Abstract

The clinical–epidemiological studies of a cluster of arthritis in Lyme, Connecticut, intersected with ongoing studies on tick-borne diseases in Long Island, New York, to set the stage for the discovery of the spirochaete agent of Lyme disease. Studies on the microbiology of spirochaetes in other parts of the country were instrumental for the cultivation of the newly discovered organism. The multinational clinical studies in Europe throughout the twentieth century on the dermatological and neurological manifestations characterized and enlarged the syndrome that we now know as Lyme borreliosis. For reasons that are discussed in this chapter, controversies have arisen among advocate patient groups and the clinicians and scientists that are at the forefront of research in Lyme borreliosis. Polarized opinions on what constitutes this disease and how to treat it have resulted in unprecedented litigation involving medical societies and advocate patient groups with no obvious end in sight.

1.1 The epidemic of oligoarticular arthritis in Connecticut and the north-east

The story of Lyme disease in Connecticut has been told on numerous occasions and has often been cited as an example of a very positive interplay among the lay community, academic medicine, and public health workers. In October 1975, two mothers, Polly Murray and Judith Mensch, from Lyme, Connecticut, contacted the Connecticut State Health Department to report that a number of children who lived in the same neighbourhood in their town had developed what they had been told was juvenile rheumatoid arthritis. Soon thereafter, a joint investigation by the Connecticut State Health Department and the Yale University School of Medicine was begun to investigate the reports made by both mothers. This fortuitous occurrence developed into a most dramatic epidemiological study that resulted in the identification of a world-wide infection.

The possibility of a focal episode of juvenile rheumatoid arthritis in Lyme kindled the interest of Dr Allen Steere, who had just joined the Division of Rheumatology at Yale, which in turn was headed by Dr Stephen Malawista, a noted rheumatologist with a long track record on inflammatory rheumatic diseases. Dr Steere, joined by Dr David Snydman of the State Health Department, put together an active surveillance system in the affected towns of Lyme, Old Lyme and East Haddam (Connecticut) to identify cases of the disorder reported by the two mothers.

The active community surveillance disclosed 39 children (Steere et al., 1977b) with recurrent attacks of swelling and pain in large joints, notably in the knees, and some for substantial periods of time. In addition, there were twelve adults, who were related to or lived near the arthritic children, with similar signs and symptoms. The surveillance showed an epidemic of oligoarticular arthritis in a focal geographic area. The focality of Lyme disease has remained a constant feature of this disease. In fact, even within these affected towns, clustering of cases was actually the norm in that many of the patients lived in several adjoining streets. Furthermore, there was also clustering
within families, with six having more than one affected member, although the manifestations of the disease may have had onsets in different years. In the first study, the prevalence of the disease was 4.3 per 1000 residents but was three times higher among children. The overrepresentation of children in Lyme disease has also remained a constant feature of this disease. This investigation essentially excluded juvenile rheumatoid arthritis as the cause of the epidemic given that the prevalence of arthritis in these Connecticut communities was 100 times greater than that expected prevalence for juvenile rheumatoid arthritis. Thus, with a high degree of certainty that the articular manifestations being reported in the three towns in Connecticut were not juvenile rheumatoid arthritis, the disease was named Lyme arthritis. With the enlarging clinical spectrum, this name was changed to Lyme disease.

The enlarging investigation revealed that approximately one-quarter of the patients had developed an erythematous cutaneous lesion that in some cases appeared to expand into reddish, often annular, concentric rings. Interestingly, the skin lesion appeared weeks before the onset of the articular manifestations. This lesion had been previously described in Sweden in 1909 by Arvid Afzelius (see below) who named it ‘erythema migrans’ because of its propensity to enlarge. Sometime later, the lesion became known as ‘erythema chronicum migrans’ to emphasize its protracted duration. Afzelius associated the lesion with the bite of *Ixodes ricinus* ticks. During the summer of 1976, the Yale investigators followed prospectively the patients with the cutaneous lesions. This lesion had been previously described in Sweden in 1909 by Arvid Afzelius (see below) who named it ‘erythema migrans’ because of its propensity to enlarge. The attending physician treated this patient successfully with penicillin (Scrimenti, 1970). Therefore, Steere and collaborators gave antibiotics to patients with erythema migrans and compared the outcomes with those in untreated patients from their investigations. The results showed that penicillin, given early in the illness, shortened the duration of erythema migrans and appeared to prevent or lessen subsequent arthritis (Steere et al., 1980b). One final important step was taken that led to successful therapy of Lyme disease with antibiotics. European erythema migrans had long been known to be responsive to antibiotic therapy, while studies demonstrating the efficacy of antibiotic therapy for this skin lesion had also appeared in the USA (Scrimenti, 1970). Therefore, Steere and collaborators gave antibiotics to patients with erythema migrans and compared the outcomes with those in untreated patients from their investigations. The results showed that penicillin, given early in the illness, shortened the duration of erythema migrans and appeared to prevent or lessen subsequent arthritis (Steere et al., 1980b).

Prior to the Connecticut epidemic, erythema migrans in North America was first described in 1969 in a case report of a hunter from Wisconsin. The attending physician treated this patient successfully with penicillin (Scrimenti, 1970). A cluster of four cases of erythema migrans that occurred in the summer of 1975 in south-eastern Connecticut was also reported before the Yale University studies (Mast and Burrows, 1976a,b). Although determining when erythema migrans first appeared in the USA is difficult, the lack of
any reports prior to 1960 indicate that Lyme disease became epidemic in the 1970s coincident with the reports from Connecticut, Long Island, New York and Massachusetts. In retrospect, the Wisconsin case was a harbinger of the subsequent emergence of Lyme disease in the upper Midwest. Moreover, it is likely that cases of Lyme disease in these endemic areas were not diagnosed as such before it gained widespread recognition. For example, in eastern Long Island, which is a major area endemic for Lyme disease, there are persistent anecdotes of a condition known as the ‘Montauk knee’ that sounds suspiciously like the monoarticular arthritis of Lyme. This entity evidently has been around for decades, and it is tempting to speculate that the Montauk knee may actually have been the late stage of Lyme disease.

