237 Syphilis (*Treponema pallidum*)

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SHORT VIEW SUMMARY

Definition
- Syphilis is a chronic, multistage sexually transmitted infection caused by the spirochete *Treponema pallidum.*

Epidemiology
- According to the World Health Organization, globally, approximately 17.7 million persons aged 15 to 49 years had venereal syphilis in 2012; an estimated 5.6 million new cases occur each year.
- Globally, more than 1 million pregnant women are estimated to be infected each year; approximately one-third of these infections will result in stillbirths or other adverse outcomes of pregnancy.
- In developing countries, transmission is largely heterosexual, whereas transmission among men who have sex with men predominates in industrialized nations.
- Genital ulcers caused by syphilis are a major cofactor for bidirectional transmission of human immunodeficiency virus (HIV).

Microbiology
- *T. pallidum* subspecies *pallidum, pertenue,* and *endemicum* cause venereal syphilis, yaws, and endemic syphilis, respectively. *Treponema carateum* causes pinta.
- Until recently, the pathogenic treponemes were considered to be uncultivatable. Continuous long-term culture of *T. pallidum* subsp. *pallidum* by cocultivation with rabbit epithelial cells was just reported.
- All pathogenic treponemes are indistinguishable with routine clinical laboratory tests.
- Humans are the only natural hosts for *T. pallidum* subsp. *pallidum.* Infection with *T. pallidum* subsp. *pertenue* has been well documented in nonhuman primates in sub-Saharan Africa.
- *T. pallidum* possesses both inner and outer membranes; its outer membrane lacks lipopolysaccharide and contains a paucity of integral membrane proteins and surface-exposed lipoproteins, hence its impressive capacity for immune evasion and its designation as "the stealth pathogen."
- *T. pallidum* must acquire essentially all nutrients from its obligate human host and generates adenosine triphosphate primarily by glycolysis.
- *T. pallidum* disseminates early during the course of infection and invades the central nervous system in a substantial percentage of persons with early syphilis.

Diagnosis
- Because *T. pallidum* cannot be cultivated in vitro, diagnosis of syphilis depends on demonstrating treponemes in clinical samples or by demonstrating reactivity in serologic tests, or both.
- Darkfield (DF) microscopy and polymerase chain reaction are useful for detecting treponemes in exudative lesions, principally chancres.
- Serodiagnosis of syphilis involves two types of serologic tests: nontreponemal and treponemal. The former detects antibodies against lipoidal antigens (primarily cardiolipin), whereas the latter detects antibodies against *T. pallidum* proteins.
- Serodiagnosis of syphilis has traditionally used an algorithm in which nontreponemal antibodies are used for screening and the results are then confirmed with treponemal antibodies. In recent years, the so-called "reverse algorithm," in which an automatable treponemal test is used to screen followed by confirmation with a nontreponemal test, has gained popularity.
- Because nontreponemal titers usually decline with therapy, nontreponemal antibody tests are used as indicators of disease activity. However, it is now recognized that nontreponemal tests remain reactive in a substantial percentage of treated patients.
- Treponemal tests usually remain reactive for life.

Therapy
- Penicillin G is the preferred form of therapy for all stages and types of syphilitic infection.
- The use of 2.4 million units of intramuscular benzathine penicillin (single dose) is the regimen recommended by the Centers for Disease Control and Prevention and the World Health Organization for early syphilis, regardless of HIV status.
- Doxycycline is the preferred alternative for nonpregnant, penicillin-allergic patients.
- Penicillin-allergic pregnant females should be desensitized.

Prevention
- Prophylactic treatment is indicated for partners exposed to known active cases within the past 90 days regardless of whether lesions are present or serologic tests are reactive in the exposed individual.
- Early identification and treatment of gestational syphilis prevent congenital infection.

Syphilis is a complex systemic illness caused by the highly invasive, noncultivable spirochete *Treponema pallidum.* It holds a special place in the history of Western medicine because of its prevalence in modern times before the advent of penicillin, the many historical personages who had or are presumed to have had the disease, and its protean clinical manifestations, for which it came to be known as "the great imitator" or "the great impostor."[1–5] The first designated and recognized medical specialists were syphilologists. Special clinics were established in Europe and North America to care for the enormous number of persons with this disorder, and its ubiquity spawned one of the first specialized medical journals, the *American Journal of Syphilis, Gonorrhea and Venereal Disease.* The identification of the causative agent, initially named *Spirochaeta pallida,* in 1906 was a milestone in biomedical research.[4]

Venereal syphilis is usually transmitted by sexual contact and, unlike most other bacterial infections, is never diagnosed in routine clinical

practice by isolation of the causative organism. Instead, diagnosis depends on detection of *T. pallidum* or *T. pallidum* DNA in patient specimens or, most commonly, reactivity in serologic assays.[5–7] The inability to isolate *T. pallidum* from patient specimens, with the consequent dependence on serologic findings, is the root cause of most of the management dilemmas that continue to surround this disorder.[8,9] Confusion and controversies also arise from the disease's protracted natural history, which is classically divided into the following stages: (1) an incubation period lasting up to 90 days (average of 3 weeks); (2) a primary stage characterized by an ulcer, the *chancre,* at the site of inoculation, often associated with regional lymphadenopathy; (3) a florid, disseminated stage (secondary syphilis), typically characterized by generalized skin rash, mucocutaneous lesions, and lymphadenopathy, but capable of involving any organ system, including the central nervous system (CNS); (4) an asymptomatic latent period lasting years, detectable only through reactive serologic tests; and, (5) in approximately one-third of untreated persons, a recrudescent, tertiary stage involving the ascending aorta (cardiovascular syphilis) or the CNS (neurosyphilis) or causing necrotizing granulomatous lesions (gumma) in almost any organ.

HISTORY

The origins and spread of venereal syphilis, and the evolutionary differentiation of the syphilis spirochete from the causes of the nonvenereal treponematoses, particularly yaws, have been long-standing sources of debate and controversy. Phylogenetic trees constructed from reference genes and complete genomic sequences demonstrate that the pathogenic treponemes form distinct clusters.[10–12] These findings definitively disprove the Unitarian hypothesis, championed by Hudson,[13,14] that the treponematoses are caused by the same bacterium but with varying modes of transmission and clinical manifestations determined by climate and demographic factors. The debate currently centers around whether venereal syphilis was imported into Europe by shipmates of Christopher Columbus in 1493 or was an established entity that erupted in epidemic form throughout Europe as a consequence of urbanization and social upheaval.[15–19] The controversy over these two mutually exclusive theories is fueled by the imprecision and uncertainties inherent in the historical record, radiocarbon dating, and paleopathologic findings believed to represent the signature of treponemal disease in skeletal remains. Unfortunately, the inability of investigators, despite exhaustive efforts, to use polymerase chain reaction (PCR) to amplify ancient treponemal DNA from pre-Columbian archeological specimens precludes definitive resolution of this controversy.[20–23] Moreover, given the high degree of similarity between the pathogenic treponemes,[10] sequence data from numerous loci, perhaps complete genomes, will be needed to resolve this issue on a genetic basis.[24] Lacking direct molecular proof, the proponents of the "New World" or "Columbian" hypothesis point to the extensive osteologic record of presumptive treponemal disease in New World pre-Columbian populations dating back 7000 years as opposed to the sporadic skeletal evidence from Old World pre-Columbian excavation sites. In a comprehensive evaluation of all extant osteologic data, Harper and colleagues[16] concluded that no case of Old World treponemal disease has a radiocarbon date that places it firmly in the pre-Columbian period. These same investigators used sequence analysis of multiple loci in modern *T. pallidum* subspecies isolates to buttress their argument that syphilis spirochetes originated in the New World,[25] although others have questioned the robustness of their phylogenic scheme.[26,27] Indeed, analysis of genetic differences in *T. pallidum* supspecies based on estimated mutation rates leads to the conclusion that the agents of yaws and venereal syphilis diverged thousands of years ago during human prehistory.[27,28] The discovery of yaws-like treponemes that infect nonhuman primates (NHPs) in Africa[29–31] strongly supports another key tenet of the "pre-Colombian" hypothesis as first proposed by Hackett[14]—that the human treponematoses originated as a zoonosis that spilled over from an NHP reservoir. *T. pallidum* subsp. *pallidum* presumably evolved during the subsequent human diaspora from Africa.

Universally agreed on is that an epidemic known as the Great Pox (as distinguished from smallpox) ravaged Europe shortly after the return of Columbus from his first voyage of discovery.[4,32] This plague broke out during the invasion of Italy in 1494 by Charles VIII of France, whose army included numerous mercenaries, some from Spain, and was accompanied by a horde of civilians, many of whom were prostitutes.[4,32] Although it cannot be proved with certainty that *T. pallidum* was the cause of this scourge, the first clear descriptions of the serious ailment dubbed "the French Disease" by contemporary physicians and chroniclers noted its sexual mode of transmission and traced its origins to the West Indies and members of Colombus's expedition.[4,32] From these primary historical accounts the Colombian hypothesis took root. The name "syphilis" derives from an epic poem, *Syphilis sive morbus Gallicus (Syphilis or the French Disease),* published in 1530 by Girolamo Fracastoro, a Veronese physician, poet, and philosopher. In his treatise, Fracastoro provided a detailed description of the clinical features of syphilis along with recommendations for treatment, ending with the allegory of Syphilus, a shepherd who contracted an illness as punishment for offending the sun god Apollo.[4] During the pandemic of the early 16th century, syphilis in adults manifested as a fulminant, often fatal, illness that progressed rapidly from genital ulceration to gummas. Whether the comparatively mild nature of the present-day ailment reflects a change in the virulence of *T. pallidum,* an adaptation of the human host, or the disappearance of a concomitantly occurring but unknown illness is an enduring mystery. A remarkable phylogenetic comparison of genomic sequences of geographically widespread *T. pallidum* strains, many obtained directly from clinical samples, has added to this conundrum.[33] This study revealed that all modern-day syphilis spirochetes diverged from a common ancestor less than 500 years ago, a time frame roughly congruent with the explosive emergence of syphilis on the European scene. Variation in outer membrane proteins (OMPs),[34] which was not examined by these investigators,[33] driven by herd immunity as the spirochete gained traction within European populations[35,36] might explain changes in its virulence properties over the ensuing centuries.

One of the difficulties in sorting through medical writings from the 17th and 18th centuries is that unequivocal clinical distinctions between syphilis, gonorrhea, and other venereal diseases did not emerge until the late 18th century. John Hunter's misguided self-inoculation experiment with urethral pus containing both *Neisseria gonorrhoeae* and *T. pallidum* served only to prolong the misconception that syphilis and gonorrhea are the same disease.[4] By the mid-19th century, however, syphilis had been distinguished from gonorrhea and its principal clinical features defined, although not without some erroneous teachings. One prominent example is the dogma of Ricord, the greatest syphilologist of the 19th century, that material from secondary syphilis lesions is noncontagious.[4]

In 1903, Metchnikoff launched the era of modern syphilology when he observed that a female chimpanzee inoculated on the clitoris with material from a syphilitic lesion developed a chancre followed by secondary syphilis. Two years later, Schaudinn and Hoffmann discovered *S. pallida* in chancre exudates and adjacent lymph node aspirates. By 1906, Wassermann had developed his complement fixation test using an extract from the liver of a syphilitic stillborn baby. Subsequently, it was shown that extracts from uninfected beef livers and hearts were equally sensitive and that a phospholipid extracted from beef heart (cardiolipin) reproduced the Wassermann reaction when mixed with lecithin and cholesterol. In 1910, Ehrlich introduced his 606th arsenic preparation, arsphenamine or salvarsan, for syphilotherapy, hailed at the time as "the magic bullet." In 1912, Nichols and Hough[37] used rabbit inoculation to isolate the organism from the cerebrospinal fluid (CSF) of a patient who developed neurosyphilis after salvarsan therapy for secondary syphilis. In addition to being the first demonstration of early CNS invasion by *T. pallidum,* their findings suggested that the CNS may serve as a sanctuary for the spirochete during inadequate therapy of early syphilis, a concern to this day.[38] Also noteworthy is that the "Nichols" isolate became the reference laboratory strain of *T. pallidum* and was the source of DNA for the *T. pallidum* genome sequencing project.[39] Of note, another interesting observation from genomic sequencing is that the phylogenetic cluster (clade) containing the Nichols strain greatly diminished in prevalence during the latter part of the 20th century and is being replaced by a second clade represented by the high-level erythromycin-resistant street-strain 14 (SS14).[12,33,40] In 1927, Dr. Julius Wagner von Jauregg was awarded the Nobel Prize in Medicine for describing malarial fever as treatment for neurosyphilis. In 1937, Thomas Parran, the US Surgeon

General from 1936 to 1948, published his landmark book *Shadow on the Land,* in which he estimated that 10% of Americans would be infected by syphilis during their lifetimes.[41] In 1943, John Mahoney of the US Public Health Service treated the first syphilis patients with penicillin,[42] the true magic bullet, work that won him the Lasker Award in 1947. Not surprisingly, syphilis rates plummeted over the next decade. Despite alarming comebacks, most notably the "drugs for sex" cocaine-fueled epidemic of the late 1980s to early 1990s[43] and the substantial upswing in cases among men who have sex with men (MSM) beginning in the late 1990s,[44] syphilis rates have never approached pre–World War II levels.

The enduring impact of syphilis on the biomedical research community extends beyond its ongoing threat to public health. In an effort to better understand the natural history of syphilis, from 1932 to 1972 the US Public Health Service conducted the "Tuskegee Study of Untreated Syphilis in the Negro Male" in which 412 indigent African-American men with latent syphilis in rural Macon County, Alabama were followed without treatment along with 192 black males without serologic evidence of syphilis.[45,46] The revelation 4 decades after the study's inception that treatment had been withheld for years despite the proven efficacy of penicillin sparked outrage and charges of abuse of authority and racial exploitation on the part of the US government and the medical profession.[47] It has also been argued that the continuance of the study was more a reflection of the lack of data and consensus about the efficacy of penicillin therapy for late syphilis than of racial bias.[46] Questions of racial bias aside, the egregious violations of patient rights brought to light the need for much more stringent regulation of research involving human subjects and led to the 1979 Belmont Report, the establishment of the National Human Investigation Board, and the requirement for institutional review boards. In 2010, the public health and medical communities were stunned by disclosures of bioethical violations even more serious than those of the Tuskegee Study.[48–50] Susan Reverby, a Wellesley College historian investigating Dr. John Cutler, one of the physicians involved in the implementation of the Tuskegee Study, inadvertently discovered that from 1946 to 1948 the US Public Health Service conducted studies in Guatemala in which male prisoners were unknowingly inoculated with *T. pallidum* and allowed to transmit syphilis to their sexual partners as part of a plan to evaluate prophylactic treatment regimens. Among the many disturbing revelations was that Parran had approved funding for the studies and appears to have followed their progress. The National Archives has posted more than 12,000 pages of documents related to this study on its website (www.archives.gov/research/health/cdc-cutler-records). A full report by the Presidential Commission for the Study of Bioethical Issues can be found at https://bioethicsarchive.georgetown.edu/pcsbi/node/5896.html.

ETIOLOGY

The causal agent of venereal syphilis is *T. pallidum* subsp. *pallidum,* which belongs to the order Spirochaetales, the family Spirochaetaceae, and the genus *Treponema.* Other members of the genus *Treponema* that can infect humans are *T. pallidum* subsp. *pertenue* (yaws), *T. pallidum* subsp. *endemicum* (bejel or endemic syphilis), and *Treponema carateum* (pinta). In addition to the pathogenic spirochetes, commensal treponemes have been isolated from humans, particularly from the oral cavity and the prepuce of uncircumcised men, and they have been identified by amplification of 16S ribosomal RNA genes from the gut microbiomes of hunter-gatherer and traditional agrarian populations.[51,52] At one time, investigators believed that commensal treponemes were nonpathogenic variants of *T. pallidum.*[53] Miao and Fieldsteel[54,55] disproved this notion by showing with DNA-DNA hybridization that *T. pallidum* subsp. *pallidum* and *pertenue* were indistinguishable and that there was no discernible homology between the DNAs of pathogenic and cultivatable treponemes. As a result, the agents of venereal syphilis, endemic syphilis, and yaws were reclassified as subspecies of *T. pallidum*; *T. carateum* retained its status as a separate species because no isolates were available for study (as is true today). The pathogenic treponemes are believed to have evolved by reductive evolution from a commensal treponeme; comparative genomics, using the *Treponema denticola* genome as a frame of reference, suggests that the divergence from a common progenitor occurred millions of years ago.[56,57] In contrast, as noted earlier, the divergence of the *T. pallidum* subspecies postdates the emergence of modern man, probably occurring within the past 20,000 years.[27,56,57]

All four pathogenic treponemes are morphologically indistinguishable and induce antibodies detected with the routine serologic tests used to diagnose venereal syphilis.[7,58] In clinical situations, distinction among the corresponding infections rests on geography, clinical manifestations, patient age, and other demographic features.[7,58] Of the four pathogens, only *T. pallidum* subsp. *pallidum* is transmitted routinely by sexual contact.[59] Because the other three are transmitted nonsexually, the diseases they cause are collectively referred to as the *endemic* or *nonvenereal treponematoses.*[58] *T. pallidum* subsp. *pallidum* is considered the most virulent because it is the only subspecies capable of regularly breaching both the blood-brain and maternal-fetal barriers.[59,60] At the opposite end of the virulence spectrum is *T. carateum,* which disseminates only to cutaneous sites and causes the least severe skin lesions. A relatively small number of nucleotide differences in the *T. pallidum* subsp. *pallidum* and *pertenue* genomes, which are 99.8% identical, appear to be responsible for profound differences in tissue tropisms and clinical manifestations.[61,62] For many years it was thought that *T. pertenue* is not transmissible by sexual activity; the discovery of genital ulceration, often severe, in NHPs infected with *T. pertenue*–like organisms[29,31,63] argues that the mode of transmission is not determined solely by genetic factors. Until recently, the pathogenic treponemes were considered to be uncultivatable.[64] In what appears to be a major breakthrough, continuous long-term culture of three *T. pallidum* subsp. *pallidum* strains by cocultivation with rabbit epithelial cells has been reported.[65] Intratesticular inoculation of rabbits, rabbit infectivity testing (RIT), remains the only means of recovering strains from clinical specimens.[66,67]

T. pallidum is approximately 0.2 μm in diameter, has tapering ends, and ranges in length from 6 to 20 μm (Fig. 237.1). Because of their small diameter, pathogenic treponemes cannot be visualized with brightfield microscopy and are best visualized with darkfield (DF) or phase-contrast microscopy (see Fig. 237.1A). Although these organisms are often described as spiral or coiled, high-resolution time-lapse microscopy has confirmed earlier reports that, like the Lyme disease spirochete *Borrelia burgdorferi, T. pallidum* has a flat-wave morphology (see Fig. 237.1A).[65,68] Within the periplasmic space are the flagellar filaments, which extend from motors at each cell pole and overlap in the middle of the cell cylinder (see Fig. 237.1B–C).[68,69] The rotation of the filaments, driven by the motors, propagates an undulating wave along the length of the bacterium capable of propelling it through complex fluids, tissue matrices, and intercellular junctions.[70,71] *T. pallidum* is often described as gram negative. In addition to this description being erroneous from a phylogenetic standpoint,[72] the syphilis spirochete lacks the genes for synthesis of lipopolysaccharide (LPS),[39] the hallmark glycolipid of gram-negative organisms, and does not take up Gram stain. Other major differences in the molecular architecture and composition of their cell envelopes further underscore the phylogenetic gulf between *T. pallidum* and gram-negative bacteria.[34,73] The outer membrane of *T. pallidum* contains an extraordinarily low density of integral membrane proteins (see Fig. 237.1D)[74–76] that, as a whole, have little sequence homology with OMPs of gram-negative bacteria.[73,77] In gram-negative bacteria, the peptidoglycan resides directly beneath the outer membrane; in *T. pallidum,* the murein layer is found midway in the periplasmic space, beneath the flagellar filaments, which rotate against it in order to transfer their motive force to the cell cylinder.[68,69] For many years, it was believed that *T. pallidum* possesses a coat of serum proteins and mucopolysaccharides that shields it from the host's immune system.[78] It is now widely accepted that the paucity of proteins and pathogen-associated molecular patterns (PAMPs) on the spirochetal surface is the basis for the bacterium's impressive capacity for immune evasion, which has earned for it the name "stealth pathogen."[34,73,79]

The genomes of pathogenic treponemes consist of single circular chromosomes of approximately 1.1 MB,[39] near the low end of the spectrum for eubacteria and only half the size of the genomes of oral treponemes.[80,81] The absence of plasmids, pathogenicity islands, transposable elements, and restriction-modification systems indicates that the organism has limited capacity for uptake of exogenous DNA, perhaps explaining why it has remained exquisitely sensitive to penicillin for more than 7 decades. The syphilis spirochete is the only pathogenic

