Clinical Manifestations of Lyme Disease

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The author discusses the clinical manifestations of Lyme disease, a multisystem inflammatory illness with protean symptomatology. The author also presents a brief historical review of the disease.

Lyme disease is a multisystem inflammatory disease caused by the spirochete, *Borrelia burgdorferi,* and spread by *Ixodes* ticks. In 1975, Steere described Lyme arthritis, an outbreak of juvenile rheumatoid arthritis, in three small towns on the east bank of the Connecticut River. Some of these patients recalled an expanding red rash, identified as erythema chronicum migrans (ECM).[1] The first report of ECM in the United States was in 1970, by Scrimenti, in Wisconsin, although the lesion had first been described in Europe in 1909.[2] The outbreak of juvenile rheumatoid arthritis in Connecticut also was linked to preceding ECM and tick bites, and over the next few years, Lyme arthritis, as it was first named, became known as Lyme disease. This occurred, in part, because of the association with cardiac disease, but also because approximately 10 percent of the patients had a neurologic syndrome essentially identical to a tick-borne neurologic syndrome in Europe, known as Bannwarth's syndrome. The multisystem, inflammatory nature of Lyme disease, a multifocal epidemic, was established.

Today in the United States, Lyme disease is identified as a multifocal 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. Ninety percent of the cases reported in the United States are from these three regions, and the total number has in-

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creased steadily each year. This increase in cases is especially notable in New Jersey, second to New York in newly reported cases of Lyme disease.

After *B. burgdorferi* was identified as the etiologic agent of Lyme disease in the United States, studies in Europe established that the same organism was the cause of ECM in Germany, Austria, and Scandinavia. In addition, two other skin lesions reported in Europe from the late 19th century, acrodermatitis chronica atrophicans (ACA) and lymphadenosis benigna cutis (LABC), and tick-borne meningopolyneuritis, or Bannwarth's syndrome, were established as being caused by infection with the same organism.

Lyme disease now is 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, *I. pacificus* in California, *I. ricinus* in Europe, *I. persulcatus* in Asia, and, possibly, *I. hyocyclus* in Australia.[3-5]

Lyme disease is an infectious disease capable of causing damage to a number of organ systems.[6,7] Stage one of the disease occurs within a month of inoculation with *B. burgdorferi,* the causative agent of Lyme disease.[8-10] The clinical syndrome at this stage includes ECM, the skin rash, and associated symptoms. Stage two of Lyme disease, which includes cardiac and/or neurologic disease, usually occurs two to three months after the initial infection, occasionally in the absence of any preceding evidence of illness suggestive of stage one. Stage three includes arthritis and/or chronic neurologic manifestations that recently have been described; these stage three manifestations may occur years after ECM, but may appear in the absence of any preceding history suggestive of earlier Lyme disease.

Stage one occurs between 1 day and 1 month after tick bite (median 7 days) and consists of ECM and associated symptoms: fever, fatigue, malaise, headache, stiff neck, arthralgia, and myalgia. About 50 to 70 percent of patients will experience ECM and, of these, 50 percent of patients will have more than one skin lesion. Regional (and occasionally systemic) lymphadenopathy may occur. Patients may develop pain on neck flexion, conjunctivitis, erythematous throat, temporomandibular joint pain, and hepatosplenomegaly and/or right upper quadrant tenderness.[11]

Nonspecific laboratory studies, like erythrocyte sedimentation rate, complete blood count, and liver function tests, are abnormal in between 20 and 50 percent of cases, but are not helpful in diagnosing Lyme disease.[11] Early in the disease, specific serologic tests may be negative and seropositivity may not occur until six to eight weeks into the illness.[12,13] *B. burgdorferi* has been cultured from biopsy specimens taken at the expanding red border of the ECM lesion.[8]

