgkin lymphoma, chronic lung disease (particularly silicosis), chronic renal failure, malnutrition, alcoholism, and immunosuppression.

It is important that *infection* with *M. tuberculosis* be differentiated from *disease*. Infection is the presence of organisms, which may or may not cause clinically significant disease. Most infections are acquired by person-to-person transmission of airborne organisms from an active case to a susceptible host. In most people primary tuberculosis is asymptomatic, although it may cause fever and pleural effusion. Generally, the only evidence of infection, if any remains, is a tiny, fibrocalcific nodule at the site of the infection. Viable organisms may remain dormant in such lesions for decades. If immune defenses are lowered, the infection may reactivate to produce communicable and potentially life-threatening disease.

Infection typically leads to the development of delayed hypersensitivity to *M. tuberculosis* antigens, which can be detected by the tuberculin (Mantoux) skin test. About 2 to 4 weeks after infection, intracutaneous injection of purified protein derivative of *M. tuberculosis* induces a visible and palpable induration that peaks in 48 to 72 hours. A positive tuberculin test result signifies T cell–mediated immunity to mycobacterial antigens. It does not differentiate between infection and disease. False-negative reactions may occur in the setting of certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression, and (notably) overwhelming active tuberculous disease. False-positive reactions may result from infection by atypical mycobacteria or prior vaccination with BCG (*Bacillus Calmette-Guerin*), an attenuated strain of *M. bovis* that is used as a vaccine in some countries.

Pathogenesis.

The pathogenesis of tuberculosis in a previously unexposed, immunocompetent person depends on the development of anti-mycobacterial cell-mediated immunity, which confers resistance to the bacteria and also results in development of hypersensitivity to mycobacterial antigens. The pathologic manifestations of tuberculosis, such as caseating granulomas and cavitiation, are the result of the hypersensitivity that develops in concert with the protective host immune response. Because the effector cells that mediate immune protection also mediate hypersensitivity and tissue destruction, the appearance of hypersensitivity also signals the acquisition of immunity to the organism. A summary of the pathogenesis of tuberculosis is shown in Figure 8-27.

Macrophages are the primary cells infected by *M. tuberculosis*. Early in infection, tuberculosis bacilli replicate essentially unchecked, while later in infection, the cell response stimulates macrophages to contain the proliferation of the bacteria.
• *M. tuberculosis* enters macrophages by endocytosis mediated by several macrophage receptors: mannose receptors bind lipoarabinomannan, a glycolipid in the bacterial cell wall, and complement receptors (already discussed) bind opsonized mycobacteria.[23]

• Once inside the macrophage, *M. tuberculosis* organisms replicate within the phagosome by blocking fusion of the phagosome and lysosome. *M. tuberculosis* blocks phagolysosome formation by inhibiting Ca\(^{2+}\) signals and the recruitment and assembly of the proteins that mediate phagosome-lysosome fusion. [84] Thus, during the earliest stage of primary tuberculosis (<3 weeks) in the nonsensitized individual, bacteria proliferate in the pulmonary alveolar macrophages and airspaces, resulting in bacteremia and seeding of multiple sites. **Despite the bacteremia, most people at this stage are asymptomatic or have a mild flulike illness.**

• The genetic makeup of the host may influence the course of the disease. In some people with polymorphisms in the *NRAMP1* gene, the disease may progress due to the absence of an effective immune response. NRAMP1 is a transmembrane protein found in endosomes and lysosomes that pumps divalent cations (e.g. Fe\(^{2+}\)) out of the lysosome. NRAMP1 may inhibit microbial growth by limiting availability of ions needed by the bacteria.[85]

• About 3 weeks after infection, a T-helper 1 (T\(_H\)1) response is mounted that activates macrophages to become bactericidal. [86] The response is initiated by mycobacterial antigens that enter draining lymph nodes and are displayed to T cells. Differentiation of T\(_H\)1 cells depends on IL-12, which is produced by antigen-presenting cells that have encountered the mycobacteria. *M. tuberculosis* makes several molecules that are ligands for TLR2, and stimulation of TLR2 by these ligands promotes production of IL-12 by dendritic cells.

