Infectious Diseases of the Fetus and Newborn Infant

FIFTH EDITION

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CHAPTER 11

Lyme Disease

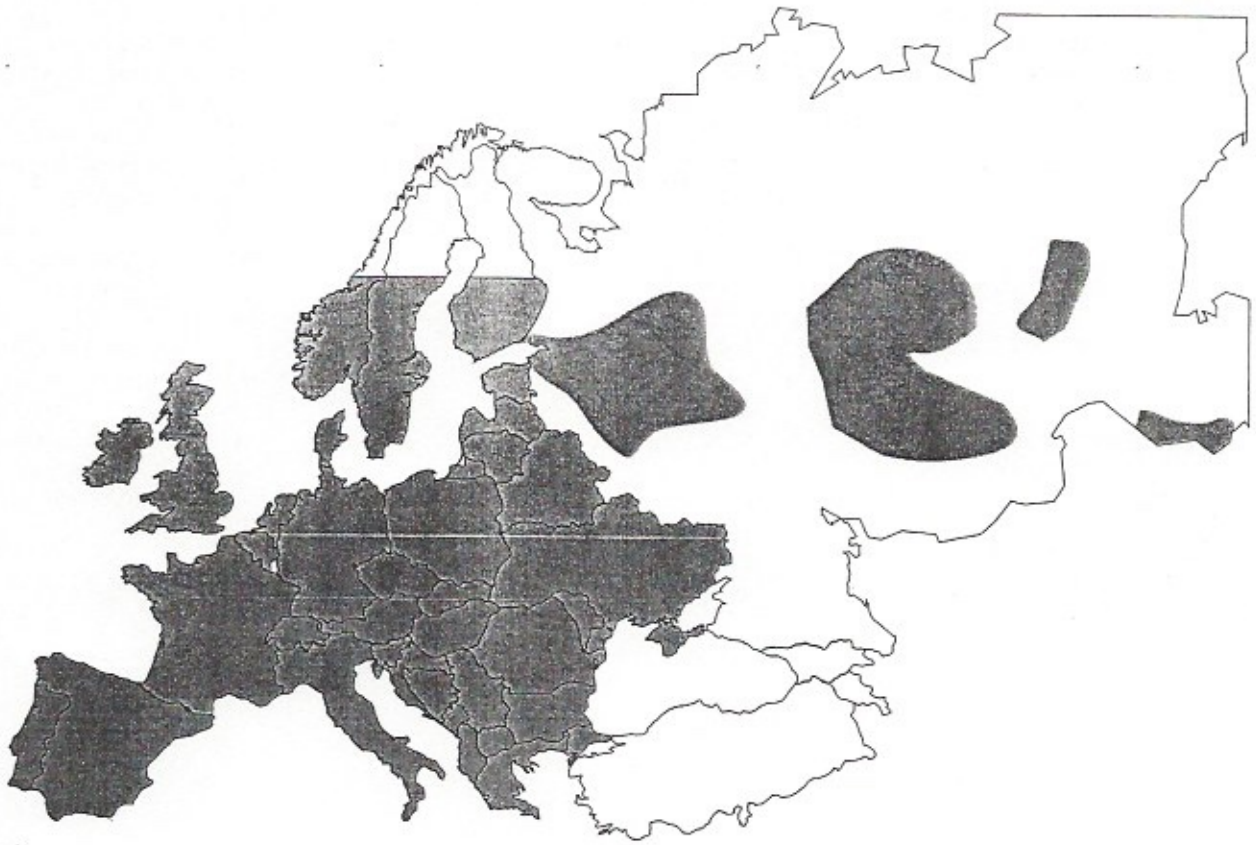
TESSA GARDNER, M.D.

Lyme disease, or Lyme borreliosis, is a tickborne zoonosis of both children and adults caused by the spirochete *Borrelia burgdorferi*.[1, 2] It has a worldwide geographic distribution and has been reported from more than 40 countries and 6 continents; the geographic distribution and number of cases reported continue to increase (Figs. 11–1 and 11–2). It is now the most common tickborne infection in the United States,[3–6] where 16,800 cases were reported to the Centers for Disease Control and Prevention (CDC) in 1998 (Fig. 11–3); in Europe,[8–10] where 2100 cases were reported to the European Union Concerted Action of Risk Assessment in Lyme Borreliosis (EUCALB) in 1994, and more than 60,000 cases were estimated to occur annually as of 1998[9]; and possibly in the world.[11–13]

Lyme borreliosis is a fairly recently recognized infection, although erythema migrans (EM), the characteristic skin lesion of early Lyme borreliosis, was first described in a Swedish woman in 1909 by Afzelius, who proposed that it was related to a zoonosis transmitted by a tick bite.[14] In 1975, Steere and associates recognized an outbreak of infectious arthritis and unusual rash similar to European EM in Old Lyme, Connecticut; they proposed that transmission occurred via an arthropod vector and named the disease Lyme arthritis.[15] Eventually, it was found to be associated with ixodid tick bites and later, when its multisystem involvement was recognized, became known as Lyme disease.

In 1981, Burgdorfer and colleagues discovered a new species of *Borrelia* in *Ixodes* ticks associated with Lyme disease, and this became known as *Borrelia burgdorferi*.[1, 16, 17] This spirochete was found to be the causative agent of North American Lyme disease[18] and of European EM,[19] as well as other European syndromes such as acrodermatitis chronica atrophicans (ACA),[20] Bannwarth's syndrome,[21] and lymphadenosis benigna cutis[22]; the entire disease complex is now known as Lyme borreliosis.

