Annu. Rev. Publ. Health. 1991. 12:85–109

LYME DISEASE: A MULTIFOCAL WORLDWIDE EPIDEMIC

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KEY WORDS: *Borrelia burgdorferi,* Ixodes ticks

INTRODUCTION

Lyme disease (LD) is a multisystem, inflammatory disease that is caused by the spirochete, *Borrelia burgdorferi,* and spread by Ixodes ticks. Since the isolation of the organism, we have clearly seen that many lessons learned from syphilis are applicable to Lyme disease. Syphilis, which is caused by *Treponema pallidum* (another spirochete), is also a multisystem disease that often is quite delayed after the initial infection. In the last few years, a better understanding of LD has helped us understand syphilis, as well.

In 1975, Steere, Malawista, and colleagues at Yale University described Lyme arthritis, an oubreak of "juvenile rheumatoid arthritis" in three small towns on the east bank of the Connecticut River (142). Over the next few years, we began to appreciate the multisystem nature of this newly described ailment, and the name "Lyme disease" came into usage. By 1990, researchers identified Lyme disease as an epidemic disease in the Northeast (from Massachusetts through Pennsylvania, with cases described as far south as the Carolinas and Georgia); the northern Midwest (primarily Minnesota and Wisconsin, as well as Michigan), and in northern California and Oregon. In the United States, 90% of the cases reported are from these three regions, and the total number has steadily increased each year. In retrospect, however, the story of *B. burgdorferi* infection began in Europe, more than a century ago.

0163-7525/91/0501-0085$02.00

In 1883, Buchwald reported an atrophic skin lesion, which, in 1902, Herxheimer and Hartmann named acrodermatitis chronica atrophicans (ACA). In 1946, Hauser reported that some patients recalled a tick bite, often at the site of the skin lesion. Occasionally, the ACA lesion had been preceded by another lesion, known as erythema chronicum migrans (ECM), also at the site of the bite.

Afzelius had described ECM previously in 1909, and in 1914 Lipschutz gave the lesion its descriptive name. In 1922, Garin and Bujadoux noted a connection between meningitis and preceding tick bite, and in 1941 Bannwarth reported tick-borne meningopolyneuritis, the syndrome that bears his name. In 1930, Hellerstrom reported that in certain patients, lymphocytic meningitis was preceded by ECM. Lenhoff described spirochetal forms in biopsies from ECM lesions in 1948, and in 1951 Hellerstrom found that ECM resolves after standard spirocheticidal therapy (including bismuth, neoarsphenamine, and penicillin). In 1955, Binder reported that ECM could be transferred by skin graft.

Scrimenti reported the first case of ECM in the Americas, which occurred in Wisconsin in 1970. Five years later, the outbreak of juvenile rheumatoid arthritis in Connecticut was also linked to proceding ECM and tick bite. Over the next few years, Lyme arthritis, became known as Lyme disease, in part because of the association with cardiac disease, but also because approximately 10% of the patients had a neurologic syndrome essentially identical to Bannwarth's syndrome. The multisystem, inflammatory nature of Lyme disease was established.

After *B. burgdorferi* was identified as the etiologic agent of LD in the United States, studies in Europe established that the same organism was the cause of ECM and ACA in Germany, Austria, and Scandinavia. Indirect immunofluorescence (IFA), enzyme-linked immunosorbent assay (ELISA), and Immunoblot for serologic testing and T-cell proliferative responses for cellular testing are now used to confirm the diagnosis of LD. Comparison of levels of specific immune reactivity between sites of inflammation and the peripheral blood help to identify locations of *B. burgdorferi*-induced inflammation. Newer techniques, like polymerase chain reaction, in situ hybridization, and immunologic antigen identification help locate organism-derived compounds at these sites.

Lyme disease is now known to have a worldwide distribution, with cases described in Africa, Asia, and Australia. The primary vector in each area has been identified as an Ixodes tick: *I. dammini* in the Northeast and Midwest, *I. scapularis* in the Southeast, and *I. pacificus* in California.

Thus, between 1883 and 1990, at least three discrete skin lesions and a multisystem, inflammatory disease have been ascribed to infection with *B. burgdorferi*. Sufficient new information has been generated to hold three

international convocations and fill three volumes (12, 131, 141); the fourth such meeting was held in June 1990, in Stockholm.

CLINICAL DESCRIPTION AND CONTROVERSIES

Lyme disease is an infectious disease, capable of causing damage to a number of organ systems (18, 31). The clinical syndrome has been divided into three relatively arbitrary stages to describe the many manifestations. Stage One usually occurs within a month of inoculation with *B. burgdorferi,* the causative agent (13, 59, 137). It includes ECM, which is the skin rash that is a marker for LD, and associated symptoms. Stage Two manifestations include cardiac and neurologic disease and usually occur two to three months after the initial infection; there may be no preceding evidence of illness suggestive of Stage One LD. Stage Three includes arthritis and chronic neurologic manifestations, which have recently been described; Stage Three may occur years after ECM, or in the absence of any preceding history suggestive of earlier LD.

Stage One occurs between one day and one month after tick bite (median seven days). It consists of ECM and associated symptoms: fever, fatigue, malaise, headache, stiff neck, arthralgia, and myalgia. About 50–70% of patients will experience ECM; of these, 50% will have more than one skin lesion. Regional (and occasionally systemic) lymphadenopathy may occur. Patients may experience pain on neck flexion, conjunctivitis, erythematous throat, or temporomandibular joint pain. A few patients have hepatosplenomegaly and/or right upper quadrant tenderness (133). Only about 30% of patients will recall a tick bite (142), although animal studies suggest that the tick must remain attached for a day or longer to transmit the disease (97).

