MEDICAL PROGRESS

LYME DISEASE

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LYME disease was described as a separate entity in 1977 because of a geographic clustering of children in Lyme, Conn., who were thought to have juvenile rheumatoid arthritis.[1] The rural setting of the case clusters and the identification of erythema migrans (Fig. 1) as a feature of the illness suggested that the disorder was transmitted by an arthropod. It soon became apparent that Lyme disease was a multisystem illness that affected primarily the skin, nervous system, heart, and joints.[2] Epidemiologic studies of patients with erythema migrans implicated certain ixodes ticks as vectors of the disease.[3-5] An important clue to the cause of the illness came with the observation that patients with erythema migrans who were treated with penicillin had a better outcome than untreated patients.[6]

In addition to providing clues about the cause of the illness, erythema migrans linked Lyme disease in the United States with certain syndromes in Europe. Early in this century, Afzelius in Sweden[7] and Lipschütz in Austria[8] described a characteristic expanding skin lesion, called erythema migrans or erythema chronicum migrans, which they attributed to *I. ricinus* tick bites. Many years later, it was recognized that erythema migrans could be followed by a chronic skin disease, acrodermatitis chronica atrophicans, which had already been described as a separate entity.[9] In the 1940s, Bannwarth defined a syndrome, preceded in a few cases by an erythema, that consisted of radicular pain followed by chronic lymphocytic meningitis and sometimes cranial or peripheral neuritis.[10] The syndrome has been called tick-borne meningopolyneuritis, lymphocytic meningoradiculitis, and chronic lymphocytic meningitis, as well as Bannwarth's syndrome. In 1948, Lennhoff described spirochete-like structures in skin specimens in several dermatologic entities, including erythema migrans.[11] The report led to the use of penicillin to treat this skin lesion in Europe.[12]

These various syndromes were brought together conclusively in 1982, when Burgdorfer and Barbour isolated a previously unrecognized spirochete, now called *Borrelia burgdorferi*,[13] from *I. dammini* ticks.[14] The spirochete was then recovered from patients with Lyme disease in the United States[15,16] and from those with erythema migrans, Bannwarth's syndrome, or acrodermatitis in Europe[17-19]; the patients' immune responses were linked conclusively with this organism. Although there are regional variations, the basic outlines of this disorder are similar worldwide, and its most common name is Lyme disease or Lyme borreliosis. Clinically, this borrelial infection is most like syphilis in its multisystem involvement, occurrence in stages, and mimicry of other diseases. Although many of its facets remain to be elucidated, reports about this borreliosis have increased dramatically in the past several years. This report reviews current studies of the causation, vector, epidemiology, clinical manifestations, pathogenesis, diagnosis, and treatment of this protean infection.

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CAUSATION

Borrelia species, along with the leptospira and treponema, belong to the eubacterial phylum of spirochetes.[20] Like all spirochetes, the borrelia species have a protoplasmic cylinder that is surrounded first by a cell membrane, then by flagella, and finally by an outer membrane, that is only loosely associated with the underlying structures.[20] The borrelia are longer and more loosely coiled than the other spirochetes, and their outer membrane is unique in that the genes encoding it are located on plasmids, an arrangement that may be advantageous to the organism in making antigenic changes in these proteins.[20] The entire outer membrane can move to one end of the cylinder, a phenomenon called capping or patching that may be important in cell adherence.[21]

The borrelia species are fastidious, microaerophilic bacteria that grow best at 33°C in a complex, liquid medium called Barbour–Stoenner–Kelly medium.[22] In one study, *B. burgdorferi* was also shown to grow in colonies on this medium that had been solidified with 1.3 percent agarose.[23] It is relatively easy to obtain a primary isolate of this spirochete from ticks, but it is difficult to do so from patients.[15,16] As compared with most bacteria, borrelia grow quite slowly; each spirochete elongates for 12 to 24 hours and then divides into two cells.[22] *B. burgdorferi* loses pathogenicity in culture, usually after 10 to 15 passages, and after that time the organisms are no longer infectious.[24]

Of the borrelia species, *B. burgdorferi* is the longest (20 to 30 μm) and narrowest (0.2 to 0.3 μm), and it has fewer flagella (7 to 11).[25] Its ratio of guanine to cytosine is between 28 and 30.5 percent, and it is 31 to 59 percent DNA homologous with other borrelia.[26] *B. burgdorferi* contains at least 30 different proteins,[27,28] but the functions of only a few of them are currently known. These include the two major outer-surface proteins, a highly charged basic protein called outer-surface protein A (30 to 32 kd)[21,29] and another called outer-surface protein B (34 to 36 kd).[30] The 66-kd polypeptide is also thought to be located on the outer

