LYME DISEASE

A Tick-Associated Disease Originally Described in Europe, but Named After a Town in Connecticut

JOHN F. ANDERSON AND LOUIS A. MAGNARELLI

LITTLE DID GERMAN PHYSICIAN ALFRED BUCHwald realize in 1883, when he described a chronic inflammation of the skin, that his observation would be the first among hundreds providing information on a serious global illness. Now known as Lyme disease or Lyme borreliosis, this human and veterinary disease is caused by a spirochete that is transferred from animals to humans by the bite of a hard-bodied tick. Although considered to be a newly recognized illness in the United States, Lyme disease or related maladies have been known in Europe for more than a century. This illness is currently the most commonly reported arthropod-associated disease in the United States.

In this article, we review highlights of the history of the clinical diagnosis of Lyme borreliosis and related diseases, the milestones leading to the discovery of the etiologic agent, *Borrelia burgdorferi*, as well as the natural history of this bacterium and its tick vectors in the United States.

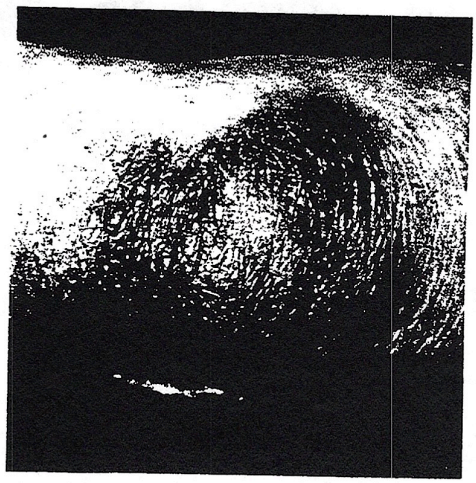
Magnarelli (left) and Anderson stand beside plaque identifying Old Lyme, CT. Lyme disease was named after this town.

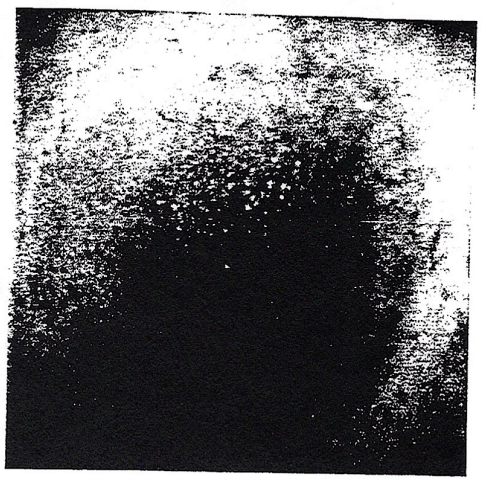
Lyme Disease and Related Disorders

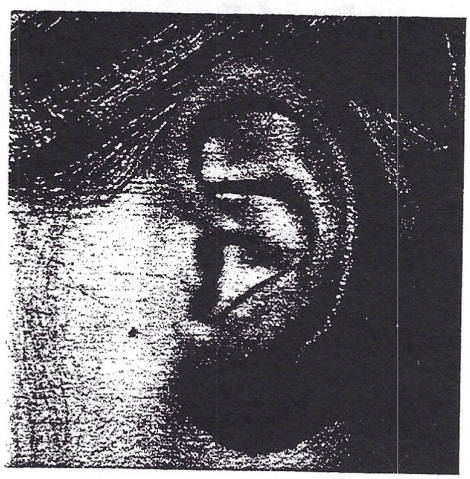
Acrodermatitis Chronica Atrophicans. Although *B. burgdorferi* remained unknown until 1981, clinical features of one of these illnesses had been described in Germany in 1883 by Buchwald as a tissue-paper-like atrophy of the skin in *Vierteljahresschrift für Dermatologie und Syphilis*. In 1902, in *Archiv für Dermatologie und Syphilis*, Karl Herxheimer and Kuno Hartmann of the dermatologischen Abtheilung des städtischen Krankenhauses in Frankfurt, Germany, further characterized the illness and called it acrodermatitis chronica atrophicans. Although relatively common in Europe, the illness is rare in the United States. The disease was first reported in a patient in the United States in 1898 and in others until 1945, but all were emigrants from Europe and presumably had acquired infections there. A couple of indigenous cases were reported in the 1980s.

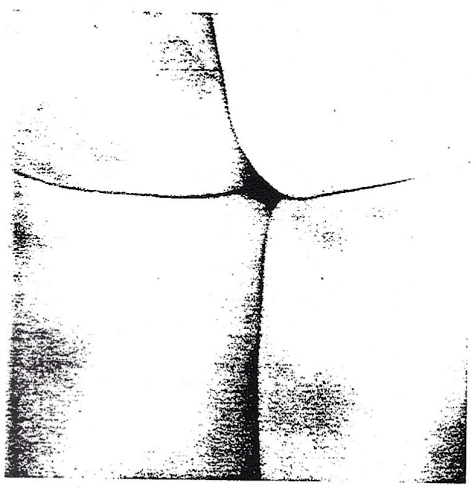
Erythema Migrans. A centrifugally annular erythema, now often heralded as the hallmark of Lyme disease, was first described and named *erythema migrans* by Swedish dermatologist Arvid Afzelius when he reported to the Dermatologischen Gesellschaft in Stockholm in October, 1909, that an elderly woman had an erythema of the skin following a bite from an *Ixodes reduvius* (L) (=*Ixodes ricinus* [L]). His report was published in 1910 in *Archiv für Dermatologie und Syphilis*. The Viennese physician Wilhelm Balban reported three similar cases in an article entitled "Erythema annulare, entstanden durch Insektenstiche," published also in *Archiv für Dermatologie und Syphilis* in 1910 but did not

*First US acquired case proven & published by dermatologist Rudy Scrimenti in Wisconsin in 1969!









(Top left) Acrodermatitis chronica atrophicans. Note the violaceous discoloration and atrophy of the skin. (Courtesy of Yale Journal of Biology and Medicine [Weber et al. 1984].)

(Top right) Erythema migrans. (Courtesy of Raven Press. [Berger et al. 1983].)