Nonspecific laboratory studies, such as erythrocyte sedimentation rate, complete blood count, and liver function tests, are not clinically helpful, even when abnormal (133). In the first weeks of the disease, specific serologic tests may be negative (30, 103, 138). Researchers have cultured *B. burgdorferi* from biopsy specimens taken at the expanding red border of the ECM lesion (138).

Two to three months following the onset of ECM, about 10–15% of untreated patients with Stage One LD will experience neurologic disease. Meningoencephalitis, meningitis, cranial nerve palsies, and peripheral neuropathies may occur (91, 95, 100). These conditions are often accompanied by extreme fatigue, malaise, headache, and photophobia; fever is usually absent. Mild encephalopathy, including difficulty with concentration and memory and emotional lability, may occur. These neurologic findings match those described in Europe in the early part of this century. They are

now known as Bannwarth's syndrome (9) or tick-borne meningopolyneuritis (53).

A lymphocytic pleocytosis is found in cerebrospinal fluid with elevated protein, but normal glucose levels (91, 100). *Borrelia burgdorferi* has been grown from the cerebrospinal fluid of patients with Lyme meningitis (138).

Pachner & Steere (91) have found neuropathic changes on nerve conduction testing; Halperin et al (46) documented axonopathy in one third of patients with peripheral neuropathy. Peripheral nerve biopsies have shown heavy epineural vessel infiltration with mononuclear cells (23, 39, 46, 62, 153). Vasculitis, but no organisms, was seen in one patient (23); luminal obliteration of perineural vessels without vasculitis was found in another (39). Researchers have not seen immune complexes, immunoglobulin, and complement in biopsy specimens (23, 46).

Stiernstedt et al (148) proposed vascular disease induced by *Borrelia burgdorferi* as a possible pathogenetic mechanism for cerebrovascular disease. Midgard & Hofstad (83) have seen vasculitis on angiographic study of a patient with LD central nervous system disease.

Most patients with encephalitic symptoms have abnormalities on electroencephalography (91). Halperin et al (46) have documented reversible neuropsychiatric testing abnormalities; they found small plaques in some patients on magnetic resonance imaging (MRI); the plaques occasionally resolved after antibiotic therapy. An insufficient number of normal individuals have had MRI to know if these plaques represent *B. burgdorferi*-induced cerebral damage or if normal individuals may have such plaques.

Cardiac disease occurs in 8–10% of previously untreated patients two to three months after ECM, occasionally in association with Stage Two neurologic disease. Steere et al (134) have reported atrioventricular conduction defects, mild congestive heart failure, and ST and T wave changes compatible with myopericarditis. Researchers have described reversible (50, 55, 101) and rarely fatal (77) myocarditis. Multifocal damage has been documented in electrophysiologic studies of individual cases (101, 134). Duray (39) described focal myonecrosis and a sparse interstitial infiltrate of polymorphonuclear cells and lymphocytes in one report of myocardial biopsies; in another report, Reznick et al found *B. burgdorferi,* myonecrosis, and perivascular mononuclear cell infiltration. The finding of an organism within the myocardium (77) suggests that direct invasion occurs in Lyme myocarditis.

Arthritis is the classic feature of Stage Three LD (136). Steere et al summarized their experience with 55 LD patients who did not receive antibiotic therapy (144). A prospective study of these patients revealed that 44 experienced articular problems over a six-year period. Of this group, ten

patients experienced arthralgias with or following ECM, occurring one day to eight weeks (mean, two weeks) after the onset of the lesion. Twenty-eight patients had polyarthritis, often migratory, four days to two years after the onset of ECM (mean, six months); half of this group had experienced preceding migratory arthralgias. Finally, chronic Lyme arthritis developed in six patients, usually affecting a single joint, with onset four months to four years after ECM (mean, 12 months); Five of these patients had experienced either arthralgia or intermittent arthritis before chronic synovitis developed. The migratory polyarthritis group is reminiscent of the original cohort of patients described by Steere et al in their initial report of Lyme arthritis (142).

The synovium in Lyme arthritis is hypertrophic and hyperplastic, with focal necrosis, vascular proliferation, and inflammatory cell infiltration. Mononuclear cell aggregates and lymphoid follicles, which resemble rheumatoid synovium, may be present (136), although there are histological differences between rheumatoid and Lyme synovitis (39). As in syphilis, endarteritis obliterans may be seen, with capillary arborization, dilatation, and congestion (60). *B. burgdorferi* has been seen rarely, in or near synovial vessels (60) or in synovial fluid (126), and it has been grown from synovial fluid (105).

Tertiary neuroborreliosis, a term that purposely draws upon the clinical analogy with tertiary neurosyphilis, includes chronic encephalomyelopathy and neuropathy (1, 90, 92). Like tertiary neurosyphilis, Stage Three neurologic LD may occur insidiously months to years after the onset of infection, even in the absence of clinically apparent preceding infection. Thus, subclinical infection may occur for long periods before the emergence of overt neurologic damage. This development raises serious concerns over the finding of asymptomatic seropositivity in a significant percentage of persons in areas endemic for LD.

One of the major controversies regarding LD is the question of which clinical conditions can be ascribed to *B. burgdorferi* infection. On the basis of seroepidemiologic and biopsy evidence, it has been suggested that many cutaneous lesions, including morphea, lichen sclerosis et atrophicans, eosinophilic fascitis, and certain other cutaneous fibrotic disorders, are due to *B. burgdorferi* (118). However, these claims are by no means definitive. Subclinical or asymptomatic infection may be prevalent in endemic areas (30, 145), so that seropositivity may represent no more than a coincidence (117).

