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Author(s): George P. Schmid
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Epidemiology and Clinical Similarities of Human Spirochetal Diseases

George P. Schmid

From the Division of Sexually Transmitted Diseases, Center for Prevention Services, Centers for Disease Control, Atlanta, Georgia

Lyme disease, first identified in 1975, is the most recently recognized of the seven human spirochetal diseases; the evolving clinical picture of Lyme disease indicates it shares many features with the other diseases. These similarities are striking in view of the diverse epidemiology of the seven diseases, which are caused by *Treponema* species (spread by human-to-human contact) or *Leptospira* or *Borrelia* species (zoonoses). These similarities include the following: (*1*) skin or mucous membrane as portal of entry; (*2*) spirochetemia early in the course of disease, with wide dissemination through tissue and body fluid; and (*3*) one or more subsequent stages of disease, often with intervening latent periods. Lyme disease shares with many spirochetal diseases a tropism for skin and neurologic and cardiovascular manifestations, whereas chronic arthritis is unique to Lyme disease. These similarities and dissimilarities offer opportunities to discover which properties unique to the pathogenic spirochetes are responsible for clinical manifestations and suggest that certain clinical features of patients with spirochetal diseases other than Lyme disease may someday be recognized in patients with Lyme disease.

Spirochetes are unusual bacteria that are widely distributed in nature. Some are free-living, while others colonize higher living organisms, ranging from molluscs and termites to humans. Other spirochetes, however, are pathogenic. Although the factors that make some spirochetes pathogenic and others not are largely unknown, the basic structure is the same (figure 1). All spirochetes have a spiral shape with two or more axial filaments attached by basal knobs to pores at the end of the cells; the fibrils of most species overlap near the middle of the cell. The filaments lie between the central protoplasmic cylinder, which contains cytoplasm and nuclear material and is bounded by a cell wall, and an outer envelope. Although contained by the cell envelope, the axial filaments, whose structure is similar to that of flagella of other bacteria, are probably responsible for cell motion [1]. Cellular motion persists at viscosities that would block the flagellar motion of other bacteria [1, 2], a factor that may be important in pathogenesis. It is thought this might enable spirochetes to remain motile in environments (such as intercellular spaces) that immobilize other bacteria.

Within the order Spirochaetales are two families: Spirochaetaceae and Leptospiraceae. Four genera belong to Spirochaetaceae and two to Leptospiraceae.

Please address request for reprints to Dr. George P. Schmid, Division of Sexually Transmitted Diseases (E02), Center for Prevention Services, Centers for Disease Control, Atlanta, Georgia 30333.

The family and genus taxonomy of spirochetes is based largely upon differences in structure or growth characteristics, while within genera species differentiation is based on such characteristics as disease manifestations (among treponemes), animal or vector tropism (among borreliae), and serologic relationship (among leptospires). Recently, DNA hybridization techniques have proven useful in characterizing some spirochetes and will undoubtedly provide a more satisfying taxonomic structure in the future.

Of the six genera, three—*Treponema*, *Borrelia*, and *Leptospira*—contain organisms pathogenic for humans; these cause seven diseases (table 1). Members of *Treponema* cause four diseases. None of the pathogenic treponemes are morphologically distinguishable; all cause serologic changes that are indistinguishable by standard syphilis serologic tests (either nontreponemal tests, such as the rapid plasma reagin [RPR] or the Venereal Diseases Research Laboratory [VDRL] test; or treponemal tests, such as the fluorescent treponemal antibody, absorbed [FTA-ABS] or the microhemagglutination-*Treponema pallidum* [MHA-TP] test), and none have been reliably propagated on artificial media. Members of *Leptospira* cause leptospirosis. The leptospires that are pathogenic have traditionally been grouped taxonomically into one species, *Leptospira interrogans*, although recent DNA homology studies indicate that there are multiple species [3]. Over 240 serovars of *L. interrogans* have been described, but the illnesses