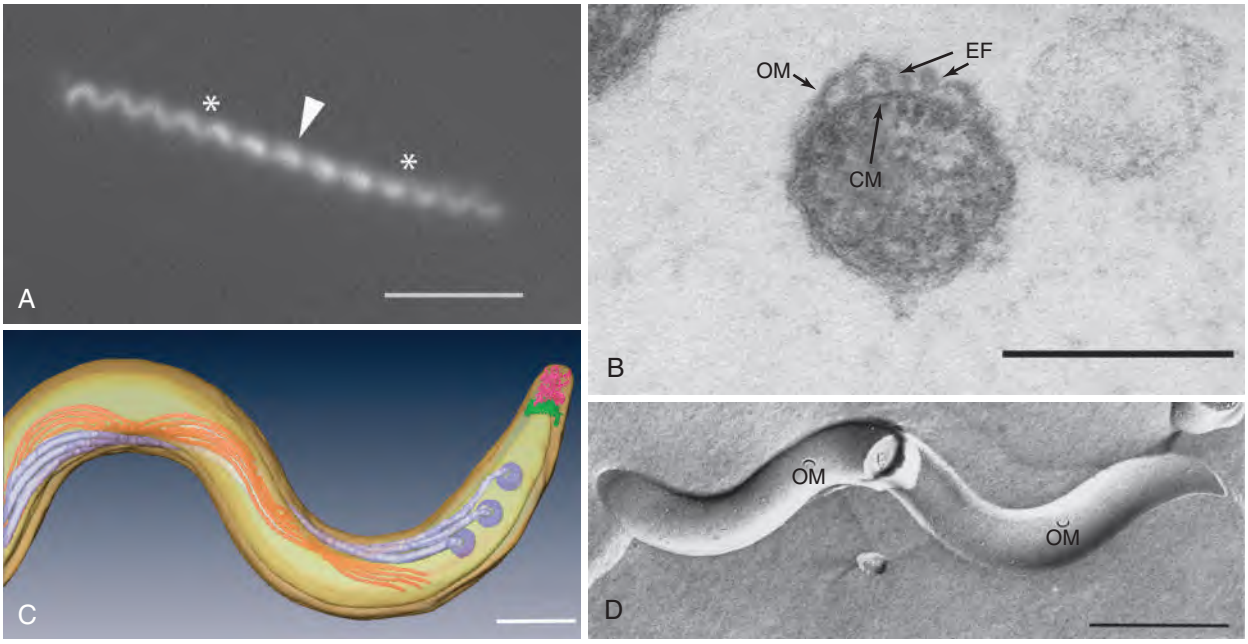

FIG. 237.1 (A) Darkfield micrograph showing the flat wave morphology of *Treponema pallidum*. Asterisks and arrowhead indicate segments oriented 90 degrees from each other. *Bar,* 10 μm. (B) Ultrathin section of *T. pallidum* showing the outer and cytoplasmic membranes (*OM* and *CM,* respectively) and flagellar filaments (endoflagella *[EF]*). *Bar,* 200 nm. (C) Top view of a surface-rendered model of *T. pallidum* generated from cryoelectron tomograms showing the outer and cytoplasmic membranes *(transparent yellow),* flagellar motors (basal bodies, *dark lavender*), flagellar filaments *(light lavender),* cytoplasmic filaments *(orange),* cap *(green),* and cone *(pink). Bar,* 200 nm. (D) Freeze-fracture electron microscopy reveals rare outer membrane proteins (particles) in the *T. pallidum* outer membrane. Convex and concave leaflets of the outer membrane are indicated. *Bar,* 500 nm. *(A courtesy Ms. Carson Karanian and Ms. Morgan Ledoyt. C from Izard J, Renken C, Hsieh CE, et al. Cryo-electron tomography elucidates the molecular architecture of* Treponema pallidum, *the syphilis spirochete.* J Bacteriol. *2009;191:7566–7580. D from Radolf JD, Bourell KW, Akins DR, et al. Analysis of* Borrelia burgdorferi *membrane architecture by freeze-fracture electron microscopy.* J Bacteriol. *1994;176:21–31.)*

treponeme whose physiology has been examined in detail, although there is no reason to believe that it differs substantively from those of the other subspecies.[34] *T. pallidum* subsp. *pallidum* replicates slowly (doubling time of approximately 30 hours in rabbits)[82] and poorly tolerates desiccation, elevated temperatures, and high oxygen tensions.[83] Because optimal replication under in vitro conditions occurs in ambient oxygen concentrations of 3% to 5%, the organism, once considered anaerobic, is now classified as a microaerophile.[83] During the course of reductive evolution, *T. pallidum* has dispensed with a vast amount of the biosynthetic machinery found in other bacterial pathogens. It is unable to synthesize fatty acids, nucleotides, enzyme cofactors, and most amino acids and must therefore scavenge all of these nutrients from its obligate human host by using a complex repertoire of cytoplasmic membrane transporters after they traverse the outer membrane via porins and other channels.[34,39,73] Lacking the components for oxidative phosphorylation, *T. pallidum* relies on glycolysis as its primary means for production of adenosine triphosphate (ATP), exploiting the abundant supply of glucose in blood and interstitial fluids. Additional ATP is likely generated through a recently discovered flavin-dependent Na/H^+ redox pump working in tandem with an A-type ATP synthase.[34] Identification of stable, genetically variable loci within the *T. pallidum* genome has made possible the development[84] and further refinement[85] of a scheme for typing syphilis strains, an essential tool for molecular epidemiologic studies. A meta-analysis of global typing studies reported the existence of at least 57 subtypes, with wide variation in geographic distribution, although a small number of subtypes predominate overall.[86] Recent studies emphasizing vaccine development have pointed to the need for a typing system that takes into account sequence variation in OMPs in *T. pallidum* strains circulating in clinical populations.[87]

EPIDEMIOLOGY

Despite the availability of effective and inexpensive antibiotic treatment, venereal syphilis continues to cause significant morbidity and mortality globally. According to the World Health Organization (WHO), globally, approximately 17.7 million persons aged 15 to 49 years had venereal syphilis in 2012, with an estimated 5.6 million new cases.[88] Although syphilis has recently reemerged in the United States and Europe[89–92] most individuals (>90%) who acquire syphilis reside in less affluent regions of the world.[93]

The number of new syphilis cases in the United States has cycled continuously since active reporting began in 1941. The advent of penicillin treatment and the establishment of aggressive syphilis-control public health campaigns toward the end of World War II led to notable decreases in the total number of new syphilis cases. As shown in Fig. 237.2, the incidence of venereal syphilis steadily decreased over several decades, with periodic outbreaks between 1986 and 1994 and between 2002 and 2011. In 2016, the rate of reported cases of primary and secondary syphilis in the United States was 8.7 cases per 100,000 population (27,814 total cases), more than four times the 2.1 per 100,000 rate at the historical nadir in 2000.[94] The upswing in the total number of early syphilis cases in the late 1980s, ascribed principally to heterosexual transmission, as would be expected, led to increases in gestational and congenital syphilis (CS) cases. The reappearance of syphilis during this time period was linked epidemiologically to the exchange of sex for drugs, especially crack cocaine.[95] The most recent surge has occurred chiefly among gay and bisexual men and other MSM,[96] a high-risk group that accounted for 58.1% of all primary and secondary syphilis cases reported to the Centers for Disease Control and Prevention (CDC) in 2016.[94] However, it is important to highlight that during the period from 2013 to 2016, syphilis rates in the United States increased in both men and women, in every region of the country, in every age group among those aged 15 years or older, and in every racial and ethnic group. The reasons for this latest increase are likely multifold and include lack of sexual inhibition resulting from the availability of effective treatment for human immunodeficiency virus (HIV), the use of the Internet to meet partners, the practice of HIV serosorting, and the increase in oral sex as a form of "safe sex."[96] Some have suggested that, risk factors notwithstanding, the oscillating pattern of syphilis outbreaks reflects changes in levels of immunity to *T. pallidum* within susceptible populations.[35] In the United States, syphilis is currently characterized by low-level endemicity with

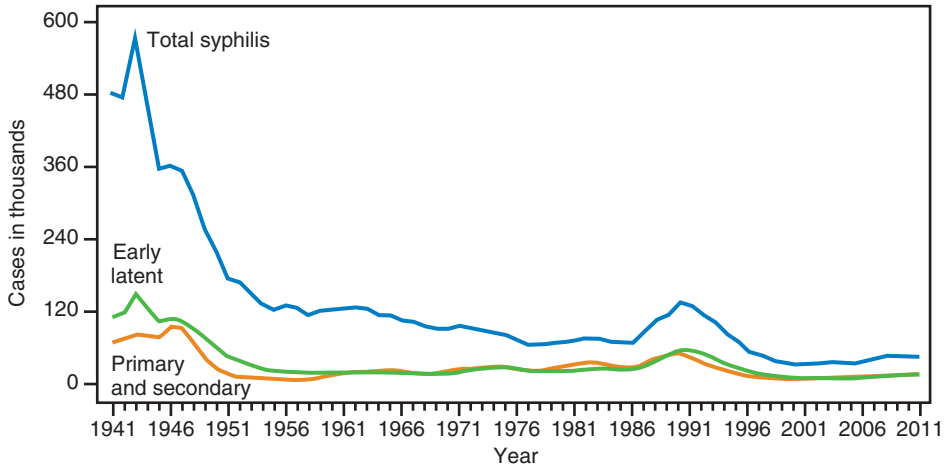

FIG. 237.2 Syphilis epidemiology in the United States: reported cases by stage of infection, 1941–2011. *(Modified from Centers for Disease Control and Prevention. STD Surveillance 2010, National Profile.* http://www.cdc.gov/std/stats10/figures.*)*

concentration among population subgroups with high rates of partner change, poor access to health services, social marginalization, or low socioeconomic status. The highest incidence of syphilis in the United States is evidenced in MSM from poor, underserved minority communities in southern states, from Maryland to Florida to eastern Texas and also in urban centers in California.[90] In addition, several other metropolitan areas throughout the country continue to report a high incidence of venereal syphilis in HIV-infected MSM.

In European and European Union member states, 24,541 new cases of syphilis were reported in 2014, with an overall incidence rate of 5.1 per 100,000 population. Similar to trends shown earlier in this chapter for the United States, close to two-thirds (63%) of reported syphilis cases were diagnosed in men who reported having sex with other men (MSM). The highest rate of syphilis was observed in Malta (11.5 per 100,000 population), followed by Lithuania (8.7), Iceland (7.7), and Spain (7.7). Rates below 2.5 per 100,000 population were observed in Croatia, Cyprus, Greece, Italy, and Slovenia.[97,98] The increase in syphilis cases in European/European Union states is also linked to changes in sexual behavior among MSM, in addition to more complete reporting and improved case detection through more rigorous testing as recommended in current international HIV management guidelines.

The social changes and disruption of medical services that followed the breakup of the Soviet Union in the late 1980s led to important increases in syphilis rates in Eastern Europe and Russia.[99,100] Although improved prevention strategies have led to a steady decrease in the overall disease burdens in this region of the world, Eastern European countries and Russia continue to report higher burdens of syphilis than their counterparts in the West. Findings from a recent review reveal that country-specific rates vary widely, with a mean syphilis incidence rate for Eastern European countries of 12.5 per 100,000 population, ranging from a high of 41 per 100,000 in Belarus to a low of 1.15 per 100,000 in Albania.[100] A report from the Russian Federation revealed that although the overall syphilis incidence declined nationally from 79.4 per 100,000 in 2004 to 28.9 per 100,000 in 2013, rates remain very high in Far Eastern, Siberian, and Northwestern Federal districts.[101] In the Tuva Republic, located in southern Siberia, the incidence rate of syphilis was estimated to be 177 per 100,000.

In China, a country where syphilis was virtually eradicated in the 1950s, the incidence and prevalence of the disease have more than quadrupled in the past several years.[102] In 2008 there were more syphilis cases in the coastal province of Guangdong than were reported in the entire European/European Union region in the same time period. Although the causes are not entirely clear, this increase in syphilis rates has been attributed to migration from rural communities to urban environments, leading to earlier sexual debut, later marriage, more lifetime partners, and increased commercial sex, including in MSM. These factors are compounded by limited syphilis screening, lack of adequate partner notification, and an overall unwillingness by the general population to access sexually transmitted disease (STD) health care services.[103]

Endemic rates of syphilis transmission have been stubbornly persistent in the resource-limited public health systems of Latin America and the Caribbean. Because syphilis is not rigorously reported, and often not recognized by health care providers in the region, country-specific disease prevalence and incidence rates most likely underestimate the true magnitude of the problem. Syphilis has been shown to be a leading cause of genital ulcerative disease in both Peru and the Dominican Republic,[104] second only to genital herpes. Likewise, in another study from Peru, the prevalence of venereal syphilis was estimated to be 10.5% among MSM and 2.0% in socially marginalized men and women.[104] In a Brazilian study, high syphilis prevalence rates were the norm in prisoners, commercial sex workers, and MSM.[105] High syphilis prevalence rates have also been documented for MSM (5% and 13%) and female sex workers (6.8% and 15.3%) in Honduras and Guatemala, respectively.[105a] In one study describing the epidemiology of venereal syphilis in Colombia, 10% of female sex workers in Bogota had serologic and clinical evidence of the disease.[106] In another study, seroprevalence rates in sexually active men and women between the ages of 18 and 24 were close to 6%.[106,107] Overall, studies from this region consistently document high syphilis prevalence among MSM, particularly in Peru, Argentina, Costa Rica, El Salvador, Honduras, Nicaragua, and Guatemala.[108–110] Throughout the region, transgender persons had the highest syphilis rates of all groups, which in this population were linked to high vulnerability as a result of low self-esteem and marginalization, and a lack of legal recognition and labor opportunities, which often leads to engagement in commercial sex work.

Regardless of geographic location, the worldwide epidemiology of syphilis has been greatly influenced by developments in the HIV epidemic. A statistical association between the two diseases became apparent at the outset of the acquired immunodeficiency syndrome (AIDS) epidemic in the early 1980s.[111] Since that time, numerous studies have documented the high rate of HIV infection among patients with syphilis.[96,112,113] Not surprisingly, this increase has disproportionately affected large metropolitan areas with well-established populations of HIV-coinfected MSM, including San Francisco, where the incidence of primary and secondary syphilis increased more than 600% (26 cases per 100,000).[114] This increase has been attributed to increased reports of unprotected sex among HIV-positive MSM and increased HIV prevalence. Simultaneously, there also has been a resurgence of traditional sexual marketplaces such as saunas and cruising grounds, together with a new and rapid growth of Internet chat rooms, increasing the opportunity for rapid and easy access to new sexual partners. The overall effect has been to join previously isolated sexual networks, increasing the size of the sexual networks and thereby reducing the time taken for the spread of syphilis to evolve. In addition, the idea that oral sex is "safer" sex and rarely associated with HIV transmission

may explain the role of oral sex in syphilis transmission.[115] During the period from 2000 to 2016, the rise in the rate of reported primary and secondary syphilis was primarily attributable to increased cases among men and, specifically, among gay and bisexual men and other MSM.[116] Rates of HIV coinfection among MSM with newly diagnosed early syphilis are as high as 50%.[117] In one study from Florida, 21% of men diagnosed with early syphilis in 2003 had acquired HIV infection by the end of 2011.[118] Although the association between syphilis and HIV infection initially was thought to simply reflect similar behavioral risk factors for acquisition and transmission, it has become apparent over the years that complex biologic relationships exist between these two diseases.[96,119,120] The presence of a syphilitic chancre can theoretically facilitate HIV transmission by either increasing the host's susceptibility to infection with the virus or the HIV-infected host's infectiousness to discordant sexual partners. The former is associated with the disruption of the protective epithelial and mucosal barriers present in genital chancres and the known enrichment of the lesion with activated lymphocytes, macrophages, and dendritic cells (DCs), all of which are potential targets and donors for HIV[121–124] and which differentially increase expression of key HIV coreceptors (i.e., CCR5 and DC-SIGN) in untreated patients.[124,125] With respect to increased infectiousness, the inflammatory response elicited by *T. pallidum* is capable of inducing HIV gene expression, thereby promoting viral replication.[126] Not surprisingly, in HIV-infected patients, CD4 counts decrease and HIV viral loads increase in individuals with untreated syphilitic coinfection.[127]

Nearly 1.0 million pregnant women are estimated to be newly infected with syphilis every year, and approximately half of pregnant women who are left untreated will experience adverse outcomes in their pregnancies. These include early fetal loss (20–28 weeks' gestation) and stillbirth (>28 weeks' gestation), neonatal death, low-birth-weight infants, and infants with clinical evidence of infection.[128] In 2008, syphilis in pregnancy contributed to 305,000 stillbirths and fetal and neonatal deaths, and an additional 215,000 infants were at increased risk of dying from low birth weight, prematurity, or complications of infection related to syphilis.[128] Of particular concern, in sub-Saharan Africa, syphilis contributes to approximately 20% of all perinatal deaths. After decreasing from 10.5 to 8.4 reported CS cases per 100,000 live births during 2008–2012, the rate of reported CS in the United States subsequently increased each year during 2012–2016. In 2016, there were a total of 628 reported cases of CS, including 41 syphilitic stillbirths, and the national rate was 15.7 cases per 100,000 live births. This rate represents a 27.6% increase relative to 2015 (12.3 cases per 100,000 live births) and a 86.9% increase relative to 2012 (8.4 cases per 100,000 live births).[129]

PATHOGENESIS

Studying syphilis pathogenesis poses a formidable and unique set of challenges. First and foremost is that *T. pallidum* has, until very recently, defied all attempts at continuous cultivation in artificial media[64,65] and therefore cannot be genetically manipulated. A second serious limitation is the lack of a facile murine model for dissecting the complex host response to this pathogen.[130,131] Although the outbred rabbit model recapitulates many facets of human disease, rabbits do not develop typical secondary lesions after intradermal inoculation, nor do they develop neurologic complications or neuropathologic effects comparable to those of humans, even when inoculated intravenously.[132,133] Investigators who wish to circumvent these deficiencies by studying infection in humans must cope with an enormous spectrum of disease manifestations, person-to-person variability in immune responses, high rates of HIV coinfection, and the fact that results from blood and skin (the two most accessible sites) represent snapshots from just two compartments of a dynamic, systemic process.[134,135] A third obstacle is the fragility of *T. pallidum,* particularly its outer membrane, a physical property that has greatly hampered efforts to identify and examine molecules that function at the host-pathogen interface.[136,137] Lastly, transcriptional and proteomic analysis of syphilis spirochetes has thus far been confined to organisms extracted from inflamed rabbit testes,[138,139] a circumstance unlikely to represent the expression profiles in human tissues during the various stages of disease. Given all of these impediments, it is not surprising that our current understanding of the microbiologic and immunologic factors that determine the outcome of human infection lags far behind that of most other common bacterial infections.

