Commentary: A Patient Looks at Lyme Disease and Guidelines

Over eight thousand Pub Med entries on Lyme disease have been posted, covering more than three decades since a spirochete, *Borrelia burgdorferi* (*Bb*), was recognized as the cause of a strange arthritic illness affecting citizens of Lyme, Old Lyme and East Haddam, Connecticut. Lyme disease incidence has steadily risen,[1] though actual incidence is not known. The Centers for Disease Control and Prevention (CDC) estimates Lyme disease cases are under-reported by factors of 6 to 12.[2] [3] In Lyme-endemic areas such as Wisconsin, high factors would be used to estimate annual incidence. Wisconsin reported 1,948 confirmed cases and 636 possible cases in 2009 for a total of 2,584, an incidence rate of 34.5 per hundred thousand residents.[4]

Lyme Disease *Guidelines*

Limits on the length of time antibiotics should be prescribed to treat Lyme disease have been adopted from clinical practice guidelines by medical insurance companies, making "covered" access to antibiotics problematic in cases where longer than standard treatment for Lyme disease might be required. Physicians dependent on third party payors may feel pressure to adhere to the treatment parameters set forth in the *Guidelines* from the Infectious Diseases Society of America,[5] even when individual patients could benefit from longer treatment. How these *Guidelines* reflect available scientific evidence to determine patient care should concern physicians, especially with Lyme disease incidence rising.

Lyme Disease Then

When 2000 and 2006 *Guidelines* author Dr. Alan Steere and other researchers from Yale University began studying oddly-affected arthritic Connecticut residents in the 1970s, reports of

US Navy Drs. Mast and Burrows in Groton, Connecticut, who had successfully treated patients presenting with red bull's-eye-like rashes, came to their attention. The Navy doctors reported that the majority of patients displaying these rashes did not develop arthritis after they gave them antibiotics, but the Yale doctors were not convinced antibiotics were the answer. In 1977 Dr. Steere and colleagues wrote, "We remain skeptical that antibiotic therapy helps."[6] From their standpoint a significant percentage of patients treated with short courses of various antibiotics went on to have neurological, musculoskeletal, and cardiac complications.[6] For one summer of their early investigations Steere and his coworkers did not treat patients with antibiotics. At that time, they did not know the causative agent of the illness they were seeing was a spirochetal bacterium.

Dr. Steere's work in Connecticut revealed the relapsing remitting nature of the odd illness. For some people infected in those early years rashes went away without antibiotics or bouts of arthritis lessened in severity with each recurrence until they disappeared completely.[7] To explain the variability of Lyme disease infection Dr. John Halperin, a *Guidelines* author, would later write, "Disease variability among patients probably is the result of multiple factors, including bacterial strain differences in virulence and organotropism, inoculum size, host immunity, and simultaneous co-infection with other tick-borne organisms." [8]

Lyme Disease Now

Without actual incidence available to physicians, many of them believe Lyme disease isn't a problem in their area, though birds have been noted as transport, [9] and, over the last ten years, the infection has been reported in forty-nine states.[10] By underestimating prevalence, physicians may rule out rule out a burgeoning cause of patient morbidity.

Lyme disease can be difficult to diagnose because physicians do not know or recognize all manifestations of the illness. Signs and symptoms vary from person to person; both objective signs and subjective symptoms may wax and wane; and preexisting conditions or newly developed syndromes may be hard to separate from the disease process itself. The *Erythema migrans* (*EM*) rash associated with Lyme disease may be well-known by physicians, but other associated presentations including carpal tunnel syndrome,[11] temporal mandibular joint syndrome (TMJ),[12] or Parsonage-Turner syndrome (acute brachial neuritis or neuralgic amyotrophy)[13] would rarely be recognized as symptoms of borreliosis. Although establishing causation is always an issue, carpal tunnel syndrome was found in 25% of patients with late-stage Lyme disease; TMJ, though far more rare, was the most aggravating arthralgia experienced by two patients with confirmed Lyme disease; and Parsonage-Turner syndrome was reported as the first manifestation of Lyme disease in four patients. More serious physical manifestations can and do occur. Physicians would rarely expect carditis,[14] paralysis and seizures[15] in children to have Lyme disease etiology and would undoubtedly initially try to rule out other causes.