(Bottom left) *Borrelia* lymphocytoma. Note reddish swelling of earlobe. (Courtesy of Yale Journal of Biology and Medicine. [Weber et al. 1984].)

(Bottom right) Multiple secondary erythema migrans lesions. (Courtesy of Raven Press. [Berger et al. 1983].)

cite Afzelius' article, and, in 1913, B. Lipschutz, also of Vienna, reported a similar case in the same journal, but, without citing Afzelius or Balban, called the disease erythema chronicum migrans.

Lipschutz's designation of the disease as erythema chronicum migrans was accepted without challenge until 1930 when Sven Hellerstrom of the dermato-syphilidologischen Klinik des Karolinischen Instituts, Stockholm, Sweden, stated in *Acta Dermato-venereologica* that Afzelius, not Lipschutz, had the priority article. Lipschutz's description, however, prevailed until recently when it was realized that the disease is not always chronic. Thereupon, in 1986, the Munich, Germany, physician Klaus Weber proposed in the *Proceedings of the Second International Symposium on Lyme disease and Related Disorders*, that the disease be known as erythema migrans because there is "no reason to foster a mistake any longer, especially since Afzelius has provided us with a term which is shorter, self-explanatory, and older."

The first case of erythema migrans in a native U.S. citizen was accurately diagnosed and described in 1970 in *Archives of Dermatology* by dermatologist R. J. Scrimenti of Milwaukee, WI. In 1976, in the *Journal of the American Medical Association*, W. E. Mast and W. M. Burrows, Jr., of the U.S. Navy, reported four people in southeastern Connecticut as also having erythema migrans.

Borrelia Lymphocytoma. A solitary cutaneous lesion, with follicles resembling those in lymph nodes, is the third and least prevalent Lyme-disease-like illness associated with skin. This was first noted in 1911 by the Swiss pathologist Jean Louis Burckhardt of the Pathologisch-Anatomischen Institut, Basel, in an article entitled "Zur Frage der Follikel-und Keimzentrenbildung in der Haut", published in *Frankfurter Zeitschrift für Pathologie*. More than 30 years later in 1943, Bo Bafverstedt of the Department of Dermatology of the Sodersjukhuset in Stockholm termed the condition lymphadenosis benigna cutis; the disease is now also known as *Borrelia*

lymphocytoma as reviewed by Klaus Weber in the *Yale Journal of Biology and Medicine* in 1984 and Eva Asbrink in *Supplementum 77* of the *Scandinavian Journal of Infectious Diseases* in 1991. It appears as a tumorlike, bluish-red swelling that often is accompanied by regional disorders of lymph nodes or lymph vessels. The nodule is often in the ear lobe of children and the areola area of the breasts of adults.

Bannwarth's Syndrome. Neurological disease following tick bite and an enlarging erythema were first noted in a single case report in 1922 by Garin and Bujadoux in *Le Journal de Medicine de Lyon.* In 1930, Sven Hellerstrom of Stockholm, unaware of the earlier publication in France, independently reported the connection between erythema migrans and meningitis; and in 1941 and 1944, Alfred Bannwarth of Universitäts-Nervenklinik in Munich, Germany, described neurologic disease in 26 patients, noted the chronic inflammatory central nervous system changes, and described the disorder as chronic lymphocytic meningitis with the clinical syndrome of neuralgia or neuritis. Unaware of the earlier reports from France and Sweden, Bannwarth missed the association of this syndrome with erythema migrans and tick bites, but other investigators often made the association and referred to the condition as tick-borne meningopolyneuritis, Bannwarth's syndrome, or syndrome of Garin-Bujadoux, Bannwarth. This neurologic manifestation is a syndrome within the clinical spectrum of Lyme disease as reviewed by Rudolph Ackermann and colleagues of the Neurologic University Clinic of Cologne, Germany, in the *Yale Journal of Biology and Medicine* in 1984, and by two independent reviews in *Supplementum 77* of the *Scandinavian Journal of Infectious Diseases,* 1991, by Wolfgang Kristoferitsch of Vienna, Austria, and John J. Halperin of the State University of New York at Stony Brook.

Lyme Disease. A clustering of arthritic children in southeastern Connecticut was reported in 1976 in *Arthritis and Rheumatism* by A. C. Steere, Stephen Malawista, and colleagues of Yale University. They initially called this syndrome Lyme arthritis and later changed the name to Lyme disease after the towns of Old Lyme and Lyme, where many of the children lived. The Yale group described the major clinical signs and symptoms of this complex disease and linked the illness to tick bites.

A multisystemic illness, Lyme disease is known to affect tissues of skin, joint, nervous system, and heart of all age groups, but infection is usually not considered to be life threatening. Progression of the illness is divided into early and late infection. Early infection is separated into localized infection, characterized by erythema migrans and sometimes regional disorders of lymph nodes or lymph vessels, and by disseminated infection. The spirochetes may then migrate to many sites via the bloodstream and lymphatic system. Characteristic symptoms include secondary annular lesions in the skin, migratory pain in joints, Bell's palsy, severe malaise, and fatigue.

According to Steere, now at Tufts University, up to 8% of the patients develop cardiac problems several weeks after tick bite. Patients most commonly have atreoventricular block, but others may develop acute inflammation of muscle tissue and the enveloping membrane, and mild left-ventricular dysfunction. Enlargement of the heart or fatal inflammation of all layers of the heart are rare.

Considerable variation occurs in the clinical expression of late infection. Patients may experience fatigue, keratitis of the eyes, episodes of arthritis usually involving only one or few large joints, acrodermatitis chronica atrophicans (rare in the United States), and syndromes of both the central and peripheral nervous systems.

Antibiotics such as oral tetracycline, doxycycline, and amoxicillin are effective during early disease. Ceftriaxone is commonly used for neurologic abnormalities. Treatment for late disease involving joints and neurologic abnormalities has been more problematic, and the response of patients often has been slow, according to Steere.

