# 17 Lyme Disease: the Great Controversy

John J. Halperin, Phillip Baker and Gary P. Wormser

## 17.1 Background

We live in interesting times. As a result of vigorous efforts by well-intentioned but misinformed patient advocates and by a small cadre of their physician supporters, Lyme disease – with fewer annual confirmed cases in the USA than varicella (Hall-Baker *et al.*, 2010) – is repeatedly characterized as epidemic, controversial and difficult to diagnose or treat. Pseudo-documentary movies (Halperin, 2009) have been produced vilifying experts in the field and purporting to demonstrate a medical conspiracy – driven supposedly by unsupported and unsupportable allegations of conflicts of interest – to hide the suffering of the victims of this disorder.

The press, politicians and advocates repeatedly portray this as a subject of substantive and legitimate scientific controversy. Yet the scientific evidence is remarkably consistent, providing no real basis for controversy (Sigal, 2007; Weissmann, 2007; Baker, 2010). That fact notwithstanding, the states of Connecticut, Maryland, Minnesota, Massachusetts, New York, Pennsylvania, Rhode Island and others have passed or considered legislation or regulations to assure the provision of demonstrably ineffective prolonged antibiotic treatment (Klempner *et al.*, 2001; Krupp *et al.*, 2003; Fallon *et al.*, 2008) for patients diagnosed with an undefined disorder termed 'chronic Lyme disease'. In 2006, the Attorney General of the state of Connecticut opened an investigation of the Infectious Diseases Society of America (IDSA) for issuing evidence-based guidelines for the diagnosis and treatment of Lyme disease, on the legally questionable theory that this clinical guideline represented an anti-trust violation. Although this remarkable action yielded no finding of any anti-trust violation (but ultimately cost the IDSA over half a million dollars in legal and other costs (IDSA, October 2010, personal communication), it did result in a detailed review of the guidelines by an independent panel that endorsed all of the guidelines' original recommendations (Lantos *et al.*, 2010). What, then, is the basis for this controversy?

This strange story begins with the disease's original characterization in the USA in the early 1970s, when a surprising number of children in Lyme and Old Lyme, Connecticut, were diagnosed as having juvenile rheumatoid arthritis. Efforts by several mothers of affected children led to a more detailed investigation. This ultimately resulted in the pioneering work of Allen Steere and others (Steere *et al.*, 1977), who identified both the tick vector and the responsible bacterial pathogen, *Borrelia burgdorferi* (Burgdorfer *et al.*, 1982; Benach *et al.*, 1983; Steere *et al.*, 1983). It also resulted in the early creation of multiple vocal patient

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support and advocacy groups, whose members have advocated strongly for the perceived needs and concerns of patients afflicted – or thought to be afflicted – with this disease (www.lymenet.org/SupportGroups/). Remarkably, active groups even formed in areas of the USA where Lyme disease is not endemic. Aided by the Internet, these groups have shared information, viewpoints and strategies to lobby for their cause, reinforcing each other's perspectives and misinformed opinions, thereby setting the stage for the current chaos.

The path from there epitomizes the law of unintended consequences. With significant support from both the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC), several academic groups – primarily those at Yale and Stony Brook – became actively involved in efforts to understand better the full scope of Lyme disease. Development of early serological tests in the 1980s led to the observation that some patients who appeared to have active, disseminated Lyme disease, in whom serological tests would be expected to be positive, did not have measurable antibody responses as evidenced by the ELISAs then in use (Dattwyler *et al.*, 1988). Although this observation was probably the result of limitations in the then-available assays (see Johnson, Chapter 4, in this volume), the notion of seronegative late Lyme disease became firmly implanted in the consciousness of patients and some healthcare providers.