Neuroborreliosis/Neurological Lyme Disease

Cortical neuronal and neuroglial cell invasion by *Borrelia burgdorferi*,[16] hypoperfusion,[17] cerebral vasculitis,[18] and low metabolic brain function[19] can occur in Lyme disease. These findings have been observed with confocal microscopy,[16] SPECT,[17] biopsy,[18] and PET.[19] Although the exact pathophysiology is not yet understood, changes in the cerebral landscape from the presence of *Borrelia burgdorferi* [20] [21] [22] [23]are believed to contribute to the mental aberrations of some patients with neuroborreliosis, much like the contribution of *Treponema pallidum* to neuropsychiatric presentations in tertiary syphilis.[24]

Schizophrenia,[25]dementia,[26] panic attacks,[27] anorexia nervosa,[28] obsessive-compulsive disorder,[29] bipolar disorder,[29] and paranoia[29] have been associated with brain-invasive *Borrelia burgdorferi*. For some patients these disorders resolve with extended or additional antibiotic therapy,[30] without the use of anti-psychotics, anti-anxiety medications, or SSRIs, which would suggest *Borrelia burgdorferi* can be the etiologic agent of at least some psychiatric disorders. [31] [32]

Depression is most frequently observed in those who have persistent *Bb* infection. After reviewing available medical literature, Dr. Brian Fallon, director of Columbia University's Lyme Disease Research Center, wrote, "Depressive states among patients with late Lyme disease are fairly common, ranging across studies from 26% to 66%."[29] Certainly anyone with chronic illness would be susceptible to depression, so the possible causal link between Lyme disease and depression has been scrutinized. When patients with fibromyalgia or depression were compared to patients with Lyme disease encephalopathy, defined by the study's researchers as "primarily manifested by disturbances in memory, mood, and sleep," the Lyme patients' difficulties were determined to be due to central nervous system dysfunction and could not be "explained as psychological response to chronic illness."[33]

Lyme Disease Controversy

Ever since Lyme disease got its name in the 1970s, controversy has centered on whether or not Lyme disease patients have persistent infection,[34] post-Lyme sequelae,[35] permanent damage from the infection,[36] auto-immune disorders as the result of past infection,[37] [38] mental illness,[39] [40]or fear and anxiety over the illness.[41] [42] To insist that Lyme disease doesn't persist is in vogue now,

though several researchers who are IDSA 2006 *Guidelines* authors have at one time or another noted what they believed to be persistent or chronic Lyme disease in patients.[43] [44] [45] [46] [47] [48]

Borrelia burgdorferi penetrates endothelial cells[49] and leaves the bloodstream to take up residence in joints,[50] myocardial tissues,[51] nervous tissues,[52] and the brain.[53] The migration of spirochetes to the central nervous system may be rapid.[54] [55] Through intracellular localization,[56] macrophage invasion,[57] cyst formation,[58]and the ability to downregulate outer surface proteins and use complement-neutralizing proteins to induce the formation of immune complexes,[59] *Bb* can escape serological and immune system detection and resist antibiotics. Evidence of persistent infection in tissues following antibiotic therapy has been found through culture,[60] direct microscopic examination,[61] and PCR analysis.[62] [63]

The progressive nature of Lyme disease was noted by Dr. Steere and his colleagues,[64] even though today they discount the progressive spiral of often debilitating symptoms patients may endure as evidence of chronic or persistent infection. Emphasizing the *Guidelines* position on chronic Lyme disease the authors wrote, "There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease."[5] By any standard, early research beliefs that antibiotics were not curative and today's IDSA position that Lyme disease does not exist in antibiotic-treated patients are impossible to reconcile. No official reconciliation of past and present data on Lyme disease has been issued.

