We have come a long way in our understanding of Lyme disease (LD). Although it was originally mistaken for juvenile rheumatoid arthritis when it first appeared in the mid-1970s as an epidemic of oligoarthritis among children and adults in eastern Connecticut, subsequent epidemiologic investigations established a probable microbial etiology for the disease [1]. This prediction was fulfilled by the discovery in 1981 of a new spirochetal bacterium, *Borrelia burgdorferi*, residing within the midgut of a new species of hard tick, *Ixodes scapularis* [2], and, shortly thereafter, by the isolation of the spirochete from a small number of patients [3, 4]. Increasingly sophisticated methods for detecting and genotyping LD spirochetes in ticks, small mammal reservoirs, and humans—an incidental host—have enabled investigators to define the disease’s enzootic cycle, major clinical manifestations, and prevalence in the United States and globally [5]. Although *B. burgdorferi* is far from an easy bacterium to study, considerable progress has been made in unraveling the mechanisms that enable this zoonotic parasite to cycle back and forth between 2 strikingly different milieus. Studies of LD pathogenesis have been greatly facilitated by the availability of the bacterium’s genomic sequence [6, 7] and by the development of techniques for genetically manipulating virulent spirochetes [8]. The development of a murine model that faithfully reproduces most clinical features of the disease represents another milestone in LD research [9]. Work in the murine model, in conjunction with in vitro and translational studies in humans, has firmly established that disease manifestations result from the inflammatory response evoked by the spirochete and its constituents [10, 11]. The borrelial genome encodes an astonishing number (>150) of lipid-modified polypeptides [6, 7], including numerous outer surface proteins (Osp’s) that are expressed at different times during the enzootic cycle [12]. Lipoprotein-mediated activation of innate immune cells is believed to be a principal trigger of acute inflammation at sites of infection [10].

Most patients with LD present with a slowly expanding annular skin lesion, erythema migrans (EM), which develops at the site of tick feeding [5]. Although ostensively localized at the time of presentation, patients with solitary EM often have impressive flulike symptoms (malaise, headache, arthralgias, myalgias) that are believed to be indicative of spirochetal dissemination [5]. Indeed, culture and/or polymerase chain reaction (PCR)–based studies indicate that as many as one-half of patients with EM are spirochetic at presentation, although spirochete concentrations in the blood are usually quite low [13]. Thus, *B. burgdorferi* appears to be a potent inducer of inflammation in vivo, and this supposition is mirrored by in vitro systems in which extremely low spirochete:cell ratios elicit the production of proinflammatory cytokines [14]. In addition to being disproportionate to the visible lesion, constitutional symptoms may take weeks to months to resolve after therapy. Physicians need to anticipate this enigmatic delayed response and not rush to re-treat.

The major clinical controversies in LD center on the small percentage of patients who do not return to a state of well-being after therapy. Two posttreatment syndromes have been distinguished [15]. The rarer one is a persistent large-joint synovitis that, on the basis of negative PCR results and culture analyses of synovial fluids, is clearly not due to persistent infection. The association between this syndrome and the HLA-DR4 histocompatibility allele [16] was the first major evidence that “treatment-resistant Lyme arthritis” is an autoimmune process. Subsequent studies demonstrating possible molecular mimicry between an immunodominant epitope of OspA and a peptide derived from lymphocyte function-
associated antigen—1 (LFA-1), an adhesion molecule expressed on the surface of T cells [17], further support an autoimmune etiology.

The far more common posttreatment syndrome is a constellation of chronic musculoskeletal and neurocognitive symptoms variously referred to as “chronic Lyme disease,” “post–Lyme disease syndrome,” or “posttreatment chronic Lyme disease” (PTCLD) [15]. Differences of opinion regarding the cause and management of PTCLD have polarized the medical community [18]. One camp holds that posttreatment symptoms are indicative of deep-seated, persistent infection requiring prolonged and intensive antibiotic therapy. The majority of physicians and scientists, the so-called mainstream camp, maintain that PTCLD is neither infective nor inflammatory in nature. Over the years, the mainstream viewpoint has slowly gained acceptance, largely because researchers have failed to garner convincing and reproducible evidence for either persistent infection or ongoing inflammation. Pivotal in this regard were the 2 randomized, multicenter trials reported by Klempern et al. in 2001 [19] that found no evidence for persistent B. burgdorferi infection in patients with PTCLD and failed to demonstrate any benefit from prolonged antimicrobial therapy (30 days of intravenous ceftriaxone plus 60 days of oral doxycycline). This study did, however, document that individuals with PTCLD experience considerable impairment in their health-related quality of life.

The follow-up study by Klempern et al. reported in this issue of The Journal of Infectious Diseases [20] has provided another piece to this complex puzzle by helping to rule out an autoimmune mechanism in PTCLD. Using banked samples from their treatment cohorts and matched samples from asymptomatic subjects who were treated for LD, these researchers were unable to establish a clear link between treatment outcome and HLA haplotype. Nevertheless, 2 cautionary notes must be sounded. First, an increased frequency of DRB1*0401 (an allele associated with antibiotic treatment-resistant Lyme arthritis) was observed but did not reach statistical significance, suggesting that the study may have been underpowered. Second, not all autoimmune processes are associated with specific HLA haplotypes, a point acknowledged by the authors.

After more than a decade of controversy, we now can state with a reasonable degree of certainty what PTCLD is not. However, we still do not understand this baffling entity and whether spirochetal infection has a causal role in its pathogenesis. In the meantime, clinicians caring for patients with PTCLD must forego costly, irrational, and potentially harmful antimicrobial regimens. Prompt recognition and treatment of early LD remains the only proven strategy for preventing long-term complications.

References