Special Articles

Lyme Disease: A Neuropsychiatric Illness

Brian A. Fallon, M.D., M.P.H., and Jenifer A. Nields, M.D.

Objective: *Lyme disease is a multisystemic illness that can affect the central nervous system (CNS), causing neurologic and psychiatric symptoms. The goal of this article is to familiarize psychiatrists with this spirochetal illness.* *Method:* *Relevant books, articles, and abstracts from academic conferences were perused, and additional articles were located through computerized searches and reference sections from published articles.* *Results:* *Up to 40% of patients with Lyme disease develop neurologic involvement of either the peripheral or central nervous system. Dissemination to the CNS can occur within the first few weeks after skin infection. Like syphilis, Lyme disease may have a latency period of months to years before symptoms of late infection emerge. Early signs include meningitis, encephalitis, cranial neuritis, and radiculoneuropathies. Later, encephalomyelitis and encephalopathy may occur. A broad range of psychiatric reactions have been associated with Lyme disease including paranoia, dementia, schizophrenia, bipolar disorder, panic attacks, major depression, anorexia nervosa, and obsessive-compulsive disorder. Depressive states among patients with late Lyme disease are fairly common, ranging across studies from 26% to 66%. The microbiology of* Borrelia burgdorferi *sheds light on why Lyme disease can be relapsing and remitting and why it can be refractory to normal immune surveillance and standard antibiotic regimens.* *Conclusions:* *Psychiatrists who work in endemic areas need to include Lyme disease in the differential diagnosis of any atypical psychiatric disorder. Further research is needed to identify better laboratory tests and to determine the appropriate manner (intravenous or oral) and length (weeks or months) of treatment among patients with neuropsychiatric involvement.*

(Am J Psychiatry 1994; 151:1571–1583)

Lyme disease (Lyme borreliosis), caused by the tick-borne spirochete *Borrelia burgdorferi*, may progress from an initial skin infection to a disabling multisystemic illness. Now the most common vector-borne infection in the United States, Lyme disease is increasing in incidence and geographic spread (1). The disease has dermatologic, arthritic, ophthalmologic, cardiac, neurologic, and psychiatric manifestations (2). In its protean manifestations, in its spirochetal etiology, and in its course (early skin localization and rapid invasion of the central nervous system [CNS]), Lyme disease is similar to syphilis (3). Like syphilis, early recognition is important to prevent an acute, treatable illness from becoming a chronic or relapsing one. Because current diagnostic tests are not always reliable, physicians must rely on clinical presentation as the basis for diagnosis. Because many of the symptoms of Lyme disease involve the CNS, patients with Lyme disease may be referred to psychiatrists both before and after diagnosis.

In this article, we present an overview of Lyme disease with a particular emphasis on its neuropsychiatric features.

Received March 16, 1992; revisions received Oct. 22, 1993, and March 30, 1994; accepted April 1, 1994. From the Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York; the Division of Therapeutics, New York State Psychiatric Institute; and the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn. Address reprint requests to Dr. Fallon, New York State Psychiatric Institute, 722 West 168th St., Unit 13, New York, NY 10032.

Supported in part by a grant to Dr. Fallon from the Lyme Research Foundation, Inc.

The authors thank Drs. W. Burgdorfer, P.K. Coyle, D.F. Klein, M.R. Liebowitz, and R.T. Schoen for comments on earlier versions of this article.

TRANSMISSION

Lyme disease is transmitted by an infected nymphal or adult female *Ixodes* tick. Smaller than the dog tick, the *Ixodes* tick may easily be missed on casual inspection. The bite is usually not painful. Transmission of the spirochete appears to require the tick to feed at least 12–24 hours (4). The ticks are most commonly carried by deer and by the white-footed mouse, but other carriers have been described as well.

DISTRIBUTION

Lyme disease has been reported throughout the United States and in numerous countries around the world. The geographic spread and the incidence in the United States have been rapidly increasing. For example, during 1992, 45 states reported 9,677 cases, representing a 19-fold increase over the 497 cases reported by 11 states in 1982 (5). The State of Connecticut, which in 1992 had the highest rate of Lyme disease in the country, reported between 1991 and 1992 a threefold increase in the proportion of infected ticks in four communities and a one and a half-fold increase in reported cases throughout the state (6). The most heavily affected areas include the Northeast (New York, New Jersey, Connecticut, Massachusetts, Rhode Island, Pennsylvania), the upper Midwest (Minnesota, Wisconsin), and the Pacific coastal region (California, Oregon).

HISTORY

Although Lyme disease was first described in the United States as an arthritic illness preceded by a rash (7), early reports in Europe described a primarily neurologic illness without any arthritis (8, 9). Psychiatric symptoms were described in some of these early reports.

In 1909 a Swedish physician described the classic Lyme rash, known as erythema chronicum migrans, noting that it developed at the site of an *Ixodes* tick bite (10). In 1922 two French doctors, Garin and Bujadoux, wrote a case entitled "Paralysis by Ticks," now thought to be the first report of Lyme meningoradiculitis (8). The patient developed erythema migrans after a tick bite, followed by radiculopathy, paralysis of a portion of one arm, anxiety, and meningitis. In 1930 Hellerstrom, of the Karolinska Institute, described a man who, 3 months after an erythema migrans rash, developed an encephalitis with psychotic symptoms, disorientation, and marked CSF abnormalities (11). In 1941 Bannwarth, a German neurologist, described the syndrome of chronic lymphocytic meningitis, which was characterized by radicular pains, lymphocytic meningitis, and peripheral nervous system involvement, especially facial palsy (9). The cases in all of these early reports, previously described as Garin-Bujadoux syndrome, Bannwarth's syndrome, and neuroborreliosis, are now considered to have been cases of Lyme disease.

In the United States, the first report of a tick-induced erythema migrans rash was in 1970 (12). In 1977 "Lyme arthritis" was described by Steere et al. (7); the article was based on an epidemiological investigation of an outbreak of presumed juvenile rheumatoid arthritis in Connecticut. In 1978 the link between Lyme arthritis and the bite of an *Ixodes* tick (13) was recognized. In 1982 Burgdorfer et al. isolated the etiologic agent of Lyme disease from an *Ixodes* tick—a spirochete now known as *B. burgdorferi* (14). Early in the history of Lyme disease, aspirin and nonsteroidal anti-inflammatory agents were used for symptoms that emerged after the erythema migrans rash (15). Subsequently, penicillin was shown to shorten the duration of illness, thus supporting an infectious etiology. While short courses (10 days) of oral or intravenous antibiotics were recommended at first, it is now recognized that some patients benefit from longer courses (6 weeks or longer) or repeated treatments (16–18).

TYPICAL CLINICAL MANIFESTATIONS OF LYME DISEASE

Within days or weeks after the bite of a tick infected with *B. burgdorferi,* a localized skin reaction may occur, consisting most typically of an erythematous annular rash (erythema migrans), which may enlarge to a size of 5 cm or greater. This early localized sign of infection may soon be followed by mild to severe flu-like symptoms.

Hematogenous dissemination may lead to early (weeks to months) heart, ophthalmologic, or nervous system involvement. Although second- or third-degree atrioventricular block is most common, rare reports of myopericarditis, left ventricle dysfunction, and cardiomegaly exist (19). Conjunctivitis can be an early manifestation of ocular involvement.

Within the first few weeks after skin infection, *B. burgdorferi* may disseminate to the CNS (20–22) where it may remain quiescent for months to years before producing symptoms (23). Because approximately one-third of infected patients do not recall the tick bite or rash and because the flu-like symptoms are nonspecific and may be mild (24), patients may not realize that they are infected until long after the initial bite. Neurologic problems, which occur in 15%–40% of patients (25), may be the presenting symptom. Early on, patients may experience headaches without any signs of inflammation in the CSF (18). Shortly thereafter, patients may develop meningitis, cranial neuritis, and motor or sensory radiculitis (26). With meningitis, symptoms may include recurrent severe headaches, stiff neck, photophobia, and, less commonly, nausea and vomiting. At this stage, objective signs are commonly present in the CSF (see the section on CNS laboratory tests). In less than half of the patients with meningitis, a mild encephalitis develops that is characterized by fluctuating

disturbances of mood, concentration, memory, and sleep. Cranial neuritis, such as Bell's palsy, occurs in 5%–10% of patients with neurologic Lyme disease (27). Other signs of peripheral nerve involvement include sensory or motor radiculoneuropathies; objective abnormalities may be evident on nerve conduction studies. Symptoms of peripheral neuropathy typically include sharp shooting pains, areas of numbness, paresthesias, weakness, or fasciculations.

