OF MICE AND MEN: LYME DISEASE 1990

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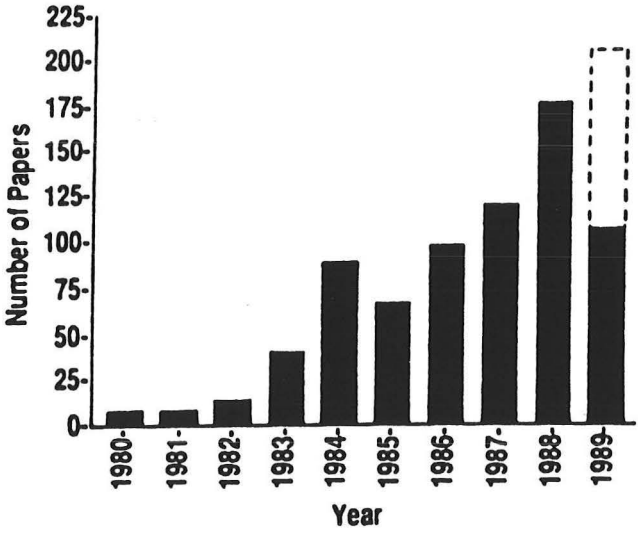
INTRODUCTION

Lyme disease or Lyme borreliosis, a multisystem infectious disorder caused by the spirochete Borrelia burgdorferi (B. burgdorferi) is the most prevalent arthropod-borne disease in the United States (1). Approximately 14,000 cases have been reported to the Centers for Disease Control since 1980 (1). In addition, it is estimated that thousands of new cases occur each year in Europe, and the disease is now known to be endemic in Asia (1). Current understanding of this entity dates from the mid 1970's when Allen Steere and colleagues at Yale University described a cluster of cases of arthritis in children and adults who lived in the vicinity of Lyme, Connecticut (2). The clinical and epidemiological studies which originated from this epidemic led to the identification of the etiological agent in 1982 and to the emergence of a comprehensive, though incomplete, understanding of the pathogenesis, clinical features and medical management of this disorder.

As shown in Figure 1, clinical and basic laboratory investigation of Lyme disease and B. burgdorferi has undergone explosive growth in recent years (3).

Figure 1: Distribution of papers on Lyme disease since 1980 with projection through 1989. Data taken from the *SCI®*.



Unfortunately, the attention of the popular media to Lyme disease has helped to fuel public anxiety about it, often in areas of the country in which it still poses only a minor threat to public health. However, it is also true that untreated Lyme Disease can have devastating sequelae and that the disease appears to be spreading beyond its original endemic foci. Today's Grand Rounds will review this rapidly evolving field. When appropriate, parallels and distinctions will be drawn between Lyme disease and venereal syphilis because it is now recognized that these two spirochetoses share a number of pathogenetic, immunologic, and clinical features.

HISTORY

Lyme disease is not an entirely new clinical entity. Its dermatological and neurological manifestations were well characterized in the European literature of the first half of the century. On the other hand, arthritis and carditis, manifestations typical of American Lyme disease, were not noted by European authorities. The convergence of the European and American experiences has enabled clinicians to develop the relatively complete clinical picture of Lyme disease that exists today. The milestones in the history of Lyme disease are outlined below.

A BRIEF HISTORY OF LYME DISEASE

1909	First description of ECM by Afzelius
1921	Afzelius' published case histories
1922	First report of neurological disease in a patient with ECM
1941	Bannworth's published series of Lyme meningitis/radiculitis
1957	Evidence for the bacterial etiology of ECM
1970	First reported case of Lyme disease in U.S.
1977	Steere's first report of Lyme arthritis
1982	B. burgdorferi isolated from I. dammini
1983	B. burgdorferi isolated from Lyme disease patients

In 1909 Arvid Afzelius described to the Swedish Dermatological Society an expanding, erythematous, annular lesion, associated with the bite of the hard tick Ixodes ricinus. He called the lesion "erythema migrans" and later added "chronicum" to designate lesions that persist for months, rather than weeks (4). In 1921, his combined cases appeared in a now frequently cited publication (5). Working independently in Vienna, Lipschutz (6) published similar findings in 1923 and speculated that an infectious agent was transmitted by the tick bite.

The first description of the neurological complications of Lyme disease appeared in 1922 when Garin and Bujadoux reported a 58 year old woman who developed erythema (not recognized by them as ECM) and meningoradiculitis following a tick bite (7). In 1930, Hellerstrom (8) called attention to the relationship between the ECM of Afzelius and meningitis, and he later speculated on its spirochetal etiology. In 1941 Bannwarth (9) described 26 patients with lymphocytic

meningitis, peripheral neuropathy, and cranial neuritis (now called Bannwarth's syndrome), although he did not relate his disorder to tick bites and ECM; his cases typify the neurological complications of Lyme disease most commonly seen today. In 1951, Hollstrom noted that penicillin had a beneficial effect on the course of a patient with ECM and meningitis (4). In 1957, Binder and associates provided indisputable evidence that ECM was caused by an infectious agent susceptible to penicillin (4). They transplanted into volunteers pieces of skin taken from the periphery of an ECM lesion; 1 to 3 weeks later all volunteers developed typical ECM which disappeared promptly following administration of penicillin (4).

The first documented case of Lyme disease in the United States was reported in 1970 by Rudolph J. Scrimenti a dermatologist in Milwaukee, WI (3,10). His patient was a 57 year old physician with ECM, headaches, and arthralgia; he was familiar enough with the European literature that he treated his patient with penicillin and saw clinical improvement. The epidemic of arthritis in Lyme, Conn. led to the realization that ECM, Bannwarth Syndrome, and Lyme arthritis were stages and manifestations of the same disorder transmitted by the bites of Ixodid ticks (11,12).

In 1982, Borrelia burgdorferi was discovered by Drs. Willy Burgdorfer, of the Rocky Mountain National Laboratory, and Jorge Benach, from the New York State Health Department. Neither was looking for the agent of Lyme disease. They were conducting a rickettsial survey of ticks on Long Island, New York. In what must be considered one of the more important serendipitous scientific discoveries of the past twenty years, instead of Rickettsiae, in the tick midguts they found spirochetes. As Burgdorfer reminisced: "I remembered the European literature... and I could not dismiss the thought that I had been led to the discovery of the long sought cause of ECM and Lyme disease" (4). Soon, the spirochetes were isolated by Burgdorfer and Alan Barbour (13). The following year two different groups independently reported that they had isolated from Lyme disease patients spirochetes that were antigenically related to those obtained from ticks (14,15).