Person-to-person transmission of spirochetes initiates the pathogenic sequence. With venereal syphilis, this typically occurs when treponemes are transferred during intimate contact, usually sexual (oral-genital as well as genital-genital, rarely kissing), with an actively infected partner. In their human inoculation studies conducted at Sing Sing Prison in the 1950s, Magnuson and colleagues[140] (see discussion of ethics) found that as few as 10 organisms of the Nichols strain could cause lesions. Thus, only miniscule amounts of infectious exudate need be exchanged when microenvironmental conditions are conducive to survival of this fastidious pathogen. Individuals with venereal syphilis are most infectious during the primary and secondary stages of disease (including secondary relapses of early latency) when moist, mucocutaneous lesions are present. Persons with early syphilis may be infectious, however, even if they lack open lesions. Micrographs showing that spirochetes are abundant within the epidermis and superficial layers of the dermis in secondary syphilitic lesions[141] suggest how minute abrasions created during sexual activity might result in infection. Transfusion syphilis, a well-recognized nonsexual mode of transmission before World War II, no longer occurs in the United States[142] but remains a significant concern in underdeveloped countries.[143] The agents of yaws, pinta, and endemic syphilis are transmitted by nonsexual contact with open lesions, usually during childhood.[58]

Syphilis spirochetes rapidly gain entry into their new host either by directly penetrating mucous membranes or via abrasions and cracks in skin. Remarkably, treponemes applied to the preputial mucosa of rabbits migrate into the subepithelium within several hours.[144] Once below the epithelial surface, they begin to multiply locally and disseminate through lymphatics and blood vessels. Why some members of the bacterial population remain localized whereas others respond to the same environmental signals by migrating away from the inoculation site is a fascinating and unresolved question. The experimental and clinical evidence that *T. pallidum* disseminates systemically early during the course of infection is overwhelming.[59,145] Brown and Pearce[146] recovered *T. pallidum* from inguinal lymph nodes and blood of rabbits within 48 hours of intratesticular inoculation, well before the onset of orchitis; these findings have been replicated with quantitative PCR.[147] Numerous reports in the early 20th century documented transmission following the transfusion of blood from seronegative donors (i.e., during the incubation period).[148] Almost any organ in the body can be invaded during the spirochetemia of early syphilis, including the CNS.[1,67,149] Using both RIT and PCR, investigators in the molecular era have confirmed that substantial percentages of patients with early syphilis without neurologic signs or symptoms harbor *T. pallidum* in their CNS.[150,151]

It is widely believed that *T. pallidum* must adhere to epithelial cells and extracellular matrix components in order to gain the "foothold" needed to establish infection[152,153]; spirochetes subsequently disseminate within tissues by coordinating adherence with motility in a series of "stop and go" movements.[71,154] Binding studies suggest that fibronectin and laminin are important substrates for this attachment-mediated form of motility.[155–157] Putative *T. pallidum* adhesins for these host molecules have been identified[152,158–160] and, in two cases (TP0435 [Tpp17] and TP0751 [pallilysin]), crystal structures have been obtained.[161,162] Light micrographs showing *T. pallidum* attached end-on to cell surfaces suggested years ago that the tip of the bacterium functions as an attachment organelle[163]; this notion has been buttressed by recent cryoelectron tomographic analyses (see Fig. 237.1C).[68,69] Chemoreceptor arrays near the cell ends translate environmental cues (chemotactic signals) into a chain of phosphorylation events that determine whether the flagellar motors turn clockwise or counterclockwise.[69,164] Directed motility does not occur unless the motors at each end of the cell turn in opposite directions.[164] How a spirochete coordinates the direction of rotation of the motors at opposite ends of the cell is a mystery.[164] Circulating treponemes bind to vascular endothelium within target organs, reaching the parenchyma by negotiating their way through the tight junctions separating endothelial cells, a process called *interjunctional penetration.*[70] Use of the Lyme disease spirochete, *B. burgdorferi,* as a

heterologous host identified TP0751 (pallilysin) as a putative adhesin for vascular endothelium.[165]

Although rare examples of intracellular treponemes have been reported,[166,167] the syphilis spirochete is believed to be incapable of establishing long-term residence in phagocytic or nonphagocytic cells.[59,168] There is also now a consensus among syphilologists that clinical manifestations result from the inflammatory processes driven by the presence of treponemes and treponemal constituents within infected tissues.[168,169] How does the spirochete flourish within the extracellular space in the face of the increasingly vigorous humoral and cellular responses it elicits as the disease progresses? Current thinking is based on an infection model that pits innate and adaptive immunity against a motile invader structurally equipped to "fly" beneath the host's "immunologic radar," perhaps even manipulating the host response to facilitate dissemination and immune evasion.[79,134,170]

Although lacking LPS, *T. pallidum* contains abundant lipoproteins, which are capable of activating macrophages and DCs via CD14- and Toll-like receptor 1/2 (TLR1/2)–dependent signaling pathways.[79,169] However, because of the bacterium's unique cell envelop architecture,[34,73,76] the vast majority of these PAMPs are not readily accessible to TLRs or other pattern recognition receptors (PRRs) expressed on the surface of innate immune cells. As a result, spirochetes can replicate at the site of inoculation, disseminate hematogenously, and then replicate at metastatic sites virtually unchecked by innate surveillance systems. At some point, and through poorly understood mechanisms, pathogen sensing is triggered and organisms are taken up by tissue-based DCs, which then traffic to draining lymph nodes to present cognate treponemal antigens to naïve B and T cells.[171] The production of opsonic antibodies enhances the uptake and degradation of spirochetes by phagocytes, allowing spirochetal PAMPs to gain access to PRRs lining the phagosomal vacuole and stimulating the production of proinflammatory cytokines, while production of interferon-γ (IFN-γ) by recruited, locally activated natural killer (NK) and $CD4^+$ and $CD8^+$ T cells bolsters macrophage-mediated clearance and inflammation.[134,170,172–174] Although these adaptive responses help to shift the balance in favor of the host, the spirochete is by no means without countermeasures. The paucity of antigenic targets on its surface,[73,76,77,160] the copious production of antibodies against subsurface lipoprotein "decoys,"[73,77,175] and the emergence of antigenically variant subpopulations via intergenomic recombination and phase variation of OMPs[176–180] collectively enable a subpopulation of bacteria to avoid opsonophagocytosis[181] and other forms of antibody-mediated clearance, prolonging disease manifestations and fueling the relapses of early latency. How, then, is the pathogen eventually contained, bringing about the quiescent stage of disease called late latency? Possibly, as infection proceeds, the antibody repertoire broadens and intensifies sufficiently to the point at which the spirochete's antigen-poor surface is overwhelmed, its capacity for antigenic variation is exhausted, or both. Nevertheless, although no longer capable of disseminating, organisms survive for years in a substantial proportion of untreated individuals, establishing niduses of inflammation that set the stage for recrudescent (i.e., tertiary) disease when, for reasons unknown, the balance shifts back in favor of the pathogen (see "Natural Course of Untreated Syphilis," later).

PATHOLOGIC FEATURES

Perivascular infiltrates composed of lymphocytes, histiocytes (macrophages), and plasma cells, accompanied by varying degrees of endothelial cell swelling and proliferation, are the histologic hallmarks of syphilis regardless of anatomic site or stage of disease (Fig. 237.3A–B).[182] Spirochetes are abundant in early syphilis lesions and often are observed in and around blood vessels (see Fig. 237.3C), occasionally even protruding into the lumen in histologic specimens (i.e., "caught in the act" of disseminating).[182–184] In contrast, with the exception of paresis (see later), spirochetes are not easily demonstrable in tertiary syphilis lesions.[182,185]

In primary syphilis, progression of the vasculopathic changes to frank endarteritis obliterans causes tissue necrosis, ultimately giving rise to a genital ulcer, the chancre. In secondary syphilis skin lesions, a wide variety of histologic patterns, including granuloma during later phases, can be superimposed on the characteristic features noted earlier.[186–188] Cutaneous infiltrates are most intense in the papillary dermis but often extend into the reticular dermis, assuming a bandlike (lichenoid) distribution. Follicles and sweat glands are frequently sleeved with inflammatory cells and, when extensive and severe, cause syphilitic alopecia. Epithelial abnormalities in secondary skin lesions include exocytosis, keratinocyte necrosis, acanthosis, microabscesses, and hyperkeratosis. Edema, papillation, and hyperplasia of the epidermis are distinctive features of condylomata lata, the highly infectious, intertriginous excrescences of secondary syphilis. Lymph nodes in secondary syphilis exhibit marked follicular hyperplasia coupled with lymphocyte depletion and histiocytic infiltration of the paracortical zones.[189] Although circulating immune complexes are detectable in patients with secondary syphilis,[190] immune complexes are not typically observed in skin.[123] Glomerular deposition of immune complexes, however, has been demonstrated in patients with nephrotic syndrome, a rare complication of secondary syphilis.[191,192]

A gumma is a circumscribed mass of granulation tissue, so named because of its rubbery or gummy gross consistency. The gumma of tertiary syphilis histologically is composed of a dense infiltrate of lymphocytes, plasma cells, epithelioid cells, and multinucleated giant cells surrounding a caseous, necrotic core; proliferating fibroblasts and fibrosis also may be present.[193] Endarteritis and perivascular inflammation help to distinguish syphilitic gummas from those caused by tuberculosis. Obliterative endarteritis involving the vasa vasorum, the nutrient vessels of the aortic adventitia, is the key pathologic lesion in cardiovascular syphilis.[194] The ascending aorta and arch are most frequently affected because the vasa vasorum are most plentiful in these regions of the aorta.[194,195] These changes eventually give rise to intimal thickening and wrinkling (producing a distinctive "tree bark" appearance), patchy medial necrosis, and adventitial scarring with destruction of elastic fibers and weakening of the aortic wall.

Asymptomatic neurosyphilis and syphilitic meningitis are due to diffuse leptomeningitis (Fig. 237.4A).[149] The pathologic features of meningovascular syphilis explain the syndrome's variable mixture of focal neurologic signs with superimposed encephalitis.[149,196,197] In general, there is diffuse thickening and lymphocytic infiltration of the meninges with two kinds of arteritis: (1) *Heubner* endarteritis, affecting large and medium-sized arteries, characterized by crescentic collagenous thickening of the intima, thinning of the media, and dense, inflammatory infiltrates (lymphocytes and plasma cells) within the adventitia (see Fig. 237.4B), and (2) *Nissl-Alzheimer* endarteritis of small vessels, characterized by the proliferation of endothelial and adventitial cells. *Paresis* and *tabes dorsalis* involve poorly understood spirochete-driven, neurodegenerative processes of brain tissue, hence their designation as "parenchymatous." In paresis, diffuse meningovascular inflammatory changes are associated with striking, progressive loss of cerebral cortical neurons, resulting in gross cerebral atrophy (greatest in the frontal and temporal lobes), and proliferation of astrocytes and glial cells. Microglial cells are hypertrophied and elongated and often contain abundant iron. Spirochetes are often readily detectable, usually in the gray matter, with little correlation between the clinical picture and the location and distribution of organisms. Tabes dorsalis (Greek for "consumption of the back") is characterized by demyelination of dorsal root ganglia with secondary wallerian degeneration of the posterior columns of the spinal cord (see Fig. 237.4C). In early tabes, the leptomeninges and dorsal roots are heavily infiltrated with lymphocytes and plasma cells. These inflammatory changes diminish as the disease becomes chronic, eventually disappearing in so-called burnt-out cases. The degenerative changes in the tabetic spinal cord can be so severe that the posterior surface of the cord is concave, rather than convex.

Immunohistochemical (IHC) analysis of the cellular infiltrates in primary and secondary syphilis lesions has provided valuable insights into the pathogenic mechanisms operative during infection. Staining with macrophage markers has confirmed that these professional phagocytes are universally present.[123,134,170,198] A long-standing point of dogma in the syphilis field, based on work done with the rabbit model, is that the cellular response to *T. pallidum* is a classic, delayed-type hypersensitivity reaction.[78] Immunostaining has revealed that this is not the case in humans. Whereas lesional T cells in rabbits are predominantly $CD4^+$ lymphocytes,[199] $CD8^+$ T cells are prominent in humans.[123,134,170,200,201] This finding has implications for both the ontogeny of the adaptive

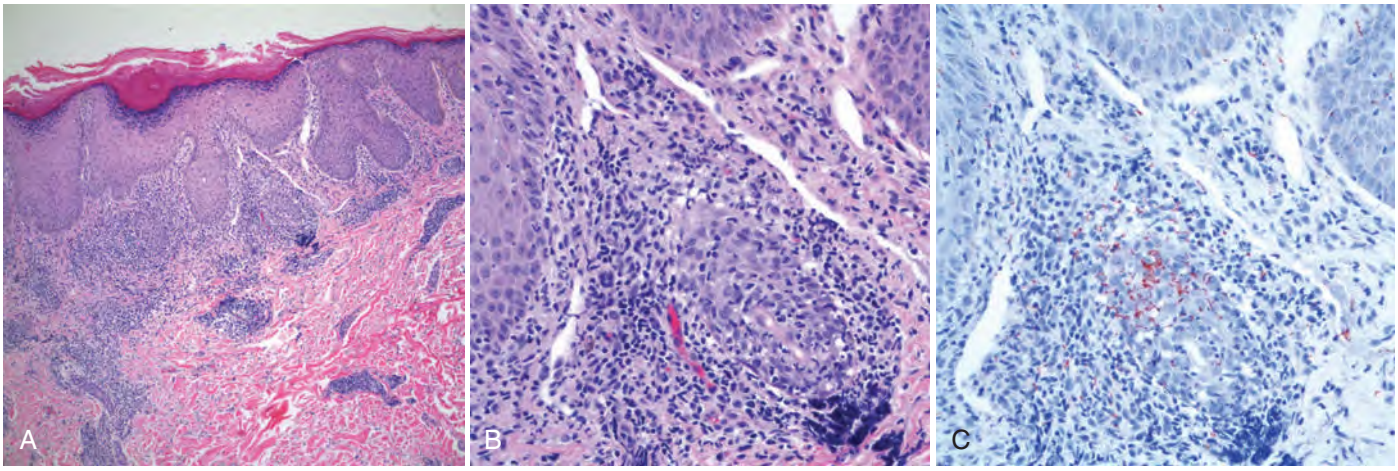

FIG. 237.3 Characteristic histopathology from a secondary syphilis skin lesion. (A) Punch biopsy specimen obtained from secondary syphilis skin lesion demonstrates a mixed infiltrate composed of lymphocytes, histiocytes, and plasma cells, accompanied by varying degrees of endothelial cell swelling and proliferation. (Hematoxylin-eosin stain, ×100.) (B) Characteristic obliterative endarteritis, ×400. (C) Immunohistochemistry staining reveals abundant spirochetes, labeled in *red,* in and around the wall of a blood vessel, ×400. *(Courtesy Drs. Adriana Cruz and Rodolfo Trujillo, Centro Internacional de Entrenamiento e Investigaciones Médicas, Cali, Colombia.)*

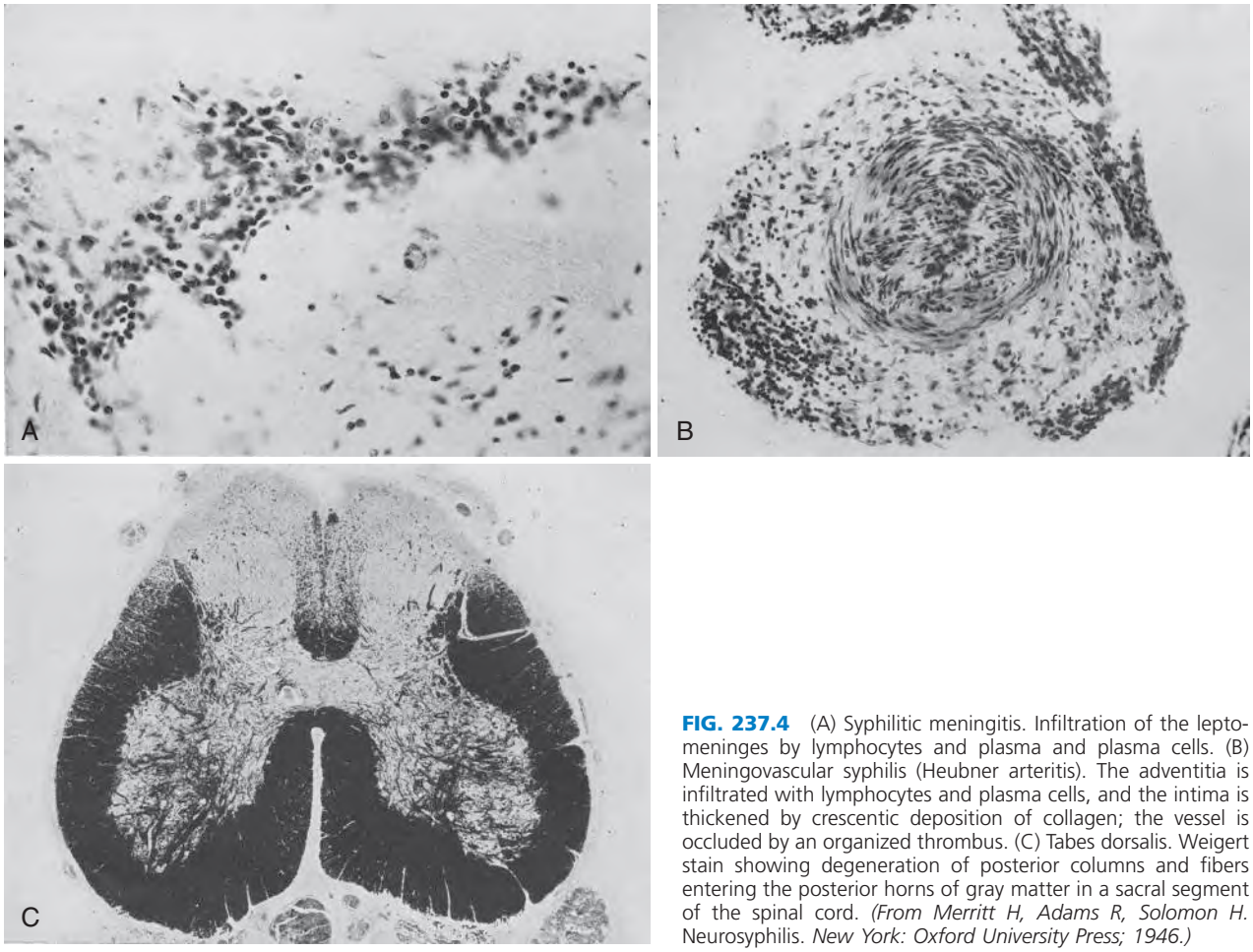

FIG. 237.4 (A) Syphilitic meningitis. Infiltration of the leptomeninges by lymphocytes and plasma and plasma cells. (B) Meningovascular syphilis (Heubner arteritis). The adventitia is infiltrated with lymphocytes and plasma cells, and the intima is thickened by crescentic deposition of collagen; the vessel is occluded by an organized thrombus. (C) Tabes dorsalis. Weigert stain showing degeneration of posterior columns and fibers entering the posterior horns of gray matter in a sacral segment of the spinal cord. *(From Merritt H, Adams R, Solomon H.* Neurosyphilis. *New York: Oxford University Press; 1946.)*

cellular response and its role in clearance of organisms. Because *T. pallidum* is an extracellular pathogen, priming and activation of $CD8^+$ T cells (resulting in local production of IFN-γ) would have to occur by cross-presentation; whether this is advantageous for the spirochete is an open question. NK cells, another potential source of IFN-γ, also have been identified in secondary syphilis skin biopsy specimens.[134,170] Evidence has been provided that *T. pallidum* promotes the development in secondary syphilis lesions of regulatory T cells, which could facilitate spirochetal persistence by producing antiinflammatory molecules.[201,202]

NATURAL COURSE OF UNTREATED SYPHILIS

Of the numerous investigations that have contributed to our understanding of syphilis, the "Oslo Study" stands out as the single greatest source of information about the natural course of the disease.[203] The study was born from the clinical impression of Boeck at the University of Oslo that the mercury-based antisyphilitics of the late 19th century were more harmful than efficacious, coupled with his astute insight that "the immune mechanisms of the body are the most important in combating the disease." In 1891, he began a prospective study of 1978 untreated patients with early syphilis who were hospitalized and closely monitored until all signs and symptoms had disappeared; enrollment ended in 1910 when arsphenamine became accepted syphilotherapy. In 1925, his successor, Bruusgaard, recognizing that Boeck's material "is hardly to be duplicated anywhere else," conducted follow-up on 473 persons (309 living and 164 dead) from the original cohort. Concerns over potential biases and shortcomings in Bruusgaard's data prompted his successor, Gjestland, in 1948 to undertake a painstaking reexamination of the available records for the 1404 patients who lived near Oslo. Because Boeck had enrolled his cohort before the availability of both DF microscopy and the Wassermann test, his diagnoses rested entirely on clinical criteria; during their reexamination, Gjestland and collaborators concluded that the great majority of individuals had, in fact, been correctly diagnosed. Among the key findings of Gjestland's comprehensive analysis was that 24% of enrollees developed one or more secondary relapses within 5 years of discharge. Two-thirds of the relapses took place within 6 months of resolution of secondary lesions, whereas nearly 90% occurred within 1 year. These observations form the basis for the 1-year time point used clinically and epidemiologically to distinguish early latent from late latent syphilis. (As of January 2018, the CDC had renamed early and late latent syphilis as *early syphilis, non-primary, non-secondary* and *syphilis, unknown duration or late,* respectively.) Twenty-eight percent eventually developed some type of late manifestation: 10% developed cardiovascular syphilis, 6.5% developed symptomatic neurosyphilis; and 16% developed benign (i.e., gummatous) tertiary disease. Many of these patients had more than one "late" complication. Of those on whom autopsy was performed, 35% of the men and 22% of the women had evidence of cardiovascular involvement, especially aortitis. Syphilis was considered the primary cause of death in 15% of the men and 8% of the women. Thus, another important finding of the Oslo Study was that untreated syphilis can be uneventful and that many persons appear to spontaneously self-cure.

