Letters

Chronic Lyme Disease: a Persistent Inflammatory Infection

Seth Pincus (*ASM News*, November 2005, p. 529–535) provides a thought-provoking review of the potential role of infection in chronic inflammatory diseases. In terms of Lyme disease, he states that "the mechanism of disease is not fully understood and may involve both infectious and postinfectious processes."

Unfortunately, most studies of chronic Lyme disease have focused on "postinfectious" causes of chronic inflammation (R. B. Stricker, A. Lautin, and J. J. Burrascano, Expert Rev. Anti Infect. Ther. **3:** 155–165, 2005). For example, molecular mimicry between *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, and the human leukocyte antigen LFA-1 has been proposed as a mechanism that elicits persistent autoreactive symptoms in chronic Lyme disease. Recently, however, this antigenic cross-reactivity was shown to be "irrelevant" in chronic Lyme disease (A. C. Steere, B. Falk, E. E. Drouin, L. A. Baxter-Lowe, J. Hammer, and G. T. Nepom, Arthritis Rheum. **48:**534–540, 2003; R. S. Kalish, J. A. Wood, W. Golde, R. Bernard, L. E. Davis, R. C. Grimson, P. K. Coyle, and B. J. Luft, J. Infect. Dis. **187:**102–108, 2003; R. B. Stricker and E. L. McNeil, Ann. Intern. Med. **140:**W6, 2004). As stated by Dr. Pincus, "there are few, if any, conclusive examples where molecular mimicry is the prime initiator of human disease."

While molecular mimicry remains unproven as a cause of chronic tick-borne disease, recent studies of *B. burgdorferi* have focused on the pathophysiological complexity of the organism (Stricker et al., Expert Rev. Anti Infect. Ther. **3:**155–165, 2005; S. E. Phillips, N. S. Harris, R. Horowitz, L. Johnson, and R. B. Stricker, Lancet **366:**1771, 2005). These studies reveal that the agent of Lyme disease is one of the most invasive and elusive bacteria known to man (Phillips et al., Lancet **366:** 1771, 2005). In fact, *B. burgdorferi* satisfies all of the criteria for persistent infection outlined by Dr. Pincus: evading immune responses through antigenic variation, cloaking with host proteins, living within cells, or occupying immunologic sanctuaries such as the central nervous system (Stricker et al., Expert Rev. Anti Infect. Ther. **3:**155–165, 2005; Phillips et al., Lancet **366:**1771, 2005). Dr. Pincus states correctly that culture of limited tissue samples is "rarely successful" in human patients with late manifestations of Lyme disease. However, extended tissue culture in animal models of Lyme disease has demonstrated persistent infection in mice, dogs, and chimps (S. E. Phillips, J. J. Burrascano, N. S. Harris, L. Johnson, P. V. Smith, and R. B. Stricker, Int. J. Epidemiol., November 2005). Thus *B. burgdorferi* provides a good example of a highly invasive and elusive infectious cause of chronic inflammatory disease.

Although treatment with antibiotics may be "controversial" in chronic Lyme disease, many patients appear to respond clinically to this therapy, supporting a role for persistent infection in chronic disease [R. B. Stricker, A. Lautin, and J. J. Burrascano, Expert Rev. Anti Infect. Ther. **3:**155–165, 2005; S. T. Donta, Clin. Infect. Dis. **25** (Suppl.)**:**S52-S56, 1997]. Conversely, the cost of incorrectly assuming a noninfectious pathogenesis of chronic Lyme disease is high: the underlying infection is allowed to proceed unabated or may even be intensified by immunosuppressive therapies, leading to further morbidity of the disease. Additional studies of antibiotic therapy are needed to address the issue of optimal therapy for chronic Lyme disease.

One other aspect of chronic inflammation that Dr. Pincus fails to mention is polymicrobial infection, which is relatively common in patients with persistent symptoms of Lyme disease (R. B. Stricker, ASM News **69:**265, 2003). Polymicrobial infection with agents such as *Babesia, Anaplasma, Ehrlichia and Bartonella* adds yet another dimension to the mechanism of chronic inflammation in tick-borne diseases.

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