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Guest Editorial

B. burgdorferi—Seek and Ye Shall Find Expanding the Envelope

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The borreliae, present on this earth for eons, evolved alongside mammalian life forms in a host-parasite relationship, no doubt long before the appearance of humankind. It should not surprise us, then, that we have much to learn about the range of diseases that the borreliae may underlie and the true scope of infection of the human inhabitants of this planet.

We are at the threshold of a new and exciting era in the understanding and conquest of Lyme borreliosis. Direct antigen detection methods may strike a discordant note with antibody testing's "perfect music of the Spheres," but when clinically validated and honed to optimal sensitivity and specificity, these will be powerful tools in the exploration of the pathogenesis and clinical manifestations of borrelial disease. Researchers as well as rank and file physicians will be able to diagnose with confidence and will have measurable indices of disease activity as these tests begin to become commercially available.

However, with these advances, we will begin to perceive just how daunting an adversary the borreliae really are and how commonly affected the populace of endemic regions. It is my prediction that a much wider range of human disease, now only hinted at, and maybe even totally unanticipated, will eventually be linked to borrelial infection in humans. The borreliae are resilient, phoenixlike. Cutting-edge direct antigen detection methods will corroborate the conclusions already quite apparent from the relatively few reports of culture isolation of borreliae from human subjects following antibiotic treatment now in the worldwide peer-reviewed literature (1–5). The rarity of such isolations should not lead to the conclusion that this phenomenon is rare but only that this has been difficult to prove conclusively with methods available until recently. Nocton et. al. (6) demonstrated polymerase chain reaction (PCR) positivity in serial synovial fluids of 100% of patients treated with conventional oral antibiotics and in 37% of those treated with longer oral and/or intravenous antibiotic regimens. The authors opined that the presence of Bb-DNA implied viable organisms. Bradley et. al. (7) had similar findings and conclusions in their study of serial synovial fluids using Bb-specific DNA detection. Borreliae are, however, tissue tropic and the absence of detection of Bb-specific DNA in body fluids does not exclude their presence in interstitial, intracellular, and parenchymal sites. The Rocky Mountain Laboratory antigen capture method, because it depends on the direct detection of the myriad blebs shed by each living borrelial spirochete, promises to have a far higher yield in tissues and fluids than DNA detection relying on genomic or even of multitarget probes (8, 9). Systematic application of direct antigen detection methods to suspect populations will reveal the true extent of the disease and define the ratio of seropositive to seronegative cases. Seronegativity may be due to T cell anergy and not only as a result of early application of antibiotic therapy (10). Claims that seronegative Lyme disease is rare or that it is common are currently unverifiable.

A tissue repository should be established for tissues from humans suspected of borrelial disease, including autopsy materials, for in depth study using all currently available classic histologic as well as cutting-edge research methods. The pathologist is, after all is said and done, the final arbiter of truth in clinical matters (11–13).

With recognition of chronic persistent infection, we will begin to look at disease pathogenesis quite differently. A persisting pathogen may induce noxious injury over not just days, weeks, or months, but years and decades, and even the natural life of the host. Slowly simmering infection can induce a wide variety of host responses, both direct and immune-mediated. The treatment approach may need to be very different in this circumstance than for a readily extirpated bacterium such as staphylococcus or streptococcus (14–17). Chronic infection may require chronic treatment. Definitive cure, while theoretically possible, may not be achieved using currently available methods in chronically infected patients. This dilemma should prompt a determined effort to develop definitive means of curing the infection (18, 19).

A focus on problems associated with prolonged antibiotic therapy (20) has diverted attention from the much more ominous and insidious spread of borrelial disease in the general population. This vast *de facto* and unintended "Tuskegee" experiment of nature has far greater long-term societal impact in terms of personal suffering, economic loss (21), disability, and death (13, 22) than complications of intensive treatment for a serious disease that are, to some degree, unavoidable.

Often, sequelae of borrelial disease are treated as independent disease entities without being traced back to the inciting etiology. For example, Goodman and colleagues found an incidence of seropositivity for *Borrelia burgdorferi* four times higher amongst patients awaiting cardiac transplantation for chronic congestive cardiomyopathy compared to a control population (23). Yet, this very costly and debilitating illness and the fabulously expensive cardiac transplantation and its aftermath is not counted in the economic impact of Lyme disease. Dementing diseases are amongst society's costliest illnesses. What percentage of patients requiring placement in long-term care facilities for organic brain syndromes really represent unrecognized and untreated end-stage chronic neuroborreliosis (24)? This question deserves to be answered.

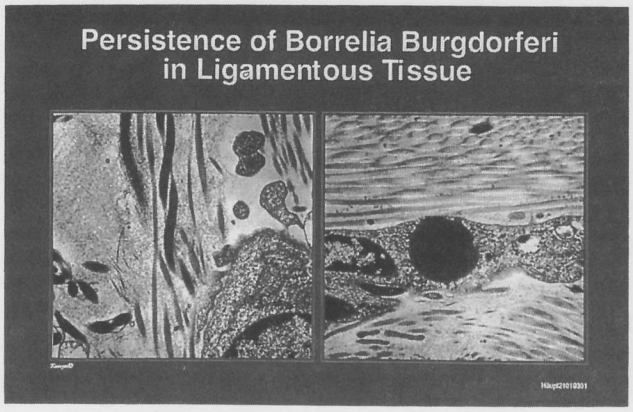

FIG. 1. Persistence of *B. burgdorferi* in the ligamentous tissue. (Reprinted with permission from *Arthritis and Rheumatism*.)