As worldwide reporting of Lyme borreliosis increases, a geographically defined "Lyme Belt" is emerging between 30 and 65 degrees North latitude in the Eastern Hemisphere, and between 25 and 50 degrees North latitude in the Western Hemisphere; there may also be a belt developing between 30 and 40 degrees South latitude in the Eastern Hemisphere. This is reminiscent of the "Malaria Belt," which has been defined by climatic conditions and the distribution of another major arthropod vector of human disease, the *Anopheles* mosquito.



A

FIGURE 11–1 *A*, The geographic distribution of Lyme borreliosis in Europe. Europe is the main area outside North America from which Lyme borreliosis has been reported. This map shows European countries from which cases of Lyme borreliosis have been reported either to the World Health Organization,[501] to the European Union Concerted Action on Risk Assessment in Lyme Borreliosis,[9, 10] or in the medical literature.[11, 12, 41–44, 48, 83, 85–87, 90, 162, 251, 268, 275, 276, 305, 310, 352, 370, 371, 381, 387, 389, 402–405, 409, 422, 432–435, 448, 503, 504, 507–523, 525–537, 539–550, 552, 553] Reliable statistics on incidence by country are not available, as reporting of cases is voluntary in most countries. The highest incidences (either 1000–20,000 cases/country or 15–140 cases/100,000 population annually) of European Lyme borreliosis have been reported from Austria, Slovenia, Poland, Sweden, Bulgaria, Denmark, Hungary, the Netherlands, Finland, the Czech Republic, Switzerland, Germany, Italy, and France; lower incidences (either <500 cases/country, or <5 cases/100,000 population annually) have been reported from Belgium, Croatia, Estonia, Greece, Ireland, Latvia, Lithuania, Luxembourg, Moldavia, Norway, Romania, Russia, Spain, the United Kingdom, and the former Yugoslavia.

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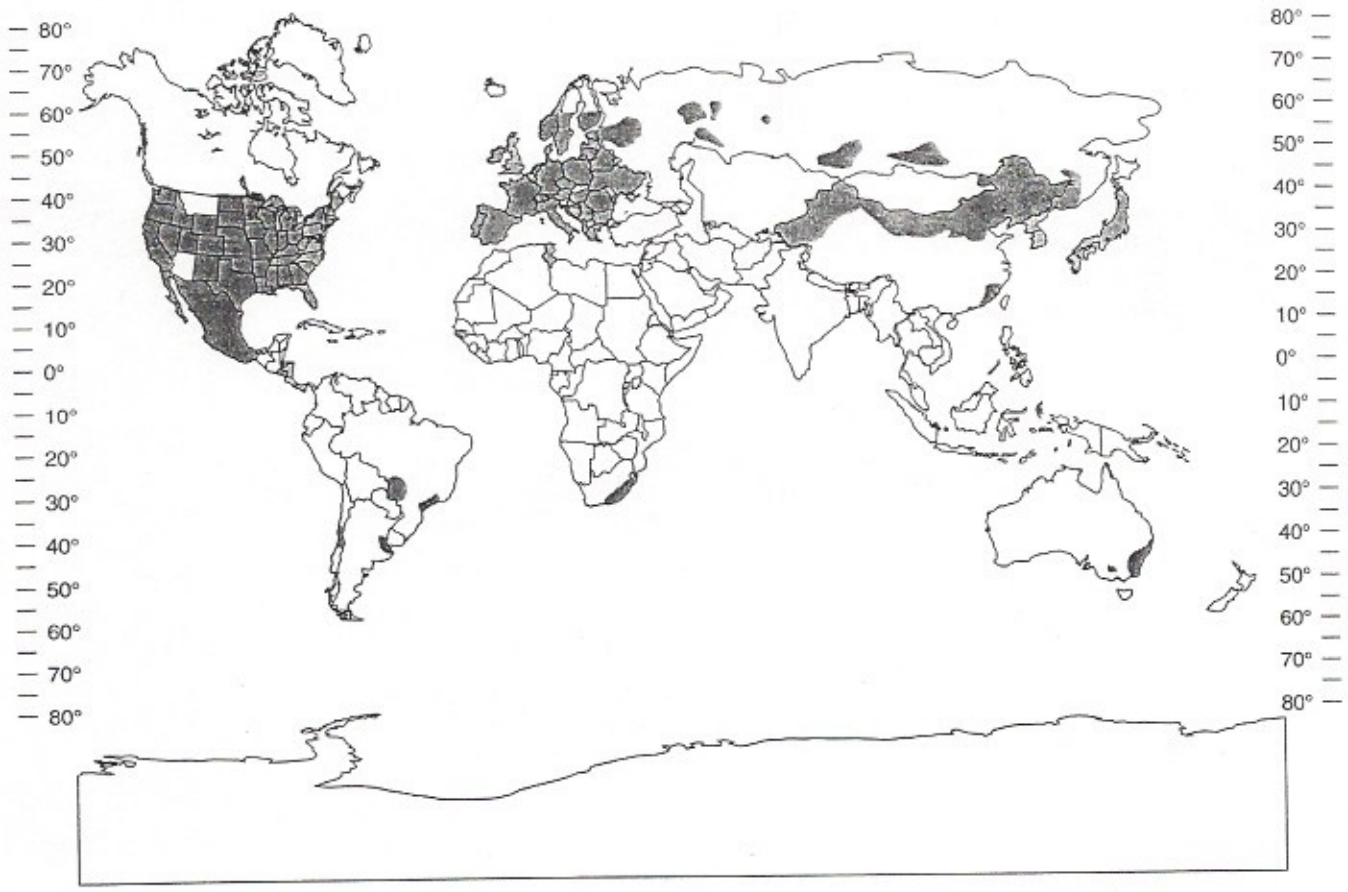
Lyme borreliosis is a multisystem infection that initially emerged as a new "great imitator"[14] because of the diversity of its clinical presentations, which comprise both early and late stages and include dermatologic, cardiac, neurologic, arthritic, and ocular manifestations.[23] However, more than 20 years since its recognition as a new disease,[15] the spectrum of its clinical manifestations has been extensively characterized, resulting in gradual loss of this reputation.[24] The existence of congenital borreliosis was suspected because of clinical similarities between the two spirochetoses Lyme borreliosis and the classic "great imitator" syphilis,[599] and the well-known association of gestational syphilis with miscarriage, early congenital infection, and late congenital infection.