1.2 The role of other tick-borne diseases in the discovery of the agent of Lyme disease

1.2.1 The tick revolution of the 1970s

In the early 1970s, an increase in the number of cases of Rocky Mountain spotted fever (RMSF) occurred in the south-east, south central and north-eastern states. This increase was amply documented and sparked a renewed interest in tick-borne diseases in this country (Benach et al., 1977; Burgdorfer, 1975). This was particularly true in Long Island and other coastal New England and the Massachusetts offshore islands that are at the northernmost limit of the geographic distribution of this disease. Parallel with the increase in the number of cases of RMSF were reports of very large populations of *Dermacentor variabilis* ticks, the vector of the causative organism of RMSF, *Rickettsia rickettsii*. Although the reasons for this spike in the prevalence of RMSF have been debated, a general consensus has not developed. Nevertheless, it is generally believed that the increase in cases of RMSF in the early 1970s resulted from a number of environmental changes that may have been occurring during these years, and possibly even earlier. One such change was the banning in the late 1960s of DDT, a chlorinated hydrocarbon pesticide that had been widely used for agricultural, suburban pest, and public health insect control. The widespread use of this pesticide may have affected tick populations as non-target organisms and may have helped keep these populations in check; banning of this pesticide may have allowed for a gradual increase in the tick populations in large geographic areas of the country. Another environmental change reflects the increased suburbanization of rural land leading to a closer relationship of wildlife with new human residents. While this demographic trend is certainly well-documented and can explain the increase in the number of cases of tick-borne diseases, it does not explain the large increases in the tick populations. To explain the latter, increases in the populations of reservoirs have been implicated as the sources of large numbers of vectors. This is particularly true in the case of deer and the *Ixodes scapularis* ticks. As mentioned earlier, the increases in cases of RMSF and its vector, *D. variabilis*, were not an isolated event. In fact, another, possibly larger and of higher public health impact, increase in the numbers of human-biting *I. scapularis* led to the epidemic of Lyme disease in the northeast and upper Midwest.

The entomological literature prior to the 1970s clearly documents the presence in the northeast of an Ixodes species whose subadult stages are ectoparasites of field rodents, notably *Peromyscus leucopus*, and whose females feed on white-tailed deer. Depending on the source, this tick species was identified as *I. muris* or as *I. scapularis*. Stepping into this taxonomic void, Spielman and coworkers described a new species using morphological characteristics of ticks collected in Massachusetts which they named *Ixodes dammini*, for Gustave Dammin, a pathologist at Harvard University (Spielman et al., 1979). This tick, once largely thought to be confined to feral hosts, assumed immediate importance as the vector to humans of *Babesia microti*, and a few years later as the vector of the aetiological agent of Lyme disease.

However, concerns that the newly named *Ixodes dammini* was not a new species prompted researchers to use genetic approaches to address this taxonomic question. Reciprocal crosses between *I. dammini* from Massachusetts and *I. scapularis* from Georgia produced offspring through the F3 generation whereas reciprocal crosses between *I. dammini* and *I. pacificus* from California (now known to be the vector of *B.
burgdorferi on the west coast (Burgdorfer et al., 1985) and I. scapularis and I. pacificus crosses produced sterile F1 progeny. Through assortive mating experiments, morphometric measurements, and chromosome and isoenzyme analyses, led Oliver and coworkers (Oliver et al., 1993) to conclude that I. dammini was not a species separate from I. scapularis, and that the name Ixodes scapularis, which had been used for more than 100 years to identify this species, had priority over the name Ixodes dammini. General acceptance of the name change resulted in the now near universal use of the I. scapularis nomenclature in the scientific literature.

Was there a ‘tick revolution’ in the 1970s and possibly even earlier? On the face of the question, it appears improbable that virtually parallel increases in the populations of two separate tick species in such geographic proximity over such a short period of time are due to chance. Convincing arguments have been proposed, but single theories do not explain all of the increases in the tick populations and of the epidemics that developed thereafter. As with other environmental events, the causes are probably multifactorial, and their consequences certainly important enough to be debated for years to come. To be sure, significant multifactorial theories have been tested with an extraordinary degree of insight. One study linked concurrent defoliation of oak trees by gypsy moths (another environmental event in the north-east in the 1970s) with changing acorn production by the defoliated oaks, deer eating acorns, and rodent reservoirs eating the pupae of the gypsy moth (Jones et al., 1998; LoGiudice et al., 2003; Ostfeld et al., 2006). This theory was characterized as an environmental chain reaction using disparate animal and plant players as the basis for the changes in vectors and reservoirs that resulted in the tick-borne epidemics of the last 30 or so years.

1.2.2 Human babesiosis

The finding of human cases of babesiosis on Nantucket Island (Massachusetts) (Ruebush et al., 1977, 1981) and on Long Island (New York) (Benach et al., 1982, 1978, 1979) was a pivotal event in the discovery of the causative organism of Lyme disease. Human babesiosis in the north-eastern USA is caused by the intraerythrocytic piroplasm Babesia microti (Homer et al., 2000; Rudzinska et al., 1976). Babesiosis is a malaria-like opportunistic infection with a broad spectrum of severity, ranging from subclinical in immunologically intact persons to fatal in elderly, immunocompromised, or cirrhotic patients. This protozoan pathogen is maintained enzootically in the white-footed mouse reservoir (Peromyscus leucopus) and is transmitted through the bite of Ixodes scapularis (Piesman and Spielman, 1980; Piesman et al., 1979; Spielman et al., 1981). The first cases of human babesiosis appeared in the 1970s in the offshore islands of Massachusetts and New York. The number of cases increased from a handful to more than one dozen in a short time, and more ominously, the severity of the illness in elderly patients, added to the detection of transfusion-transmitted and transplacental cases, required investigation by federal and state public health officials (Esernio-Jenssen et al., 1987; Grabowski et al., 1982). The finding of transfusion-acquired cases resulted in a ban on blood collection from the enzootic areas by the local blood banks. A very clear disease pattern emerged from the increasing number of cases (Dammin et al., 1981; Meldrum et al., 1992; Rosner et al., 1984; Ruebush et al., 1981). The typical patient was 50 years old or older and presented with non-periodic fever and chills, myalgia, fatigue, haemolytic anaemia, and haematuria. A number of patients had been splenectomized with a fatality rate of around 10% in this subset. In fact, studies with experimental animal models also have documented that advanced age is a risk factor for more severe disease (Habicht et al., 1983; Vannier et al., 2004). The parasitaemia varied markedly and did not always correlate with clinical severity (Dammin et al., 1981; Filstein et al., 1980; Meldrum et al., 1992; Rosner et al., 1984; Ruebush et al., 1981). In some immunocompromised patients, the parasitaemia was only reduced with red blood cell exchanges (Cahill et al., 1981), and even in these cases, it persisted at low levels for months. Importantly, in the intervening years since the first cases of babesiosis were discovered, its geographic distribution has not changed markedly. While single cases of B. microti infection have been reported from areas other than coastal New England and New York, the large majority of the
reported cases remains clustered geographically in the same endemic areas.