In 1932 the US Public Health Service began a prospective comparative study (the infamous Tuskegee study of 1932 to 1972, see earlier) involving 412 African-American men with untreated syphilis of 3 or more years' duration and 192 uninfected, matched controls.[45,46] It should be noted that when this study was initiated, there was no consensus about the usefulness of arsenicals for treatment of persons with latent syphilis or even the need to treat such individuals, especially older than the age of 50. Indeed, as noted earlier, a consensus on the need to treat latent syphilis was slow to develop even after the efficacy of penicillin for early syphilis became well established.[204] Serial reports from this study underscored the excess cardiovascular morbidity and mortality resulting from untreated syphilis.[45,194] In his analysis of autopsy data from the first 20 years of the study, Peters and colleagues[205] found that 50% of patients who had been infected for 10 years had cardiovascular involvement and that cardiovascular and neurosyphilis were the primary causes of death among the 40% of syphilitic patients who had died during this period. Of the 41% of survivors at 30 years of follow-up, 12% had evidence of late, predominantly cardiovascular, syphilis.[206]

In a third large study published in 1946, Rosahn[207] used a novel approach, postmortem examination, to assess the outcome of untreated syphilis. Of a total of 3907 cases encompassing all diseases, 380 were found to involve clinical, laboratory, or postmortem evidence of syphilis. Only 77 (39%) of the 198 untreated cases demonstrated anatomic changes consistent with syphilis; in 31 of these, syphilis was not the cause of death. Twenty percent of the untreated individuals, therefore, were thought to have died from complications of late syphilis. Rosahn believed that the sizable percentage of individuals who appeared to have self-cured mirrored the findings from the Oslo Study (only the Bruusgaard data were available at the time). Of the anatomic lesions attributable to syphilis, 83% were cardiovascular, 8% were neurologic, and 9% were gummas. Cardiovascular syphilis was almost certainly overrepresented in this series because it involved hospitalized persons who came to autopsy. An interesting sidelight was the observation that continued reactivity of serologic tests, what we now call the serofast state,[208] can occur without apparent histologic evidence of disease.

A schematic depicting the course of untreated syphilis is shown in Fig. 237.5.[182,209–211] The incubation period is a median of 3 weeks but may vary from 10 to 90 days depending on the size of the inoculum.[212] The primary stage begins with the appearance of the chancre at the site of inoculation. This usually painless, solitary lesion does not develop in every case or may go unnoticed, particularly in women or MSM. The secondary or disseminated stage becomes evident 4 to 10 weeks after the appearance of the chancre and is associated with the highest treponemal burdens in the bloodstream and tissues. After weeks to several months, the untreated patient then enters a period of latency during which the diagnosis can be made only by serologic testing (unless a relapse occurs). As per the revised terminology described earlier, latency is divided into *early syphilis, non-primary, non-secondary* (infectious relapses and/or spirochetemia common) and *late syphilis of unknown duration* (relapses, spirochetemia, or both unlikely) stages.

Late syphilis refers to both clinically inapparent latent infection and the tertiary syndromes (benign gummas, cardiovascular syphilis, and neurosyphilis) that develop in approximately one-third of untreated cases. Cardiovascular syphilis typically involves the aortic arch.[194] The skin, bones, liver, CNS, and spleen are the most commons sites in which gummas develop.[1] As noted earlier, although invasion of the CNS occurs during early syphilis, individuals usually do not develop neurologic complications at this stage. Asymptomatic neurosyphilis may resolve spontaneously, persist indefinitely, or progress to one of the "early" neurosyphilis syndromes, meningitis and meningovascular syphilis, within the first 1 to 10 years of infection, or one of the "late" parenchymatous syndromes, general paresis and tabes dorsalis, 10 or more years after infection.[149,213,214]

Whether coinfection with HIV worsens the manifestations of syphilis or accelerates the course of the disease, or both, has been a contentious issue for more than 2 decades. Since the late 1980s, a number of case reports and small series have documented ophthalmologic and neurologic complications, as well as unusual or highly destructive nonneurologic syphilis syndromes in HIV-infected patients.[215–217] The sheer volume of cases led many authorities to conclude that infection with HIV poses a profoundly increased risk of complications, particularly neurologic, during active syphilis.[96,216,217] To the surprise of many, a multicenter prospective study sponsored by the CDC did not bear this out.[151,218] The differences in clinical presentation between HIV-infected and HIV-uninfected patients were marginal. Although HIV-infected patients with primary syphilis tended to present with more genital ulcers and genital ulcers were present more frequently in HIV-infected patients with secondary syphilis, manifestations of disseminated infection, including neurologic and ophthalmologic complications, were not worsened by concomitant HIV infection. Thus, if atypical and aggressive presentations of syphilis do occur more frequently among HIV-infected patients, they likely represent a small percentage of total cases, an assessment shared by several groups.[96,211,219,220] The effectiveness of current antiretroviral regimens should further mitigate concerns about the ability of HIV infection to adversely affect the natural course and manifestations of syphilis.[221] Interesting to note, no correlation has been observed between HIV status and isolation or detection of *T. pallidum* in CSF,[150,151] suggesting that the bacterium's inherent invasiveness, rather than the

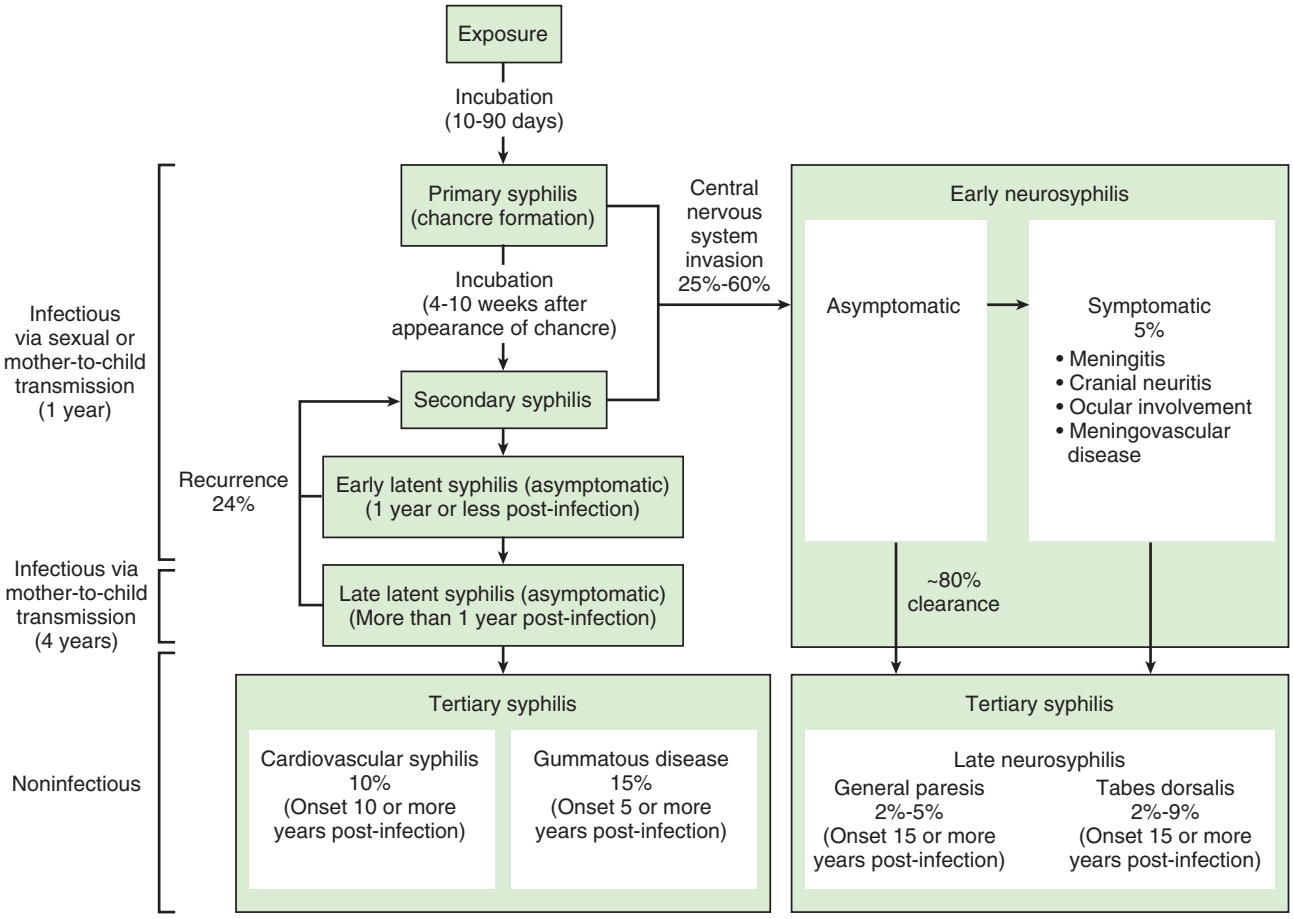

FIG. 237.5 Natural course of untreated syphilis. As of January 2018, the Centers for Disease Control and Prevention renamed early and late latent syphilis as *early syphilis, non-primary, non-secondary* and *syphilis, unknown duration or late,* respectively. *(Modified from Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem.* JAMA. *2003;290:1510–1514.)*

integrity of host immune defenses, is the primary determinant of CNS invasion during early syphilis.

The effect of early syphilis on HIV viral load also has been examined by several groups.[222–224] Most,[222–225] but not all,[226,227] studies found that active syphilis causes transient increases in viral loads and decreases in CD4 count that return to baseline with effective antimicrobial therapy. Besides diminishing the dangers of untreated syphilis to the coinfected individual, lowering viral loads in semen by treatment of syphilis has important public health implications for this at-risk population.

CLINICAL MANIFESTATIONS

Several excellent summaries of the spectrum of clinical manifestations in acquired syphilis are available.[209–211,228]

Primary Syphilis

Syphilis commences clinically when spirochetes replicating at the site of inoculation induce a local inflammatory response sufficient to generate a macule, which over the course of 1 to 2 weeks becomes papular and then ulcerates, producing the defining lesion of primary syphilis, the chancre.[1,182,230] The base of the typical chancre (Fig. 237.6A) is smooth, clean, and without exudate; the borders are raised and have a characteristic, cartilaginous consistency. Unlike the exquisitely painful genital ulcers caused by *Haemophilus ducreyi* (chancroid) and herpes simplex virus (herpes genitalis), the classic chancre is painless and nontender on examination; spirochetal infiltration of cutaneous sensory nerves may explain this phenomenon. Multiple chancres frequently occur, especially in persons who are coinfected with HIV.[218] Chancres that do not conform to the classic features are extremely common, representing more than half of the cases in one large series.[230]

The chancre forms wherever spirochetes are inoculated. The external genitalia are most frequently involved. In one study, penile lesions in men (presumably heterosexual) were located, in decreasing order of frequency, on the prepuce, coronal sulcus, shaft, corona, glans, frenum, and urethral meatus.[230] In women, lesions were located on the labia majora, labia minora, fourchette, and perineum[230]; occasionally chancres occur on the cervix, presenting as a painless discharge. Among heterosexuals, a much greater percentage of men present with primary syphilis because intravaginal chancres tend to go unnoticed; a male-to-female ratio of 9:1 was noted in one large study.[231] Similarly, chancres in MSM often go unnoticed because they occur within the rectum. Chancres in the anal area may be exquisitely painful and mistaken for anal fissures. As with anogenital ulcers, sexual orientation is a determining factor for the location of oral chancres. In heterosexuals, they typically occur on the upper lip in men and on the tongue in women, whereas in MSM they tend to be located on the tongue (see Fig. 237.6B).[232] Genital chancres are often accompanied by inguinal adenopathy, frequently bilateral, consisting of moderately enlarged, discrete, painless nodes, whereas cervical adenopathy often accompanies chancres in the oral cavity (see Fig. 237.6C). The chancre heals on its own within 3 to 6 weeks, leaving either no trace or a thin atrophic scar; the lymphadenopathy may persist longer.

Primary syphilis must be differentiated principally from herpes simplex virus infections, chancroid, and traumatic suprainfected genital lesions. Primary genital herpes usually begins as a painful erythematous rash that develops into clusters of vesicles accompanied by regional lymphadenopathy and systemic symptoms. It runs a 10- to 14-day course in immunocompetent patients. Recurrent genital herpes is less florid and is characterized by mild to moderately painful vesicles and no lymphadenopathy. Chancroid is characterized by one or more extremely

FIG. 237.6 (A) Classic penile chancre. (B) Oral chancre. (C) Bilateral cervical lymphadenopathy in same patient as in (B). *(B and C courtesy Dr. Kevin Dieckhaus. Copyright 2013.)*

painful, exudative, indurated ulcers associated with tender, eventually suppurative, lymphadenopathy. The ulcer has irregular, overhanging edges and bleeds easily (e.g., when scrapings are collected for a DF examination). Early venereal warts, granuloma inguinale, lymphogranuloma venereum, tuberculosis, atypical mycobacterial infections, tularemia, sporotrichosis, anthrax, rat-bite fever, or any genital ulcer may resemble early primary syphilis.

Secondary Syphilis

The manifestations of secondary syphilis, the often florid, systemic stage of the infection, are protean and are largely responsible for the disease's legendary reputation as "the great imitator."[1,209–211,229,233,234] The vast majority (>95%) of cases involve the skin and mucous membranes. With rare exceptions, secondary syphilis rashes are macular, papular, papulosquamous, annular, or pustular, or various combinations thereof.[229] Although often described as nonpruritic, in one series 40% of patients complained of itch, which could be severe.[235] The rash of secondary syphilis usually begins on the trunk and proximal extremities as bilateral, pink to red, discrete macular lesions 3 to 10 mm in diameter that are usually overlooked by the patient. These lesions often evolve from macules into brownish red papules (hence the term *maculopapular*); in a few patients, they progress to pustular lesions termed *pustular syphilids*. In one study of more than 200 patients, 94% and 66% of patients with maculopapular and papular lesions, respectively, presented within 4 weeks of the onset of rash as opposed to only 1 of 11 patients with pustular lesions.[236] Scaling is minor with most papular lesions but can be pronounced enough to resemble guttate psoriasis; hyperkeratotic plaques also are not unusual. Lesions are generally widespread and symmetrically distributed, although it is not uncommon for the rash to be anatomically limited. Involvement of palms and soles (Fig. 237.7A–B), either as part of the generalized eruption or as an isolated finding, is a characteristic feature of the maculopapular rash (see Fig. 237.7C) that helps in distinguishing secondary syphilis from psoriasis and pityriasis rosea. When the hair follicles are involved, patchy alopecia or thinning and a loss of eyebrows and beard may develop (see Fig. 237.7D). Lesions teeming with spirochetes, referred to as *mucous patches,* may develop on labial (see Fig. 237.7E), lingual, gingival, buccal, palatal, or pharyngeal mucosa, as well the moist surfaces of the genitalia. The typical mucous patch is an oval-shaped, shallow ulcer with a slightly raised border covered by a grayish-white or silvery membrane. In warm, moist intertriginous areas, the papules can enlarge, coalesce, and erode to produce painless, broad, moist, gray-white to erythematous papillary excrescences termed *condylomata lata* (see Fig. 237.7F). Generalized lymphadenopathy with firm, nontender nodes is a common physical finding in secondary syphilis; enlargement of the epitrochlear lymph nodes should always suggest the diagnosis.[1] Constitutional symptoms are also common and include low-grade fever, malaise, pharyngitis, anorexia, weight loss, arthralgias, and myalgias. During relapses of secondary syphilis, the skin lesions tend to be less florid, asymmetrically distributed, and more infiltrated.

Lues maligna is an unusual and severe variant of secondary syphilis eruption. Patients with this form of the disease may look systemically ill and present with rapidly developing polymorphic, ulcerating, rupioid (i.e., with heaped-up crusts) lesions sparing the palms and soles. Long recognized to affect debilitated persons, the condition has recently been reported most often in patients with HIV infection.[237–240]

Secondary syphilis can involve virtually any organ system, often causing diagnostic delay or confusion when not accompanied by telltale mucocutaneous signs. Subclinical elevations of liver enzymes, principally alkaline phosphatase, occur in up to 50% of patients.[241] The rare,

FIG. 237.7 Secondary syphilis lesions. (A) Characteristic palmar rash. (B) Plantar rash with hyperkeratosis. (C) Syphilitic exanthem—posterior trunk. (D) Syphilitic patchy alopecia. (E) Syphilitic oral mucous patch. (F) Male genital condylomas. *(Courtesy Dr. Adriana Cruz, Centro Internacional de Entrenamiento e Investigaciones Médicas, Cali, Colombia.)*

symptomatic hepatitis is characterized by a disproportionately elevated serum alkaline phosphatase level, mildly increased aminotransferases, and usually normal bilirubin. The histologic picture includes portal inflammation, mild hepatocellular necrosis, noncaseating granulomas, and rarely cholestasis. The gastrointestinal tract, particularly the stomach, may also become extensively infiltrated, ulcerated, or both, and the condition can be mistaken for lymphoma or carcinoma.[242,243] Epigastric or abdominal pain, early satiety, and nausea and vomiting are the most common gastrointestinal symptoms. All of the structures of the eye may be involved in secondary syphilis: the cornea (interstitial keratitis), the anterior chamber (iritis and anterior uveitis), the vitreous and choroid (posterior uveitis and chorioretinitis), and the optic nerve (optic neuritis).[244–247] Vitritis can be so dense that it obscures visualization of the retina.[248] The presence of cotton-wool spots in a patient with HIV infection can result in confusion between chorioretinitis due to syphilis and cytomegalovirus (CMV); retinal hemorrhage, a characteristic feature of CMV, does not occur with syphilis. Otosyphilis manifests with sudden or progressive sensorineural hearing loss, tinnitus, vertigo, and dysequilibrium.[249] The most common type of skeletal lesion is periostitis, most frequently involving the tibia, but also the sternum, skull, and ribs. Rarely, destructive bony lesions occur.[250,251] Symmetrical tenosynovitis and/or arthritis involving wrists, knees, and ankles also have been reported.[252] Syphilitic meningitis and stroke syndromes are well-recognized neurologic complications of secondary syphilis (see later). Although pneumonia is most typically associated with severe CS (see later), rare cases of pulmonary involvement in adults have been reported in the pre- and post-HIV eras.[253–255]

Latent Syphilis

Latent syphilis is, by definition, the stage during which serologic tests are reactive without clinical manifestations. Important to note, the term does not mean that the disease process is quiescent, only that clinical signs and symptoms are not evident. Stokes described syphilis as "the relapsing disease par excellence," recognizing that the immune system may require years before it can contain the spirochete, even if unable to fully eradicate it in many instances.[1] The Oslo Study is only one of several in the prepenicillin era that documented a high rate of relapse in early syphilis. Although the percentages differ, they concurred insofar as the preponderance of relapses occurred during the first 1 to 2 years,[1] observations that led to the somewhat arbitrary 1-year demarcation between early latent and late latent syphilis. However, the fact that asymptomatic pregnant women can transmit the infection to their infants in utero 5 or more years after infection clearly demonstrates that recurrent episodes of "silent" spirochetemia occur for prolonged periods.[1,60] In reality, there is no clear biologic demarcation between early latency, when the disease is still systemically active, and late latency, when it is active but anatomically contained.

Mucocutaneous relapses are by far the most common form of infectious relapse and the ones with greatest public health significance because of their potential for disease transmission.[229] The cutaneous lesions of secondary relapses tend to be less florid than initial secondary outbreaks, asymmetrically distributed, and often confined to the mouth, genital, and anal regions. Relapsing lesions have a greater tendency to assume annular forms; mucous patches and condylomata lata also are common. Late mucocutaneous relapses can manifest as localized destructive lesions, resembling gummas. A small percentage of relapses involve noncutaneous sites, such as bone (usually tibial periostitis), eye (usually iritis), liver, other viscera, and the CNS. These are probably flare-ups of infectious foci established earlier.

Tertiary Syphilis

Tertiary syphilis is a (usually) slowly progressive, destructive inflammatory process that can affect any organ in the body to produce clinical illness 5 to 30 or more years after the initial infection.[145,182,210] It is generally subdivided into neurosyphilis, cardiovascular syphilis, and gummatous syphilis. Although customary and convenient, inclusion of neurosyphilis among the tertiary syndromes is technically inaccurate because, as noted earlier (also see Fig. 237.5), not all forms of neurosyphilis occur as late disease. Since the introduction of penicillin, once-common forms of tertiary disease have become so rare that most

practitioners have never seen a case. These changes partly reflect the diminished prevalence of syphilis in the United States and other industrialized countries in the postantibiotic era, but also are attributed to the widespread use of antibiotics for unrelated conditions with the consequent "inadvertent" treatment of latent syphilis. In an oft-cited series of 241 cases published in 1972, Hooshmand[256] proposed that patients no longer presented with the classic neurosyphilitic syndromes as a result of widespread exposure to antibiotics. Most authorities now believe that the laboratory criteria used in that study for the diagnosis of these putative "forme frustes" of neurosyphilis were inadequate.[214] In fact, since that series many cases of patients with identifiable neurosyphilis syndromes have been published. Nevertheless, there is no question that the presentation of neurosyphilis has undergone a significant shift in recent years as paresis and tabes dorsalis have been replaced by meningeal and meningovascular syndromes.[210,211,257]

Neurosyphilis

The neurosyphilis syndromes are arguably the most confusing to practitioners for several reasons (for an excellent recent review, see Ghanem[258]). One is the baffling array of signs and symptoms *T. pallidum* can inflict on the CNS, which pose a diagnostic challenge to even the most experienced and well-trained clinician. Another is the unpredictable nature of the disease. Syphilologists have long pondered the question of why some individuals develop neurosyphilis and others do not.[149] Whether the answer(s) lie in the putative neuroinvasive properties of particular strains of *T. pallidum*[133,259] or in polymorphisms within the human genome that influence the responses elicited by spirochetes once within the CNS,[260] or a combination of the two, remains to be determined. A third reason is that neurosyphilis belies the entrenched concept that syphilis proceeds via an orderly and stereotypical temporal sequence. To the contrary, because the CNS is invaded during the spirochetemic episodes of early syphilis, neurologic manifestations can occur during any stage of the disease. In addition, clinicians often have trouble grasping the fact that asymptomatic CNS infection (often termed "neuroinvasion") is a frequent occurrence in early syphilis that does not usually require specific management, and that *T. pallidum* can be present in the spinal fluids of patients with early syphilis in the absence of neurologic symptoms and CSF abnormalities.[8,9,211,258,261] Lastly, the classification scheme for neurosyphilis developed by Merritt and colleagues[149] in the 1940s, still widely used today,[258] tends to convey the impression that patients always present with distinct neurologic syndromes. The reality, however, recognized by the scheme's creators[149] and underscored by contemporary neuroimaging modalities,[262] is that overlap syndromes with combinations of meningeal, vascular, and parenchymatous features frequently occur.