Maternal-fetal transmission of *B. burgdorferi* was first reported in 1985 by Schlesinger and co-workers.[25] As the number of reported cases of Lyme disease continues to increase, there have been increasing reports of gestational Lyme disease associated with adverse outcomes and suspected congenital Lyme borreliosis.[25–48] Although a homogeneous congenital Lyme borreliosis syndrome has not yet emerged, there are several features that are common among the 66 adverse outcomes of pregnancies complicated by gestational Lyme borreliosis reviewed later in this chapter (including miscarriage during the



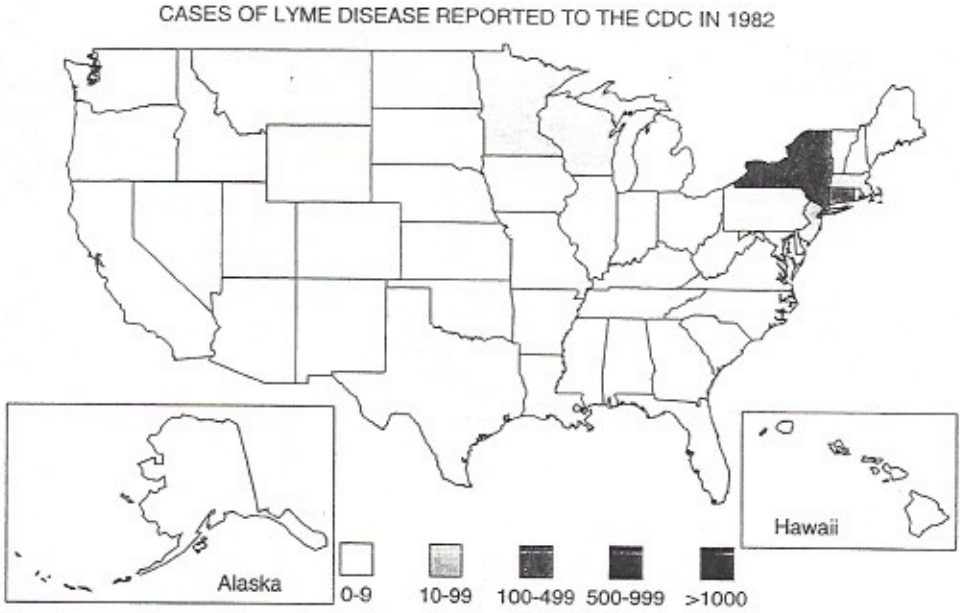
B

FIGURE 11–1 *Continued. B,* The worldwide geographic distribution of Lyme disease in temperate zone "Lyme Belts." In addition to North America and Europe, Lyme borreliosis is also endemic in Asia, mainly in China and Japan, and it has been reported from countries on three other continents and the Caribbean, including Argentina, Australia, Brazil, Chile, Egypt, Honduras, Israel, Mexico, Mozambique, Puerto Rico, South Africa, Taiwan, and Tunisia, although some of these cases may not have been indigenously acquired. The existence of indigenous cases in Central and South America, the Caribbean, Australia, and central and southern Africa is still uncertain.[164, 165, 303, 344, 349–351, 374, 388, 439, 448, 449, 451–453, 455, 456, 506, 554–561, 563, 566–569] Ixodid ticks infected with *Borrelia burgdorferi* have been found in Korea, and in several subarctic and subantarctic circumpolar islands (Egg and St. Lazaria Islands of Alaska, Flatey Island of Iceland, Campbell Island of New Zealand, and the Crozet Islands), but no cases of Lyme borreliosis have been reported yet from these areas.[165, 555] The geographic distribution of Lyme disease cases forms two belts—a 35-degree-wide northern temperate zone belt between 30 and 65 degrees North latitude in the Eastern Hemisphere, and another one slightly more southerly between 15 and 50 degrees North latitude in the Western Hemisphere. These include the majority of the Asian, European, North African, and North American cases. In addition, the cases from Australia, southern Africa, and South America appear to be clustered in a temperate zone belt between 10 and 40 degrees South latitude, but more cases are needed to determine if this is a true Southern Hemisphere "Lyme Belt."