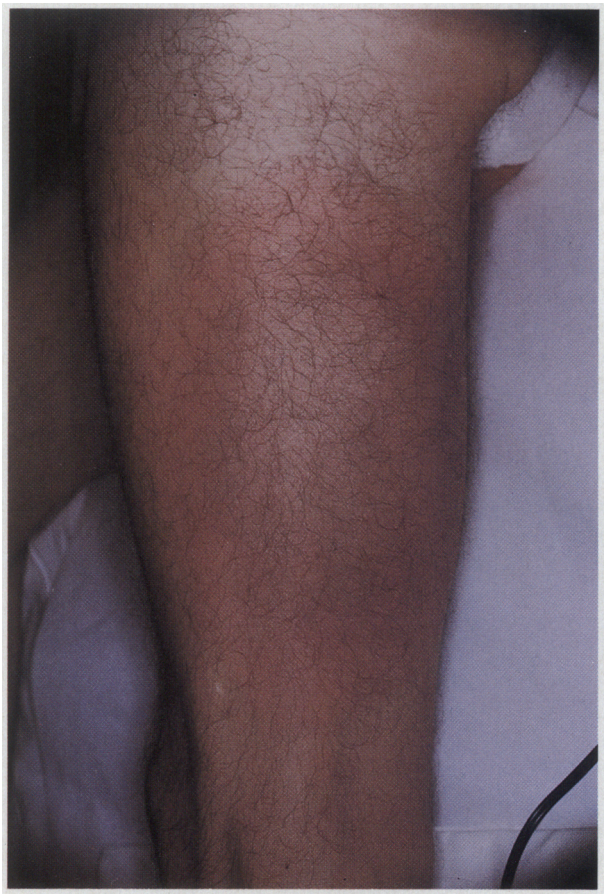

Figure 1. Patient with Erythema Migrans.
The characteristic lesion begins as a red macule or papule that expands to form a large annular erythema with a bright red outer border and partial central clearing. However, not all lesions have this characteristic appearance, and they may be lacking altogether.

membrane.[31] The 41-kd antigen is located on the flagellum, and it is similar to the flagellar antigens of other spirochetes.[32] The 58- or 60-kd antigen appears to be a heat-shock protein that is cross-reactive with an equivalent antigen (58 to 65 kd) in a wide range of bacteria.[33] In one study, the cell wall of *B. burgdorferi* was found to contain a lipopolysaccharide with endotoxin-like properties, similar to gram-negative, rough-form polysaccharide[34]; in another study, the organism lacked a lipopolysaccharide with the properties of endotoxin.[35]

All the isolates of *B. burgdorferi* examined to date have had four to nine pieces of extrachromosomal plasmid DNA.[36,37] These include the typical supercoiled variety, but also an unusual type of linear plasmid that has not been found in other prokaryotic organisms.[37] Currently, the function of only one of these plasmids has been clearly delineated. It is a 49-kb linear plasmid, parts of which have been cloned and shown to produce from a common promoter the two chief outer-surface proteins of the spirochete, A and B.[38,39] From different isolates or from different passages of the same isolate, the two proteins may vary in their molecular weights and reactivity with monoclonal antibodies.[24,29] In addition, outer-surface protein B may not be produced in culture.[24,40] These in vitro observations suggest that the outer membrane of the organism undergoes antigenic variation during the course of the infection, but this variation seems to be minor as compared with that in relapsing-fever borrelia. Plasmids may also code for proteins that are important in pathogenicity, since the loss of infectivity of isolates after passage has been correlated with the loss of particular plasmids in culture.[24,41]

Certain differences have been noted between American and European isolates of *B. burgdorferi* in morphology,[25] outer surface proteins,[42] plasmids,[36] and DNA homology.[43] In general, European isolates have been more diverse than American isolates.[25,40,42] In a hamster model, inoculation with one strain of the spirochete from the East Coast of the United States protected against infection with another strain from the East Coast, but not against strains from the West Coast and Europe.[44] This diversity may account for clinical variations in the disease in different geographic regions. Although different immunotypes or subtypes of *B. burgdorferi* — or even closely related species — surely exist, there is no currently accepted system of subclassification.

Vector and Animal Hosts

The Lyme disease spirochete is transmitted by certain ixodes ticks that are part of the *I. ricinus* complex. These include *I. dammini* in the northeastern and midwestern United States,[5,45] *I. pacificus* in the western United States,[46] *I. ricinus* in Europe,[47] and *I. persulcatus* in Asia.[48] Although a number of ixodid ticks are found in Australia, the vector there has not yet been identified. Ixodid ticks are also indigenous to Africa and South America, but it is not clear whether Lyme borreliosis occurs on those continents. *B. burgdorferi* has been demonstrated in other species of ticks[49] and in mosquitoes and deer flies,[50] but only ticks of the *I. ricinus* complex seem to be important in the transmission of the spirochete to humans.

Ticks of the *I. ricinus* complex feed once during each of the three stages of their usual two-year life cycle. Typically, larval ticks take one blood meal in late summer, nymphs feed during the following spring and early summer, and adults during that autumn.[51] In the United States, the preferred host for both the larval and nymphal stages of *I. dammini* is the white-footed mouse, *Peromyscus leucopus*.[45] It is critical that both of the tick's immature stages feed on the same host, because the life cycle of the spirochete depends on horizontal transmission: from infected nymphs to the mice in early summer, and in late summer from the infected mice to larvae, which then molt to become infected nymphs that begin the cycle again in the following year.[52] The fact that white-footed mice are tolerant to infection with *B. burgdorferi* is also crucial. The mice are capable of remaining spirochetemic through-

out the summer, and they have no inflammatory response associated with the infection.[45] After a larval tick feeds on an infected mouse, the spirochetes remain confined to the midgut of the tick until the following year, when as a nymph it attaches itself to another host. The organisms then migrate to the tick's salivary glands and are injected with its saliva as it feeds.[53,54] In experimental studies, the ticks must often remain attached for 24 hours or more before transmission occurs.[55] Infection rates among *I. dammini* may be amazingly high. In Connecticut, the Lyme disease spirochete has been found in 10 to 35 percent of these ticks,[15,50,56] and on Shelter Island, N.Y., the infection rate exceeds 50 percent.[57]