Later-stage illness (months to years after infection) generally affects the joints, eyes, skin, or CNS. Arthritic involvement begins with migratory arthralgias and, in 60% of untreated patients, develops into an inflammatory arthritis, typically affecting the large joints, such as the knee (28). Ophthalmologic involvement may consist of localized inflammation such as uveitis, iritis, or optic neuritis (29, 30). A late dermatologic manifestation of Lyme disease, acrodermatitis chronica atrophicans, is seen almost exclusively in Europe (31).

Late neurologic involvement may be manifested by encephalomyelitis or encephalopathy (18, 23, 32). Encephalomyelitis, an uncommon late manifestation of Lyme disease, may have quite severe and diverse presentations, including spastic paraparesis, transverse myelitis, cerebellar syndromes, hemiparesis, and movement disorders (18, 32). More common in late Lyme disease is an encephalopathy characterized by subtle to severe cognitive changes and a polyradiculoneuropathy (23). In this stage of illness, the CSF may appear normal (18, 21) (see section on CNS laboratory tests). Other accompanying symptoms of later infection include profound fatigue, sleep disturbance, photophobia, auditory hyperacusis, extreme irritability or emotional lability, word-finding problems, dyslexic-like errors when speaking or writing, and spatial disorientation (23, 33). Disturbances in other sensory modalities, such as taste and smell, have been reported (33, 34). These symptoms may fluctuate in intensity so that symptoms are present on some days but not others. The profile of persistent, marked fatigue and cognitive deficits associated with late-stage Lyme disease is similar to the symptom profile of the chronic fatigue syndrome (35). Whether the late-stage symptoms of Lyme disease are due to persistent infection or to a postinfectious immune activation is an important question that requires further elucidation.

Because patients with encephalopathy or encephalitis may experience marked mood lability, irritability, and sleep disturbance, the distinction between an organic mood disorder and a concomitant primary major depression may be quite difficult to make.

ATYPICAL NEUROLOGIC MANIFESTATIONS OF LYME DISEASE

Because the clinical spectrum of Lyme disease continues to expand, physicians who work in endemic areas should keep Lyme disease in the differential diagnosis of any atypical neurologic illness with multisystemic features. Case reports, for example, have linked a variety of neurologic syndromes to late Lyme disease; these include blindness (30), progressive dementias (32, 36, 37), seizure disorders (34, 38, 39), the Tullio phenomenon (40), strokes (41), extrapyramidal disorders (42), amyotrophic lateral sclerosis (43), Guillain-Barré syndrome (44), and progressive demyelinating-like syndromes mimicking multiple sclerosis (23).

CENTERS FOR DISEASE CONTROL (CDC) CRITERIA FOR DIAGNOSIS

Lyme disease surveillance by the CDC began in 1982, and in 1991 Lyme disease became nationally reportable. For epidemiologic surveillance studies (1), the CDC requires history of exposure in an endemic area and either 1) a physician-diagnosed erythema migrans rash of at least 5 cm in diameter or 2) laboratory confirmation of exposure to *B. burgdorferi* and at least one systemic manifestation. Systemic manifestations must be either musculoskeletal (arthritis), neurologic (lymphocytic meningitis, cranial neuritis, radiculopathy, encephalomyelitis with intrathecal antibody production), or cardiac (second- or third-degree atrioventricular conduction delays). Laboratory confirmation requires the isolation of *B. burgdorferi*, the demonstration of diagnostic levels of *B. burgdorferi* immunoglobulin (Ig) M or IgG antibodies in serum or CSF, or a rising specific antibody titer on serum samples taken from acutely ill and convalescent patients.

These criteria have been useful for epidemiologic studies, but not all patients with Lyme disease will meet this case definition. About one-third of patients do not recall the erythema migrans rash; serologic testing may be unreliable (45); and the clinical spectrum of Lyme disease continues to expand beyond the manifestations currently included in the CDC case definition.

LABORATORY TESTING

Because *B. burgdorferi* is difficult to culture, indirect methods are used to detect the presence of the spirochete. Currently available serologic tests, such as the enzyme-linked immunosorbent assay (ELISA) and the indirect immunofluorescence assay, rely on the immune response following exposure to *B. burgdorferi*, but they can be unreliable, with both false positive and false negative results (45). In a recent study, over half of the 45 laboratories studied reported falsely negative values in a known positive serum sample from a patient with Lyme disease (46). The Western blot is also often used to examine the serum for antibodies against epitopes that are specific for *B. burgdorferi* (e.g., 31 kD, 34 kD, or 39 kD bands). Other laboratory tools are emerging—such as urine antigen tests (47), cell-mediated immunoassay (48), immune complex assays (49), polymerase chain reaction assays (50, 51), and borreliacidal

TABLE 1. Neuropsychological Test Results Among Patients With Disseminated Lyme Disease

Study	N	Diagnosis	Comparison Subjects	Neuropsychological Tests[a]	Results
Logigian et al. (23)	27	Late neurologic Lyme disease	None	California Verbal Learning Test, Wechsler Memory Scale, Wisconsin Card Sorting Test, Trail Making Test, Rey-Osterrieth Complex Figure Test, Finger Tapping Test, Hooper Visual Organization Test, Benton Face Discrimination Test, Boston Naming Test, Token Test, Oral Word Association Test	56% had memory deficits
Kaplan et al. (56)	20[b]	Lyme encephalopathy	11 fibromyalgia and 11 nonpsychotic depressed patients	California Verbal Learning Test, Wechsler Memory Scale, Rey-Osterrieth Complex Figure Test, MMPI, Beck Depression Inventory	Lyme disease patients were significantly more impaired on memory tests
Halperin et al. (27)	17	Neurologic Lyme disease	None	California Verbal Learning Test, Wechsler Memory Scale, Symbol Digit Modalities, Booklet Category Test, Block Design, Purdue Pegboard	Impaired memory, attention, conceptual ability, and motor function; improvement with antibiotics
Krupp et al. (57)	15	Late Lyme disease and cognitive symptoms	10 Healthy age- and sex-matched subjects	WAIS-R[c], Trail Making Test, Booklet Category Test, Oral Word Association Test, Wechsler Memory Scale, Selective Reminding Test	Lyme disease patients had significantly impaired verbal fluency and memory

[a]Neuropsychological tests were not administered by individuals who were blind to medical diagnosis.
[b]A subgroup of patients from the study by Logigian et al. (23).
[c]Subtests of information, vocabulary, similarities, digit span, block design, object assembly, and digit symbol.

antibody tests (52)—but these are not yet well standardized across laboratories.

Several *B. burgdorferi* antigens are shared by other spirochetes. For example, both *B. burgdorferi* and the etiologic agent of syphilis, *Treponema pallidum*, may cause a positive finding on the fluorescent treponemal antibody absorption test; results of nontreponemal tests, such as the rapid plasma reagin and Venereal Disease Research Laboratory tests, are usually negative in Lyme disease (18). Patients with syphilis or periodontal disease (oral spirochetes) may have falsely positive Lyme ELISA serologies and a common 41 kD antibody to flagellar antigen evident on Western blot.

Falsely negative test results may occur for a variety of reasons. If tested too soon after initial infection, the patient may not yet have mounted an antibody response (53). In addition, antibiotic treatment early in the infection may abrogate the humoral immune response (54). In some cases, free antibodies may not be detected because the borrelia antibodies are bound within circulating immune complexes (55). Finally, interlaboratory variability in antigenic standardization of Lyme assays may result in false negative as well as false positive results (46).