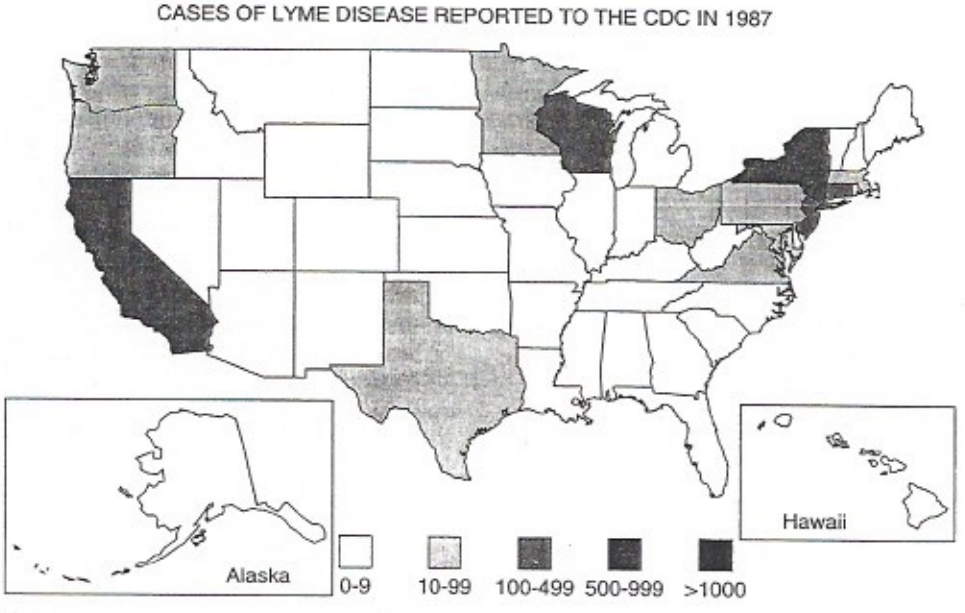
first 20 weeks of gestation with a high frequency of fetal cardiac abnormality; severe early congenital infection with fulminant neonatal sepsis and meningoencephalitis and a high frequency of cardiac abnormality; mild early congenital infection with growth retardation and mild cardiac abnormality; and late congenital infection with growth retardation, developmental delay, and neurologic, cutaneous, dental, and skeletal involvement).

THE ORGANISM

Borrelia organisms are arthropod-borne spirochetes that infect birds, domestic and wild animals, and humans.[49, 50, 52] It is now recognized that *B. burgdorferi* is a phenotypically and genotypically heterogeneous genospecies complex, and the name has been modified to *Borrelia burgdorferi sensu lato* to reflect this. There are several genospecies of *Borrelia burgdorferi sensu lato: Borrelia burgdorferi sensu stricto, Borrelia andersonii, Borrelia garinii, Borrelia afzelii, Borrelia valaisiana, Borrelia lusitaniae, Borrelia japonica, Borrelia tanukii, Borrelia turdae,* and several genetically distinct genomic groups that have not yet achieved genospecies status.[51–71, 884] *B. burgdorferi sensu stricto, garinii,* and *afzelii* have been associated with human Lyme borreliosis[55]; *B. valaisiana* DNA has been found in EM lesions of two patients by polymerase chain reaction (PCR)[72]; and strains similar to strain 25015 in



A



B

FIGURE 11–2 The increase in the number of cases and expansion of the geographic distribution of Lyme disease in the United States from 1982 through 1998. The number of cases of Lyme disease reported to the Centers for Disease Control and Prevention (CDC) by state health departments in *(A)* 1982, *(B)* 1987, and *(C)* 1998.[4, 461] National surveillance began in 1982, and Lyme disease became a notifiable disease in 1990.[3] Cases of Lyme disease have also been reported to the Canadian Laboratory Centre for Disease Control (LCDC), mostly from southern areas that border Lyme-endemic areas of the northeastern, upper midwestern, and northwestern United States.[479]

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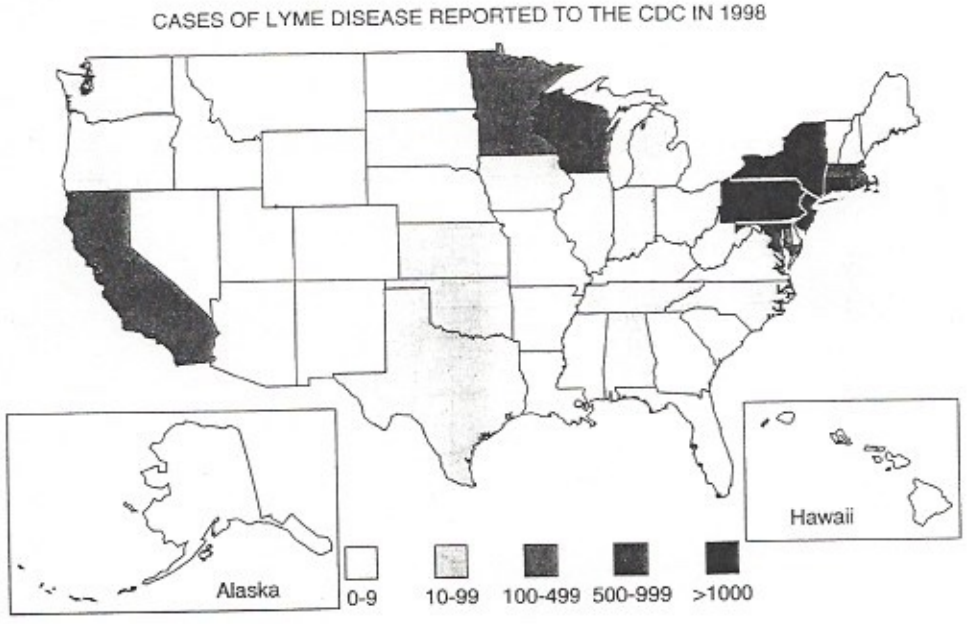