MICROBIOLOGY

On the basis of DNA-DNA hybridization studies (Table 1) (16), the Ixodes tick spirochete was classified as a separate species of the genus Borrelia and named Borrelia burgdorferi in honor of its discover. B. burgdorferi is a slowly growing (doubling time approximately 20 hours) microaerophilic, fastidious bacterium that grow best in a complex mixture called modified Barbour-Stoenner-Kelly medium.

TABLE 1. DNA homologies between Lyme disease spirochetes and other spirochetes (16)

ORGANISM	REL. BINDING RATIO
Ixodes damini spirochete	100
Ixodes ricinus spirochete	100
Human CSF isolate	76
Borrelia hermsii	59
Borrelia turcicatae	46
Borrelia parkeri	37
Treponema phagedenis	2
Treponema denticola	2
Leptospira interrogans	1
Leptospira biflexa	1

Like all spirochetes, B. burgdorferi consists of an outer membrane surrounding a cytoplasmic membrane and a helically shaped protoplasmic cylinder (17). Compared to T. pallidum, B. burgdorferi is larger and has fewer and wider spirals; the tip structures of both organisms also are different. The organelles of motility, called endoflagella, are located in the periplasmic space between the outer and cytoplasmic membranes. T. pallidum has three to six endoflagella while B. burgdorferi typically has between eight and eleven (17). The outer membrane is a relatively fragile phospholipid bilayer; the best available biochemical data indicate that it does not contain lipopolysaccharide (18,19). The absence of lipopolysaccharide is a major biochemical difference between the double-membraned spirochete and conventional gram negative bacteria.

Considerable effort has gone into defining the composition of B. burgdorferi in the hopes of identifying molecules that contribute to the virulence of the organism, the immunopathogenesis of Lyme disease, or both. At the present time only a few of the organism's protein antigens have been defined at the molecular level. These include the 31-kDa Osp A and 34-kDa Osp B outer membrane proteins, the 41-kDa endoflagellar protein, and the 60-kDa heat shock protein (1,17,19). While the 41- and 60-kDa proteins appear to be antigenically invariant, Osps A and B vary considerably among North American and European strains (17,20), and it has been speculated that these differences account for the different clinical manifestations of Lyme disease in the United States vs. Europe (20).

B. burgdorferi possesses an unusual linear chromosome and two forms of plasmids--supercoiled circles and large linear plasmids; the latter are duplex pieces of DNA with covalently closed ends (19). Both Osps A and B are co-expressed off

burgdorferi attenuates the virulence of the organism and appears to correlate with loss of one or more plasmids (22). Loss of plasmids and virulence during repeated passage of B. burgdorferi isolates complicates larboratory investigations of Lyme disease pathogenesis.

ENTOMOLOGY AND EPIDEMIOLOGY

As described above, the association between ECM and tick bites was originally established by European investigators (4). In addition to the large proportion of patients with ECM-like lesions (2), several features of the original Lyme, Conn. epidemic suggested the likelihood of transmission by arthropods. These included [1] clustering of cases in sparsely inhabited, woody areas along the eastern shore of the Connecticut River, [2] peak occurrence in summer months, and [3] the lack of simultaneous disease among co-inhabitants. Shortly afterwards the same investigators reported that a significant proportion of patients recalled tick bites at the sites of ECM development (23). The thirty-fold greater prevalence of ECM in communities on the east side of the Connecticut River also correlated with the distribution of I. dammini (23). In a follow-up study, Steere and colleagues corrleated the distribution of Lyme disease cases throughout the United States with the geographic foci of I. dammini (Northeast and upper Mid West) and of I. pacificus (in the Western U.S) (24).

Lyme disease is transmitted to humans by five of the six species of Ixodid (I. ricinus "complex") ticks--I. dammini, I. pacificus, and possibly I. scapularis in the United States; I. ricinus in Europe, and I. persulcatus in Asia (1,25,26). The proportion of infected ticks appears to be a major determinant of the prevalence of Lyme disease in an endemic area; in some areas of the Northeastern United States, infection rates for I. dammini exceed 50% (25,26). Although B. burgdorferi has been demonstrated in mosquitoes, deer flies, and non-Ixodes ticks, their importance as vectors for disease transmission remains to be determined (27). The recent appearance of Lyme disease in areas outside of the known ranges of the Ixodid ticks, however, indicates the importance of other less well characterized vectors of Lyme disease.

Ticks transmit the bacterium when they feed, and the likelikhood of transmission depends upon the length of time the tick feeds. Transmission is unlikely when ticks feed for less than 24 hours and highly likely when they feed to repletion (28). Rapid removal of attached ticks, therfore, can be an extremely effective preventive measure. B. burgdorferi live in the midgut of infected ticks in close association with the microvillar brush border and the intercellular spaces of the gut epithelium. The organism is infrequently recovered from the saliva of infected ticks. Infection most likely occurs when midgut contents are regurgitated during feeding (29).

During their multi-year lifespans, Ixodid ticks develop through three distinct stages during which each individual tick feeds on three different host animals

(25,26). As shown in Table 2, all five species feeds on many different kinds of hosts, including small-, medium-, and large-sized animals. In the case of I. dammini, the white-footed mouse is particularly important for subadult ticks, while adults have a predilection for the white-tailed deer. Although all three feeding stages parasitize humans, humans are invariably incidental hosts (25,26).

Table 2. Significant hosts for *Ixodes* ticks harboring borreliae.

