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GUEST COMMENTARY

Lyme Disease: the Sensible Pursuit of Answers

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Disease is very old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible.

—John Martin Charcot, *De l'Expectation en Médecine*

In 1989, Preac-Mursic et al. published a landmark article (30) documenting recovery by culture of living *Borrelia burgdorferi* from patients who had been previously treated with regimens believed to cure the disease. Included was one patient who had been treated with 10 days of intravenous ceftriaxone and from whose spinal fluid the organism was grown following treatment (30). This report was greeted with skepticism and disbelief from some quarters, with suggestions that the cultures must have been contaminated or that the report was otherwise erroneous. Since then there have been a number of corroborating reports confirming survival of *B. burgdorferi* in humans despite aggressive antibiotic treatment, including the use of the best available intravenous antibiotics (12, 22). These apparently anomalous observations, which reveal the deficiencies of the existing paradigm for Lyme disease, have been very hard for the medical community to reconcile, and they presage a revolution in our conceptualization of this disease (15). Such a shift will be necessary to deal effectively with the biologic realities of *B. burgdorferi* infection (1).

Emerging scientific research is beginning to clarify how it is possible for a bacterial infection to resist eradication by the powerful antibiotics employed against it. Montgomery et al. reported on the intracellular localization of *B. burgdorferi* within macrophages and the recovery of spirochetes in culture from these cells (29). Klempner, Georgilis, and coworkers demonstrated very convincingly that *B. burgdorferi* can adopt an intracellular location within fibroblasts and that the organism can be grown from such cells in vitro after treatment of the tissue cultures with ceftriaxone (9, 14). Ma et al. reported on the intracellular localization of *B. burgdorferi* within human umbilical vein endothelial cells in vitro (25). In a recent editorial Mahmoud points out that infections due to intracellular pathogens are notoriously difficult to treat and cure (26). Interestingly, *B. burgdorferi* was not among the list of pathogens cited. The author suggested that the outcome of infections due to intracellular pathogens may be genetically regulated. Steere et al. have suggested that genetic regulation may be a feature of infections due to *B. burgdorferi*; they found the illness more problematic in individuals bearing HLA-DR 2, 3, or 4 alleles (33). The key to the development of methods to combat such infections, Mahmoud argues, is increased understanding of adhesion to and internalization in host cells by these pathogens. Garcia Monco et al. (8), Coburn et al. (1a), and others are intensively studying this process in *B. burgdorferi* infection.

These observations lead one to the conclusions that certain subsets of patients with Lyme disease may require prolonged antibiotic treatment and that presently available chemotherapeutic modalities may be suppressing but not eradicating the infection. Thus, individuals who have demonstrated relapses following aggressive treatment may require an open-ended antibiotic approach provided that they are deriving clinical benefit and not experiencing any adverse effects and that they wish to be treated (24). Oral antibiotics often suffice to keep patients well, and these are certainly preferable in terms of convenience and cost. It should be emphasized, however, that all oral regimens should be designed to adequately treat not only the musculoskeletal system and other peripheral locations but also the central nervous system (7, 17, 19). Unfortunately, some patients do not respond adequately to oral medication, particularly those with serious central nervous system involvement, and in such individuals, prolonged intravenous treatment may be necessary. In one such case, *B. burgdorferi* was grown from spinal fluid despite treatment for 21 days with parenteral cefotaxime and 4 months with minocycline (22). This patient had had virtually no opportunity for reinfection in the interim. Cerebrospinal fluid pleocytosis which had been present for several years and which failed to improve with a prior course of 21 continuous days of intravenous cefotaxime resolved completely with 13 weeks of a "pulse" cefotaxime regimen (11) consisting of 4 g every 8 h for 24 h weekly. Significant neurologic injury had already occurred in this patient. However, because of the known plasticity of the human central nervous system, it is hoped that suppression of the infectious agent with extended treatment will at least avoid or slow further microbe-induced damage and that perhaps some recovery of neurologic function may occur in time.