White-tailed deer, which are not involved in the life cycle of the spirochete, are the preferred host for *I. dammini*'s adult stage,[58] and they seem to be critical to the survival of the ticks.[59] However, the ticks have been found on at least 30 types of wild animals and 49 species of birds.[55,60-62] If deer are removed from an established focus, the tick may be able to adapt and survive on other animal hosts.[59] Although zoonotic infection with *B. burgdorferi* is widespread within endemic focuses, illness is not known to develop in wild animals.[56,60-62] In contrast, clinical Lyme disease does occur in domestic animals, including dogs, horses, and cattle.[63-65]

Epidemiology

According to the Centers for Disease Control, Lyme disease is now the most common vector-borne infection in the United States.[66] From 1980 through 1988, 13,795 cases were reported, primarily from three areas of the country: from Massachusetts to Maryland in the northeast, Wisconsin and Minnesota in the midwest, and California and Oregon in the west.[67] However, sporadic cases were identified in 43 states. In Europe, it is also estimated that thousands of new cases of Lyme borreliosis occur each summer, particularly in Germany, Austria, Switzerland, France, and Sweden, although cases have now been reported in most European countries.[68] In the Soviet Union, cases have been recognized from the Baltic republics to the Pacific Ocean.[48] Patients with the disease have also been found in China, Japan, and Australia.[69-71] The infection is usually acquired when nymphal ticks feed between May and July, but only a minority of the patients remember the bite because of the small size of the ticks.[72] Adult ticks occasionally transmit the disease when they feed in the autumn. People of all ages and both sexes are affected.

The earliest known American cases occurred only 25 years ago in residents of Cape Cod and Connecticut.[73] Since then, the infection has spread, particularly in the coastal areas of the northeastern United States. The best documented example of this spread is the recent outbreak in Ipswich, Mass.[74] In 1980, *I. dammini* became established in a nature preserve that had many deer. During the next seven years, clinical symptoms of Lyme disease developed in 35 percent of the 190 residents of the area adjacent to the preserve. In other outbreaks, 16 percent of the 162 permanent residents of Great Island, Mass., had the illness, in most instances between 1972 and 1979[73]; and 7.5 percent of the 200 people who participated in a study on Fire Island, N.Y., had the disorder during a five-year period.[75] In these two places, 6 to 8 percent of the residents had evidence of subclinical infection.[73,75]

How does one explain the rapid spread and focal epidemics of Lyme disease in the northeastern United States in recent years? Although the infection may have been present in North America for centuries, Matuschka and Spielman have postulated that during the development of the United States, deer and probably this disease survived in only a few isolated areas, such as Naushon Island near Cape Cod.[52] In the 20th century, as farmland reverted to woodland in the northeast, the habitat for deer improved, their numbers increased, they migrated to new areas, and federal programs protected them. At the same time, rural areas where deer and the deer tick lived became heavily populated with susceptible suburbanites who had never been exposed to the spirochete. The situation seems to be different on the West Coast and in Europe. On the West Coast, Lyme disease occurs sporadically, and only 1 to 3 percent of *I. pacificus* ticks are infected.[46,76] This has been attributed to the fact that the nymphal stage feeds predominantly on lizards rather than mice, and lizards are not susceptible to infection with the spirochete.[76] In Europe, Lyme borreliosis is already widely established in the remaining forested areas, and there is little room for spread.

Clinical Manifestations and Pathogenesis

Lyme disease generally occurs in stages, with different clinical manifestations at each stage. Before the use of antibiotic therapy for this infection, the typical patient in Connecticut first had erythema migrans (stage 1), sometimes followed several weeks or months later by meningitis or Bell's palsy (stage 2), and often followed months or years later by arthritis (stage 3).[72] The problem with this classification is that each system — skin, neurologic system, and joints — may be affected either early or late in the illness.

Asbrink has proposed a modified plan,[77] analogous to that used in classifying syphilis, in which Lyme borreliosis is essentially divided into early and late infection. Early infection consists of stage 1 (localized erythema migrans), followed within days or weeks by stage 2 (disseminated infection) and within weeks or months by intermittent symptoms. Late infection, or stage 3 (persistent infection), usually begins a year or more after the onset of the disease. A patient may have one or all of the stages, and the infection may not become symptomatic until stage 2 or 3.

Early Infection: Stage 1 (Localized Erythema Migrans)

After it is injected by the tick, *B. burgdorferi* spreads locally in the skin in 60 to 80 percent of patients and results in erythema migrans (Fig. 1), which

is sometimes accompanied by fever, minor constitutional symptoms, or regional lymphadenopathy.[72,73] The spirochete has been seen at this stage and cultured from the skin lesion more readily than at any other time in the illness.[78] At this time, the patient's mononuclear cells respond minimally to *B. burgdorferi* antigens,[79] and specific antibody to the spirochete is often lacking.[80] Even in untreated patients, erythema migrans lesions usually fade within 3 to 4 weeks (range, 1 day to 14 months), but they may recur.[72]

Early Infection: Stage 2 (Disseminated Infection)

Within days or weeks after inoculation, the Lyme disease spirochete may spread in the patient's blood or lymph to many sites (Table 1). The spirochete has been recovered several times from blood during this stage,[15,16] and it has also been seen in small numbers in specimens of myocardium, retina, muscle, bone, synovium, spleen, liver, meninges, and brain.[81] In the rat model of the disease, *B. burgdorferi* can be cultured from all organs five days after inoculation, but positivity gradually disappears from most sites.[82] It seems likely that this also occurs in patients.