	Animal hosts for indicated stage	
Tick species	Larval and nymphal ticks	Adult ticks
I. dammini	Rodents, insectivores, birds	Deer, canids
I. scapularis	Skinks, birds, rodents	Deer, bear, canids, hogs
I. pacificus	Lizards, birds, rodents	Deer, bear, canids
I. dentatus	Rabbits, birds	Rabbits
I. ricinus	Rodents, insectivores, birds	Deer, canids, hares, cattle
I. persulcatus	Rodents, insectivores, birds	Deer, canids, hares, cattle

The tick developmental cycle begins in early spring when engorged females deposit eggs from which larvae emerge 6 to 8 weeks later (1,25,26). In late summer, the larvae feed on small rodents and develop into nymphs. In early spring or summer of the following year, the nymphs feed on small rodents, birds, or medium-sized vertebrates. The nymphs become adults in late summer or early fall and then attach to larger hosts, such as deer or cattle, for mating and feeding. Adult males attach to the latter host for mating but rarely feed (1,25,26). The white footed mouse, Peromyscus leucopus, the preferred host for both the larval and nymphal stages of I. dammini, is the major spirochetal reservoir and, as such, is crucial to perpetuation of B. burgdorferi in an endemic area (1,25,26,30). Early in the summer, mice become infected by feeding nymphs. They are amazingly tolerant to infection, remaining persistently spirochetemic for months, and can, therefore, infect feeding larvae later in the summer. Maintenance of high levels of B. burgdorferi in an endemic area appears to require that both immature forms feed on the same host species and that the hosts be both susceptible and tolerant to infection. Deer, which harbor adult ticks, are relatively unimportant as reservoirs of B. burgdorferi. They are necessary, however, for completion of the tick life cycle (i.e. mating) and for maintenance of the tick population in an endemic area (1,25,26,30). In contrast to the Northeast, cases of Lyme disease are sporadic on the West Coast. This is presumably because immature forms of I. pacificus feed predominantly on lizards and lizards not susceptible to spirochete infection (1).

Is American Lyme disease a new entity that is increasing in incidence or has it merely been underdiagnosed for many years? Clinical and epidemiological data suggest that its true incidence is increasing. Although ECM was a distinctive marker for this disorder, Steere et al. (2) noted that older physicians practicing in the area of the original outbreak did not recognize the lesion. Comparative serological and surveillance data from Southeastern Connecticut revealed that between 1977 and 1985 its incidence had increased from 129 to 453 per cent in towns known to be endemic for Lyme disease and that it had spread northward into towns not involved in the original surveillance studies (31). From 1988 to 1989, the number of confirmed cases in Texas rose from 28 to more than 80 (personal communication, Dr. Jeffry Taylor, Texas Dept. of Public Health). Since the original epidemic, other outbreaks have also been described.

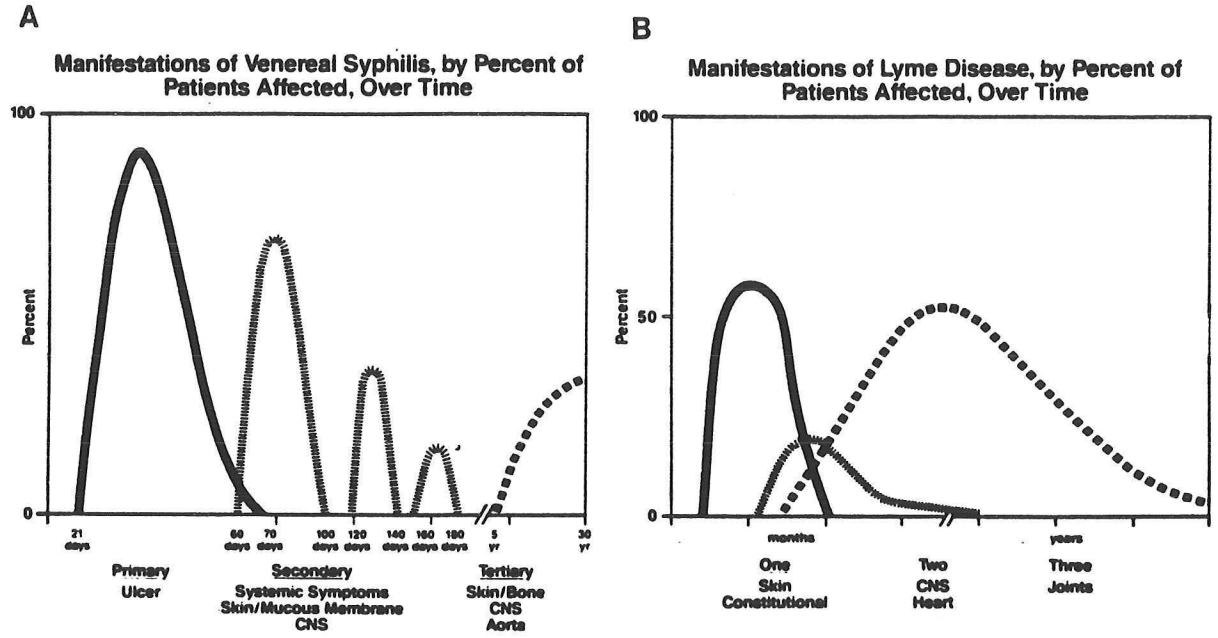
One of the best documented occurred in the community of Ipswich, Massachusetts. From 1980 to 1987, these investigators demonstrated progressive spread of Lyme disease from a nature preserve to the outlying inhabited areas. The authors theorized that the growth of the deer population in an area already heavily populated by white-footed mice allowed for an explosive increase of the Ixodid tick population and the introduction of Lyme disease into the adjacent humans (32). A similar dynamic, increased numbers of deer in proximity to humans, is thought to underlie the increasing incidence of Lyme disease in many other areas of the United States. However, this does not explain the emergence of Lyme disease in areas outside the range of Ixodes ticks. In the latter cases, one must speculate that B. burgdorferi has been introduced into regions where other vectors are capable of perpetuating the zoonotic cycle. Evidence has been generated suggesting that birds, which also may harbor borreliae, can function as reservoirs and disperse them over long distances (25,26).

PATHOGENESIS

Syphilis is the prototypical spirochete infection in that it progresses through relatively well defined stages of clinical activity separated by periods of remission (Figure 2A). Over the years, syphilologists have come to recognize that significant overlap exists between these stages (e.g. severe neurological disease during secondary syphilis). This is because asymptomatic, hematogenous dissemination of T. pallidum occurs early in the course of infection; in some patients this results in unexpectedly early disease manifestations.

Lyme disease also progresses through stages analogous to those of syphilis (Figure 2B). The overall usefulness of this scheme however, is diminished by the fact that in the individual Lyme disease patient significant overlap between the various stages may occur. Simultaneous with or shortly after the appearance of ECM (the equivalent of the syphilitic chancre) at the site of the tick bite, a large proportion of patients have constitutional symptoms and/or other clinical evidence of systemic dissemination (e.g. secondary ECM, lymphadenopathy) (1,2, 11,12).

