as a protuberant, soft, painless mass. As the lesion enlarges, its borders become raised and indurated. Disfiguring scars may develop in untreated cases and are sometimes associated with urethral, vulvar, or anal **strictures**. Regional lymph nodes typically are spared or show only nonspecific reactive changes, in contrast to chancroid.

Microscopic examination of active lesions reveals marked epithelial hyperplasia at the borders of the ulcer, sometimes mimicking carcinoma (pseudoepitheliomatous hyperplasia). A mixture of neutrophils and mononuclear inflammatory cells is present at the base of the ulcer and beneath the surrounding epithelium. The organisms are demonstrable in Giemsa-stained smears of the exudate as minute, encapsulated coccobacilli (Donovan bodies) in macrophages. Silver stains (e.g., the Warthin-Starry stain) may also demonstrate the organism.

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 unusual glycolipids and lipids including mycolic acid, which makes them acid-fast, meaning they will retain stains even on treatment with a mixture of acid and alcohol. They are weakly gram positive.

Tuberculosis

Tuberculosis is a serious chronic pulmonary and systemic disease caused most often by *M. tuberculosis*. The source of transmission is humans with active tuberculosis who release mycobacteria present in sputum. 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. According to the World Health Organization (WHO), tuberculosis is estimated to affect more than a billion individuals worldwide, with 8.7 million new cases and 1.4 million deaths each year. But there is significant progress toward WHO targets for reduction in cases of tuberculosis. Globally, between 2010 and 2011, new cases of tuberculosis fell at a rate of 2.2%, and mortality has decreased by 41% since 1990. Infection with HIV makes people susceptible to rapidly progressive tuberculosis; 13% of the people who developed tuberculosis in 2011 were HIV-positive. In 2011 there were 10,528 new cases of tuberculosis in the United States, 62% of which occurred 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 older adults, immigrants from high-burden countries, racial and ethnic minorities, 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 active disease. Most infections are acquired by person-to-person transmission of airborne organisms from an active case to a susceptible host. In most healthy 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 pulmonary 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 be reactivated, producing 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 (PPD, or 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 signifies T-cell–mediated immunity to mycobacterial antigens* but does not differentiate between infection and active 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 outcome of infection in a previously unexposed, immunocompetent person depends on the development of anti-mycobacterial T-cell–mediated immunity.** These T cells control the host response to the bacteria and also result in development of pathologic lesions, such as caseating granulomas and cavitation.

Infection by *M. tuberculosis* proceeds in steps, from initial infection of macrophages to a subsequent T_H1 response that both contains the bacteria and causes tissue damage (Fig. 8-24). Early in infection, *M. tuberculosis* replicates essentially unchecked within macrophages, while later in infection, the cell response stimulates macrophages to contain the proliferation of the bacteria. The steps in infection are the following.

- *Entry into macrophages. M. tuberculosis* enters macrophages by phagocytosis mediated by several receptors expressed on the phagocyte, including mannose binding lectin and CR3.
- *Replication in macrophages. M. tuberculosis* inhibits maturation of the phagosome and blocks formation of the phagolysosome, allowing the bacterium to replicate unchecked within the vesicle, protected from the microbicidal mechanisms of lysosomes. The bacterium blocks phagolysosome formation by inhibiting Ca^{2+} signals and the recruitment and assembly of the proteins that mediate phagosome-lysosome fusion. Thus, during the earliest stage of primary tuberculosis (<3 weeks) in the nonsensitized individual, bacteria proliferate in the pulmonary alveolar macrophages and air spaces, resulting in bacteremia and seeding of multiple sites. Despite the bacteremia, most people at this stage are asymptomatic or have a mild flu-like illness.
- Multiple pathogen associated molecular patterns (Chapter 6) of *M. tuberculosis*, including lipoproteins and glycolipids, are recognized by innate immune receptors, including Toll-like receptors such as TLR2.