early syphilis who have such findings do indeed have asymptomatic neurosyphilis and should be treated for neurosyphilis; such treatment is particularly important in patients with concurrent HIV infection. Before the advent of penicillin, the risk of development of clinical neurosyphilis in untreated asymptomatic persons was roughly proportional to the intensity of CSF changes, with the overall cumulative probability of progression to clinical neurosyphilis ~20% in the first 10 years but increasing with time. Most experts agree that neurosyphilis is more common in HIV-infected persons, while immunocompetent patients with untreated latent syphilis and normal CSF probably run a very low risk of subsequent neurosyphilis. In several recent studies, neurosyphilis was associated with a rapid plasma reagin (RPR) titer of ≥1:32, regardless of clinical stage or HIV infection status.

SYMPTOMATIC NEUROSYPHILIS The major clinical categories of symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis. The last category includes general paresis and tabes dorsalis. The onset of symptoms usually occurs <1 year after infection for meningeal syphilis, up to 10 years after infection for meningovascular syphilis, at ~20 years for general paresis, and at 25–30 years for tabes dorsalis. Neurosyphilis is more frequently symptomatic in patients who are co-infected with HIV, particularly in the setting of a low CD4+ T lymphocyte count. In addition, recent evidence suggests that syphilis infection worsens the cognitive impairment seen in HIV-infected persons and that this effect persists even after treatment for syphilis.

Meningeal syphilis may present as headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status. This condition may be concurrent with or may follow the secondary stage. Patients presenting with uveitis, iritis, or hearing loss often have meningeal syphilis, but these clinical findings can also be seen in patients with normal CSF.

Meningovascular syphilis reflects meningitis together with inflammatory vasculitis of small, medium, or large vessels. The most common presentation is a stroke syndrome involving the middle cerebral artery of a relatively young adult. However, unlike the usual thrombotic or embolic stroke syndrome of sudden onset, meningovascular syphilis often becomes manifest after a subacute encephalitic prodrome (with headaches, vertigo, insomnia, and psychological abnormalities), which is followed by a gradually progressive vascular syndrome.

The manifestations of *general paresis* reflect widespread late parenchymal damage and include abnormalities corresponding to the mnemonic *paresis: p*ersonality, *a*ffect, *r*eflexes (hyperactive), *e*ye (e.g., Argyll Robertson pupils), *s*ensorium (illusions, delusions, hallucinations), *i*ntellect (a decrease in recent memory and in the capacity for orientation, calculations, judgment, and insight), and *s*peech. *Tabes dorsalis* is a late manifestation of syphilis that presents as symptoms and signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia. Symptoms include ataxic wide-based gait and foot drop; paresthesia; bladder disturbances; impotence; areflexia; and loss of positional, deep-pain, and temperature sensations. Trophic joint degeneration (Charcot's joints) and perforating ulceration of the feet can result from loss of pain sensation. The small, irregular Argyll Robertson pupil, a feature of both tabes dorsalis and paresis, reacts to accommodation but not to light. *Optic atrophy* also occurs frequently in association with tabes.

Other Manifestations of Late Syphilis The slowly progressive inflammatory process leading to tertiary disease begins early during infection, although these manifestations may not become clinically apparent for years or decades. Early syphilitic aortitis becomes evident soon after secondary lesions subside, and treponemes that trigger the development of gummas may have seeded the tissue years earlier.

CARDIOVASCULAR SYPHILIS Cardiovascular manifestations, usually appearing 10–40 years after infection, are attributable to endarteritis obliterans of the vasa vasorum, which provide the blood supply to large vessels; *T. pallidum* DNA has been detected by PCR in aortic tissue. Cardiovascular involvement results in uncomplicated aortitis, aortic regurgitation, saccular aneurysm (usually of the ascending aorta), or coronary ostial stenosis. In the preantibiotic era, symptomatic cardiovascular complications developed in ~10% of persons with late untreated syphilis. Today, this form of late syphilis is rarely seen in the developed world. Linear calcification of the ascending aorta on chest x-ray films suggests asymptomatic syphilitic aortitis, as arteriosclerosis seldom produces this sign. Only 1 in 10 aortic aneurysms of syphilitic origin involves the abdominal aorta.

