In Lyme disease, musculoskeletal symptoms can persist after treatment, which has led to the hypothesis that the causal organism itself may escape antibiotic therapy. The controversy that surrounds this question extends beyond patients, physicians, and scientists, as public health organizations struggle with how the disease should be diagnosed and treated. Is Lyme disease an infection that resolves, or is the spirochetal agent resilient and evasive? In this issue of the JCI, Bockenstedt et al. address this issue and present compelling evidence that the residues of nonviable spirochetes can persist in cartilaginous tissue long after treatment and may contribute to antibiotic-refractory Lyme arthritis.

The controversy

The controversy in its broadest scope is in terms of opinions about diagnostic criteria for Lyme disease and the duration of antibiotic therapy (3, 4). Is Lyme disease an infection that resolves, as most bacterial infections do, in the face of an effective immune response, antibiotics, or a combination of the two? Or is the spirochetal agent — *Borrelia burgdorferi* in North America — unaccountably more resilient and evasive than numerous in vitro and in vivo studies in the laboratory and clinic would have us conclude? The controversy extends beyond academic and public health circles and now encompasses state and federal legislative bodies as well as widespread litigation, including an antitrust suit by Connecticut’s attorney general against the Infectious Diseases Society of America (4).

Earlier in the controversy’s history, one could roughly characterize the disputants as academic clinicians, microbiologists, and public health epidemiologists on one side and a group of practitioners, mainly without academic affiliations but supported by national and local patient advocacy groups, on the other side. The great majority of papers on antibiotic susceptibilities and therapy protocols in experimental infections and controlled clinical trials bolstered claims of the first group that *B. burgdorferi* infection, with some exceptions, was cured by courses of single antibiotics within — at most — a few weeks (5). By this account, if some symptoms and disability continued through or recurred after appropriate antibiotic therapy, this plausibly was a postinfection phenomenon, such as Reiter’s syndrome and Sydenham’s chorea. In the case of *B. burgdorferi* infection, this was termed “post–Lyme disease syndrome” (6, 7). The other side of the dispute generally preferred the term “chronic Lyme disease,” with its implication of ongoing infection (8).

There was an occasional paper that reported results that challenged the prevailing view about the spirochete’s susceptibility in vitro or in vivo to antibiotics of the β-lactam, tetracycline, and macrolide classes (9, 10). But these provocative reports did not discernibly influence professional opinion makers or alter the research priorities of governmental funding agencies. They did not lead to wider, independent testing of these alternative hypotheses, which by implication entailed lengthier treatments at minimum and radically different therapies at the extreme. Those advocating unconventional treatment measures continue to cite as justification the evidence from a handful of subsequently published articles, but, in my view, most investigators in the Lyme disease research field did not attach much credence to these reports. If this was complacency, it was shaken by unsettling reports from three research groups, who from a partisan’s view, were among the academic and public health “establishment.”

Questioning convention

In 2002, Bockenstedt et al. reported the persistence of *B. burgdorferi* DNA in tissues and its uptake into xenodiagnostic ticks feeding on mice that had been treated for infection several weeks to months previously (11). The authors concluded that whatever was persisting in the mouse and was transmitted from mouse to tick (though no further) was not infectious in the usual sense and called these spirochetes “attenuated.” This interpretation recalled publications from the 1960s — the heyday of attention on posttreatment “L-forms” and other cell-wall-deficient bacteria and their possible association with recurrent or chronic disease (reviewed in ref. 12). Hodzic et al. reported a similar duration of PCR positivity of tissues after treatment “L-forms” and other cell-wall-deficient bacteria and their possible association with recurrent or chronic disease of the *β*-lactam, tetracycline, and macrolide classes (9, 10). But these provocative reports did not discernibly influence professional opinion makers or alter the research priorities of governmental funding agencies. They did not lead to wider, independent testing of these alternative hypotheses, which by implication entailed lengthier treatments at minimum and radically different therapies at the extreme. Those advocating unconventional treatment measures continue to cite as justification the evidence from a handful of subsequently published articles, but, in my view, most investigators in the Lyme disease research field did not attach much credence to these reports. If this was complacency, it was shaken by unsettling reports from three research groups, who from a partisan’s view, were among the academic and public health “establishment.”
Sible posttreatment spirochetes in their mouse model. But more important were the experiments using real-time imaging of transgenic fluorescent \textit{B. burgdorferi} in mice and the transplantation of cartilaginous tissue to naive mice to assess antigenicity and mitogenicity (2). The results of these latter experiments provide compelling evidence that there are residues of the bacteria in the form of protein if not transcribable DNA continuing to cause mischief long after bacterial life has ceased. The authors, with justification, propose that this accounts for the phenomenon of antibiotic-refractory Lyme arthritis as well perhaps as less distinctive musculoskeletal manifestations after treatment.