Two to three months following the onset of ECM, about 10 to 15 percent of untreated patients with stage one Lyme disease will experience neurologic disease. Meningoencephalitis, meningitis, cranial nerve palsies, and peripheral neuropathies may occur, often in combination, and often accompanied by extreme fatigue, malaise, headache, and photophobia.[14-16] Fever usually is absent. Mild encephalopathy, including difficulty with concentration and memory, and irritability and emotional liability may occur. These neurologic findings are essentially identical to those described in Europe, in the early part of this century and now known as Bannwarth's syndrome[17] or tick-borne meningopolyneuritis.[18]

A lymphocytic pleocytosis is found in the cerebrospinal fluid, with elevated protein, but normal glucose levels.[14,16] The spinal fluid is normal in stage one Lyme disease, even in the presence of headache; a few cases have had serial lumbar punctures, demonstrating that meningoencephalitis of stage two disease evolves. The meningitis of Lyme disease is indistinguishable from that of enterovirus, virtually epidemic in the state in the early fall. *Borrelia burgdorferi* has been grown from the cerebrospinal fluid of patients with Lyme meningitis.[8]

Neuropathic changes have been found on nerve conduction testing;[14] axonopathy was documented in one third of patients with peripheral neuropathy.[19] Peripheral nerve biopsies have shown heavy epineural vessel infiltration with mononuclear cells,[19-23] but the organism has not been found at the site of inflammation. Vasculitis was seen in one case;[20] luminal obliteration of perineural vessels without vasculitis was found in another case.[21] Immune complexes, immunoglobulin, and complement have not been seen in biopsy specimens.[19,20]

Vascular disease caused by *B. burgdorferi* may be the underlying mechanism for one report of cerebrovascular disease[24] and vasculitis has been seen on angiographic study of one patient with Lyme disease central nervous system (CNS) disease.[25]

Most patients with encephalitic symptoms have abnormalities on electroencephalography[14] and reversible neuropsychiatric testing abnormalities have been documented;[19] in some patients, small plaques have been found on magnetic resonance imaging (MRI), occasionally resolving after antibiotic therapy.[19] 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. In collaboration with Dr. Jonathan Willard-Mack, a neuropsychologist at UMDNJ-Robert Wood Johnson Medical

School, and Dr. Robert Chabot, a clinical electroneurophysiologist at New York University School of Medicine, the staff of the Lyme Disease Center at UMDNJ-Robert Wood Johnson Medical School is studying this population; we have found there to be widespread, often severe, abnormalities on both neuropsychologic testing and quantitative electroencephalography, some of which may resolve after therapy.

Cardiac disease occurs in 8 to 10 percent of previously untreated patients, two to three months after ECM, occasionally in coincident with stage two neurologic disease. Atrioventricular conduction defects, mild congestive heart failure, and ST and T wave changes compatible with myopericarditis have been reported.[26] Reversible[27-29] and rarely fatal[30] myocarditis has been described. The multifocal damage documented in electrophysiologic studies of individual cases is likely the explanation for the multiple levels of heart block occasionally described, in rapid succession, in individuals with Lyme disease carditis.[26,29] Focal myonecrosis and a sparse interstitial infiltrate of polymorphonuclear cells and lymphocytes was described in one series of myocardial biopsies,[21] while *B. burgdorferi,* myonecrosis, and perivascular mononuclear cell infiltration was found in another.[29] The finding of an organism within the myocardium suggests that direct invasion occurs in Lyme myocarditis.[30]

Arthritis is the classic feature of stage three Lyme disease,[31] and the reason the first epidemic of Lyme disease was described 15 years ago. Steere summarized experience with 55 patients with Lyme disease who did not receive antibiotic therapy. These patients had been infected before the efficacy of antibiotics had been appreciated, so they represent the only collection of patients where the natural evolution of Lyme arthritis has been studied.[32] A prospective study of these patients revealed that 44 patients (80 percent) experienced articular problems over the course of a six-year period. This included: 10 patients (18 percent) who experienced arthralgias with or following ECM, one day to eight weeks (mean, two weeks) after the onset of the lesion; 28 patients (51 percent) with polyarthritis, often migratory, present four days to two years after the onset of ECM (mean, 6 months); 14 patients with preceding migratory arthralgias; and 6 patients (11 percent) with chronic Lyme arthritis, usually affecting a single joint (most often the knee), with onset 4 months to four years after ECM (mean, 12 months). Five of these 6 patients had experienced either arthralgia or intermittent arthritis prior to developing chronic synovitis. The migratory polyarthritis group is reminiscent of the original cohort of patients described by Steere.[1]