• Mature T\(_H\)1 cells, both in lymph nodes and in the lung, produce IFN-\(\gamma\). **INF-\(\gamma\) is the critical mediator that enables macrophages to contain the *M. tuberculosis* infection.** IFN-\(\gamma\) stimulates formation of the phagolysosome in infected macrophages, exposing the bacteria to an inhospitable acidic environment. IFN-\(\gamma\) also stimulates expression of inducible nitric oxide synthase, which produces nitric oxide, capable of destroying several mycobacterial constituents, from cell wall to DNA.

• In addition to stimulating macrophages to kill mycobacteria, the T\(_H\)1 response orchestrates the formation of granulomas and caseous necrosis. Macrophages activated by IFN-\(\gamma\) differentiate into the “epithelioid histiocytes” that characterize the granulomatous response, and may fuse to form giant cells. In many people this response halts the infection before significant tissue destruction or illness. In other people the infection progresses due to advanced age or immunosuppression, and the ongoing immune response results in tissue destruction due to caseation and cavitation. Activated macrophages also secrete TNF, which promotes recruitment of more monocytes. The importance of TNF is underscored by the fact that patients with rheumatoid arthritis who are treated with a TNF antagonist have an increased risk of tuberculosis reactivation.

• In addition to the T\(_H\)1 response, NK-T cells that recognize mycobacterial lipid antigens bound to CD1 on antigen-presenting cells, or T cells that express a \(\gamma\delta\) T-cell receptor, also make IFN-\(\gamma\). However, it is clear that T\(_H\)1 cells have a central role in this process, since defects in any of the steps in generating a T\(_H\)1 response result in absence of resistance and disease progression.

In summary, immunity to *M. tuberculosis* is primarily mediated by T\(_H\)1 cells, which stimulate macrophages to kill the bacteria. This immune response, while largely effective, comes at the cost of hypersensitivity and accompanying tissue destruction. Reactivation of the infection or re-exposure to the bacilli in a previously sensitized host results in rapid mobilization of a defensive reaction but also increased tissue necrosis. Just as hypersensitivity and resistance are correlated, so, too, the loss of hypersensitivity (indicated by tuberculin negativity in a previously tuberculin-positive individual) may be an ominous sign that resistance to the organism has faded.
Clinical Features of Tuberculosis.

The many clinical-pathologic patterns of tuberculosis are shown in Figure 8-28. **Primary tuberculosis is the form of disease that develops in a previously unexposed, and therefore unsensitized, person.** About 5% of newly infected people develop clinically significant disease. The elderly and profoundly immunosuppressed persons may lose their immunity to *M. tuberculosis* and so may develop primary tuberculosis more than once. With primary tuberculosis the source of the organism is exogenous.

In most people, the primary infection is contained, but in others, primary tuberculosis is progressive. The diagnosis of progressive primary tuberculosis in adults can be difficult. In contrast to secondary tuberculosis (apical disease with cavitation; see below), progressive primary tuberculosis more often resembles an acute bacterial pneumonia, with lower and middle lobe consolidation, hilar adenopathy, and pleural effusion; cavitation is rare, especially in people with severe immunosuppression. Lymphohematogenous dissemination may result in the development of *tuberculous meningitis* and *miliary tuberculosis* (discussed below).

**Secondary tuberculosis is the pattern of disease that arises in a previously sensitized host.** It may follow shortly after primary tuberculosis, but more commonly it appears many years after the initial infection, usually when host resistance is weakened. It most commonly stems from reactivation of a latent infection, but may also result from exogenous reinfection in the face of waning host immunity or when a large inoculum of virulent bacilli overwhelms the host immune system. Reactivation is more common in low-prevalence areas, while reinfection plays an important role in regions of high contagion.

Secondary pulmonary tuberculosis classically involves the apex of the upper lobes of one or both lungs. Because of the pre-existence of hypersensitivity, the bacilli elicit a prompt and marked tissue response that tends to wall off the focus of infection. As a result, the regional lymph nodes are less prominently involved early in secondary disease than they are in primary tuberculosis. On the other hand, cavitation occurs readily in the secondary form. Indeed, cavitation is almost inevitable in neglected secondary tuberculosis, and erosion of the cavities into an airway is an important source of infection because the person now coughs sputum that contains bacteria.

