Treponema

Clinical Manifestations

Treponemes cause diverse clinical manifestations. In patients with acquired venereal syphilis, there is an initial genital tract lesion (primary stage) followed by disseminated lesions (secondary stage) and, in approximately one-third of untreated individuals, cardiovascular and neurologic problems (tertiary stage). Infection during pregnancy (congenital syphilis) may result in fetal death or birth defects. Yaws, pinta, and endemic syphilis, the nonvenereal treponematoses, are usually present as skin or mucous membrane lesions. Soft tissue and bone lesions also can occur with yaws and endemic syphilis.

Structure and Biology

Treponemes are helically coiled, corkscrew-shaped cells, 6 to 15 μm long and 0.1 to 0.2 μm wide. They have an outer membrane which surrounds the periplasmic flagella, a peptidoglycan-cytoplasmic membrane complex, and a protoplasmic cylinder. Multiplication is by binary transverse fission. Treponemes have not yet been cultured in vitro.

Classification and Antigenic Types

Classification of the pathogenic treponemes is based primarily upon the clinical manifestations of the respective diseases they cause. Treponema pallidum subsp pallidum causes venereal syphilis; T pallidum subsp pertenue causes yaws; T pallidum subsp endemicum causes endemic syphilis; and T carateum causes pinta. Venereal syphilis is transmitted by sexual contact; the other diseases are transmitted by close nonvenereal contact.

Pathogenesis

Treponemes are highly invasive pathogens which often disseminate relatively soon after inoculation. Evasion of host immune responses appears to be, at least in part, due to the unique structure of the treponemal outer membrane (i.e., its extremely low content of surface-exposed proteins). Although treponemes lack classical lipopolysaccharide (endotoxin), they possess abundant lipoproteins which induce inflammatory processes.

Host Defenses

Various studies suggest that both cellular and humoral processes contribute to host defenses against treponemal infection. Clearance of treponemes from local sites appears to be due to phagocytosis by macrophages.

Epidemiology

Humans are the only source of treponemal infection; there are no known nonhuman reservoirs. Venereal syphilis is distributed worldwide, and over the past several decades has become a significant public health problem in many underdeveloped countries. Infectivity rates correspond to the most sexually active age groups. Following
the adoption of penicillin as the mainstay of syphilotherapy, the number of new syphilis cases progressively
decreased until 1958, after which the trend reversed and a steady increase has occurred. The late 1980’s
experienced a major increase in the incidence of early syphilis cases which was largely related to crack cocaine
usage among inner city minorities. Improved surveillance methods have helped to control this syphilis epidemic.
Despite extensive eradication campaigns, yaws remains widespread in the tropics. Pinta remains endemic in
Central and South America, and endemic syphilis is present in certain regions of the Middle East. The
pathogenic treponemes have many cross-reacting antigens, and untreated infection is believed to confer partial
protection against the other treponemal diseases.

**Diagnosis**

Diagnosis relies heavily on clinical manifestations. In addition, the finding of treponemes within exudative
lesions and positive serology aids the diagnosis.

**Control**

Control of venereal and nonvenereal treponematoses is based upon active surveillance and treatment of contacts.
Penicillin treatment eradicates all stages, including congenital infection in pregnancy.

**Introduction**

The genus Treponema contains both pathogenic and nonpathogenic species. Human pathogens cause four
treponematoses: syphilis (T pallidum subsp pallidum), yaws (T pallidum subsp pertenue), endemic syphilis (T
pallidum subsp endemicum), and pinta (T carateum). Nonpathogenic treponemes may be part of the normal
flora of the intestinal tract, the oral cavity, or the genital tract. Some of the oral treponemes have been associated
with gingivitis and periodontal disease.
Clinical Manifestations