CNS LABORATORY TESTS FOR LYME DISEASE

The results of laboratory testing among patients with neurologic Lyme disease vary depending on the stage of the illness. In very early CNS involvement (meningismus) or late-stage infection (encephalopathy), the CSF may appear normal (18). When clinical signs of meningitis or encephalitis are present, a spinal tap may reveal a mononuclear pleocytosis, mildly increased protein, and, in some cases, an elevated IgG index or oligoclonal immunoglobulins. Intrathecal anti-*B. burgdorferi* antibody production is present in 70%–90% of patients with Lyme meningitis (18). Magnetic resonance imaging (MRI) studies may demonstrate punctate white matter lesions on T_2 weighted images, similar to those seen in demyelinating disorders, such as multiple sclerosis. EEG studies may show diffuse slowing or epileptic discharges, but this is uncommon.

In patients with late Lyme encephalopathy, results of brain MRI and EEG studies are generally normal. Functional brain imaging using quantitative brain perfusion single photon emission computed tomography (SPECT), however, may reveal hypoperfusion, particularly in the cerebral white matter, even in patients with no CSF or MRI abnormalities (E.L. Logigian et al., unpublished data, 1994). Objective deficits may be seen on neuropsychological testing (23, 27, 56, 57) (table 1). In about half of these patients, typical markers of CSF infection (pleocytosis, elevated protein, intrathecal antibody production) cannot be found (18). Current experimental research using sensitive ELISA and Western blot techniques has demonstrated the continued presence of spirochetal antigens among many patients with encephalopathy whose CSF otherwise tests normal (21). In some of these patients, results of standard antibody testing of both the serum and the CSF have been negative, but the immune complex dissociation assay revealed bound *B. burgdorferi*-specific antibody (58).

Given the limitations of diagnostic tests, clinicians need to consider clinical factors that would aid in the diagnosis of Lyme disease. These include a history of an

erythema migrans rash or *Ixodes* tick bite, exposure to a Lyme endemic area, and the combination of neuropsychiatric and extraneural symptoms. Because Lyme disease is a multisystemic illness, patients whose neuropsychiatric symptoms start after a flu-like illness should be asked about a history of other symptoms of Lyme disease, including rashes, joint pains, arthritis, cardiac problems, changes in vision, and radicular pains or cranial nerve palsies.

NEUROPSYCHOLOGICAL FINDINGS

Most studies have found that patients with Lyme encephalopathy have subtle impairments in memory, concentration, learning, and conceptual ability. Typically, the deficits suggest frontal lobe involvement, affecting short-term memory, verbal fluency, or executive cognitive functions (table 1). Logigian et al. (23), in a study of 27 patients with chronic neurologic Lyme disease, found that 15 of the 27 had quantifiable memory deficits. In order to determine whether psychological factors might account for the memory impairment among Lyme disease patients, Kaplan et al. (56) compared 20 patients with Lyme encephalopathy with 11 fibromyalgia patients and 11 nonpsychotic depressed patients on a neuropsychological test battery. They found that the Lyme disease patients showed greater impairment on standardized memory tests than either of the comparison groups and that the impairment was independent of the number of somatic complaints and the presence of depression.

Cognitive impairments among patients with late Lyme encephalopathy often improve with antibiotic treatment (23, 27), suggesting that active spirochetal infection causes the encephalopathy. In Halperin et al.'s study (27) of patients with late Lyme borreliosis, serial neuropsychological testing before and after a course of intravenous antibiotics revealed marked improvement on tests of memory, attention and concentration, conceptual ability, and psychomotor and perceptual motor function. Noteworthy is that many patients with cognitive deficits did not have clinical evidence of focal CNS disease. Results of EEGs, CSF studies, and other laboratory investigations were often normal. MRI scans were abnormal in some of the patients with severe memory impairment, revealing hyperintense T_2 white matter lesions suggestive of edema or inflammation. Some patients with late Lyme encephalopathy continue to have residual neuropsychological deficits after antibiotic treatment.

Krupp et al. (57) compared 15 patients with Lyme disease who had complaints of persistent cognitive difficulty 6 months after antibiotic treatment to 10 healthy comparison subjects matched in age and education. Compared to the healthy subjects, the Lyme disease patients exhibited marked impairment on memory tests. In that study, the memory impairment was not correlated with serum or CSF anti-*B. burgdorferi* antibody titers and was not explained by MRI findings or depression. Fatigue, however, a nonspecific marker of chronic Lyme disease, was correlated with memory impairment; this suggested to the authors that the persistent encephalopathy could be an indirect effect of systemic infection elsewhere in the body. The authors noted that persistent neuropsychological deficits were somewhat more common among patients who had received only oral rather than intravenous therapy. In addition, of the six Lyme patients with no objective neuropsychological test deficits but subjective complaints of memory impairment, five had the highest depression scores of the entire group of 15, suggesting that depression in some Lyme patients may account for the subjective experience of cognitive dysfunction.

PSYCHIATRIC MANIFESTATIONS OF LYME DISEASE

A limited but ever increasing literature is beginning to suggest that psychiatric disorders may be part of the clinical profile of Lyme disease. Before reviewing this literature, we present the following case.

Ms. A, a previously healthy 18-year-old college freshman, suddenly developed severe and sustained anxiety, depersonalization, and panic attacks associated with insomnia and appetite loss. She consulted the university health services. After evaluation by both a psychologist and an internist, rest was recommended, under the assumption that these symptoms represented an adjustment reaction to being away from home. As her symptoms worsened, Ms. A began to fear that she was going crazy.

Two weeks later, Ms. A returned home on a medical leave of absence. An extensive medical workup revealed no abnormalities except for a positive Lyme ELISA titer. A Western blot for *B. burgdorferi* also came back positive. Ms. A insisted on getting a spinal tap. Although the cell count and total protein were normal, the CSF revealed IgG antibodies to *B. burgdorferi*. The diagnosis of CNS Lyme disease was made. The patient was treated with a 6-week course of intravenously administered antibiotics, and over the course of the following 3 months she felt 80% better.

Noteworthy in this case is that a diagnosis of Lyme disease was never considered by the college's counselor and internist. The private community physician also did not suspect Lyme disease, but because the patient lived in an endemic area and because Lyme disease is well-known as the "new great imitator" (59), this doctor included a Lyme test in the battery of blood tests. After the ELISA results came back positive, the patient recalled a large annular rash several months earlier that had been followed by a brief period of moderate headaches and uncharacteristic fatigue. Ms. A did not have any joint pain, radiculopathy, cranial nerve palsies, or cardiac symptoms. Her primary manifestation of Lyme disease was psychiatric. Because Ms. A's CSF studies demonstrated borrelial antibodies and because her psychiatric symptoms resolved so rapidly after intravenous antibiotic treatment, active CNS infection was presumed to have been the cause of the severe anxiety and depersonalization. Had Ms. A's serologic Lyme test re-

sults come back falsely negative, the diagnosis of Lyme disease would have been missed. It should be emphasized, however, that careful history taking by a clinician well-versed in the clinical spectrum of Lyme disease would have suggested the diagnosis even in the absence of positive serologic test results.

The psychiatrist's evaluation becomes complicated when psychiatric symptoms emerge after the patient has already received a standard course of antibiotic treatment. Such a situation developed with Ms. A.

One year later, Ms. A developed a return of anxiety with panic attacks and agoraphobia. In addition, she developed rare déjà vu episodes, repetitive musical hallucinations, and intrusive obsessional thoughts and images. Results of a repeat spinal tap were normal on routine testing with a nonreactive CSF ELISA for *B. burgdorferi* antibodies. An EEG after sleep deprivation revealed intermittent slowing in the right and left temporal areas with rare sharp waves. Ms. A was treated for 6 months with imipramine, with complete resolution of her panic attacks and agoraphobia. With time, the obsessional thoughts, déjà vu experiences, and musical hallucinations also resolved.

Although the panic disorder and obsessive-compulsive disorder may have been mere epiphenomena with the Lyme disease, the lack of a family history of these disorders and the normal premorbid history suggest that Lyme disease may have triggered these symptoms. Severe anxiety and panic attacks have been previously described in Lyme disease (60). Obsessive-compulsive disorder has been associated with CNS infections, such as the encephalitis epidemic of 1916–1922 (61), and has also been associated with Lyme disease (62); antineuronal antibodies triggered by systemic infection may induce certain subtypes of obsessive-compulsive disorder (63). Persistent infection could not be completely ruled out in Ms. A's case, given the fact that patients with late CNS Lyme disease may have no demonstrable CSF abnormalities on currently available testing. However, because of the absence of other systemic Lyme symptoms and the improvement with psychiatric medications, this patient has continued to be treated symptomatically and observed for the possible reemergence of signs of CNS infection.