Localized secondary tuberculosis may be asymptomatic. When manifestations appear, they are usually insidious in onset. Systemic symptoms, probably related to cytokines released by activated macrophages (e.g., TNF and IL-1), often appear early in the course and include malaise, anorexia, weight loss, and fever. Commonly, the fever is low grade and remittent (appearing late each afternoon and then subsiding), and night sweats occur. With progressive pulmonary involvement, increasing amounts of sputum, at first mucoid and later purulent, appear. Some degree of hemoptysis is present in about half of all cases of pulmonary tuberculosis. Pleuritic pain may result from extension of the infection to the pleural surfaces. Extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved.

The diagnosis of pulmonary disease is based in part on the history and on physical and radiographic findings of consolidation or cavitation in the apices of the lungs. Ultimately, however, *tubercle bacilli must be identified.* Acid-fast smears and cultures of the sputum of patients suspected of having tuberculosis should be performed. Conventional cultures require up to 10 weeks, but culture in liquid media can provide an answer within 2 weeks. **PCR amplification of *M. tuberculosis* DNA allows for even more rapid diagnosis.** PCR assays can detect as few as 10 organisms in clinical specimens, compared with more than 10,000 organisms required for smear positivity. However, culture remains the gold standard because it also allows testing of drug susceptibility. Multidrug resistance is now seen more commonly than it was in past years: hence, all newly diagnosed cases in the United States are assumed to be resistant and are treated with multiple drugs. The prognosis is generally good if infections are localized to the lungs, except when they are caused by drug-resistant strains or occur in aged, debilitated, or immunosuppressed individuals, who are at high risk for developing miliary tuberculosis (see below).
All stages of HIV infection are associated with an increased risk of tuberculosis. The use of highly active antiretroviral therapy (HAART) reduces the risk of tuberculosis in people with HIV infection, but even with HAART, people infected with HIV are more likely to get tuberculosis than the uninfected. A low CD4 count before starting HAART is an important risk factor for development of tuberculosis, which underscores the role of the immune response in keeping reactivation of \textit{M. tuberculosis} in check. The manifestations of tuberculosis differ depending on the degree of immunosuppression. People with less severe immunosuppression (CD4+ T-cell counts >300 cells/mm$^3$) present with usual secondary tuberculosis (apical disease with cavitation). People with more advanced immunosuppression (CD4+ T-cell counts <200 cells/mm$^3$) present with a clinical picture that resembles progressive primary tuberculosis. The extent of immunodeficiency also determines the frequency of extrapulmonary involvement, rising from 10% to 15% in mildly immunosuppressed people to greater than 50% in those with severe immune deficiency. Other atypical features of tuberculosis in HIV-positive people include an increased frequency of false-negative sputum smears and tuberculin tests (the latter due to “anergy”), and the absence of characteristic granulomas in tissues, particularly in the late stages of HIV. The increased frequency of sputum smear-negativity is paradoxical because these immunosuppressed patients typically have higher bacterial loads. The likely explanation is that cavitation and bronchial damage are more in immunocompetent individuals, resulting in more bacilli in expelled sputum. In contrast, the absence of bronchial wall destruction due to reduced T-cell–mediated hypersensitivity results in the excretion of fewer bacilli in the sputum.

\textbf{Morphology.}

\textbf{Primary Tuberculosis.} In countries where infected milk has been eliminated, primary tuberculosis almost always begins in the lungs. Typically, the inhaled bacilli implant in the distal airspaces of the lower part of the upper lobe or the upper part of the lower lobe, usually close to the pleura. As sensitization develops, a 1- to 1.5-cm area of gray-white inflammation with consolidation emerges, known as the Ghon focus. In most cases, the center of this focus undergoes caseous necrosis. Tubercle bacilli, either free or within phagocytes, drain to the regional nodes, which also often caseate. This combination of parenchymal lung lesion and nodal involvement is referred to as the Ghon complex (Fig. 8-29). During the first few weeks there is also lymphatic and hematogenous dissemination to other parts of the body. In approximately 95% of cases, development of cell-mediated immunity controls the infection. Hence, the Ghon complex undergoes progressive fibrosis, often followed by radiologically detectable calcification (Ranke complex), and despite seeding of other organs, no lesions develop.

Histologically, sites of active involvement are marked by a characteristic granulomatous inflammatory reaction that forms both caseating and noncaseating tubercles (Fig. 8-30A to C). Individual tubercles are microscopic; it is only when multiple granulomas coalesce that they become macroscopically visible. The granulomas are usually enclosed within a fibroblastic rim punctuated by lymphocytes. Multinucleate giant cells are present in the granulomas. Immunocompromised people do not form the characteristic granulomas (Fig. 8-30D).