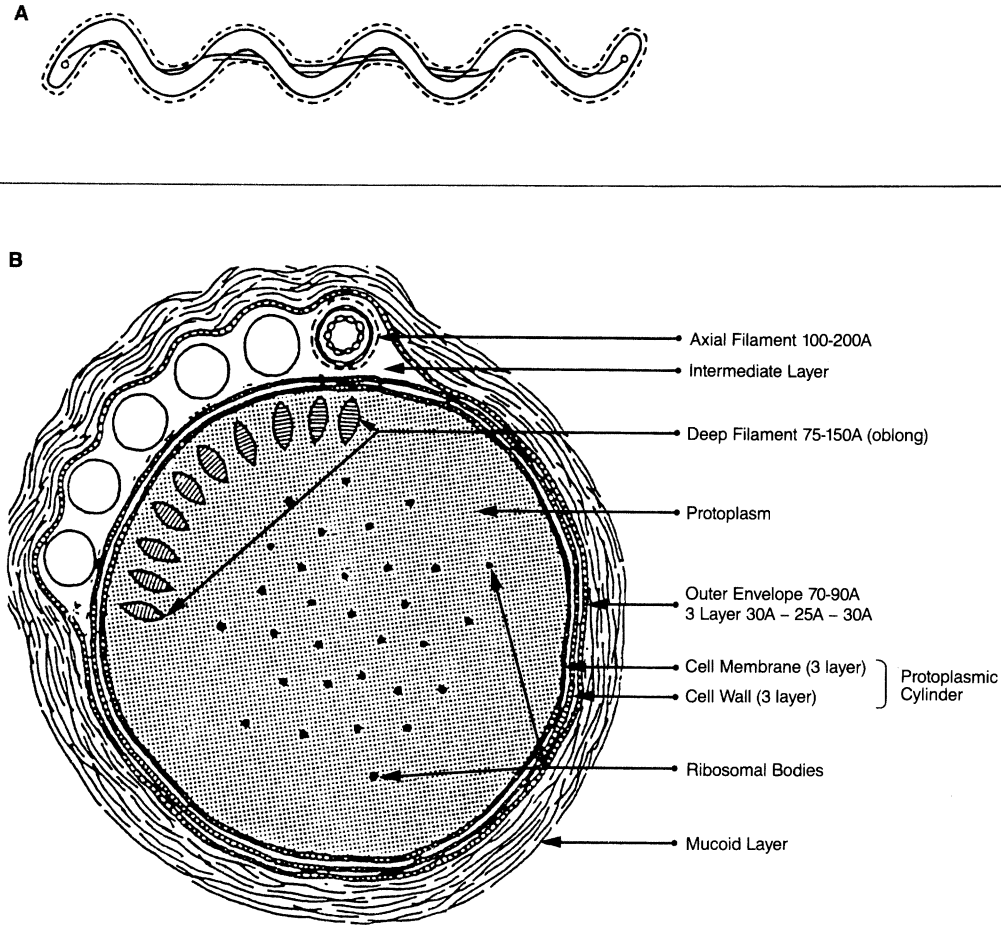

Figure 1. (*A*) Diagram of a spirochete with one axial filament [40]. (*B*) Cross-section of spirochete with six axial filaments [41].

caused by these serotypes differ principally in degree of clinical severity. Members of *Borrelia* cause two dissimilar diseases, relapsing fever and Lyme disease. Many species of relapsing fever borreliae, currently differentiated primarily on the basis of their tropism for a louse or a tick vector, cause relapsing fever, while only one species—*Borrelia burgdorferi*—causes Lyme disease.

Table 1. Human spirochetal diseases and their etiologic agents.

Infecting organism	Disease
Treponema	
T. carateum	Pinta
T. pallidum subspecies *pertenue*	Yaws
T. pallidum subspecies *endemicum*	Syphilis, endemic (nonvenereal)
T. pallidum subspecies *pallidum*	Syphilis, venereal
Leptospira interrogans	Leptospirosis
Borrelia	
Borrelia species	Relapsing fever
B. burgdorferi	Lyme disease

Epidemiologically, spirochetal diseases follow one of two patterns. The treponemal diseases are a result of close skin-to-skin contact between humans, and there is no recognized animal reservoir of the treponemes that cause human disease. The remaining spirochetes (*Leptospira*, *Borrelia*) are zoonotic; that is, they have an animal reservoir in nature and infect humans via the direct or indirect contact of the latter with the animal reservoir.