A serosurvey conducted in Shelter Island (New York) was carried out to detect asymptomatic individuals that could transmit *B. microti* through blood banking procedures and to determine the prevalence and incidence of serologically reactive but asymptomatic babesiosis (Filstein et al., 1980). Healthy individuals at high risk of exposure to ticks were surveyed during a single transmission season. Paired sera obtained in June and October 1978 were tested for antibodies to *B. microti* using the newly developed indirect immunofluorescence test (Chisholm et al., 1978). Point prevalence values of 4.4% in June and 6.9% in October were obtained. Six of 102 persons tested in both months showed at least a fourfold rise in titre of antibodies to *B. microti* for an incidence of 6% for the season. Control sera from inland areas did not show any significant reactivity to *B. microti*, but of the six persons who seroconverted, four had histories of tick bites during the transmission season. Of note, this serosurvey identified a number of individuals who reported a history of erythema migrans and who also had antibodies to *B. microti*. These individuals did not have clinical babesiosis but retrospective inquiries yielded histories compatible with early Lyme disease. Sera banked from these individuals were used several years later to strengthen the association between *B. burgdorferi* and Lyme disease (Burgdorfer et al., 1982). This association between subclinical exposure to *B. microti* and signs of Lyme disease proved to be a common occurrence that underscored the close natural history of both pathogens. This pattern also underscored the opportunistic nature of babesiosis and the high degree of susceptibility of healthy persons to infection with *B. burgdorferi*.

The sharing of reservoir and vector hosts by *B. microti* and *B. burgdorferi* leads to frequent coinfection in nature (Anderson et al., 1986; Piesman et al., 1987; Piesman et al., 1986) and in patients (Benach and Habicht, 1981; Krause et al., 1992b; Sweeney et al., 1998). Evidence for coinfection in humans was noted before the discovery of *B. burgdorferi*. Clinical histories consistent with Lyme disease were elicited from patients who had antibodies to *B. microti* in the serosurvey in 1978 (Filstein et al., 1980). Subsequently, in 1980 a number of patients with clinical babesiosis reported erythema migrans at the onset of the disease (Benach and Habicht, 1981). Although serological confirmation of Lyme disease was not possible at the time, subsequent serological confirmation of coinfection or coexposure was obtained shortly after *B. burgdorferi* was discovered. Clinical coinfection was further documented in a series of patient studies (Benach et al., 1985; Grunwaldt et al., 1983). The existence of clearly established human cases of coinfection with *B. burgdorferi* and *B. microti* led to clinical and animal model studies to determine whether the course of illness is more severe following coinfection (Hilton et al., 1999; Krause et al., 1996; Wang et al., 2000). In the clinical arena, there are conflicting results. One study reported greater severity of Lyme disease (Krause et al., 1996), while another did not report any synergistic interactions between the two diseases (Wang et al., 2000). Experimental studies of coinfection in mice did not show any synergy leading to greater severity of either infection (Coleman et al., 2005), but another study showed greater arthritis severity in double infections (Moro et al., 2002).

### 1.2.3 Borrelia research in Montana and Minnesota

The medium defined by Kelly for the *in vitro* cultivation of *Borrelia hermsii* greatly facilitated the studies of Stoenner on the biology of relapsing fever and made possible the subsequent discovery of the *Borrelia* agent of Lyme disease (Kelly, 1971). Burgdorfer pioneered relapsing fever research as early as 1954, and his work was instrumental in institutionalizing investigations on the tick–borne *Borrelia* at the Rocky Mountain Laboratory (Burgdorfer, 1954, 1970; Davis and Burgdorfer, 1954). Research on relapsing fever *Borrelia* continued with the studies of Stoenner, and then Barbour on the antigenic variation of these organisms (Barbour et al., 1982; Stoenner, 1974; Stoenner et al., 1982). The early *Borrelia* work at the Rocky Mountain Laboratory was paralleled by the seminal studies, also on relapsing fever, of Russell Johnson at the University of Minnesota. His manuscripts (Johnson, 1977) were required reading for all the investigators that joined this field after the identification of the agent of Lyme disease.
1.3 The discovery of the spirochaete

The discovery of the Lyme disease spirochaete was the result of a convergence of events that were occurring in different geographic areas of the USA although not necessarily in isolation from each other:

1. The collaboration between Burgdorfer and Benach centred around the Long Island, New York, endemic areas of several tick-borne diseases, and led to joint investigations that yielded the isolation of the organism.

2. The state of readiness at the Rocky Mountain Laboratory to culture spirochaetes in Kelly’s medium was another factor in the discovery of the organism.

3. The description of an enlarging clinical spectrum for Lyme disease by Steere, Malawista, and coworkers permitted the clinical identification of cases outside of the Lyme, Connecticut, area.

The serosurveys for babesiosis in 1978 and 1979 in Shelter Island, New York, had provided serum specimens from individuals with clinically inapparent babesiosis, but who gave a history of erythema migrans and joint manifestations that had been diagnosed as Lyme disease by Dr Edgar Grunwaldt, the internist on Shelter Island. These sera, stored in our serum bank at Stony Brook University, were used for establishing the aetiology of one of the organisms that were seen in *Ixodes scapularis* adults collected from Shelter Island. One such organism was a microfilaria seen in the haemolymph of the ticks. On dark-field microscopy, spirochaetes were seen and later cultured in Kelly’s medium. In addition to the banked sera, we provided the serum of a faculty member, a physician at Stony Brook University, who had suffered from many of the manifestations Lyme disease for some time. These sera reacted with the newly cultured spirochaetes, initially thought to be a species of *Treponema*, and these findings were reported in Science (Burgdorfer et al., 1982). In short order, spirochaetes were isolated from patients with Lyme disease by two groups, thus fulfilling Koch’s postulates; both studies were reported in the same issue of the New England Journal of Medicine in 1983 (Benach et al., 1983; Steere et al., 1983). Spirochaetes were subsequently isolated from the skin of patients with erythema migrans (Berger et al., 1985).