Asymptomatic Neurosyphilis

Asymptomatic neurosyphilis is defined by the presence of one or more CSF abnormalities (pleocytosis, elevated protein concentration, or reactive CSF Venereal Disease Research Laboratory [VDRL] test) in persons with serologic evidence for syphilis but no neurologic signs or symptoms. The recognition that neurologically asymptomatic patients with early syphilis can have abnormal spinal fluids and that these changes are potential harbingers of symptomatic neurosyphilis predates the discovery of *T. pallidum*. Rabbit isolation studies in the 1920s and 1930s,[1,149,263,264] since confirmed,[150,151] established definitively that CSF abnormalities are the consequence of CNS invasion by *T. pallidum* during early syphilis. Studies using rabbit inoculation from this same period,[263] also confirmed in the modern era,[150,151] revealed that up to 25% of ostensibly normal CSF samples from patients with early syphilis can harbor *T. pallidum*. The cumulative incidence of CSF abnormalities in untreated early syphilis peaks at somewhere between 30% and 50% of patients during the first 12 to 18 months of infection.[149,265]

Asymptomatic CNS infection can follow three distinct, not easily predictable paths.[185,258,266–268] In a substantial percentage of patients with either early or late syphilis, the abnormalities resolve spontaneously; in the remainder, they either persist without development of overt neurologic symptoms or worsen with the eventual appearance of a neurosyphilitic syndrome. Hence, the general trend over time is for asymptomatic neurosyphilis to decrease in frequency, due to either progression or resolution, while the proportion of symptomatic neurosyphilis increases. Accordingly, on the basis of examining more than 2200 patients, Merritt and colleagues[149] maintained that the incidence of late asymptomatic neurosyphilis was in the vicinity of 10%, well below the peak values noted earlier for early syphilis. Several tenets about the complex relationship between asymptomatic and symptomatic neurosyphilis emerged from the preantibiotic era and continue to be useful today: (1) asymptomatic neurosyphilis is always the forerunner of meningeal, vascular, and parenchymatous syndromes; (2) asymptomatic neurosyphilis during late syphilis carries a worse prognosis than asymptomatic neurosyphilis during early infection; (3) the likelihood of progression from asymptomatic to symptomatic neurosyphilis increases in rough proportion to the degree of CSF abnormalities; and (4) if the spinal fluid remains normal during the first 2 years of infection, or if it is abnormal but reverts to normal, symptomatic neurosyphilis will not develop.

Although the clinical importance of diagnosing asymptomatic neurosyphilis was well appreciated in the preantibiotic era, there was a diversity of opinion as to when lumbar puncture should be done,[1] just as there is today.[9,269] The Europeans, influenced by Ravaut, argued for later spinal fluid examination to avoid overtreating persons whose CNS infections were going to resolve spontaneously. Americans, led by Moore, advocated early examination of the spinal fluid to identify persons with severe CSF abnormalities (the so-called "paretic formula") who would benefit from more intensive arsenical therapy. The issue faded into the background as it became evident that neurorelapse was uncommon in patients with early syphilis given intramuscular benzathine penicillin G (BPG). However, as discussed later, it has resurfaced in the HIV era as a result of numerous case reports suggesting that single-dose intramuscular BPG predisposes to CNS relapse in the absence of a fully competent immune system,[215] along with clinical studies suggesting a higher prevalence of asymptomatic neurosyphilis among patients with early syphilis who are coinfected with HIV.[270–272]

Syphilitic Meningitis

Syphilitic meningitis typifies the ambiguity of syphilis staging for CNS disease because it is a true overlap syndrome, occurring as either an early or a late manifestation (see Fig. 237.5). Approximately 10% of cases occur in persons with a rash of secondary syphilis, and most occur during the first 2 years of infection. Even when meningitis is the sole presenting manifestation, more than half of patients recall having a chancre or a secondary syphilis rash, or both, an unusual occurrence in patients with parenchymatous syndromes. On the other hand, there are many documented instances of patients presenting with this form of neurosyphilis in late syphilis or in which it complicates late forms of neurosyphilis, or both. Although headache and meningismus mimicking many other causes of aseptic meningitis are not uncommon in patients with secondary syphilis, the full-blown meningeal syndrome is rare, representing less than 10% of all cases of neurosyphilis.[213] In their classic series, Merritt and Moore[213] could find only 80 well-authenticated cases over a 15-year period in three general hospitals, and they estimated, on the basis of their survey of the literature, that it may complicate between 0.3% and 2% of early syphilis cases (probably an overestimate, even at the low end, in our experience). In addition to signs and symptoms indicative of increased intracranial pressure (e.g., nausea, vomiting, headache), which occurred in nearly all cases, these authors distinguished three syndromic variants: (1) acute hydrocephalus without focal signs unrelated to increased intracranial pressure; (2) meningitis of the vertex, presenting with seizures, focal neurologic deficits (e.g., hemiplegia, aphasia), and changes in sensorium; and (3) basilar meningitis with cranial nerve palsies, especially of nerves III, VI, VII, and VIII. Eighth cranial nerve involvement can be unilateral or bilateral and can affect either or both the acoustic and vestibular nerves. The differential diagnosis is broad and includes viral causes of aseptic meningitis and meningoencephalitis; neuroborreliosis; tuberculous and fungal meningitis; parameningeal processes (e.g., abscess); and noninfectious processes such as sarcoidosis and carcinomatous meningitis. Reactive serologic tests for syphilis in blood and CSF, along with the subacute onset of signs and symptoms, help to distinguish meningeal syphilis from the numerous other infectious and noninfectious entities in the differential diagnosis.

Meningovascular Syphilis

Meningovascular syphilis comprises those syndromes in which focal neurologic signs due to infarction are the dominant presenting feature.[149] Like syphilitic meningitis, meningovascular syphilis represents an early-late overlap syndrome, although weighted more toward the late end of the temporal spectrum (see Fig. 237.5). The spinal cord, brainstem, or cerebrum may be involved separately or together, although the majority of patients in the large series by Merritt and colleagues[149] had vascular syndromes referable to the middle cerebral artery. Accordingly, the most common focal findings were contralateral hemiplegia or hemiparesis, homonymous hemianopsia, and aphasia. Recent case reports underscore the potentially catastrophic outcomes resulting from involvement of the posterior cerebral circulation.[273,274] In the 42 cases reviewed by Merritt and colleagues,[149] only 25% of patients gave a history of primary or secondary syphilis. These authors attributed 3% of their neurosyphilis cases at Boston City Hospital to meningovascular syphilis. This proportion is likely much lower than the current incidence. In a large series from India in which magnetic resonance imaging (MRI) was used, 11 of 35 patients were classified as having focal neurologic symptoms attributable to ischemia.[262] The relatively young age of patients with meningovascular syphilis (30–50 years) helps to distinguish this syndrome from atherosclerotic stroke, hence the clinical dictum that a stroke in a young or middle-aged individual always should raise suspicions of syphilis. As with atherosclerotic stroke, onset may be sudden ("syphilitic apoplexy"). However, a substantial proportion of patients have prodromal symptoms, such as headache, vertigo, insomnia, irritability, and personality and behavioral changes, weeks to months before the thrombotic event. Merritt and colleagues[149] attributed these affective and cognitive changes to the leptomeningeal component of the underlying pathologic condition. MRI showing significant cortical atrophy in many cases suggests that paretic-type changes are also contributory.[262] In the series by Merritt and colleagues,[149] only 5 of the 42 patients had neurologic deficits, suggesting involvement of more than one blood vessel. In recent case reports in which MRI and magnetic resonance angiography were used, however, imaging revealed diffuse and often bilateral involvement,[257] as one might expect with a CNS vasculitis. Meningovascular syphilis may also rarely involve the spinal cord, resulting in infarction of the anterior or, less commonly, posterior spinal arteries. In contrast to patients with involvement of cerebral vessels, the spinal variant lacks prodromal symptoms and is usually sudden in onset. Because of its semiacute course and association with global alterations in cerebral function, meningovascular syphilis has to be differentiated from chronic meningitides, as well as rheumatologic causes of cerebral vasculitis, particularly systemic lupus erythematosus, Wegener granulomatosis, and polyarteritis nodosa, and, in patients with a history of genital ulcers, Behçet disease.

Parenchymatous Syndromes

The parenchymatous syndromes, general paresis and tabes dorsalis, the last to occur in the neurosyphilis temporal sequence (see Fig. 237.5), involve distinct, poorly understood, neurocytotoxic mechanisms in addition to the vascular-based inflammatory and ischemic changes that cause symptomatology in meningeal and meningovascular syphilis.[185,258] In the preantibiotic era, these two syndromes accounted for one-half to two-thirds of all cases of neurosyphilis, and both were fourfold to sevenfold more common in men than women. As one indicator of how common they were, according to Stokes,[1] paresis accounted for 11% of neuropsychiatric admissions in the United States and 5% to 7% of cases of mental disease in the French, German, American, and Russian armies. The virtual disappearance of tabes dorsalis, which is disproportionate to the decline in the incidence of paresis, is one of the most striking changes in the epidemiology of neurosyphilis. Because the American Association of Neurology no longer recommends screening for paresis as part of a routine dementia evaluation,[275] it is important to maintain vigilance for this relatively rare but still encountered dementing illness. In case reports,[276–279] and in the experience of the authors, a substantial degree of reversibility can be seen when paresis is promptly recognized and treated.

Merritt and colleagues[149] described general paresis as a chronic, spirochetal meningoencephalitis that severely disturbs the structure and function of the cerebral cortices, particularly the frontal and temporal lobes. In one of the largest case series in the postantibiotic era (from the United Kingdom), the interval between infection and admission varied between 4 and 41 years (mean, 21 years).[280] The typical clinical picture is a slow, often insidious, onset of neuropsychiatric disturbances coupled with progressive deterioration in cognitive function. The presentation, however, may be abrupt. In the British series, the duration of symptoms varied between 24 hours and 5 years and approximately 20% of patients had seizures.[280] As the disease worsens, patients experience loss of motor control to the point of paralysis along with worsening loss of bowel and bladder control. Untreated paresis is fatal. The constellation of signs and symptoms can be remembered with the mnemonic PARESIS: *p*ersonality (emotional lability, paranoia); *a*ffect (carelessness in appearance); *r*eflexes (hyperactive); *e*ye (Argyll Robertson pupils [Fig. 237.8])[281]; *s*ensorium (illusions, delusions, especially megalomania, hallucinations); *i*ntellect (decreased recent memory, judgment, insight); and *s*peech (slurred). The dramatic postmortem pathologic findings described by Merritt and colleagues[149] have been demonstrated on a number of occasions in patients with MRI, now an essential tool for making the diagnosis.[276,277,282,283] In several instances, subacute changes in personality and cognition in concert with temporal abnormalities at MRI have been confused with herpes encephalitis (Fig. 237.9).[284–287] Kodama and colleagues[276] concluded from a small series ($n = 7$) that mesial temporal lobe atrophy at MRI carries a poor prognosis for improvement after antimicrobial therapy.

The demyelinating process in the posterior spinal cords of patients with tabes dorsalis eventually results in the development of an ataxic, wide-based gait and foot slap; paresthesias; shooting or lightning pains (sudden onset, rapid radiation, and disappearance); bladder disturbances; fecal incontinence; impotence; loss of position and vibratory sense; absent ankle and knee jerk reflexes; and loss of deep pain and temperature sensation. The characteristic "lightning" or lancinating pains experienced by at least 75% of patients are usually present at the outset of the disease, typically affecting the lower extremities, and occurring episodically.

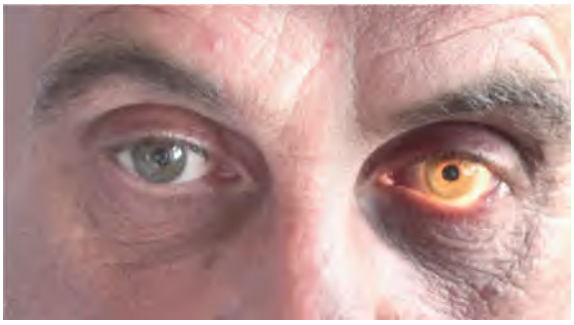

FIG. 237.8 Argyll Robertson pupils in a patient with tabes dorsalis. A 47-year-old man with a history of human immunodeficiency virus (HIV) infection presented with an 8-month history of severe paroxysmal shooting pains in his legs, progressive difficulty in walking, tinnitus, and urinary incontinence. He had a fully suppressed HIV viral load and a $CD4^+$ count of 400 cells/mm^3 while receiving antiretroviral therapy. The physical examination showed Argyll Robertson pupils, which are nonreactive to bright light but briskly constrict when focusing on a near object (see video at https://www.nejm.org/doi/10.1056/NEJMicm1507564?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov). Magnetic resonance imaging showed high signal changes in the dorsal columns of the thoracic spine, and samples of blood and cerebrospinal fluid were positive for syphilis on Venereal Disease Research Laboratory (VDRL) testing and *Treponema pallidum* particle agglutination assay. The patient was treated with intravenous penicillin for 14 days, and gabapentin was started for the neuropathic leg pains. Tabes dorsalis is a form of neurosyphilis that is characterized by degeneration of the nerves in the dorsal columns of the spinal cord. Along with Argyll Robertson pupils, the condition is associated with ataxia and loss of proprioception. After treatment, the patient's symptoms and mobility slowly improved, although the shooting pains in his legs have continued despite pharmacotherapy. The serum VDRL level fell appropriately, and the result on VDRL testing of the cerebrospinal fluid was negative. *(From Osman C, Clark TW. Tabes dorsalis and Argyll Robertson pupils.* N Engl J Med. *2017;375:e40.)*

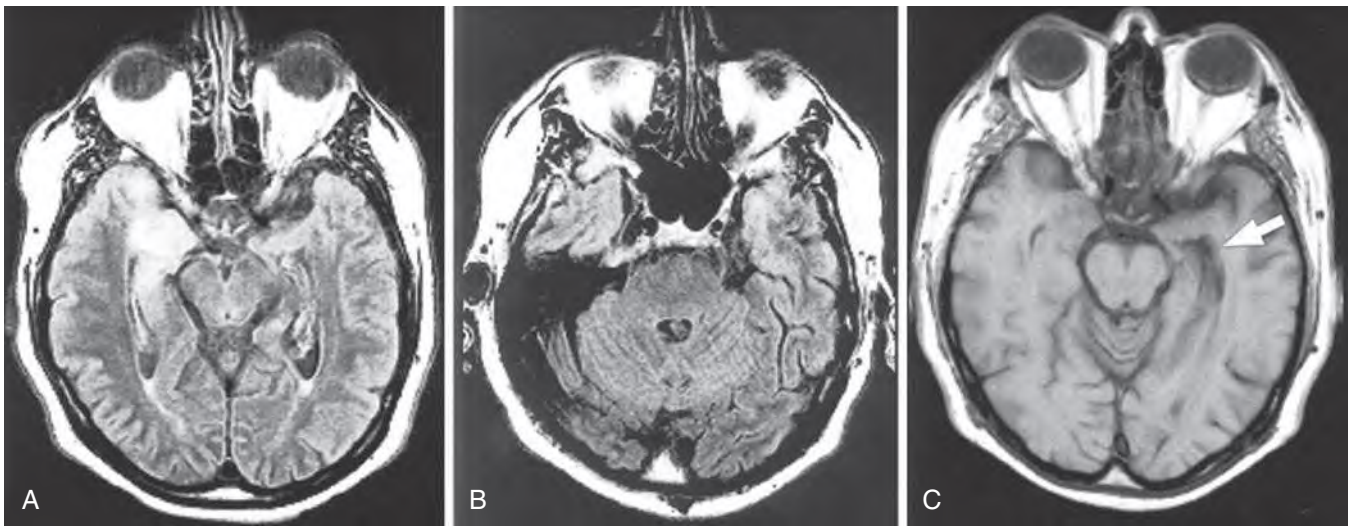

FIG. 237.9 Magnetic resonance images of general paresis in a 50-year-old man with a 3-month history of progressive dementia and seizures. (A) Axial fluid-attenuated inversion recovery (FLAIR) image obtained at midbrain level. (B) Axial FLAIR image obtained at the level of the pons. Asymmetrical bilateral signal hyperintensity in the mesial temporal lobes is greater on the right side than on the left. (C) Axial T1-weighted image obtained at the level of the low midbrain showing mild left temporal lobe atrophy, evidenced by dilatation of the temporal horn *(arrow). (From Bash S, Hathout GM, Cohen S. Mesiotemporal T2-weighted hyperintensity: neurosyphilis mimicking herpes encephalitis.* Am J Neuroradiol. *2001;22:314–316.)*

Some patients, 10% to 20%, experience visceral crises. In the most common gastric form, the individual experiences recurrent episodes of sudden, agonizing epigastric pain with nausea and vomiting that can last for days and mimic surgical emergencies. Intestinal, rectal, and laryngeal crises can also occur. Decrease or loss of tendon and patellar reflexes with preservation of muscle strength is a common, relatively early, neurologic finding. Ataxia was regarded as such a cardinal symptom of tabes that it was once called "progressive locomotor ataxy"; between 50% and 80% of patients exhibit a positive Romberg sign. Trophic degenerative joint disease, Charcot joints, and traumatic ulcers or sores on the lower extremities and feet resulting from the loss of proprioception and sensation were once prominently featured in textbooks. Degenerative ocular changes are also common components of the tabetic syndrome. The Argyll Robertson pupil (see Fig. 237.8), although not limited to tabes or even syphilis, is a characteristic late feature.[281] Primary optic atrophy occurs over a period of months to years, beginning peripherally and proceeding to the center of the nerve, producing progressive concentric constriction of the visual fields with retention of normal vision, referred to as "gun barrel" sight.[288]

Central Nervous System Gumma

The CNS gumma, the rarest form of neurosyphilis, was uncommon even in the preantibiotic era. In a review of 2203 brain tumors published in 1932, Cushing[289] found only 12 cases, and Merritt and colleagues[149] found only 5 well-documented cases over a 15-year span at the Boston City Hospital. Nevertheless, sporadic reports continue to appear in the modern literature.[193,290,291] Because of the likelihood that a CNS gumma will initially be mistaken for a tumor or other type of space-occupying lesion (e.g., toxoplasmosis in an AIDS patient), this entity well exemplifies the reputation of syphilis as the great mimicker. The pathologic features of gumma within the CNS are no different than those occurring outside it. Merritt and colleagues[149] considered gumma of the CNS to be a chronic, localized form of syphilitic meningitis that extends from the pia mater into the adjacent brain or spinal cord. In a comprehensive review of the literature, Fargen and colleagues[193] found that two-thirds of the lesions occurred in the cerebral convexities, of which the majority were located in the frontal lobes or frontoparietal region. The pituitary was the most common site outside the cerebral hemispheres.

Ocular Syphilis

Ocular complications may occur as part of a neurosyphilis syndrome, often asymptomatic neurosyphilis, or as an isolated manifestation.[149,244,246,247,292] Anterior or posterior uveitis or panuveitis, the most common abnormalities, can occur during either early or late syphilis (see Chapter 115). Other ocular syndromes include episcleritis, vitritis, retinitis, papillitis, interstitial keratitis, acute retinal necrosis, and retinal detachment. Primary optic atrophy is unique to late syphilis and is most associated with tabes dorsalis.[149,288] The differential diagnosis includes tuberculosis, rheumatoid arthritis, sarcoidosis, toxoplasmosis, histoplasmosis, and ocular *Toxocara canis* infections. The presence of pupillary abnormalities distinguishes syphilis from these other processes. Unless scarring has occurred, improvement with treatment can be dramatic.