Despite this marked epidemiologic difference, all the spirochetal diseases share remarkable similarities in their pathogenesis and resultant clinical manifestations. These similarities include a skin or mucous membrane portal of entry (often with a

resultant skin lesion that may centrifugally expand over time); spirochetemia early in the course of disease, with wide dissemination throughout tissues, and body fluids; and then one or more subsequent stages of disease, often with intervening latent periods. Illness such as this is found in few nonspirochetal diseases and suggests that the pathogenic spirochetes share relatively unique virulence characteristics.

Treponemal Infections

Three of the four treponemal diseases—pinta, yaws, and endemic syphilis—are collectively referred to as the nonvenereal treponematoses. They are not spread by sexual activity, and, hence, disease is not initially manifest in the genital area. The fourth treponemal disease, syphilis, is a venereal disease, and the initial manifestations occur in the genital area.

The inability to morphologically or genetically distinguish *Treponema pallidum* subspecies *pallidum*, *T. pallidum* subspecies *pertenue*, and *T. pallidum* subspecies *endemicum* has led to the hypothesis that they arose from a common ancestor; although *Treponema carateum* remains a separate species, it is included in the common ancestor theory [4, 5]. Presumably, an early treponeme (perhaps *T. carateum*) occurred in tropical areas and was spread by close, nonvenereal skin-to-skin transmission; from this treponeme, *T. pallidum* subspecies *pertenue* evolved. Transmission depended upon warm and often humid environmental conditions, as the treponemes in open skin lesions thrived in these conditions. In colder and less humid areas (encountered either as people migrated or the organism adapted), the transmission of the treponemes became less efficient, but the treponeme found that it could survive well in warm and humid oral lesions (*T. pallidum* subspecies *endemicum*), and thus transmission occurred through oral secretions on shared, contaminated drinking and eating vessels. With syphilis, the proper conditions were met by the warmth and humidity in the genital area (alternatively, a genetic mutation may have occurred in the organism causing endemic syphilis). Because cross-immunity occurs among the treponemes, syphilis began to be the dominant treponemal infection when hygienic conditions improved or more clothing began to be worn (covering sores) and yaws, pinta, and endemic syphilis did not develop in childhood to afford protective immunity.

Pinta. Found only in the Western Hemisphere, pinta was a prevalent disease in semi-arid areas of Brazil, Colombia, Cuba, southern Mexico, and Venezuela, with scattered foci in other Central and South American countries and the Caribbean. As late as the early 1950s, 2% of the population of Mexico and Colombia were thought to be infected [6]. Currently, pinta is found only in remote parts of Mexico and northern South America [7].

Pinta is alone among the spirochetal diseases in having only skin manifestations, and it appears to be the least contagious. Pinta is also unusual among the nonvenereal treponematoses in affecting individuals of all ages—not primarily children (although the majority of the infected are children or adolescents). The first manifestation of illness, a primary papule or plaque at the site of inoculation, appears 2–3 weeks after inoculation (figure 2). The skin lesion enlarges by local extension and coalescence, and during this stage spirochetemia probably occurs.

Three to 9 months after inoculation, secondary skin lesions—called pintids—appear on the body and also enlarge in a centrifugal manner; repetitive crops may occur over years, causing pinta to be infectious for years—far longer than the other treponemal diseases [4]. Both the lesions of primary and secondary pinta undergo pigmentary changes, becoming copper-colored and then gray or blue. With the onset of "tertiary" pinta 1–3 years later, skin lesions become atrophic and depigmented and may be difficult to differentiate from vitiligo. Treponemes are easily found in the infectious primary and secondary lesions. With onset of "tertiary" pinta, treponemes become difficult to find; the lesions tend to be dry and, hence, are not a ready source of transmission (probably the reason pinta is the least infectious of the treponemal diseases). It has been suggested that vectors may play a role [8]. Systemic symptoms do not occur.

Yaws. Yaws is a globally important disease and had a significant worldwide tropical distribution before 1960. In the early 1950s, it was thought that there were 50 million cases of yaws in the world, with at least 25 million in tropical Africa [6]. In the 1950s and 1960s, however, the World Health Organization sponsored yaws eradication programs that used the recently developed, single-dose, repository penicillin regimens such as PAM (procaine penicillin G in oil with aluminum stearate) or benzathine penicillin. These programs became priorities in many nations and achieved great success by seeking out and