Because syphilis exhibits diverse clinical manifestations that mimic many other infectious and noninfectious disorders (Fig. 36-1), it has earned a reputation as “the great imitator.” Yaws, pinta, and endemic syphilis also have highly variable manifestations. Treponemal infections are unique in that they are characterized by distinct clinical stages. Multiplication of the organisms at the initial site of entry produces the primary stage. The dissemination of treponemes to other tissues results in the secondary stage. After a relatively prolonged period, in some cases 20 to 30 years, the tertiary or late stage evolves. Treponema pallidum subsp pallidum, the most invasive of the pathogenic treponemes, produces highly destructive lesions in almost any tissue of the body, including the central nervous system. Treponema carateum is the least invasive and causes only cutaneous disease. Treponema pallidum subspp pertenue and endemicum are intermediate in invasiveness and cause destructive lesions in bones and soft tissues.

Figure 36-1  Clinical manifestations of syphilis
Venereal syphilis is the prototype treponemal disease and the only treponematosis of significance in developed countries. Clinical manifestations of syphilis are complex and the periods associated with each stage vary greatly. (Fig. 36-2 depicts averages.) After an incubation period of 10 to 90 days, extensive multiplication of treponemes at the site of entry produces erythema and induration. The resultant papule eventually progresses to a superficial ulcer with a firm base called a hard chancre. (Haemophilus ducreyi causes soft chancre, which differs in that it is flat, centrally umbilicate, tender, and painful.) Numerous treponemes are present in this highly contagious, open lesion. Regional lymph nodes enlarge, causing regional lymphadenopathy. After 2 to 6 weeks of symptoms, this primary lesion heals, leaving only remnants of scar tissue.

After an asymptomatic period of 2 to 24 weeks, the secondary or disseminated stage begins. Organisms multiply in many different tissues. Clinical manifestations include slight fever, generalized lymphadenopathy, malaise, and a mucocutaneous rash. The rash initially appears on the palms and soles and eventually spreads to other areas. The rash may be macular, papular, follicular, papulosquamous, or pustular. Superficial sores (mucous patches) may occur on mucous membranes of the mouth, vagina, or anus, while wart-like lesions called condylomata lata may form in moist intertriginous areas. All of these lesions teem with treponemes and are highly contagious. Deposition of immune complexes consisting of treponemal antigens and host antibodies in glomerular basement membranes may produce nephrotic syndrome. Two to six weeks after the onset of secondary syphilis, host defenses bring about healing. About 25 percent of untreated patients experience recurrences of this secondary stage in the first several years following infection.

The period between secondary and tertiary syphilis, termed latency, can last for many years. Early latency refers to the first 4 years when secondary relapses may occur; late latency is the asymptomatic period beyond 4 years.
During this latter period, the patient harbors infectious organisms, especially in the spleen and lymph nodes and blood serology remains positive. Tertiary syphilis can affect almost any tissue. Approximately 80 percent of fatalities are caused by cardiovascular involvement, while most of the remaining 20 percent are from neurologic involvement. Cardiovascular problems are usually attributed to local inflammation induced by the multiplication of treponemes within the wall of the thoracic aorta. The subsequent aortitis produces complications such as aneurysms and coronary artery stenosis. Neurologic syphilis may be meningeal, meningovascular, parenchymatous, or various combinations thereof. If the parenchymatous form involves the brain, it is called generalized paresis; if it involves the spinal column, it is called tabes dorsalis. Complications of neurosyphilis include dementia, loss of proprioception, strokes, and blindness. For unclear reasons, cardiovascular syphilis is much less common than during the pre-antibiotic era. Gummas are highly destructive tertiary syphilitic lesions that usually occur in skin and bones but may also occur in other tissues. They are necrotizing granulomas with numerous lymphocytes, giant cells, and epithelioid cells, but few treponemes. A delayed hypersensitivity response to the small numbers of treponemes in the lesions may be responsible for the development of gummatous disease. Gummas also have become rare in the post-antibiotic era.