In assessing patients in the early 1980s, all with typical signs and symptoms of active Lyme disease, many were noted to have objectively demonstrable cognitive slowing and memory difficulty (Halperin *et al.*, 1988, 1990; Logigian *et al.*, 1990; Krupp *et al.*, 1991), just like many patients with other active infectious or inflammatory disorders. This gave rise to the notion – in some circles– that such symptoms are an essential part of the Lyme disease symptom complex, rather than the non-specific toxic-metabolic encephalopathy seen in patients with many inflammatory diseases. From there, it was a short if illogical step to conclude that these symptoms were sufficiently typical of Lyme disease that their presence – in the absence of more specific abnormalities or even positive serological tests – justified a diagnosis of *B. burgdorferi* infection and treatment with antibiotics. As these same symptoms also occur in approximately 2% of otherwise healthy individuals at any given time (Luo *et al.*, 2005), this logic has indeed been problematic. Even worse, these symptoms were misinterpreted as evidence of *central nervous system* (CNS) infection by *B. burgdorferi* – a terrifying prospect for symptomatic individuals – despite the fact that early work clearly showed that the vast majority of these patients *did not have active nervous system infection* (Halperin *et al.*, 1992) (see Halperin, Chapter 13, this volume). All of these false assumptions set the stage for a medical 'perfect storm'.

Reinforced by information from support groups and the Internet, patients with a common but non-specific symptom complex became convinced that their difficulties were caused by an infection for which the diagnostic tools were deeply flawed. Even more frightening, they believed that, if left untreated, this infection would result in irreversible brain damage. Not surprisingly, some physicians – who came to be known as 'Lyme literate physicians' or LLMDs – began treating such patients with aggressive courses of antibiotics. When treatment responses were less than satisfactory – and despite the fact that this microorganism has never been shown to develop antibiotic resistance – many patients and LLMDs were reluctant to acknowledge that the underlying premises and logic were deeply flawed. Instead, they invoked a series of ever more creative conjectures – substantiated only by inaccurate or misinterpreted snippets of information – as to why this infection was apparently so difficult to treat. These included assertions that *B. burgdorferi* cells adopt a cell-wall-free or cyst form (Brorson and Brorson, 1998, 1999; MacDonald, 2006) and/or that they hide intracellularly. Such conclusions were based primarily on extrapolations from *in vitro* studies, without supporting evidence that this was of any clinical relevance (Wormser *et al.*, 2006).

As many of these LLMDs became increasingly invested in this deeply flawed

disease model, the response to treatment became the final element in this self-reinforcing logic. Early work indicated that patients with acute, active early Lyme disease, as indicated by the presence of an erythema migrans (EM) skin lesion (when large numbers of spirochaetes are presumably present), sometimes exhibited a Jarisch–Herxheimer-like reaction within 24 h after initiation of treatment (Weber *et al.*, 1988; Maloy *et al.*, 1998). This led to the notion that any worsening of symptoms during treatment constituted 'Herxing', regardless of the duration of symptoms or treatment at the time of the worsening. The logical inconsistency of postulating that treatment-resistant disease was due to a small number of undetectable bacteria, while at the same time concluding that symptoms arising or worsening during antibiotic therapy were due to the release of large amounts of pharmacologically active bacterial products, was either discounted or never considered. However, this then completed the very tidy but circular conceptual model. If patients improved, even transiently, after treatment, this validated the diagnosis and justified further treatment; the possibility of a placebo effect or natural fluctuation in symptom severity was either never considered or completely rejected. If patients worsened, this was considered to be due to a Jarisch–Herxheimer reaction, similarly validating the diagnosis. If there were no response to therapy, this validated the assumption that this infection is highly resistant to standard antimicrobial therapy.

At this point, it is informative to examine in more detail some of the key myths that together resulted in this irrational construct.

## 17.2 Laboratory Myths – Seronegative Lyme Disease

### 17.2.1 Serology

In 1988, using early whole-cell-sonicate ELISA assays for the serodiagnosis of Lyme disease, a group of scientists at the State University of New York at Stony Brook (SUNY-SB) identified 17 patients who had been treated early in the course of Lyme disease but still had symptoms interpreted as evidence of active infection (Dattwyler *et al.*, 1988). Although none of these patients had significant elevations of antibody by ELISA, all had evidence of T-cell immunoreactivity against *B. burgdorferi*, using a T-cell proliferation assay subsequently found to be non-specific and therefore now felt not to be useful diagnostically.

To appreciate how infected individuals could be 'seronegative', it is important to understand the factors involved in developing an ELISA for the serodiagnosis of any infection, including infection caused by *B. burgdorferi*. As many bacterial antigens are shared among *B. burgdorferi* and other related and unrelated groups of microorganisms, there is considerable immunological cross-reactivity, often leading to false-positive serological results (Magnarelli *et al.*, 1987). Consequently, assays must be designed to balance sensitivity and specificity. The greater the sensitivity, the more likely an assay will detect low levels of antibodies specific for *Borrelia* antigens (as detailed by Johnson, Chapter 4, this volume). However, the assay will then also detect weak cross-reactivities that are not diagnostically significant or meaningful.