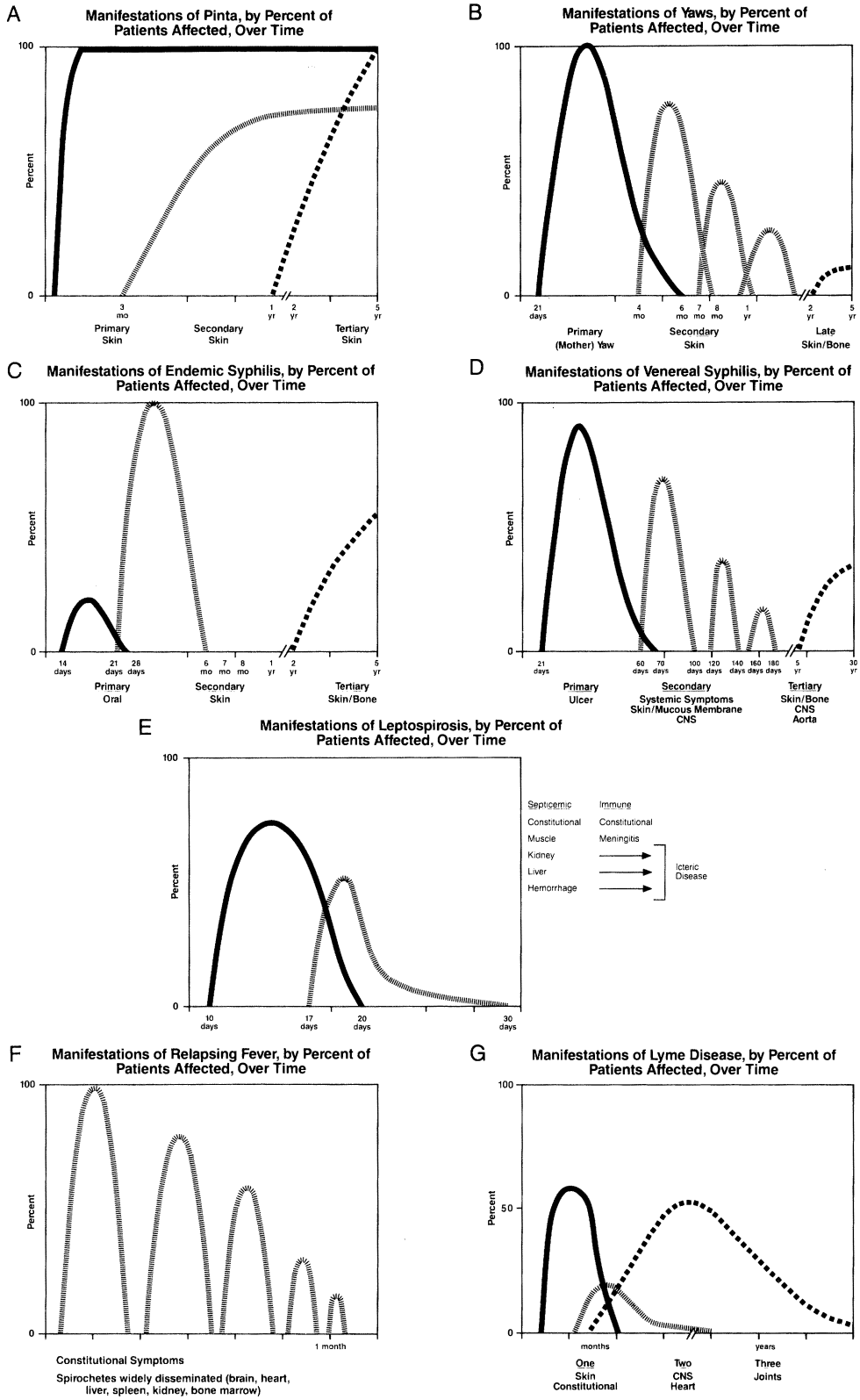

Figure 2. Clinical courses of seven human spirochetal diseases (by percentage of persons affected), divided into clinical stages of disease with major organ involvement of each stage noted: (*A*) pinta, (*B*) yaws, (*C*) endemic syphilis, (*D*) syphilis, (*E*) leptospirosis, (*F*) relapsing fever, and (*G*) Lyme disease.

treating both those with active cases and asymptomatic household contacts [9]. By 1980, yaws was eliminated as a significant health problem in many countries but is now becoming resurgent in some areas as control programs have lost effectiveness [10]. Currently, significant numbers of cases are found in northern South America and the Caribbean, equatorial Africa, Micronesia, and Burma [7]. Yaws remains a disease of rural areas and one where infection remains common under crowded and primitive living conditions [6].