Although the list of the disease's possible manifestations is long (Table 1), disseminated infection is often associated with characteristic symptoms in the skin, nervous system, or musculoskeletal sites.[72] Secondary annular skin lesions, which occur in about half the patients, resemble the primary erythema migrans lesion, but they are generally smaller and migrate less. Excruciating headache and mild stiffness of the neck are common, but they typically occur in short attacks lasting only hours. Cerebrospinal fluid is usually normal during the first days of these symptoms. The musculoskeletal pain of Lyme disease is generally migratory in joints, bursae, tendons, muscle, and bone, lasting only hours or days in a given location. At this stage, patients often appear quite ill, and they frequently have debilitating malaise and fatigue, which may be the predominant symptoms. Except for fatigue, the symptoms are typically intermittent and changing. Widely disseminated hematogenous infection seems to be more common in the United States than in Europe.

By this time, patients' mononuclear cells begin to have heightened responsiveness to *B. burgdorferi* antigens and mitogens,[79] less suppressor-cell activity than normal,[83] and decreased natural-killer-cell activity.[84] The specific IgM response, which is often directed first against the 41-kd flagellar antigen of the spirochete,[28] peaks between the third and the sixth week[15] but may persist.[28] The specific IgM response is frequently associated with evidence of the polyclonal activation of B cells, including elevated total serum IgM levels[85] and the presence of cryoprecipitates,[85] circulating immune complexes,[86] and occasionally, rheumatoid factor,[87] antinuclear antibodies, or anticardiolipin antibodies.[88] Gradually, specific IgG antibody develops, primarily of the IgG1 and IgG3 subclasses,[89] to an increasing array of spirochetal polypeptides, particularly the 31-, 34-, and 66-kd outer-surface proteins, the 41-kd flagellar antigen, and the 55/58-kd antigen.[28] Immune antibodies are required for the serum-mediated killing of the spirochete by the classical complement pathway.[90] Both polymorphonuclear leukocytes and monocytes readily phagocytose and kill the spirochete.[91] Histologically, all affected tissues show an infiltration of lymphocytes with plentiful plasma cells.[81] Plasma-cell precursors are large and can resemble immunoblasts

Table 1. Manifestations of Lyme Disease by Stage.*

System†	Early Infection		Late Infection
	Localized (Stage 1)	Disseminated (Stage 2)	Persistent (Stage 3)
Skin	Erythema migrans	Secondary annular lesions, malar rash, diffuse erythema or urticaria, evanescent lesions, lymphocytoma	Acrodermatitis chronica atrophicans, localized scleroderma-like lesions
Musculoskeletal system		Migratory pain in joints, tendons, bursae, muscle, bone; brief arthritis attacks; myositis‡; osteomyelitis‡; panniculitis‡	Prolonged arthritis attacks, chronic arthritis, peripheral enthesopathy, periostitis or joint subluxations below lesions of acrodermatitis
Neurologic system		Meningitis, cranial neuritis, Bell's palsy, motor or sensory radiculoneuritis, subtle encephalitis, mononeuritis multiplex, myelitis‡, chorea‡, cerebellar ataxia‡	Chronic encephalomyelitis, spastic parapareses, ataxic gait, subtle mental disorders, chronic axonal polyradiculopathy, dementia‡
Lymphatic system	Regional lymphadenopathy	Regional or generalized lymphadenopathy, splenomegaly	
Heart		Atrioventricular nodal block, myopericarditis, pancarditis	
Eyes		Conjunctivitis, iritis‡, choroiditis‡, retinal hemorrhage or detachment,‡ panophthalmitis‡	Keratitis
Liver		Mild or recurrent hepatitis	
Respiratory system		Nonexudative sore throat, nonproductive cough, adult respiratory distress syndrome‡	
Kidney		Microscopic hematuria or proteinuria	
Genitourinary system		Orchitis‡	
Constitutional symptoms	Minor	Severe malaise and fatigue	Fatigue

*The classification by stages provides a guideline for the expected timing of the illness's manifestations, but this may vary from case to case.

†Systems are listed from the most to the least commonly affected.

‡The inclusion of this manifestation is based on one or a few cases.

or Reed–Sternberg cells.[81] Some degree of vascular damage, including mild vasculitis or hypercellular vascular occlusion, may be seen in multiple sites,[81] suggesting that the spirochete or immune complexes may have been present in and around blood vessels.

After hematogenous spread, *B. burgdorferi* seems to be able to sequester itself in certain niches. How the organism does this remains a mystery. Perhaps it can coat itself with a "slime" layer that includes host proteins, or perhaps it is able to survive in certain intracellular sites, but there is no proof for either hypothesis. After several weeks or months, as the infection begins to localize, about 15 to 20 percent of the patients in the United States develop frank neurologic involvement.[92,93] Although there are many possible abnormalities, meningitis with superimposed cranial or peripheral neuropathy is common.[93] Encephalitic signs are subtle if present; they include somnolence, poor memory, and mood change. In Europe, the first neurologic sign is characteristically radicular pain, which is followed by the development of a pleocytosis in the cerebrospinal fluid, but meningeal or encephalitic signs are frequently absent.[94,95]

In patients with meningitis, cerebrospinal fluid typically has a lymphocytic pleocytosis of about 100 cells per cubic millimeter, often with elevated protein but normal glucose levels.[92-95] The Lyme disease spirochete has been cultured from spinal fluid several times.[15,18] Mononuclear cells responsive to *B. burgdorferi* are concentrated there[96]; specific IgG, IgM, or IgA antibody to the spirochete is produced intrathecally, and oligoclonal bands may be present.[97,98] In addition to their reactivity to *B. burgdorferi,* T-cell clones from cerebrospinal fluid may react with a host of autoantigens, including myelin basic protein, peripheral myelin, cardiolipin, and galactocerebrosides.[99] Although myelin basic protein itself has not been found in cerebrospinal fluid, antibody to it has been demonstrated in a few patients.[100] It is not known whether autoreactivity causes tissue damage or is a secondary epiphenomenon.

