Atypical primary lesions are common. The clinical appearance depends on the number of treponemes inoculated and on the immunologic status of the patient. A large inoculum produces a dark-field-positive ulcerative lesion in nonimmune volunteers but may produce a small dark-field-negative papule, an asymptomatic but seropositive latent infection, or no response at all in some individuals with a history of syphilis. A small inoculum may produce only a papular lesion, even in nonimmune individuals. Therefore, syphilis should be considered even in the evaluation of trivial or atypical dark-field-negative genital lesions. The genital lesions that most commonly must be differentiated from those of primary syphilis include those caused by herpes simplex virus infection **(Chap. 216)**, chancroid **(Chap. 182)**, traumatic injury, and donovanosis **(Chap. 198e)**. Regional (usually inguinal) lymphadenopathy accompanies the primary syphilitic lesion, appearing within 1 week of lesion onset. The nodes are firm, nonsuppurative, and painless. Inguinal lymphadenopathy is bilateral and may occur with anal as well as with external genital chancres. The chancre generally heals within 4–6 weeks (range, 2–12 weeks), but lymphadenopathy may persist for months.

Secondary Syphilis The protean manifestations of the secondary stage usually include mucocutaneous lesions and generalized nontender lymphadenopathy. The healing primary chancre may still be present in ~15% of cases, and the stages may overlap more frequently in persons with concurrent HIV infection. The skin rash consists of macular, papular, papulosquamous, and occasionally pustular syphilides; often more than one form is present simultaneously. The eruption may be very subtle, and 25% of patients with a discernible rash may be unaware that they have dermatologic manifestations. Initial lesions are pale red or pink, nonpruritic, discrete macules distributed on the trunk and proximal extremities; these macules progress to papular lesions that are distributed widely and that frequently involve the palms and soles **(Fig. 206-3; see also Figs. 25e-18 and 25e-19)**. Rarely, severe necrotic lesions (*lues maligna*) may appear; they are more commonly reported in HIV-infected individuals. Involvement of the hair follicles may result in patchy alopecia of the scalp hair, eyebrows, or beard in up to 5% of cases.

In warm, moist, intertriginous areas (commonly the perianal region, vulva, and scrotum), papules can enlarge to produce broad, moist, pink or gray-white, highly infectious lesions (*condylomata lata*; **see Fig. 25e-20**) in 10% of patients with secondary syphilis. Superficial mucosal erosions (*mucous patches*) occur in 10–15% of patients and commonly involve the oral or genital mucosa **(see Fig. 25e-21)**. The typical mucous patch is a painless silver-gray erosion surrounded by a red periphery.

Constitutional signs and symptoms that may accompany or precede secondary syphilis include sore throat (15–30%), fever (5–8%), weight loss (2–20%), malaise (25%), anorexia (2–10%), headache (10%), and meningismus (5%). *Acute meningitis* occurs in only 1–2% of cases, but CSF cell and protein concentrations are increased in up to 40% of cases, and viable *T. pallidum* organisms have been recovered from CSF during primary and secondary syphilis in 30% of cases; the latter finding is often but not always associated with other CSF abnormalities.

Less common complications of secondary syphilis include hepatitis, nephropathy, gastrointestinal involvement (hypertrophic gastritis, patchy proctitis, or a rectosigmoid mass), arthritis, and periostitis. Ocular findings associated with secondary syphilis include pupillary abnormalities and optic neuritis as well as the classic iritis or uveitis. The diagnosis of ocular syphilis is often considered in affected patients only after they fail to respond to steroid therapy. Anterior uveitis has been reported in 5–10% of patients with secondary syphilis, and *T. pallidum* has been demonstrated in aqueous humor from such patients. Hepatic involvement is common in syphilis; although it is usually asymptomatic, up to 25% of patients may have abnormal liver function tests. Frank syphilitic hepatitis may be seen. Renal involvement usually results from immune complex deposition and produces proteinuria associated with an acute nephrotic syndrome. Like those of primary syphilis, the manifestations of the secondary stage resolve spontaneously, usually within 1–6 months.