Figures 2A and 2B



Positive blood cultures for B. burgdorferi have been obtained from a number of such patients (14,15,33), including some who have not developed an antibody response to the organism (33). Pathological evidence for dissemination of spirochetes also has been obtained in the first stage of Lyme disease. Inflammatory changes are found in virtually every organ and spirochetes can be detected ocasionally as well (34). Finally, the substantial number of reports describing diverse organ system involvement during acute Lyme disease (1) argues strongly for the rapid dissemination of spirochetes in early infection. For these reasons, it can be very difficult to separate stages one and two; many authorities prefer to distinguish between acute and chronic Lyme disease rather than utilize the above staging system. As will be discussed later, consideration of the time course of spirochete dissemination also has major implications for treatment of early Lyme disease.

As with syphilis, the clinical manifestations of Lyme disease reflect the complex interplay between host immunological defenses and the bacterium. In both spirochetoses, a perivascular inflammatory response consisting of lymphocytes and plasma cells is a prominent histopathological feature (34,35). Spirochetes are occasionally visualized in proximity to the involved blood vessels. In both diseases, endothelial cells of involved vessels appear to be "activated", and this may be important at the cellular and molecular level for disease progression (34,35). In chronic forms of Lyme disease, blood vessels of involved structures show more pronounced pathologic changes, including endarteritis obliterans as in Lyme synovitis. Occasionally, frank vasculitic changes analogous to those of tertiary syphilis are seen (34,35).

The close relationship between the immune response to B. burgdorferi and the clinical manifestations of Lyme disease is emphasized further by the fact that chronic Lyme disease, particularly arthritis, is often characterized by an extraordinarily intense inflammatory response in the face of a paucity of organisms (35-7). The latter observation, the poor response to antibiotic therapy shown by many patients, and the statistical correlation between HLA-DR2 and chronic arthritis have been cited as evidence that autoimmunity ("molecular mimicry") contributes to Lyme disease pathogenesis (1,37). Nevertheless, the fact that spirochetes can be found in many forms of chronic Lyme disease suggests that the intense inflammatory response characteristic of this stage is driven by the continued antigenic stimulus of a small number of organisms (34-8).

Finally, we are only now beginning to understand the cellular and molecular mechanisms by which B. burgdorferi invades cells. In vitro, the organism attaches to a wide variety of cell types, perhaps reflective of its ability to cause widespread disease (39). Most intriguing is the recent observation that the spirochete can attach to and penetrate cultured human umbilical vein endothelial cells (36,40). This may be the in vitro equivalent of the transendothelial migration that spirochetes must undergo prior to stromal invasion of different organs (33-8).

CLINICAL MANIFESTATIONS

Lyme disease may be brief and inconsequential or chronic and a significant cause of disability. Asymptomatic infection in endemic areas appears to be relatively common (1). Recognition of the diverse manifestations of Lyme disease, "the new great imitator" as opposed to syphilis, the "old great imitator" represents a major challenge to the practitioner. Nevertheless, differentiation of Lyme disease from other clinical disorders is imperative because of the availability of specific antimicrobial therapy.

A. Dermatologic.

ECM, the cutaneous hallmark of Lyme disease, is an annular, centrifugally expanding lesion that occurs in approximately 50% of patients (12,41,42). Approximately one third of patients recall receiving a tick bite in the 3 to 21 days prior to the onset of ECM (12). ECM typically begins as a painless, painful, and/or pruritic macule or papule; the thigh, groin and axilla are the most commonly involved sites. It expands as a confluent erythema or target-like lesion and can reach considerable size (occasionally diameters greater than 60 cm). Atypical variants with central scaling, vesicles, or purpura are described (12,41,42). Secondary lesions, numbering from one to more than 20, occur in as many as 50% of patients (12,41,42).

A small percentage of untreated patients will experience recurrences of ECM from one to 14 months after the original lesion (12). A large number of nondermatological signs and symptoms occur in ECM patients (Tables 3 and 4) (12) and probably reflect reflect hematogenous dissemination of B. burgdorferi with

systemic release of cytokines (Il-1, TNF etc.). Patients often report the constitutional symptoms as being extraordinarily debilitating.

Table 3. Early Symptoms of Lyme Disease

	Patients ($n=314$)
	n(%)
Malaise, fatigue, and lethargy	251 (80)
Headache	200 (64)
Fever and chills	185 (59)
Stiff neck	151 (48)
Arthralgias	150 (48)
Myalgias	135 (43)
Backache	81 (26)
Anorexia	73 (23)
Sore throat	53 (17)
Nausea	53 (17)
Dysesthesia	35 (11)
Vomiting	32 (10)
Abdominal pain	24 (8)
Photophobia	19 (6)
Hand stiffness	16 (5)
Dizziness	15 (5)
Cough	15 (5)
Chest pain	12 (4)
Ear pain	12 (4)
Diarrhea	6 (2)

Table 4. Early Signs of Lyme Disease

	Patients ($n=314$)
	n(%)
Erythema chronicum migrans*	314 (100)
Multiple annular lesions	150 (48)
Lymphadenopathy	
Regional	128 (41)
Generalized	63 (20)
Pain on neck flexion	52 (17)
Malar rash	41 (13)
Erythematous throat	38 (12)
Conjunctivitis	35 (11)
Right upper quadrant tenderness	24 (8)
Frank arthritis	19 (6)
Splenomegaly	18 (6)
Hepatomegaly	16 (5)
Muscle tenderness	12 (4)
Periorbital edema	10 (3)
Evanescent skin lesions	8 (3)
Abdominal tenderness	6 (2)
Testicular swelling	2 (1)

* Required for inclusion in this study.

ECM lesions have a relatively high culture positivity rate for B. burgdorferi (1,14,42).

Two other skin lesions, acrodermatitis chronica atrophicans (ACA) and lymphadenosis benigna cutis (LABC), are also associated with B. burgdorferi infection and occur almost exclusively among European Lyme disease patients. Both lesions are characterized by intense lymphocytic infiltration of the dermis, often in a perivascular distribution (43-5). ACA is a patchy erythematous swelling, usually on an extremity, that progresses to induration, thickening, and hyperpigmentation; in its late stages it may be indistinguishable from localized scleroderma (morphea) or lichen sclerosis atrophicans (43,44). LABC manifests as bluish nodules with a predilection for the ear lobes of children and the nipple areas of adults (45).