The synovium in Lyme arthritis resembles

rheumatoid synovium,[21,31,33] although there are distinct differences between rheumatoid and Lyme synovitis.[21] In Lyme disease, there is hypertrophy and hyperplastic changes, with focal necrosis, vascular proliferation, and chronic inflammatory cell infiltration. Mononuclear cell aggregates and lymphoid follicles may be present, suggesting that there is an ongoing local immunologic reaction within the joint.[34] As in syphilis, endarteritis obliterans may be seen, with capillary arborization, dilatation, and congestion.[33] *B. burgdorferi* has been seen rarely in or near synovial vessels[33] or in synovial fluid,[35] and has been grown from synovial fluid.[36]

Tertiary neuroborreliosis is a term that purposely draws upon the clinical analogy with tertiary neurosyphilis. This late form of Lyme disease includes chronic encephalomyelopathy and neuropathy,[37-39] and, like tertiary neurosyphilis, stage three neurologic Lyme disease may develop insidiously months to years after the onset of infection, even in the absence of clinically apparent preceding infection. Subclinical infection thus may occur for long periods prior to the emergence of overt neurologic damage; this raises serious concerns over the finding of asymptomatic seropositivity in a significant per-

cent of people in areas endemic for Lyme disease. Clinical experience with this population is limited, and the true clinical spectrum of this stage of Lyme disease currently is being defined. Claims that amyotrophic lateral sclerosis,[40] multiple sclerosis,[41] and Alzheimer's disease[42] are due to infection with *B. burgdorferi* have been laid to rest. Many individual cases of neurologic damage have been stated as due to *B. burgdorferi* infection merely because the patient has a positive serologic test, a circumstance that does not guarantee causality.

One of the major controversies in the study of Lyme disease is the question of what clinical conditions can be ascribed to *B. burgdorferi* infection. On the basis of sero-epidemiologic and biopsy evidence, it has been suggested that a number of cutaneous lesions, including morphea, lichen sclerosus et atrophicus, eosinophilic fascitis, and other cutaneous fibrotic disorders, are due to *B. burgdorferi,* although these claims are by no means definitive.[43] Subclinical or asymptomatic infection may be quite prevalent in endemic areas, so that seropositivity may represent no more than a coincidence.

Another area of major concern relates to *B. burgdorferi* infection occurring during pregnancy. Shortly after the Lyme disease 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 complicated by Lyme disease, 14 normal births and 5 adverse outcomes were noted.[46-49]

Also, there is no evidence that Lyme disease can be passed by sexual or other intimate contact. There is evidence, however, that *B. burgdorferi* can survive in blood[50] and various blood products[51] for as long as six to eight weeks. Whether Lyme disease can be spread by transfusion is unclear.[52]

Lyme disease diagnosis can be aided by the use of serologic and cellular testing. However, Lyme disease remains a clinical diagnosis. In the absence of a set of well-substantiated criteria for the diagnosis of Lyme disease, i.e. Jones' criteria for rheumatic fever, there is no substitute for a careful history and physical done by a well-prepared health care provider, and confirmed by serologic evidence of preceding infection.