Continuing field investigations headed by Edward Bosler of our laboratory, isolated the spirochaetes from the blood of white-footed mice collected in Shelter Island and from the same areas where the serosurveys of 1978 and 1979 had been carried out (Bosler et al., 1983). The isolation of the *Borrelia* organisms from *Peromyscus leucopus* served to identify the main reservoir of this organism. This finding, also published in Science in 1983, was subsequently confirmed in several studies from other parts of the country (Burgdorfer et al., 1988). Interestingly, deer, long thought to be involved in the zoonotic cycle of the spirochaete, proved to be a relatively incompetent host (Telford et al., 1988). Canine Lyme disease was identified through our continuing studies on Long Island (Lissman et al., 1984). Dr Barry Lissman, a veterinarian in private practice in our area, had been a prior collaborator in our studies on tick-borne disease. A few years earlier, Dr Lissman and our group had characterized for the first time the canine cases of Rocky Mountain Spotted Fever (Lissman and Benach, 1980). Attuned to the problem of high tick burdens in Long Island dogs, Dr Lissman had seen a series of animals with lameness and arthritis that were heavily infested by both *I. scapularis* and *D. variabilis*. The discovery of the spirochaete permitted the testing of canine serum against this agent with strongly positive results. Moreover, we were able to grow the *Borrelia* from blood samples from dogs with this syndrome (Lissman et al., 1984).

The transmission of the organism by the feeding of *I. scapularis* ticks was subsequently verified (Benach et al., 1987; Ribeiro et al., 1987).

Dr Robert Lane in California and Dr Burgdorfer were able to grow the *Borrelia* organism from *Ixodes pacificus* ticks, thus identifying a third endemic area in the western USA (Burgdorfer et al., 1985). In 1983, at the first International Meeting on Lyme Disease at Yale University in New Haven, Connecticut, a group of investigators that had been instrumental in the discovery and characterization of the Lyme disease spirochaete agreed that the new organism would be named *Borrelia burgdorferi*, after Willy...
Burgdorfer. Dr Johnson wrote the taxonomic study proposing this name (Johnson et al., 1984). Years later, taxonomists in Europe determined that Lyme disease spirochaetes in Europe were sufficiently diverse to warrant separate species designations (Belfaiza et al., 1993; Canica et al., 1993). This led to the naming of B. garinii and B. afzelii as well as the designation of the original isolate as B. burgdorferi sensu stricto, with the entire complex being B. burgdorferi sensu lato (Baranton et al., 1992) (see Chapter 9). More recently, B. japonica and other Borrelia species of unknown infectivity were described (Kawabata et al., 1993).

A notable milestone in the therapy of Lyme disease was made by Dattwyler et al. (1987, 1988a) with the introduction of ceftriaxone as the choice antibiotic (see Chapter 18). Barthold developed a murine model of Lyme arthritis and carditis that has provided the basis for numerous studies on pathogenesis and host responses (Barthold et al., 1988) (see Chapter 14). The genetic transformation barrier for B. burgdorferi was broken by the work of Samuels (Samuels, 1995; Samuels et al., 1994a,b) and Rosa and coworkers (Rosa et al., 1996, 2005) (see Chapter 8). These studies have already permitted important research on gene product function in conjunction with the genome of B. burgdorferi (Fraser et al., 1997) (see Chapter 2).

1.4 The European evidence of one hundred years

Although Lyme disease was named for the place where it was first described in the USA, the disorder had been present in Europe for a long time, mainly as a dermatological and neurological disorder, in contrast with the original rheumatological presentation in the USA. Furthermore, many years before, several European scientists had linked this disorder to an infectious agent transmitted by a tick bite. The historical hallmarks are presented in Table 1.1.

1.4.1 Erythema migrans and Azfelius

The first description of the most frequent and worldwide pathognomonic skin lesion of what we now know as Lyme borreliosis or Lyme disease, was given at the beginning of the twentieth century by Arvid Azfelius (1857–1923), one of the founders of the Swedish Society of Dermatology. In 1909 he presented before the society an elderly woman with an expanding annular erythema with central fading that had developed at the site of a bite by the tick Ixodes reduvius (Azfelius, 1910). Because of its expansion pattern he named this lesion erythema migrans and suggested that it was due to a tick-transmitted infection. A few years later, the Austrian dermatologist, Lipschütz, described another patient with a similar condition that lasted for 7 months, and suggested naming it erythema chronicum migrans (ECM) on the basis of its duration (Lipschütz, 1918). He did not speculate on its aetiology. In 1921 Azfelius reported six additional patients with a similar skin lesion, and two more were presented before the Swedish Society of Dermatology by other authors (Azfelius, 1921). All of the patients had a previous tick bite, a fact that was held by Azfelius as evidence that a tick bite (Ixodes ricinus) was implicated in this entity. In 1930, another Swedish dermatologist, Sven Hellerström, from the Karolinska Institute, reported a patient who developed lymphocytic meningitis three months after an ECM, and suggested that both conditions were related (Hellerström, 1930). In the years to follow, other similar cases were discussed by Hellerström, who suggested a common aetiology for the skin lesion and for the accompanying meningitis. Other European authors reported additional patients with meningitis following erythema migrans (Dalsgaard-Nielsen, 1948; Gelbjerg-Hansen, 1945; Zwelleger, 1946). In 1936, Askani from the Dermatology Clinic at the University of Heidelberg reviewed the significance of ticks as vectors of human and animal pathogens and concluded that ECM was caused either by a toxin or by a living pathogen from the salivary glands of ticks (Askani, 1936). Together with Hellerström’s findings, this became the preliminary evidence for the salivary route of transmission during tick feeding.

The cause of ECM remained elusive, and Hellerström mentioned a possible role for spirochaetes, at that time being investigated by Carl Lennhoff, also a member of the Dermatology Clinic at the Karolinska Institute. Lennhoff claimed to have developed a staining technique (based on the interaction of mercuric chloride with spirochaetes) that permitted him to identify
spirochaetal elements in many different skin lesions of unknown aetiology, including psoriasis, zoster, varicella, lymphadenosis benigna cutis, and erythema migrans, among others (Lennhoff, 1948). Although his staining method appeared suitable for demonstrating spirochaetes in culture, it was not suitable for identifying these microorganisms in smears or in tissue sections of ECM lesions. In fact, to Lennhoff’s disappointment, the structures that he thought were spirochaetes turned out to be artefacts.