Otosyphilis

Syphilis can cause hearing loss via two mechanisms during early or late infection. One is osteitis of the temporal bone with destructive changes in the membranous cochlea and labyrinth. The other is inflammation and atrophy of cranial nerve VIII, typically insidious and often bilateral.[293] Merritt and colleagues[149] found that 10 of their 80 cases of syphilitic meningitis had involvement of the acoustic or vestibular branches of the eighth cranial nerve, or both, whereas 57 of their 203 cases of tabes dorsalis had hearing impairment. Involvement of cranial nerve VIII typically begins with high-frequency hearing loss and progresses to a complete unilateral or bilateral loss of cochlear and vestibular function.[294] Syphilitic labyrinthitis has been known to mimic Meniere disease. In the postantibiotic era, otosyphilis has become liberally defined as an unexplained sensorineural hearing loss in the presence of a reactive treponemal serologic test.[295,296] As noted by Pletcher and Cheung,[297] this definition lacks a clear causal relationship between syphilis and the clinical symptoms. Nevertheless, in such cases, treatment is usually indicated because there are no diagnostic measures that can reliably eliminate the possibility of syphilis.

Cardiovascular Syphilis

In the preantibiotic era, asymptomatic aortitis was considered to be highly prevalent; in fact, Moore[298] maintained that the majority of patients with long-standing syphilis have subclinical aortitis undetectable on radiographs or at clinical examination. Despite the marked decline in incidence since World War II, syphilitic involvement of the aorta continues to occur, although the diagnosis is often not suspected clinically or made before surgery or postmortem examination.[194,299,300] Dilation of the proximal portion of the aorta and linear calcification of the anterolateral wall of the ascending aorta are suggestive radiographic signs. Weakening of the aortic valve ring and distortion of the cusps

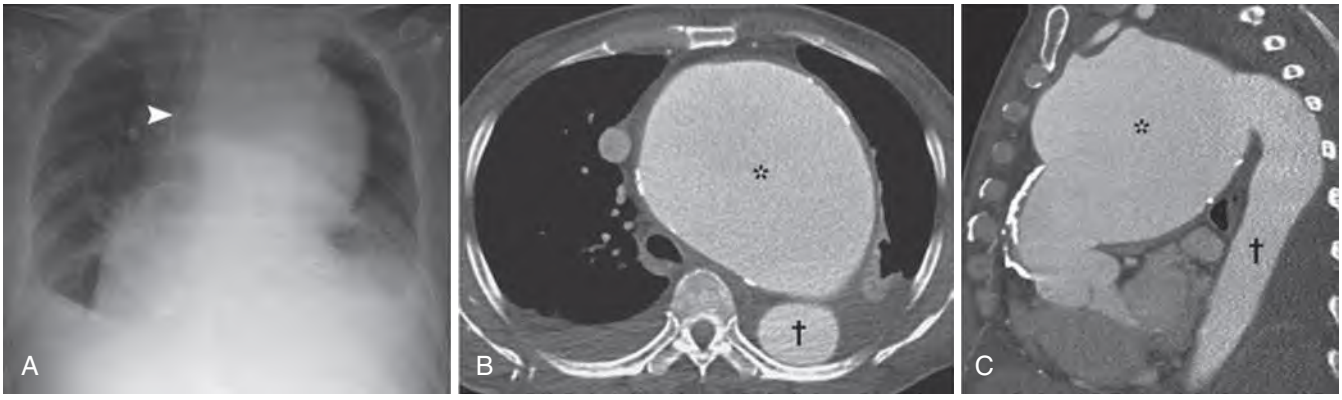

FIG. 237.10 Cardiovascular syphilis in a 76-year-old man with progressive dyspnea and leg swelling. (A) Chest radiograph showing a mediastinal mass with tracheal deviation *(arrowhead).* (B) Contrast-enhanced computed tomogram of the chest showing a large saccular aortic aneurysm. (C) Sagittal reconstruction image. Asterisks in (B) and (C) indicate aneurysm; daggers show normal descending aorta. *(From Rajab TK, Gallegos RP. Images in clinical medicine. Giant syphilitic aortic aneurysm.* N Engl J Med. *2011;364:1258.)*

results in aortic regurgitation, the most common complication of syphilitic aortitis, and in approximately 20% of these cases, coronary ostial stenosis. Fibrosis of the media also contributes to the development of ostial stenosis and, rarely, can cause severe coronary occlusion even in the absence of dilation of the aortic root.[301] Surprisingly, syphilitic aneurysm is the least common complication, occurring only one-third as frequently as aortic insufficiency and producing clinically apparent, albeit often devastating, manifestations in only 5% to 10% of patients with aortitis. A recent case report emphasized the importance of considering syphilis in patients who present with aortic regurgitation and myocardial infarction.[302] Syphilitic aneurysms are usually saccular, although they may be fusiform; because of the diffuse scarring in the aortic wall, they tend not to dissect (Fig. 237.10). Approximately 50% of aneurysms occur in the ascending aortic arch and have been designated the "aneurysm of signs" because they attain great size with few symptoms. In a recent surgical series, Roberts and colleagues[303] stated that the key to recognizing cardiovascular syphilis at surgery was the diffuse nature of the involvement of the tubular portion of the ascending aorta with complete or virtual sparing of the sinus portion. Aneurysm of the innominate artery is a rare complication of ascending aortitis.[299,304] Next most frequently involved (30%–40%) is the transverse arch, designated the "aneurysm of symptoms" because of its location in proximity to a number of mediastinal structures. The minority of aneurysms, 10% to 15%, occur in the descending arch; a small percentage occur below the sixth vertebral body or, even more rarely, below the thorax.[305]

Late Benign (Gummatous) Syphilis

The gumma is a necrotizing granulomatous lesion that occurs in late syphilis. These indolent lesions are most commonly found in the skin, om mucocutaneous surfaces, and in the skeletal system but can develop in any organ. They may be single or multiple and vary in size from small defects to large tumor-like masses (Fig. 237.11). They are of clinical importance principally because of their local destructiveness or cause of masslike effects, or both.[306] The cutaneous manifestations range from superficial nodules to deep granulomatous lesions, which may break down to form punched, ragged ulcers resembling pyoderma gangrenosum.[307] Involution is followed by the development of thin, atrophic, noncontractile scars arranged in arciform patterns. Gummatous hepatitis may cause low-grade fever, epigastric pain, and tenderness and eventually cirrhosis *(hepar lobatum).* Gummas of the gastrointestinal tract can ulcerate or cause leathery fibrotic changes in the bowel wall, simulating carcinoma and causing stricture.[308] Gummas of bone, originating from the metastasis of spirochetes to the periosteum during early syphilis, may result in fractures and joint destruction of long bones and radicular signs and symptoms when occurring in vertebra.[309–311] Gumma of the upper respiratory tract can lead to perforation of the nasal septum or palate.[1,182] Gummas must be distinguished from other infectious and noninfectious causes of granuloma (tuberculosis, deep fungal infections, and sarcoidosis) and neoplasm. Penicillin treatment results in rapid improvement and thus is diagnostic.

FIG. 237.11 Cutaneous syphilitic gumma. *(From Chudomirova K, Chapkanov A, Abadjieva T, Popov S. Gummatous cutaneous syphilis.* Sex Transm Dis. *2009;36:239–240.)*

LABORATORY DIAGNOSIS

Diagnosis of syphilis is stage dependent and requires a combination of clinical and laboratory criteria as shown in Table 237.1.[5–7,211] Because *T. pallidum* cannot be cultivated on artificial media, laboratory diagnosis relies on direct detection of the pathogen in patient specimens or reactivity in serologic tests, or both. Direct detection of *T. pallidum* in clinical material is the only means of establishing a microbiologic diagnosis. At one time, direct detection was limited to visualization of live (i.e., motile) treponemes with DF microscopy and silver staining of treponemes in paraffin-embedded tissues. IHC detection has largely supplanted silver staining, and PCR has greatly expanded the range of clinical specimens in which treponemes can be detected, although it is still not a routine diagnostic tool, and no US Food and Drug Administration–approved PCR test for syphilis is on the market. Serologic tests are unquestionably the mainstay of syphilis diagnosis. In addition to supplementing direct detection, they are the only means of establishing a probable diagnosis when lesional specimens are not available or cannot be obtained. Syphilis serodiagnosis depends on the use of assays measuring two distinctly different types of antibody reactivities, the so-called "nontreponemal" and "treponemal" tests. Traditionally, serodiagnosis of syphilis has been performed by screening for nontreponemal antibodies and confirming reactivity with a treponemal test. Reverse-sequence algorithms in which sera are first tested by an automated treponemal assay and, when reactive, followed by a nontreponemal test have transformed the landscape of syphilis serodiagnosis while also creating unforeseen dilemmas, particularly when screening low-prevalence populations.[312,313] Nontreponemal

TABLE 237.1 Clinical and Laboratory Criteria for Diagnosis of Syphilis

Presumed Incubating Syphilis Requiring Treatment

Persons who have had sexual contact within the last 90 days with a person diagnosed with early syphilis
Persons who have had sexual contact >90 days previously with a person diagnosed with early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain
Sex partners of persons with late latent syphilis or syphilis of undetermined duration who have nontreponemal test titers >1 : 32

Early Syphilis
Primary

Confirmed (Requires 1 and 2 or 3)
1. One or more chancres (ulcers)
2. Identification of Treponema pallidum in lesion exudate by DF microscopy
3. Detection of T. pallidum DNA in lesion exudate with PCR

Probable (Requires 1 and Either 2 or 3)
1. One or more lesions compatible with chancres
2. Reactive nontreponemal test
3. Reactive treponemal test

Secondary

Confirmed (Requires 1 and Either 2, 3, or 4)
1. Localized or diffuse mucocutaneous lesions consistent with secondary syphilis
   a. Macular, papular, follicular, papulosquamous, or pustular rash
   b. Condylomata lata (anogenital region or mouth)
   c. Mucous patches (oropharynx or cervix)
2. Identification of T. pallidum in lesion exudates with DF microscopy
3. Identification of T. pallidum in skin biopsy with silver or immunohistochemical staining
4. Detection of T. pallidum DNA in tissue with PCR

Probable (Requires 1 and 2)
1. Skin or mucous membrane lesions consistent with secondary syphilis
2. Reactive nontreponemal test titer ≥4 and a reactive confirmatory treponemal test

Early Syphilis, Non-Primary, Non-Secondary

(formerly early latent; no confirmed case classification)

(Requires: A. 1, 2, 4, 5; B. 1, 3, 4, 5; C. 4, 5 and 6, 7, or 8)
1. Absence of signs and symptoms of syphilis
2. No prior history of syphilis
3. A prior history of syphilis
4. Documented seroconversion or fourfold or greater increase in nontreponemal test titer during the previous 12 months
5. Documented seroconversion of a treponemal test during the previous 12 months
6. A history of symptoms consistent with primary or secondary syphilis during the previous 12 months
7. A history of sexual exposure to a partner who had confirmed or probable primary or secondary syphilis or probable early latent syphilis (documented independently as duration <1 year)
8. Reactive nontreponemal and treponemal tests in a person whose only possible exposure occurred within the preceding 12 months

Syphilis, Unknown Duration or Late

(formerly *late latent*; initial infection occurred greater than 12 months previously or insufficient evidence to conclude that infection was acquired during the previous 12 months; *no confirmed case classification*)

(Requires 1, 2, and Either 3 or 4)
1. Absence of signs and symptoms of syphilis
2. A reactive nontreponemal and treponemal test
3. No prior history of syphilis
4. A prior history of syphilis and a current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer

Late Syphilis
Benign (Gummatous) and Cardiovascular

Confirmed (Requires 1 and 2 or 3)
1. Clinically compatible case (e.g., inflammatory lesions of the skin, bones, or cardiovascular system)
2. Identification of treponemes in tissue sections with silver or immunohistochemical staining
3. Detection of T. pallidum DNA in tissue with PCR

Probable (Requires 1, 2, and 3)
1. Clinically compatible case
2. A reactive serum treponemal test
3. Absence of clinical signs or symptoms consistent with neurosyphilis

Neurosyphilis

Confirmed (Requires 1, 2, and Either 3, 4, or 5)
1. Clinical signs consistent with neurosyphilis
2. A reactive serum treponemal test
3. A reactive VDRL in CSF
4. Detection of T. pallidum DNA in CSF or tissues with PCR
5. Identification of treponemes in tissue with silver or immunohistochemical staining

Probable (Requires 1, 2, and 3)
1. Clinical signs consistent with neurosyphilis
2. A reactive serum treponemal test
3. Elevated CSF protein or leukocyte count in the absence of other known causes

Continued

TABLE 237.1 Clinical and Laboratory Criteria for Diagnosis of Syphilis—cont'd

Congenital Syphilis: Neonatal

Confirmed (Requires 1 and 2 or 3)

1. Clinically compatible case (e.g., hepatosplenomegaly, rash, condylomata lata, jaundice, anemia)
2. Demonstration of T. pallidum by microscopic examination of specimens from lesions, amniotic fluid (antenatal), placenta, umbilical cord, nasal discharge, or autopsy material
3. Detection of T. pallidum DNA in lesions, tissue, blood, CSF, or a combination of these, by PCR

Probable (Requires 1 or 2 and 3)

1. Infant born to a mother who had untreated or inadequately treated syphilis at delivery, regardless of findings in the infant
2. An infant or child with a reactive treponemal test result
3. One of the following additional criteria
   a. Clinical signs or symptoms of congenital syphilis on physical examination
   b. Evidence of congenital syphilis on radiographs of long bones
   c. Abnormal CSF cell count or protein without other cause
   d. Reactive VDRL in CSF
   e. Reactive treponemal antibody absorbed—19S-IgM antibody test or IgM enzyme-linked immunosorbent assay

Syphilitic Stillbirth

1. A fetal death that occurs after a 20-week gestation
2. Fetus weighs >500 g and the mother had untreated or inadequately treated syphilis at delivery

CSF, Cerebrospinal fluid; *DF,* darkfield; *IgM,* immunoglobulin M; *PCR,* polymerase chain reaction; *VDRL,* Venereal Disease Research Laboratory.

Modified from the Centers for Disease Control and Prevention. STD Surveillance Case Definitions. https://wwwn.cdc.gov/nndss/conditions/syphilis/case-definition/2018/. Accessed January 27, 2018. Reproduced from Jorgensen JH, Pfaller MA, Carroll KC, et al, eds. Manual of Clinical Microbiology. *11th ed. Washington, DC: ASM Press; 2015. © 2015 American Society for Microbiology. Used with permission. No further reproduction or distribution is permitted without the prior written permission of American Society for Microbiology.*

tests have a unique role in management because they are used as surrogate markers for disease activity during screening and gauging the adequacy of therapeutic response. For detailed information on diagnostic tests for syphilis, the reader is referred to work by Sena and colleagues.[7] A report by the Association of Public Health Laboratories (APHL) summarizing the findings of an expert consultation panel on syphilis diagnostics convened by the CDC in 2009 can be found at https://www.aphl.org/programs/infectious_disease/std/Documents/ID_2009Jan_Laboratory-Guidelines-Treponema-pallidum-Meeting-Report.pdf.[314]

Direct Examination for Spirochetes Darkfield Microscopy and Direct Fluorescent Antibody Test for *Treponema pallidum*

DF microscopy is a simple, rapid method for detecting live *T. pallidum* in clinical specimens.[7,315] In experienced hands, DF microscopy is capable of detecting organisms in suspensions containing a minimum of 10^4 to 10^5 spirochetes per milliliter. The method is most applicable to moist, exudative lesions of primary and secondary syphilis, which typically contain high concentrations of treponemes. Other specimens, such as lymph node aspirates, amniotic fluid, and nasal discharge from infants with suspected CS, also may contain spirochetes at sufficient concentration for successful DF examination. Detailed descriptions of the DF procedure can be found in Sena et al.,[7] Larsen et al.,[315] and Wheeler et al.[316] Briefly, the surface of the lesion should be cleansed with nonbactericidal saline and gently abraded with dry gauze. The serous exudate is then transferred to a glass slide, covered with a cover slip, and examined; the suspension can be thinned by adding a drop of nonbacteriostatic saline. Because the test relies on observation of motile treponemes, the specimen should be examined as rapidly as possible, ideally within 20 minutes. Visualization of a single motile treponeme is considered diagnostic. DF microscopy should not be performed on oral lesions because *T. pallidum* cannot be distinguished easily from commensal oral spirochetes. Given the many biologic and technical factors that determine the success of the technique, it must be emphasized that a negative result does not rule out the diagnosis of syphilis. DF microscopy also cannot distinguish *T. pallidum* from the other pathogenic treponemes, although this is rarely a cause for diagnostic uncertainty. In recent years, the DF technique has fallen into disfavor because it requires a microscope outfitted with a special condenser and a highly trained microscopist. A 2014 survey of national reference and large clinical laboratories in Latin America and the Caribbean revealed that only 2 of 69 participating facilities still performed DF microscopy.[317] Nevertheless, the fact that at least 15% of patients with DF-positive primary syphilis have nonreactive serologic tests[6,318] underscores the continued need for proficiency with DF microscopy, an opinion endorsed by an expert panel convened by the CDC.[314]

The direct fluorescent antibody test for *T. pallidum* (DFA-TP) identifies *T. pallidum* in touch preparations by immunostaining with either a fluorescein isothiocyanate (FITC)–conjugated polyclonal or monoclonal antibody.[7,315,319] Because motility is not required for interpretation of DFA-TP, slides can be fixed and processed at a later time. DFA-TP with a *T. pallidum*–specific monoclonal antibody can be performed on all mucocutaneous lesions of primary and secondary syphilis, including specimens from anal and oral sites. Although DFA-TP is at least as sensitive as DF microscopy and more specific, it has never gained wide acceptance because of its technical complexity, its instrumentation requirements, and the poor availability of antibody conjugates. In fact, the most recent European guidelines recommend against DFA-TP testing.[320]

Visualization of *Treponema pallidum* in Tissues

Silver impregnation is the traditional method for detection of *T. pallidum* in formalin-fixed tissues. The Dieterle technique is believed to be more sensitive than Warthin-Starry staining.[321] Although used with great success in countless cases, silver staining is prone to artifacts, has limited sensitivity, and is not specific for *T. pallidum.* Spirochetes other than *T. pallidum* will stain with this method; *B. burgdorferi,* which induces similar histopathologic changes, is the one most likely to cause diagnostic confusion in regions where the endemic treponematoses do not occur and Lyme disease is common.[320,322] In 1992, Ito and colleagues[323] introduced the use of an FITC-labeled *T. pallidum*–specific monoclonal antibody for immunostaining of processed tissues. As with the DFA-TP, the technique has never become popular. Recently, impressive results have been reported with use of commercially available polyclonal anti–*T. pallidum* antibodies and avidin-biotin immunoperoxidase staining to detect treponemes in paraffin-embedded skin biopsy specimens.[134,141,170,183,324] In head-to-head comparisons, immunohistochemistry compares favorably with PCR for detection of treponemes in tissue samples[325] and has the advantage of enabling assessment of the spatial distribution of spirochetes in samples and their relationship to matrix, vascular, and cellular components of syphilitic infiltrates.[183,325,326]

Polymerase Chain Reaction Detection of *Treponema pallidum*

Despite the numerous studies published since the first use of PCR for molecular detection of *T. pallidum* in the early 1990s,[327,328] a commercially available or approved, standardized test has yet to be introduced within

or outside the United States.[5,7] Of the many gene targets, *polA (tp0105)* and *tpn47 (tp0574)* have been the most extensively used and appear to be more or less comparable in sensitivity and specificity when properly optimized.[329,330] Although PCR can detect *T. pallidum* in a wide variety of specimen types, including embedded and archived tissues, its usefulness, not surprisingly, appears to be greatest for genital ulcers and other exudative lesions, which typically contain high concentrations of treponemes.[7] A meta-analysis found that the sensitivity and specificity of PCR for genital ulcer swabs were approximately 80% and 95%, respectively, with DF microscopy used as the gold standard; these authors concluded that PCR was more useful for confirming than excluding a diagnosis of primary syphilis.[329] It is important to note, however, that head-to-head comparisons have repeatedly demonstrated that PCR can detect spirochetes in DF-negative samples from patients with a high suspicion of primary syphilis.[331–336] Studies using conventional and real-time PCR indicate that PCR analysis of blood, even during early syphilis, has limited diagnostic usefulness,[329] probably because of variability in the concentrations of circulating organisms and the limited amount of blood that can be processed for amplification; degradation of DNA during frozen storage of blood may also be a factor.[234] In a study from China, *T. pallidum* was detected in the serum or plasma of 50% of patients with secondary syphilis compared with 21% and 13% for individuals with primary and early latent disease, respectively.[337–339]

Serologic Tests

Syphilitic infection elicits two different types of antibody responses, designated as "nontreponemal" and "treponemal."[6,340] The term *nontreponemal,* derived from the long-held belief that the inciting antigens are lipids liberated from inflamed tissues, is probably a misnomer given that cardiolipin is a major phospholipid constituent in *T. pallidum.*[341] In addition to lacking sensitivity in primary and late syphilis, nontreponemal antibodies can be elicited in conditions with no relationship to syphilis, so-called biologic false positives (BFPs; see later). Beginning with the fluorescent treponemal antibody absorption (FTA-ABS) test, treponemal tests were developed to address the lack of specificity of the nontreponemal tests.[6,340] The need to achieve higher throughput with decreased laboratory costs prompted the development of automatable immunoassays that use recombinant antigens instead of *T. pallidum* lysates. Rapid point-of-care (RPOC) tests have been developed to meet the need for on-site testing in developing countries with limited public health and laboratory infrastructures. None of the currently available serologic tests can distinguish venereal syphilis from the endemic treponematoses. Serum is the specimen of choice for both nontreponemal and treponemal tests; however, plasma may also be used in the rapid plasma reagin (RPR) card test and the toluidine red unheated serum test (TRUST).[342,343] Although syphilis screening in low-risk adults has been largely abandoned, systematic reviews provide convincing evidence in favor of syphilis screening for pregnant women and adults and adolescents at increased risk of infection.[5,344]

Nontreponemal Tests

The nontreponemal antibody tests in widespread use today are the descendants of the original Wassermann test. The standard nontreponemal test is the VDRL slide test in which heat-inactivated serum is tested for its ability to flocculate or agglutinate a standardized suspension of a cardiolipin, cholesterol, and lecithin and read microscopically at ×100.[5] Most laboratories and blood banks now use the RPR card test, which uses finely divided charcoal particles as a visualizing agent, for routine screening and following the response to therapy, whereas VDRL testing is used exclusively for CSF. As a general rule, RPR titers on the same serum specimens tend to be higher than VDRL titers. TRUST is a macroflocculation assay in which the charcoal is replaced with toluidine red; its sensitivity is equivalent to that of the RPR test, whereas its specificity is slightly higher.[342,343]

Nontreponemal tests are reported as the highest dilution giving a fully reactive result.[315] A four-fold change in titer using the same nontreponemal test method is necessary to demonstrate a significant difference and should be performed in the same laboratory and, if possible, on the same day. Sera with extremely high nontreponemal titers may give weakly reactive, atypical, or even negative "rough" reactions at low dilutions because antibody excess prevents the agglutination reaction. Most laboratories circumvent this "prozone" phenomenon, which occurs in approximately 1% to 2% of sera from patients with secondary syphilis and occasionally in HIV-infected patients,[315,345] by routinely titrating all samples to at least 16 dilutions. In untreated patients, the degree of reactivity of nontreponemal tests roughly correlates with the stage of disease and inversely with treponemal burdens. Approximately 30% of patients with early primary syphilis have nonreactive nontreponemal tests.[318] The greater sensitivity of treponemal tests for detecting early infection is a principal argument for screening using the "reverse algorithm" (see later).[346,347] Nearly all patients with secondary syphilis will have nontreponemal test titers of at least 1 : 8. Although there have been rare case reports of HIV-reactive syphilis patients with nonreactive nontreponemal tests,[348,349] a nonreactive nontreponemal test (i.e., one without a prozone) essentially rules out the diagnosis of secondary syphilis. Approximately one-third of patients with tertiary syphilis will have nonreactive nontreponemal tests; these are presumed to be cases in which the inflammatory response is largely burned out, but nevertheless these patients still require stage-specific treatment (see later).