An area of great interest is defining the true extent of neurologic manifestations of LD. Claims that amyotrophic lateral sclerosis (76), multiple sclerosis (29), and Alzheimer's disease (94) are due to infection with *B. burgdorferi* have been laid to rest. Many individual cases of neurologic

damage have been attributed to *B. burgdorferi* infection merely because the patient has a positive serologic test, a circumstance that does not guarantee causality.

Another area of major concern is *B. burgdorferi* infection that occurs during pregnancy. Shortly after the LD epidemic in the Northeast was appreciated, reports of adverse outcomes of pregnancy began to appear. In a review of 19 pregnancies between 1976 and 1984 that were complicated by LD, Markowitz et al (78) noted 14 normal births and 5 adverse outcomes. Complications included rash, syndactyly, congenital heart anomalies, cortical blindness, prematurity, and intrauterine death. Toxemia of pregnancy has been attributed to pregnancy-related *B. burgdorferi* infection (69). Claims have been made that *B. burgdorferi* may cause fetal anomalies and fetal demise (70, 104, 155). A few large studies have been organized to evaluate the true risk of such infection. A prospective study found no evidence that asymptomatic seropositivity had any effect on pregnancy outcome (38), and a study in New York found no association between anti-*B. burgdorferi* antibody in cord blood and congenital malformations in the babies (157). A Swiss study found no reason to screen for LD during pregnancy (86), whereas a small Italian study found that LD during pregnancy might predispose to stillbirth (24). Thus, the theory that *B. burgdorferi* infection causes adverse pregnancy outcomes has not been proven. The ongoing study of Dlesk et al (38) hopefully will gain enough entrants to answer this question definitively.

There also is no evidence that LD can be passed by sexual or other intimate contact. There is evidence, however, that *B. burgdorferi* can survive in blood (10) and various blood products (11) for as long as 6–8 weeks (L. H. Sigal, unpublished observations). Whether LD can be spread by transfusion is unclear (8).

DIAGNOSIS AND DIAGNOSTIC TESTING

In early studies of LD, the presence of ECM was required to assure that diagnosis, as ECM was the only pathognomonic feature of the disease (133). Because LD has been described in more geographic areas and has been implicated in more clinical situations, a case definition became necessary. In 1982 and 1983, the Centers for Disease Control stated that ECM in an endemic area, or ECM and two or more organ systems affected in a nonendemic area, would be accepted as a case of LD. Since 1984, this has been changed: ECM or laboratory confirmation of infection (serologic positivity or isolation of *B. burgdorferi* from the site of disease) and one or more organ systems affected in an endemic area; ECM and two or greater

organ systems affected in a nonendemic area; or ECM plus laboratory confirmation of infection (26). In New York State, a case is defined as a history of ECM or symptoms compatible with late disease, plus serologic evidence of preceding infection with *B. burgdorferi*, plus a history of exposure in an area (county) known to be endemic (89).

As has been well documented recently, serologic testing for LD is not well standardized, and interlaboratory variation makes interpretation difficult (52, 68, 115). An excellent summary of the issues involved in serologic tests and their interpretation appeared as part of the Third Symposium on LD (71). Cross-reactivity in serological tests for LD and other spirochetal infections can occasionally pose a problem (75). Additionally, infection with *B. burgdorferi* can cause serologic false-positivity for other organisms, perhaps because the organism nonspecificity stimulates immunoglobulin production, which is known as polyclonal B cell activation (122). Different techniques (including IFA, ELISA, and Western immunoblotting) and modification of these techniques are available. A recent antibody-capture enzyme immunosorbent assay shows promise as a more sensitive test for specific antibodies (15). Different preparations of the organism have been tried, with mixed results (49, 74). Antibodies bound in immune complexes have also been identified, which suggests another means of early serologic confirmation of the diagnosis (112).

One effective use of both serologic and cellular testing is to determine levels of specific immune reactivity at closed space sites of inflammation. In arthritis (123) and meningitis (93) caused by *B. burgdorferi*, there is evidence that antigen-sensitive cells are concentrated at the site of inflammation, and specific antibodies have been found concentrated within the cerebrospinal fluid of patients with Lyme neurologic disease (120, 147).

Recent editorials caution on the overuse of LD serologic testing (82) and repeat the need for a national program of standardization of these tests (51, 72). Many kits for rapid determination of serologic reactivity in doctor's offices are now available and more are soon to be marketed, which may further muddy the waters. One suggestion for practitioners in endemic areas is to use an academically oriented laboratory for diagnostic serologic tests.

As noted above, measurable levels of IgM and IgG immunoglobulin may not be present for up to eight weeks after the tick bite (116), so the timing of the test is crucial in its interpretation (71). Early, even incomplete, antibiotic therapy may blunt or abrogate the humoral immune response to the organism, which would render the patient inappropriately seronegative (116). Lyme disease, however, remains a clinical diagnosis. Without a set of well-substantiated criteria for the diagnosis of LD (like the Jones criteria for rheumatic fever), there is no substitute for a careful history and physical done

by a well-prepared health care provider that is confirmed, as needed, by serologic evidence of preceding infection.