In 1949, Schaltenbrand (1949) from the Neurological Clinic at the University of Würzburg showed that the nervous system disorders associated with ECM were different from those of the central European tick-borne encephalitis. He speculated on the relationship between the anatomical location of the tick bite and the subsequent neurological manifestations and assumed that ECM meningitis was caused by an unidentified viral agent associated with I. ricinus. He also described prompt improvement after treatment with corticosteroids and tetracycline. In 1950, Hellerström at the Annual Meeting of the Southern Medical Association in Cincinnati, Ohio, presented a study ‘ECM Afzelius with meningitis (Hellerström, 1950).’ He reviewed several cases in which both erythema migrans and subsequent meningocerebrospinal symptoms occurred after tick bites. He also discussed the still unsolved cause of ECM and wondered whether the sheep tick, I. ricinus, could be a vector of spirochaetes. He pointed out that ‘spirochaetes have been known to cause circular erythemas that subside in the centre and advance peripherally, and to affect the nervous system.’ Hellerström injected tick salivary gland extracts into the skin of patients and healthy people and noted an intense

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<th>Year</th>
<th>Author, country of origin</th>
<th>Hallmark</th>
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<tr>
<td>1883</td>
<td>Alfred Buchwald, Germany</td>
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<td>1902</td>
<td>Herxheimer and Hartman</td>
<td>Further characterization of ACA</td>
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<td>1910</td>
<td>Arvid Afzelius, Sweden</td>
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<td>1918</td>
<td>Lipschütz, Austria</td>
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<td>1922</td>
<td>Garin and Bujadoux, France</td>
<td>Description of meningopolyneuritis after tick bite and probable EM</td>
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<td>1930</td>
<td>Hellerström, Sweden</td>
<td>Description of meningitis following EM. Suggested common aetiology for both conditions</td>
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<td>1943</td>
<td>Bo Bäfverstedt, Sweden</td>
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<td>1944</td>
<td>Bannwarth, Germany</td>
<td>Further descriptions of meningopolyneuritis after EM</td>
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<td>1948</td>
<td>Carl Lennhoff, Germany</td>
<td>Reported seeing spirochaetes in biopsy specimens (turned out to be artefacts)</td>
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<td>1949</td>
<td>Hellerström, Sweden</td>
<td>Suggested that a spirochaete might be involved</td>
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<td>1949</td>
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<td>Successful treatment of ACA with penicillin</td>
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<td>1951</td>
<td>Hollström, Sweden</td>
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<td>1955</td>
<td>Binder et al., Germany</td>
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<td>1974</td>
<td>Weber, Germany</td>
<td>Successful response of ECM to antibiotics</td>
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<td>1984–1985</td>
<td>Ackermann et al., Germany and Sweden</td>
<td>Cultivation of B. burgdorferi in skin and fluids</td>
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reaction in the former, whereas only a weak response was obtained in the later. In 1951, a colleague of Hellerström, Hollström, reported on the successful use of penicillin in treating ECM (Hollström, 1951). Despite the accumulating evidence, and perhaps because spirochaetes had never been found in association with ticks of the genus *Ixodes*, the search for spirochaetes in ticks was not pursued and the cause of ECM remained obscure. In 1955, Binder and coworkers (1955) succeeded in transmitting ECM from human to human by transplanting pieces of skin taken from the peripheral zone of a lesion of a patient with ECM. In each of the three volunteers, typical lesions developed within 1 to 3 weeks, and a subpassage was equally successful. In each case, treatment with penicillin caused the lesions to disappear within a few days. These experiments clearly suggested that the cause of ECM was an infectious agent susceptible to penicillin.

A rickettsial cause of ECM was suggested in 1962 by Degos et al. in France (Degos et al., 1962). Based on results obtained by Giroud’s slide agglutination test, they reported six of seven patients with significant titres against the epidemic typhus agent, *Rickettsia prowazekii*, the murine typhus rickettsia, *R. mooseri*, and the boutonneuse fever agent, *R. conorii*. Although these results could not be confirmed, the notion that ECM is caused by a rickettsia was kept alive by the electron microscopic demonstration of rickettsia-like microorganisms in macrophages of two ECM patients (Sandbank and Feuerman, 1979).

In 1974, Klaus Weber, from Munich, successfully treated a patient with ECM and meningitis with antibiotics (penicillin and chloramphenicol) and concluded that this nervous disorder was a bacterial illness (Weber, 1974). He ruled out spirochaetes as the causative agent because ‘these microorganisms are transmitted by argasid and not ixodid ticks.’ He also referred to the negative results of S. Hard who attempted to infect larval, nymphal, and adult *I. ricinus* by allowing them to feed on the erythematous ring of an ECM lesion (Hard, 1966). Subsequent dark field examination of tick tissues showed no spirochaetes, and transmission experiments with nymphal ticks that had fed on the lesion as larvae proved negative. He pursued further the rickettsial hypothesis and examined the sera of 13 ECM patients for the detection of antibodies to 14 different rickettsial antigens (Sandbank and Feuerman, 1979; Weber, 1981). All tests were negative.

### 1.4.2 Garin-Bujadoux, Bannwarth and the neurological spectrum

In 1922, two French neurologists, Charles Garin and Antoine Bujadoux, from Lyons, gave the first description of neurological complications after a tick bite and of a skin lesion that, although not recognized as such, was compatible with erythema migrans (Garin and Bujadoux, 1922). They reported on a 58-year-old man who developed a reddish, painful and expanding skin lesion, accompanied by inguinal lymphadenopathy, 3 weeks after having been bitten by a tick on his left buttock. This was followed by excruciating bilateral sciatic pain, intercostal pain, and finally a painful unilateral right brachial plexopathy with amyotrophy of the deltoid muscle. He required morphine, obtaining only partial relief. Four months after disease onset the pain had decreased significantly, and he was left with deltoid amyotrophy and weakness. Serological test for syphilis (Wassermann test) was weakly positive, but the authors were aware that ‘in certain tick-transmitted diseases such as relapsing fever and Rocky Mountain Spotted Fever these test can be positive’[sic.]. They ruled out syphilis as the cause, and presented the case as an example of ‘paralysie par les tiques’ (tick palsy), although they also argued that this disorder could be caused by a tick-borne virus. However, in contrast to their patient, they noted that those cases of tick palsy in the literature were not accompanied by a previous skin lesion. Furthermore, tick palsy is usually caused by *Dermacentor* tick bites, while their patient had been bitten by *Ixodes hexagonus*, the hedgehog tick.