<u>What Do the *Guidelines* Recommend?</u>

Treatment for Tick Bites

For patients who reach their doctor's office within 72 hours of an *Ixodes scapularis* tick bite, the 2006 *Guidelines* recommend physicians prescribe a single 200 mg dose of doxycycline if the bite occurred in a Lyme disease endemic area and if there was evidence of tick engorgement. This prescription is based on a study by Drs. Nadelman, Fish, and Wormser (all *Guidelines* authors) et al which showed that an *EM* rash developed in only one of 235 subjects treated with doxycycline compared to eight of 247 subjects in the placebo arm.[65] Seven of the nine subjects who developed *EM* showed serologic evidence of *Bb* infection with positive ELISA results; four of four who had skin biopsies were positive; and one subject in the doxycycline arm who developed an *EM* was negative on ELISA but had positive IgM antibodies on immunoblot by CDC criteria.[66] The remaining subject who developed an *EM* was equivocal on ELISA and negative for IgM and IgG antibodies on immunoblot, but did not return for blood tests later in the study period. There was no evidence of seroconversion of asymptomatic individuals in the placebo or doxycycline group.

Nadelman et al findings should be considered carefully before choosing or accepting the single-dose doxycycline protocol for tick bites. Research has demonstrated that early antibiotic intervention to halt Lyme disease infection may preclude the development of antibodies.[67] For this reason Nadelman et al may not have detected antibodies in treated study participants who were indeed infected but did not have an *EM* rash. In other words, doxycycline may have prevented antibodies from developing, without eliminating infection that could have become evident based on clinical manifestations after the six week follow up period, yet Nadelman et al discount this possibility.[68] [69] [70]

Lyme Disease Rash

In 1970, preceding Dr. Steere's Connecticut investigations by half a decade, Dr. Rudolph Scrimenti reported that his patient, a Wisconsin grouse hunter, developed an *Erythema migrans* rash after a tick bite. Forty years later this characteristic rash of Lyme disease is still being missed in diagnoses. A 2009 Johns Hopkins study revealed 23% of patients who had an *EM* were not diagnosed correctly.[71] The rash is not so distinctive that it cannot be mistaken, especially if there is no clear history of tick attachment or engorgement. Lyme disease rashes vary in size, shape, and some may have necrotic or vesicular centers,[72] so reliance on a rash with a clearing center to diagnose Lyme disease infection is inappropriate. In a vaccine trial 59% of the identified *EM* rashes had homogenous erythema while only 9% demonstrated central clearing (i.e., the bull's-eye rash).[73]

When Stony Brook University researchers headed by Dr. Benjamin Luft studied twenty strains of *Borrelia burgdorferi*, they found ten strains produced only an *EM* rash and there was no evidence of invasive disease.[74] In light of the Stony Brook findings, the effectiveness of tick bite prophylaxis from Nadelman et al should be reconsidered. These two studies illustrate how clinical practice guidelines may lack external validity or pertinence to the individual patient. Yale University's Dr. Harold Krumholz cautions,

"The evidence on which we base practice guidelines . . . is almost always imperfectly suited for direct translation into practice settings. Because clinical decisions in practice must go far beyond evidence, guideline authors almost always rely on expert opinion to provide useful advice. Even when evidence from randomized trials is available, study samples and settings are often narrowly defined, which raises questions about their relevance to typical clinical practice."[75]

Early-Late Lyme Disease

Guidelines authors designated doxycycline, amoxicillin, and cefuroxime axetil as first-line agents for Lyme disease, reserving intravenous ceftriaxone for joint or neurologic infections. Three to four weeks of antibiotic therapy is the *Guidelines* treatment standard, regardless of patient-specific factors such as duration of illness. For patients with arthritis, the *Guidelines* suggest physicians may prescribe another three to four weeks of antibiotics if the initial course did not clear the infection. Further re-treatment is not recommended.