Before the widespread adoption of the two-tier testing approach in 1995 following a CDC-sponsored conference on Lyme serodiagnosis (Dressler *et al.*, 1993; Anon., 1995), laboratories tried to design single assays to optimize accuracy. This included limiting false-positive results attributable to cross-reactivity by adopting stringent end points for ELISAs (see Johnson, Chapter 4, this volume). However, adoption of the Western blot as an essential component of a two-tiered sequential test represented a major advance, as it enabled the use of validated criteria to confirm the specificity of weakly positive or borderline ELISA results, i.e. results that, in earlier ELISAs, probably would have been considered negative. It is likely that the 17 patients included in the above-described SUNY-SB study included individuals with false-negative ELISAs who would be positive with current assays, patients with post-treatment persistent

symptoms and perhaps patients who did not really have Lyme disease. Using the currently recommended two-tier approach, most laboratory experts now feel that, except in the first 3–6 weeks of infection before an antibody response has developed sufficiently to be detectable, seronegative Lyme disease is extraordinarily rare.

Although the preceding history explains the origins of the myth of seronegativity, there is another, often repeated variation of this argument that is more difficult to understand, namely that serological results become temporarily falsely negative *during and because of* antibiotic treatment, i.e. the presence of antibiotics in the patient's system in some way interferes with either the production of antibodies at the time, or the assays for them. Patients often relate that they were told 'the test was negative because I was on antibiotics'. Not only is there no evidence – or even theoretical rationale – to support such an assertion, there is no precedent for this with reference to any other infectious disease.

These two untenable explanations for false-negative serologies are very different from the situation in which a patient is *cured* very early in infection, in which circumstance the rapid removal of all antigens certainly can lead to an aborted antibody response, because none of the infecting organisms is present long enough to elicit the response. Observations on rabbits infected experimentally with *Treponema pallidum* (syphilis) provide a useful perspective on this point. Rabbits that received penicillin while incubating infection were 'either cured or subsequently developed clinically recognizable lesions' (Hollander *et al.*, 1952). Single subcurative doses of penicillin prolonged the 'incubation period of experimental syphilis… up to a limit of 30–40 days', but when lesions developed, all of the animals became seropositive.

### 17.2.2 Other diagnostic tests

Because of the technical difficulty of culturing *B. burgdorferi* using conventional laboratory methods, and because of the presumed small number of organisms present in readily obtainable samples, microbiological diagnosis of Lyme disease is generally impractical. Even the extremely technically sensitive and specific PCR, adopted as an alternative to culture, is of remarkably low diagnostic sensitivity with many types of clinical specimens (Lebech *et al.*, 2000; Avery *et al.*, 2005; Roux *et al.*, 2007), again presumably because of the low number of microorganisms present. On the other hand, PCR can detect fragments of DNA from long-dead organisms; DNA has been detected in tissues as long as 7 years after an infection has been microbiologically cured (Rovery *et al.*, 2005). Thus, although such fragments may be specific for *B. burgdorferi*, their presence does not prove active infection.

Consequently, diagnosis has relied almost exclusively on demonstrating a specific host antibody response to the microorganism. However, this too has important pitfalls. The presence of specific antibody – which commonly persists for long periods of time after infection – indicates past or present exposure to relevant borrelial antigens, and does not prove active infection (Hammers Berggren *et al.*, 1993). For most other infections, serological testing typically relies on the demonstration of a fourfold or greater change in antibody titre. In contrast, for Lyme disease the convention has been to rely on a single serological determination.