**Structure and Biology**

Treponemes are helically coiled, corkscrew-shaped organisms 6 to 15 μm long and 0.1 to 0.2 μm wide. The organisms stain poorly with aniline dyes. Treponemes in tissues can be visualized by silver impregnation methods. Live treponemes, which are too slender to be seen by conventional light microscopy, can be visualized by using dark-field microscopy. Treponema pallidum subsp. pallidum exhibits characteristic motility that consists of rapid rotation about its longitudinal axis and bending, flexing, and snapping about its full length.

Treponema pallidum subsp. pallidum is a fastidious organism that exhibits narrow optimal ranges of pH (7.2 to 7.4), Eh (−230 to −240 mV), and temperature (30 to 37°C). It is rapidly inactivated by mild heat, cold, desiccation, and most disinfectants. Traditionally this organism has been considered a strict anaerobe, but it is now known to be microaerophilic. Treponemes multiply by binary transverse fission. The in vivo generation time is relatively long (30 hours). Despite intense efforts over the past 75 years, *T. pallidum* subsp. pallidum has not been successfully cultured in vitro. Viable organisms can be maintained for 18 to 21 days in complex media, while limited replication has been obtained by co-cultivation with tissue culture cells. The other three pathogenic treponemes also have not been successfully grown in vitro.
The composition of T pallidum subsp pallidum (dry weight) is approximately 70 percent proteins, 20 percent lipids, and 5 percent carbohydrates. This lipid content is relatively high for bacteria. The lipid composition of T pallidum is complex, consisting of several phospholipids, including cardiolipin, and a poorly characterized glycolipid which is biochemically and immunologically distinct from lipopolysaccharide. While antigenic analysis of T pallidum subsp pallidum has been hampered by the inability to grow this organism in vitro, this situation has largely been circumvented through the use of modern molecular techniques, including monoclonal antibodies and recombinant DNA. During the course of infection, antibodies develop to a number of treponemal proteins, most notably the lipoproteins and flagella.

**Figure 36-5  Proposed structure of treponemal outer and cytoplasmic membranes**

Abbreviations: OM, outer membrane; Ef (endoflagella or periplasmic flagella); LP1, 2, lipoproteins; pg, peptidoglycan; CM, cytoplasmic membrane. (From Cox DL, Chang P, McDowall AW, and Radolf JD: The outer membrane, not a coat of host proteins, limits the antigenicity of virulent Treponema pallidum. Infect Immun 60:1076, with permission.

Although treponemes possess both outer and cytoplasmic membranes (Fig. 36-4), they differ considerably in structure from enteric Gram-negative bacteria. Figure 36-5 is a diagrammatic cross-section of T pallidum subsp pallidum. The organism has an outer membrane containing an extremely low density of surface-exposed transmembrane proteins. Typically, three flagella originate from each end of the bacterium, and, winding about
the bacterium within the periplasmic space, overlap at the midpoint. The presence of peptidoglycan in the cell wall, originally surmised on the basis of the bacterium’s exquisite sensitivity to penicillin, has been confirmed by biochemical analysis. Unlike Gram-negative bacteria in which the peptidoglycan underlies the outer membrane, in treponemes the murein layer overlies the cytoplasmic membrane. The cytoplasmic membrane covers the protoplasmic cylinder; this membrane contains the majority of the bacterium’s integral membrane proteins and is particularly abundant in lipid-modified polypeptides (lipoproteins).

Pathogenesis

Untreated syphilis is a slowly evolving chronic disease that transpires in stages separated by asymptomatic intervals. Humans are the only natural host for T pallidum subsp pallidum, and infection occurs through sexual contact. The organisms penetrate mucous membranes or enter minuscule breaks in the skin. Experiments in both humans and rabbits using standardized inocula indicated that less than 10 organisms are capable of producing infection. In women the initial lesion is usually on the labia, the walls of the vagina, or the cervix; in men it is on the shaft or glans of the penis. A chancre also may occur on lips, tongue, tonsils, anus, or other skin areas. The observation, made in a number of in vitro studies, that T pallidum subsp pallidum and subsp pertenue specifically attach to numerous cell types is believed to reflect the ability of these bacteria to infect diverse tissues and organs. To disseminate away from the site of initial entry, organisms must traverse the viscous ground substance between tissue cells. There is evidence that Treponema pallidum subsp pallidum elaborates an enzyme capable of degrading hyaluronic acid within the ground substance, thereby potentially facilitating hematogenous dissemination of organisms.