B. Neurologic.

The full spectrum of neurological disorders attributable to Lyme disease remains to be defined. Some clinical syndromes (e.g. meningoradiculitis, cranial neuritis) are undeniably associated with it, while others (e.g. encephalopathy and multiple sclerosis type syndromes) are less well established. Current difficulties in diagnosing Lyme disease (described below), particularly the reliance upon serodiagnosis, account for many of the controversies over the neurological spectrum of the disorder (45).

As described above, a large amount of evidence supports the contention that hematogenous dissemination and central nervous system invasion by B. burgdorferi occur early in Lyme disease. In addition to the minor neurological complaints (somnolence, headache, stiff neck) seen in many ECM patients (1,12,45), approximately 40% of patients with frank neurological involvement still have detectable ECM lesions (46). All told, about 15% to 20% of ECM patients develop frank neurological symptoms, often recurrent in nature, within weeks to months following infection (1). The most common pattern of acute neurological illness is the "classical triad" of meningitis (often meningoencephalitis), sensory and/or motor radiculitis, and cranial neuritis (Table 5) (46,47). However,

TABLE5. Type of neurologic involvement

Patient	Age	Meningitis	Encephalitis	Cranial Neuritis	Radiculoneuritis		Myelitis
					Motor	Sensory	
A.	9	+	+				
B.	18	+	+		+		
C.	58	+	+	+		+	+
D.	9		+				
E.	20	+		+			
F.	33	+	+		+		
G.	49	+	+	+	+	+	
H.	56	+	+	+		+	
I.	22	+	+	+			
J.	10	+	+				
K.	15	+	+				
L.	8	+	+				
M.	27	+	+				
N.	22	+		+	+		
O.	14	+	+	+	+		
P.	66			+		+	
Q.	4			+			
R.	32			+			
Total		14	13*	10	5	4	1

presentations with individual components of the triad are also well recognized. Of the cranial neuropathies, unilateral and bilateral Bell's palsies are the most frequently encountered and the best documented (1,46-48) Typical locations for the radiculoneuritis syndromes are shown in Figure 3 (47).

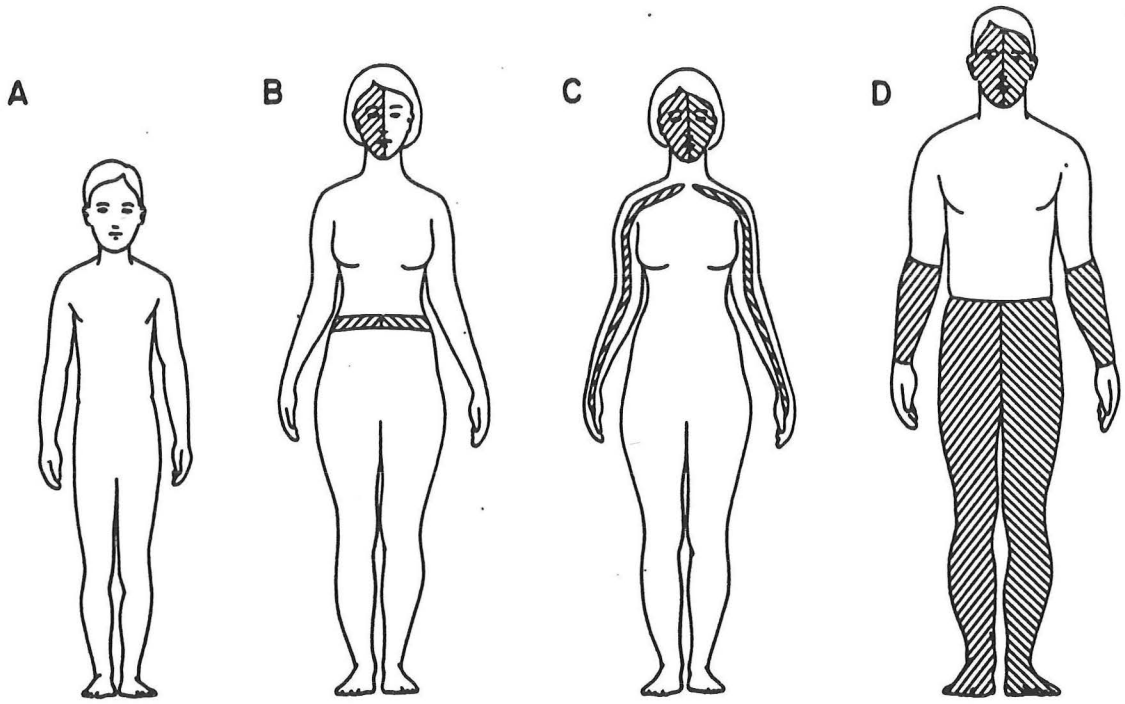


Figure 3

Cerebrospinal fluid abnormalities are usually those of an "aseptic" meningitis; plasma cells may also be noted and are an important clue to diagnosis (46,48). In patients with Bannwarth syndrome one can often demonstrate markedly elevated IgG synthetic rates in the central nervous system and intrathecal production of specific antibodies against B. burgdorferi (47).

Finally, in recent years evidence has also arisen that patients with chronic or late Lyme disease (diagnoses primarily by reactive serological tests) may develop peripheral neuropathies with widespread nerve conduction abnormalities and central nervous system involvement ranging from cognitive difficulties and/or mild encephalopathy to severe encephalitis/vasculitis syndromes (49-50).

C. Rheumatologic

During the past 15 years, Steere and co-workers have carefully characterized Lyme arthritis, the most distinctive feature of the American form of the disease (2,11,12,51). In their original series (2), most patients experienced brief, recurrent attacks of asymmetric swelling and pain in a few large joints, especially the knee, within weeks after the appearance of ECM. In a subsequent longitudinal study, they found that within six months of onset of ECM, seven of 12 patients experienced joint complications ranging from migratory arthralgias to intermittent monoarticular or oliogarticular arthritis (11). Later they found that some patients with intermittent arthritis can develop a chronic, occasionally deforming, synovitis similar to rheumatoid arthritis (52).