Although adoption of the two-tier testing strategy has provided a reasonable compromise between sensitivity and specificity, test interpretation requires an appreciation of three key elements. Firstly, the criteria used for the Western blot are only to be applied in patients with positive or borderline ELISAs. Without this much measurable antibody, blots should not even be performed. Secondly, the IgM criteria are intended for use only in individuals with early infection (Anon., 1995). By 4–8 weeks after exposure to *B. burgdorferi*, the much more specific IgG antibody response should be developing and is of much greater diagnostic value (Wormser *et al.*, 2006). In patients with disease of 1–2 months duration or longer, isolated IgM responses are far more likely to be cross-reactive and not specific for

*B. burgdorferi*. Thirdly, the bands selected for use in the Western blot were chosen not because they are unique to *B. burgdorferi* but rather on the basis of statistical considerations that included an analysis of those combinations of bands that provided the best predictive values for well-characterized specimens known to have been obtained from individuals with and without Lyme disease (Dressler *et al.*, 1993). Obviously, laboratories using criteria other than these must establish the validity of their own criteria based on equally rigorous scientific assessments.

Efforts continue to develop simpler and more sensitive and specific diagnostic tests for Lyme disease. Although the C6 ELISA assay shows some promise (Philipp *et al.*, 2003; Vermeersch *et al.*, 2009), with accuracy that appears comparable to the two-tier approach, there have not yet been sufficient comparative studies to judge which methodology is preferable.

## 17.3 Clinical Myths: Lyme Disease is a Clinical Diagnosis Based Entirely on Symptomatology

### 17.3.1 Background

Infectious diseases are associated with a wide array of symptoms. Some symptoms are sufficiently unusual outside the context of that particular disease to have a meaningful positive predictive value supporting that diagnosis. Others are common to a broad range of inflammatory disorders and thus have no diagnostic specificity. As is the case with laboratory diagnostic tests, the extent to which particular clinical signs or symptoms support a diagnosis depends on their sensitivity and specificity. For the diagnosis of Lyme disease, some findings (e.g. EM, bilateral facial nerve palsies or childhood facial nerve palsies) are quite unusual, occurring in very few circumstances apart from Lyme disease. If these occur in an individual living in an endemic area where there is a risk of recent exposure to infected ticks, the probability of the patient having Lyme disease is quite high.

Other signs or symptoms are of intermediate specificity. Unilateral facial nerve palsy in an adult, radicular pain without a mechanical cause, relapsing large joint oligoarthritis and heart block in an otherwise healthy young individual are less diagnostic. However, such symptoms are suggestive of the diagnosis and, if there has been potential exposure, it is appropriate to consider Lyme disease in the differential diagnosis. Further along the continuum would be lymphocytic meningitis. This can be caused by Lyme disease, but there is heavy epidemiological and symptomatic overlap between this and enteroviral meningitis. Although it would be reasonable to consider Lyme disease in the appropriate context, one must also realize that in many of these patients there will actually be a viral aetiology. At the other end of the spectrum are many symptoms (e.g. fatigue, malaise, headaches, diffuse aches and pains, cognitive slowing) that are common to virtually all inflammatory disorders. If these symptoms are present in the absence of more distinctive and definitive features, they are of no predictive value for the diagnosis of Lyme disease. In this context, even obtaining a serological test is ill-advised, as it is more likely to be misleading than helpful.

One historic footnote bears mentioning. In the early 1980s, the academic group at SUNY-SB developed a collaboration with several primary care physicians in eastern Long Island, who were seeing many patients with Lyme disease. In an effort to cast a broad net to identify other symptoms that might be related to the infection, they created a database that included a standard review of systems. This completely generic review of systems subsequently became the questionnaire used by many LLMDs as a Lyme-specific symptom inventory.

### 17.3.2 The assertion that 'Lyme disease is a clinical diagnosis'

Every diagnosis in medicine relies ultimately on an ill-defined process termed 'clinical judgement'. 'Clinical judgement' assumes that an appropriately knowledgeable

physician will carefully and correctly gather all relevant clinical, laboratory and epidemiological data and reach a logical conclusion that is congruous with usual and acceptable medical practice. While King Louis XIV of France famously asserted that he was the law ('Le loi, c'est moi'), diagnoses advanced by physicians are not inherently correct simply because they are asserted by a physician, however sincere the intentions may be.