Latent Syphilis Positive serologic tests for syphilis, together with a normal CSF examination and the absence of clinical manifestations of syphilis, indicate a diagnosis of latent syphilis in an untreated person. The diagnosis is often suspected on the basis of a history of primary or secondary lesions, a history of exposure to syphilis, or the delivery of an infant with congenital syphilis. A previous negative serologic test or a history of lesions or exposure may help establish the duration of latent infection, which is an important factor in the selection of appropriate therapy. *Early latent* syphilis is limited to the first year after infection, whereas *late latent* syphilis is defined as that of ≥1 year's duration (or of unknown duration). *T. pallidum* may still seed the bloodstream intermittently during the latent stage, and pregnant women with latent syphilis may infect the fetus in utero. Moreover, syphilis has been transmitted through blood transfusion or organ donation from patients with latent syphilis. It was previously thought that untreated late latent syphilis had three possible outcomes: (1) persistent lifelong infection; (2) development of late syphilis; or (3) spontaneous cure, with reversion of serologic tests to negative. It is now apparent, however, that the more sensitive treponemal antibody tests rarely, if ever, become nonreactive without treatment. Although progression to clinically evident late syphilis is very rare today, the occurrence of spontaneous cure is in doubt.

Involvement of the CNS Traditionally, neurosyphilis has been considered a late manifestation of syphilis, but this view is inaccurate. CNS syphilis represents a continuum encompassing early invasion (usually within the first weeks or months of infection), months to years of asymptomatic involvement, and, in some cases, development of early or late neurologic manifestations.

ASYMPTOMATIC NEUROSYPHILIS The diagnosis of asymptomatic neurosyphilis is made in patients who lack neurologic symptoms and signs but who have CSF abnormalities including mononuclear pleocytosis, increased protein concentrations, or CSF reactivity in the Venereal Disease Research Laboratory (VDRL) test. CSF abnormalities are demonstrated in up to 40% of cases of primary or secondary syphilis and in 25% of cases of latent syphilis. *T. pallidum* has been recovered by inoculation into rabbits of CSF from up to 30% of patients with primary or secondary syphilis but less frequently by inoculation of CSF from patients with latent syphilis. The presence of *T. pallidum* in CSF is often associated with other CSF abnormalities, but organisms can be recovered from patients with otherwise normal CSF. Although the prognostic implications of these findings in early syphilis are uncertain, it may be appropriate to conclude that even patients with

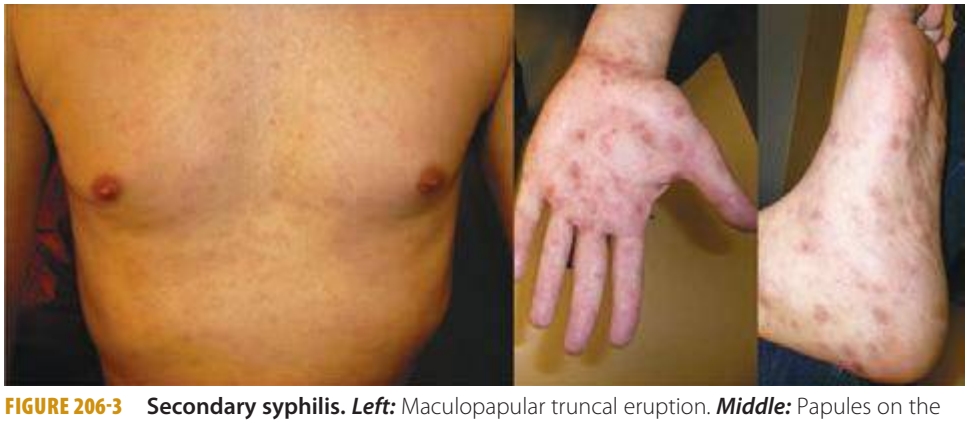

FIGURE 206-3 **Secondary syphilis.** ***Left:*** Maculopapular truncal eruption. ***Middle:*** Papules on the palms. ***Right:*** Papules on the soles. *(Courtesy of Jill McKenzie and Christina Marra.)*