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An Appraisal of “Chronic Lyme Disease”

TO THE EDITOR: Feder et al. (Oct. 4 issue)¹ review the great controversy surrounding “chronic Lyme disease.” For most patients with this diagnosis, the authors advocate against the use of antibiotics.

But before the decision is made not to use antibiotics for patients with post-tick-bite symptoms, anaplasma, babesia, bartonella,² and ehrlichia must be ruled out. These tick-borne² intracellular pathogens are difficult to diagnose and can establish long-term, persistent infection.³⁻⁵ Anaplasma, babesia, and bartonella are underdiagnosed: the nonspecific symptoms of infections with these organisms tend to be ascribed to the more easily identifiable Lyme disease, which often accompanies them.²⁻⁶ Indeed, when studied prospectively, 65 of 161 patients with Lyme disease (40%) were coinfecting with babesia, and 11 of 161 (7%) with anaplasma.⁶ Accurate diagnosis of these infections helps steer successful treatment: babesia³ and bartonella⁵ are especially difficult to eradicate. Accurate diagnosis is also important, since babesia³ and anaplasma⁴ can spread through blood transfusion.

As Feder et al. note, “chronic Lyme disease” is often unrelated to borrelia. If symptoms occur after a tick bite in the absence of evidence of active borrelia infection or if they persist despite anti-borrelia treatment, another tick-borne infection should be suspected. If such an infection is found, the patient may indeed benefit from appropriate antibiotics.

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TO THE EDITOR: Feder et al. fail to adequately inform readers about the science underlying the “chronicity” debate. Multiple researchers have documented *Borrelia burgdorferi*’s ability to penetrate human cells. In demonstrating the presence of the organism inside neurons and glial cells, Livengood and Gilmore established that it can exist in an intracellular state within a protected site,¹ characteristics favoring persistence and necessitating longer courses of antibiotics. *B. burgdorferi*’s pleomorphic abilities also favor persistence. One study suggested that penicillin, ceftriaxone, and doxycycline are ineffective against the bacteria in its cystic form.² The study by Yrjänäinen et al. revealed that *B. burgdorferi* can survive standard therapy, lending further credence to the theory of bacterial persistence.³ Krupp et al. found that retreatment was beneficial; 69% of the treatment group, as compared with 23% of the placebo group, had significant improvement in fatigue.⁴

“Clinical assessment remains the most important method for determining the efficacy of treatment.”⁵ Persistent symptoms in patients with late Lyme disease suggest treatment failure and the need for a new approach.

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TO THE EDITOR: The patient community discussed in the article by Feder et al. does not suffer from “mild and self-limiting subjective symptoms.” These symptoms are disabling, precluding employment and school attendance. Patients have severe pain and cognitive dysfunction. Antibiotics have helped many such patients reclaim their lives.

A careful reading of the article shows that a diagnosis of Lyme disease is all but impossible without certain objective symptoms. These symptoms determine which patients receive the diagnosis, are treated, and are enrolled in research studies. Table 1 of the article shows objective symptoms present in a minority of patients. Erythema migrans rash may be undetected or misdiagnosed in persons infected with *B. burgdorferi*. Thus, many infected persons do not receive the diagnosis.

Patients who are seronegative for *B. burgdorferi* often do not lack an antibody response. A patient may have a strong positive response (IgG or IgM) to two genus-species-specific immunoblot bands for *B. burgdorferi* and have negative serologic test results because of the existing test criteria. For these reasons, some doctors may treat patients without qualifying clinical or serologic evidence of Lyme disease. In my view, many of these patients are helped greatly by treatment.

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TO THE EDITOR: The article by Feder et al. on the proper therapy of chronic Lyme disease addresses a very timely concern. Unfortunately, the authors' statement that there are no “scientific data” that support persistent *B. burgdorferi* infection in the face of negative serologic test results is erroneous. In 1988, we reported on 17 patients who had all

had erythema migrans, received inadequate antibiotic therapy, had vigorous T-cell blastogenesis to borrelia antigens, and were seronegative on the basis of enzyme-linked immunoassay.^{1,2} The majority of these patients had improvement after definitive antibiotic therapy. Seronegative infection was confirmed by other laboratories using polymerase-chain-reaction (PCR) assays to document the presence of microbes in seronegative patients.^{3,4} Abrogation of a humoral response by removal of the bulk of microbial antigens has been seen in other settings, including infection with *Treponema pallidum*. Although the use of repeated courses of antibiotics for a putative borrelia infection is unsupported and may cause serious morbidity,⁵ persons with evidence of previously inadequately treated Lyme disease may be seronegative and may benefit from adequate antibiotic therapy. Fortunately, erythema migrans is now more readily recognized, and occult Lyme disease is rarer. In the absence of antibiotic treatment, most persons become seropositive.

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TO THE EDITOR: The appraisal of chronic Lyme disease by Feder et al. requires reevaluation. The strong recommendations made by the authors are based on a relatively small number of subjects, do not reflect clinical evidence, and do not take into account the International Lyme and Associated Diseases Society (ILADS) clinical practice guidelines.

It is time the medical community acknowledged Lyme disease as another example of “clinical equipoise” — an absence of consensus within

the clinical community — and established publishing standards accordingly.

When clinical equipoise exists, it is even more critical for the medical community to be able to evaluate conflicting positions, the basis for the medical evidence cited, study criteria, and professional agendas and conflicts of interest that may exist. Only by airing these different points of view will the medical and scientific communities reach a better understanding of controversial topics such as chronic Lyme disease.

Currently, medical experts in support of the ILADS clinical practice guidelines are rarely, if ever, included in the process of scientific reviews. In the spirit of good science, I would suggest that this be changed.