Conditions other than treponemal infection can elicit antilipoidal antibodies that cause reactivity in a nontreponemal test with a negative treponemal test result, termed a *biologic false-positive* reaction.[350] Acute BFP reactions, defined as lasting less than 6 months, are associated with transient diseases or conditions such as malaria, brucellosis, and mononucleosis. Recently, smallpox vaccination was shown to produce BFP reactions.[351] Causes of chronic BFP reactions, defined as lasting more than 6 months, include autoimmune diseases, particularly systemic lupus erythematosus, HIV infection, intravenous drug use, and leprosy. Patients with hepatitis C infection are noted to be five times more likely to have BFP reactions than hepatitis C–negative controls.[352] Acute BFP titers tend to be higher than chronic BFPs. Aging and pregnancy have also been cited as causes of BFP reactions, but it is likely that other underlying conditions were responsible for the false-positive test results. For example, in a Swedish study of 5170 pregnant women, eight of nine BFPs were positive for reasons other than pregnancy.[353] A BFP is not necessarily indicative of a disease state. A study of 19,067 Jamaicans revealed that 0.59% of the general population had false-positive VDRL results.[354] The relationship between the anticardiolipin (i.e., nontreponemal) antibodies of syphilis and those associated with the antiphospholipid (aPL) syndrome, a cause of BFP tests for syphilis, was once a source of confusion. It is now recognized that aPL "autoimmune" antibodies are distinct and directed against β_2-glycoprotein I, a cardiolipin-binding hemostasis control protein.[208,211,261,355–360]

Treponemal Tests

Conventional treponemal tests (i.e., the FTA-ABS and *T. pallidum* particle agglutination [TPPA] tests) and the majority of newer commercially available treponemal assays measure both immunoglobulin G (IgG) and IgM without distinguishing the immunoglobulin class responsible for reactivity. This property accounts for their high level of sensitivity for syphilitic infection of all stages but also their inability to distinguish active from inactive disease. It is important to remember, therefore, that a reactive treponemal test usually remains reactive for life. On the other hand, treponemal tests should always be performed when primary syphilis is suspected because of their greater sensitivity than nontreponemal tests (86% vs. 70%), becoming reactive 1 to 2 weeks after the appearance of the chancre.[5,318] Treponemal tests also should be performed for suspected tertiary syphilis even when nontreponemal tests are nonreactive. Although reactive treponemal tests in this context are sufficient evidence for treatment, they are not definitive evidence that syphilis is the underlying process.

The formats of treponemal tests have changed substantially over the years.[7,315] The first to come into widespread use was the FTA-ABS test. In this test, a serum sample, adsorbed with an extract of the cultivatable treponeme *Treponema phagedenis* Reiter (Sorbent) to remove cross-reactive antibodies generated against commensal microbiota, is used to immunolabel treponemes fixed to glass slides. Labeled organisms are demonstrated by means of an FITC-conjugated antihuman immunoglobulin antibody, and the sample is scored by eye based on fluorescence intensity. Because of the subjectivity involved and the need for expensive microscopy equipment, the CDC no longer regards the FTA-ABS test as

the gold standard treponemal test and does not recommend it for routine usage.[361] The microhemoagglutination–*T. pallidum* (MHA-TP) assay is a passive hemagglutination assay of formalinized, tanned erythrocytes sensitized with *T. pallidum* antigen that can be used to test preabsorbed patient sera. The TPPA test, which uses gelatin particles sensitized with *T. pallidum* antigens, has supplanted the MHA-TP. Since the 1980s, numerous enzyme-linked immunoassays (EIAs) and chemiluminescent immunoassays (CIAs) have been developed for syphilis diagnosis, the majority of which use recombinant *T. pallidum* antigens to detect IgM or IgG, usually both. In head-to-head comparisons, the TPPA compares favorably with other treponemal tests currently on the market, including EIAs and CIAs using recombinant antigens. Unlike the immunoassays, the TPPA assay is not automatable and, because it is read manually rather than spectrophotometrically, tends to be subjective and cannot be readily digitized. Detailed information on the newer formats used for treponemal tests can be found in the work of Sena and colleagues.[362]

Many laboratories handling large patient volumes have switched to a "reverse algorithm" in which screening is performed with an automatable treponemal EIA or CIA followed by a nontreponemal test when the former is reactive.[5,344,346,361,363–366] Head-to-head comparison of the traditional and reverse sequence indicates that the latter is more sensitive, particularly for patients with primary and latent disease. However, individuals with so-called 'discordant' serologic test results (i.e., immunoassay reactive, nontreponemal test nonreactive) also may have treated infection. Taking a careful clinical history is important because previously treated asymptomatic individuals will require no further management. For persons with discordant serologic findings and without a history of treatment, a TPPA test or comparably sensitive immunoassay should be performed.[361,364] If a second treponemal test result is positive, persons with a history of previous treatment will require no further management unless sexual history suggests likelihood of reexposure. In this instance, a repeat nontreponemal test in 2–4 weeks is recommended to evaluate for early infection, and those without a history of treatment for syphilis should be offered it. If the second treponemal test is nonreactive, the clinician may decide that no further evaluation or treatment is indicated or that treatment is indicated for individuals at high risk. Practitioners should be aware of data, based on use of the TPPA assay as the confirmatory treponemal test, indicating that discordant test results in individuals at low risk of syphilis have a high likelihood of being immunoassay false positives. This situation is commonly encountered during prenatal screening. Mmeje and colleagues[367] found that 80% of women in a low-risk clinical setting with discordant prenatal serologic findings had nonreactive TPPA tests and that a majority of these individuals had nonreactive repeat CIA tests. These data support CIA retesting of low-risk patients with discordant serologic findings and negative TPPA test results, reserving treatment for those with a reactive follow-up test.[261] Given these caveats, the CDC and the US Preventive Services Task Force have been reluctant to endorse the reverse algorithm and have opted instead to provide guidance for clinicians and facilities that use it.[261,344]

Syphilis Serologic Tests in HIV Infection

There is now consensus that serologic tests for syphilis perform well in persons coinfected with HIV.[261] However, some caveats should be borne in mind. First, HIV-infected individuals may have a higher incidence of false-positive nontreponemal test results.[368,369] Second, nontreponemal test titers in HIV-infected individuals tend to be higher at presentation (including prozone phenomena) and remain persistently elevated after treatment.[112,151,370,371] These serologic findings may reflect the B-cell dysregulation associated with HIV infection. Third, there are the well-documented, although extremely rare, cases of HIV-infected patients with secondary syphilis and nonreactive syphilis serologies.[348,372] If serologic test results are negative in an HIV-infected individual with suspected secondary syphilis, skin biopsy for histopathologic examination and direct detection of *T. pallidum* should be performed.

Rapid Point-of-Care Tests

Resource-poor countries often cannot meet the personnel and laboratory demands for reliable syphilis serology testing. In addition, when syphilis serologic assays are performed off site, delays in diagnosis can result in missed opportunities for treatment and intervention, a grave concern in regions with high rates of CS. RPOC tests address these problems.[5,373,374] WHO established the ASSURED criteria to define the characteristics of an ideal RPOC test: *a*ffordable, *s*ensitive, *s*pecific, *u*ser-friendly, *r*apid and robust, *e*quipment free, and *d*eliverable to those who need them.[375] Most of the commercially available RPOC tests for syphilis are immunochromatographic strip assays that use recombinant *T. pallidum* antigens to detect IgM and IgG antibodies in whole blood from fingerstick specimens and can be performed in approximately 20 minutes. Numerous rapid tests have been evaluated in diverse clinical and community settings and shown to fulfill the ASSURED criteria and reduce disease burden[5,376] An RPOC test that simultaneously detects nontreponemal and treponemal antibodies has shown excellent sensitivity and specificity with archived samples and performed well on site in China.[377,378] Rapid, dual HIV and syphilis tests are now available and have been shown to be more cost-effective than single tests and to prevent more adverse pregnancy outcomes.[379]

Tests for Neurosyphilis

Contributing to the complexity of diagnosing neurosyphilis is deciding which patients should undergo lumbar puncture. As discussed earlier, CSF abnormalities are common in patients with early syphilis without neurologic symptoms, and a substantial proportion of patients with early syphilis have treponemes in their CNS, yet (see later) randomized trials have failed to demonstrate a benefit of enhanced therapy in patients either without or with HIV coinfection.[151,380] Consequently, the CDC does not recommend routine lumbar puncture in patients with early syphilis, regardless of HIV status.[261] Several studies have suggested that serum RPR titers greater than or equal to 32 or CD4 counts below 350 in HIV-infected patients indicate a higher risk of asymptomatic neurosyphilis[270,381,382]; the long-term benefits of lumbar puncture and more intensive therapy in this patient subset remain unproven.[9] Because of the low yield, the CDC no longer recommends routine lumbar puncture in patients with late syphilis to identify asymptomatic neurosyphilis.[261] Of course, patients with reactive serologies and neurologic symptoms or findings should always undergo lumbar puncture regardless of disease stage.[261]

Unfortunately, no gold standard exists for the laboratory diagnosis of neurosyphilis.[38] Although a reactive CSF VDRL test constitutes definitive evidence of neurosyphilis, a presumptive diagnosis can be based solely on the presence of an elevated CSF protein or pleocytosis, or both. Given the limited and conflicting data on performance,[383,384] the CSF RPR test is currently not recommended in place of the CSF VDRL test. The CSF FTA-ABS assay has high sensitivity but low specificity because reactivity may be due to the passive transfer of IgG antitreponemal antibodies across the blood-brain barrier rather than intrathecal production of antibodies.[385] Because of the lack of specificity, the CDC does not recommend performing treponemal tests on CSF, although it is worth noting that a nonreactive treponemal test rules out the diagnosis. Methods for discriminating between intrathecal production and passive diffusion of treponemal antibodies have been devised but are cumbersome, are difficult to interpret, and cannot be used to assess therapeutic response.[386,387] In a study of 40 patients diagnosed with symptomatic neurosyphilis (30 patients with early syphilis, 10 with late), only 17 had PCR-positive spinal fluids.[338] As is often the case in studies of neurosyphilis, the criteria used by these investigators to diagnose neurosyphilis have been called into question.[339] In any event, a positive result of PCR assay on CSF in a symptomatic patient provides strong support for a diagnosis of neurosyphilis, whereas a negative PCR does not rule it out.

THERAPY

Principles of Syphilotherapy

There is no evidence that the susceptibility of *T. pallidum* to penicillin has diminished over the 70 years it has been used. Parenterally administered aqueous penicillin G is the preferred therapy for all forms and stages of syphilis. However, as discussed later, the preparation used, dosage, and duration of therapy vary with the stage of disease and manifestations to be treated. Table 237.2 presents guidelines for the treatment of syphilis based on current CDC recommendations.[261] Clement and coworkers[388] have published an extensive literature review evaluating the quality of evidence for the CDC guidelines.

TABLE 237.2 Recommended Therapy for Syphilis (Based on 2015 Centers for Disease Control and Prevention Sexually Transmitted Disease Treatment Guidelines[a])

STAGE	PATIENTS NOT ALLERGIC TO PENICILLIN	PATIENTS ALLERGIC TO PENICILLIN[a]	ALTERNATIVE REGIMENS[a]
Early syphilis[b] (primary, secondary, early latent), adults	BPG 2.4 MU IM in a single dose	Doxycycline, 100 mg PO bid for 14 days *or* Tetracycline hydrochloride, 500 mg PO qid for 14 days *or* Desensitization to penicillin in pregnant women, treat with BPG	Ceftriaxone, 1–2 g IM or IV daily for 10–14 days *or* Azithromycin[c] 2 g PO
Late latent, syphilis of unknown duration, adults, or nonneurologic tertiary syphilis	BPG 2.4 MU IM at weekly intervals × 3 (7.2 MU total)	Doxycycline, 100 mg PO bid for 28 days *or* Tetracycline hydrochloride, 500 mg PO qid for 28 days	Ceftriaxone (dosage and duration unknown)
Neurosyphilis, otic syphilis, and ocular syphilis, adults[d]	Aqueous crystalline penicillin G, 18–24 MU per day given as 3–4 MU IV q4h or continuous infusion for 10–14 days *or* Procaine penicillin G, 2.4 MU IM, plus probenecid, 0.5 g PO qid, daily for 10–14 days	Ceftriaxone, 2 g IM or IV daily for 14 days	
Pregnancy[c]	Stage-appropriate treatment with penicillin as for nonpregnant patients; penicillin-allergic patients should be desensitized and treated with penicillin		
Congenital syphilis	Aqueous crystalline penicillin G, 100,000–150,000 units/kg/day, administered as 50,000 units/kg/day IV q12h during the first 7 days of life and q8h thereafter for a total of 10 days *or* Procaine penicillin G, 50,000 units/kg IM daily for minimum of 10 days	Not applicable	
Older infants (>30 days old) and children with a diagnosis of congenital syphilis	Aqueous crystalline penicillin G 200,000–300,000 units/kg/day IV, administered as 50,000 units/kg q4–6h for 10 days In selected cases, treatment can be given with benzathine penicillin G,[b] 50,000 units/kg/day, up to 2.4 MU IM in a single dose or procaine penicillin G 50,000 units/kg IM daily for minimum of 10 days		

[a]Therapeutic regimens other than penicillin have not been well studied, especially in patients with syphilis duration longer than 1 year; therefore, careful follow-up is mandatory. Ceftriaxone should be used cautiously in patients with a well-documented history of penicillin allergy. There are insufficient data to recommend ceftriaxone for penicillin-allergic pregnant patients.
[b]HIV-infected and HIV-uninfected patients. Available data indicate that additional doses of BPG, amoxicillin, or other antibiotics in early syphilis do not enhance efficacy, regardless of HIV status.
[c]Azithromycin as a single 2-g dose PO appears to be as effective as 2.4 MU IM BPG for early syphilis. However, mutations in *Treponema pallidum* that confer resistance to azithromycin are geographically widespread. For this reason, azithromycin should be used with caution only when treatment with BPG or doxycycline is not feasible. *Azithromycin should not be used in pregnant women or in men who have sex with men.*
[d]In light of the extensive track record with the use of high-dose intravenous penicillin for neurosyphilis, penicillin-allergic patients probably should be desensitized. Data for the use of ceftriaxone as alternative therapy for neurosyphilis are limited. If concern exists about the safety of ceftriaxone, skin testing and, if necessary, desensitization should be performed.
BPG, Benzathine penicillin G; *HIV,* human immunodeficiency virus; *MU,* million units.

Because *T. pallidum* cannot be cultivated, it has never been possible to use conventional in vitro methods to assess its susceptibility to antimicrobials or rationally design therapeutic regimens. Some success in defining the spirochete's susceptibility to antimicrobials other than penicillin has been achieved in vitro by inhibiting incorporation of radiolabeled amino acids into protein[40] or replication during coculture with mammalian cells[40,389] and by assessing response to treatment in the rabbit model.[390–393] Beginning with the initial observations of the effectiveness of penicillin in 1943,[42] the principles underlying successful treatment of syphilis with this mainstay antimicrobial have had to be extrapolated from pharmacokinetic data, animal experimentation, and clinical trials.[394,395] Early investigations established that *T. pallidum* is exquisitely sensitive to penicillin but that the determinants of cure differed from those observed with other penicillin-sensitive organisms (e.g., streptococci). To be effective, a minimal serum concentration of 0.02 μg/mL had to be maintained for at least 7 to 10 days. Maintaining adequate serum levels of penicillin without prolonged interruptions was found to be more important than the total dose administered. As elegantly stated by Eagle and colleagues,[396] "*Treponema pallidum* is … one of the most sensitive, as well as one of the most resistant of all bacteria to the action of penicillin. It is one of the most sensitive in terms of the smallest concentration, which is bactericidal; it is one of the most resistant in terms of the time for which it must be exposed to that concentration in order to be killed." This unusual dose-time relationship can be attributed directly to the bacterium's extraordinarily slow rate of replication in mammalian tissues, rather than a lack of targets for β-lactams.[39,82,397] Once the principles for successful therapy had been deduced, the rationale for the use of depot formulations of penicillin G for treatment of individual patients became evident, as did the possibility of using them as the basis for public health control programs.[394,398] Of the various long-acting

preparations developed in the early penicillin era, BPG was found to provide the most sustained levels of antibiotic. A single intramuscular injection of 2.4 million units of BPG yields treponemicidal concentrations lasting as long as 3 to 4 weeks.[394]

Incubating or Early Syphilis

Presumptive or epidemiologic treatment should be given to anyone who has been exposed to a patient with primary, secondary, or early latent syphilis within the preceding 90 days, even if he or she is seronegative and has no evidence of infection at examination. Persons without physical findings who were exposed more than 90 days before the diagnosis of infectious syphilis in a sex partner should be treated presumptively if serologic test results are not immediately available and follow-up is uncertain.[261] If serologic test results in such individuals are negative, no treatment is necessary. Eagle and colleagues[399] showed in the rabbit model that much smaller doses of penicillin are necessary to abort incubating syphilis than to eradicate established infection. However, to ensure adequate safety margins, prophylactic treatment schedules are the same as those used for patients with clinically evident early infection, 2.4 million units of BPG. This regimen has been reported to be 100% effective for preventing infection in contacts of persons known to have early syphilis.[400,401]

Therapy for patients with early syphilis needs to accomplish two objectives: (1) resolution of infectious mucocutaneous lesions, critically important from a public health standpoint, and (2) eradication of spirochetes to resolve manifestations and prevent sequelae, including tertiary complications. Initial studies of penicillin using miniscule doses by today's standards made clear the drug's remarkable effectiveness in accomplishing the first objective. Although they do not meet contemporary standards for clinical trials, studies of single-dose BPG for early syphilis conducted in the 1950s and 1960s were well enough conducted and involved large enough numbers of patients for meaningful conclusions to be drawn regarding the second.[9,394,401,402] On the whole, investigators reported excellent clinical and serologic responses with posttreatment follow-up periods up to several years. Treatment failures were uncommon (collectively, approximately 5%) and usually were due to lack of reversion of nontreponemal test titers, a serologic phenomenon no longer considered unequivocally to be indicative of failure to eradicate treponemes. Rare, overt (i.e., clinical) failures were usually judged to be reinfections. In a large comparison of multiple therapeutic regimens, Schroeter and colleagues[401] found a single intramuscular injection of 2.4 million units of BPG to be equivalent to 4.8 million units of procaine penicillin G given daily for 8 days or in three divided doses over 6 days. As discussed at length earlier, syphilologists have long been keenly aware of the potential for the CNS to serve as a reservoir for relapse. Particularly important, therefore, were follow-up studies showing that patients with early syphilis who were given single-dose BPG had normal CSF values 2 years after treatment.[403–405] On the basis of these results, clinicians dispensed with routine examination of spinal fluid 2 years after treatment, an important milestone in syphilis management.