C

FIGURE 11–2 *Continued*

genomic group DN127 occasionally have been associated with Lyme disease.[83, 865] The other genospecies are involved in enzootic cycles of maintenance of *B. burgdorferi* in nature, but have not yet been isolated from patients with Lyme borreliosis.[55, 56] There is a newly described uncultivable *Borrelia* species, *Borrelia lonestarii*, which has been found in the Lone Star tick, *Amblyomma americanum*, and may be associated with Lyme-like disease in the southern United States.[73] Certain genospecies have been associated more frequently with certain clinical manifestations.[10, 74–76] *B. lonestarii* and a new species, *Borrelia miyamotoi*,[77] may be more closely related to the relapsing fever borreliae than to *B. burgdorferi sensu lato*.[73, 77]

Borrelia burgdorferi as the Etiologic Agent of Lyme Borreliosis

In 1981, Burgdorfer and associates discovered (isolated) a new species of *Borrelia* in *Ixodes dammini* (later renamed *Ixodes scapularis*[78]) ticks from a Lyme-endemic area in New York, demonstrated elevated antibody titers to this spirochete in convalescent sera of patients with Lyme disease, and proposed that this spirochete was involved in the etiology of Lyme disease.[1, 17]

In 1982, Berger and colleagues demonstrated rare spirochetes, similar to the *I. dammini (scapularis)* spirochete, by Warthin-Starry silver stain in skin biopsy specimens of untreated patients with EM skin lesions; they were able to isolate spirochetes from one specimen, thus supporting a spirochetal etiology for EM.[79] In 1985, Berger and co-workers grew the *I. dammini (scapularis)* spirochete from several skin biopsy specimens of EM lesions[79] and thus confirmed this spirochete as the etiologic agent of North American EM.

In 1983, Steere and associates isolated the new spirochete, which was subsequently named *Borrelia burgdorferi*, from blood, spinal fluid, and joint fluid of American Lyme disease patients and from *I. dammini (scapularis)* ticks in a Lyme-endemic area of Connecticut; they

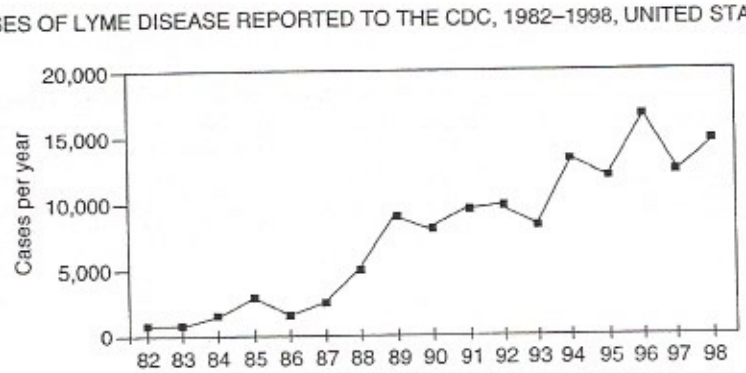

FIGURE 11–3 The number of cases of Lyme disease in the United States reported to the CDC by the individual state health departments has increased steadily from 1982 to 1998.[4, 461] Lyme disease became a reportable disease in 1990.[3]

demonstrated serum IgM and IgG antibody titer increases in these patients directed against this spirochete.[18] Simultaneously in 1983, Benach and colleagues isolated the same spirochete from the blood of patients with American Lyme disease and demonstrated similar seropositivity in these patients.[80] Both groups proposed the *I. dammini (scapularis)* spirochete as the etiologic agent of Lyme disease.[18, 80] In the same year, Barbour and co-workers, including Burgdorfer, isolated a new spirochete, similar to the *I. dammini (scapularis)* spirochete, from *Ixodes ricinus* ticks from an EM-endemic area of Switzerland.[81]

Ryberg and associates, including Burgdorfer, in 1983 demonstrated significant levels of IgM and IgG serum antibodies against the North American Lyme disease spirochete in sera of European patients with lymphocytic meningoradiculitis (Bannwarth's syndrome); they proposed the Lyme disease spirochete as the etiologic agent of Bannwarth's syndrome.[21]

In 1984 and 1985, Asbrink, Hovmark, and colleagues isolated the *I. ricinus* spirochete from skin biopsy specimens of European patients with EM,[19] acrodermatitis chronica atrophicans,[19, 20] and lymphadenosis benigna cutis[22]; antibody titer elevations against this spirochete were demonstrated in these patients, thus confirming the spirochetal etiology of these European skin diseases. In 1987, de Koning and co-workers demonstrated spirochetes, morphologically consistent with *B. burgdorferi*, in European EM and lymphadenosis benigna cutis skin lesions, in synovia of patients with European Lyme arthritis, and in spinal fluid of a patient with European Bannwarth's syndrome, and thus confirmed the spirochetal etiology of these additional European diseases.[82]

Some genospecies, such as *B. burgdorferi sensu stricto, garinii*, and *afzelii*, have been associated with human Lyme borreliosis, and others, such as *B. japonica*, only with tick vectors and reservoir hosts but not yet with human disease.[55, 56] *B. valaisiana* DNA has been found in EM lesions of two patients by PCR[72]; *B. burgdorferi sensu lato* isolates similar to strain 25015 of group DN127 were found in the cerebrospinal fluid (CSF) and EM of nine Slovenian patients[83, 884]; and *B. burgdorferi* genospecies DN127 was isolated from one patient with borrelial lymphocytoma.[74]

