T. pallidum rapidly penetrates intact mucous membranes or microscopic abrasions in skin and, within a few hours, enters the lymphatics and blood to produce systemic infection and metastatic foci long before the appearance of a primary lesion. Blood from a patient with incubating or early syphilis is infectious. The generation time of *T. pallidum* during early active disease in vivo is estimated to be ~30 h, and the incubation period of syphilis is inversely proportional to the number of organisms inoculated. The 50% infectious dose for intradermal inoculation in humans has been calculated to be 57 organisms, and the treponeme concentration generally reaches 10^7/g of tissue before a clinical lesion appears. The median incubation period in humans (~21 days) suggests an average inoculum of 500–1000 infectious organisms for naturally acquired disease; the incubation period rarely exceeds 6 weeks.

The primary lesion appears at the site of inoculation, usually persists for 4–6 weeks, and then heals spontaneously. Histopathologic examination shows perivascular infiltration, chiefly by CD4+ and CD8+ T lymphocytes, plasma cells, and macrophages, with capillary endothelial proliferation and subsequent obliteration of small blood vessels. The cellular infiltration displays a T_H1-type cytokine profile consistent with the activation of macrophages. Phagocytosis of opsonized organisms by activated macrophages ultimately causes their destruction, resulting in spontaneous resolution of the chancre.

The generalized parenchymal, constitutional, and mucocutaneous manifestations of secondary syphilis usually appear ~6–8 weeks after the chancre heals, although primary and secondary manifestations may overlap. In contrast, some patients may enter the latent stage without ever recognizing secondary lesions. The histopathologic features of secondary maculopapular skin lesions include hyperkeratosis of the epidermis, capillary proliferation with endothelial swelling in the superficial dermis, dermal papillae with transmigration of polymorphonuclear leukocytes, and—in the deeper dermis—perivascular infiltration by CD8+ T lymphocytes, CD4+ T lymphocytes, macrophages, and plasma cells. Treponemes are found in many tissues, including the aqueous humor of the eye and the cerebrospinal fluid (CSF). *T. pallidum* invades the CNS during the first weeks or months of infection, and CSF abnormalities are detected in as many as 40% of patients during the secondary stage. Clinical hepatitis and immune complex–induced glomerulonephritis are relatively rare but recognized manifestations of secondary syphilis; liver function tests may yield abnormal results in up to one-quarter of patients with early syphilis. Generalized nontender lymphadenopathy is noted in 85% of patients with secondary syphilis. The paradoxical appearance of secondary manifestations despite high titers of antibody (including immobilizing antibody) to *T. pallidum* may result from immune evasion due to antigenic variation or changes in expression of surface antigens. Secondary lesions generally subside within 2–6 weeks, and the infection enters the latent stage, which is detectable only by serologic testing. In the preantibiotic era, up to 25% of untreated patients experienced at least one generalized or localized mucocutaneous relapse, usually during the first year. Therefore, identification and examination of sexual contacts are most important for patients with syphilis of <1 year's duration.

As stated earlier, about one-third of patients with untreated latent syphilis developed clinically apparent tertiary disease in the preantibiotic era, when the most common types of tertiary disease were the gumma (a usually benign granulomatous lesion); cardiovascular syphilis (usually involving the vasa vasorum of the ascending aorta and resulting in aneurysm); and late symptomatic neurosyphilis (tabes dorsalis and paresis). In Western countries today, specific treatment for early and latent syphilis and coincidental therapy (i.e., therapy with antibiotics that are given for other conditions but are active against treponemes) have nearly eliminated tertiary syphilis. Asymptomatic CNS involvement, however, is still demonstrable in up to 40% of persons with early syphilis and 25% of patients with late latent syphilis, and cases of general paresis and tabes dorsalis are being reported from China. The factors that contribute to the development and progression of tertiary disease are unknown.