Lyme disease has become the most prevalent arthropod-associated disease in the United States. Robert Craven and David Dennis of the Centers for Disease Control (CDC) reported more than 40,000 cases from 1982 to 1991 and stated that 81% of all reported vector-borne illnesses from 1986 to 1990 were caused by Lyme disease. All but the states of Hawaii, New Mexico, and Montana reported residents with Lyme disease in 1991, although Alaska's one case had been contracted elsewhere. Disease incidence in 1991 was highest

A multisystemic illness, Lyme disease is known to affect tissues of skin, joint, nervous system, and heart of all age groups, but infection is usually not considered to be life threatening.

in Connecticut, New York, Rhode Island, New Jersey, and Delaware where rates per 100,000 population were 37.4, 18.8, 17.7, 10.9, and 10.6%, respectively. In 1993, CDC reported that Lyme disease accounted for more than 90% of all vectorborne illnesses in the United States in 1992 with a provisional total of 9,677 cases.

Lyme disease is one of seven known human spirochetal diseases. The others are pinta, yaws, venereal syphilis, nonvenereal syphilis, leptospirosis, and relapsing fever. There are common disease features among these seven illnesses as reviewed in 1989 by G. P. Schmid of the CDC in *Supplement 6 of Reviews of Infectious Diseases*. Three similarities among the seven diseases include (1) spirochetal entry through the skin or mucous membranes, (2) spirochetemia before or during onset of clinical illness, and (3) dissemination of spirochetes to various organs that is followed by latent periods between subsequent stages of disease.

CDC reported more than 40,000 cases from 1982 to 1991 and stated that 81% of all reported vector-borne illnesses from 1986 to 1990 were caused by Lyme disease.

The Etiologic Agent—A Spirochete

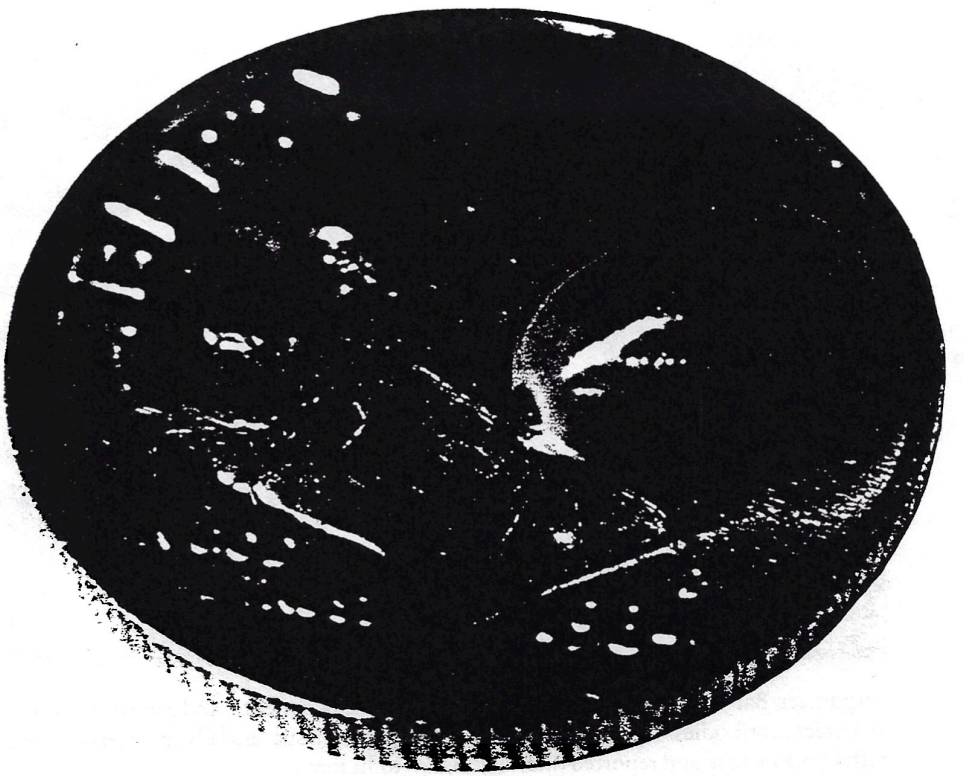
Spirochetes are slender, helically coiled, motile, gram-negative bacteria possessing periplasmic flagella. Those associated with arthropods are currently known to be associated with two ecologically diverse groups: (1) woodeating insects including a cockroach, *Cryptocercus punctulatus* Scudder, and termites, and (2) bloodsucking arthropods, namely soft and hard bodied ticks, and lice. The medically important species are in the genus *Borrelia*. Spirochetes causing relapsing fever were discovered more than a century before the etiologic agent of Lyme disease was recognized.

Epidemic Relapsing Fever-Causing Spirochete. Epidemic relapsing fever-causing organisms were the first *Borrelia* to be observed. Placing his compound microscope on the bed table beside patients acutely ill with relapsing fever during an epidemic in Berlin in 1867 and 1868, a 25-year-old medical doctor by the name of Otto Obermeier periodically drew blood from his patients during the febrile attack, immediately examined the blood microscopically, and observed myriads of living and actively motile spirilla-like organisms moving among the red blood cells. Rudolf Virchow at Charite' Krankenhaus in Berlin, for whom Obermeier was an intern, prohibited him from publishing his observation until he could infect laboratory animals. The epidemic crashed and Obermeier had to wait five more years before he was to witness another epidemic and again observe these insidious motile, helical microbes in the blood of more patients. This time, in 1873, Virchow encouraged Obermeier to report his findings to the Berliner Medicinischer Geselkshaft. It was during this second epidemic that this 30-year-old physician tried to infect himself with blood from a patient. Obermeier was unsuccessful in causing infection with relapsing fever-causing spirochetes—probably because he drew blood from a patient during the phase of the illness when few, if any, infectious organisms were present. However, he later was to try a similar, but this time fatal, experiment with blood from a patient ill with cholera. Two to three weeks later he was to succumb to the infection.

The spirochete observed by Obermeier was initially named *Spirochaete recurrentis* by H. Lebert of Breslav, Germany, in 1874, one year after Obermeier's article was published. The following year, in 1875, Ferdinand Cohen in *Beiträge zur Biologie der Pflanzen* designated the spirochete after Obermeier and named it *Spirochaeta obermeieri*, but *recurrentis* had priority, and the species is known as *Borrelia recurrentis* today. Later, the genus was named for A. Borrel, a microbiologist at the Pasteur Institute in Paris, by the Amsterdam microbiologist M. Swellengrebel.