\textbf{Secondary Tuberculosis.} The initial lesion is usually a small focus of consolidation, less than 2 cm in diameter, within 1 to 2 cm of the apical pleura. Such foci are sharply circumscribed, firm, gray-white to yellow areas that have a variable amount of central caseation and peripheral fibrosis (Fig. 8-31). In immunocompetent individuals, the initial parenchymal focus undergoes progressive fibrous encapsulation, leaving only fibrocalcific scars. Histologically, the active lesions show characteristic coalescent tubercles with central caseation. Tubercle bacilli can often be identified with acid-fast stains in early exudative and caseous phases of granuloma formation but are usually too few to be found in the late, fibrocalcific stages. Localized, apical, secondary pulmonary tuberculosis may heal with fibrosis either spontaneously or after therapy, or the disease may progress and extend along several different pathways.

\textbf{Progressive pulmonary tuberculosis} may ensue in the elderly and immunosuppressed. The apical lesion
expands into adjacent lung and eventually erodes into bronchi and vessels. This evacuates the caseous center, creating a ragged, irregular cavity that is poorly walled off by fibrous tissue. Erosion of blood vessels results in hemorrhage into the cavities. With adequate treatment the process may be arrested, although healing by fibrosis often distorts the pulmonary architecture. The cavities, now free of inflammation, may persist or become fibrotic. If the treatment is inadequate or if host defenses are impaired, the infection may spread via airways, lymphatic channels, or the vascular system. Miliary pulmonary disease occurs when organisms draining through lymphatics enter the venous blood and circulate back to the lung. Individual lesions are either microscopic or small, visible (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma (the adjective “miliary” is derived from the resemblance of these foci to millet seeds). Miliary lesions may expand and coalesce, resulting in consolidation of large regions or even whole lobes of the lung. With progressive pulmonary tuberculosis, the pleura is invariably involved, and serous pleural effusions, tuberculous empyema, or obliterative fibrous pleuritis may develop.

Endobronchial, endotracheal, and laryngeal tuberculosis may develop by spread through lymphatic channels or from expectorated infectious material. The mucosal lining may be studded with minute granulomatous lesions that may only be apparent microscopically.

Systemic miliary tuberculosis occurs when bacteria disseminate through the systemic arterial system. Miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis, but could involve any organ (Fig. 8-32).

Isolated tuberculosis may appear in any of the organs or tissues seeded hematogenously and may be the presenting manifestation. Organs that are commonly involved include the meninges (tuberculous meningitis), kidneys (renal tuberculosis), adrenals (formerly an important cause of Addison disease), bones (osteomyelitis), and fallopian tubes (salpingitis). When the vertebrae are affected, the disease is referred to as Pott disease. Paraspinal “cold” abscesses in these patients may track along tissue planes and present as an abdominal or pelvic mass.

Lymphadenitis is the most frequent presentation of extrapulmonary tuberculosis, usually occurring in the cervical region (“scrofula”). In HIV-negative individuals, lymphadenitis tends to be unifocal and localized. HIV-positive people, on the other hand, almost always have multifocal disease, systemic symptoms, and either pulmonary or other organ involvement by active tuberculosis.

In years past, intestinal tuberculosis contracted by the drinking of contaminated milk was a fairly common primary focus of disease. In countries where milk is pasteurized, intestinal tuberculosis is more often caused by the swallowing of coughed-up infective material in patients with advanced pulmonary disease. Typically the organisms are seed to mucosal lymphoid aggregates of the small and large bowel, which then undergo granulomatous inflammation that can lead to ulceration of the overlying mucosa, particularly in the ileum.

Leprosy

Leprosy, or Hansen's disease, is a slowly progressive infection caused by *Mycobacterium leprae* that mainly affects the skin and peripheral nerves and results in disabling deformities. *M. leprae* is likely to be transmitted from person to person through aerosols from asymptomatic lesions in the upper respiratory tract. Inhaled *M. leprae*, like *M. tuberculosis*, is taken up by alveolar macrophages and disseminates through the blood, but replicates only in relatively cool tissues of the skin and extremities. Despite its low communicability, leprosy remains endemic among an estimated 10 to 15 million people living in poor tropical countries.