Physicians willing to offer additional antibiotic therapy to those who remain ill after standard therapeutic regimens for Lyme disease have been employed are constrained by the *Guidelines* admonishment, "Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) subjective symptoms." Although infections disease treatment should be directed by the resolution of signs and symptoms, the *Guidelines* take the position that subjective symptoms lasting more than six months following what is deemed to be adequate treatment cannot be causally related to Lyme disease. This position and corresponding prohibition against further treatment should be disconcerting to physicians who know other infectious diseases such as hepatitis and tuberculosis require lengthy antimicrobial regimens and that one-size-fits-all guidelines cannot cover every patient seen in clinical practice; patients must be assessed individually.[76]

Failing Standard Lyme Disease Treatment

A physician encountering a patient who doesn't respond to "standard Lyme disease treatment" may look for alternative interventions via guidelines, even though few treatment options are listed in the current *Guidelines*. Antibiotics commonly prescribed for bacterial infections,

innovative or off-label treatment protocols, and additional alternative interventions for Lyme disease are targeted in the *Guidelines* section "Therapeutic modalities not recommended." The zoonosis vying for prevalence among infected ticks, *Bartonella henselae*,[77] is also included in this section:

"Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are *not* recommended for treatment of patients with any manifestation of Lyme disease: first-generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-*Bartonella* therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others."[5]

Refuting the entire list of therapies not recommended by *Guidelines* authors would require a lengthy document, but singling out one potentially effective proposed intervention highlights how guidelines may circumscribe innovation in medicine: Evidence for the advantageous use of intravenous immunoglobulin (IVIG) for Lyme disease patients, specifically those who suffer from neuroborreliosis, was presented to the American Academy of Neurology (AAN) last year. Dr. Amiram Katz of Orange, Connecticut told AAN members that thirty Lyme disease patients who were given IVIG (2g/kg per month) for at least six months had improvement of their neurological examination with respect to sensation, Achilles reflex, and Romberg tests. Physicians would naturally assume all interventions "not recommended" have been studied repeatedly and sufficient evidence to discount their efficacy in Lyme disease has been produced, though that would be incorrect.[78]

Lyme Disease Tests

To compound the difficulty of diagnosing Lyme disease, screening tests are notoriously poor indicators of the infection.[79] [80] In fact, an October 2005 study from Johns Hopkins found commercial tests may miss 75% of Lyme disease infections.[81] To reach that conclusion, the two-year long study used culture, two-tier serology (ELISA or VIDAS assays followed by Western Blotting), and PCR analysis. To achieve 100% diagnostic accuracy all three test methods had to be combined. Culturing *Borrelia burgdorferi* is a three-week process unavailable to the average physician; PCR testing results were deemed poor by the study group; and the CDC-recommended two-tier serologic testing based on antibodies was accurate in just 18% of the samples tested.

Direct detection tests would aid Lyme disease diagnosis. Currently-used tests rely on indirect evidence□antibodies□and the assumption that the body's immune system unfailingly produces them in response to invading *Bb*. The timing of these antibody tests can be critical for accurate results. For example, many physicians test patients who present with an *EM* rash not knowing that a number of patients won't test positive at that time; rash is considered an early sign of Lyme disease, often there has been insufficient time for a humoral response to develop.[82] Another important testing caveat mentioned previously: early antibiotic intervention for Lyme disease can abrogate the body's antibody production against *Bb*.[83] In short, some patients who fail the antibiotic therapy prescribed early in the course of their infection may not test positive later. Seronegative Lyme disease has been recognized since 1988,[44] and others have reported seronegative patients with persistent infection.[84]

In addition to these diagnostic challenges, physicians are handicapped by tests missing important

serological information. Two *Borrelia burgdorferi*-specific Western Blot test bands, 31 and 34, are not reported by common laboratories. These bands mark two outer surface proteins (OspA and OspB) of the Lyme bacterium, which are upregulated in late disease while other bands are downregulated. By discounting bands 31 and 34 we reduce the chance that late-stage patients will test positive.[85] Without positive test results patients may not receive additional and appropriate treatment, even though commercially-available common serology tests are insufficiently sensitive to rule out Lyme disease. No "gold standard" test exists.