Blood from a patient with incubating syphilis may be infectious long before the appearance of a chancre, as transfused blood from patients with incubating syphilis has transmitted the infection. Although neurological symptoms may not become apparent until years after infection, invasion of the central nervous system by T pallidum occurs relatively early. A high proportion of patients with early syphilis have CSF abnormalities, despite a lack of neurological symptoms and treponemes often can be recovered by rabbit inoculation with either normal or abnormal spinal fluids during this period. Conversely, a normal spinal fluid examination two or more years after infection indicates a low risk of subsequent development neurosyphilis. Other target tissues include lymph nodes, skin, mucous membranes, liver, spleen, kidneys, heart, bones, joints, larynx, and eyes. It is generally believed that the motility of the organisms contributes to the invasiveness of these bacteria. Studies with cultured human endothelial cells have demonstrated that T pallidum rapidly penetrates between tight endothelial cell junctions, and this may be the mode of invasion at the various sites of dissemination.
The most prominent and widespread histopathologic feature of syphilitic infection is perivascular inflammation. This typically consists of proliferation of adventitial cells; perivascular cuffing with lymphocytes, monocytes and plasma cells; and swelling and proliferation of endothelial cells (Fig. 36-6). Occasionally these changes progress to frank vasculitis with ischemic necrosis of tissues. Granulomatous changes are characteristic of tertiary disease but may be seen in secondary syphilis as well. Treponema pallidum subsp pallidum appears to lack potent toxins, and it is believed that tissue damage results from the host’s cellular inflammatory response. Treponemal lipoproteins have been shown to be capable of activating relevant immune effector cells, most notably macrophages and endothelial cells. While evasion of host cellular and humoral immune responses is presumably prerequisite to establishment of persistent infection, the mechanisms responsible for this are poorly understood. It is known, however, that the surface of the organism reacts poorly with specific antibodies; the paucity of surface-exposed proteins is believed to explain this phenomenon (Fig. 36-5). Circulating immune complexes containing treponemal antigens are regularly present in secondary syphilis and may contribute to clinical manifestations, most notably the nephrotic syndrome occasionally seen in the secondary stage of the disease.

**Host Defenses**

Several clinical studies support the notion that humans develop some degree of resistance to treponemal infection. The Oslo study, begun in the early 1900s, involved over 2,000 untreated primary and secondary syphilis patients observed for 30 to 50 years. Approximately 25 percent of these patients developed secondary syphilis and 13 percent developed tertiary syphilis. The fact that 75 percent of the patients did not progress beyond primary syphilis has been taken to indicate the development of some degree of immunity. The Sing-Sing study, in which human volunteers were intradermally inoculated with virulent T pallidum subsp pallidum demonstrated that resistance to infection occurs in late syphilis. The precise contribution of humoral and cellular immune mechanisms to host defenses in syphilitic infection is not clear. Treponemes are capable of disseminating hematogenously despite high titers of circulating antibodies directed against numerous treponemal proteins. On the other hand, the presence of both organisms and antibody-synthesizing host cells (i.e., plasma cells) in the same tissue areas suggests some role for antibodies. Passive transfer of immune serum does not protect experimental syphilitic rabbits against challenge inoculation, although some modification of treponemal lesions occurs. Injection of immune serum before T pallidum subsp pallidum challenge lengthens the incubation period, reduces the severity of lesions, and speeds healing. Thus, antibodies appear to be partially but not solely responsible for healing and immunity. A mononuclear and plasma cell infiltrate occurs early in infection and is especially prominent in perivascular areas.
Immunohistochemical studies indicate that a large proportion of the mononuclear cells are macrophages, while the lymphocytes are a mixture of CD4+ and CD8+ T cells. The roles of these immune cell types are still being clarified. In vitro, macrophages readily phagocytose and process treponemal organisms and histopathological studies suggest a similar process occurs in vivo. Activated macrophages, in turn, amplify T cell stimulation.