One conceptualization of the different possible states between a viable, proliferating bacterium and its total absence as well as the predicted outcomes of the different detection measures is shown in Figure 1. This depicts a spirochete and a cell-wall–active antibiotic, but would apply to other types of bacteria and, in modified form, to antibiotics that have other targets. The spirochete shown missing a cell wall may replicate in this state and revert to the usual morphology corresponding to descriptions of L-forms. Beyond this state, there may possibly be replication, but neither reversion nor the possibility of transmission. Finally there are membrane blebs, which may or may not contain nucleic acids, and then only proteins. Either of the last two states could be what Bockenstedt et al. observed (2).

**A wider angle view**

Drawing back from the close-up shot on this Lyme disease controversy, can we see connections in the background with other infectious diseases and their posttreatment outcomes? Would these in-depth studies of persistence of pathogen viability and residual DNA and proteins in a host have arisen in the absence of a medical and social controversy that inspired Congressional investigations, advocacy and counter groups among lay individuals and practitioners, picketers at medical meetings, and numerous lawsuits? In my view, yes. I think that the nosology of post–Lyme disease syndrome has utility and that investigations along the lines of the work described here will yield further insights not just about Lyme disease but about other postinfection sequelae, including reactive arthritis, some forms of chronic fatigue syndrome, and perhaps other disorders yet to be rec-

---

**Figure 1**

Detectable remains of spirochete infection. Following antibiotic treatment and host immune attack, an intact, replicating spirochete may descend to a state where only proteins of the bacteria remain detectable in the host tissue. The first transition is from the effect of a cell wall–active antibiotic. This can result in some cells that don’t have cell walls (also called L-forms or protoplasts) and, consequently, are not affected by the antibiotic anymore, but can still replicate (the circular arrow indicates replication of that form of cell). These cells can revert to normal bacteria with cell walls in the absence of the antibiotic. The next step down are intact cells that contain DNA and protein, but that cannot revert and may or not be able to replicate. Then there is autolysis or immune-mediated breakup of the bacteria into vesicles that contain both DNA and protein or protein alone (under these conditions, free DNA would be rapidly degraded by nucleases). Finally, with the destruction or turnover of the bacterial nucleic acid, only protein remains. The cells become spherical or pleomorphic in the absence of cell wall.
ognized. While the authors’ findings on experimental infections of laboratory mice may not change opinions on appropriate antibiotic therapy for patients, they point to testable hypotheses on the mechanisms for lingering illness after treatment of infection (18, 19) and laboratory means to identify persistent antigenic and mitogenic stimulation.

With PCR and sensitive antigen detection methods so readily at hand, we may neglect more direct but time-consuming and artful gauges of viability. Almost 50 years ago, Gutman, Turck, Petersdorf, and Wedgwood reported in the JCI the survival of bacterial variants in antibiotic-treated patients with pyelonephritis (20). They used painstaking methods in a pre-PCR microbiology lab for “separation of bacterial variants from classical organisms.” These remain in the urine were uncultivable by routine procedures but, according to the authors, lived to cause disease again.

Address correspondence to: Alan Barbour, Departments of Medicine and Microbiology & Molecular Genetics, University of California Irvine, 3012 Hewitt Hall, Irvine, California 92697-4028, USA. Phone: 949.824.5626; Fax: 949.824.8598; E-mail: abarbour@uci.edu.