NEW DIAGNOSTIC TESTING: NEW ANTIGEN PREPARATIONS, ANTIGEN TESTING, POLYMERASE CHAIN REACTION

Newer diagnostic tests for LD have been developed and many show great promise. As noted above, some of the serologic negativity in patients may be because of binding of the specific antibodies in immune complexes; these antibodies are then unable to bind in the assay being used. Isolation of these immune complexes may be helpful in such cases (113).

Modification of the assays being used also may be helpful. The antibody capture technique may be able to decrease nonspecific binding, and thus is more sensitive and as specific as assays currently being used (15). Nonspecific binding by the test sera may be decreased by absorption of the sera with other microorganisms to remove these antibodies; this has been tried, with mixed results (30, 44).

Berger et al (16) used the organism cultured from an individual; however, this procedure did not increase the efficacy of serologic testing. Nevertheless, differential responsiveness to individual components of *B. burgdorferi* suggests that fractions of the organism may offer a better antigenic preparation for use in ELISA (45, 48, 49, 74).

Infected *Peromyscus leucopus* (white-footed field mice) shed large numbers of viable *B. burgdorferi* in their urine (22, 113), which suggests that the isolation of organism-derived proteins in the urine might lend itself to diagnosing LD (54). Although enough information is not yet available to assess this technique, detection of antigen does not differentiate between live and dead organisms (see below, Pathogenesis).

B. burgdorferi-derived nucleic acids can be identified in tissue (114), which allows a sensitive method for implicating the organism in local inflammation. An individual copy of a gene from a microorganism can be copied rapidly and accurately in vitro until 1 million copies are present in the test tube, by using a new technology called polymerase chain reaction. Thus, a fluid or tissue specimen with one copy of a gene can be probed and this genetic evidence of infection can be detected. This technique has been used in LD (102; M. A. Liebling, unpublished observations) to identify *B. burgdorferi*-derived genetic materials in the blood and cerebrospinal fluid of patients with LD. Although this technique is potentially very sensitive, it is prone to false-positive testing because of contamination. It also suffers from the same problem as noted above for antigen detection; after effective ther-

apy, genetic materials may persist, so that this test does not help the physician determine if further therapy is indicated.

PATHOGENESIS

B. burgdorferi can elicit many immunologic responses and changes in the host (119). Therefore, the means by which this pathogen may cause tissue damage may be quite complicated. The organism clearly is present at many of the sites of inflammation. Complement fixation by the organism and local polymorphonuclear cell activation may cause local damage. Production of in situ immune complexes may act as a focus of persisting inflammation or producing vasculitis. *B. burgdorferi* can elicit the production of immunologically active compounds from monocyte/macrophages, including interleukin-1 and tumor necrosis factor (cachectin), which may affect immune cells locally and alter the function of fibroblasts and endothelial cells at the site of inflammation. Thus, the presence of live organism certainly plays a role in the pathogenesis of LD.

The persistence of dead organism may act as a focus of local or systemic inflammation; long after antibiotics have killed *B. burgdorferi,* there may be persistent inflammation, as immune mechanisms continue to react with the effete organism. All the mechanisms noted above could continue for months until the host's macrophages can eliminate the residue. This mechanism may explain the delayed response to antibiotics and the peristence of nonspecific symptomatology long after the end of (ultimately) curative antibiotic therapy.

Occasionally, a molecule found in a microorganism resembles a component of the potential host. In this circumstance, known as molecular mimicry, the immune response against the microorganism might identify and attack the host component and lead to host damage. There is evidence that a *B. burgdorferi* molecule, the flagellin, resembles a specific human axonal protein (125). Immunologic reactivity with flagellin might then cause tissue damage. Thus, another possible immunopathogenetic mechanism must be considered in LD. However, any suggestion that immunomodulatory therapy might be an effective treatment of LD is premature at this time.

VACCINE DESIGN

No human vaccine for LD is currently available. Passive immunization of hamsters with serum from rabbits previously inoculated with *B. burgdorferi* led to protection from subsequent inoculation of the hamsters with the organism; normal rabbit serum was ineffective (56). Passive immunization with allogeneic anti-*B. burgdorferi* serum prevented the development of Lyme

arthritis in the LSH strain of hamster (106). Active immunization with dead *B. burgdorferi* also protected hamsters (57). An animal vaccine for LD is under development, and a human vaccine is being planned. The fact that the immunopathogenesis of LD may, in part, include autoimmunity predicated upon molecular mimicry (125) suggests that the safety and efficacy of whole organism vaccines may be problematic.

THERAPY AND PROGNOSIS

Antibiotic therapy in Stage One disease usually results in resolution of disease and prevents progression to later stages. Oral therapy is recommended for early disease. There is no evidence that intravenous drugs are necessary, even for severe Stage I disease. The only comparative study of antibiotic therapy in early disease suggested that either penicillin or tetracycline was more effective than erythromycin (1000 mg in 4 divided dosages for 10 days) in preventing progression to later disease; 20 days of tetracycline was no better than 10 days of treatment (139). There are many proposed antibiotic regimens for early disease, and there is no evidence that one drug is superior to another. Tetracycline, amoxicillin, ampicillin, and penicillin have been used with good success, at 4 divided dosages of 1000–2000 mg per day. Doxycycline at 100 mg 2–3 times a day is also effective. There is no evidence that the addition of probenecid to therapy with the penicillins adds any efficacy. Other agents, including cefuroxime axetil, cefixime, and minocycline have also been used. Initial studies of azithromycin, a new macrolide antibiotic with greater anti-*B. burgdorferi* activity than erythromycin, are encouraging. The optimum duration of therapy has not been determined, although current practice is generally to continue treatment for 3–4 weeks.