A six year longitudinal study of 55 untreated patients, published in 1957, has provided the most comprehensive picture of Lyme arthritis yet available (51). From one day to eight weeks after the onset of ECM, eighteen percent of the patients experienced short episodes of joint, periarticular, and/or musculoskeletal pain; none of these patients had objective joint abnormalities (Figure 4). Approximately half of the cohort (51%) developed one or more episodes of frank arthritis, usually monoarticular or oligoarticular arthritis in large joints, from four days to two years after onset of ECM (Figure 4). In these patients, the frequency and duration of attacks diminished with time (Figure 5). Temperomandibular joint involvement was also frequent.

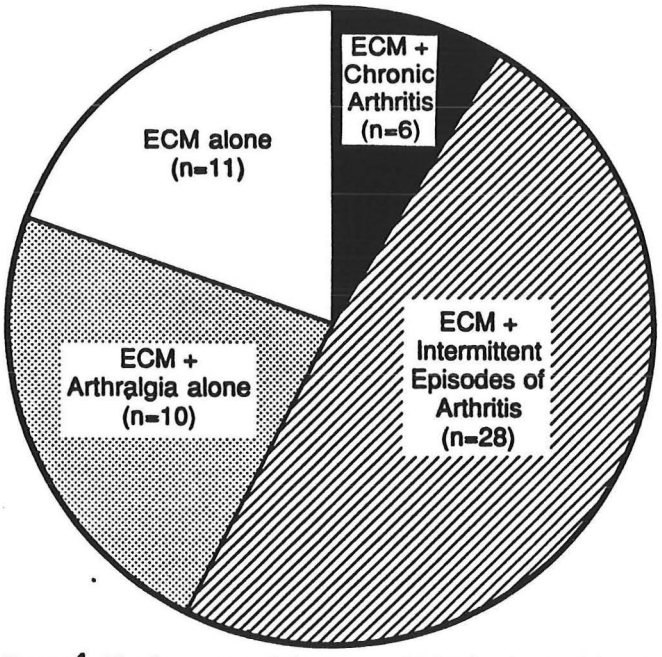


Figure 4. The frequency of the types of joint involvement in patients with Lyme arthritis. The spectrum ranges from arthralgias, to intermittent episodes of arthritis, to chronic arthritis.

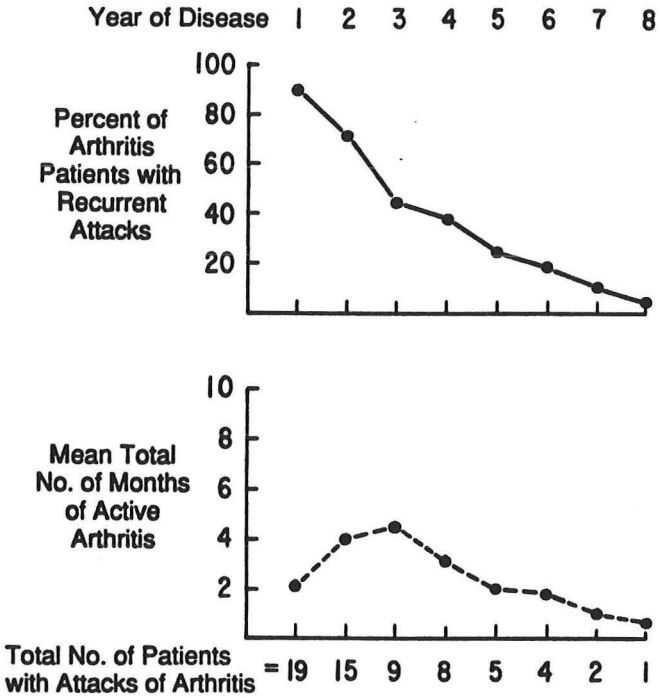


Figure 5. The percentage of arthritis patients with recurrent attacks (*top*) and the mean total number of months of active arthritis by year of disease (*bottom*). Nineteen of the 21 patients had attacks of arthritis during the first year of illness, and the number of patients who continued to have recurrences decreased by 10% to 20% each year. The mean total number of months of active arthritis was 4 and 5 months during the second and third years of illness and decreased to 2 months or less by the fifth year.

Six of the 55 patients (11%) developed chronic arthritis in one to three large joints from 4 months to 4 years after disease onset (Figure 4); in five the persistent arthritis was preceded by intermittent attacks. Four of the patients had involvement of one or both knees, while the other two patients had hip and shoulder involvement, respectively. One patient developed radiographic evidence of joint erosion. In three patients, the arthritis subsided spontaneously within 1.5 to three years.

In addition to arthritis, other rheumatological complications of Lyme disease have been reported. These include myositis, spondyloarthropathy, osteomyelitis, and panniculitis (1, 53).

D. Cardiac

Occurring in between 4% and 10% of untreated patients, carditis is the least frequently encountered major complication of Lyme disease (54,55). Initially described only in the United States, European cases are now also being reported (55,56). The myocarditis of Lyme disease is diffuse, as determined by both electrocardiographic changes, Gallium-67 myocardial scanning, and, in a limited number of cases, endomyocardial biopsy (54-7). However, patients present most commonly with symptoms due to complete or high-grade heart block rather than left ventricular dysfunction (54-58). Surface EKGs and His bundle studies indicate that the block is almost always supra-Hisian (54,55,58).

Hospitalization and continuous monitoring are advisable for patients with second degree or complete A-V block and for first degree block when the PR interval is greater than 0.30 seconds (55). The prognosis for patients with Lyme carditis is excellent with the majority of patients returning to normal sinus rhythm within days to weeks (54,55,58). A small number of patients have required implantation of permanent pacemakers (55). As shown in Table 8, carditis is usually seen in association with other stigmata of acute Lyme disease, thereby facilitating the diagnosis. However, cardiac involvement may be isolated and/or chronic (56,57). Recently, histopathologic and microbiologic evidence has been provided that the continued presence of spirochetes drives the intense inflammator response in the myocardium (56,57).

DIAGNOSIS

Diagnosis of Lyme disease is relatively straightforward when a patient in an endemic area presents with classical stigmata, such as ECM. Physicians practicing outside endemic areas are less likely to be familiar with the disease and are particularly prone to mistake it for another disorder. Because of the beneficial effects of antimicrobial therapy, it is incumbent that Lyme disease be included in the differential diagnosis of patients with compatible neurologic, rheumatologic, and/or cardiac disorders.