The course of untreated syphilis was studied retrospectively in a group of nearly 2000 patients with primary or secondary disease diagnosed clinically (the Oslo Study, 1891–1951) and was assessed prospectively in 431 African-American men with seropositive latent syphilis of ≥3 years' duration (the notorious Tuskegee Study, 1932–1972). In the Oslo Study, 24% of patients developed relapsing secondary lesions within 4 years, and 28% eventually developed one or more manifestations of tertiary syphilis. Cardiovascular syphilis, including aortitis, was detected in 10% of patients; 7% of patients developed symptomatic neurosyphilis, and 16% developed benign tertiary gummatous syphilis. Syphilis was the primary cause of death in 15% of men and 8% of women. Cardiovascular syphilis was documented in 35% of men and 22% of women who eventually came to autopsy. In general, serious late complications were nearly twice as common among men as among women.

The Tuskegee Study showed that the death rate among untreated African-American men with syphilis (25–50 years old) was 17% higher than the rate among uninfected subjects and that 30% of all deaths were attributable to cardiovascular or, to a lesser extent, CNS syphilis. Anatomic evidence of aortitis was found in 40–60% of autopsied subjects with syphilis (vs 15% of control subjects), whereas CNS syphilis was found in only 4%. Rates of hypertension were also higher among the infected subjects. The ethical issues eventually raised by this study, begun in the preantibiotic era but continuing into the early 1970s, had a major influence on the development of current guidelines for human medical experimentation, and the history of the study may still contribute to a reluctance of some African Americans to participate as subjects in clinical research.

CLINICAL MANIFESTATIONS

Primary Syphilis The typical primary chancre usually begins as a single painless papule that rapidly becomes eroded and usually becomes indurated, with a characteristic cartilaginous consistency on palpation of the edge and base of the ulcer. Multiple primary lesions are seen in a minority of patients. In heterosexual men the chancre is usually located on the penis **(Fig. 206-2; see also Fig. 25e-17)**, whereas in MSM it may be found in the anal canal or rectum, in the mouth, or on the external genitalia. Oral sex has been identified as the source of infection in some MSM. In women, common primary sites are the cervix and labia. Consequently, primary syphilis goes unrecognized in women and homosexual men more often than in heterosexual men.

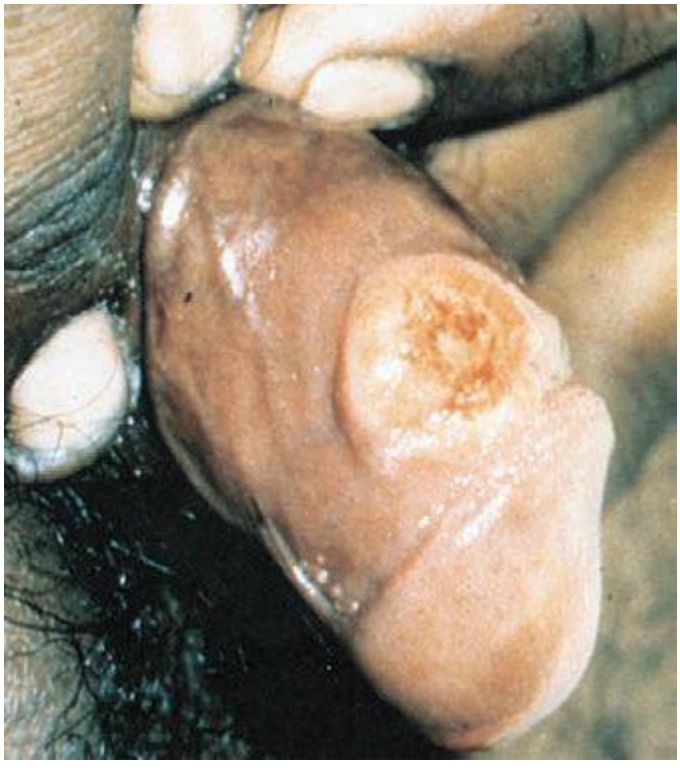

FIGURE 206-2 **Primary syphilis** with a firm, nontender chancre.