Yaws affects children 2–15 years of age, who, together with those with latent cases between primary and secondary stages, serve as a reservoir of infection. Infection is spread by skin-to-skin contact from primary or secondary yaws lesions. The initial manifestation of yaws is a primary skin lesion, called the "mother yaw," which develops a mean of 21 days after inoculation (figure 2). This lesion is a papilloma or ulcerated papilloma. The mother yaw persists 3–6 months, and spirochetemia occurs during this period. Shortly after (or occasionally before) the lesion heals, secondary skin lesions similar to those of the primary lesion appear on the body, and these persist for several months; multiple crops may occur for up to 5 years after the initial infection. The large majority of persons then have no stigmata of disease, although latency may continue, as about 10% of individuals subsequently develop late (or tertiary) yaws. This stage is characterized by nodular or ulcerated nodular lesions of the skin, sometimes with underlying periostitis leading to bony destruction and deformities. Rhinopharyngitis mutilans, a disfiguring gummatous ulceration of the nasal area, is particularly characteristic. Treponemes are easily found in the primary or secondary skin lesions but not in the late stages. As in pinta, systemic symptoms do not occur.

Neurologic or aortic complications in late yaws are thought not to occur. The issue has not been definitively settled, however, since some workers have described neurologic abnormalities in cases of late yaws [11].

Endemic syphilis. Nonvenereal, or endemic, syphilis is an uncommon infection caused by *T. pallidum* subspecies *endemicum*. Although endemic and venereal syphilis share a name, the diseases they cause are quite different; in endemic syphilis the late lesions resemble those of yaws or late benign syphilis and no aortic or neurologic abnormalities are found.

At one time, endemic syphilis was widespread and was the only nonvenereal treponematosis that had a significant distribution outside the area between the Tropic of Cancer and the Tropic of Capricorn; this distribution did not include the Western Hemisphere [7]. Unlike the areas where pinta and yaws occur, these endemic areas are arid and dry. Endemic syphilis was also a target of eradication programs because, although the prevalence of active disease in endemic areas was estimated to be only 3%–5% (less than that of yaws), the rate of tertiary disease is higher in endemic syphilis than in yaws, although not as severe [5]. As a result of these programs, the distribution of endemic syphilis is now restricted to parts of the Arabian peninsula and Africa [12].

As with yaws, endemic syphilis affects children. The initial manifestations of endemic syphilis are thought to be shallow, painless ulcers on the mucous membranes of the mouth (figure 2). This suggests that the disease is spread by saliva, and shared eating utensils have been suggested as the principal mode of spread. However, the oral lesions are often not noticed or do not occur, and the initial manifestation of disease is often disseminated lesions of the mucous membranes or intertriginous areas (lesions similar to the condylomata lata of venereal syphilis) or a disseminated skin rash. Subsequently, a latent period occurs until tertiary disease—with gummata of the nasopharynx, skin, or bone, similar to but less severe than those found in yaws—occurs in as many as 50% of cases.

Venereal syphilis. Venereal syphilis has worldwide distribution and is spread via sexual intercourse. In the United States 39,673 cases of primary or secondary syphilis occurred in fiscal year 1988 [13].

Treponema pallidum subspecies *pallidum* (and probably the other treponemes) is highly infectious, with a calculated ID_{50} for humans of $\leqslant 57$ organisms [14]. The initial lesion, which occurs a mean of 21 days following inoculation, is a painless ulcer that occurs most commonly on the genitalia (figure 2). The ulcer persists for 2–6 weeks before healing; spirochetemia is thought to occur early in the course of syphilis, even before the appearance of the ulcer.

After the ulcer heals (or occasionally while it is still present) many patients develop secondary syphilis, characterized by disseminated skin and mucous membrane lesions and systemic symptoms. The spinal fluid is infected in one-third of secondary cases, although only a small number of patients have symptoms referable to the CNS. This stage lasts 2–6 weeks. Relapses occur in about one-fourth of pa-

tients, usually in the first year. A small number of patients develop uveitis [15], hepatitis, and glomerulonephritis, the last being due to an immune-complex nephritis [16].