Within a few hours to days of the onset of therapy, approximately 15% of patients may experience a remarkable worsening of signs and symptoms of disease (139), which is often accompanied by fever, chills, malaise, headache, and myalgia. These patients may experience a rise in the peripheral blood white cell count and, occasionally, increases in liver function tests. All of these abnormalities are relatively mild and usually resolve within a day or so. This phenomenon, first described in syphilis, is known as the Jarisch-Herxheimer reaction. Such reactions are also found early in the therapy of other Borrelial infections and of Brucellosis, where the reaction may be life threatening.

If untreated, ECM will spontaneously resolve in a median of 28 days, although it may persist for as long as 14 months. Progression to later disease is most frequent in patients with more serious early manifestations (144), but progression may follow mild or inapparent Stage One LD (99).

Oral or parental antibiotics are effective in treatment of Stage Two LD. The suggested route, dosage, and duration of therapy varies with the type of manifestations (77, 91, 139, 143, 146).

The arthritis of LD is generally treated with intravenous antibiotics, including penicillin (20 million units per day in 6 divided dosages), cefotaxime (3 grams twice a day), and ceftriaxone (1 gram twice a day). Chloramphenicol, at dosage appropriate to body mass, is also effective. Steere et al (137) reported that Lyme arthritis was successfully treated with intravenous penicillin in 55% of patients. *B. burgdorferi* is sensitive to ceftriaxone (58), and this agent has been used successfully (33). One study suggests that subsequent treatment with ceftriaxone is effective in patients who have failed to respond to penicillin (34). There is preliminary evidence to suggest that prolonged oral therapy (one month) may be effective in treatment of late disease (67), but these studies must be confirmed.

The most appropriate therapy for Stage Three neurologic disease is probably intravenous antibiotics, as used for other late manifestations of LD, although there is not enough clinical experience to know if late neurologic damage is totally reversible. There are anecdotes that claim slow, but impressive, resolution.

Based on the premise that *B. burgdorferi* is a slowly growing organism, some groups have suggested that therapy for late LD should include intravenous courses for six weeks or longer and prolonged oral "maintenance" therapy for up to 18–24 months. It is not evident that these regimens are any more effective than the more traditional approaches noted above; however, it is certainly believable that the longer regimens are associated with more side effects and more expense to the patient or the third-party payer.

One argument made in favor of more prolonged therapy is the persistence of symptoms and the occasional apparent "progression" to later manifestations, often in the presence of persistent elevated levels of anti-*B. burgdorferi* antibody. The general experience has been that it may take as long as six months for some patients with arthritis to fully resolve after antibiotic therapy (137), and continuous achiness and nonspecific symptoms may occur after therapy of other late manifestations of LD. This problem may be because of the persistence of *B. burgdorferi*-derived antigens at the site of disease, which is a focus for prolonged inflammation, as described above. Our experience suggests that symptoms will develop in some patients after LD, including fibromyalgia, which are not due to ongoing infection and are not amenable to further antibiotic therapy (121). Many patients referred to the Lyme Disease Center at Robert Wood Johnson Medical School have been subjected to many courses of oral and intravenous therapy for complaints clearly not due to *B. burgdorferi* infection, but which have been mistakenly attributed to LD (121). Not every complaint in a patient who has had LD (or,

for that matter, in an individual with serum antibodies to *B. burgdorferi*) is necessarily because of *B. burgdorferi* infection.

One indisputable fact is that the earlier a patient is treated, the less likely that person is to experience later manifestations. The overwhelming majority of patients with treated Stage I LD will be cured. Fatalities due to *B. burgdorferi* infection are very rare. The only LD fatalities reported in the American literature were because of carditis [although in one, coexisting babesiosis complicated the clinical picture (77)], and possibly because of adult respiratory distress syndrome related to LD (61). There is also a brief French report of a case of Lyme meningoradiculitis, which was complicated by encephalitis and phrenic paralysis (81). Permanent heart block due to LD was reported from the Netherlands (35). Lyme meningitis resolves with antibiotic therapy (65).

Lyme arthritis has proven somewhat less responsive to antibiotic therapy. In the initial report, 55% of patients treated with intravenous penicillin resolved; later studies suggest a better response rate to therapy with third generation cephalosporins. Nonetheless, some patients have required other forms of treatment, including hydroxychloroquine (as a remittive agent) and synovectomy (132).

A controversial issue in the therapy of LD is the status of asymptomatic persons who happen to test positive for antibodies to *B. burgdorferi*. We do not know how many, if any, of these individuals will ever experience tissue damage because of this infection. The policy at the Lyme Disease Center at Robert Wood Johnson Medical School is that if a true seropositive result is obtained on an individual without any preceding history of LD, oral therapy for one month, as for Stage One disease, is given.

EPIDEMIOLOGY OF THE DISEASE, TICK (AND OTHER POSSIBLE) VECTORS, AND HOSTS

As mentioned above, LD was first described as Lyme arthritis. In these early studies, LD patients occasionally recalled a preceding tick bite (142). Subsequent field studies documented that there were far fewer cases of LD on the west bank of the River, in parallel with the smaller number of deer, mice, and ticks (154). When cases were described elsewhere in the US, the distribution of LD was found to match that of Ixodes ticks (140).