Lyme Disease Reporting Criteria

For the CDC to confirm Lyme disease infection each case must have specific signs of the illness: an *EM* rash, Bell's palsy, visibly swollen joints, Lymphocytic meningitis, radiculoneuropathy, 2nd or 3rd degree atrioventricular block, or encephalomyelitis confirmed with higher numbers of Lyme antibodies in CSF than in sera. Additional serologic confirmation is also required: patients must have a positive ELISA or IFA followed by a positive Western Blot. Unfortunately, most physicians do not know that CDC requirements for positive Lyme disease Western Blots were set in place for CDC surveillance purposes *only* and were not meant to be diagnostic. Misunderstanding CDC Lyme disease case specifics□signs of the illness and test interpretation─has been so pervasive that early in the new millennium a congressional committee issued this directive:

"The Committee is distressed in hearing of the widespread misuse of the current Lyme disease surveillance case definition. While the CDC does state that this ['] surveillance case definition was developed for national reporting of Lyme disease: it is NOT appropriate for clinical diagnosis,' the definition is reportedly misused as a standard of care for healthcare reimbursement, product (test) development, medical licensing hearings, and other legal cases. The CDC is encouraged to aggressively pursue and correct the misuse of this definition. This includes issuing an alert to the public and physicians, as well as actively issuing letters to places misusing this definition."[86]

The CDC did not comply with the congressional committee's recommendations unless one sentence found on the CDC's Division of Vector-Borne Disease webpage "Lyme disease reporting," under the heading "2008 Case Definition" and above the heading "Clinical presentation," serves as sufficient physician notification.[87]

Influence and Opposition in Guidelines

Due to the prevailing influence of the Infectious Diseases Society of America's 8,600 members, only their own clinical practice guidelines for the treatment of Lyme disease reach most physicians. A link to the 2006 IDSA *Guidelines* can be found on the CDC's Vector-Borne Infectious Disease website. Another set of clinical practice guidelines from the International Lyme and Associated Diseases Society (ILADS) used to be available, along with the IDSA *Guidelines*, at the National Guidelines Clearinghouse, but the ILADS guidelines have been withdrawn. Nevertheless, ILADS guidelines for the treatment of Lyme disease may still be viewed at www.ilads.org.

In contrast to the IDSA position that Lyme disease is cured with, at most, two months of antibiotic therapy, ILADS physician members believe Lyme disease can be difficult to diagnose and that persistent forms of the illness require longer treatment.

Borrelia burgdorferi reproduces slowly in the body; spirochetes divide approximately once every twenty-four hours.[88] Since antibiotics work most effectively on replicating bacteria, those that replicate slowly, like *Borrelia*, require antibiotics for a lengthier time period, unlike bacteria that cause Strep throat, which replicates every twenty minutes and is customarily treated with seven to ten days of antibiotics. With these time frames in mind, physicians and patients may

wonder why the standard of care for slow-replicating *Borrelia burgdorferi* would often be the same or less than that of a common Streptococcal infection.

Divergent standards of care and opinion should be considered during the guidelines creation process because various guidelines committees have reviewed the same evidence and reached entirely different conclusions; yet, in a commentary on guidelines reform Drs. Allan Sniderman and Curt Furberg note such considerations are rare.[89] In some areas of medicine expert opinion may stand in for the evidence normally reviewed by guidelines committees,[75] consequently, evidence-based guidelines (EBGs) may not be based on sound science.[90] Sniderman and Furberg contend expert opinion may play a heavy hand in guidelines recommendations "Because gaps in evidence are inevitable, they must be filled with judgments, and judgments tend to preserve previous positions. Thus what has been decided is often already decided by the deciders." ILADS physicians have asked on numerous occasions to serve on IDSA Lyme disease guidelines panels; their requests have been denied.