LATE BENIGN SYPHILIS (GUMMA) Gummas are usually solitary lesions ranging from microscopic to several centimeters in diameter. Histologic examination shows a granulomatous inflammation, with a central area of necrosis due to endarteritis obliterans. Although rarely demonstrated microscopically, *T. pallidum* has been detected by PCR or recovered from these lesions, and penicillin treatment results in rapid resolution, confirming the treponemal stimulus for the inflammation. Common sites include the skin and skeletal system; however, any organ (including the brain) may be involved. Gummas of the skin produce indolent, painless, indurated nodular or ulcerative lesions that may resemble other chronic granulomatous conditions, including tuberculosis, sarcoidosis, leprosy, and deep fungal infections. Skeletal gummas most frequently involve the long bones, although any bone may be affected. Upper respiratory gummas can lead to perforation of the nasal septum or palate.

Congenital Syphilis Transmission of *T. pallidum* across the placenta from a syphilitic woman to her fetus may occur at any stage of pregnancy, but fetal damage generally does not occur until after the fourth month of gestation, when fetal immunologic competence begins to develop. This timing suggests that the pathogenesis of congenital syphilis, like that of adult syphilis, depends on the host immune response rather than on a direct toxic effect of *T. pallidum*. The risk of fetal infection during untreated early maternal syphilis is ~75–95%, decreasing to ~35% for maternal syphilis of >2 years' duration. Adequate treatment of the woman before the 16th week of pregnancy should prevent fetal damage, and treatment before the third trimester should adequately treat the infected fetus. Untreated maternal infection may result in a rate of fetal loss of up to 40% (with stillbirth more common than abortion because of the late onset of fetal pathology), prematurity, neonatal death, or nonfatal congenital syphilis. Among infants born alive, only fulminant congenital syphilis is clinically apparent at birth, and these babies have a very poor prognosis. The most common clinical problem is the healthy-appearing baby born to a mother with a positive serologic test

Routine serologic testing in early pregnancy is considered cost-effective in virtually all populations, even in areas with a low prenatal prevalence of syphilis. Low-tech point-of-care tests have been developed and are being widely implemented to facilitate antenatal testing in resource-poor settings. A recent study demonstrated the high cost-effectiveness of using these tests for screening (with subsequent treatment) in sub-Saharan Africa. Adverse outcomes were reduced, with 64,000 fewer stillbirths, 25,000 fewer neonatal deaths, and up to 25,000 fewer live births of infants with syphilis. The intervention would remain cost-effective even if the current syphilis seroprevalence among pregnant women declined from its present 3.1% to 0.4%. Where the prevalence of syphilis is high or when the patient is at high risk of reinfection, serologic testing should be repeated in the third trimester and at delivery. Neonatal congenital syphilis must be differentiated from other generalized congenital infections, including rubella, cytomegalovirus or herpes simplex virus infection, and toxoplasmosis, as well as from erythroblastosis fetalis.

The manifestations of congenital syphilis include (1) early manifestations, which appear within the first 2 years of life (often at 2–10 weeks of age), are infectious, and resemble the manifestations of secondary syphilis in the adult; (2) late manifestations, which appear after 2 years and are noninfectious; and (3) residual stigmata. The earliest manifestations of congenital syphilis include rhinitis, or "snuffles" (23%); mucocutaneous lesions (35–41%); bone changes (61%), including osteochondritis, osteitis, and periostitis detectable by x-ray examination of long bones; hepatosplenomegaly (50%); lymphadenopathy (32%); anemia (34%); jaundice (30%); thrombocytopenia; and leukocytosis. CNS invasion by *T. pallidum* is detectable in 22% of infected