Between 1941 and 1944, Bannwarth in Germany reported several patients who suffered meningitis with evidence of cranial or peripheral neuropathy (Bannwarth, 1941, 1944). In his first report, he described 14 patients with lymphocytic meningitis and severe radicular pain in the trunk and extremities. Pain was migrating, neuralgic and more intense at night. Facial palsy was present in six patients, unilateral in two of them, and bilateral in four. Bannwarth, however,
did not make the connection between prior tick bites or ECM, which one of the patient seemed to have had, and the neurological disturbances, and favoured, instead, an allergic or rheumatic aetiology.

In 1985 Ackermann et al. reported on eight patients with chronic progressive encephalomyelitis and intrathecal synthesis of specific antibodies against *B. burgdorferi* who improved following parenteral antibiotic therapy (Ackermann et al., 1985). This is the first report of central nervous system involvement in Lyme borreliosis, and was followed by larger series (Ackermann et al., 1987). The protean manifestations of the neurological disorder created some confusion with other neurological diseases of uncertain origin, including multiple sclerosis or Guillain–Barré syndrome, among others (Kristoferitsch, 1991; Schmutzhard et al., 1989). In the 1970s and 1980s, Horstrup and Ackerman reviewed the manifestations of this entity in Europe. They (Hörstrup and Ackermann, 1973), and others (Weber, 1974) insisted on an infectious aetiology even before the spirochaetal origin of Lyme disease was discovered.

1.4.3 Acrodermatitis chronica atrophicans (ACA) and lymphadenosis benigna cutis

ACA was first described in the late nineteenth century by Buchwald (Buchwald, 1883) and then clearly characterized by Herxheimer and Hartmann in 1902 (Herxheimer and Hartman, 1902). Many patients with this intriguing disorder remembered having been bitten by the sheep tick, *I. ricinus*, and some reported subsequent development of ECM-like skin lesions. In 1942, R. H. Kahie, a German dermatologist, noted that six of seven patients with ACA had a positive serological response against *Treponema pallidum*. Ten years later, his mentor, Dr Grüneberg, confirmed these results and speculated that the reactions must have been caused by a group-specific spirochaete as the causative agent of ACA (Grüneberg, 1954).

In the 1940s, the beneficial effect of penicillin on ACA was demonstrated (Thyresson, 1949), and Gotz showed in the 1950s that it was a transmissible condition (Gotz, 1954, 1955). He successfully transplanted affected skin of a patient into four volunteers, including himself, and recorded a clinical picture similar to ACA (i.e. inflammation that lasted for as long as 312 days and promptly disappeared after treatment with penicillin). Gotz speculated the aetiologic agent to be a large virus, but, lacking evidence, he concluded that the cause of ACA would continue to be an open question. In 1955, Lohel showed antibodies against spirochaetes in mice inoculated with blood from ACA patients (Lohel, 1955). His claim of ACA being a spirochaetosis, however, was rejected. The geographical distribution in Europe and the observation that most patients had been from rural areas further strengthened the suspicion that the tick *Ixodes ricinus* was the vector.

Lymphadenosis benigna cutis, or borrelial lymphocytoma, was first described by Bäfverstedt, another Swedish dermatologist, in 1943 as a benign skin condition characterized by the appearance of lymphoreticular tissue in the epidermis and subcutaneous layers (Bäfverstedt, 1943). He also mentioned a possible association with cases of ACA. In the ensuing years, it was successfully transmitted and treated with penicillin, again reinforcing the idea of an infectious aetiology.

1.4.4 A missing articular manifestation in Europe?

The rheumatological aspects of Lyme disease became evident after the initial epidemic of arthritis in Lyme, Connecticut was first reported (see above). On the other hand, the European descriptions of this disease consisted primarily of a cutaneous and neurological disorder. This notion, that American Lyme disease primarily affects the joints while European Lyme disease is primarily neurological, may represent an acquisition bias. That dermatologists and neurologists in Europe were well aware of this disease, while in the USA rheumatologists led by Stephen Malawista became involved in the arthritis epidemic may at least partially account for this notion. However, a German patient (Herzer et al. in 1976) developed an expanding skin lesion, neurological abnormalities and arthritis following a tick bite (Herzer et al., 1983). This patient insisted on her disease being related to the prior tick bite, but was not diagnosed until she read an article on the lay press about the presentation of Lyme disease in the
USA. She was then told that Lyme arthritis did not exist in Europe.

Although joint manifestations had been observed in European patients with erythema migrans, ACA, and lymphocytic meningitis (Bannwarth, 1941; Benjamowistch and Maschkilleisson, 1933; Erbslöh and Kohlmeyer, 1968; Gans, 1933, 1952; Hoövelborn, 1931; Hopf, 1966; Jessner, 1922; Jessner and Loewenstamm, 1924; Schaltenbrand, 1949), the initial reports on European Lyme disease after the discovery of its aetiology basically neglected the rheumatological aspects to the point that they were regarded as curiosities (Ackermann et al., 1980; Hewitt et al., 1980). In fact, the Second International Symposium on Lyme Disease and Related Disorders, held in Vienna in 1985, did not include any studies by European rheumatologists. In the meantime, an increasing number of reports of Lyme arthritis from several European countries have accrued, suggesting that this joint manifestation may have been overlooked or at least underestimated (Herzer, 1983, 1991; Herzer et al., 1983).

1.4.5 Linking the aetiology of the European syndromes to Borrelia burgdorferi

In the early 1980s, the clinical spectrum of a disorder of still unknown aetiology had been clearly delineated, particularly in its cutaneous and neurological manifestations, and investigators had concluded that it was caused by an infectious agent, probably a spirochaete, and that it was transmitted by Ixodid ticks. Soon after the discovery of the Lyme agent in the USA, B. burgdorferi was finally isolated from European patients with EM by Swedish and German investigators (Ackermann et al., 1984; Asbrink et al., 1984; Wilske et al., 1985). In 1983, Asbrink et al. from Sweden, succeeded for the first time in isolating B. burgdorferi from the skin of a patient with ACA (Asbrink et al., 1984), thus demonstrating that this cutaneous disease was also part of the spectrum of Lyme disease.