Beginning ~5 years after primary infection, tertiary syphilis develops in about one-third of cases. About 15% of patients develop late benign syphilis, with gummata of the skin, bone, or internal organs. Alternately, two organ systems are targets of tertiary syphilis: the CNS and the aorta. About 8% of patients develop CNS disease, which takes one of three forms. The first form, meningovascular syphilis, is an arteritis and commonly manifests itself as a seizure or stroke. The second, general paresis, is caused by direct invasion of the brain substance, and patients undergo personality changes and dementia. The third, tabes dorsalis, is a result of demyelination of the posterior columns and manifests as attacks of body pain that last several days (lightning pains)—perhaps similar to the pain experienced by persons with acrodermatitis chronica atrophicans—or a loss of proprioception, resulting in a broad-based gait; impotence and bladder dysfunction are also common. Syphilitic aortitis occurs in ~10% of patients, with degeneration of the wall of the aorta. Syphilitic myocarditis has been argumentatively described [17, 18].

Leptospira and Borrelia Infections

The remaining spirochetal diseases are zoonoses. Their epidemiology differs, however. Leptospirosis affects many mammals, including humans. It has as its reservoir animals, often rodents, that excrete leptospires in the urine as a result of a chronic infection in the distal tubule. Humans become infected as a result of direct or indirect contact with the infected urine. Relapsing fever is a disease that also affects animals but that has as its vector human lice (in the case of louse-borne relapsing fever [LBRF]) or ticks (in the case of tick-borne relapsing fever [TBRF]).

Leptospirosis. Leptospirosis has a worldwide distribution but is most common in developing countries and warm climates, where contact with animals or water contaminated with their urine is most likely to occur. Infection occurs via direct contact with animal blood or urine (e.g., farmers or abattoir workers) or, more commonly, via indirect contact with contaminated water (e.g., workers in rice paddies or swimmers). In the United States, leptospirosis is most common in Hawaii, where it is an important occupational hazard of taro farming, which entails wading in shallow water. In the United States, ~100 cases of leptospirosis are reported each year [19].

Leptospires enter the body through mucous membranes or abrasions. Clinical illness begins abruptly 2–20 days later with the abrupt onset of fever, headache, and myalgia (figure 2). These symptoms mark the beginning of the septicemic stage, during which spirochetemia occurs and leptospires can be found in the blood, CSF, kidneys, and other organs [20]. Although a variety of skin rashes have been described in the septicemic stage, there is no consistent appearance of or pattern to the rashes. Thus, it seems unlikely that direct skin invasion by leptospires causes the rash, although this has been reported [21].

The septicemic stage of leptospirosis lasts 4–7 days. Direct damage to the body by the leptospires is the basis of initial illness. Following the appearance of antibody, these symptoms subside as the leptospires disappear from all organs except the aqueous humor and kidneys, which are protected sites. Following a quiescent period of 1–3 days, the second stage of illness—the immune stage—begins, and illness is thought to be related to the patient's immune response to the leptospires. The subsequent course of illness depends upon which of two clinical syndromes develops: anicteric leptospirosis (90% of cases) or icteric leptospirosis (10% of cases).

In anicteric leptospirosis, the immune stage is generally of lesser duration and severity than the septicemic stage. The most important features of the immune stage are meningitis, which clinically resembles aseptic meningitis, and leptospiruria; fever may not be prominent. Commonly, in anicteric leptospirosis, the septicemic phase is mild and patients seek medical attention with the symptoms of aseptic meningitis and no clear preceding illness. Conversely, not all patients with a septicemic stage develop a clinically apparent immune stage.

Other symptoms may develop during the immune stage. Nonmeningitic neurologic manifestations, including encephalitis, nerve palsies, and myelitis, may last for weeks to months. Uveitis typically appears late, even months, after the onset of disease.

Unlike the relatively mild illness of anicteric leptospirosis, the illness of icteric leptospirosis results in death in up to 10% of cases. Its hallmarks are jaundice and azotemia, which begin in the latter part of the septicemic phase and tend to obscure the biphasic nature of the illness. Cardiovascular involve-

ment, often with myocarditis, may be manifested by shock. There is a hemorrhagic diathesis in icteric leptospirosis, and death occurs from hemorrhage, cardiovascular collapse, or renal failure.