Unilateral or bilateral facial palsy is the most common cranial neuropathy, and it may be the only neurologic abnormality.[101] The peripheral neuritis is usually an asymmetric motor, sensory, or mixed radiculoneuropathy of the limbs or trunk.[92-95] Electrophysiologic studies of affected extremities suggest primarily axonal nerve involvement with some demyelination of both the proximal and distal nerve segments.[93,102] Histologically, the lesions show predominantly axonal injury with perivascular infiltration of lymphocytes and plasmacytes around epineural blood vessels.[81,102] Spirochetes have not been seen in these lesions. However, IgM antibodies to *B. burgdorferi* have been shown to bind to normal human axons, suggesting that molecular mimicry between spirochetal and host proteins may have a role in peripheral nerve lesions.[103] Stage 2 neurologic abnormalities usually last for weeks or months, but they may recur or become chronic.

Within several weeks after the onset of the disease, 4 to 8 percent of the patients have cardiac involvement.[104] The most common abnormality is fluctuating degrees of atrioventricular block (first-degree, Wenckebach, or complete heart block), but some patients have acute myopericarditis, mild left ventricular dysfunction, or rarely, cardiomegaly or fatal pancarditis.[105] The duration of cardiac abnormalities is usually brief (between three days and six weeks)[104]; complete heart block rarely persists for more than a week, and the permanent insertion of a pacemaker is not necessary.[106] According to case reports, patients during this period of the illness have had fatal adult respiratory distress syndrome,[107] recurrent hepatitis,[108] myositis,[109] osteomyelitis,[110] panniculitis,[111] and serious involvement of the deeper tissues of the eye, including iritis followed by panophthalmitis[112] or choroiditis with exudative retinal detachments.[113] In Europe, patients may have an unusual skin lesion called a lymphocytoma; intensely red and violet nodular lesions appear most commonly on the ear lobe or nipple of the breast.[77]

A mean of six months after the onset of the disease (range, two weeks to two years), commonly after intermittent episodes of arthralgia or migratory musculoskeletal pain, about 60 percent of the patients in the United States begin to have brief attacks of asymmetric, oligoarticular arthritis, primarily in the large joints, especially the knee.[114] Some attacks may affect the periarticular structures, including the peripheral entheses.[114,115] The reasons for the activity or latency of *B. burgdorferi* are not clear, but this pattern is characteristic of the involvement of the joints in this infection. White-cell counts in the joint fluid range from 500 to 110,000 per cubic millimeter and consist of predominantly polymorphonuclear leukocytes. Immune complexes, which correlate with the total granulocyte count, are uniformly present.[86]

Late Infection: Stage 3 (Persistent Infection)

Although the pattern varies, episodes of arthritis often become longer during the second and third years of the illness, lasting months rather than weeks, and chronic arthritis — defined as a year or more of continual joint inflammation — characteristically begins during this period.[114-116] Typically, only one or a few large joints are affected, most commonly the knee. Synovial lesions show villous hypertrophy, the deposition of fibrin, a heavy infiltrate of mononuclear cells, the intense expression of HLA-DR on many cell types, and sometimes a few spirochetes in and around blood vessels along with a form of endarteritis obliterans.[117,118] In two instances, the Lyme disease spirochete has been cultured from joint fluid,[119,120] and mononuclear cells responsive to *B. burgdorferi* are concentrated there.[79] In severe cases, chronic Lyme arthritis may lead to the erosion of cartilage and bone[114-116,121] and, rarely, to permanent joint disability.[114] The production of interleukin-1, which can be stimulated directly by *B. burgdorferi,* is found in joint

fluid,[122] as are elevated levels of collagenase and prostaglandin E_2[123]; this lymphokine is likely to be one of the mediators that cause synovial proliferation and activate collagenase. The number of patients who have recurrences decreases by 10 to 20 percent each year, and even patients with chronic arthritis rarely have continual joint inflammation for more than several years.[114] The involvement of the joints is similar in the United States and Europe, but it seems to be a less frequent manifestation of the illness in Europe.[121]

As with a number of rheumatic diseases, chronic Lyme arthritis appears to have an immunogenetic basis involving D-locus alleles of the major histocompatibility complex. These class II histocompatibility molecules, which are located primarily on B cells and macrophages, present peptide fragments of foreign antigens to T helper cells that initiate the immune response against the antigens. In an initial study of 10 patients with chronic Lyme arthritis, 7 had HLA-DR2 and 4 had HLA-DR4.[116] In a recent study of 80 patients with Lyme arthritis, those with chronic joint involvement had a significantly increased frequency of HLA-DR4, often combined with HLA-DR3 or DR2, and these patients often did not respond to multiple courses of antibiotic therapy.[124] Thus, in genetically susceptible people, *B. burgdorferi* may trigger an immune response with autoreactive features that continues for some time after the organism has been killed.