This spirochete was imported into the United States about 1834 and caused epidemics in people living on both coasts; including residents of Philadelphia in 1844 and in Chinese laborers in California in 1874. The spirochete is transmitted among humans by body lice, *Pediculus humanus humanus* L., as first suggested by F. P. Mackie in 1907 in the *British Medical Journal*, and documented by Charles Nicolle and colleagues in 1912 in *Comptes Rendus des Seances de L'Académie des Sciences*. Transmission to humans occurs by contaminating abraded skin with hemolymph from crushed lice. Epidemic relapsing fever no longer occurs in the United States, but it is present in parts of Europe, Asia, Africa, and South America.

Endemic Relapsing Fever-Causing Spirochetes. The importance of borreliae in soft-bodied ticks was initially demonstrated when

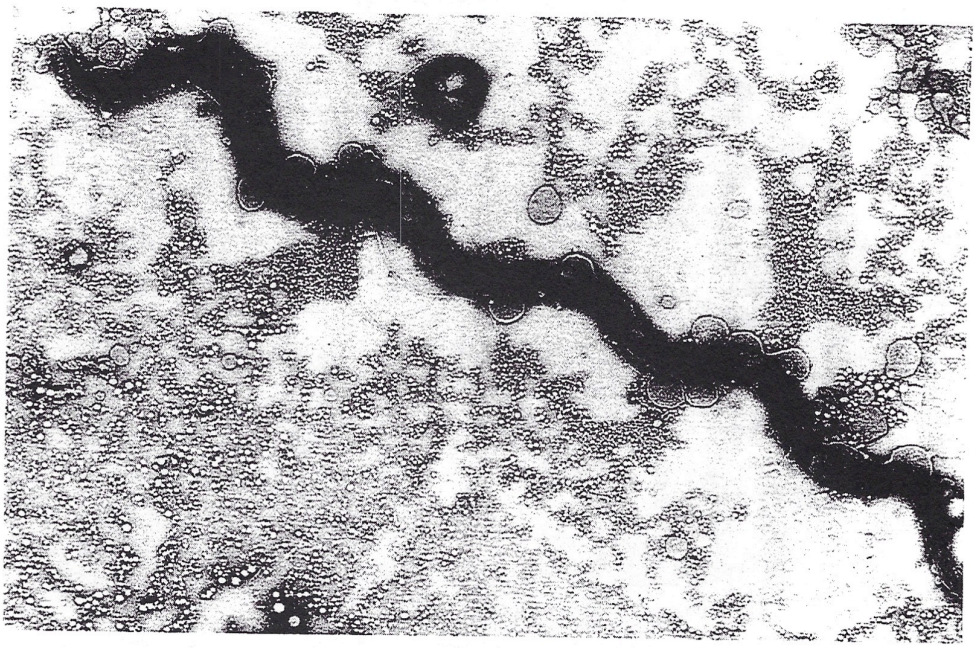


Unfed and fully fed adult female *I. scapularis*. (Courtesy of Pfizer Central Research.)

E. Marchoux and A. Salimbeni fed soft-bodied ticks on chickens and successfully infected them with *Borrelia anserina* as they reported in *Annales de L'Institut Pasteur* in 1903. Thereupon, at least three articles appeared by P. H. Ross and A. D. Milne in 1904 in the *British Medical Journal,* by J. E. Dutton and J. L. Todd in 1905 in *The British Medical Journal,* and Robert Koch in 1905 in *Deutsche Medizinische Wochenschrift* reporting on the association of relapsing fever-causing borreliae in humans with bites from soft-bodied ticks. Dutton died at Kosongo in Congo territory in Africa in 1905 from relapsing fever at the age of 29 after accidentally infecting himself during a postmortum examination. Todd also contracted the illness but survived.

Endemic relapsing fever-causing borreliae vectored by soft-bodied ticks are reported from all continents except Australia. The first focus in the United States was documented in Colorado in 1914, and many others have been identified in western states in subsequent decades. One or more borreliae causing this disease, namely *B. turicatae, B. parkeri,* and *B. hermsi,* occur naturally from Texas, Oklahoma, and Kansas, westward to California, and northward into Washington, Idaho, and British Columbia, Canada. Humans can acquire the infection while visiting caves, cabins, or animal shelters inhabited by infected *Ornithodorus hermsi* Wheeler, Herms and Meyer, *O. turicata* (Duges), *O. rudis* Karsch, and *O. parkeri* Cooley ticks. Transmission of spirochetes to humans occurs via coxal fluid or salivary secretions of the tick.

Lyme Disease-Causing Spirochetes. The causative agent of Lyme disease remained elusive until 1981 when Willy Burgdorfer of the National Institute of Health, Rocky Mountain Laboratories in Hamilton, MT, observed spirochetes in adult *Ixodes scapularis* Say, the black legged tick, from Shelter Island, NY. (J. H. Oliver of Georgia Southern University and colleagues documented in 1993 in the *Journal of Medical Entomology* the conspecificity of *Ixodes scapularis* and *Ixodes dammini* Spielman, Clifford, Piesman, and Corwin. *Ixodes scapularis* is the priority name, though Andrew Spielman of Harvard University contends that *Ixodes dammini* is a distinct species as he and colleagues wrote in the 1979 edition of the *Journal of Medical Entomology.*). Alan Barbour, then of the Rocky Mountain Laboratories, successfully isolated the seminal B31 strain by using a modification of a medium published in *Science* magazine for the growth of *Borrelia hermsi* by Richard Kelly of Baptist Memorial Hospital Medical Center in Memphis, TN, in 1971. Using their isolate as antigen,



B. burgdorferi. (Courtesy of The American Society of Microbiology. [Anderson et al. 1989].)

Burgdorfer, Barbour, and colleagues were able to detect antibodies in patients diagnosed with Lyme disease and reported their findings in *Science* magazine in 1982.

The following year, A. C. Steere and colleagues at Yale, and J. L. Benach and colleagues of the New York State Health Department at Stony Brook, reported the isolation of these spirochetes from humans. At the same time, E. M. Bosler and colleagues at the New York State Health Department, and we along with our colleagues, reported the first isolations of these borreliae from small and medium-sized wild animals, namely white-footed mice, *Peromyscus leucopus* (Rafinesque), and a raccoon, *Procyon lotor* (L.).