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. Even for severe stage one disease, there is no evidence that intravenous drugs are necessary. The only comparative study of antibiotic therapy in early disease suggested that either penicillin or tetracycline was more effective than erythromycin (1,000 mg in four divided doses for 10 days) in preventing progression to later disease; 20 days of tetracycline was no better than 10 days of treatment.[53] 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 doses of between 1,000 and 2,000 mg per day, in four divided doses; doxycycline at 100 mg two or three times a day also is effective. There is no evidence that the addition of probenecid to therapy with the penicillins is necessary to increase efficacy of penicillin therapy. Other agents, including cefuroxime axetil, cefixime, and minocycline have 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 generally is to treat for three to four weeks.

There may be a remarkable worsening of signs and symptoms of disease,[53] often accompanied by fever, chills, malaise, headache, and myalgia, in approximately 15 percent of patients, within a few hours to days of the onset of therapy. This may be accompanied by a rise in the peripheral blood white cell count, and occasionally by increases in liver function tests. All of these abnormalities are relatively mild and usually resolve within a day or so. This phenomenon was first described in syphilis, and is known as the Jarisch-Herxheimer reaction. Such reactions also may be experienced early in the therapy of other borrelial infections, and of brucellosis, where the reaction may be life threatening. It appears that antibiotic therapy causes the disruption of many of the organisms and causes the liberation of many borrelial components. When these circulating proteins, polysaccharides, and lipids are identified by the immune system, there is a sudden, systemic response, with exacerbation of symptoms—the Jarisch-Herxheimer reaction.

If untreated, ECM spontaneously will 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,[32,54] but progression may follow mild or inapparent stage one Lyme disease.[55]

Oral or parenteral antibiotics are effective in treatment of stage two Lyme disease; the suggested route, dose, and duration of therapy varies with the type of manifestations.[14,30,42,53,56]

The arthritis of Lyme disease generally is treated with intravenous antibiotics, including penicillin (20 million units per day in six divided doses), cefotaxime (3 g twice a day), and ceftriaxone (1 g twice a day). Chloramphenicol, at doses appropriate to body mass, also is effective in the treatment of Lyme disease. In 55 percent of the cases reported by

Steere,[57] Lyme arthritis was treated successfully with intravenous penicillin. *B. burgdorferi* is sensitive to ceftriaxone and this agent has been used successfully.[58] One study suggests that subsequent treatment with ceftriaxone is effective in patients who have failed to respond to penicillin.[58] There is preliminary evidence to suggest that prolonged oral therapy (one month) may be effective in treatment of late disease but these studies must be confirmed.[59]

The most appropriate regimen for the treatment of stage three neurologic disease probably is intravenous antibiotics, as used for the other late manifestations of Lyme disease. There is not enough clinical experience to be definitive about this, however, or 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 slow-growing organism, some groups have suggested that therapy for late Lyme disease should include intravenous courses for six weeks or longer and prolonged oral maintenance therapy, up to 18 to 24 months. At this time, there is no proof that these regimens are any more effective than the more traditional approaches; there is every reason to believe that the longer regimens are associated with more side effects and more expense to the patient.

One argument in favor of more prolonged therapy is the persistence of symptoms and the occasional apparent "progression" to later manifestations, often in the presence of persisting elevated levels of anti-*B. burgdorferi* antibody. The general experience has been that it may take six months or longer for arthritis to fully resolve after antibiotic therapy;[57] persisting nonspecific symptoms may occur after therapy of other manifestations of Lyme disease. This may be due to the persistence of *B. burgdorferi*-derived antigens at the site of disease, serving as a focus for prolonged inflammation.[34] Our experience suggests that some patients develop symptoms after Lyme disease (including fibromyalgia) that are not due to ongoing infection and are not amenable to further antibiotic therapy.[60] Many patients referred to the Lyme Disease Center at Robert Wood Johnson Medical School have been subjected to many, unnecessary courses of oral and intravenous therapy for complaints clearly not due to persisting or new *B. burgdorferi* infection, but which have been mistakenly attributed to Lyme disease.[60] It is crucial to recall that not every complaint in a patient who has had Lyme disease (or, for that matter, in an individual with serum antibodies to *B. burgdorferi*) is necessarily due to *B. burgdorferi* infection.