There is clustering of genospecies from patients with different clinical manifestations, such as EM, ACA, neuroborreliosis, arthritis, and carditis[55, 67, 74–76, 84–89]; this clustering suggests the possibility of differences in pathogenicity and organotropism of strains of different phenotypes and genotypes, which may be related to differences in clinical syndromes associated with these strains.[51–53]

In North America, where ACA does not occur, *B. burgdorferi sensu stricto* is the only agent of human Lyme disease, and is associated with all North American manifestations of Lyme disease, EM, neuroborreliosis, arthritis, and carditis.[5] In Europe, ACA is associated predominantly with *B. afzelii*, and occasionally with *garinii* or *sensu stricto*[67, 74–76, 85–87, 89]; EM with all three genospecies (*B. burgdorferi sensu stricto, garinii, afzelii*)[74–76, 85, 89]; neuroborreliosis predominantly but not exclusively with *B. garinii*[74–76, 85, 87, 88]; arthritis predominantly with *sensu stricto* and sometimes with *garinii*[75, 76]; and carditis with *sensu stricto* and occasionally with *garinii*.[75, 76]

Within genospecies, there may be strains that are more pathogenic than others, as may be involved in the clustering of strains isolated from European patients with disseminated Lyme borreliosis in one sub-branch of *B. garinii*,[55] the clustering of *B. garinii* strains associated with adult neuroborreliosis in Osp A serotype 4, and the clustering of *garinii* associated with pediatric neuroborreliosis in Osp A serotype 6.[88]

A large study by the EUCALB, of over 2000 patients with Lyme borreliosis in 15 European countries during 12 months in 1994, found that the incidence of Lyme borreliosis per 100,000 population increased from Western to Eastern Europe, with higher incidences east of the Netherlands, France, and Italy.[10]

Morphology

Borrelia burgdorferi[56, 81, 91–98, 218] is a long (10 to 30 micrometers in length), narrow (0.18 to 0.25 micrometer in diameter), irregularly and loosely coiled, helical, motile, flexible spirochete with tapered ends and sheathed flagellae.

It has an inner and an outer cell membrane and four to eight flagellae, located in the periplasmic space between the inner and outer trilaminar cell membranes. These membranes, which are inserted at each end and extend toward the middle of the spirochete, allow it to move efficiently through viscous solutions and presumably enhance its ability to disseminate in body tissues. The trilaminar outer membrane structure is similar to, but more fluid than, that of gram-negative bacteria, and it contains the embedded outer surface membrane lipoproteins and a lipopolysaccharide with weak endotoxin-like activity.[100] The flexible cell wall is located just outside the cytoplasmic membrane.[99] In addition to the typical *B. burgdorferi* morphology, morphologic variants have been found in tissue biopsies.[101–103]

Molecular Biology

B. burgdorferi has several major antigens that can be separated by polyacrylamide gel electrophoresis and characterized antigenically by reactivity in Western blots with *B. burgdorferi*–specific polyclonal and monoclonal antibodies.[51, 52, 92, 93, 104, 105]

The 83- to 100-kilodalton (kd) antigen p83/100 is *Borrelia* genus–specific,[51, 106, 107] cross reacts minimally with other bacteria,[104] is associated with either the flagella or the protoplasmic cylinder, and is a chromosomally encoded immunodominant antigen of *B. burgdorferi sensu lato*, which has minor homology with the muscle and cytoskeletal proteins myosin and troponin, and contains an amino acid sequence that is a common cell recognition signal of integrins and may be involved in spirochetal attachment to cells.[106] The constant-molecular-weight, major immunodominant 60-kd common antigen HSP60, and the 70-kd antigen HSP70 are heat shock proteins that function as flagellin chaperones, are encoded by chromosomal genes, and cross react broadly with other bacteria.[104, 109, 882] The 35-kd protein, a *B.*

burgdorferi sensu lato–specific lipoprotein encoded by a chromosomal gene, is expressed early in human infection and is an important immunodominant marker for early human infection.[110] There are several other significant antigens, including the 39-kd molecular weight protein, some encoded by chromosomal and some by plasmid genes.[882]

The 41-kd flagellar antigen p41 is the other major protein of the organism[51, 52]; it has a uniform molecular weight in all *B. burgdorferi* strains,[51] is encoded by a highly conserved gene (with 96–97% sequence homology between strains) located on the main chromosome,[111] and is the antigen most often recognized in Lyme borreliosis patient sera.[112] *B. burgdorferi* flagellin has an epitope that shares amino acid homology with the N-terminal amino acid sequences of human chaperonin, a 60-kd heat shock protein,[113] and has some cross-reactivity with other spirochetes.