Legislating Lyme Disease

Physicians have had their medical licenses restricted, revoked, or been forced into retirement for treating Lyme disease with longer than standard therapeutic regimens.[91] [92] [93] In response to the arbitrary actions of state medical boards, patients have been working with elected officials to safeguard access to Lyme-treating physicians. Rhode Island, Massachusetts, and Connecticut achieved physician protection through legislation.

The Connecticut legislation recognizes Lyme disease should be a clinical diagnosis because tests cannot always confirm the infection. It prohibits the Connecticut State Medical Examining Board

from persecuting physicians who make a clinical diagnosis of Lyme disease in the absence of positive tests and/or treat these patients with longer than standard courses of antibiotics.

Minnesota appeared poised to follow these states' legislative achievements; however, in March of this year a compromise was reached between the Minnesota Board of Medical Practice, interested parties, and state legislators who had introduced a "doctor protection bill." To avoid Lyme disease legislation that would direct Board of Medical Practice actions, the Board chose to post a resolution on its website, acknowledging that the science of Lyme disease is "unsettled." For this reason, the " . . . Board will engage in a moratorium for a time period not to exceed five years, on the investigation, disciplining, or issuance of Corrective Action Agreements based solely on long term prescription or administration of antibiotic therapy for 'chronic lyme disease' . . . "[94]

Those infected with *Borrelia burgdorferi* cannot always find adequate care where they live; they may travel hours or days to see Lyme disease specialists. Wisconsin patients with late-stage disease often seek treatment in other states. Governor Jim Doyle, in his 2008 Lyme disease proclamation, recognized the paucity of Wisconsin physicians willing to make a clinical diagnosis of the illness, and to treat, and re-treat patients.[95]

Lyme Disease Treatment Studies

Because antibiotics can suppress but not eradicate *Bb* infections,[96 97 98 99] Lyme disease patients may relapse after treatment,[100] though providing lengthier antibiotic therapy is not a panacea. In his "Diagnostic Hints and Treatment Guidelines" Dr. Joseph Burrascano points out, "We have to

recognize that in some patients, Lyme Borreliosis may not be curable in a strict bacteriologic sense, and open-ended, ongoing suppressive antibiotic therapy may be necessary."[101]

Lyme disease treatment studies seem to bolster Dr. Burrascano's beliefs. Published studies have found both no effect[102] and beneficial effect from antibiotic therapy.[103] [104] [105] Retrospective studies have shown that the longer patients are followed after completing short-term antibiotic therapy, the higher the rate of failure.[106] [107] [108] Nonetheless, in an uncontrolled study of 277 patients by former 2006 *Guidelines* panelist Dr. Sam Donta, the longer patients were treated, the greater their improvement.[109]

More Lyme disease treatment studies are needed, although external validity will continue to be an issue; the infected population is heterogeneous, affected, as Dr. Halperin noted, by complex confounding factors in addition to coinfection with other tick-borne diseases,[8] which must be recognized before effective care can be delivered. Norman Latov, MD, PhD says medical decision making should automatically encompass complex confounding factors and that ". . . strict EBGs allow neither common sense nor clinical judgment."[110] Dr. Latov concludes evidence-based guidelines have effectively ". . . created uncertainty and mistrust, undermining patient confidence in physicians and our medical system."