The one indisputable fact is that the earlier a patient is treated, the less likely that person is to progress to later manifestations of Lyme disease. The overwhelming majority of patients with treated stage one Lyme disease will experience a cure. Fatalities due to *B. burgdorferi* infection are very rare. The only Lyme disease fatalities reported in the English language literature were due to carditis [although in one, coexisting babesiosis complicated the clinical picture[30]] and possibly due to adult respiratory distress syndrome related to Lyme disease.[61] There also is a brief French report of a fatal case of Lyme meningoradiculitis, complicated by encephalitis and phrenic paralysis.[62] Nonfatal permanent heart block due to Lyme disease was reported from the Netherlands,[63] but all other cases of conduction defect have been reversible. Lyme meningitis resolves with antibiotic therapy.[56]

Lyme arthritis has proved somewhat less responsive to antibiotic therapy. In the initial report, 55 percent of patients treated with intravenous penicillin resolved; later studies suggest a better response rate to therapy with third-generation cephalosporins, including cefotaxime and ceftriaxone. Nonetheless, some patients have required other forms of treatment, including hydroxychloroquine (as a remittive agent) and synovectomy.[6] An understanding of the immunopathogenesis of this disease is helpful in appreciating the persistence of inflammation and symptoms in some patients; a full review of this topic is beyond the scope of this paper, but can be found elsewhere.[34]

A controversial issue in the therapy of Lyme disease is the status of asymptomatic people who happen to test positive for antibodies to *B. burgdorferi*. It is not known how many, if any, of these people ever will experience tissue damage due to this infection. The policy at the Lyme Disease Center is that if a true seropositive result is obtained on an individual without any preceding history of Lyme disease, oral therapy for one month, as for stage one disease, is given.

Should a tick be found on your patient it should be removed with thin tweezers or forceps, using antiseptic precautions. 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 act as a syringe and regurgitate into the wound, causing transfer of *B. burgdorferi*.

Even if an engorged tick is found, it is estimated that in an endemic area only 10 percent of tick bites actually transmit the disease.[64] This suggests 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. If this experience is extrapolated to repeated prophylaxis of large numbers of residents in endemic areas, the cost and potential morbidity of therapy would be tremen-

dous; in some endemic areas, individuals would be on constant antibiotic prophylaxis from April to October for their repeated tick exposures. In addition, prophylactic therapy may give a false sense of security and lead individuals to abandon preventive techniques. Our suggestion is that if no skin rash develops and no signs or symptoms suggestive of Lyme disease develop, the bitten individual should return for blood testing at six to eight weeks after the bite; if seropositive, the patient then can be treated with an oral regimen. Some suggest that a blood test done 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.

CONCLUSIONS

Lyme disease has been described by the press and broadcast media as being the scourge of the 1980s and 1990s; reporters speak of Lyme disease as being second to AIDS as a public health problem in the United States. Well-meaning physicians have stated that prolonged and repeated therapy is necessary to suppress Lyme disease, and that rarely, if ever, is it cured. Reports of medical problems thought due to *B. burgdorferi* infection appear in the medical literature, supported by only a positive serologic test. The tests practitioners use to document exposure to *B. burgdorferi* have been unfairly derided as being nearly useless, because of cross-reactivity, inaccuracy, and lack of standardization. The end result has been that patients in endemic areas often feel their physicians do a poor job of diagnosing and treating Lyme disease, that the tests and therapeutic agents are profoundly flawed, and that Lyme disease should represent a real cause for alarm.[65]

Given the perception by many patients of Lyme disease as a mysterious, difficult-to-diagnose disease, with an ever-expanding and poorly defined, clinical spectrum, it is not surprising that many patients have seized upon Lyme disease as the ultimate explanation for all of their ills. It is no wonder that many patients view Lyme disease with alarm, bordering on hysteria.