Pathogenesis.
M. leprae is an acid-fast obligate intracellular organism that grows very poorly in culture but can be propagated in the armadillo. It proliferates best at 32° to 34°C, the temperature of the human skin and the core temperature of armadillos. Like M. tuberculosis, M. leprae secretes no toxins, and its virulence is based on properties of its cell wall. The cell wall is similar enough to that of M. tuberculosis that immunization with BCG confers some protection against M. leprae infection. Cell-mediated immunity is reflected by delayed-type hypersensitivity reactions to dermal injections of a bacterial extract called lepromin.

M. leprae causes two strikingly different patterns of disease. People with the less severe form, tuberculoid leprosy, have dry, scaly skin lesions that lack sensation. They often have asymmetric involvement of large peripheral nerves. The more severe form, lepromatous leprosy, includes symmetric skin thickening and nodules. This is also called anergic leprosy, because of the unresponsiveness (anergy) of the host immune system. Cooler areas of skin, including the earlobes and feet, are more severely affected than warmer areas, such as the axilla and groin. In lepromatous leprosy, widespread invasion of the mycobacteria into Schwann cells and into endoneural and perineural macrophages damages the peripheral nervous system. In advanced cases of lepromatous leprosy, M. leprae is present in sputum and blood. People can also have intermediate forms of disease, called borderline leprosy.

The T-helper lymphocyte response to M. leprae determines whether an individual has tuberculoid or lepromatous leprosy.\[85\] People with tuberculoid leprosy have a T\(_{H1}\) response associated with production of IL-2 and IFN-\(\gamma\). As with M. tuberculosis, IFN-\(\gamma\) is critical to mobilizing an effective host macrophage response. Lepromatous leprosy is associated with a weak T\(_{H1}\) response and, in some cases, a relative increase in the T\(_{H2}\) response. The net result is weak cell-mediated immunity and an inability to control the bacteria. Occasionally, most often in the lepromatous form, antibodies are produced against M. leprae antigens. Paradoxically, these antibodies are usually not protective, but they may form immune complexes with free antigens that can lead to erythema nodosum, vasculitis, and glomerulonephritis.

**Morphology.** Tuberculoid leprosy begins with localized flat, red skin lesions that enlarge and develop irregular shapes with indurated, elevated, hyperpigmented margins and depressed pale centers (central healing). Neuronal involvement dominates tuberculoid leprosy. Nerves become enclosed within granulomatous inflammatory reactions and, if small (e.g., the peripheral twigs), are destroyed (Fig. 8-34). Nerve degeneration causes skin anesthesias and skin and muscle atrophy that render the person liable to trauma of the affected parts, leading to the development of chronic skin ulcers. Contractures, paralyses, and autoamputation of fingers or toes may ensue. Facial nerve involvement can lead to paralysis of the eyelids, with keratitis and corneal ulcerations. On microscopic examination, all sites of involvement have granulomatous lesions closely resembling those found in tuberculosis, and bacilli are almost never found, hence the name “paucibacillary” leprosy. The presence of granulomas and absence of bacteria reflect strong T-cell immunity. Because leprosy pursues an extremely slow course, spanning decades, most patients die with leprosy rather than of it.

Lepromatous leprosy involves the skin, peripheral nerves, anterior chamber of the eye, upper airways (down to the larynx), testes, hands, and feet. The vital organs and CNS are rarely affected, presumably because the core temperature is too high for growth of M. leprae. Lepromatous lesions contain large aggregates of lipid-laden macrophages (lepra cells), often filled with masses (“globi”) of acid-fast bacilli (Fig. 8-35). Because of the abundant bacteria, lepromatous leprosy is referred to as “multibacillary”. Macular, papular, or nodular lesions form on the face, ears, wrists, elbows, and knees. With progression, the nodular lesions coalesce to yield a distinctive leonine facies. Most skin lesions are hypoesthetic or anesthetic. Lesions in the nose may cause persistent inflammation and bacilli-laden discharge. The peripheral nerves, particularly the ulnar and peroneal nerves where they approach the skin surface, are symmetrically invaded with mycobacteria, with minimal inflammation. Loss of sensation and trophic changes in the hands and feet follow the nerve lesions. Lymph nodes contain aggregates of bacteria-filled foamy macrophages in the paracortical (T-cell) areas and reactive germinal centers. In advanced disease, aggregates of macrophages are also present in the splenic red
The testes are usually extensively involved, leading to destruction of the seminiferous tubules and consequent sterility.