Diagnosis in any given patient requires the appropriate balancing of all the different data elements. A 3-year-old, living in Lyme, Connecticut, with summertime facial nerve palsy probably has Lyme disease. The child might have a negative serology as this disorder may occur before a measurable antibody response has developed. In this case, the initiation of presumptive treatment might well be reasonable. If that child's father developed acute radicular pain in January after lifting heavy furniture, the probability of the radiculitis being related to Lyme disease is extremely low, even if his serology were positive. If the child's mother has been completely healthy but feeling exhausted and absented-minded ever since the child and her twin sibling were born, it is unlikely that the fatigue and forgetfulness are due to Lyme disease. In this sense, Lyme disease is a clinical diagnosis in which a capable physician will synthesize all available data specific to that patient. Then, informed by the broader set of evidence-based medical knowledge, that physician will adopt a diagnostic and treatment strategy consistent with current, reasonable medical thinking and practice.

## 17.4 The Symptom Described as 'Brain Fog'

The CNS can be affected in one of three ways in patients with Lyme disease (Halperin, 2010; Halperin, Chapter 13, this volume). The most common has nothing to do with brain infection. Individuals with systemic inflammatory or infectious disorders commonly feel tired and cognitively slowed in the absence of any brain infection or direct involvement of any sort. Actual CNS infection by *B. burgdorferi* almost always manifests as meningitis. By definition, this disorder consists of inflammation of the lining of the brain, a rather uncomfortable process that is uniformly benign. Very rarely, patients develop parenchymal brain or spinal cord involvement, a disorder most accurately termed encephalomyelitis. Affected patients generally have focally abnormal neurological examinations, abnormal brain or spinal cord magnetic resonance imaging (MRI) scans and inflammatory cerebrospinal fluid (CSF). Many will have demonstrable local production of anti-*B. burgdorferi* antibodies in the CSF. Although this encephalitis typically causes focal neurological abnormalities, very rarely it may present just as cognitive difficulty. When cognitive difficulties are substantial, or the brain MRI demonstrates significant and potentially related parenchymal abnormalities, CSF should be examined. Inflammatory changes in the CSF would then lead to the diagnosis of encephalitis, with corresponding treatment.

Unfortunately, it has become commonplace for patients and their treating physicians to assume that the first, common disorder (a toxic-metabolic encephalopathy) – often referred to by patients as 'brain fog' – represents evidence of what, in fact, is the very, very rare phenomenon of direct brain infection (encephalomyelitis) by *B. burgdorferi*, and that this will progress to severe irreversible brain damage. This assumption has been reinforced by the indiscriminate use of brain single photon emission computed tomography (SPECT) imaging, which, with remarkable frequency, is interpreted as showing cerebral vasculitis in patients with normal neurological examinations, CSF, brain MRI imaging and even brain vascular imaging. Most neurologists find this juxtaposition to be conceptually perplexing, if not frankly irrational. Given this misconception, it should not be surprising that affected patients are so terrified by the misguided fear of a brain-damaging infection that they are willing to undergo extensive and expensive testing and treatment, often at their own expense. Fortunately, the very rare cases of Lyme encephalomyelitis can be

diagnosed quite easily (Ljostad and Mygland, 2009). The key to correct diagnosis is, as always, sound clinical judgement.

## 17.5 The Assertion that Lyme Disease is a Potentially Lethal infection

One of the more curious aspects of *B. burgdorferi* infection is how generally benign it actually is. Although heart block and encephalomyelitis could conceivably be lethal, there are only extraordinarily rare cases suggesting Lyme disease was a factor in a patient's death. Although advocacy groups occasionally cite examples of patients dying from this infection, the objective data contain remarkably little to support this notion. A few case reports suggest that Lyme carditis might have contributed to patients' demise (Marcus *et al.*, 1985; Lamaison, 2007; Tavora *et al.*, 2008). There are probably as many case reports of deaths due to inappropriate treatment (Patel *et al.*, 2000; Holzbauer *et al.*, 2010). A group at the CDC recently reviewed US death certificate data (Kugeler *et al.*, 2011) from 1999 to 2003. The diagnosis of Lyme disease was listed on 119 of the reviewed death certificates from this period. However, among these, only one patient had symptoms consistent with Lyme disease. It is important to understand that diagnoses listed on death certificates include previously made diagnoses, often with no independent review or substantiation, and in reviewing these data the authors did not have access to medical records or any information other than the terminal events. If this one patient actually did die for reasons related to Lyme disease, a comparison with Lyme disease incidence data during the same period would suggest a mortality rate of approximately 1 per 100,000 of the population. Certainly, in any disease with such extraordinarily low suspected mortality, a causal relationship must be highly suspect.