Lyme disease has become a major health concern in a growing number of communities. Much has been learned about the disease, although much study is needed. The problem is manageable, if we can convince all of our patients that Lyme disease is a cause for concern, not panic; vigilance, not hysteria. ■

REFERENCES

1. Steere AC, Malawista SE, Snydman DR, et al.: Lyme arthritis. An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum* 20:7-17, 1977.
2. Scrimenti RJ: Erythema chronicum migrans. *Arch Dermatol* 102:104-105, 1970.
3. Steere AC, Malawista SE, Craft JE, et al.: International symposium on Lyme disease. *Yale J Biol Med* 57:445-705, 1984.
4. Stanek GL, Flamm H, Barbour AG, Burgdorfer W: Proceedings of the second international symposium on Lyme disease and related disorders. *Zbl Bakt Hyg A* 263:1-495, 1986.
5. Benach JL, Bosler EM: Third international symposium on Lyme disease and related disorders. *Ann NY Acad Sci* 539:1-513, 1988.
6. Steere AC: Lyme disease. *N Engl J Med* 321:586-596, 1989.
7. Sigal LH: Lyme disease: A worldwide borreliosis. *Clin Exp Rheumatol* 6:411-421, 1988.
8. Steere AC, Grodzicki RL, Kornblatt AN, et al.: The spirochetal etiology of Lyme disease. *N Engl J Med* 308:733-740, 1983.
9. Benach JL, Bosler EM, Hanrahan JP, et al.: Spirochetes isolated from the blood of two patients with Lyme disease. *N Engl J Med* 308:740-742, 1983.
10. Johnson RC, Schmid GP, Hyde FW, et al.: *Borrelia burgdorferi* sp. nov.: Etiologic agent of Lyme disease. *Intern J Sys Bacteriol* 34:496-497, 1984.
11. Steere AC, Bartenhagen NH, Craft JE, et al.: The early clinical manifestations of Lyme disease. *Ann Intern Med* 99:76-82, 1983.
12. Craft JE, Grodzicki RL, Steere AC: Antibody response in Lyme disease: Evaluation of diagnostic tests. *J Infect Dis* 149:789-795, 1984.
13. Russell H, Sampson JS, Schmid GP, et al.: Enzyme-linked immunosorbent assay and indirect immunofluorescence assay for Lyme disease. *J Infect Dis* 149:465-476, 1984.
14. Pachner AR, Steere AC: The triad of neurologic manifestations of Lyme disease: Meningitis, cranial neuritis, and radiculoneuritis. *Neurology* 35:47-53, 1985.
15. Pfister HW, Einhaupl KM, Wilske B, Preac-Mursic V: Bannwarth's syndrome and enlarged neurological spectrum of arthropod-borne borreliosis. *Zbl Bakt Hyg A* 263:343-347, 1986.
16. Reik L Jr, Steere AC, Bartenhagen NH, et al.: Neurologic abnormalities of Lyme disease. *Medicine* 58:281-294, 1979.
17. Bannwarth A: Chronische lymphocytare meningitis, entzundliche polyneuritis und rheumatismus. Ein beitrag zum problem allergie und nervensystem. *Arch Psychiatr Nervonkr* 113:284-376, 1941.
18. Horstrup P, Ackermann R: Durch zecker ubertragene meningopolyneuritis (Garin-Bujadoux-Bannwarth). *Fortsch Neurol Psychiatr* 41:583-606, 1973.
19. Halperin JJ, Pass HL, Anand AK: Nervous system abnormalities in Lyme disease. *Ann NY Acad Sci* 539:24-34, 1988.
20. Camponova F, Meier C: Neuropathy of vasculitic origin in a case of Garin-Bujadoux-Bannwarth's syndrome with positive *Borrelia* antibody response. *J Neurol* 233:698-726, 1986.
21. Duray PH: The surgical pathology of human Lyme disease. An enlarging picture. *Am J Surg Pathol* 11:47-60, 1977.
22. Kristoferitsch W: Neuropathies in cases of acrodermatitis chronica atrophicans. *Ann NY Acad Sci*

539:35-45,, 1988.