Lyme disease has occurred as focal epidemics in three areas of the United States; 90% of cases are found in the Northeast, the northern Midwest, and the Pacific Northwest. Newly developing foci were documented in New Jersey (17, 111), Westchester County, NY (158), Suffolk County, NY (14), Ipswich, Mass. (65), and greater Philadelphia (4a). In each area, there has been a rapid increase in the number of cases. In the "home" of LD, there has

been a three- to eight-fold increase near the mouth of the Connecticut River, and a spread of LD into inland and southern Connecticut. The highest incidence, however, is still on the east bank of the river (25).

New York State now has the dubious distinction of having the largest number of LD cases, and Rhode Island has the highest state-wide incidence (73, 84, 152). However, state figures obscure the focal nature of the disease; incidence figures in a given small area may approach 1 in 1000 residents (152). In Mount Kisco, NY, the prevalence rate in 1987 was 5 per 1000 residents (A. Curran, Westchester County Department of Health surveillance data). Approximately 4% of the residents of Lyme, Conn. have had LD (25); in smaller communities, 16% of the summer residents of Great Island, Mass. (145), and 7.5% of the summer residents of Shelter Island, NY (47), have had LD.

Nationwide, the 1988 figures represent a ninefold increase in cases compared with 1982, and a twofold increase compared with 1987 (84). In 1987–1988, 11 states reported their first cases of LD (84). Preliminary 1989 figures suggest further increases, especially in the central Midwest (84) and in the South Atlantic states. Georgia, for example, had a twelvefold increase between 1988 and 1989. The geographic distribution of *I. dammini* and *B. burgdorferi* extends into northern and inland areas not yet endemic for LD, which suggests that there may be new areas of disease in the future (7).

The increased number of cases of reported LD is probably due to many factors, including increased awareness on the part of both physicians and patients, more aggressive case finding, and the rapid development of new foci of disease (17). However, the absolute increase in cases, which is attributable to increased exposure to the vector, is probably from increased recreational, occupational, and residential exposure (17).

Lyme disease is spread by different species of Ixodes ticks, in different areas of the world. In the Northeast and northern Midwest, *Ixodes dammini,* the deer tick, is the primary vector of LD; in the West, it is *I. pacificus,* the black-legged tick (19). On the other continents other Ixodes ticks have been implicated: *I ricinus* in Europe; *I. persulcatus* in the transUral Soviet Union, China, and Japan; and possibly *I. hyocyclus* in Australia (118).

The life cycle of *I. dammini* includes dependence on hosts for each of its three stages of development. Eggs are laid in the early spring. Larvae, which emerge about one month later, seek and acquire a blood meal, usually from a white-footed field mouse. Once this is accomplished, usually between July and September, the larvae undergo a prolonged metamorphosis and emerge as nymphs in the earlier spring of the following year. The nymphs, too, single-mindedly seek a single blood meal, again usually provided by a mouse, from May through July. Having sated themselves, the nymphs molt. Adult male and female *I. dammini* emerge in the fall and obtain their blood meal, during

the late fall and early winter, their preferred host being the white-tailed deer. Once engorged, the female drops to the ground and lays her eggs, and the two-year cycle starts again (20, 129).

In the Northeast and Midwest, *Peromyscus leucopus*, the white-footed field mouse, is the usual host for the larva and nymph *I. dammini*, and *Odocoileus virginianus*, the white-tailed deer, is the usual host for the adult stage. In general, *I. dammini* larvae do not carry *B. burgdorferi* (20), but acquire the organism with their first blood meal, typically from the field mouse. In *I. ricinus*, the sheep tick and principal vector in Europe, there is evidence to suggest transovarial passage of the organism (130). *P. leucopus* is a competent reservoir for *B. burgdorferi:* It is densely infested with the vector, *I. dammini;* it is the predominant host for the vector; and it has a persistent spirochetemia, which efficiently infects the vector (66, 79). The timing of the life cycle of *I. dammini* is crucial to the amplification of LD, because it is the infected nymph that then infects mice with *B. burgdorferi* before the initial blood meal of the larva. One generation of infected *I. dammini* thus is capable of passing *B. burgdorferi* on to the next. Deer are the primary hosts of adult *I. dammini* (159), insuring that the eggs can be laid, but *O. virginianus* does not act as a reservoir of *B. burgdorferi* infection (149). The crucial nature of the deer-tick interaction is clear: If, as was done on Great Island, the deer population is eliminated, the number of larval ticks and the number of new cases of LD are substantially diminished (159).

Other animals may be infected with *B. burgdorferi*, including many different mammals (3, 4, 21, 98) and birds (5, 156). Although humans can spread louse-borne Borrelial infections by distributing the lice, birds with infected ticks may distribute LD to new areas (5, 156). Once an infected tick gains a blood meal from a local mammalian potential reservoir, a new focus of LD may be established. The new outbreaks of LD in the South Atlantic states may, in part, be due to such avian distribution along migratory paths. Other deer may act as hosts to infected ticks; in California, black-tailed deer and the exotic species fallow and axis deer were found to carry *B. burgdorferi* (63).

Jack rabbits in Texas are seropositive for *B. burgdorferi*, which suggests intense exposure to the organism (21). The cotton-tailed rabbit, *Sylvilagus floridans*, found throughout the Western hemisphere, is usually infested with *I. dentatus* in the Eastern US; 50% of the *I. dentatus* isolated in one study carried *B. burgdorferi* (150). *I. spinalpis* infests rabbits in the Western US (150). Although *I. dentatus* rarely bites humans (3), *I. dammini, I pacificus*, and *I. scapularis* can feed on either humans or rabbits; thus, rabbits may represent a hidden enzootic cycle (151) and may introduce heterogeneous *B. burgdorferi* into the process (6).