Relapsing fever. Relapsing fever is divided into LBRF, caused by *Borrelia recurrentis*, and TBRF, caused by any of the other relapsing fever borreliae. Because borreliae are difficult to grow, only limited phenotypic and genotypic work has been done to categorize them [22]. The difficulty in identifying *Borrelia* species by usual bacteriologic methods has led to a categorization of relapsing fever borreliae by the agent-vector relationship, such that, for example, *Borrelia* that infect *Ornithodoros turicata* ticks are speciated as *Borrelia turicatae*. Recent studies of DNA homology suggest that these different species are closely related and that this categorization may soon be challenged. Relapsing fever borreliae, unlike *Borrelia burgdorferi*, undergo antigenic phase variations during the clinical course of illness.

Although LBRF has been reported from all the inhabited continents except Australia, the only current focus of disease is in Africa, principally in Ethiopia. The only host for *B. recurrentis* is humans. Because lice live for only 3 weeks and transovarial passage of *B. recurrentis* does not occur, close contact between infected and susceptible persons is required for propagation of infection. Thus, LBRF often occurs in epidemic fashion in times of disaster, when housing is crowded and hygienic conditions are poor.

TBRF has also been reported from all the inhabited continents except Australia (where Lyme disease has occurred, although the vector is unknown [23]). In the United States, two species of ticks transmit *Borrelia* to humans: *Ornithodoros hermsi* with its agent, *B. hermsii*, and *O. turicata* with its agent, *B. turicatae*; *Ornithodoros parkeri* with its agent, *B. parkeri*, may rarely transmit infection. These ticks have ranges west of the Mississippi River. One case of probable TBRF occurred in Ohio in 1975, however, but the vector is unknown [24].

Infected ticks transmit infection through salivary secretions, transmit borreliae transovarially, and can remain infective for many years without feeding. These tick vectors are soft ticks that are active at night, feed quickly (in 10–20 minutes), and whose bite is relatively painless; hence, the bite is often unnoticed. Since TBRF depends upon human intrusion into tick-infested areas, cases are sporadic or limited to small outbreaks.

Differences in clinical illness caused by the various *Borrelia* species are primarily differences in degree of severity; LBRF is more severe than TBRF. After an incubation period of ~5–9 days, spirochetes invade the bloodstream and illness begins abruptly with fever, headache, and myalgia (figure 2) [25, 26]. The intensity of headache, along with Kernig or Brudzinski signs, suggest CNS infection, and spirochetes have been found in the CSF and brain of humans [27, 28]; the brain is a favored target in animals [28]. The first attack lasts 3–6 days and ends by crisis, with an abrupt drop in temperature followed by prostration and hypotension. If death occurs, it generally does so at this time as a result of myocardial collapse; myocarditis occurs and spirochetes may be seen in the myocardium and within cardiac vessels [27]. A petechial or macular rash occurs in up to one-fourth of patients, usually at the first remission, and spirochetes have been visualized in skin biopsies [29]. Zero to three relapses then occur in LBRF and three to five in TBRF.

Relapses are due to the ability of borreliae to change antigenic structure and escape lysis by antibody and phagocytosis by leukocytes, which are responsible for the clearing of spirochetes from the blood and improvement between relapses. Traditionally, it has been thought that spirochetes in protected sites (liver, spleen, bone marrow, CNS) underwent this antigenic change and caused a relapse when they reached a critical level and reentered the bloodstream. More recent animal work suggests that low-level spirochetemia may be continuous and that relapses occur when the new serotypes reach a critical level [22].

Lyme disease. *B. burgdorferi*, which can be differentiated from relapsing fever borreliae both phenotypically and structurally, is also separable from them by DNA homology [30].

In the United States, the only recognized vectors of Lyme disease are ticks (*Ixodes dammini*, *Ixodes pacificus*, and *Amblyomma americanum*). *B. burgdorferi* has been recognized in additional tick species, however, as well as in hematophagous insects (deer flies, horse flies, and mosquitoes), making these potential vectors of Lyme disease [31]. Consistent with this theory, the geographic distribution of reported cases of Lyme disease does not neatly correspond to the distribution of the recognized vectors.