23. Vallat JM, Hugon J, Lubeau M, et al.: Tick-bite meningoradiculoneuritis: Clinical, electrophysiologic, and histologic findings in ten cases. *Neurology* 37:749-753, 1987.

24. Stiernstedt G, Skoldenberg B, Garde A, et al.: Clinical manifestations of *Borrelia* infections of the nervous system. *Zbl Bakt Hyg A* 263:289-296, 1986.

25. Midgard R, Hofstad H: Unusual manifestations of nervous system *Borrelia burgdorferi* infection. *Arch Neurol* 44:781-783, 1987.

26. Steere AC, Batsford WP, Weinberg M, et al.: Lyme carditis: Cardiac abnormalities of Lyme disease. *Ann Intern Med* 93:8-16, 1980.

27. Hansen K, Madsen JK: Myocarditis associated with tickborne *Borrelia burgdorferi* infection. *Lancet* i:1324, 1986.

28. Jacobs JC, Rosen JM, Szer IS: Lyme myocarditis diagnosed by gallium scan. *J Pediatr* 105:950-952, 1984.

29. Reznick JW, Braunstein DB, Walsh RL, et al.: Lyme carditis electrophysiologic and histopathologic study. *Am J Med* 81:923-927, 1986.

30. Marcus LC, Steere AC, Duray PH, et al.: Fatal pancarditis in a patient with coexistent Lyme disease and babesiosis. *Ann Intern Med* 103:374-376, 1985.

31. Steere AC, Gibofsky A, Patarroyo ME, et al.: Chronic Lyme arthritis. Clinical and immunogenetic differentiation from rheumatoid arthritis. *Ann Intern Med* 90:896-901, 1979.

32. Steere AC, Schoen RT, Taylor E: The clinical evolution of Lyme arthritis. *Ann Intern Med* 107:725-731, 1987.

33. Johnston YE, Duray PH, Steere AC, et al.: Lyme arthritis spirochetes found in synovial microangiopathic lesions. *Am J Pathol* 118:26-34, 1985.

34. Sigal LH: Lyme disease: Immunologic manifestations and possible immunopathogenetic mechanisms. *Sem Arthritis Rheum* 18:151-167, 1988.

35. Snydman DR, Schenkein DP, Berardi VP, et al.: *Borrelia burgdorferi* in joint fluid in chronic Lyme arthritis. *Ann Intern Med* 104:798-800, 1986.

36. Schmidli J, Hunziker T, Moesli P, Schaad UB: Cultivation of *Borrelia burgdorferi* from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. *J Infect Dis* 158:905-906, 1988.

37. Ackermann R, Rehse-Kupper B, Gollmer E, Schmidt R: Chronic neurologic manifestations of erythema migrans borreliosis. *Ann NY Acad Sci* 539:16-23, 1988.

38. Pachner AR: Spirochetal diseases of the central nervous system. *Neurol Clinics* 4:207-222, 1986.

39. Pachner AR, Steere AC: CNS manifestations of third stage Lyme disease. *Zbl Bakt Hyg A* 263:301-306, 1986.

40. Mandell H, Steere AC, Reinhardt BN, et al.: Lack of antibodies to *Borrelia burgdorferi* in patients with amyotrophic lateral sclerosis. *N Engl J Med* 320:255-256, 1989.

41. Coyle PK: *Borrelia burgdorferi* antibodies in multiple sclerosis patients. *Neurology* 39:760-761, 1989.

42. Pappolla MA, Omar R, Saran B: Concurrent neuroborreliosis and Alzheimer's disease: Analysis of the evidence. *Hum Pathol* 20:753-757, 1989.