Many clinicians and scientists admit that seronegative Lyme disease exists but maintain that it is a rare phenomenon. Indeed, for study purposes, many academic centers have specifically excluded patients presenting with symptoms possibly compatible with Lyme disease who are seronegative. This may be a serious conceptual and methodologic error. Present understanding of the human immune response to *B. burgdorferi* infection is rudimentary. Antibody response, although strong and invariable in some individuals, may wax and wane over time. Diagnostic serologic titers may be undetectable in other patients for reasons that are presently poorly understood. At least four research groups have suggested the presence of immune complexes in the sera and/or cerebrospinal fluid of patients with Lyme disease (3, 5, 10, 32). In patients for which a state of antigen excess exists, free antibodies may escape detection and may be revealed only after use of methods to dissociate such immune complexes. Thus, the very patients who are unable to generate detectable levels of free antibodies, who are least

apt to contain the infection, and who may present with the more serious illness among those with Lyme disease are least likely to be offered treatment. For example, the patient described above was seronegative for the first 5 years of her illness, during which time she sustained severe and irreversible neurologic injury. Western immunoblot serologic results were inconclusive at the time *B. burgdorferi* was isolated from the CSF, highlighting the fallacy of the use of this test as a "gold standard" for the confirmation of Lyme disease. An antigen-capture assay developed by the Rocky Mountain Laboratory of the National Institute for Allergy and Infectious Diseases (6) demonstrated shedding of *B. burgdorferi*-specific antigen in the urine of many patients who were suspected of having Lyme disease but who were seronegative with usual antibody tests (21). The availability of such direct antigen detection methods, the polymerase chain reaction, and other approaches which directly demonstrate the presence of the pathogen, once clinically validated, will foster more rational pharmacotherapy for Lyme disease. Results of such assays will promote recognition of that which astute clinicians have long inferred from the careful study of their patients, that seronegativity is a real phenomenon in Lyme disease, occurring in both early and late stages (4, 21).

Acceptance of the possibility of seronegative disease makes empirical treatment for patients in whom Lyme disease is clinically suspected imperative, even if serologic tests are negative. Obviously, such commitment to therapy should occur only after thorough but expeditious efforts have failed to identify another cause for the symptoms. Early occurrence of irreversible neurologic injury, although rare (23, 28), may be avoided by prompt and specific therapy for such patients.

The increasing realization that Lyme disease, once entrenched, may be a chronic persisting infection refractory to cure with presently available therapeutic approaches in some patients gives added cogency to the argument in favor of preventive antibiotic treatment of deer tick bites, particularly when ticks have been attached long enough to become engorged. Eradication of the spirochete before dissemination and adoption of an intracellular location is of great advantage (16, 18, 20).

Chronic persisting infection not yielding to antibiotic treatment presents a dilemma for the patient, the physician, and for insurance companies that are contractually obliged to pay for medically necessary treatment (34). The solution is not denial of the reality of patient illness or imposition of arbitrary restrictions on allowable durations of treatment but the design of more effective and less costly treatments that can keep patients well. Aside from prevention of the illness in the first place, methods achieving sure cure for those already infected must be developed. Antibiotics may not be the answer. Rather, application of new techniques of molecular biology to interfere irreversibly with key metabolic or reproductive processes of the bacterium wherever it may be found in the body, including intracellular sites, may provide more effective targeted therapy in the future (2, 13, 27, 31, 35).

A major shift in paradigm is underway regarding the nature of Lyme disease and the treatment of infected patients. Objective markers for disease activity, presently research tools (4, 6, 21), will permit the true scope of chronic persisting infection and seronegative disease to be appreciated. This will allow the effectiveness of various treatment options to be gauged and guide the development of superior approaches. Lyme disease, complex and mysterious, will continue to pose difficult problems for us, for our patients, and for our society as human intelligence strives to fathom and checkmate *B. burgdorferi*, a biologic "evil genius."

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