B. burgdorferi has several major outer surface lipoproteins—Osp A,[114] Osp B,[114] Osp C,[114, 116] Osp D,[117] Osp E,[118] Osp F,[118] and pG[119]—that are encoded by plasmids.[114, 120, 882] The 18-kd EppA protein (exported plasmid protein A) is thought to be either an outer membrane or a secreted protein.[121] Osp A has the least variability and the greatest homology (77–83%) of the three major *B. burgdorferi* genospecies[108, 114, 122]; Osp B has high variability[114]; and Osp C has the highest variability and exhibits polymorphism of its amino acid sequences and Osp C–encoding gene sequences.[114, 120, 123] Osp C is expressed early in infection,[124, 125] and, despite this heterogeneity, the three major genospecies have common as well as genospecies-specific Osp C immunogenic epitopes recognized by patient sera.[108, 125] Osp A has an immunodominant epitope that shares amino acid sequence homology and encoding DNA sequence homology with human leukocyte function–associated antigen-1 (LFA-1), which is a candidate arthritogenic autoantigen that may be involved in the immunopathogenesis of Lyme arthritis.[126]

The smaller, variable-molecular-weight outer surface membrane lipoproteins of *B. burgdorferi* are species-specific, and antigenic modulation, variation in size, antigenicity, and expression of these outer surface proteins have been found.[51, 52, 92, 93, 129, 130] In 1998, Kawabata and associates reported that *B. burgdorferi sensu stricto* strain 297 has VMP-like proteins coded by VMP-like sequences (Vls) located in multiple copies on the 20 kilobase pair plasmid.[130] In 1997, Zhang and colleagues described a system in *B. burgdorferi sensu stricto* strain B31 that produces extensive antigenic variability in a surface lipoprotein.[131] *B. burgdorferi* Vls is expressed in patients with Lyme borreliosis,[130] and the system of antigenic variability may enhance evasion of the host immune response.[130, 131]

B. burgdorferi also has nonprotein antigens, composed of lipid-carbohydrate-, and phosphorus-containing compounds, which react with Lyme disease patient sera but are of unknown significance.[132]

The genome of *B. burgdorferi* has been sequenced.[133, 882] *B. burgdorferi sensu stricto* strain B31 has a large linear chromosome of 910, 725 base pairs (about 900 kbp) and at least 17 plasmids (10 linear plasmids ranging in size from 17 to 56 kbp, and 7 circular plasmids ranging from 9 to 32 kbp) with a combined total of 533,000 base pairs (about 500 kbp) of double-stranded DNA with an average G plus C content of 28.6%.[882] The linear chromosome has been sequenced and contains 853 genes that encode proteins needed for DNA replication, transcription, translation, energy metabolism, and solute transport, but not for cellular biosynthesis. Eleven of the plasmids (ranging from about 9 to 54 kbp in size), containing 430 genes, have been sequenced. The functions of most of these genes are unknown, but they may be involved in antigenic variation and immune evasion; some, such as the 53- to 58-kbp linear plasmid in *B. burgdorferi sensu stricto, garinii,* and *afzelii,* and the 90- to 105-kbp linear plasmid in *B. japonica,* encode outer surface proteins A and B. Others, such as the 26- to 27-kbp circular plasmid, encode Osp C. Fifty-nine percent of the chromosomal genes have known biologic roles, 12% match genes in other organisms with unknown roles, and 29% are new genes; these percentages for plasmid genes are 16, 26, and 58, respectively.[882] Almost all of the membrane proteins of *B. burgdorferi* are lipoproteins, and 8% of its genes encode 105 putative lipoproteins, which is a much greater percentage than occurs with most other bacteria; six percent of the genes encode proteins involved in spirochetal motility and chemotaxis.[882]

Although North American and European *B. burgdorferi sensu stricto* isolates tend to cluster into separate subbranches by DNA analysis,[55] there are genetic similarities between some isolates from the two continents, suggesting some previous interchange of strains between the two continents.[62]

Among the different genospecies,[657, 117, 134] there are differences in the number, size, and sequences of the linear and circular plasmids, as well as their presence or absence, which correlate with the expression of the outer surface proteins they encode. The Osp A– and Osp B–encoding linear plasmid is present in all *B. burgdorferi sensu lato* genospecies (although some individual isolates may lack the Osp B gene, and this plasmid may be lost in culture). Almost all North American and European strains express Osp A and it shows the least antigenic variability between genospecies[120]; Osp A serotyping has been used to divide *B. burgdorferi sensu lato* into different phenotypes,[105] which correlate with different genotypes by Osp A gene sequencing. The Osp C gene is located on a 26-kbp circular plasmid that is present in all genospecies, but its expression, both qualitatively and quantitatively, is variable; most European strains express Osp C, but Osp C has been found to be cryptic in North American strains, where it is expressed only in strains that have lost all plasmids other than the Osp C–encoding and Osp AB–encoding plasmids.[116] The Osp D gene is highly conserved and is present in 24, 50, and 90%, respectively, of isolates of *B. burgdorferi sensu stricto, afzelii,* and *garinii*; its encoding plasmid has significant size variability, ranging from 36 to 40 kbp, and contains varying numbers of copies of a 17-kbp repeating sequence bordering a variable region with evidence of homologous recombinational events.[117] The Osp E and Osp F genes are located in tandem on the

45-kbp linear plasmid.[118] The pG gene is located on a 48-kbp linear plasmid that has some sequence homology to the Osp EF gene and is detectable in most strains of *B. burgdorferi sensu stricto* and *B. afzelii*, but not in *B. garinii* or *B. japonica*.[119] There is p83/100 gene heterogeneity in *B. garinii*, but not in either *B. burgdorferi sensu stricto* or *B. afzelii*; *B. garinii* strains could be separated into two major subtypes on the basis of p83/100 gene sequence variation, one corresponding to Osp A serotype 4 and the other to serotypes 3, 5, 6, and 7.[106] The EppA protein gene is located on the 9-kbp circular plasmid, and loss of this plasmid has been associated with loss of virulence during passage of *B. burgdorferi* in culture.[121]