43. Sigal LH: Response of mononuclear cells to *Borrelia burgdorferi*. *Ann Intern Med* 103:808, 1985.

44. Markowitz LE, Steere AC, Benach JL: Lyme disease during pregnancy. *JAMA* 255:3394-3396, 1986.

45. MacDonald AB: Human fetal borreliosis, toxemia of pregnancy, and fetal death. *Zbl Bakt Hyg A* 263:189-200, 1986.

46. MacDonald AB, Benach JL, Burgdorfer W: Stillbirth following maternal Lyme disease. *NY State J Med* 87:615-616, 1987.

47. Schlesinger PA, Duray PH, Burke BA, et al.: Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. *Ann Intern Med* 103:67-68, 1965.

48. Weber K, Bratzke HJ, Neubert U, Wilske B, Duray PH: *Borrelia burgdorferi* in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. *Pediatr Infect Dis* 7:286-289, 1988.

49. Dlesk A, Broste SK, Harkins PG, et al.: Lyme seropositivity (LS+) and pregnancy (PG) outcome in the absence of symptoms (Sx) of Lyme disease (LD). *Arthritis Rheum* 32:S46, 1989.

50. Baron SJ, Fister RD, Cable RG: Survival of *Borrelia burgdorferi* in blood products. *Transfusion* 29:581-583, 1989.

51. Baranton G, Saint-Girons I: *Borrelia burgdorferi* survival in human blood samples. *Ann NY Acad Sci* 539:444-445, 1988.

52. Aoki SK, Holland PV: Lyme disease—another transfusion risk? *Transfusion* 29:646-650, 1988.

53. Steere AC, Hutchinson GJ, Rahn DW, et al.: Treatment of the early manifestations of Lyme disease. *Ann Intern Med* 99:22-26, 1983.

54. Sigal LH, Moffat CM, Steere AC, Dwyer JM: Cellular immune findings in Lyme disease. *Yale J Biol Med* 57:595-598, 1984.

55. Reik L Jr, Burgdorfer W, Donaldson JO: Neurologic abnormalities in Lyme disease without erythema chronicum migrans. *Am J Med* 81:73-78, 1986.

56. Steere AC, Pachner AR, Malawista SE: Neurologic abnormalities of Lyme disease: Successful treatment with high-dose intravenous penicillin. *Ann Intern Med* 99:767-772, 1983.

57. Steere AC, Green J, Schoen RT: Successful parenteral penicillin therapy of established Lyme arthritis. *N Engl J Med* 312:869-874, 1974.

58. Dattwyler RJ, Halperin JJ, Pass H: Ceftriaxone as effective therapy in early Lyme disease. *J Infect Dis* 155:1322-1325, 1987.

59. Liu NY, Dinerman H, Levin RE, et al.: Randomized trial of doxycycline versus amoxicillin-probenecid for the treatment of Lyme arthritis: Treatment of nonresponders with IV penicillin or ceftriaxone. *Arthritis Rheum* 32:S46, 1989.

60. Sigal LH: Experience with the first 100 patients referred to a Lyme disease center. *Am J Med* 88:577-581, 1990.

61. Kirsch M, Ruben FL, Steere AC, et al.: Fatal adult respiratory distress syndrome in a patient with Lyme disease. *JAMA* 259:2737-2739, 1988.

62. Melet M, Gerard A, Voiriot P, et al.: Meningoradiculonevrite mortelle au cours d'une maladie de Lyme. *La Presse Medicale* 15:2075, 1986.

63. deKooning J, Hoogkaamp-Korstanje JAA, van der Linde MR, Crijns HJGM: Demonstration of spirochetes in cardiac biopsies of patients with Lyme disease. *J Infect Dis* 160:150-153, 1989.

64. Costello CM, Steere AC, Pinkerton RE, Feder HM Jr: Prospective study of tick bites in an endemic area for Lyme disease. *J Infect Dis* 159:136-139, 1989.

65. Sigal LH, Taragin MI: Public awareness and anxiety concerning Lyme disease in an endemic area. IV International Conference on Lyme Borreliosis, Stockholm, Sweden, 1990.