In Europe, *B. burgdorferi* was soon thereafter isolated from patients with erythema migrans, acrodermatitis chronica atrophicans, *Borrelia* lymphocytoma, and Bannwarth's syndrome by several scientists including Eva Asbrink, Anders Hovmark, and colleagues at the Sodersjukhuset in Stockholm, Sweden, Rudolf Ackerman and colleagues at the Neurologic University Clinic of Cologne, Germany, Hans-Walter Pfister of the Neurologische Klinik der Universität, Munich, Germany, and colleagues, and Uwe Neubert of the Universität, Munich. It should be noted that the infectious etiology of erythema migrans, acrodermatitis chronica atrophicans, and *Borrelia* lymphocytoma was recognized in Europe in the 1940s and 1950s, many years before borreliae were isolated from patients. Penicillin had been shown to be effective in treating patients, and each of the skin diseases had been successfully transferred from human to human.

The spirochete was named *Borrelia burgdorferi* in 1984, in honor of Willy Burgdorfer, by R. C. Johnson of the University of Minnesota and colleagues, who also demonstrated that these spirochetes could be isolated more easily from tissues of rodent organs, such as spleen and kidney, than from blood. The original culture medium used to make the first isolations from ticks, humans, and wild mammals has been improved and is called Barbour–Stoenner–Kelly medium. Ear punch biopsies and urinary bladders increasingly are being used to isolate borreliae from rodents as first reported by R. J. Sinsky and Joe Piesman of the University of Alabama at Birmingham, T. G. Schwan and colleagues of the Rocky Mountain Laboratories, and S. M. Callister and colleagues of the Gundersen Medical Foundation. Although recently discovered, *B. burgdorferi* was demonstrated to be present in *I. scapularis* collected in the 1940s on Long Island, NY, by D. H. Persing, then of Yale University, and colleagues, who used the polymerase chain reaction.

In contrast to borrelial isolates from humans and ticks in Europe, those in the United States have relatively homogeneous protein profiles in polyacrylamide gels. In Europe, Guy Baranton and colleagues of the Institut Pasteur proposed in the *International Journal of Systematic Bacteriology* in 1992 that three species be designated for the isolates from

I. ricinus and humans in Europe, namely *B. burgdorferi, B. garinii,* and VS461 (=*B. afzelii*), and in Japan, Y. Yanagihara and colleagues of the University of Shizuoka named the borreliae from *Ixodes ovatus Borrelia japonica.* Isolates from human skin, blood, and the central nervous system in the United States have been indistinguishable from one another and, with one exception, from spirochetes cultured from *I. scapularis* and rodents in the eastern United States. Although variants from the standard B31 strain have been reported from *I. pacificus* Cooley and Kohls, *I. neotomae* Cooley, and rodents in California by M. L. Bissett and Warren Hill of the California Department of Health Services, and R. N. Brown, R. S. Lane, and J. A. Pascocello of the University of California, Berkeley, and from *I. dentatus* Marx, cottontail rabbits, *Sylvilagus floridanus* Allen, and four isolates from larval *I. scapularis* in New York State by us and our colleagues, none of these variants from strain B31 has yet to be isolated from humans and, therefore, none is known to be associated with human disease.

Natural History

***Ixodes ricinus* Complex of Vectors.** Before Burgdorfer's observation in 1981, knowledge of the association of borreliae with hard-bodied ticks was limited to an African and Australian disease in cattle and horses caused by *Borrelia theileri* and transmitted by *Rhipicephalus evertsi* Neumann, *Boophilus decoloratus* (Koch), and *B. microplus* (Canestrini). Following the finding of borreliae in *I. scapularis,* borreliae were soon isolated in three other species within the *Ixodes ricinus* complex including *I. pacificus* in the United States and two Old World species, *I. ricinus* and *I. persulcatus* Schulze.

I. ricinus-type ticks are similar in appearance, require relatively high humidities when not on host animals, and inhabit woodlands, wooded pastures, brushy areas, or moorlands. They feed on three different animals in their life, parasitize humans in all three feeding stages, and feed as subadults on a relatively large number of small, medium, and large-sized animals. The females feed and mate with males on large and sometimes medium-sized mammals, and females may mate with males on vegetation as well. The generation time may vary among species; that of *I. scapularis* is approximately two years, though in extreme northern latitudes in Europe and Asia, the duration of a generation of *I. ricinus* or *I. persulcatus* may be five or six years. However, regardless of the species and number of years the tick remains alive, the aggregate time spent feeding on host animals is no more than two to three weeks. The tick spends most of its life in soil or on vegetation.

North American Tick Vectors. *Geographical Distribution.* The two North American species collectively inhabit large areas of land. *I. scapularis* is relatively common throughout most of New England, parts of Maine, New York, New Jersey, Pennsylvania, Delaware, Maryland, and is also frequently collected in states as far south as Florida and as far west as Texas. It is relatively abundant in the upper midwest, particularly parts of Minnesota, Wisconsin, and Illinois. It also occurs in Iowa, Michigan, Indiana, and Ohio, and a dense population is established in Long Point, Ontario, Canada, as recently confirmed by I. A. Barker and colleagues of the University of Guelph. *I. pacificus* is common in habitats along the Pacific Coast from southern California northward to southwestern British Columbia, Canada, with inland populations in parts of Nevada, Utah, and Idaho. Additionally, Carl Olson and colleagues of the University of Arizona recently have found specimens in mountainous areas of Arizona.

Host Animals. Ixodes scapularis and *I. pacificus* feed on at least 119 species and 80 species, respectively. Subadults of the two species feed on mammals, birds, and lizards, though lizards are rare within the northern geographical range of *I. scapularis. Ixodes pacificus* subadults have a predilection for lizards. Adults of each species feed preferentially on large and to a lesser extent on medium-sized mammals.

The relatively recent increase in numbers of *I. scapularis*...appears to be related to land-use patterns and limited hunting programs that have allowed white-tailed deer to increase.

Seasonal Appearance. The seasonal appearance of the egg, larval, nymphal, and adult stages varies among the two North American species. That of *I. scapularis* in northern United States is as follows. Adult females feed and mate in October through early December, on warm days in winter, and again in early spring (March into early May) of the following calendar year. Feeding continues for approximately 9–11 days.