In some areas of New York 100% of *I. dammini* ticks carry the organism (18), and in endemic areas 40% infection rates are common (73). In contrast,

rate of infection of *I. scapularis* is usually 1% or less (73). *I. pacificus* infection rates may be as high as 10% (64), but are usually about 1–2% (18). The competence of the reservoirs in the various locations of endemic LD have a profound influence on the different tick infection rates, which in turn affect human infection rates. Thus, *P. leucopus,* which is a competent reservoir, helps amplify infection with *B. burgdorferi* in the Northeast and Midwest. However, the main hosts for nymphal *I. scapularis* and *I. pacificus* are skinks and other small lizards (127). The skink is not a competent reservoir for *B. burgdorferi,* so infection with the organism is not amplified in the South and the West.

Other ticks may also be involved in the transmission of LD. In New Jersey, another Ixodid tick, *Amblyomma americanum,* the Lone Star tick, may carry *B. burgdorferi* (107). *A. americanum* may be a secondary vector for LD (108). Occasionally other ticks, including Dermacenter (64), another Ixodid tick, and Ornithodoros (18), an Argasid tick, may carry *B. burgdorferi.* However, there is no evidence that these species serve as major vectors of LD. Individual reports suggest that other hematophagous insects, including fleas, mosquitoes, flies, stable flies, and flying insects may spread LD (5, 14, 98), perhaps by passive transfer, but the primary vector remains the Ixodid tick.

WHY NOW, WHY HERE?

I. dammini was first identified on Naushon Island, off the coast of Massachusetts, in the early 1920s. Since the 1970s, it has been collected from an increasingly large area of the US. In 1904, examples were identified in Ontario Province. This species was probably the same tick that visiting naturalists described as abundant in central New York in 1749, but virtually gone from the same area by the mid 1800s (31).

The recent expansion of LD and the domain of *I. dammini* parallel the change in abundance of deer. Before the 1600s, Native Americans engaged in a deliberate policy of forest burning to provide themselves with farmland. By the mid-1600s, virtually all large animals in southern New England and the mid-Atlantic region had been destroyed, the result of hunting for food and bartering with the colonists. After the settlers had displaced the original occupants of the region, agriculture kept the area deforested into the 1900s. Attempts to eradicate Texas cattle fever early in the twentieth century included a nationwide attempt to eradicate deer. Thus, when our first (and only) environmentalist President, Theodore Roosevelt, wished to go big game hunting, there were no deer to hunt on the continental US. He, and others, had to go to Africa or across a narrower body of water to the Elizabeth Islands, especially Naushon, where deer had long survived.

As agriculture failed in the East, and the nation was fed by the farmers of the Midwest and West, Eastern forests were gradually reestablished in the 1800s, and undergrowth, shrubbery and brush thrived again. With the earlier destruction of the forest, there had been destruction of the undergrowth, the preferred environment for field mice. Thus, a return of forest land increased the habitat for the mice.

Deer populations were reestablished in the East in the 1930s (for example, deer were taken from the upper peninsula of Michigan and imported to Nantucket Island). By the 1950s, deer were commonplace. [A parallel story of diminished and then increasing deer populations can be told in Europe during and after World War II. Deer population is a less crucial determinant of *I. ricinus* levels; unlike *I. dammini* adult *I. ricinus* have many potential hosts (31, 80).] We do not know if the imported deer carried with them *I. dammini* or whether the deer were infested by the small number of ticks that had survived on Naushon, Gardiner, and Shelter Islands and in Ontario. We do know, however, that with the increased number of deer has come an increased number of *I. dammini* and focal epidemics of LD (80, 128).

PUBLIC HEALTH CONCERNS AND PREVENTION STRATEGIES

Lyme disease has become a major public health problem in endemic areas, and these areas have expanded in recent years. As noted above, the increased number of cases of LD is attributable to greater exposure to a larger number of infected ticks. Humans are accidental hosts for *B. burgdorferi;* this disease is a zoonosis, which affects the animals noted above. Humans are only recently involved.

Forestry workers in endemic areas are at increased risk for seropositivity (37, 85), as are farmers (36), but an outdoor occupation is not required. Parks in suburban New York are an area of increased risk for LD (43), and even a private yard may not be safe. In areas of high incidence in Westchester, there is an average of one tick per square meter of lawn (41). A survey of patients with LD identified that 68.6% acquired the disease in their yard; 11.4% in school or camp; and 8.6%, in parks (42).

Recent work has suggested that dogs in areas with LD may also be afflicted. Serologic surveys of dogs may identify new foci of human LD; dogs may be used as sentinels of new areas of infection (40). Having pets, either dogs (2, 64, 88) or cats (32, 64, 135), or farm animals (135) may increase a person's risk of contracting LD, although this has been disputed (27).

Prevention of the disease can be accomplished at many levels of effort (110). Individuals can decrease their risk by taking simple precautions. Once the areas that contain the most ticks are identified—brush and undergrowth,

especially in areas frequented by deer, and the lawn-shrub interface where field mice live—these areas should be avoided, where practical. When spending time outside, a person should tuck trousers into socks and wear long-sleeved shirts; nymphs live in low brush and grab onto a passing leg, then crawl upward to find a dining site. Wear light-colored clothing to spot the tiny tick more easily. It may take many hours, or even days, for a tick to bite and begin its blood meal, so there is time to remove ticks before any damage can be done (87, 96). At the end of an outdoor activity, inspect yourself and others; a shower will wash off any nonattached ticks. Tick repellents are very effective and, when used as directed, safe; application to shoes and socks may be especially useful. There is evidence that pets may carry ticks into the home; animals should be inspected carefully and frequently.