Lyme disease should be included in the differential diagnosis of a wide range of neurologic syndromes. The National Neurologic Research Bank holding tissues for various neurologic diseases including multiple sclerosis, Alzheimer's disease, and motor neurone disease should begin to be systematically evaluated for evidence of borrelial etiology and pathogenesis using the newer direct antigen detection methods (25). Theoretic conceptualizations already developed for other "slow" infections of the central nervous system (CNS) may find application in borrelial disease of the CNS (26). In depth evaluation of some patients previously thought to have multiple sclerosis has uncovered significant evidence of CNS and/or systemic borrelial infection and good response to *intensive* antibiotic treatment (27, 28).

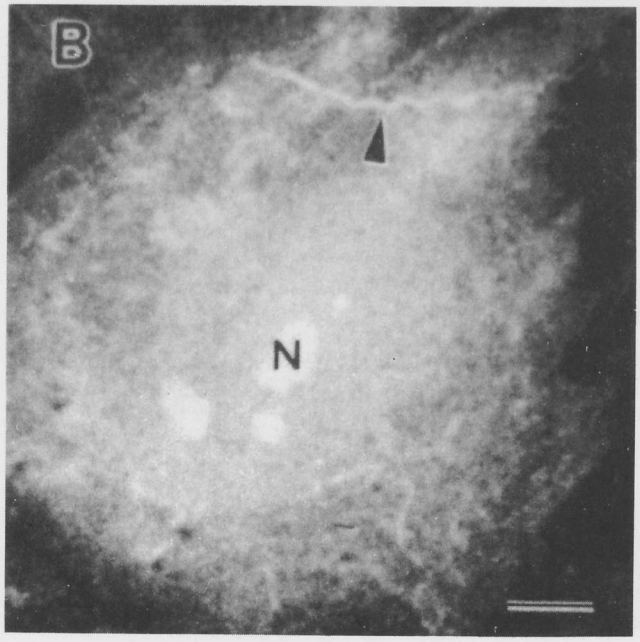

FIG. 2B. Representative confocal microscopic image of optically sectioned fibroblast cocultured with *B. burgdorferi* for 24 hours. Serial section 2.4 m below cell surface shows clear intact spirochete adjacent to perinuclear region of fibroblast. Typical periodicity of spiral shape of *B. burgdorferi* is apparent. Nucleus, nucleoli (N), and mitochondria are visible. (Reprinted with permission from *Journal of Infectious Diseases*.)

The role of borrelial infection also needs to be systematically studied using modern methods in psychiatric syndromes (29) (including derangements leading to domestic violence, suicide, and homicide), attention deficit disorder, various arthritides, "idiopathic" or "autoimmune" diseases, chronic fatigue syndrome, and fibromyalgia. Stunning electron photomicrographs of Haupl and colleagues demonstrate Lyme spirochetes nestled parallel to collagen fibers from synovial tissue removed from a patient previously intensively treated for Lyme disease (3) (see Fig. 1). Klempner and colleagues' beautiful confocal photomicrographs conclusively prove intracellular localization of borreliae within human fibroblasts (30) (see Fig. 2). Is it not likely then, that Lyme disease-associated fibromyalgia with pain localized to fibroblast-produced collagen-rich fasciae and entheses may not be due to the persistence of living borreliae? Although their conclusions were otherwise, the data of Dinerman and Steere clearly demonstrated antibiotic responsiveness of symptoms in their series of patients with Lyme disease-associated fibromyalgia (31).

While the reality and extent of chronic persistent infection needs to be more widely recognized, it also must be acknowledged that there may be self-perpetuating immune-mediated mechanisms of injury that may coexist with active infection or be operative following eradication of the pathogen. For the latter circumstance, antibiotic treatment of a prolonged nature would be futile. Sorting out which cases are due to chronic persistent infection and which are not will be a major achievement of direct antigen detection methods. Creative immune-modulating interventions may prove more effective in inducing remission and averting ongoing injury than antibiotic treatment for this subset of patients, or these may have a combined role with antibiotic therapy in patients having active infection (32).

We should be humble before this disease. Until there is general agreement on a "gold standard" for diagnosis of active Lyme disease, presently available standard and research assays must be viewed as approximations of the truth only (33). Likewise, limits placed on the geographic range of the infection must be greeted with extreme skepticism, as success in documenting the nearly ubiquitous borreliae in a given natural setting depends largely on the determination and experience of the investigator.

At the present time, there exists no substitute for the clinical judgement of an experienced treating physician knowledgeable about the manifold presentations of the disease, adept in listening to the patient and in observing, as in other natural phenomena, the interaction of host and pathogen. Skillful application of antibiotics continues to be the mainstay of treatment for what is, first and foremost, an infectious disease.

Science is all about measuring things. Once objective measures of disease activity are widely available, rational approaches to treatment will replace those based on convention or blind obedience to authority, and the medical neglect now so frequent in chronic Lyme borreliosis will take its well-deserved place in the history of medicine, and not in modern practice.

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