Engorged females detach, drop to the ground, and crawl to the duff area of soil. Each female lays 1,000–3,000 eggs in a single cluster in May, June, or early July. Upon hatching, larval ticks feed for three to five days on an animal in late July, August, or early September, and then fall to the ground fully fed. Surviving in the moist duff or perhaps in moist soil of an animal burrow, most remain in their fully fed condition through the winter and molt into nymphs in late spring of the following year. Nymphs feed for three to five days on hosts principally in late May, June, and early July before detaching and falling to the ground. Fully fed nymphs molt into adults in the duff primarily in October and November. By contrast, larvae and nymphs of *I. pacificus* are abundant from March through June, and adults are most active from November through May.

The accumulating evidence suggests that, in the years ahead, *I. scapularis* will continue to expand its range, become more numerous, and become a serious problem to more people.

Acquisition and Transmission of Spirochetes. Ticks acquire their spirochetes while feeding on infected animals, though on rare occasions, unfed larvae are infected transovarially. Acquisition and transmission of the spirochete by *I. scapularis* in northern United States are favored by the generation time of two years which allows the seasonal appearance of nymphs before larvae. Primarily appearing in late July through early September, larvae often feed on reservoir-competent infected host animals, such as white-footed mice, which previously had been parasitized about two months before by infected nymphs. In Lyme disease foci, white-footed mice often are infected universally. This inverted seasonal appearance of nymphs preceding larvae helps ensure the infection of rodents before uninfected larvae begin feeding, thereby ensuring infection of the next generation of ticks. Borreliae are transstadially passed by competent vectors, such as *I. scapularis*. Thus, nymphs, which become infected as larvae, are able to infect the animals they parasitize.

Although *B. burgdorferi* has been isolated from or detected in at least 22 wild or domestic mammals, eight birds, and humans, there are some animals that are suitable hosts for ticks but are incompetent reservoirs for the spirochete. Studies by Sam Telford, III, and T. N. Mather and colleagues at Harvard University have reported the incompetence of white-tailed deer, *Odocoileus virginianus* (Zimmerman), and gray catbirds, *Dumetella carolinensis* (L.). R. S. Lane and J. E. Loye of the University of California–Berkeley, report the western fence lizard, *Sceloporus occidentalis* Baird and Girard, to be incompetent. Therefore, uninfected nymphal and adult *I. pacificus* and *I. scapularis* likely had fed earlier either on reservoir incompetent hosts, or on competent hosts that were uninfected. Alternatively, they could have fed on infected animals and either not acquired the spirochete during feeding or ingested bacteria during feeding but not successfully transstadially passed the bacteria.

Many articles have been published on the isolation of *B. burgdorferi* from ticks and animals in the northeastern, midwestern, south central, and western United States, but, until recently, none has reported its isolation in the southeastern United States, although we and our colleagues and others have detected spirochetes in ticks and documented significant titers of antibody in wild animals to these spirochetes. It is therefore interesting to note that J. H. Oliver and colleagues have recently isolated *B. burgdorferi* from *I. scapularis*, the cotton mouse, *Peromyscus gossypinus* LeConte, and the cotton rat, *Sigmodon hispidus* Say and Ord, from Georgia and Florida.

Prevalence of infection of *I. scapularis* is significantly higher in northern United States than that of *I. scapularis* collected in southern states or of *I. pacificus*. Prevalence of *I. scapularis* nymphs and adults in the north is about 20–25% and 50%, respectively, whereas infection rarely exceeds 3% in the south or in *I. pacificus* adults. R. S. Lane and colleagues have suggested that the lower infection rate in the latter ticks from the western United States may be a result of reservoir incompetence of the western fence lizard, the seasonal peak of larval abundance occurring before that of nymphs, and infrequent feeding by nymphs on reservoir competent rodents.

Humans acquire infections from ticks that transfer spirochetes during feeding, either by salivation as documented by J.M.C. Ribeiro and colleagues at Harvard University, regurgitation, or by both methods. Joe Piesman and colleagues report that *I. scapularis* nymphs are unlikely to transmit borreliae during their first 24 hours of attachment, but almost always successfully transfer spirochetes after

they have been attached for three days. It is therefore important to find and remove ticks as quickly as possible after they have become attached so as to reduce risk of acquiring Lyme disease.

Abundance and Spread of I. scapularis. The relatively recent increase in numbers of *I. scapularis* in northeastern and midwestern woodlands, brushy and edge habitats, and in lawns and parks within woodland settings appears to be related to land-use patterns and limited hunting programs that have allowed white-tailed deer to increase. Adult *I. scapularis* feed preferentially on white-tailed deer, and we and other entomologists, namely Andrew Spielman and his former students Joe Piesman, M. L. Wilson, and S. R. Telford, III, at Harvard University; A. J. Main, formerly of Yale University; K. C. Stafford, III, at the Connecticut Agricultural Experiment Station; and Tom Daniels and Durland Fish at the New York Medical College have stressed the importance of deer in maintaining dense populations of *I. scapularis*.

It is interesting to note that ticks were abundant in the pristine eastern hardwood forests in the mid 1700s and then declined to very low levels in the next 120 years. From the diary of Swedish botanist Pehr Kalm, we learn that near Saratoga, NY, on 24 June 1749, "The woods abound with woodlice" (Kalm called them *Acarus americanus* L. =*Amblyomma americanum* (L.), but J. C. Bequaert of Harvard University in 1945 suggested the species had to be otherwise). In the latter part of the next century, Asa Fitch, the state entomologist of New York, wrote in 1872, "The most common tick of our country, the wood tick from its inhabiting the woodlands, and not occurring in cleared and cultivated grounds, though formerly abundant throughout the northern and middle states, has now become nearly or quite extinct." During the time between the writings of these two scientists, the forests were cut, agriculture often replaced forest, and the large wild mammals were reduced to extremely low levels. In the 120 years since Fitch wrote of the absence of ticks in New York, a large portion of agricultural land has reverted to forest, deer have returned in great abundance, and *I. scapularis* has become established in many wooded areas.