It has been recognized only recently that *B. burgdorferi* may cause syndromes of both the central and peripheral nervous systems more than a year after the initial infection. However, the spectrum of these abnormalities and suitable diagnostic tests are still being investigated. Of the several late syndromes of the central nervous system that have been described, the most clearly defined is progressive encephalomyelitis, reported by Ackermann in 48 patients in West Germany.[125] These patients had spastic paraparesis, bladder dysfunction, ataxia, seventh- or eighth-cranial-nerve deficits, or cognitive impairment, including dementia. The diagnosis was proved by the demonstration of intrathecal production of antibody to *B. burgdorferi*. In the United States, a few patients have been reported with possible late neurologic abnormalities due to Lyme disease, including subacute encephalitis,[126,127] dementia,[128] and syndromes suggestive of demyelination (in some instances, accompanied by hypodense areas compatible with demyelination on magnetic-resonance-imaging scans).[126,128] Although these patients had serologic evidence of Lyme disease, they did not have intrathecal production of antibody to *B. burgdorferi* or were not tested for it.

More commonly, patients in the United States have subtle syndromes of the central or peripheral nervous systems late in the illness. Halperin et al. described patients with intermittent distal paresthesia or radicular pain more than a year after the onset of the disease.[129] Although their physical examinations were usually normal, they had electromyographic evidence of axonal neuropathy. The greatest diagnostic problem has been in patients who have subtle symptoms of the central nervous system, such as memory loss, somnolence, or behavioral changes, after the more classic symptoms of Lyme disease have disappeared.[130] The intrathecal production of antibody to *B. burgdorferi* has been an inconsistent finding in these patients, and it may be difficult to tell whether their symptoms are due to active central nervous system infection with the spirochete. Several patients have now been described with a keratitis similar to syphilitic keratitis that began years after their initial infection.[131,132]

The best example of prolonged latency followed by persistent infection in Lyme borreliosis is acrodermatitis chronica atrophicans, the late skin manifestation of the disorder, which has been observed primarily in Europe.[77] This skin lesion usually begins insidiously with bluish-red discoloration and swollen skin on an extremity. Erythema migrans may have been present at the same site years earlier. The lesion's inflammatory phase may persist for many years or decades, and it gradually leads to atrophy of the skin. *B. burgdorferi* has been cultured from such lesions as long as 10 years after their onset.[19] In acrodermatitis the rete ridges of the epidermis are typically lost, and a mononuclear-cell infiltrate and telangiectasia are present throughout the underlying dermis.[19] In some patients, scleroderma-like skin lesions can occur concomitantly.[19,77] In longstanding cases, chronic joint and bone involvement, including periostitis and subluxations of the small joints, may be seen underlying the cutaneous lesions, suggesting the spread of the spirochete by direct extension.

Congenital Infection

The transplacental transmission of *B. burgdorferi* has now been reported in two infants whose mothers had Lyme borreliosis during the first trimester of pregnancy.[133,134] Both infants died during the first week of life, one because of congenital cardiac malformations[133] and the other of encephalitis.[134] In both, spirochetes were seen in various fetal tissues stained with Dieterle's silver stain, but cultures and serologic testing were not done. In a retrospective review of 19 cases of Lyme disease during pregnancy, 5 were associated with adverse fetal outcomes.[135] Since all of the outcomes differed, they could not be linked conclusively to maternal Lyme disease. In a recent study of 463 infants from endemic or nonendemic areas, no association could be established between congenital malformations and the presence of detectable antibody to *B. burgdorferi* in cord blood, and no infant had IgM antibody to the spirochete.[136] Although it is likely that the Lyme disease spirochete can probably cause an adverse fetal outcome, it seems to be unusual.

Diagnosis

Because the culture or direct visualization of *B. burgdorferi* from patient specimens is difficult, serology is currently the only practical laboratory aid in

diagnosis. Although indirect immunofluorescence was first used to evaluate the antibody response in Lyme disease, most investigators now prefer the more sensitive and specific enzyme-linked immunosorbent assay (ELISA).[137-139] After the first several weeks of infection, almost all patients with Lyme disease have elevated antibody titers to *B. burgdorferi*.[137-139] However, serologic testing for the disorder is not yet standardized, and the results obtained from different laboratories or commercial kits may vary.[140] It cannot be emphasized too strongly that serologic results must be interpreted with caution; the physician must beware of false negative and, more commonly, false positive results.

False negative results occur primarily during the first several weeks of infection. At that time, serum samples taken during the infection's acute phase are negative in most patients by standard indirect ELISA.[80] However, by capture IgM ELISA, about 90 percent of such patients can be shown to have an IgM response to *B. burgdorferi* when serum samples from both the acute and convalescent phases are tested.[141] Recently, 17 patients were reported who had fatigue, arthralgia, mild arthritis, headache, and in some instances, peripheral neuropathy, despite earlier antibiotic therapy for erythema migrans.[142] All the patients were seronegative, but their mononuclear cells showed proliferative responses to *B. burgdorferi*. However, healthy control subjects may also have this laboratory finding.[143]