The availability of serological testing following the discovery of B. burgdorferi enabled investigators to obtain evidence for the spirochaetal aetiology of the meningopolyneuritis of Garin-Bujadoux and Bannwarth and other less frequent neurological manifestations. Cultivation of the spirochaete from the cerebrospinal fluid of some patients confirmed the conclusions drawn from serological studies (Allal et al, 1986; Pfister et al., 1989; Preac Mursic et al., 1984).

1.5 The rocky road of Lyme disease

1.5.1 The vaccine

The scientific body of work that led to the development of a commercial vaccine for Lyme disease can be considered a major outcome of the interdisciplinary approach that uncovered the major biological features of B. burgdorferi and its natural history in both the vector and the vertebrate host (see Chapter 17). The cationic lipoproteins, OspA and OspB (Benach et al., 1988; Bergström et al., 1989; Brandt et al., 1990), which are prominent in the electrophoretic profile of cultured B. burgdorferi, were the first to be studied for their role in eliciting an immune response (Barbour et al., 1983; Johnson et al., 1986). The protective role of antibodies to OspA was revealed by passive immunizations of previously infected scid mice with anti-OspA monoclonal antibodies (Barthold and Bockenstedt, 1993; Fikrig et al., 1992b, 1994). Using sera from patients with Lyme disease, passive protection of mice was accomplished but only if the sera contained antibodies to OspA (Zhong et al., 1997). Moreover, two additional studies provided evidence for a role for passive immunization and in the attenuation and resolution of chronic disease (Fikrig et al., 1990; Schaible et al., 1990). The lipid moiety turned out to be critical for the immunogenicity of OspA, since only the full-length lipidated molecule protected mice from challenge (Bockenstedt et al., 1993; Erdile et al., 1993; Weis et al., 1994). Clearly, the lipidation is important biologically but also for conferring immunogenicity to the molecule. In addition, antigens expressed by B. burgdorferi in culture could be different from those present in ticks or the mammalian host (Gern et al., 1993; Schaible et al., 1993a). This observation led to studies on the extent and nature of the protection that could be elicited following challenge with antigenically diverse strains of this organism. Furthermore, determining if vaccine preparations could protect from challenge with spirochaetes

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transmitted by ticks became critical. The antibody response to tick or needle inoculated cultured spirochaetes is dependent on the amount of antigen given. Inocula of 1000 cultured spirochaetes or fewer, or tick exposure, generated antibodies to a diverse group of antigens but not to OspA/B. In contrast, higher doses of cultured organisms developed antibodies to these two antigens (Gern et al., 1997; Schaible et al., 1993b).

There were also geographic differences in some areas of the American continent; protection could be achieved by OspA vaccination followed by challenge with infected ticks (Telford et al., 1993). Although OspA can induce a robust antibody response when administered as a purified protein, Lyme disease patients had long been known not to develop antibodies to OspA in the early stages of the disease. This ostensible paradox was subsequently explained on the basis that expression of OspA is down-regulated as the tick begins to feed on a host (Schwan et al., 1995). In this manner, the OspA vaccine would induce an antibody to an antigen that is not present in the host as it is lost during transmission from the tick to the host. If this was the case, how can the OspA subunit vaccine be protective? Attempts to answer this question showed that the vaccine was protective by eliminating the organisms that expressed OspA in the feeding tick (de Silva et al., 1996; Fikrig et al., 1992a). Thus, the mode of action of the OspA vaccine is to block transmission by inducing the formation of antibodies that eliminate spirochaetes in the midgut of the feeding tick (de Silva et al., 1996). That antibodies had an effect in the vector underscores the uniqueness of this vaccine paradigm. Antibodies to OspA have a remote effect on B. burgdorferi, affecting the organisms outside of the host where the antibodies were developed. This was a novel approach to a vaccine (Connolly and Benach, 2005).

Based on the effectiveness of the antibody response to OspA, two commercial recombinant lipidated, adjuvant-containing, OspA vaccines were formulated, tested and marketed in the USA. The US Food and Drug Administration (FDA) licensed a vaccine, LYMErix, on 21 December 1998, for persons 15–70 years of age. This licensed vaccine was a subunit formulation containing recombinant OspA (rOspA). Two vaccine studies demonstrated the effectiveness of a triple-dose vaccine regimen that protected 100% of the volunteers after the second year in one trial (Steere et al., 1998) and 92% in another (Sigal et al., 1998). Three doses of 0.5 ml (30 μg) of rOspA vaccine administered by intramuscular injection at 0, 1 and 12 months were required for optimal protection in subjects who were between 15 and 70 years of age. The duration of protective immunity for longer than 1 year after the third dose of immunization was not determined at that time. Unfortunately, safety and efficacy of the rOspA vaccine were not established for persons older than 70 years or younger than 15 years of age, two age groups that have been traditionally overrepresented in this disease (Steigbigel and Benach, 1998). Volunteers and patients that received this vaccine developed a positive serological pattern that distinguished their response from that of patients.

As of February 2002, the LYMErix vaccine was withdrawn from the commercial market in the USA. The reasons for its removal from the market were poor market penetration, and not issues related to the vaccine’s safety, immunogenicity, or efficacy. Cross-reactivity of OspA with self-antigens may have caused some doubts about the possibility of an autoimmune response (Gross et al., 1998). IgG antibodies to OspA had been shown to correlate with severe and prolonged arthritis, furthering additional concerns about autoreactivity (Akin et al., 1999; Krause et al., 1992a).

On 22 January 2002, officers from the Lyme Disease Association (LDA) and International Lyme and Associated Disease Society (ILADS) met with both scientists and administrators from the Food and Drug Administration (FDA) to express concerns about the vaccine’s track record on safety and effectiveness. This meeting was made possible at a request of a Congressman from New Jersey. The evidence presented included the occurrence of joint and muscle pain after receiving the vaccine. On 25 February, a month or so after meeting, the LDA received written answers to their questions from FDA officials. Coincidentally, on or about the same time, Glaxo SmithKline had withdrawn LYMErix from the market (http://www.lymediseaseassociation.org/Vaccine_LYMERIXMeeting.html).
1.5.2 The Lyme disease treatment controversy

Although the role of the advocacy groups in the withdrawal of the vaccine may be difficult to assess, it underscores the controversy involving public advocate groups and members of the academic medicine establishment as growing bitter and increasingly litigious. The internet is literally brimming with information that supports the existence of a sharp division of opinion regarding the nature and management of Lyme disease that began almost 20 years ago (Barinaga, 1992).