Ticks should be removed with thin tweezers or forceps, and antiseptic precautions should be used. Old wives' tales suggest that kerosene, petroleum jelly, or a lit match or cigarette are effective in tick removal; these methods should be eschewed, as they may cause the tick to regurgitate into the wound and cause infection.

Even if an engorged tick is found, Costello et al (28) estimate that in an endemic area only 10% of tick bites actually transmit the disease, which suggests that prophylactic antibiotic therapy of all tick bites is not necessary. In one study, the risk of adverse reactions from the antibiotic therapy was as great as the risk of seroconversion if no prophylaxis was given. When this experience is extrapolated to repeated prophylaxis of large numbers of residents in endemic areas, the cost and potential morbidity of therapy is tremendous. In addition, prophylactic therapy may give a false sense of security and lead individuals to abandon preventive techniques. We suggest that if no skin rash develops and no signs or symptoms of LD develop, a bitten individual should return for blood testing six to eight weeks after the bite. If seropositive, the patient can then be treated with an oral regimen. Some researchers suggest that a blood test at the time of the bite is indicated. True seropositivity would suggest prior exposure to *B. burgdorferi,* and, if treatment of asymptomatic seropositivity is considered advisable, therapy could be started at that time.

If a person lives in an area known to support a deer population, ticks carrying the organism may be on the lawn. Thus, local prevention may be indicated. One commercially available product consists of cardboard tubes that contain cotton soaked in an acaricide; mice take the cotton and use it for their nests. Any ticks present will be killed by the acaricide. This product does provide some protection, but unless all the other homeowners in the area use it, a mouse from the next yard can come onto the protected property and deposit ticks. Also, deer may deposit ticks on the lawn, and these ticks may not interact with mice or the treated nest. Finally, if use of this product leads

the individual to become lax in personal preventive measures, a disservice has been done.

The use of granular acaricide may temporarily decrease the tick population locally. Ongoing studies suggest that this may be an effective means of decreasing the risk of LD, although the risk to children and pregnant women must be considered. Spraying yards with a variety of chemical acaricides usually does not allow acaricide to reach the primary habitat of the tick, i.e. the leaf litter on the ground and the underside of vegetation; thus, this method is not very effective (109, 127). Spraying larger areas at risk is not an appropriate and effective response to LD in endemic areas.

There is little else that can be done practically on a community-wide basis. On Great Island, removal of all deer was effective, but this cannot be done on the mainland. (This is perhaps the only issue that has ever united hunters, the gun lobby, and environmentalists). If we could eradicate all field mice, the ticks would probably search for a new host, in all likelihood the residents of the community. Controlled clear burning decreases the habitat for mice, but is also not practical in suburbia or more rural settings. Brush grows back, and deer, mice, and other animals return; birds might reintroduce *I. dammini* and *B. burgdorferi*.

PUBLIC HYSTERIA

The press and broadcast media have described LD as the scourge of the 1980s and 1990s and speak of LD as second only to AIDS as a public health problem in the US. Well-meaning physicians have stated as fact that LD is only very rarely cured, and that prolonged and repeated antibiotic regimens are necessary to suppress (but rarely cure) the ailment. The medical literature contains many reports of medical problems thought due to *B. burgdorferi* infection, claims supported by only a positive serologic test. The very tests practitioners use have been unfairly derided as being nearly useless, because of cross-reactivity, inaccuracy (especially early in the disease), and lack of standardization. The end result has been that patients in endemic areas often feel that their physicians do a poor job of diagnosing and treating LD, that the tests and therapeutic agents are profoundly flawed, and that LD should represent a cause for alarm (124).

Given their perception of LD as a mysterious, difficult to diagnose disease with an ever expanding and poorly defined clinical spectrum, it is no wonder that many patients have seized upon LD as the ultimate explanation for all of their ills. Given the perception of the poor quality for testing, the inability of physicians to diagnose the disease, and the inefficacy of therapy, it is no wonder that many patients view LD with alarm that borders on hysteria. Ill-advised physicians and lay groups have exacerbated the situation: If the

tests are less than 100% accurate, how can you say that I don't have LD? If antibiotics are less than 100% effective, how can you tell me that I don't need further therapy? If I don't feel 100% improved, how can you tell me that I am cured and that I don't need more medicine?

What is the answer to these problems? Health care providers and planners must better educate physicians, patients, health officers, and veterinarians about the risks, manifestations, and treatment of LD. As increasing numbers of cases occur in a new area, local physicians are more aware of the disease and its signs and symptoms, are more adept at using the diagnostic laboratory tests available, and are more knowledgeable about therapy and prognosis.

We also must better educate the public about the kinds of personal and community-wide efforts that can be made to decrease the prevalence of LD. The time is long overdue for state and local health officials to become the major source of information of knowledge. They must take this role back from the "medical journals" available at the supermarket check-out. Educational materials have been developed by many groups, including our own at Robert Wood Johnson Medical School.

Finally, we must do a better job of exposing the charlatans. We must insist on scientific proof of assertions that have passed into the lay conventional wisdom. We must cooperate with the academic centers that perform clinical studies, so that a sufficient number of patients are included to provide answers to the many questions. We must insist that there are funds for such research, even in a time of fiscal restraint.

Lyme disease has become a major health concern in a growing number of communities. The problem is manageable, if we can convince our patients that Lyme disease is a cause for concern, not panic; vigilance, not hysteria.

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