

## EDITORIALS



## Reinfection versus Relapse in Lyme Disease

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Lyme disease, which is caused by the tickborne spirochete *Borrelia burgdorferi*, is increasing in frequency; it is spreading to new geographic locations, and it is a particular problem in the northeastern United States.<sup>1</sup> Before the discovery of the causative agent, it was learned that natural infection, without antibiotic treatment, often occurred in stages.<sup>2</sup> The infection usually began with an expanding skin lesion called erythema migrans, sometimes followed weeks later by neurologic or cardiac involvement, and often followed months later by arthritis. Attacks of arthritis commonly recurred over a period of several years, and occasionally, erythema migrans reappeared faintly before episodes of arthritis. Thus, in untreated patients, relapse of the original infection was the rule.

Today, all manifestations of Lyme disease are usually treated successfully with oral or intravenous antibiotic therapy for 2 to 4 weeks, depending on the manifestation, as recommended by the Infectious Diseases Society of America.<sup>3</sup> However, a small percentage of patients who previously had erythema migrans that was treated with antibiotics still have recurrent erythema migrans at new body sites during subsequent Lyme disease transmission seasons; this clinical and epidemiologic pattern suggests reinfection.<sup>4</sup> In contrast, in patients who previously had Lyme arthritis, which is a late disease manifestation, erythema migrans seems to recur rarely, if at all. Thus, the expanded immune response of late disease appears to be protective against reinfection, at least in most patients, whereas the immature immune response of early disease does not.

In this issue of the *Journal*, Nadelman et al.<sup>5</sup> describe the use of three molecular typing systems to subtype the strains of *B. burgdorferi* caus-

ing infection in patients with more than one episode of erythema migrans. Of 22 paired isolates obtained from 17 patients, the second isolate always had a different subtype than the first. This observation adds further weight to previous clinical observations that recurrent erythema migrans after antibiotic treatment is caused by reinfection rather than relapse of the original infection.

Furthermore, in another study in the United States, *B. burgdorferi* was cultured from skin-biopsy specimens of erythema migrans lesions before antibiotic therapy, and a second biopsy was performed after treatment. All post-treatment cultures yielded negative results<sup>6</sup>; these findings provide further support for the adequacy of recommended treatment regimens.<sup>3</sup>

It has still been questioned whether patients have persistent infection after erythema migrans because subjective symptoms — primarily pain, neurocognitive symptoms, or fatigue — may persist or begin after the resolution of the skin lesion with antibiotic therapy. Although the frequency of such symptoms decreases with time, perhaps 10% of patients (though the reported percentages have been quite variable) have symptoms for at least 6 months after treatment.<sup>7</sup> However, these symptoms do not appear to respond to further antibiotic therapy. In the largest study of antibiotics for post-Lyme disease symptoms, 129 patients who had persistent subjective symptoms after standard courses of antibiotic therapy for Lyme disease were randomly assigned to receive intravenous ceftriaxone for 30 days followed by 60 days of oral doxycycline or intravenous and oral placebo for the same durations.<sup>8</sup> A total of 180 days after starting the study drug, the numbers of patients with a con-

dition that worsened, stayed the same, or improved were similar in both study-drug groups, suggesting that such symptoms did not result from persistent infection.

An analogous situation may occur with Lyme arthritis. Although most patients with Lyme arthritis have a response to recommended antibiotic therapies,<sup>3</sup> a small percentage of patients have persistent synovitis for months or several years after receiving oral and intravenous antibiotic therapy for 2 or 3 months; this condition is called antibiotic-refractory arthritis. Rather than persistent infection, infection-induced autoimmunity,<sup>9</sup> retained spirochetal antigens,<sup>10</sup> or both may play a role in this outcome.

The issue of relapse versus reinfection has a broader context because of patient-advocacy groups that promote months or years of antibiotic therapy for “chronic Lyme disease.”<sup>11</sup> Moreover, chronic Lyme disease has become a common diagnosis for medically unexplained pain or neurocognitive or fatigue symptoms, even when there is little or no evidence of previous *B. burgdorferi* infection. Even so, these patients are said to have persistent infection, which can be suppressed only with months or years of antibiotic therapy, and the therapy must be restarted when symptoms recur. As concluded by the Infectious Diseases Society of America, there is no evidence of persistent *B. burgdorferi* infection in human patients after recommended courses of antibiotic therapy.<sup>3</sup> Although *B. burgdorferi* infection may persist for years in untreated patients, the weight

of evidence is strongly against persistent infection as the explanation for persistent symptoms in antibiotic-treated patients with Lyme disease.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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## Diagnostic Exome Sequencing — Are We There Yet?

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Advances in technology are rapidly changing the field of medical genetics in both the research laboratory and the clinic. With the use of next-generation, or massively parallel, DNA sequencing, it is possible to determine the sequence of essentially all genes in an individual's genome — referred to as the exome — within a matter of days.

This technology became widely available in 2005, and the first proof-of-principle experiment showing the power of exome sequencing for the discovery of genes associated with disease was published a few years later.<sup>1</sup> Since then, exome

analysis has been used in the research setting to identify the genetic cause of dozens of disorders, including intellectual disability.<sup>2-4</sup>

A couple of years ago, Veltman and colleagues used exome sequencing to test the hypothesis that sporadic intellectual disability is caused by de novo mutations (genetic changes that are present in affected persons but not in their parents).<sup>2</sup> Now de Ligt, Veltman, and colleagues<sup>5</sup> report in the *Journal* results obtained with a similar approach in a diagnostic setting to identify genetic causes of severe intellectual disability in 100 patients.