**Epidemiology**

Humans are the only source of treponemal infection; there are no known nonhuman reservoirs. Venereal syphilis is distributed worldwide, and over the past several decades has become a significant public health problem in many underdeveloped countries. Infectivity rates correspond to the most sexually active age groups, being highest in the 20-to-24 year age group, slightly lower in the 15- to 19-year age group, and lower still in the 25- to 29-year age group. The peak incidence of syphilis was observed in 1946 to 1947 (Fig. 36-7). In the late 1940s, it was discovered that *T. pallidum* is exquisitely sensitive to penicillin G, and penicillin was found to be effective in eradicating syphilis of all clinical stages as well as the congenital infection. Following the adoption of penicillin as the mainstay of syphilotherapy, the number of new syphilis cases progressively decreased until 1958, after which the trend reversed and a steady increase has occurred. The late 1980’s experienced a major increase in the incidence of early syphilis cases which was largely related to crack cocaine usage among inner city minorities. Improved surveillance methods have helped to control this syphilis epidemic. Approximately one to 10 percent of persons with gonorrhea may have concurrent syphilitic infection. Because gonorrhea has a shorter incubation period (two to eight days) and has painful symptoms, the patient seeks treatment before syphilitic lesions develop. Most regimens used to treat gonorrhea also eradicate incubating syphilis. Despite extensive eradication campaigns, yaws remains widespread in the tropics. Pinta remains endemic in Central and South America, and endemic syphilis is present in certain regions of the Middle East. The pathogenic treponemes have many cross-reacting antigens, and untreated infection is believed to confer partial protection against the other treponemal diseases. In areas in which yaws is endemic, the incidence of syphilis is low. After effective campaigns to eradicate yaws, the incidence of syphilis eventually increases. Similar epidemiologic observations have been made after the local eradication of pinta and endemic syphilis.

**Diagnosis**

Definitive diagnosis of syphilis is complicated by the inability to cultivate *T. pallidum* subsp. pallidum in vitro. Clinical manifestations, demonstration of treponemes in lesion material, and serologic reactions are used for diagnosis. In many cases, clinical manifestations are highly characteristic. If manifestations include one or more
cutaneous exudative lesions, motile treponemes can often be visualized within lesion exudate by dark-field microscopy.

Serologic tests are a mainstay of syphilis diagnosis. They are the only means of identifying asymptptomatically infected individuals. More than 200 serologic tests have been developed over the years and fall into two general categories: (1) “nontreponemal” tests, which measure antibodies directed against lipid antigens, principally cardiolipin, thought to be derived from host tissues and (2) “treponemal,” which detect antibodies directed against protein constituents of *T. pallidum* subsp *pallidum*. Examples of the former are the Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) tests; examples of the latter are the Fluorescent *T. pallidum* Antibody-Absorption (FTA-ABS) and Microhemagglutination for *T. pallidum* (MHA-Tp) tests. Both treponemal and nontreponemal serological tests have been highly standardized by the Centers for Disease Control and Prevention (CDC). The sensitivity of the nontreponemal and treponemal tests varies with the stage of the disease. The results of nontreponemal tests usually parallel the extent of infection; titers tend to be highest during secondary syphilis and subside during subclinical infection (latency) or following antibiotic therapy. The treponemal tests often remain reactive for life.