Although *I. scapularis* is spreading into new areas of the northeastern and midwestern United States, there is no evidence of its spreading into new foci in the southern states, or of *I. pacificus* expanding into ranges in the western United States. Birds, and to a lesser extent mammals, are probably the major natural vehicles for bringing *I. scapularis* into new areas. Our studies in Connecticut, those of G. R. Battaly and colleagues in New York, A. R. Weisbrod and R. C. Johnson in Minnesota, T. L. Schulze and colleagues in New Jersey, and R. G. McLean and colleagues of CDC have documented the importance of birds as hosts for subadult *I. scapularis*. S. A. Manweiler and colleagues in California suggest birds to be less important in the dispersal of *I. pacificus*.

Relatively new distribution records for *I. scapularis* in the northern United States and Canada have been reported in Illinois (J. K. Bouseman and U. D. Kitron and colleagues), Kansas (S. C. White, S. J. Upton, and D. E. Mock), Iowa (Nixon Wilson and M. G. Novak and colleagues), Maine (H. S. Ginsberg and C. P. Ewing, R. P. Smith and colleagues, and P. W. Rand and colleagues), Rhode Island (M. C. Carroll and colleagues), Massachusetts (C. C. Lastavica and colleagues), New York State (D. J. White and colleagues), Indiana (R. R. Pinger and Todd Glancy), Virginia (J. F. Levine and colleagues), Maryland (F. P. Amerasinghe and colleagues), Wisconsin (M. S. Godseg and colleagues; J. B. French, Jr., and colleagues; S. M. Callister and colleagues; and M. D. Sharon and colleagues), western Pennsylvania (R. D. Lord and colleagues), in the greater Philadelphia area, northern New England and Maine, and Connecticut (J.F.A. and L.A.M.), and Prince Edward Island, Canada (Harvey Artsob and colleagues). Although *I. scapularis* may not establish and become abundant in all of the above mentioned sites, the accumulating evidence suggests that, in the years ahead, *I. scapularis* will continue to expand its range, become more numerous, and become a serious problem to more people.

We believe that *I. scapularis* will remain relatively abundant and will continue to spread...so long as deer remain numerous and there is an absence of effective natural enemies.

Natural Enemies. No effective natural enemies are known for *I. scapularis* or *I. pacificus*. A chalcid wasp, *Hunterellus hookeri* Howard, which was introduced from Paris, France, in 1926 into Naushon Island, MA, became established on *I. scapularis*. Although rates of parasitism of about 33% and 20%

have been relatively recently recorded on Naushon Island and Prudence Island, RI, by T. N. Mather and colleagues, and by Renjie Hu and colleagues, *I. scapularis* remains abundant on both islands.

Possible Role of Other Ticks and Insects as Vectors. Other species of ticks that feed on humans and biting insects such as tabanids, mosquitoes, and fleas have been implicated as possible vectors of *B. burgdorferi.* For example, erythema migrans was reported by T. L. Schulze of the New Jersey Health Department and colleagues to develop following bites by *A. americanum* from which J. A. Rawlings in Texas has isolated *B. burgdorferi. Ixodes cookei* Packard has been suggested by J. E. Hall and colleagues in West Virginia as a possible vector. We have detected spirochetes in tabanids, and more than one author has reported erythema migrans developing after a deer fly bite. Vector competency has not been determined under experimental conditions, and more research is needed to determine the importance of these arthropods.

Although most attention has focused on spirochetes escaping from their enzootic cycle and entering into human populations, there are borreliae that seemingly are maintained almost exclusively in enzootic cycles involving ticks that seldom, if at all, feed on humans. Sam Telford, III, and colleagues at Harvard University, and we and our colleagues, have studied *I. dentatus* which feeds on cottontail rabbits and, as juveniles, also on birds in eastern United States. The *B. burgdorferi* isolates from cottontail rabbits and from *I. dentatus* often have different protein profiles in polyacrylamide gels than those from *I. scapularis* and rodents. Although not yet isolated from humans, these borreliae could infect humans via a rare bite from an infected *I. dentatus* or by an *I. scapularis* that feeds first on a cottontail rabbit and subsequently on a human. In California, R. N. Brown and R. S. Lane have reported on variable *B. burgdorferi* isolates from the dusky-footed woodrat, *Neotoma fuscipes* Baird, and *I. neotomae.* Unknown to feed on humans, *I. neotomae* feeds on rodents and lagomorphs. The borreliae are passed among woodrats and, to a lesser degree, to the California kangaroo rat, *Dipodomys californicus* (Merriam), by bites of *I. neotomae.* Possibly, these borreliae could be passed to humans when *I. pacificus* feeds on an infected rodent and in a subsequent stage on humans. Old world *Ixodes* that likely have a role in the ecology of Lyme disease are *I. hexagonus* Leach, as documented by Lise Gern and colleagues in Neuchatel, Switzerland, and *I. ovatus* Neumann, as reported by Kenji Miyamoto and colleagues in Asahikawa, Japan.

Outlook

We believe that *I. scapularis* will remain relatively abundant and will continue to spread into new wooded and brushy environments in the northeastern and midwestern United States so long as deer remain numerous and there is an absence of effective natural enemies. This species will not only be a formidable obstacle to our enjoyment of woodlands in unpopulated recreational areas but, also, and more importantly, to our enjoyment of yards, parks, and woodlands in some of the most densely human-inhabited areas in the United States. As emphasized by R. C. Falco and Durland Fish in Westchester County, NY, Lyme disease is peridomestic and many people acquire their tick bites near or in their yards.

Much less information is available on the outlook of Lyme disease within the southern geographical range of *I. scapularis.* Compared with numbers of documented cases of Lyme disease in the northeastern and midwestern United States, those in southern states have been relatively few except for the numbers reported from Georgia in 1989, when 715 cases were reported compared with 23 in 1992. It will be interesting to learn in the years ahead if numbers of *I. scapularis* in the more northern southern states such as Virginia, West Virginia, North Carolina, and others, increase as they have recently done in Pennsylvania. There are currently no reports of increasing numbers of these ticks in the south. Recent studies in Oklahoma (S. W. Mukolwe and A. A. Kocan and colleagues), Texas (G. J. Teltow and J. A. Rawlings and colleagues), Georgia (J. H. Oliver, Jr., and his students Jordi Galbe, H. J. Hutcheson, and Angela James; and by G. L. Mahnke and colleagues), North Carolina (J. F. Levine and colleagues), Alabama (Shirley Luckhart and colleagues), Arkansas (J. T. Kardatzke and colleagues), and Virginia (D. E. Sonenshine and colleagues) suggest involvement of lizards, birds, rodents, deer, *I. scapularis, A. americanum,* and possibly other arthropods in the natural history of Lyme disease in southern states.