Lyme disease variably begins with constitutional symptoms (fever, headache, myalgia) and erythema chronicum migrans (ECM) (figure 2), which appear 3–32 days after a tick bite [32]. Not all patients, how-

ever, have constitutional symptoms or ECM. ECM persists for ~3 weeks, during which time lesions increase in size; multiple lesions may occur. These multiple lesions, as well as many manifestations of subsequent stages of disease, undoubtedly result from spirochetal dissemination to target organs.

While the skin lesion is present (or shortly thereafter), the second stage of disease, characterized by cardiac or neurologic manifestations, begins. About 8% of patients develop various degrees of heart blockage, enlargement, or failure. Although the etiology of these manifestations is uncertain, spirochetes have been found in myocardial tissue, where a mononuclear cell infiltrate occurs [33]. Many patients complain of a headache and stiff neck, suggesting that *B. burgdorferi* commonly enters the CNS, even though results of examination of the CSF are normal early in the course of disease. More specific neurologic symptoms—most commonly meningitis or encephalitis with CSF pleocytosis, cranial nerve palsies, and peripheral neuropathies—occur in 15% of patients. *B. burgdorferi* has been isolated from CSF [34].

Arthritis, the third stage, occurs in 60% of cases and typically begins when other symptoms are present. The arthritis is initially intermittent, migrating, and without joint swelling, but after several months it tends to affect large joints and be accompanied by swelling. In most people with arthritis, attacks cease after months to a few years, but ~10% of patients develop chronic arthritis. The chronic arthritis clinically and pathologically resembles rheumatoid arthritis; spirochetes have been visualized in synovial biopsies from such patients [35].

Other manifestations that have been reported include uveitis [36], a disseminated skin rash resembling secondary syphilis [37], and possibly renal tubular excretion of spirochetes [38]. In Europe two chronic diseases of the skin, acrodermatitis chronica atrophicans and lymphadenosis benigna cutis, both of which are responsive to antimicrobial therapy, have been associated with ECM. Spirochetes have been recovered from skin lesions of patients with acrodermatitis chronica atrophicans years after onset [39].

Clinical Similarity of Spirochetal Diseases

While there is epidemiologic diversity among the spirochetal diseases, most striking is the similar overall pattern of these diseases: skin or mucous membrane exposure, spirochetemia preceding or coincident with the onset of clinical illness, dissemination of spirochetes to body organs, and then latent periods of various duration between one or more subsequent stages of disease. In most of the diseases, organisms are able to persist in the body for extended periods, and late manifestations of disease appear to be due to the presence of viable spirochetes. The finding of viable spirochetes in acrodermatitis chronica atrophicans and the response of chronic Lyme arthritis to antimicrobial agents suggest that the same event occurs in Lyme disease.

The tropism of Lyme disease for the skin, CNS, and the heart has counterparts in other spirochetal diseases, an observation that suggests similar pathophysiologic processes. Skin lesions occur in pinta, yaws, endemic syphilis, syphilis, and Lyme disease; in four of these—pinta, endemic syphilis, syphilis, and Lyme disease—centrifugally spreading skin lesions occur (in endemic and venereal syphilis, these occur in late benign syphilis). Late atrophy of the skin occurs in yaws, possibly in endemic syphilis, syphilis, and Lyme disease. CNS disease occurs in syphilis, possibly yaws, leptospirosis, relapsing fever, and Lyme disease. In each, spirochetes enter the CSF, often with minimal or no symptoms. Peripheral nerve dysfunction occurs in leptospirosis, relapsing fever, and Lyme disease, while tabes dorsalis occurs in syphilis. Myocardial disease, probably with direct invasion of the myocardium, is found in leptospirosis, relapsing fever, possibly syphilis, and Lyme disease. Constitutional symptoms of fever, headache, and myalgia occur commonly in secondary syphilis, leptospirosis, relapsing fever, and Lyme disease. Jarisch-Herxheimer reactions, uncommon in other microbiologic illnesses, commonly occur in these same four diseases. Chronic arthritis, however, occurs uniquely in Lyme disease (with the possible exception of syphilis).

The similarities and dissimilarities in pathophysiology and disease manifestations of spirochetal diseases offer opportunities to discover what properties unique to *B. burgdorferi* or to the other pathogenic spirochetes are responsible for these manifestations. Similarly, clinical features characteristic of other spirochetal illnesses but not yet associated with Lyme disease may, in the future, be recognized in patients with Lyme disease.

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