Even before the advent of HIV, some authorities had begun to question the use of single-dose BPG therapy for early syphilis on the basis of isolated case reports of neurorelapse of primary or secondary syphilis in patients treated with BPG, along with evidence that 2.4 million units of intramuscular BPG fails to achieve detectable levels of penicillin in CSF.[400,406,407] However, as noted earlier, serious reservations emerged in the late 1980s as a result of numerous case reports and small series suggesting that the incidence of BPG treatment failures in HIV-infected patients exceeded the norms from the pre-AIDS era.[215–217] To address this urgent therapeutic issue, the CDC conducted a multicenter, randomized controlled trial comparing 2.4 million units of intramuscular BPG with enhanced therapy (2.4 million units of intramuscular BPG plus oral amoxicillin-probenecid) in a cohort of 541 neurologically asymptomatic patients with early syphilis (101 and 440 persons, respectively, with and without HIV infection). The findings were reassuring. Not only were the presenting clinical manifestations similar in the HIV-infected and HIV-uninfected patients, but serious CNS or eye complications following treatment were not observed in patients randomized to either regimen. Important to note, although serologic responses were poorer overall among the HIV-infected patients, there was no evidence that enhanced therapy improved clinical or serologic outcomes in patients with early syphilis either with or without HIV infection.[151] Critics of the study have maintained that it was underpowered and did not include a long enough follow-up period and that the comparison should have included high-dose intravenous penicillin G, the standard regimen for neurosyphilis.[408] However, a systematic review of the literature published in 2011 found that no data from well-controlled trials supporting the viewpoint that HIV-infected patients with early syphilis should routinely receive more intensive therapy.[409] Indeed, the only other large-scale treatment trial deemed to be of good quality,[408] a comparison of azithromycin and BPG conducted in Tanzania,[410] also failed to observe a difference in treatment response among HIV-infected and HIV-uninfected patients given 2.4 million units of BPG for early syphilis during 9 months of follow-up. Since then, two studies comparing a single dose versus three doses of BPG also failed to establish superiority of the multidose regimen in patients with syphilis who were coinfected with HIV.[380,411] Thus, there is now more than ample evidence,[412] backed by extensive clinical experience, for the CDC's recommendation of a single intramuscular injection of 2.4 million units of BPG as primary treatment of early syphilis in all individuals without neurologic or ophthalmologic findings regardless of HIV status.[261] At the same time, the authors acknowledge that there are many practitioners who believe that treatment of uncomplicated early syphilis in patients with HIV coinfection requires, at a minimum, three weekly injections of 2.4 million units of BPG.[8]

Latency

Inasmuch as patients with latent syphilis by definition lack signs and symptoms, the primary objective of treatment during latency is to prevent secondary relapses in early latency and late sequelae in all. In women of childbearing years, prevention of congenital infection is also an important therapeutic goal.[60] In early latency, spirochetes are actively replicating, although outbreaks are muted or contained, or both, compared with secondary disease, presumably because of an increasingly effective immune response. The rationale for using single-dose BPG to treat early latent syphilis, therefore, is the same as for primary and secondary infection. Nevertheless, assessing therapeutic efficacy in early latency is difficult because there is no way to determine which patients are at risk for secondary relapses, and years of follow-up would be required to establish whether treatment has prevented late complications. Despite limited published data,[402,413] decades of clinical experience suggest that a single dose of BPG is extremely effective at preventing secondary relapses.

Assessing therapeutic efficacy in late latency is even more problematic because the decline in nontreponemal tests can be extremely slow and, as has long been recognized, does not occur in a substantial percentage of patients.[208,394,414] Although no microbiologic data exist, it is assumed that spirochetes in late syphilis are replicating slowly (if at all) and therefore require more prolonged contact with penicillin than in early disease[395]—hence the recommendation for three weekly injections of 2.4 million units of BPG for treatment of all nonneurologic forms of late syphilis. Appropriately, Clement and coworkers[388] evaluated the evidence for this regimen, as well as those described for all forms of tertiary syphilis, as based primarily on expert consensus. According to CDC guidelines, for the purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., >1:32) should be assumed to have early syphilis.[261] However, the CDC cautions against using serologic titers to differentiate early latent from late latent syphilis. When the duration of infection cannot be ascertained, caregivers should opt for the late latent treatment regimen.

Tertiary Syphilis

The CDC recommends that all persons with tertiary syphilis should be tested for HIV and receive a CSF examination before the initiation of therapy; individuals with CSF abnormalities should be treated with a neurosyphilis regimen (see later).[261]

Cardiovascular and Gummatous Syphilis

As with late latent syphilis, spirochetes in tertiary lesions are presumed to be replicating slowly.[395] Consequently, the rationale for using 7.2

million units of intramuscular BPG in three divided doses in non-neurologic forms of tertiary syphilis is the same. As one would anticipate, there is a paucity of data supporting the efficacy of this regimen for tertiary disease. An additional problem in assessing responses in late syphilis is that only inflammation, not destruction and scarring that already have occurred, will resolve with therapy. The primary treatment objective for tertiary syphilis, therefore, is to eradicate spirochetes so as to prevent further tissue damage. The literature contains a number of case reports documenting the penicillin responsiveness of gumma, although in many of these, penicillin formulations other than BPG were used. Consistent with the authors' experience, two reports[415,416] show prompt resolution of gumma in response to single-dose intramuscular BPG. Although penicillin therapy for cardiovascular syphilis has been accepted since the late 1940s and there are data from as far back as the 1950s to support its efficacy in arresting disease progression and symptomatic deterioration,[194,298] there are no trials supporting the use of BPG. There is also global disparity in treatment guidelines. Although US, European, and WHO guidelines recommend 7.2 million units of intramuscular BPG, Australian guidelines call for either intravenous penicillin for 15 days or daily intramuscular procaine penicillin for 20 days.[300] The CDC acknowledges that some clinicians elect to treat cardiovascular syphilis with high-dose intravenous penicillin.[261]

Neurosyphilis

Although recommendations for treatment of neurosyphilis once included 7.2 million units of intramuscular BPG and the large majority of patients (at least 80%) do, in fact, respond to this regimen, accumulated evidence for treatment failures, as well as the inability of BPG to achieve treponemicidal levels in the CSF, led the CDC to stop recommending it.[400] Aqueous penicillin G, 18 to 24 million units daily, administered as 3 to 4 million units intravenously every 4 hours or as a continuous infusion for 10 to 14 days, is the currently recommended regimen; failures with this regimen are virtually nonexistent. If compliance can be ensured, procaine penicillin 2.4 million units intramuscularly daily with probenecid 500 mg four times a day for 10 to 14 days can be considered as an alternative. Although not mandatory, CDC guidelines allow for follow-up of intravenous therapy with three divided doses of BPG to ensure prolonged penicillinemia for comparable treatment of nonneurologic tertiary syphilis. Otosyphilis and ocular syphilis, both frequently associated with neurosyphilis, should be treated as such regardless of the results of lumbar puncture.

Penicillin Allergy

Penicillin allergy presents one of the most serious challenges in the routine management of syphilis because it deprives the practitioner of the most powerful weapon for combating the disease. A careful history should always be obtained, therefore, before one decides that penicillin is contraindicated, and if necessary and possible, consultation with a subspecialist should be sought. Penicillin-allergic patients whose compliance with therapy or follow-up is questionable should be desensitized and treated with BPG. Doxycycline and tetracycline have long-established track records as alternatives to penicillin with a reasonable amount of published data, some recent and including HIV-infected persons, indicating efficacy comparable to that of BPG.[400,401,417–420] Clement and coworkers[388] gave alternative tetracycline and doxycycline regimens a rating indicative of support from randomized clinical trials, although lower in overall quality than the evidence for BPG. Doxycycline is preferred both because of its twice-daily administration, ensuring better compliance, and its lipophilicity, enabling it to cross the blood-brain barrier. Pharmacokinetics data and limited clinical studies suggest that ceftriaxone is effective for treating both early and late syphilis, including neurosyphilis,[419,421–423] although the optimal dose and duration of therapy for either have not been determined. Clinicians opting for ceftriaxone must be mindful of a risk, albeit probably small, of cross-reactivity in persons with anaphylactic-type hypersensitivity to penicillin.[424,425] Enthusiasm for azithromycin, which can be as efficacious as BPG when administered orally as a single 2-g dose,[410] has been tempered by the discovery of geographically widespread (including the United States) macrolide-resistant strains of *T. pallidum* associated with A2058G or A2059G mutations in the bacterium's 23S rRNA genes.[426–431] In light of this disappointing development, azithromycin should be used cautiously, with careful follow-up, and not at all in pregnant patients or in MSM.[261]

Gestational Syphilis

Syphilis in pregnancy poses great risk to both the mother and her unborn child.[5,60,432–434] Thus, treatment objectives are twofold: resolution of infection in the mother and prevention of in utero infection of the fetus. Every case of CS represents an opportunity missed to make the diagnosis antenatally.[435] All women should be screened serologically during the early stages of pregnancy and, for those at high risk, at delivery as well. Infected pregnant patients should receive penicillin at dosage schedules appropriate for the stage of syphilis as recommended for nonpregnant patients. Prospective studies have demonstrated the efficacy of BPG to prevent CS,[436] although pharmacokinetics data and case reports do raise some doubt as to whether one intramuscular injection of BPG is sufficient once the fetus is already infected.[437] Some clinicians administer a second injection of BPG, although there are no controlled data to support the practice. Consultation with an obstetrician or maternal-fetal subspecialist is strongly recommended in the event of sonographic evidence of syphilitic infection in the fetus because complications (a form of Jarisch-Herxheimer [JH] reaction, see later), such as preterm labor and fetal distress, can be precipitated by treatment. There is no satisfactory alternative to penicillin for the treatment of syphilis during pregnancy. If the patient has a well-documented or skin test–proven penicillin allergy, desensitization is strongly recommended, given penicillin's track record in preventing CS, the inability to use tetracycline derivatives in this setting because of their adverse effects on the fetus, the well-recognized risk for treatment failure with macrolides, and the paucity of data for ceftriaxone.[261]

JARISCH-HERXHEIMER REACTION

The JH reaction is a systemic reaction resembling bacterial sepsis that usually begins 6 to 8 hours after the initial treatment of syphilis with effective antibiotics, especially penicillin.[298,438,439] It is particularly common when secondary syphilis is treated but can occur at any stage. On the basis of work done with relapsing fever, another spirochetal infection in which severe JH reactions commonly occur,[440,441] this phenomenon is likely a cytokine storm caused by the abrupt release of lipoproteins and other PAMPs from lysed treponemes. The JH reaction in syphilis consists of the abrupt onset of fever, chills, myalgias, headache, tachycardia, hyperventilation, vasodilation with flushing, and mild hypotension. It lasts from 12 to 24 hours and occurs with varying degrees of severity. Localized forms of the JH reaction also may occur in patients with ocular syphilis, neurosyphilis, and cardiovascular syphilis.[298,442,443] In the case of cardiovascular syphilis, a JH reaction can result in sudden death due to aneurysmal rupture or coronary occlusion. Patients should be warned of the possibility of the reaction before treatment; in cardiovascular syphilis, an argument can be made for prophylactic treatment. The JH reaction can be prevented or treated with an antiinflammatory agent such as aspirin every 4 hours for a period of 24 to 48 hours. Prednisone can also abort the reaction, though no data exist as to when it should be used.[439]

Response to Therapy

Once disease manifestations have resolved after treatment, typically within weeks, decline in nontreponemal test titers is the only means of monitoring therapeutic response over prolonged periods. At one time, it was believed that nontreponemal test results decline rapidly (i.e., within 3 months) and become nonreactive ("serorevert") in most appropriately treated patients with primary and secondary syphilis.[357,394,444–446] Romanowski and coworkers[447] deserve much credit for showing definitively that the nontreponemal antibody response to therapy of early syphilis is often slow and incomplete. Their report, along with the serologic data presented in the randomized treatment trial published by Rolfs and colleagues[151] several years later, led to less stringent criteria for an adequate serologic response. This is currently defined as a fourfold decrease in nontreponemal titer no later than 1 year after therapy for early syphilis and 2 years for late latent syphilis.[261] Even so, serologic titers do not change substantially (i.e., remain positive at the initial titer or decline only one dilution) in 15% to 20% of patients with early

syphilis and in an even higher, although not well defined, proportion of patients treated for latent syphilis.[211] Serologic cure is primarily associated with younger age, higher baseline nontreponemal titers, and earlier syphilis stage.[208,448] A major question is whether patients who do not demonstrate serologic response benefit from additional treatment. Sena and coworkers[449] found that only 27% of 82 HIV-negative "serofast" patients exhibited serologic response after retreatment during an additional 6 months of follow-up. CSF examination to exclude neurosyphilis should be considered for patients who do not achieve a fourfold decline during the appropriate interval after therapy,[261] especially those in whom close follow-up and serologic monitoring cannot be ensured. Although some experts doubt that many serofast patients will turn out to have neurosyphilis (the authors' experience as well),[450] a recent report from China found CSF abnormalities considered indicative of asymptomatic neurosyphilis in 34% of serofast patients.[358] Many patients will have persistent low-level titers despite a fourfold or greater decline after treatment. Evaluation of serologic data from a multicenter treatment trial treatment[359] found, quite remarkably, that only 17% of patients with an appropriate decline in nontreponemal titer at 6 months achieved seroreversion 12 months after therapy, with the seroreversion rate highest for primary infection.[360] There is no evidence that such individuals benefit from lumbar puncture or additional therapy,[261] nor are there anecdotal reports suggesting frequent neurologic relapses in this group.[450] More than six decades after the demonstration of the efficacy of penicillin therapy, the biologic significance of persistent, low nontreponemal titers is unknown. It has been proposed that this phenomenon represents a failure of the immune response to halt production of antilipoidal antibodies as a result of B-cell tolerance[208] rather than the failure of therapy to eradicate treponemes hiding within a CNS niche, as was once believed.[208,451]

Pleocytosis, long regarded as the hallmark of an active inflammatory process,[1,149] should resolve within weeks to months after appropriate therapy for neurosyphilis. When positive, CSF VDRL findings should be monitored quantitatively but may not normalize. An elevated protein may, likewise, persist indefinitely.

Congenital Syphilis

Although early diagnosis and treatment of women with gestational syphilis can prevent CS, persistently high rates of venereal syphilis in the general population combined with a lack of access to prenatal care in many regions of the world have seriously hampered efforts to control the disease.[128,452–455] Globally, the magnitude of CS rivals that of HIV infection in neonates.[452] WHO estimates have indicated that 1.0 million pregnant women have active syphilis and that up to one-third of such pregnancies result in early fetal death (22–28 weeks' gestation), stillbirth (>28 weeks), neonatal death, preterm or low-birth-weight infants, and newborns with congenital infection.[5,128] In the United States, the incidence of CS increased by 38% (8.4–11.6 cases per 100,000) from 2012–2014, reversing a decade long decline in its overall incidence. In 2015, the CDC confirmed that the incidence of CS has continued to increase, reaching a two-decade high at 12 cases per 100,000 live births.[456] The rise in the incidence of CS has been most pronounced among whites, with a 69% increase. However, the overall prevalence remained highest in African Americans (35.2 cases per 100,000), Hispanics (15.5 cases per 100,000), and Native Americans (10.3 cases per 100,000). A total of 19 states, including California, Florida, Louisiana, Michigan, and New York, have reported dramatic increases in new cases of CS. The most common risk factor for developing CS in the United States continues to be lack of prenatal care (around 21% of affected pregnancies) or inadequate care.[456]

Although the problem of CS in sub-Saharan Africa and, more recently, China and the United States has received a good deal of attention, CS in Latin America and the Caribbean has been largely unnoticed, in spite of what appears to be a public health problem of alarming dimensions. In 2012, Colombia's National Institute of Health Surveillance System (Sistema Nacional de Vigilancia en Salud Pública [SIVIGILA]) reported rates of GS/CS many times greater than those in the United States and Western Europe, and in a retrospective study in a predominantly black, indigent population of Colombia's Pacific coastal region the reported rate rivaled rates in sub-Saharan Africa.[457] A similar problem exists in Haiti and other Caribbean nations.[458] The picture of both venereal syphilis in the general population and pregnant women and, by extension, CS is not one of a vanishing disease. Rather, this potentially deadly GS/CS dyad requires continued monitoring, early and effective screening, and treatment strategies to help reverse this trend of increasing disease burden.

The vast majority of CS cases are believed to arise in utero.[459] The fetus can be infected during any stage of syphilitic infection in the mother, but it is most likely to occur during the spirochetemia associated with untreated primary and secondary syphilis,[460–462] and less frequently during early latency (60%–90% vs. 40% in early latent and <10% in late latent syphilis).[460,461] Findings from a PCR-based study underscored the pathogenic and prognostic importance of spirochetemia during pregnancy; the investigators found that miscarriage, stillbirth, and neonatal death, respectively, occurred in 81%, 73%, and 83% of syphilitic mothers who were PCR positive in blood.[463] Although fetal syphilis can occur during the first trimester,[464] the risk to the offspring increases significantly during the second and third trimesters. Fetal infection is characterized by early hepatic dysfunction and placental involvement, followed by spread of the spirochete into the amniotic fluid and the appearance of severe hematologic anomalies.[462] In mothers who acquire syphilis during pregnancy, compromise of the fetus can be more severe and, in some instances, lead to multiorgan compromise.[462] Not surprisingly, up to 7% of fetuses with CS are stillborn.[465–467] Death in the newborn period is usually the result of liver failure, severe pneumonia, hypopituitarism, or pulmonary hemorrhage.

No other form of syphilis better exemplifies the remarkable invasiveness of *T. pallidum* than CS. The presence of spirochetes in the placenta and umbilical cord supports transplacental invasion of maternal bloodborne spirochetes as the major route of transmission to the infant.[468] Macroscopically, the infected placenta is generally large, thick, and pale, weighing up to one-third as much as the fetus.[469,470] Histologically it reveals focal proliferative villitis with necrosis and focal infiltration of maternal lymphocytes and plasma cells, endothelial and adventitial proliferation of villous vessels leading to small blood vessel obliteration, large and immature villi, extensive stromal hyperplasia, and, in some cases, multiple small gumma indicative of miliary spread of the bacterium.[469–472] Spirochetes can often be detected in the placenta with silver stain, immunohistochemistry, or PCR.[468,473] Intrauterine growth retardation, a commonly associated finding in the infected newborn, is thought to reflect inadequate nutrition of the fetus as a result of syphilitic placentitis.[60,474–476] Necrotizing funisitis, an inflammatory process involving the matrix of the umbilical cord, characterized by perivascular inflammation and obliterative endarteritis, is, for all practical purposes, pathognomonic of CS.[477] Indeed, CS should be suspected clinically whenever the umbilical cord is swollen and discolored red, white, and blue, resembling a "barber's pole."[477,478]

The clinical, laboratory, and radiographic features present in the newborn period or within the first 2 years of life, or both, comprise early CS, whereas those that manifest after 2 years of age comprise late CS (Table 237.3). Depending on the degree of systemic involvement, the clinical presentation of early CS can range from life-threatening disease (i.e., fetal hydrops) to an otherwise normal-appearing newborn with only minimal laboratory and radiographic anomalies.[60] The earliest sign of CS is usually rhinitis (snuffles), which is soon followed by a diffuse, maculopapular, desquamative rash with extensive sloughing of the epithelium, particularly on the palms, on the soles, and about the mouth and anus (Fig. 237.12). In contrast to acquired syphilis in the adult, a vesicular rash and bullae, also known as *pemphigus syphiliticus,* may develop. These lesions are teeming with spirochetes and histologically have the characteristic obliterative endarteritis and perivascular mononuclear cuffing on microscopic examination that are found in lesions of acquired syphilis. Newborn hair may be brittle and sparse; infantile alopecia, especially affecting the eyebrows, is considered suggestive of CS. At the nares, lips, and anus, the initial lesions may be indistinguishable from the mucous patches of secondary syphilis but then become deeply fissured and hemorrhagic, leading to Parrot radial scars of late CS, which are also known as *rhagades.*[479]

Multiple organs can be affected in newborns with early CS.[480,481] Liver involvement is common; indeed, more than 30% of infected