Two terms relevant to syphilis serodiagnostic testing are sensitivity and specificity. The perfect test, not yet developed, would detect 100 percent of the treponemal infections and would be nonreactive in all other diseases. Sensitivity refers to the ability to detect the tested variable, in this case syphilis. A false-negative occurs when serum from a syphilitic patient fails to react. Specificity refers to the ability to recognize when the variable is not present (i.e., to exclude syphilis in nonsyphilitic patients). A false-positive occurs when serum from a nonsyphilitic patient reacts positively. In general, treponemal tests are more sensitive and more specific than the nontreponemal tests. However, mathematical models have shown that maximal sensitivity and specificity are achieved if patients are screened with a nontreponemal test and positive sera confirmed by a treponemal test. A number of clinical conditions may cause false-positive nontreponemal tests. These include leprosy, tuberculosis, malaria, infectious mononucleosis, collagen disorders, systemic lupus erythematosus, rheumatoid arthritis, pregnancy, and drug abuse. Individuals with false-positive nontreponemal tests are identified by virtue of the fact that their treponemal tests are nonreactive.

Congenital syphilis is difficult to diagnose in asymptptomatically infected neonates because maternal antibodies (IgG) which pass through the placenta and enter the fetal circulation cause reactivity in both nontreponemal and treponemal tests. In uninfected infants, such maternal antibodies disappear by 3 months. Because of the presence of maternal antibodies in the newborn, quantitative VDRL or RPR tests should be performed monthly.
over the first 6 months. If the titer increases or stabilizes and does not decrease, congenital syphilis is indicated and the baby should be treated accordingly.

Control

Table 36-2 Effective and Ineffective Preventive Measures against Syphilis

The current worldwide prevalence of syphilis emphasizes the need for continued preventive measures and strategies. Unfortunately, effective measures are limited (Table 36-2). Short of abstinence, the condom remains the method of choice for prevention of sexual transmission. Topical application of antibiotics, chemicals, creams, or lotions and thorough washing with soap and water after sexual contact are highly ineffective. A vaccine appears to be the only hope for future control of syphilis. Despite intense research in this area, only limited progress has been made. Two other control measures are important. The first is to educate people about the early clinical manifestations of primary syphilis, so that they can seek treatment before infecting others. The second, for which epidemiology programs have been established, is to trace contacts of syphilitic patients; these contacts are then treated prophylactically before onset of clinical manifestations.

Penicillin remains the drug of choice for treating syphilis. Penicillin resistance has not yet emerged, unlike the situation for gonorrhea. In non-penicillin-allergic patients without central nervous system involvement, infection is usually treated with benzathine penicillin G, a long-acting penicillin preparation which produces treponemicidal levels in serum for up to ten days. Patients with central nervous system involvement (neurosyphilis) should receive high dose intravenous penicillin for 10 to 14 days. Penicillin-allergic, nonpregnant patients with early syphilis can be treated with tetracycline. Penicillin-allergic, pregnant patients and patients with neurosyphilis must be desensitized to penicillin because of the lack of effective alternative therapies. A Jarisch-Herxheimer reaction occasionally follows treatment of secondary syphilis. This systemic reaction is associated with the rapid death of treponemes. Between 2 and 12 hours after antibiotic therapy, headache, malaise, slight fever, chills, muscle aches, and intensification of syphilitic lesions occur. These manifestations
resolve in fewer than 12 hours. This benign reaction requires no prophylactic measures and, importantly, indicates effective therapy.

Both nontreponemal and treponemal antibodies remain detectable for long periods, even after effective treatment. The recommended procedure for verifying a cure involves tracking the nontreponemal antibodies until they are undetectable or reach a stable, low titer. Nontreponemal tests in patients with primary and secondary syphilis should be nonreactive within 6 to 12 months and 12 to 18 months after treatment, respectively. A cure may be difficult to verify in patients with long standing infection; in these patients, nontreponemal and treponemal antibodies may be detected years after treatment.

Other Treponematoses

Yaws

Yaws, caused by T pallidum subsp pertenue, predominates in the tropical areas of Africa, South America, India, Indonesia, and the Pacific Islands. Its highly contagious nature is indicated by an estimated 50 million cases worldwide. Transmission occurs through nonsexual human-to-human contact. Most cases are in children and adolescents. In endemic areas, 75 percent of the population contract yaws before reaching 20 years of age.