Lyme Disease and *Guidelines* Conclusions

Lyme disease is more common and more complicated than in the past. Infection caused by two strains of the Lyme bacterium have been found in the same person[111] and, even though some strains of *Borrelia burgdorferi* did not appear to produce invasive infection in Stony Brook

studies, Bartonella,[112] Babesia,[113] and Ehrlichia/Anaplasma[114] can accompany the bacterium, altering the diagnostic picture. In Lyme disease-endemic areas like Wisconsin, twenty-eight to thirty per cent of ticks may carry one or more of these additional pathogens.[115] Tick transmission of Lyme disease and coinfections notably increases morbidity.[116] [117] [118] The Ehrlichial bacterium, Anaplasma, prevalent in Wisconsin,[119] was determined by researchers at Johns Hopkins to "enhance reductions in transendothelial electrical resistance" to help *Bb* enter the brain.[120]

While most patients respond to short-term treatment for Lyme disease or Anaplasmosis, unknown numbers of patients are coinfected and may not respond readily to standard therapy. Babesiosis, indigenous to Wisconsin[113]and the most common Lyme disease co-infection,[121] is treated with antibiotics and antimalarials. In severe cases, Babesiosis may require exchange transfusion.[122] As coinfections proliferate[123] [124] and Lyme disease continues to rise[10] more patients are bound to fail treatment. Twenty-one reports of death from Lyme disease have been presented.[125] [126] [127]

Haplessly, Lyme disease is believed by many to be an acute illness only. Perceiving Lyme disease as a progressive systemic illness, like Dr. Steere and his colleagues did in the past, may provide a more accurate and realistic view of the spectrum of infection. Physicians need to recognize the potential seriousness of Lyme disease infection, and that persistent symptoms, though subjective and easily dismissed, may be due to persistent disease. Symptoms can come on slowly and be disregarded by patients and their physicians, and seemingly unrelated disorders in disparate body systems may not be aggregated by physician or patient, thus, *Borrelia burgdorferi*, the unifying etiological agent of patient morbidity, can be overlooked.

For thirty-four hundred patients who participated in a chronic Lyme encephalopathy study a mean time of 1.2 years passed between the onset of their symptoms and treatment.[128] Delayed treatment has consequences. Fifteen to twenty per cent of patients ill for more than one year failed longer-than-standard and higher-than-standard dose antibiotic treatment regimens in the mid to late 1980s; nevertheless, in this same patient population additional antibiotic therapy delivered better outcomes for eighty to eighty-five percent of the patients treated by the Stony Brook Lyme disease clinic.[129]

Lyme disease is under-recognized and under-reported. Laboratory tests for Lyme disease have poor sensitivity, clinical diagnosis can be difficult, and physicians have been subjected to adverse actions by medical boards and insurers for deviating from "standard treatment protocols." In an editorial on practice guidelines, Canada's Dr. van Walraven contends,

". . . valid reasons might explain the dissonance between physician behavior and guideline recommendations . . . compliance with guidelines does not necessarily translate into appropriate patient care. This requires both a valid guideline and a patient to whom the application of the guideline is appropriate."[130]

The benefit of antibiotic intervention to prevent or mitigate serious complications and preserve quality of life seems reasonable, although what can be done to preserve physician autonomy and accommodate those whose Lyme disease symptoms persist after treatment remains to be seen. The outcome of a lengthy review of the controversial 2006 *Guidelines* simply preserved the status quo□no changes were made. On stasis in medicine David Kocurek, Ph.D. argues:

"When keepers of medical knowledge reject change and new understanding, stagnation and dogma follows. When that dogma persists for its own sake, to protect reputation, or worse, only to sustain tradition or financial interests, it then becomes dangerous and sets up the high probability for sub-standard patient care."[131]

To reduce the potential for inadequate care and assist successful outcomes, physicians need greater knowledge of insidious, intransigent *Borrelia burgdorferi*. Without definitive tests, a definitive cure can not be known. Therefore, while medicine unravels the intricacies of Lyme disease and the coinfections that may accompany it, physicians must have flexibility to treat patients to the best of their ability. As long as controversy over Lyme disease treatment continues, physicians should be guided by nothing more, and nothing less, than their patient's response to intervention and the principles of informed consent, especially when standard treatment fails.[132]

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