Ixodes pacificus in the western United States, like *I. scapularis* in the southern United States, does not seem to be spreading into new geographical areas or increasing in abundance. There is no current indication that prevalence of Lyme disease along the Pacific

Coast will approach levels currently reported in the northeastern United States.

Acknowledgments

We thank Bonnie Hamid for assistance. This article was supported by NIH Grant AI30548 and Centers for Disease Control grants U50/CCU106598 and U50/CCU106581.

References & Suggested Readings

Anderson, J. F., L. A. Magnarelli, R. B. LeFebvre, T. G. Andreadis, J. B. McAninch, G-C. Perng & R. C. Johnson. 1989. Antigenically variable *B. burgdorferi* isolated from cottontail rabbits and *I. dentatus* in rural and urban areas. J. Clin. Microbiol. 27: 13–20.

Andriole, V. T., [ed.] 1989. Lyme disease and other spirochetal diseases. Rev. Infect. Dis. 11 (Suppl.) 6: S1433–S1525.

Barbour, A. G. & D. Fish. 1993. The biological and social phenomenon of Lyme disease. Science (Washington, DC) 260: 1610–1616.

Benach, J. L. & E. M. Bosler, [eds.] 1988. Lyme disease and related disorders. Ann. N.Y. Acad. Sci. 539: 1–513.

Berger, B. W., O. J. Clemmensen & A. B. Ackerman. 1983. Lyme disease is a spirochetosis. Am. J. Dermatopathol. 5: 111–124.

Burgdorfer, W., A. B. Barbour, S. F. Hayes, J. L. Benach, E. Grunwaldt & J. P. Davis. 1982. Lyme disease—a tick-borne spirochetosis? Science (Washington, DC) 216: 1317–1319.

Centers for Disease Control and Prevention. 1993. Lyme disease—United States, 1991–1992. Morbidity and Mortality Weekly Report 42: 345–348.

Ginsberg, H. S., [ed.] 1993. Ecology and environmental management of Lyme disease. Rutgers University Press, New Brunswick, NJ.

Johnson, R. C., [ed.] 1989. Lyme disease. Rheumatic disease clinics of North America. 15: 627–825. Sanders, Philadelphia.

Lane, R. S., J. Piesman & W. Burgdorfer. 1991. Lyme borreliosis: Relation of its causative agent to its vectors and hosts in North America and Europe. Annu. Rev. Entomol. 36: 587–609.

Oliver, J. H., M. R. Owsley, H. J. Hutcheson, A. M. James, C. Chen, W. S. Irby, E. M. Dotson & D. K. McLain. 1993. Conspecificity of the ticks *Ixodes scapularis and I. dammini* (Acari: Ixodidae). J. Med. Entomol. 30: 54–63.

Reik, L., Jr. 1991. Lyme disease and the nervous system. Thieme Medical, New York.

Skoldenberg, B. & G. Stiernstedt, [eds.] 1990. Lyme borreliosis 1990—Proceedings of the IV International Conference on Lyme Borreliosis held in Stockholm, Sweden, June 18–21, 1990. Scand. J. Infect. Dis. (Suppl.) 77: 1–157.

Spielman, A., C. M. Clifford, J. Piesman, and M. D. Corwin. 1979. Human babesiosis on Nantucket Island, USA: description of the vector, *Ixodes (Ixodes) dammini*, n. sp. (Acarina: Ixodidae). J. Med. Entomol. 15: 218–234.

Spielman, A., M. L. Wilson, J. F. Levine & J. Piesman. 1985. Ecology of *Ixodes dammini*-borne human babesiosis and Lyme disease. Annu. Rev. Entomol. 30: 439–460.

Stanek, G., H. Flamm, A. G. Barbour & W. Burgdorfer, [eds.] 1987. Lyme borreliosis. Proceedings of the Second International Symposium on Lyme Disease and related disorders, Vienna, 1985. Verlag, NY.

Steere, A. C. 1989. Lyme disease. New Eng. J. Med. 321: 586–596.

Steere, A. C., S. E. Malawista, J. E. Craft, D. K. Fisher & M. Garcia-Blanco, [eds.] 1984. Lyme disease. First International Symposium. Yale J. of Biol. and Med. New Haven, CT.

Weber, K., G. Schierz, B. Wilske & V. Preac-Mursic. 1984. European erythema migrans disease and related disorders, pp. 15–21. *In* A. C. Steere, S. E. Malawista, J. E. Craft, D. K. Fischer & M. Garcia-Blanco [eds.], Lyme Disease, First International Symposium. Yale Journal of Biology and Medicine, New Haven, CT.

◆

Born in Fargo, ND, John F. Anderson received his B.S. in zoology and his M.S. degree in entomology at North Dakota State University. He received his Ph.D. in medical entomology from the University of Illinois where his mentor was William R. Horsfall. Anderson joined the Connecticut Agricultural Experiment Station in New Haven as an assistant entomologist, became head of the Department of Entomology, and became State Entomologist in 1969—a position he held until 1987, when he became director. Louis A. Magnarelli was born in Syracuse, NY, and attended the State University of New York at Oswego for his undergraduate studies. He received his M.S. degree in biology from the University of Michigan and his Ph.D. in medical entomology from Cornell University. Magnarelli began his work at the Connecticut Agricultural Experiment Station in 1975 and became department head in entomology and became state entomologist in 1987. In addition to these positions, he became vice director in 1992. Both authors have research appointments in the Department of Epidemiology at Yale University, and both juggle their administrative responsibilities with their research on ticks and microbial pathogens. Correspondence should be sent to The Connecticut Agricultural Experiment Station, P.O. Box 1106, New Haven, CT 06504.