The Lyme Disease Foundation (LDF) was founded in 1988 by Karen Vanderhoof-Forschner and her husband Thomas E. Forschner as a non-profit corporation to foster education and research on this disease. The LDF was remarkably successful in meeting its goals, and over the years, it was instrumental in educating the public about Lyme disease through its outreach programs, videos, and conferences held in various parts of the country. Researchers in this field were given an opportunity to present their work at their venues, and many did. On the other hand, the LDF also sponsored the alternative views to treatment that ultimately fostered polarization between the research establishment and some of the patients. Other advocacy organizations followed the lead of the LDF. Notably, the Lyme Disease Association (LDA) and International Lyme and Associated Disease Society (ILADS) have become quite active in patient advocacy and education. At the very core of the controversy is the belief by some patient advocates and some of their doctors that Lyme disease is a chronic infection that can only be treated with unusually long courses of antibiotic therapy. From this core, other contentious issues follow such as, for example, the reluctance of insurance companies to pay for long-term antibiotic treatment. The insurance companies base their refusal to cover these lengthy treatments on the lack of scientific evidence showing that long-term antibiotic therapy is beneficial (see Chapter 18).

How did we get to this state of affairs? In approaching this topic, we could have delved deeply into the internet sites that reflect the views of advocacy groups. We chose not to as there is sufficient material in the internet to fill this volume, and not all material is useful to understand the genesis of this social phenomenon. There are obviously some legitimate reasons that may have assisted in the development of the controversy, and these relate to the natural history of Lyme disease and the idiosyncrasies of its agent *B. burgdorferi* (Barbour and Fish, 1993).

- Lyme disease produces non-specific symptoms, often separated in time. Its most compelling sign, the erythema migrans, has a variable morphology, and can be absent or not noticed. The neurological manifestations are protean, and often subtle and non-specific and this results in some confusion for the patients (García-Moncó and Benach, 1995).
- Many patients deny a history of the tick bite, mostly because they never saw or recognized the very small nymph.
- *Borrelia burgdorferi* is fastidious. Even laboratory-adapted strains grow slowly, so that cultures of the spirochaetes are not useful for iron-clad diagnoses that are the norm for other bacterial diseases. Hence, serology has become the only means of laboratory diagnosis of Lyme disease. This, too, presents some confounding problems. The antibodies are long lived and do not provide a means to determine a cure. Although clearly not the intended result, a study showing that there is seronegative Lyme disease alerted patients to the notion that they could also have this disease without serological evidence (Dattwyler et al., 1988b).
- Treatment-refractory Lyme disease has been reported in the academic medicine literature (Drouin et al., 2008; Kannian et al., 2007; Steere et al., 2006). In the mind of some patients, a bona fide treatment failure is the main indication for long-term antibiotic therapy.

Despite some of the problems presented by the diagnostic and clinical features of Lyme disease, many advances have been made to solve the problems outright or mitigate them so that this disease can be diagnosed and treated with a degree of certainty that is equal to that of other infections. The scientific community, under the auspices of the Centres for Disease Control, assembled a panel of experts to standardize the

The same is true for treatment. For a number of years, chronic Lyme disease has been studied in patient populations using different clinical research approaches (Marques, 2008). In short, despite the diversity of the studies, their results are markedly similar. Lyme disease is generally treatable with the recommended therapies of antibiotics, making prolonged treatment unnecessary. The efficacy of treatment of chronic Lyme disease was evaluated in a randomized, placebo-controlled clinical trial for both seropositive and seronegative patients with persistent symptoms after having received initial antibiotic therapy for the illness. The study showed that the quality of life did not improve after long-term antibiotic therapy. The implicit recommendation was that long-term antibiotic therapy is not warranted. In fact, the Data Safety Monitoring Board of this project recommended that the study be discontinued because there was no difference in treatment efficacy between groups (Klempner et al., 2001). Post treatment chronic Lyme disease patients who have symptoms show no evidence of objective cognitive impairment. Continuing antibiotics was not more effective than placebo (Kaplan et al., 2003). Halperin et al provided evidence-based recommendations on the treatment of neuroborreliosis and post-Lyme syndrome. They found that adults and children respond well to recommended antibiotic therapy. In contrast, there is no compelling evidence that prolonged treatment with antibiotics has any beneficial effect in post-Lyme syndrome (Halperin et al., 2007). A multi-author review tackled the chronic Lyme disease issue and reached the predictable and forceful conclusion that there is no evidence in support of long-term antibiotic therapy (Feder et al., 2007).

An expert panel of the Infectious Diseases Society of America (IDSA) provided evidence-based guidelines for the management of patients with Lyme disease. These guidelines list the doses and durations of recommended antimicrobial therapy for both treatment and prevention of Lyme disease. The guidelines also provide a list of therapies to be avoided and proposed a definition of the post-Lyme disease syndrome (Wormser et al., 2006). As a result of these guidelines, an antitrust investigation against the IDSA was started by the Attorney General of the State of Connecticut alleging that the restrictive recommendations prevent patients from receiving care that is not included in the guidelines (www.lymediseasesassociation.org). The IDSA provided a rebuttal standing by the guidelines (www.idsociety.org). In May 2008, the IDSA reached an agreement with the Connecticut Attorney General that ends the investigation. The agreement allows for the guidelines to remain. However, in this agreement with the Attorney General, the IDSA will call for another special review of the guidelines. To this end, the IDSA will convene a review panel to conduct a comprehensive and up-to-date evaluation of the scientific literature, in order to determine whether the 2006 guidelines need to be changed. At the time of this writing, the IDSA issued a call for applications for scientists to participate in this review panel.

While The Attorney General’s investigation of the 2006 IDSA guidelines never questioned the medical evidence, there were concerns with the process leading to the recommendations, and the agreement to revisit the guidelines reflects these concerns. As part of the review process, scientists have been invited to submit information about themselves to meet selection criteria for the review panel. The review panel will consider all new and past evidence and determine whether, and how, the guidelines should be revised. If the panel recommends revisions, they will be carried out as per the IDSA Standards and Practice Guidelines Committee.
The views held by the advocacy groups on treatment and even on the very definition of what constitutes Lyme disease are at odds with the views of the scientific community. The potential for harm resulting from long-term antibiotic treatment, not to mention the harm to the patient caused by treating a disease that they may not have, are the main reasons to double the efforts by the scientific community to have its voice heard by the patients. This is not an easy task as advocacy groups demand complete responsibility for the health care that they want to receive and question the very authority of science (Aronowitz, 1991).

References