**Syphilis**

Syphilis is a chronic venereal disease with multiple presentations. The causative spirochete, *T. pallidum* subsp. *pallidum*, hereafter referred to simply as *T. pallidum*, is too slender to be seen in Gram stain, but it can be visualized by silver stains, dark-field examination, and immunofluorescence techniques (Fig. 8-36). Sexual contact is the usual mode of spread. Transplacental transmission of *T. pallidum* occurs readily, and active disease during pregnancy results in congenital syphilis. *T. pallidum* cannot be grown in culture.

**Primary Syphilis.**

This stage, occurring approximately 3 weeks after contact with an infected individual, features a single firm, nontender, raised, red lesion (chancre) located at the site of treponemal invasion on the penis, cervix, vaginal wall, or anus. The chancre heals in 3 to 6 weeks with or without therapy. Spirochetes are plentiful within the chancre and can be seen by immunofluorescent stains of serous exudate. Treponemes spread throughout the body by hematologic and lymphatic dissemination even before the appearance of the chancre.

**Secondary Syphilis.**

This stage usually occurs 2 to 10 weeks after the primary chancre and is due to spread and proliferation of the spirochetes within the skin and mucocutaneous tissues. Secondary syphilis occurs in approximately 75% of untreated people. The skin lesions, which frequently occur on the palms or soles of the feet, may be maculopapular, scaly, or pustular. Moist areas of the skin, such as the anogenital region, inner thighs, and axillae, may have *condylomata lata*, which are broad-based, elevated plaques. Silvery-gray superficial erosions may form on any of the mucous membranes but are particularly common in the mouth, pharynx, and external genitalia. All these painless superficial lesions contain spirochetes and so are infectious. Lymphadenopathy, mild fever, malaise, and weight loss are also common in secondary syphilis. The symptoms of secondary syphilis last several weeks, after which the person enters the latent phase of the disease. Superficial lesions may recur during the early latent phase, although they are milder.

**Tertiary Syphilis.**

This stage is rare where adequate medical care is available, but it occurs in approximately one third of untreated patients, usually after a latent period of 5 years or more. Tertiary syphilis has three main manifestations: cardiovascular syphilis, neurosyphilis, and so-called benign tertiary syphilis. These may occur alone or in combination.

*Cardiovascular syphilis*, in the form of syphilitic aortitis, accounts for more than 80% of cases of tertiary disease. The aortitis leads to slowly progressive dilation of the aortic root and arch, which causes aortic valve insufficiency and aneurysms of the proximal aorta (see Chapter 11).

*Neurosyphilis* may be symptomatic or asymptomatic. Symptomatic disease manifests in several ways, including chronic meningovascular disease, tabes dorsalis, and a generalized brain parenchymal disease called *general paresis*. These are discussed in Chapter 28. Asymptomatic neurosyphilis, which accounts for about one third of neurosyphilis cases, is detected when a patient's CSF exhibits abnormalities such as pleocytosis (increased numbers of inflammatory cells), elevated protein levels, or decreased glucose. Antibodies stimulated by the spirochetes, discussed below, can also be detected in the CSF, and this is the most specific test for
neurosyphilis. Antibiotics are given for a longer time if the spirochetes have spread to the CNS, and so patients with tertiary syphilis should be tested for neurosyphilis even if they do not have neurologic symptoms.

So-called benign tertiary syphilis is characterized by the formation of gummas in various sites. Gummas are nodular lesions probably related to the development of delayed hypersensitivity to the bacteria. They occur most commonly in bone, skin, and the mucous membranes of the upper airway and mouth, although any organ may be affected. Skeletal involvement characteristically causes local pain, tenderness, swelling, and sometimes pathologic fractures. Involvement of skin and mucous membranes may produce nodular lesions or, rarely, destructive, ulcerative lesions that mimic malignant neoplasms. Gummas are now very rare because of the use of effective antibiotics and are seen mainly in individuals with AIDS.

Congenital Syphilis.