Reviews

In 1990 two review articles appeared in Germany which suggested that psychiatric symptoms may be part of the picture of Lyme disease (64, 65). After an extensive review of the neurologic literature, Omasits et al. (64) concluded: "psychiatric manifestations can at times be predominant, ranging from agitated depressive states to the clinical picture of dementia." Kohler (65) described a staging of psychiatric symptoms, with depression occurring in early CNS disease and organic mood and psychotic disorders occurring in late-stage disease. Although Kohler's report was suggestive, there was no mention of prospectively collected data to support the staging description.

The sparse world literature on the psychiatric manifestations of Lyme borreliosis is methodologically limited. Most of the literature consists of case reports and uncontrolled small series. When standardized measures were used, they were generally self-report depression items that examined one point in time without a comparison group. Despite these marked methodological problems, the case reports and small series are provocative.

Psychiatric Case Reports

Case reports have linked Lyme disease to a vast array of neuropsychiatric symptoms, including paranoia (37, 62, 66–68), thought disorder (66), delusions (62, 66), auditory hallucinations (62, 67), olfactory hallucinations (34), visual hallucinations (69), stereotypies (67), anorexia nervosa (70), obsessions or compulsions (62, 70), major depression (37, 58, 64), disorientation (37, 69, 70), confusion (34, 37, 70), violent outbursts (62, 70), mood lability (60, 62, 67, 70), panic attacks (60, 62), mania (60, 62), personality changes (34, 37), catatonia (67), and dementia (36, 37). In three of these cases (66, 67, 69), it was not until the onset of a psychotic disorder that the patient was brought to medical attention. In two of these cases, no other symptoms of systemic Lyme disease were evident at initial presentation, although a careful history revealed neck and radicular pains 4–6 months earlier. Four patients were hospitalized for a psychiatric illness (62, 66, 67, 70) before it was recognized that the psychiatric symptoms might be caused by CNS Lyme disease. One patient's mania and movement disorder led to hospitalization for a neuropsychiatric evaluation, but Lyme disease was not considered and therefore not diagnosed until several months after discharge (60). Two patients had such extensive multisystemic symptoms that somatization disorder would have been hard to rule out had these two patients not had positive results on serologic tests and a normal premorbid history (60). Many of the patients had abnormalities noted on EEG, CSF, or structural brain imaging (34, 60, 62, 66–68, 70). In one patient (68), *B. burgdorferi* was successfully cultured from the CSF. In two other patients (37, 70), pathological studies of brain tissue revealed *B. burgdorferi*-like spirochetes.

Among the 11 well-described cases, nine patients were treated with intravenous antibiotics for presumed CNS infection (34, 60, 62, 66–68, 70). Duration of intravenous antibiotics ranged from 10 days (one course) to 29 weeks (three courses). Although all patients responded well to antibiotic treatment, relapses occurred in several patients (37, 60, 62, 68). One 47-year-old man with seropositive Lyme disease manifested primarily by depression and memory deficits had an initial excellent response to intravenously administered antibiotics; he relapsed 5 months later, was not re-treated, was institutionalized in a state psychiatric hospital with an organic mood syndrome and progressive frontal-type dementia, and died at age 52. The neuropathological examination revealed degeneration of the substantia nigra and thalamus, with spi-

TABLE 2. Psychiatric Disorders in Larger Series of Patients With Lyme Disease

Study	N	Diagnosis	Measures	Comparison Group	Results	Comments
Logigian et al. (23)	27	Late neurologic Lyme disease	MMPI (score >70 signified depression)	None	26% had extreme irritability; 33% were depressed	89% had encephalopathy
Barr et al. (71)	88	Lyme disease	Beck Depression Inventory, Spielberger anxiety scale	Seronegative patients	Significantly more depression among seropositive patients	
Belman et al. (72)	96 children	Neurologic Lyme disease	Neurologic examination	None	38% had behavioral changes (irritability, lability, poor attention)	Most common symptom was headaches
Krupp et al. (57)	15	Late Lyme disease and cognitive symptoms	Center for Epidemiologic Studies Depression Scale neuropsychological battery	10 healthy age- and sex-matched subjects	Lyme disease patients were significantly more depressed	The most depressed patients did not have abnormal neuropsychological findings
Fallon et al. (73)	51	Chronic, seropositive Lyme disease	Survey using DSM-III-R criteria	30 non-Lyme disease patients with arthritis	Lyme disease patients were significantly more likely to have DSM-III-R depression (66% versus 23%)	32% of Lyme disease patients reported panic attacks (versus 19% of comparison patients; n.s.)
Halperin et al. (27)	17	Neurologic Lyme disease	Beck Depression Inventory	None	Mean Beck scores did not show depression	Depressed patients may have been excluded from study
Kaplan et al. (56)	20[a]	Lyme encephalopathy	Beck Depression Inventory, MMPI	11 fibromyalgia and 11 nonpsychotic depressed patients	Mean Beck scores were not significantly different between groups	Only 13 of the 20 patients completed the Beck inventory
Reik et al. (74)	18	Neurologic Lyme disease	Clinical interview	None	39% had mood lability and irritability; 22% had marked depression	Lyme disease diagnosed by history of erythema migrans or Lyme disease arthritis
Ackermann et al. (32)	44	*Borrelia* encephalomyelitis	Clinical interview	None	12 patients had mild memory and mood problems; 2 patients had dementia-like deficits	Diagnosis based on intrathecal production of Bb antibodies and clinical features

[a]A subgroup of patients from the study by Logigian et al. (23).

rochetes evident in the substantia nigra (37). A flare-up of symptoms shortly after the initiation of antibiotics was reported in four of these patients (60, 62); in one case (62), the antibiotic treatment may have precipitated a manic episode. This treatment-initiated flare-up may reflect an inflammatory response to spirochetal lysis and antigen release, similar to the Jarisch Herxheimer reaction that occurs in the treatment of syphilis. In addition to worsening systemic symptoms (e.g., arthralgias, weakness, shooting pains), this reaction may include worsening neuropsychiatric symptoms, such as depression, anxiety, or photophobia (33).

Psychiatric Series

Nine reports (23, 27, 32, 56, 57, 71–74) of larger series of Lyme patients are summarized in table 2. Irritability, mood lability, or depression were reported in seven of the nine studies, with a frequency ranging from 26% to 66% of the sample. Of the four controlled studies, three (57, 71, 73) reported that depression was greater or more frequently reported by the Lyme disease group. Noteworthy is that all of these studies were composed of patients with disseminated Lyme disease, primarily with late neurologic symptoms consistent with encephalopathy. The patients with Lyme encephalomyelitis (32) showed the most extreme illness, with two patients suffering from dementia-like syndromes. The one study of children with neurologic Lyme disease (72) indicated that behavioral or mood disturbances were the second most common symptom, resulting in mood lability, decreased interest in play, or poor school performance. Six of the 96 children in this series were thought to have psychiatric disturbances unrelated to Lyme disease.

Three of the studies relied on a clinical interview for psychiatric assessment (32, 72, 74). One used a survey based on DSM-III-R (73). Five used standardized self-report instruments (23, 27, 56, 57, 71). In one survey of 51 seropositive patients (73), the cumulative frequency of DSM-III-R major depression since the onset of illness was three times higher among the Lyme patients than among a medically ill comparison group, even though the comparison group was both older and

ill far longer. In addition, among the Lyme patients who reported major depression, most (90%) denied a prior history of depression. It should be noted that none of the nine published series used structured psychiatric diagnostic interviews, and six of the nine studies relied solely on self-report measures. Although all of the studies in table 2 have methodological flaws (small sample size, unclear inclusion/exclusion criteria, biased samples, use of nonstandardized instruments, retrospective or cross-sectional data rather than a prospective design, reliance on patient self-report rather than a structured clinical interview conducted by an individual who was blind to the patient's diagnosis), the preponderance of evidence supports the notion that Lyme disease may be associated with marked mood changes.