It has been proposed that the high level of variability of Osp C[115] and D,[117] and the existence of a VMP-like system[130, 131] may be involved in immune evasion by *B. burgdorferi*. Evasion of the immune response by a *B. burgdorferi* strain expressing a truncated Osp B also raised this as a possible immune escape mechanism.[135, 136]

Differential gene expression, which has been found in *B. burgdorferi*, has also been suspected to be involved in infectivity, invasion, and dissemination, and in evasion of the host immune response to the infection[120, 137]; it may also have a role in differential organotropism. Abundant Osp A and Osp B, and no Osp C, are expressed by *B. burgdorferi* in unfed tick midguts. The beginning of tick feeding and the arrival of the blood meal in the tick midgut trigger downregulation of Osp A and B, and upregulation of Osp C expression of *B. burgdorferi* in the engorged tick midgut.[138–140] Although Osp A and B are not expressed initially after infection, they are eventually expressed, in particular in patients with chronic Lyme arthritis. Although Osp E and Osp F are expressed by *B. burgdorferi* in ticks and in the mammalian host, it appears that the Osp E and F homologues, the Erp proteins (Osp EF–related proteins), form a gene group that is differentially expressed at different stages of the spirochete's life cycle; the Osp E homologue, p21, which has 70% amino acid homology with Osp E, and the Osp F homologues, pG, bbk2.10, and bbk2.11, are expressed only in the mammalian host and not in the spirochete in culture or in ticks.[119, 127, 141] Expression of p21 does not occur even in engorged ticks, only in the mammalian host; antibody to p21 is found in 28 to 33% of patients with early or late Lyme disease, including Lyme arthritis, indicating its expression during Lyme disease.[127] Confirmation of differential gene expression during Lyme disease was first reported in 1998, when p35 (the 35-kd protein) and p37 (the 37-kd protein) messenger RNA (mRNA), but not Osp A mRNA, was found in EM skin biopsies and Lyme arthritis synovium, consistent with upregulation of p35 and p37 and the downregulation of Osp A.[141] The protein EppA (exported plasmid protein A) is downregulated at the transcriptional level in cultured *B. burgdorferi*, is expressed only in the mammalian host, and is associated with virulent strains of *B. burgdorferi*.[121] Temperature increases, as occur with ingestion of the blood meal by the tick, and even increases in culture temperature from 23° C to 35° C, induce downregulation of Osp A expression, and upregulation of Osp C, Osp E, Osp F, and of the Osp EF homologues, the Erp proteins.[128, 140, 142] As Osp A is downregulated and disappears, the spirochete becomes resistent to antibody against Osp A; this is important in vaccine development, as is discussed in the section Prevention: Vaccine Development.

B. burgdorferi produces none of its own proteolytic enzymes. It acquires a host-derived activated proteolytic complex consisting of plasmin, plasminogen, and a urokinase-type plasminogen activator, which arrives at the tick midgut in the blood meal, binds to Osp A while it is still expressed, and coats the spirochete; this complex is presumably able to dissolve extracellular matrix, facilitate dissemination of the spirochete to the tick salivary glands for transmission to the host, and then enhance spirochete dissemination in host tissues, where the host-derived antigens cause the spirochete to be invisible immunologically to the host.[143–146] Surface antigens of *B. burgdorferi*, particularly Osp A, are also involved in binding of the spirochete to collagen fibers, vascular endothelium, and other cells,[147] including antigen-presenting cells,[148] and in triggering a variety of events in host cells, ranging from expression of adhesion molecules to production of cytokines and other factors involved in the immunopathogenesis of the infection,[149, 150] as is discussed in the section Pathology and Pathogenesis.

Some antigens of *B. burgdorferi* have epitopes that share homology and cross react with host epitopes, leading to molecular mimicry,[151] such as *B. burgdorferi* Osp A and human leukocyte function–associated antigen-1 (LFA-1),[126] and possibly p83/100 and the human muscle and cytoskeletal proteins myosin and troponin,[106] *B. burgdorferi* flagellin, and human axonal heat shock protein 60.[113] This is discussed further in the sections Pathology and Pathogenesis, and Interactions with the Immune System: Correlation of Clinical Manifestations with HLA Type.

Taxonomy

Borrelia burgdorferi,[51, 94] the etiologic agent of Lyme borreliosis, is a member of the order Spirochaetales, the family Spirochaetaceae, the genus *Borrelia*, and the species *burgdorferi*. Borreliae are more closely related genetically to *Spirochaeta* than to *Treponema*, and all borreliae are transmitted by arthropods.[99]

B. burgdorferi was initially divided into four phenotypes,[92] and later into eight serotypes[51, 52, 105, 259] on the basis of antigenic diversity of Osp A as determined by reactivity with various monoclonal antibodies and by Osp A gene sequencing.[105] It was also initially divided into three genotype subspecies, based on DNA homology and ribosomal RNA restriction endonuclease pattern analysis,[50, 53] and corresponding to phenotypes based on major protein antigenicity, with 76 to 100% DNA homology within groups, and 46 to 74% between groups.[53]

As more isolates of *B. burgdorferi* have been studied by various methods, it has become clear that *B. burgdorferi* has phenotypic and genotypic heterogeneity.* On the basis of phenotypic and genotypic differences from

*See references 13, 51–66, 68, 70, 100, 105, 115, 117, 123, and 884.