Congenital syphilis occurs when *T. pallidum* crosses the placenta from an infected mother to the fetus. Maternal transmission happens most frequently during primary or secondary syphilis, when the spirochetes are most numerous. Because the manifestations of maternal syphilis may be subtle, routine serologic testing for syphilis is mandatory in all pregnancies. Intrauterine death and perinatal death each occurs in approximately 25% of cases of untreated congenital syphilis.

Manifestations of congenital disease are divided into early (infantile) and late (tardive) syphilis, depending on whether they occur in the first 2 years of life or later. Early congenital syphilis is often manifested by nasal discharge and congestion (snuffles) in the first few months of life. A desquamating or bullous rash can lead to sloughing of the skin, particularly of the hands and feet and around the mouth and anus. Hepatomegaly and skeletal abnormalities are also common.

Nearly half of untreated children with neonatal syphilis will develop late manifestations, which are discussed below.

Serologic Tests for Syphilis.

Serology remains the mainstay of diagnosis, although microscopy and PCR are also useful. Serologic tests include nontreponemal antibody tests and antitreponemal antibody tests. Nontreponemal tests measure antibody to cardiolipin, a phospholipid present in both host tissues and *T. pallidum*. These antibodies are detected in the rapid plasma reagin and Venereal Disease Research Laboratory (VDRL) tests. Nontreponemal tests typically become positive 4 to 6 weeks after infection, and so immunofluorescence of exudate from the chancre is important for diagnosis early in infection. The nontreponemal tests are nearly always positive in secondary syphilis, but they usually become negative in tertiary syphilis. The VDRL and rapid plasma reagin tests are used as screening tests for syphilis and to monitor response to therapy, since these tests become negative after successful treatment of infection. False-positive VDRL test results are not uncommon and are associated with certain acute infections, collagen vascular diseases (e.g., systemic lupus erythematosus), drug addiction, pregnancy, hypergammaglobulinemia of any cause, and lepromatous leprosy.

Treponemal antibody tests measure antibodies that specifically react with *T. pallidum*. These include the fluorescent treponemal antibody absorption test and the microhemagglutination assay for *T. pallidum* antibodies. These tests also become positive 4 to 6 weeks after infection, but unlike nontreponemal antibody tests, they remain positive indefinitely, even after successful treatment. They are not recommended as primary screening tests because they are significantly more expensive than nontreponemal tests. While more specific than the nontreponemal tests, false-positive treponemal antibody tests can also occur.

Serologic response may be delayed, absent, or exaggerated (false-positive results) in people co-infected with syphilis and HIV. However, in most cases, these tests remain useful in the diagnosis and management of syphilis even in people infected with HIV.
Morphology. In primary syphilis a chancre occurs on the penis or scrotum of 70% of men and on the vulva or cervix of 50% of women. The chancre is a slightly elevated, firm, reddened papule, up to several centimeters in diameter, that erodes to create a clean-based shallow ulcer. The contiguous induration creates a button-like mass directly adjacent to the eroded skin, providing the basis for the designation hard chancre (Fig. 8-38). On histologic examination, treponemes are visible at the surface of the ulcer with silver stains (e.g., Warthin-Starry stain) or immunofluorescence techniques. The chancre contains an intense infiltrate of plasma cells, with scattered macrophages and lymphocytes and a proliferative endarteritis (see Fig. 8-8). The endarteritis, which is seen in all stages of syphilis, starts with endothelial cell activation and proliferation and progresses to intimal fibrosis. The regional nodes are usually enlarged due to nonspecific acute or chronic lymphadenitis, plasma cell–rich infiltrates, or granulomas.

In secondary syphilis widespread mucocutaneous lesions involve the oral cavity, palms of the hands, and soles of the feet. The rash frequently consists of discrete red-brown macules less than 5 mm in diameter, but it may be follicular, pustular, annular, or scaling. Red lesions in the mouth or vagina contain the most organisms and are the most infectious. Histologically, the mucocutaneous lesions of secondary syphilis show the same plasma cell infiltrate and obliterator endarteritis as the primary chancre, although the inflammation is often less intense.