In order to investigate the extent to which CNS infection with *B. burgdorferi* may contribute to the association between depression and Lyme disease, biological studies of depressed patients with Lyme disease, examining the CSF for evidence of direct infection or immune modulators, should be conducted. As in the investigation of depression in other medical illnesses, the multifactorial etiology of depression in Lyme disease needs to be addressed through examination of such factors as severity of illness, extent of pain, degree of disability, concomitant central neurologic symptoms or signs, psychodynamic factors, socioeconomic stressors, and family and personal history of psychiatric illness. Brain imaging studies (regional cerebral blood flow, SPECT, positron emission tomography) looking for evidence of metabolic dysfunction would also be of considerable interest.

MICROBIOLOGY OF *B. BURGDORFERI*

The microbiology of *B. burgdorferi* sheds light on why Lyme disease is an illness that at times can be relapsing and remitting and that can be refractory to normal immune surveillance and standard antibiotic regimens. The causative agent of Lyme disease—the spirochete *B. burgdorferi*—has a long replication time, comparable in this respect to *Mycobacterium tuberculosis*. Rapidly transmitted throughout the body, *B. burgdorferi* is known to invade the CNS within the first few weeks after initial infection (20–22). *B. burgdorferi* is known to be neurotropic, leaving the CSF to adhere to glial cells or other brain tissue (75). Once in the CNS, *B. burgdorferi,* like *T. pallidum,* may remain latent, only to cause illness months to years later (23).

Much of the genetic material in *B. burgdorferi* is contained in plasmids (76), resulting in the possibility of significant antigenic variability. This includes marked variability in the expression of surface antigens, with consequent alterations in immunogenicity. Such changes could lead to resistance to normal immunologic functions—for example, through a failure of the *B. burgdorferi*-specific antibody to induce phagocytosis—as well as to evasion of routine laboratory detection. Recent animal research (77) has found that the spirochete may undergo genetic alteration once it is sequestered in the CNS, thus resulting in a new strain of spirochete that is different from the infecting peripheral spirochete. The remarkable strain variation of *B. burgdorferi* may account for the differences between the presentation of Lyme disease in Europe and in the United States (78–80). For example, in Continental Europe, arthritic involvement is less common, and most cases of neurologic Lyme disease have prominent CSF abnormalities. Late-stage neurologic Lyme disease in the United States, on the other hand, is less likely to show CSF abnormalities on routine testing (81).

During growth, *B. burgdorferi* appears to shed membranous material (blebs) from its surface. These blebs coat the spirochete and have been found free in the CSF, serum, and urine (21, 82, 83). The blebs appear to interact specifically with IgM molecules. It is hypothesized that in some cases, the blebs may bind all of the free circulating *B. burgdorferi*-specific IgM antibodies, thereby enabling the organism itself to escape immune surveillance. In addition, the blebs possess potent, nonspecific mitogenic activity that may cause an inappropriate and ineffective stimulation of the immune system. This could initiate autoimmune disease processes (84).

B. burgdorferi has been shown to be capable of persisting in human hosts despite extensive antibiotic treatment (17, 85–88). Because in vitro studies demonstrate that *B. burgdorferi* can be recovered from antibiotic-treated fibroblast monolayers (89) and because *B. burgdorferi* has been shown to lodge inside human fibroblasts (89), mouse macrophages (90), and human endothelial cells (91), researchers conclude that the intracellular location may enable the spirochete to remain inaccessible to antibiotics and normal immune surveillance. Sequestration in other antibiotic- and immunologically privileged sites (e.g., CNS, joints, anterior chamber of the eye) may also account for persistent illness despite antibiotic treatment (20).

Several features are known to contribute to an organism's resistance to standard lengths of antibiotic treatment. These features include an intracellular location (92), long replication time, genetic variability, and the ability to become sequestered in difficult-to-penetrate sites. *B. burgdorferi* appears to possess all of these characteristics.

PATHOGENESIS OF CNS LYME DISEASE

A consistent finding in pathological studies is that the spirochete *B. burgdorferi* is rarely recovered from the affected organ, such as the CNS. Features consistent with a focal vasculitis, however, have been found in both the central and the peripheral nervous systems of patients with neurologic Lyme disease (93, 94). Scientists now believe that a small number of organisms can cause significant neurologic dysfunction either through a *B. burgdorferi*-initiated immune response directed specifically against neural tissue or through the trigger-

ing of a nonspecific inflammatory response (93). The immune response may remain active when spirochetal antigens are still present, as in an ongoing infection, or when a postinfectious autoimmune process has been triggered against host tissue.

Evidence exists to support the role of both specific and nonspecific immune processes in the production of CNS Lyme disease. Evidence of specific processes includes the production of *B. burgdorferi*-specific immune complexes and T cell responses within the CSF (95, 96), autoantibodies to neural tissue (97), and cross-reactivity of *B. burgdorferi* antibodies with neural tissue (98). Evidence of nonspecific processes includes an elevation of neurotoxins, such as quinolinic acid, in the CSF of Lyme patients but not normal comparison subjects (99). Of particular interest is that nonspecific products of immune activation, such as kynurenines or quinolinic acid, can be excitotoxic to neurons and have been linked to memory loss (100), anxiety and depression (101), seizures (101), and the chronic fatigue syndrome (102). In HIV-infected patients, elevations of quinolinic acid in the CSF tend to be correlated with the degree of neuropsychological deficits (100). Further investigation in this area is needed.

LYME DISEASE AND SYPHILIS

Several authors have noted similarities between Lyme disease and syphilis (3, 59, 103). Both are caused by a spirochete: syphilis by *T. pallidum* and Lyme disease by *B. burgdorferi*. Both start with skin inoculation and a localized skin reaction, followed by a disseminated multisystemic infection. Both may progress in stages. Both can cause meningitis, encephalitis, cognitive deficits, cranial neuropathy, and vasculitis. Both diseases can, in rare cases, lead to the Tullio phenomenon (40), characterized by nausea and nystagmus in response to sound stimulation. (This syndrome was previously considered pathognomonic for syphilis.) Antibiotic treatment of both diseases may lead to an initial worsening of symptoms, including neuropsychiatric ones (33, 104). The mechanism of injury in both infections is thought to be primarily indirect: one of immunopathogenesis, not a direct effect of the spirochete itself.

Both *T. pallidum* and *B. burgdorferi* can rapidly invade the CNS, within the first few weeks after infection. Both spirochetes can remain latent for long periods of time before the onset of disease. Both spirochetes can pass through or between endothelial cells (105, 106), thereby enabling dissemination and extensive tissue involvement. Both may persist in the host to cause a chronic infection.

Unlike *T. pallidum*, which is generally transmitted from host to host, the Lyme spirochete is carried by a vector. Furthermore, radiculopathy and peripheral neuropathy are features of Lyme disease that syphilis does not share.

Neurosyphilis is known to be associated with memory problems, depression, mania, psychosis, and personality changes, such as irritability, emotional lability, and apathy (107). Recent evidence suggests that Lyme borreliosis, the "new great imitator" (59), may be associated with a similarly wide spectrum of psychiatric disorders. What Hollos and Ferenczi (108) wrote about syphilis in 1925 bears analogy to the present state of knowledge about Lyme disease:

> The psychical symptomatology of paresis is by no means only an intellectual deterioration. On the contrary, it contains almost all the mental symptoms that occur in other psychoses, very frequently the most characteristic symptoms of mania, of melancholia, of paranoia, and of dementia praecox. In many cases the diagnosis for a long time oscillates between a "functional psychosis" and paresis, and only the beginning of pupillary stiffness, a facial palsy, or the finding of a "positive Wasserman," is the determining factor.

FUTURE DIRECTIONS IN RESEARCH

There are two areas of major clinical significance in which current knowledge about Lyme disease remains incomplete: diagnosis and the optimal treatment for patients with persistent symptoms.

Because currently available serologic tests are not always reliable, Lyme disease remains a clinical diagnosis that is based on a constellation of typical patterns. Diagnostic difficulty arises when patients present with symptoms that are nonspecific or atypical for Lyme disease. If these patients test positive for *B. burgdorferi*, they may be told that they have falsely positive test results. If they test negative, they may be told that they clearly do not have Lyme disease. Although the latter conclusions may be accurate in many cases, the absence of reliable laboratory tests makes such conclusions impossible to draw definitively. Although the prevalence of patients with seronegative Lyme disease is not known, such patients clearly do exist (48, 55, 109). Faced with diagnostic uncertainty, some clinicians may choose not to treat in order to avoid the risks of antibiotic therapy (110). Other clinicians who work in endemic areas may recommend an empirical trial of antibiotics because of what they judge to be a greater risk that a potentially multisystemic chronic infection may progress if untreated (17).