Laboratory confirmation of Lyme disease is often essential, particularly in nonendemic areas. A patient with a compatible clinical syndrome is considered to have Lyme disease if a confirmatory test, usually serological, is reactive and other diseases, particularly syphilis, are ruled out. Unfortunately, each of the available laboratory modalities has significant limitations with which the clinician must be familiar.

Identification of B. burdorferi in clinical specimens is the definitive means of confirming a diagnsosis of Lyme disease. Presently, this can be accomplished

either by in vitro cultivation in BSKII medium or by histological techniques. In addition to being extremely slow (usually weeks), isolation of B. burgdorferi from clinical specimens is not very reliable. For example, in the seminal work by Steere et al. (14) only three isolates were made from 56 cultured specimens (Table 6). It does not appear as if more recent investigators have improved substantially on these isolation rates (33). Isolation rates are highest in ECM and ACA, the distinctive cutaneous forms of Lyme disease in which cultural confirmation is probably least necessary (59).

Table 6. Isolation of *I. dammini* Spirochetes in Cultured Specimens from 56 Patients.

Material	No. of Cultures	No. Positive
Blood		
Whole	28	0
Plasma near buffy coat	27	0
Resuspended plasma pellet	25	1
Skin (ECM)		
Biopsy	18	1
Scraping	23	0
Cerebrospinal fluid	5	1
Lymph-node aspirate	10	0
Urine	6	0

B. burgdorferi stains well using Warthin-Starry or Dieterle silver stain and it also can be detected using various specific monoclonal and polyclonal antibodies (59). However, histopathological and immunohistochemical methods are postive in only a minority of specimens (59). Recently, the polymerase chain reaction (PCR) has shown promise as an exquisitely sensitive and highly specific method for detection of the spirochete in clinical specimens (60).

Since the discovery that Lyme disease patients have elevated titers of serum antibodies against the Ixodes tick spirochete (14), detection of antibodies to B. burgdorferi has become the mainstay of laboratory diagnosis. Enzyme-linked immunosorbent assays (ELISAs) and immunoblotting have replaced indirect immunofluorescence as the formats of choice (1,59,61). In the past five years, the antibody response to this pathogen has been extraordinarily well characterized, both in terms of time course and the specific antigens being recognized. Patients with early Lyme disease produce primarily IgM antibodies, the majority of which appear to be directed against the 41-kDa (endoflagellar protein) (Figure 6). In the later stages of disease, IgM titers fall, while elevated IgG titers can be detected against a number of proteins, including the pathogen- specific Osps A and B (Figure 6).

Despite their usefulness, serological tests are not without their pitfalls as both false negative and false positive results commonly occur. The majority of false negative results occur in early disease, primarily because the antibody response to B. burgdorferi develops slowly (59,61,62). Up to 50% of such patients may have undetectable levels of both IgM and IgG antibodies (59,61,62). In other words, a negative serological test does not rule out Lyme disease in a patient who has been symptomatic for a short period of time (days to weeks).

Increased sensitivity has been claimed for both immunoblotting and antibody capture ELISA as compared to conventional ELISA (63,64). In the later stages of disease, however, serological tests approach 100% sensitivity (1,59,61,65). Patients with "seronegative late" disease, a controversial phenomenon, may be an exception to this latter statement (66). On the other hand, reactive serological tests do not necessarily mean that a patient's symptom complex is due to Lyme disease, especially for patients from endemic areas where seroprevalence rates approach 10% (1). Some of the more poorly substantiated manifestations of Lyme disease in the literature may represent a serendipitous occurrence of a reactive serological test in a patient with an unrelated clinical problem.

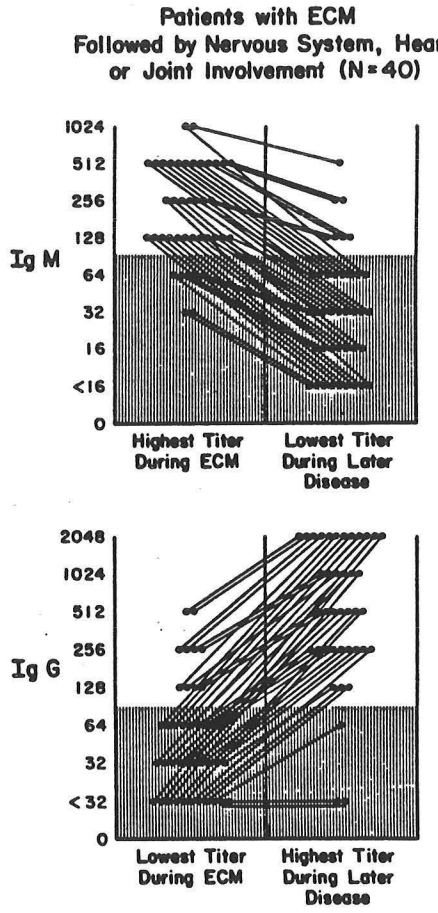


Figure 6

The majority of tests performed by commercial laboratories utilize the ELISA format and antigen derived from whole organisms. The most serious drawback to these assays is their lack of specificity and reproducibility. Specificity problems arise from the fact that all human sera contain antibodies directed against commensal spirochetes that cross-react with B. burgdorferi. Titers agains such cross-reactive antigens can be extremely elevated in other spirochete diseases, especially relapsing fever and syphilis (59,61,62,65,67). Treponemal tests for syphilis (e.g. the MHA-Tp) circumvent this problem by adsorbing cross-reactive antibodies from the test sera, however no adsorption step is routinely performed in Lyme testing. Problems with reproducibility (68) arise from the fact the none of the commercially available tests have been standardized as was done for syphilis tests by the Centers for Disease Control in the 1960s.

Investigators have employed several strategies to solve the problem of nonspecificity. The simplest approach has been to adsorb cross-reactive antibodies using various spirochete preparations (65,67). Another approach has been to use immunoblotting to be help recognize antibody responses against B. burgdorferi-specific antigens (69,70). Finally, other investigators have attempted to isolated B. burgdorferi-specific antigens from cultivated spirochetes for use as serodiagnostic antigens (71).