The primary lesion, or mother yaw, develops within 2 to 4 weeks at the site of skin entry as a painless erythematous papule or group of papules. Lesions enlarge and ulcerate, exuding a serous fluid with a bloody tinge that is swarming with organisms. These lesions heal within one to several months, leaving an atrophic, depressed scar. The treponemes disseminate, and, within 1 to 12 months, secondary lesions evolve that are quite similar to the mother yaw. Crops of these lesions develop initially on the face and moist areas of the body and then spread to the trunk and arms. Infection of the soles and palms is characteristic, as it is in syphilis. Elevated granulomatous papules may enlarge to a diameter of 5 cm and then heal, leaving areas of depigmentation. Successive crops of these lesions occur for many months. Histopathology is similar to that observed in syphilis, with minimal vascular changes and no endothelial cell proliferation. The late destructive stage, sometimes called tertiary yaws, involves treponemal infection of the bones and periosteum, especially the long bones of legs and forearms, and the bones of the feet and hands. Pathologic findings are similar to those seen in the tertiary stage of syphilis. Highly destructive gummas also may occur within the bones and soft tissues. Diagnosis depends on geographic location, clinical manifestations, demonstration of treponemes within exudates, and positive serology. In areas in which syphilis and yaws coexist, definitive diagnosis is unnecessary since both can be readily eradicated by penicillin.
Pinta

Pinta, caused by T. carateum, is endemic in the tropical areas of Central and South America. Recently, the total number of cases has been estimated at 500,000. Transmission occurs through human-to-human nonsexual contact. Most cases initially occur in children and adolescents. The primary lesion develops within 2 to 6 months at the site of skin entry as a flat, erythematous papule or group of papules. These lesions and occasional satellite lesions enlarge over several months and produce plaques with scaly surfaces. Secondary lesions occur after 2 to 18 months or longer and involve ulceration and hyperchromic patches. Typically the hands, feet, and scalp are infected. Late stages of pinta involve patches of hyperchromia and achromia, irregular acanthosis, and epidermal atrophy. Lesions heal initially with hyperpigmentation but, over time, become depigmented and hyperkeratotic due to scarring. The treponemes disturb normal melanin pigmentation and produce the characteristic skin manifestations within 2 to 5 years. The different stages of this disease are not clearly separated, and overlap of manifestations is common. Diagnosis relies on geographic location, clinical manifestations, demonstration of organisms in exudates, and positive serology. Penicillin is the antibiotic of choice. Contrary to syphilis and yaws, in which the lesions heal rapidly following antibiotic treatment, pinta lesions may require 1 year to fully resolve. After primary or early secondary manifestations, skin pigmentation returns to normal. In later manifestations, however, pigmentation remains altered permanently.

Endemic Syphilis

Endemic syphilis, caused by T. pallidum subsp. endemicum, is found in the desert areas of the Middle East and Central and South Africa. Transmission is through human-to-human nonsexual contact. Most cases are contracted by children past the age of two years. Transmission of endemic syphilis, like that of yaws and pinta, is associated with poor hygiene. Clinical manifestations can be quite similar to those of syphilis and yaws. The site of entry is usually the mucous membranes of the eyes and mouth. The primary lesion, a small papule, is detectable in only one percent of cases. After two to three months, secondary lesions or plaques develop in mucous membranes, skin, muscles, and bone. These oozing papules erode, harden, become condylomatous, and eventually heal. Clinical manifestations are then not apparent for 5 to 15 years (latency). Late endemic syphilis develops in the skin and skeletal system. Skin lesions may be superficial, nodular, or tuberous, or they may be highly destructive, deep gummas. Destructive bone lesions frequently localize in the tibia. Diagnosis depends on geographic location, clinical manifestations, treponemes in the exudate, and positive serology. Penicillin eradicates endemic syphilis.