False positive serologic results, particularly with IgM, may occur both in healthy subjects and in patients with a variety of other diseases, including syphilis (although the Venereal Disease Research Laboratory test is negative), Rocky Mountain spotted fever, autoimmune diseases, and neurologic disorders.[144-146] Most current ELISAs use sonicated whole spirochetes as the antigen in the test. Several groups have reported improved sensitivity, specificity, or both using a preparation of the 41-kd flagellar antigen alone,[147] a flagellin-enriched preparation,[31] or preparations of outer surface proteins,[31,148] but these assays are not yet widely available. Immunoblotting has been advocated as a method of identifying false positive results, since patients with Lyme disease who have positive results by ELISA will also have them on immunoblotting, whereas control subjects usually will not.[145] In addition to the problem of false positive laboratory results, 5 to 10 percent of the patients in the United States[73,75] and more in Europe[149] have asymptomatic *B. burgdorferi* infections. If these patients have symptoms caused by another disease, they may be attributed wrongly to Lyme borreliosis.

Differential Diagnosis

Lyme disease's great range of presentations can make recognition difficult. However, with its recent attention from the media, Lyme disease has probably become an overdiagnosed infection. Several examples deserve comment. The late neurologic abnormalities of Lyme disease are currently the greatest diagnostic problem because the spectrum of abnormalities has not yet been defined. However, we do not think that *B. burgdorferi* causes classic clinical pictures of multiple sclerosis, amyotrophic lateral sclerosis, or Alzheimer's disease.[146] A more common problem is the patient with vague, subjective symptoms. Headache, musculoskeletal pain, and fatigue are frequent symptoms of Lyme disease, and they may occur between episodes marked by objective abnormalities or after apparently adequate courses of antibiotic therapy. Patients with those symptoms, however, have also had objective signs of Lyme disease. Patients who have fibromyalgia or the chronic fatigue syndrome alone do not have Lyme disease.

Treatment

Before the cause of Lyme disease was known, clues emerged suggesting that it might be caused by a spirochete, and treatment studies based on the experience with syphilis were undertaken. It was first learned that patients with erythema migrans who were treated with penicillin had a better outcome than untreated patients.[6] Then tetracycline was found in a randomized study to be superior to penicillin V or erythromycin in the treatment of early Lyme disease.[150] At the same time, it became clear that patients with stage 2 neurologic abnormalities could be treated effectively with high-dose intravenous penicillin,[151] but the results were not as good in patients with arthritis.[152]

Antibiotic sensitivities to *B. burgdorferi* have now been determined in vitro and in experimental animals.[153-155] Although the methodology for such studies is not standardized, there is general agreement that *B. burgdorferi* is highly sensitive to tetracycline, but unlike *Treponema pallidum*, it is only moderately sensitive to penicillin.[153-155] Ampicillin, ceftriaxone, and imipenem are also highly active against *B. burgdorferi;* but oxacillin and chloramphenicol are only moderately active; and the aminoglycosides, ciprofloxacin, and rifampin have no activity. Erythromycin is very active against the spirochete in vitro, but not as effective in vivo.

Although recommendations for treatment are likely to be modified as further patient studies are completed, the current guidelines are given in Table 2. For early Lyme disease — localized stage 1 or disseminated stage 2 infection — oral tetracycline is generally an effective antibiotic.[150] However, doxycycline (a long-acting tetracycline) may be preferable, since it achieves better tissue levels, is taken only twice a day, and is associated with minimal gastrointestinal distress.[156] Penicillin V is less active against *B. burgdorferi* than amoxicillin or penicillin G, but penicillin G is unsuitable because oral doses are absorbed erratically.[156] Amoxicillin therefore appears to be the best choice in children and an acceptable alternative to doxycycline in adults. Studies comparing the efficacy of these drugs in the treatment of early Lyme disease are currently in progress. With each regimen, the du-

Table 2. Treatment Regimens for Lyme Disease.

MANIFESTATION	REGIMEN*
Early infection*	
Adults	Tetracycline, 250 mg orally 4× daily, 10–30 days†
	Doxycycline, 100 mg orally 2× daily, 10–30 days†‡
	Amoxicillin, 500 mg orally 4× daily, 10–30 days†‡
Children (≤8 yr)	Amoxicillin or penicillin V, 250 mg orally 3× daily or 20 mg/kilogram of body weight/day in divided doses, 10–30 days
	In case of penicillin allergy:
	Erythromycin, 250 mg orally 3× daily or 30 mg/kilogram/day in divided doses, 10–30 days‡
Neurologic abnormalities (early or late)*	
General	Ceftriaxone, 2 g intravenously 1× daily, 14 days§
	Penicillin G, 20 million U intravenously, 6 divided doses daily, 14 days§
	In case of ceftriaxone or penicillin allergy:
	Doxycycline, 100 mg orally 2× daily, 30 days‡
	Chloramphenicol, 250 mg intravenously 4× daily, 14 days‡
Facial palsy alone	Oral regimens may be adequate
Cardiac abnormalities	
First-degree atrioventricular block (PR interval <0.3 sec)	Oral regimens, as for early infection
High-degree atrioventricular block	Ceftriaxone, 2 g intravenously 1× daily, 14 days‡
	Penicillin, 20 million U intravenously, 6 divided doses daily, 14 days‡
Arthritis (intermittent or chronic)†	Doxycycline, 100 mg orally 2× daily, 30 days
	Amoxicillin and probenecid, 500 mg each orally 4× daily, 30 days
	Ceftriaxone, 2 g intravenously 1× daily, 14 days
	Penicillin, 20 million U intravenously, 6 divided doses daily, 14 days
Acrodermatitis	Oral regimens for 1 month usually adequate

*Treatment failures have occurred with all these regimens, and retreatment may be necessary.