The consequences of the specificity and reproducibility problem may be enormous. Since many patients have complaints compatible with but not due to Lyme disease, false positive serological tests can result in psychological trauma and inappropriate administration of antimicrobial therapy. Since such patients do not respond to therapy, they are then labeled as "refractory". It is my opinion that a large proportion of patients from nonendemic areas have been diagnosed with Lyme disease on the basis of falsely positive serological tests.

TREATMENT

Antimicrobial regimens for the treatment of Lyme disease are still evolving. For this reason, the current recommendations (Table 8) are somewhat controversial and revisions will undoubtedly occur as new data become available.

Even before the bacterial etiology of Lyme disease was discovered, clinical evidence supported the efficacy of antimicrobial therapy for ECM (1,72). In 1980, Steere and co-workers (73) followed up these anecdotal reports with a randomized, controlled study of oral antimicrobials (penicillin V, tetracycline, and erythromycin) for early Lyme disease. Their study provided conclusive evidence that oral penicillin V and tetracycline decrease the duration of ECM and associated symptomatology. However, ECM recurred in a small number of treated patients. Even more disturbing, oral antimicrobials had no effect on the subsequent occurrence of neurologic or cardiac disease and only diminished, but did not eliminate, subsequent arthritis (73). The occurrence of late sequelae despite appropriate therapy of early disease has been noted by other investigators (1,74).

In recent years the determinants of successful therapy have been better defined with the result that the reasons for the treatment failures in early disease are now clearer. First, as with T. pallidum, prolonged exposure to an antimicrobial is required to kill B. burgdorferi (75). Second, unlike with T. pallidum, penicillin has relatively poor activity against B. burgdorferi compared with ampicillin (or amoxicillin), tetracycline and the third generation cephalosporin, ceftriaxone (75,76) (Table 7). Finally, since B. burgdorferi disseminates early in the course of infection, effective antimicrobial levels must be reached in sites such as joints and central nervous system at this stage if relapses are to be prevented. On the basis of these findings, regimens for early disease have been formulated that include high dose

Table 7. MBCs of seven antimicrobial agents for *Borrelia burgdorferi*.

Antimicrobial agent	MBC (μg/mL)	
	Mean	Range
Penicillin G	8.7	3.2–12.8
Amoxicillin	1.9	0.4–3.2
Ceftriaxone	0.05	0.02–0.08
Erythromycin	0.13	0.04–0.16
Tetracycline	1.8	0.8–3.2
Doxycycline	1.0	0.4–3.2
Ciprofloxacin	4.0	0

amoxicillin or doxycycline to ensure adequate tissue penetration (Table 8). Patients treated with one of these regimens require close follow up. Furthermore, early Lyme disease patients who are extremely symptomatic or who have significantly abnormal CSF might fare better with parenteral antibiotics from the start.

Treatment of late Lyme disease appears to be even more problematic. In the early 1980s, Steere and colleagues (78) established the efficacy of high dose intravenous penicillin for late Lyme disease. However, they, and others noted a significant rate (as high as 50% in some series) of penicillin treatment failures in such patients (73,78). One possible explanation is that immunological,

Table 8 Treatment of Lyme disease.

Type of disease, drug	Adult dosage	Pediatric dosage
Early		
Amoxicillin	500–1,000 mg tid × 21 d	40 mg/(kg·d), divided, × 21 d
plus probenecid (optional)	500 mg tid × 21 d	
Doxycycline	100 mg bid or tid × 21 d	
Erythromycin*	250 mg qid × 10–21 d	30 mg/(kg·d), divided, × 10–21 d
Neurologic		
Mild (Bell's palsy)		
Doxycycline	100 mg bid or tid × 21–30 d	
Amoxicillin	500–1,000 mg tid	
plus probenecid	500 mg tid × 21–30 d	
More serious CNS disease		
Penicillin G	24 million units/d, divided, × 14–21 d	250,000 units/(kg·d) iv, divided (q4h), × 14–21 d
Ceftriaxone	2 g/d × 14 d	75–100 mg/(kg·d) iv
Cardiac		
Mild		
Doxycycline	100 mg bid or tid × 21 d	
Amoxicillin	500–1,000 mg tid × 21 d	40 mg/(kg·d), divided, × 21 d
plus probenecid	500 mg tid × 21 d	
More serious		
Penicillin G	24 million units/d, divided, × 14–21 d	250,000 units/(kg·d) iv, divided (q4h), × 14–21 d
Ceftriaxone	2 g/d × 14 d	75–100 mg/(kg·d) iv
Arthritis		
Ceftriaxone	2 g iv × 14–21 d	75–100 mg/(kg·d) iv
Doxycycline†	100 mg bid × 30 d	
Amoxicillin	500–1,000 mg tid × 21 d	
plus probenecid	500 mg tid × 30 d	

* Alternative therapy.
† Under investigation.

unaffected by the antimicrobials. On the presumption that cidal levels of penicillin G may still not be reached in sites such as joints and central nervous system, Dattwyler and colleagues (79,80) compared the efficacy of penicillin G to that of ceftriaxone, an agent with excellent cidal activity against B. burgdorferi, a prolonged half-life, and excellent tissue penetration (including passage across the blood-brain barrier). Their data indicate that ceftriaxone is superior to penicillin G (Table 9). Their study also supports the thesis that microbiologic treatment failure, rather than autoimmune processes, predominate in chronic Lyme disease. It remains to be seen, however, whether ceftriaxone will become the definitive therapeutic agent for this complex infection.

TABLE 9 Symptoms of Lyme Borreliosis in Randomized Study Comparing Parenteral Penicillin to Ceftriaxone

	Penicillin[a]		Ceftriaxone[b]	
	Before[c]	After[d]	Before[c]	After[d]
Arthritis	7 (70%)	5 (50%)	9 (75%)	0 (0%)
Peripheral neuropathy	3 (30%)	1 (10%)	7 (60%)	0 (0%)
Fatigue	8 (80%)	5 (50%)	10 (85%)	1 (8%)
Carditis	1 (10%)	0 (0%)	0 (0%)	0 (0%)

[a]Ten patients received penicillin G, 3×10^6 units, six times daily for 10 days.
[b]Twelve patients received ceftriaxone, 2 g, twice daily for 14 days.
[c]No. of patients with symptoms (% of patients) prior to therapy.
[d]No. of patients with re-exacerbation of symptoms within 6 months of completion of therapy.

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