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TO THE EDITOR: As an infectious-diseases consultant practicing in a highly Lyme-endemic area for more than 30 years, I have often seen patients who, convinced that they have chronic Lyme infection, leave my office disappointed or even angry at my refusal to prescribe prolonged antibiotic treatment. The article by Feder et al. is a valuable resource that I have already installed on my desktop. I salute the authors' efforts to refute those who would offer potentially hazardous treatment that is not evidence based, bolstered by reams of meaningless data from "special" laboratories and from Web sites rife with testimonials but bereft of scientific evidence. The balance between compassion for patients in distress and adherence to the evidence is exemplary and should be a help to patients and to their physicians. Good intentions do not justify improper treatment.

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THE AUTHOR REPLIES: My colleagues and I agree with Mayer and Merz that *Ixodes scapularis* ticks can transmit *Anaplasma phagocytophilum*, *Babesia microti*, or rarely, both of these pathogens, and that in the right clinical setting, appropriate diagnostic testing for these agents is warranted.¹ There is no evidence that these or any other ticks transmit bartonella.¹ There is also no evidence for the existence of chronic anaplasma infection in humans,

nor is there any published clinical evidence that an active tick-borne coinfection is the explanation for symptoms in the vast majority of patients with post-Lyme disease syndrome.²

Maloney raises several issues that we fully address in our article. *B. burgdorferi*, like other spirochetes, predominantly resides in the extracellular matrix. Moreover, patients with post-Lyme disease syndrome who received a 2-month course of doxycycline, an antibiotic that enters cells, had no greater improvement than those who received placebo.²

Holmes attaches undue significance to serologic reactivity that fails to meet conventional guidelines for seropositivity. It is important to recognize that reactivity to one or more antigens of *B. burgdorferi* on immunoblot occurs in more than 50% of the general population because of the production of cross-reactive antibodies directed at either other bacteria or nonbacterial antigens. Indeed, the principal reason that the U.S. Public Health Service recommended both two-tier testing and the use of evidence-based criteria for interpreting immunoblots in 1995 was to reduce the number of false positive results. Use of immunoblot criteria with poor specificity contributes to substantial numbers of misdiagnosed cases and furthers public misperceptions of Lyme disease.

We disagree with Volkman. Seronegativity is unexpected in patients with any manifestation of late Lyme disease (e.g., Lyme arthritis).¹ Cell-proliferation assays do not provide adequate evidence for the existence of seronegative Lyme disease because this method has an unacceptably high rate of false positive results (in one study the specificity was only 33%).³ Similarly, certain studies using PCR assays in patients with possible Lyme disease also failed to meet high-level standards for scientific evidence. False positive results for the detection of DNA of *B. burgdorferi* by PCR testing are well recognized.⁴ Approaches to improving the reliability of PCR tests include avoiding nested-primer protocols, sequencing amplicons to confirm their identity, and using positive controls with distinctive sequences. Positive results may be confirmed by amplification of multiple gene targets and testing in separate laboratories in different locations.

The term "clinical equipoise," used by Cameron, is difficult to justify in view of the published reports of five double-blind, randomized, placebo-controlled clinical trials that have con-

vincingly demonstrated that antibiotic treatment of post-Lyme disease symptoms is not in the best interests of patients.⁵ Our article summarizes the consensus among clinicians who practice evidence-based medicine, such as Drapkin, whom we thank for his comments.

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Primary Percutaneous Coronary Intervention

TO THE EDITOR: Several studies have evaluated the role of combination medical therapies administered upstream of primary percutaneous intervention (PCI). As noted in the review of the time to treatment in PCI, by Nallamothu et al. (Oct. 18 issue),¹ these trials have failed to demonstrate a survival benefit from either full-dose fibrinolysis plus PCI or reduced-dose fibrinolysis in combination with glycoprotein IIb/IIIa antagonists plus PCI in patients with ST-elevation myocardial infarction. However, there is evidence of improved outcomes with early administration of glycoprotein IIb/IIIa antagonists as compared with administration in the catheterization laboratory.² A Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or 3 was significantly more frequent in the group in which glycoprotein IIb/IIIa antagonists were administered early than in the late-administration group, and there was a trend toward a reduction in mortality.² A TIMI flow grade of 2 or 3 before PCI is associated with a decrease in adverse events and improved 1-year outcomes.^{2,3} Other studies have revealed decreased 30-day mortality and reinfarction rates with the use of the glycoprotein IIb/IIIa inhibitor abciximab.⁴ Thus, these data support early administration of glycoprotein IIb/IIIa inhibitors to improve outcomes in patients undergoing primary PCI.

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TO THE EDITOR: In their review of primary PCI, Nallamothu et al. reaffirm the importance of the time to treatment and underscore the point that the superiority of PCI over thrombolysis is limited in time, "reaching equipoise between 60 and 120 minutes." Therefore, facilitated PCI by means of pretreatment with tissue plasminogen activator (t-PA) was seen as a logical option. But as the authors emphasize, this combination actually increased mortality. The incompatibility of t-PA with PCI may be related to t-PA's procoagulant effect and the significant rate of coronary reocclusion.¹ In contrast, prourokinase follows another fibrinolytic paradigm² and has a very different mode of action.³ Indeed, prourokinase caused no measurable thrombin generation and little reocclusion (1.4%),⁴ indicating that the above complications should not be seen as an inevitable accompaniment of all thrombolytic agents.

Therefore, it is surprising that in their discussion of future challenges, the authors do not include a thrombolytic agent that is compatible with PCI. Surely, the optimal reperfusion strategy would be immediate thrombolysis followed by PCI, thereby also addressing the critical issue