Definitive treatment guidelines for Lyme disease have not been established because knowledge about this illness continues to evolve. However, because of the rapid CNS invasion, aggressive treatment is recommended as early as possible (18). General guidelines consist of 3–4 weeks of oral antibiotics for patients without evidence of central neurologic involvement or 4–6 weeks of intravenous antibiotics for patients with central neurologic involvement. In many cases, following these guidelines results in a remission of symptoms. However, in some cases, relapse occurs after antibiotics are stopped (23).

Because intravenous antibiotic treatment is expensive

and the need for long-term treatment is not yet proven, some insurance companies are now denying reimbursement for repeated courses of intravenously administered treatment; denial of reimbursement is based on the argument that the efficacy of long-term or repeated antibiotic treatment has not been established (111). Yet clinical experience suggests that some patients with central neurologic involvement may require repeated intravenously administered treatment. Several lines of evidence support this clinical observation. First, some patients with Lyme encephalopathy respond well to additional courses of antibiotics (23, 27). Second, several case reports document the persistence of the spirochete or symptoms in patients who have already had the recommended 4–6-week course of antibiotics (17, 85–88). Third, newer diagnostic techniques are able to detect the presence of *B. burgdorferi* antigens in some previously treated, persistently symptomatic patients (21). Fourth, as noted earlier, the microbiology of *B. burgdorferi* makes it clear why standard courses of antibiotics might be ineffective in some cases.

Some patients do not get better with repeated treatment. Persistent symptoms in these patients may result from permanent damage or from a postinfectious autoimmune process (112). Prospective microbiological and clinical studies are needed to identify risk factors that may predispose certain patients to develop chronic Lyme disease and to distinguish those patients who will respond to prolonged or repeated antibiotic treatment from those who will not.

CONCLUSIONS

The neuropsychiatric effects of many infectious illnesses, bacterial (neurosyphilis, tuberculosis), parasitic (neurocysticercosis, toxoplasmosis), fungal (coccidiomycoses, cryptococcosis), and viral (herpes simplex, HIV), are well known. Also well known are the prominent neuropsychiatric manifestations of illnesses, such as systemic lupus erythematosus and multiple sclerosis, that cause CNS inflammation. Early in the history of many of these illnesses, the psychiatric symptoms were thought to be functional in nature. Women suffering from multiple sclerosis were thought to be hysterical. Early depression and cognitive decline in patients with AIDS were thought to represent purely an emotional reaction to a serious illness. Later research provided objective evidence that CNS pathology caused by infection or inflammation was associated with each of these psychiatric syndromes.

The spectrum of neuropsychiatric syndromes associated with Lyme disease is only beginning to be elucidated by clinical studies and case reports. At the same time, biological studies and brain imaging techniques suggest a physiological basis for such syndromes through one or more of the following mechanisms: direct infection in the CNS; specific, localized autoimmune reactions; or secondary but centrally active immunologic responses to systemic infection.

This article emphasizes the biological substrate of the neuropsychiatric symptoms associated with Lyme disease. The complicated secondary emotional reactions to this illness that relate to particular aspects of its symptoms, including fluctuating course, bizarreness of symptoms, cognitive disability, chronic pain, and the uncertainties surrounding its diagnosis and management, have been discussed in greater detail elsewhere (33).

In addition to the dermatologic and arthritic manifestations, the breadth of neuropsychiatric symptoms in Lyme disease should be recognized. The lessons painfully learned in syphilis apply here: delays in diagnosis and treatment can result in a treatable, acute illness becoming a chronic one with, in some cases, devastating consequences.

REFERENCES

1. White DJ, Chang HG, Benach JL, Bosler EM, Meldrum SC, Means RG, Debbie JG, Birkhead GS, Morse DL: The geographic spread and temporal increase of the Lyme disease epidemic. JAMA 1991; 266:1230–1236
2. Burgdorfer W: Lyme Borreliosis: ten years after the discovery of the etiologic agent, Borrelia burgdorferi. Infection 1991; 4: 257–262
3. Lukehart SA, Marra C: A comparison of syphilis and Lyme disease: central nervous system involvement, in Lyme Disease: Molecular and Immunologic Approaches. Edited by Schutzer SE. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1992
4. Piesman J, Mather T, Sinskt R, Spielman A: Duration of tick attachment and Borrelia burgdorferi transmission. J Clin Microbiol 1987; 25:557–558
5. CDC: Lyme Disease—United States 1991–1992. MMWR 1993; 42:345–348
6. State of Connecticut Department of Public Health: Lyme Disease Update. Connecticut Epidemiologist 1993; 13:9–12
7. Steere AC, Malawista SE, Snydman DR, Shope RE, Andiman WA, Ross MR, Steele FM: Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum 1977; 20:7–17
8. Garin Ch, Bujadoux A: Paralysie par les tiques. J Med Lyon 1922; 3:765–767
9. Bannwarth A: Chronische lymphocytare meningitis, entzundliche polyneuritis and "rheumtisums." Arch Psychiatr Nervenkr 1941; 113:284–376
10. Afzelius A: Erythema chronicum migrans. Acta Derm Venereol (Stockh) 1921; 2:120–125
11. Hellerstrom M: Erythema chronicum migrans Afzelii. Acta Derm Venereol (Stockh) 1930; 11:315–321
12. Scrimenti RJ: Erythema chronicum migrans. Arch Dermatol 1970; 102:104–105
13. Steere AC, Broderick TF, Malawista SE: Erythema chronicum migrans and Lyme arthritis: epidemiologic evidence for a tick vector. Am J Epidemiol 1978; 108:312–321
14. Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Brunwaldt E, Davis JP: Lyme disease—a tick-borne spirochetosis? Science 1982; 216:1317–1319
15. Gilliland BC, Petersdorf RG: Infectious arthritis, in Principles of Internal Medicine. Edited by Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD. New York, McGraw-Hill, 1983
16. Lavoie PE, Lyme disease (Lyme Borreliosis), in Conn's Current Therapy 1991. Edited by Rakel RE. Philadelphia, WB Saunders, 1991
17. Liegner KB: Lyme disease: the sensible pursuit of answers. J Clin Microbiol 1993; 31:1961–1963