## 17.6 Treatment – The Myth that More (and more and more…) is Better

Numerous studies have now shown that Lyme disease – even in the presence of nervous system infection – can readily be treated with fairly short courses of conventional antibiotics. Well performed studies have repeatedly demonstrated no meaningful or lasting benefit (Klempner *et al.*, 2001; Krupp *et al.*, 2003; Oksi *et al.*, 2007; Fallon *et al.*, 2008) of prolonged courses of treatment. These findings are completely consistent with the known biology of *B. burgdorferi*, as well as the cumulative knowledge of treatment effects with innumerable other bacterial infections. Despite this, the notion of a need for longer-duration treatment continues in some circles.

At least three considerations should be kept in mind. Firstly, as already discussed, many patients being treated for 'chronic Lyme disease' do not have an infection with *B. burgdorferi*, or any other identifiable bacterium. Hence, no amount of antibiotic will cure them.

Secondly, as is the case for many infections, some or all of a patient's symptoms may continue even after the infection has been cured. If a patient has facial nerve palsy, the nerve must still recover from whatever damage it has incurred, even after the precipitating infection has disappeared. An inflamed knee may continue to be painful and swollen, even after the infection has been eradicated. Many patients with significant infections (e.g. bacterial pneumonia) will continue to feel tired and ill for weeks or months after microbiological cure. As symptoms attributed to Lyme disease often do not resolve immediately with treatment and presumed microbiological cure, one can readily understand why patients might feel that the recommended treatment duration is arbitrary and that antibiotic therapy should continue until all symptoms resolve. However, the data for Lyme disease, as in a myriad of other infections, demonstrate that this seemingly logical conclusion is incorrect.

Finally, one very real limitation of our diagnostic technology is that there is no definitive laboratory test that confirms cure of the infection. As the immune response typically remains demonstrable for an extended period of time after successful treatment, there is an understandable desire for another laboratory test to which the

patient can turn as confirmation that the disease is cured. In the absence of such a test, the patient's uncertainty merges with widely perpetuated misinformation leading to a desire for ever more antibiotic treatment.

## 17.7 Continuing non-specific Symptoms – the Myth that Bacteria Must be Lurking Somewhere…

Several theories have been advanced to explain the persistence of subjective symptoms in patients who have resolved their objective evidence of infection (e.g. EM skin lesion) following antibiotic treatment. One is that spirochaetes persist in unidentified tissue sites and thereby cause fatigue and other non-specific symptoms. Theories on the mechanism of persistence include the persistence of *B. burgdorferi* intracellularly. Those who invoke this theory apparently do not appreciate that this microbial strategy would not be protective against the antimicrobial effects of tetracyclines, a class of antibiotics that penetrate well into cells. Thus, a persuasive argument against this theory should be the observation that 8 weeks of doxycycline treatment was no more effective than placebo in two studies of patients with post-Lyme disease syndrome (Klempner *et al.*, 2001). In addition, if this theory were valid, refractory disease and/or persistent symptoms would be anticipated to occur significantly more commonly in β-lactam-treated patients with Lyme disease compared with tetracycline-treated individuals, which has never been demonstrated (Ljostad *et al.*, 2008).

Another theory is that *Borrelia* and other spirochaetes form cysts that insulate them both from the host's immune defenses and from the effects of antibiotic therapy. Interestingly, those who have supported this notion have never defined what exactly is meant by a 'cyst'. What is clear, however, is that under unfavorable *in vitro* growth conditions, spirochaetes may undergo morphological changes and develop a rounded appearance. These rounded forms could be a survival strategy, as they may remain viable for a period of time. In one experiment, *B. burgdorferi* that had been cultured in the absence of serum, a necessary ingredient in growth media, survived for 8 days, although they were no longer viable at 2 weeks (Alban *et al.*, 2000). Even those who reported previously on 'cyst' formation by *Borrelia* have now revised their nomenclature and instead refer to this morphological appearance as 'round bodies', a term apparently intended to encompass and replace prior descriptions such as coccoid bodies, globular bodies, spherical bodies, granules, cysts, L-forms, sphaeroplasts and vesicles (Brorson *et al.*, 2009).