†The duration of therapy is based on clinical response.

‡The antibiotic has not yet been tested systematically for this indication in Lyme disease.

§The appropriate duration of therapy is not yet clear for patients with late neurologic abnormalities, and it may be longer than two weeks.

ration of therapy (10 to 30 days) is guided by the clinical response, and some patients then require retreatment with oral or intravenous therapy. Among patients treated early in the disease, the specific antibody response will usually disappear within months,[28] and they may become reinfected in subsequent summers.[157] However, we have not observed reinfection after the treatment of arthritis.

In the initial randomized study of antibiotic therapy for early Lyme disease, about half the patients continued to experience minor symptoms after antibiotic treatment, such as headache, musculoskeletal pain, and fatigue.[147] The occurrence of these later symptoms correlated with the severity of the initial illness and not with the choice of antibiotic (tetracycline, penicillin, or erythromycin) or the duration of therapy (10 or 20 days). It is unclear whether such symptoms result from a depleted number of live spirochetes, parainfectious phenomena, or both.

Are there circumstances that make oral therapy inappropriate for disseminated stage 2 infection? We use intravenous therapy in all patients with objective neurologic abnormalities except those with facial palsy alone and no abnormalities of the cerebrospinal fluid. Although intravenous penicillin is generally effective in the treatment of neurologic abnormalities,[151,158] ceftriaxone is now commonly used, because it crosses the blood–brain barrier more readily and requires only once-a-day administration.[159] In patients who are allergic to ceftriaxone or penicillin, doxycycline or chloramphenicol may be acceptable alternatives.[158,160] Intravenous penicillin or ceftriaxone therapy has become standard in patients with high-degree atrioventricular block or cardiomegaly.

The treatment of stage 3 joint or neurologic abnormalities has generally been more problematic than that of Lyme disease's other manifestations, and the response, particularly in patients with arthritis, may be slow. In a double-blind, placebo-controlled trial of patients with established Lyme arthritis, 7 of 20 who received intramuscular penicillin G benzathine responded, as compared with 0 of 20 who received placebo.[152] Similarly, only 11 of 20 patients who received intravenous penicillin were cured.[152] In a subsequent study of 23 patients with late neurologic and arthritic manifestations of the disorder, Dattwyler et al. reported that 5 of 10 who received intravenous penicillin did not respond, as compared with 1 of 13 who received ceftriaxone.[159] However, in a recent study of patients with Lyme arthritis, the frequency of treatment failure was similar in all groups, including those who received oral doxycycline, amoxicillin–probenecid, intravenous penicillin, and ceftriaxone.[161] Antibody titers to *B. burgdorferi* declined fourfold to sixfold within a year after successful treatment, but all the patients remained seropositive.

Do corticosteroids have a role in the treatment of Lyme borreliosis? In one study, their use before antibiotic therapy was associated with the failure of antibiotic treatment,[159] but in another it was not.[161] In a retrospective review of 124 patients with facial palsy due to Lyme disease, the duration of the palsy was similar in those who received antibiotics alone, antibiotics and steroids, and no treatment.[101] Before antibiotics were used to treat Lyme disease, prednisone (40 to 60 mg per day) was used with dramatic success in the treatment of Lyme carditis.[104] Thus, if patients with severe cardiac involvement do not respond quickly to antibiotic therapy, steroids may be indicated. In patients with arthritis who do not respond to antibiotic therapy, we occasionally use intra-articular steroids.

Several other treatment questions remain unresolved. One concerns prophylactic antibiotic therapy for tick bites. In a small study comparing penicillin V and placebo, the risk of acquiring Lyme disease was less than one would expect, given the infection rate in ticks, and it was similar to the risk of an adverse reaction to penicillin.[162] It is unclear whether and how asymptomatic infection should be treated. Acroder-

matitis is known to have developed in one patient after five years of seropositivity.[73] The appropriate treatment for Lyme disease during pregnancy is also unclear. A pregnant woman in Europe whose erythema migrans was treated with oral antibiotics had an infant who died of possible Lyme encephalitis,[134] and some physicians therefore give high-dose intravenous penicillin to all women with Lyme disease during pregnancy. Whether this is necessary remains questionable. No vaccine is yet available.

Summary

Within the last decade, Lyme borreliosis has emerged as a complex new infection whose distribution is worldwide. The disorder is caused by a recently recognized spirochete, *B. burgdorferi*, transmitted by ticks of the *I. ricinus* complex. Certain species of mice are critical in the life cycle of the spirochete, and deer appear to be crucial to the tick. Although the disorder's basic outlines are similar everywhere, there are regional variations in the causative spirochete, animal hosts, and clinical manifestations of the illness. In the United States, Lyme disease commonly begins in summer with a characteristic skin lesion, erythema migrans, accompanied by flu-like or meningitis-like symptoms. Weeks or months later, the patients may have neurologic or cardiac abnormalities, migratory musculoskeletal pain, or arthritis, and more than a year after onset, some patients have chronic joint, skin, or neurologic abnormalities. After the first several weeks of infection, almost all patients have a positive antibody response to the spirochete, and serologic determinations are currently the most practical laboratory aid in diagnosis. Treatment with appropriate antibiotics is usually curative, but longer courses of therapy are often needed later in the illness, and some patients may not respond.

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