18. Coyle PK: Neurologic Lyme disease. Semin Neurol 1992; 12: 200–208
19. Reznick JW, Braunstein DB, Walsh RI, Smith C, Wolfson PM, Gierke IW, Gorelkin I, Chandler RW: Lyme carditis: electrophysiologic and histopathologic study. Am J Med 1986; 5:923–927
20. Luft BJ, Steinman CR, Neimark HC, Muralidhar B, Rush T, Finkel MF, Kunkel M, Dattwyler RJ: Invasion of the CNS by Bb in acute disseminated infection. JAMA 1992; 267:1364–1367
21. Coyle PK, Deng Z, Schutzer SE, Belman AL, Benach J, Krupp LB, Luft B: Detection of Borrelia burgdorferi antigens in cerebrospinal fluid. Neurology 1993; 43:1093–1097
22. Garcia-Monco JC, Villar BF, Alen JC, Benach JL: Borrelia burgdorferin in the central nervous system: experimental and clinical evidence for early invasion. J Infect Dis 1990; 161: 1187–1193
23. Logigian EL, Kaplan RF, Steere AC: Chronic neurologic manifestations of Lyme disease. N Engl J Med 1990; 323:1438–1444
24. Steere AC, Bartenhagen NH, Craft JE, Hutchinson GJ, Newman JH, Rahn DW, Sigal LH, Spieler PN, Stenn KS, Malawista SE: The early clinical manifestations of Lyme disease. Ann Intern Med 1983; 99:76–82
25. Reik L: Lyme Disease and the Nervous System. New York, Thieme, 1992
26. Pachner AR, Steere AC: The triad of neurologic manifestations of Lyme disease: meningitis, cranial neuritis, and radiculoneuritis. Neurology 1985; 35:47–53
27. Halperin JJ, Pass HL, Anand AK, Luft BJ, Volkman DJ, Dattwyler RJ: Nervous system abnormalities in Lyme disease. Ann NY Acad Sci 1988; 539:24–34
28. Steere AC, Malawista SE, Hardin JA, Ruddy S, Askenase PW, Andiman WA: Erythema chronicum migrans and Lyme arthritis: the enlarging clinical spectrum. Ann Intern Med 1977; 86: 685–698
29. Flach AJ, Lavoie PE: Episcleritis, conjunctivitis, and keratitis as ocular manifestations of Lyme disease. Ophthalmology 1990; 97:973–975
30. Steere AC, Duray PH, Danny JH, Kaufman MD, Wormser GP: Unilateral blindness caused by infection with Lyme disease spirochete, Borrelia burgdorferi. Ann Intern Med 1985; 103:382–384
31. Asbrink E, Hovmark A, Hederstedt B: The spirochetal etiology of acrodermatitis chronica atrophicans Herxheimer. Acta Derm Venereol (Stockh) 1984; 64:506–512
32. Ackermann R, Rehse-Kupper B, Gollmer E, Schmidt R: Chronic neurologic manifestations of Erythema migrans borreliosis. Ann NY Acad Sci 1988; 539:16–23
33. Fallon BA, Nields JA, Burrascano JJ, Liegner K, DelBene D, Liebowitz MR: The neuropsychiatric manifestations of Lyme borreliosis. Psychiatr Q 1992; 63:95–115
34. Reik L, Smith L, Khan A, Nelson W: Demyelinating encephalopathy in Lyme disease. Neurology 1985; 35:267–269
35. Krupp LB, Mendelson BW, Friedman R: An overview of chronic fatigue syndrome. J Clin Psychiatry 1991; 52:403–410
36. MacDonald AB, Miranda JM: Concurrent neocortical borreliosis and Alzheimer's disease. Hum Pathol 1987; 18:750–761
37. Waniek C, Prohovnik I, Kaufman MA: Rapid progressive frontal type dementia associated with Lyme disease and subcortical degeneration, in Abstracts of the VII Annual International Scientific Conference on Lyme Borreliosis. Hartford, Conn, Lyme Disease Foundation, 1994
38. Reik L, Burgdorfer W, Donaldson JO: Neurologic abnormalities in Lyme disease without erythema chronicum migrans. Am J Med 1986; 81:73–77
39. Brogan GX, Homan CS, Viccellio P: The enlarging clinical spectrum of Lyme disease: Lyme cerebral vasculitis, a new disease entity. Ann Emerg Med 1990; 19:572–576
40. Nields JA, Kveton JF: Tullio phenomenon and seronegative Lyme borreliosis (letter). Lancet 1991; 338:128–129
41. Kohler J, Kern U, Kaper J, Rhese-Kupper B, Thoden U: Chronic central nervous system involvement in Lyme borreliosis. Neurology 1988; 38:863–867
42. Kohlhepp W, Kuhn W, Kruger H: Extrapyramidal features in central Lyme borreliosis. Eur Neurol 1989; 29:150–155
43. Halperin JJ, Kaplan GP, Brazinsky S, Tsai TF, Cheng T, Ironside A, Wu P, Delfiner J, Golightly M, Brown RH: Immunologic reactivity against Borrelia burgdorferi in patients with motor neuron disease. Arch Neurol 1990; 47:586–594
44. Clavelou P, Beytout J, Vernay D, Aumaitre O, Dordain G, Tournilhac M: Neurologic manifestations of Lyme disease in the northern parts of the Auvergne (abstract). Neurology 1989; 39(suppl 1):350
45. Magnarelli LA: Laboratory diagnosis of Lyme disease. Rheum Dis Clin North Am 1989; 15:735–745
46. Bakken LL, Case KL, Callister SM, Bourdeau NJ, Schell RF: Performance of 45 laboratories participating in a proficiency testing program for Lyme disease serology. JAMA 1992; 268: 891–895
47. Hyde FW, Johnson RC, White TJ, Shelburne CE: Detection of antigens in urine of mice and humans infected with Borrelia burgdorferi, etiologic agent of Lyme disease. J Clin Microbiol 1989; 27:58–61
48. Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG: Seronegative Lyme disease. New Engl J Med 1988; 319:1441–1446
49. Schutzer SE, Coyle PK, Brunner M: Identification of specific borrelia burgdorferi components in circulating antigen-antibody complexes, in Lyme Disease: Molecular and Immunologic Approaches. Edited by Schutzer SE. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1992
50. Rosa PA, Schwan TG: A specific and sensitive assay for the Lyme disease spirochete, borrelia burgdorferi, using the polymerase chain reaction. J Infect Dis 1989; 160:1018–1029
51. Nocton JJ, Dressler F, Rutledge BJ, Rys PN, Persing DH, Steere AC: Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis. New Engl J Med 1994; 330:229–234
52. Callister SM, Schell RF, Lim LCL, Jobe DA, Case KL, Bryant GL, Molling PE: Detection of borreliacidal antibodies by flow cytometry. Arch Intern Med 1994; 154:1625–1632
53. Grodzicki RL, Steere AC: Comparison of immunoblotting and indirect enzyme-linked immunosorbent assay using different antigen preparations for diagnosing early Lyme disease. J Infect Dis 1988; 157:790–797
54. Shrestha M, Grodzicki RL, Steere AC: Diagnosing early Lyme disease. Am J Med 1985; 78:235–240
55. Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J: Sequestration of antibody to Borrelia burgdorferi in immune complexes in seronegative Lyme disease. Lancet 1990; 335: 312–315
56. Kaplan RF, Meadows ME, Vincent LC, Logigian EL, Steere AC: Memory impairment and depression in patients with Lyme encephalopathy: comparison with fibromyalgia and nonpsychotically depressed patients. Neurology 1992; 42:1263–1267
57. Krupp LB, Masur D, Schwartz J, Coyle PK, Langenbach LJ, Fernquist SK, Jandorf L, Halperin JJ: Cognitive functioning in late Lyme borreliosis. Arch Neurol 1991; 48:1125–1129
58. Coyle PK, Schutzer SE, Belman AL, Krupp LB, Dheng Z: Cerebrospinal fluid immunologic parameters in neurologic Lyme disease, in Lyme Disease: Molecular and Immunologic Approaches. Edited by Schutzer SE. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1992
59. Pachner AR: Neurologic manifestations of Lyme disease, the new "Great Imitator." Rev Infect Dis 1989; 11(suppl 6):S1482–S1486
60. Fallon BA, Nields JA, Parsons B, Liebowitz MR, Klein DF: Psychiatric manifestations of Lyme borreliosis. J Clin Psychiatry 1993; 54:263–268
61. von Economo C: Encephalitis Lethargica: Its Sequelae and Treatment. London, Oxford University Press, 1931, pp 118–131
62. Fallon BA, Schwartzberg M, Bransfield R, Zimmerman B, Scotti A, Weber CA, Liebowitz MR: Late stage neuropsychiatric Lyme disease: differential diagnosis and treatment. Psychosomatics (in press)