There are at least three fundamental concerns with these theories that persistence of symptoms is due to persistence of borrelial cells. One is that carefully performed microbiological evaluations have failed to find evidence of *B. burgdorferi* infection in treated patients with persistent subjective symptoms, including studies that have focused on occult CNS infection (Klempner, 2002; Kaplan *et al.*, 2003; Krupp *et al.*, 2003; Fallon *et al.*, 2008). The second is that four NIH-sponsored, randomized, placebo-controlled trials of intensive antibiotic retreatment of patients in the USA with persistent symptoms found that additional antibiotic therapy either provided no measurable benefit or a benefit so modest or ambiguous that it was outweighed by the risks associated with the treatment (Klempner *et al.*, 2001; Krupp *et al.*, 2003; Fallon *et al.*, 2008). The third is the absence of a plausible mechanism by which spirochaetal persistence, in the absence of a focus of inflammation or elaboration of a toxin, could cause fatigue and other non-specific symptoms. There is clearly ample precedent for latent infections to be asymptomatic, as illustrated by the persistence of *Mycobacterium tuberculosis* in one-third of the world's population.

## 17.8 The State of the Medical Literature – the Assertion of the Controversy

The group that calls itself ILADS – the International Lyme and Associated Diseases

Society – has published a document it titled 'Evidence-based guidelines for the management of Lyme disease' (Cameron *et al.*, 2004) and repeatedly asserts that there is a wealth of information that is being ignored by the medical establishment. However, a detailed review (Buerden *et al.*, 2010) of the ILADS document demonstrates that it references no Class I, Class II or even Class III evidence that rebuts the conclusions of the IDSA (Wormser *et al.*, 2006) or American Academy of Neurology (Halperin *et al.*, 2007) guidelines. Moreover, the IDSA guideline has now been reviewed in detail by an independent panel, formed by a process and with membership approved in advance by the Connecticut Attorney General. After more than a year spent reviewing *all* the available data, the panel found that the conclusions of the original guideline were completely appropriate and that all relevant information had been considered (Lantos *et al.*, 2010).

Unable to fight facts with facts, advocacy groups have chosen to accuse the guidelines' authors of conflicts of interest, a contention sadly supported by statements by the Connecticut Attorney General in a press conference at the termination of his investigation. What is never mentioned, however, is that the legal document that ended the investigation had no allegations, conclusions or reference to there being any conflicts of interest among the panelists (or of there being any anti-trust violation) (Poretz, 2008) – a conclusion further supported by the findings of the independent guideline review panel.

The concept that the recommendations could be influenced by conflicts of interest is a curious one. Firstly, the conclusions are in agreement with all other guidelines published by respected medical organizations (Halperin *et al.*, 2007; Ljostad and Mygland, 2009; O'Connell, 2009; Mygland *et al.*, 2010; British Infection Association, 2011). Moreover, the guidelines recommend short courses of inexpensive generic antimicrobials and testing approaches that are widely available from multiple commercial sources. The guideline contained no mention of vaccines. Consequently, following the guidelines' recommendations could in no way enrich any of the authors. (In contrast, the authors of the ILADS guideline included a principal in a company that markets Lyme disease diagnostic testing favored by LLMDs, as well as practitioners who derive substantial clinical practice revenue from providing the care recommended in their guideline – none of which was mentioned in that document.) Some have suggested that the IDSA guideline might serve to advance the authors' academic careers, but most of the authors have already achieved senior academic rank. For them, working on this guideline constituted a tremendous amount of work with the only reward being the anticipated reaction from patient advocacy groups and LLMDs. In summary, there was nothing in the guideline that could lead to personal profit for any of the authors.

It is clear that, despite focusing their rage and indignation on the authors of the various guidelines, the advocacy groups' real fight is with the notion of evidence-based medicine. The ILADS guideline demonstrates a remarkable lack of understanding of this process. Included statements consistently refer primarily to the authors' personal anecdotal observations. Many outside ILADS would welcome a rigorous, scientific study of the issues they raise. If a fraction of the time, money and energy that has been spent on inappropriate care and advocacy had instead been invested in scientific studies to understand better the pathophysiology of the disorder they refer to as 'chronic Lyme disease', we would probably all be in a much better position to help the unfortunate individuals whose lives have been severely disrupted by this symptom complex.

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