Tertiary syphilis most frequently involves the aorta; the CNS; and the liver, bones, and testes. The aortitis is caused by endarteritis of the vasa vasorum of the proximal aorta. Occlusion of the vasa vasorum results in scarring of the media of the proximal aortic wall, causing a loss of elasticity. There may be narrowing of the coronary artery ostia caused by subintimal scarring with resulting myocardial ischemia. The morphologic and clinical features of syphilitic aortitis are discussed in greater detail with diseases of the blood vessels (Chapter 11). Neurosyphilis takes one of several forms, designated meningovascular syphilis, tabes dorsalis, and general paresis (Chapter 28). Syphilitic gummas are white-gray and rubbery, occur singly or multiply, and vary in size from microscopic lesions resembling tubercles to large tumor-like masses. They occur in most organs but particularly in skin, subcutaneous tissue, bone, and joints. In the liver, scarring as a result of gummas may cause a distinctive hepatic lesion known as hepar lobatum (Fig. 8-39). On histologic examination, the gummas have centers of coagulated, necrotic material and margins composed of plump, palisading macrophages and fibroblasts surrounded by large numbers of mononuclear leukocytes, chiefly plasma cells. Treponemes are scant in gummas and are difficult to demonstrate.

The rash of congenital syphilis is more severe than that of adult secondary syphilis. It is a bullous eruption of the palms and soles of the feet associated with epidermal sloughing. Syphilitic osteochondritis and periostitis affect all bones, but lesions of the nose and lower legs are most distinctive. Destruction of the vomer causes collapse of the bridge of the nose and, later on, the characteristic saddle nose deformity. Periostitis of the tibia leads to excessive new bone growth on the anterior surfaces and anterior bowing, or saber shin. There is also widespread disturbance in endochondral bone formation. The epiphyses become widened as the cartilage overgrows, and cartilage is found in displaced islands within the metaphysis.

The liver is often severely affected in congenital syphilis. Diffuse fibrosis permeates lobules to isolate hepatic cells into small nests, accompanied by the characteristic lymphoplasmacytic infiltrate and vascular changes. Gummas are occasionally found in the liver, even in early cases. The lungs may be affected by a diffuse interstitial fibrosis. In the syphilitic stillborn, the lungs appear pale and airless (pneumonia alba). The generalized spirochetemia may lead to diffuse interstitial inflammatory reactions in virtually any other organ (e.g., the pancreas, kidneys, heart, spleen, thymus, endocrine organs, and CNS).

The late manifestations of congenital syphilis include a distinctive triad of interstitial keratitis, Hutchinson teeth, and eighth-nerve deafness. In addition to interstitial keratitis, the ocular changes include choroiditis and abnormal retinal pigmentation. Hutchinson teeth are small incisors shaped like a screwdriver or a peg, often with notches in the enamel. Eighth-nerve deafness and optic nerve atrophy develop secondary to
Pathogenesis.

There are no good animal models of syphilis, and *T. pallidum* has never been grown in culture (it lacks genes for making nucleotides, fatty acids, and most amino acids). As a result, our scant knowledge of *T. pallidum* pathogenesis comes mainly from observations of the disease in humans.

Proliferative endarteritis occurs in all stages of syphilis. The pathophysiology of the endarteritis is not known, although the scarcity of treponemes and the intense inflammatory infiltrate suggest that the immune response plays a role in the development of these lesions. Regardless of the mechanism, much of the pathology of the disease, such as syphilitic aortitis, can be ascribed to the vascular abnormalities.

The immune response to *T. pallidum* reduces the burden of bacteria, but it may also have a central role in the pathogenesis of the disease. The T cells that infiltrate the chancre are T<sub>H1</sub> cells, suggesting that activation of macrophages to kill bacteria may cause resolution of the local infection. Although there are many plasma cells in the syphilitic lesions and treponeme-specific antibodies are readily detectable, the antibody response does not eliminate the infection. The outer membrane of *T. pallidum* seems to protect the bacteria from antibody binding. The mechanism of this effect is not well understood, but either the paucity of bacterial proteins in the membrane or absorption (coating) of the membrane by host proteins may play a role. The immune response is ultimately inadequate, since the spirochetes disseminate, persist, and cause secondary and tertiary syphilis.

In passing, it should be noted that antibiotic treatment of syphilis, in patients with a high bacterial load, can cause a massive release of endotoxins, resulting in a cytokine storm that manifests with high fever, rigors, hypotension, and leukopenia. This syndrome, called the Jarisch-Herxheimer reaction, is seen not only in syphilis but in other spirochetal diseases, such as Lyme disease, and can be mistaken for drug allergy.