63. Swedo SE, Leonard HL: Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood. Pediatrics 1994; 93:323–326
64. Omasits M, Seiser A, Brainin M: Recurrent and relapsing borreliosis of the nervous system. Wien Klin Wochenschr 1990; 102:4–12
65. Kohler VJ: Lyme disease in neurology and psychiatry. Fortschr Med 1990; 108:191–194
66. Roelcke U, Barnett W, Wilder-Smith E, Sigmund D, Hacke W: Untreated neuroborreliosis: Bannwarth's syndrome evolving into acute schizophrenia-like psychosis. J Neurol 1992; 239: 129–131
67. Pfister HW, Preac-Mursic V, Wilske B, Rieder G, Forderreuther S, Schmidt S, Kapfhammer HP: Catatonic syndrome in acute severe encephalitis due to Borrelia burgdorferi infection. Neurology 1993; 43:433–435
68. Diringer MN, Halperin JJ, Dattwyler RJ: Lyme meningoencephalitis: report of a severe, penicillin-resistant case. Arthritis Rheum 1987; 30:705–707
69. Burrascand JJ: Lyme disease presenting as organic psychosis (abstract). Sixth Annual Lyme Disease Scientific Conference, 1993. Hartford, Conn, Lyme Disease Foundation
70. Pachner AR, Duray P, Steere AC: Central nervous system manifestations of Lyme disease. Arch Neurol 1989; 46:790–795
71. Barr WB, Hilton E, Warum F, Flash V, Solomon S: Assessment of depression in late Lyme disease (abstract). Neurology 1991; 41S:120
72. Belman AL, Iyer M, Coyle PK, Dattwyler R: Neurologic manifestations in children with North American Lyme disease. Neurology 1993; 43:2609–2614
73. Fallon BA, Nields JA, DelBene D, Liebowitz MR, Klein DF: Depression and Lyme disease: a controlled survey, in New Research Program and Abstracts, 144th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1991
74. Reik L, Steere AC, Bartenhagen NH, Shope RE, Malawista SE: Neurologic abnormalities of Lyme disease. Medicine 1979; 58: 281–294
75. Garcia-Monco JC, Fernandez-Villar B, Benach JL: Adherence of the Lyme disease spirochete to glial cells and cells of glial origin. J Infect Dis 1989; 160:497–506
76. Barbour AG, Garon CF: Linear plasmids of the bacterium Borrelia burgdorferi have covalently closed ends. Science 1987; 237: 409–411
77. Pachner AR, Itano A: Borrelia burgdorferi infection of the brain: characterization of the organism and response to antibiotics and immune sera in the mouse model. Neurology 1990; 40:1535–1540
78. Hanrahan JP, Benach JL, Coleman JL, Bosler EM, Morse DL, Cameron DJ, Edelman R, Kaslow RA: J Infect Dis 1984; 150:489–596
79. Steere AC, Taylor E, Wilson ML, Levine JL, Spielman A: Longitudinal assessment of the clinical and epidemiological features of Lyme disease in a defined population. J Infect Dis 1986; 154:295–300
80. Schwan TG, Burgdorfer W, Garon CF: Changes in infectivity and plasmid profile of the Lyme disease spirochete, Borrelia burgdorferi, as a result of in vitro cultivation. Infect Immun 1988; 56:1831–1836
81. Coyle PK: Antigen detection and cerebrospinal fluid studies, in Lyme Disease. Edited by Coyle PK. Philadelphia, Mosby Year Book, 1992
82. Garon CF, Dorward DW, Corwin MD: Structural features of Borrelia burgdorferi—the Lyme disease spirochete: silver staining for nucleic acids. Scanning Microsc Suppl 1989; 3:109–115
83. Dorward DW, Schwan TG, Garon CF: Immune capture and detection of Borrelia burgdorferi antigens in urine, blood, or tissues from infected ticks, mice, dogs, and humans. J Clin Microbiol 1991; 29:1162–1170
84. Whitmire WM, Garon CF: Specific and nonspecific responses of murine B cells to membrane blebs of Borrelia burgdorferi. Infect Immun 1993; 61:1460–1467
85. Preac-Mursic V, Weber K, Pfister HW, Wilske B, Gross B, Baumann A, Prokop J: Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection 1989; 17: 355–359
86. Haupl T, Hahn G, Rittig M, Krause A, Schoerner C, Schonherr U, Kalden JR, Burmester GR: Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum 1993; 36:1621–1626
87. Hassler D, Riedel K, Zorn J, Preac-Mursic V: Pulsed high-dose cefotaxime therapy in refractory Lyme borreliosis (letter). Lancet 1991; 338:193
88. Liegner KB, Shapiro JR, Ramsay D, Halperin AJ, Hogrefe W, Kong L: Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting Borrelia burgdorferi infection. J Am Acad Dermatol 1993; 28:312–314
89. Georgilis K, Peacocke M, Klempner MS: Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. J Infect Dis 1992; 166:440–444
90. Montgomery RR, Nathanson MH, Malawista SE: The fate of Borrelia burgdorferi in mouse macrophages: destruction, survival, recovery. J Immunol 1993; 150:909–915
91. Ma Y, Sturrock A, Weis JJ: Intracellular localization of Borrelia burgdorferi within human endothelial cells. Infect Immun 1991; 59:671–678
92. Mahmoud AF: The challenge of intracellular pathogens (editorial). N Engl J Med 1992; 326:761–762
93. Benach JL, Garcia Monco JC: Aspects of the pathogenesis of neuroborreliosis, in Lyme Disease: Molecular and Immunologic Approaches. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1992
94. Duray PH: Target organs of Borrelia burgdorferi infections: functional responses and histology, in Lyme disease: molecular and immunologic approaches. Edited by Schutzer SE. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1992
95. Coyle PK, Schutzer SE, Belman AL, Krupp LB, Golightly MG: Cerebrospinal fluid immune complexes in patients exposed to Borrelia burgdorferi: detection of Borrelia specific and non-specific complexes. Ann Neurol 1990; 28:739–744
96. Pachner AR, Steere AC, Sigal LH, Johnson CJ: Antigen-specific proliferation of CSF lymphocytes in Lyme disease. Neurology 1985; 35:1642–1644
97. Garcia-Monco JC, Coleman JL, Benach JL: Antibodies to myelin basic protein in Lyme disease patients. J Infect Dis 1988; 158:667–668
98. Sigal LH, Tatum AH: Lyme disease patients' serum contains IgM antibodies to Borrelia burgdorferi that cross react with neuronal antigens. Neurology 1988; 38:1439–1442
99. Halperin JJ, Heyes MP: Neuroactive kynurenines in Lyme borreliosis. Neurology 1992; 42:43–50
100. Heyes MP, Brew JB, Martin A, Price RW, Salazar AM, Sidtis JJ, Yergey JA, Mouradian MM, Sadler AE, Keilp J, Rubinow D, Markey SP: Quinolinic acid in cerebrospinal fluid and serum in HIV-I infection: relationship to clinical and neurological status. Ann Neurol 1991; 29:202–209
101. Lapin IP: Behavioral and convulsant effects of kynurenines, in Quinolinic Acid and the Kynurenines. Edited by Stone TW. Boca Raton, Fla, CRC Press, 1988
102. Heyes MP, Saito K, Crowley JS, Davis LE, Demitrack MA, Der M, Dilling LA Elia J, Kruesi MJP, Lackner A, Larsen SA, Lee K, Leonard HL, Markey SP, Martin A, Milstein S, Mouradian MM, Pranzatelli MR, Quearry BJ, Salazar A, Smith M, Strauss SE, Sunderland T, Swedo SW, Tourtellotte WW: Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurologic disease. Brain 1992; 115:1249–1273
103. Miklossy J, Kuntzer T, Bogousslavsky J, Regli F, Janzer RC: Meningovascular form of neuroborreliosis: similarities between neuropathological findings in a case of Lyme disease and those occurring in tertiary neurosyphilis. Acta Neuropathol 1990; 80: 568–572
104. Thomas EW: Syphilis: Its Course and Management. New York, Macmillan, 1949, pp 112–113
105. Comstock LE, Thomas DD: Penetration of endothelial cell

monolayers by Borrelia burgdorferi. Infect Immun 1989; 57: 1626–1628
106. Thomas DD, Navab M, Haake DA, Fogelman AM, Miller JN, Lovett MA: Treponema pallidum invades intercellular junctions of endothelial cell monolayers. Proc Natl Acad Sci USA 1988; 85:3608–3612
107. Rundell JR, Wise MG: Neurosyphilis: a psychiatric perspective. Psychosomatics 1985; 26:287–295
108. Hollos S, Ferenczi S: Psychoanalysis and the Psychic Disorder of General Paresis. New York, Nervous and Mental Disease Publishing Co, 1925, p 2
109. Keller TL, Halperin JJ, Whitman M: PCR detection of Borrelia burgdorferi DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. Neurology 1992; 42:32–42
110. Appropriateness of parenteral antibiotic treatment for patients with presumed Lyme disease: a joint statement of the American College of Rheumatology and the Council of the Infectious Diseases Society of America. Ann Intern Med 1993; 119:518
111. Stevens S: Suits seen rising to force coverage of untested therapies. Physicians Financial News, Dec 15, 1993, pp 1, 36
112. Sigal LH: Possible autoimmune mechanisms in Lyme disease, in Lyme Disease: Molecular and Immunologic Approaches. Edited by Schutzer SE. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1992