Lyme Disease: A Unique Human Model for an Infectious Etiology of Rheumatic Disease

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Lyme disease is a complex immune-mediated multi-system disorder that is infectious in origin and inflammatory or "rheumatic" in expression. Through its epidemiologic characteristics, large numbers of a seasonally synchronized patient population are readily available for prospective study. Lyme disease has a known clinical onset ("zero time"), marked by the characteristic expanding skin lesion, erythema chronicum migrans, and a clearly defined pre-articular phase. At least some manifestations of the disorder are responsive to antibiotics, and the causative agent—a spirochete—is now known. These advantages make Lyme disease unique as a human model for an infectious etiology of rheumatic disease.

Lyme disease (formerly Lyme arthritis) was recognized in November 1975 because of unusual geographic clustering of children with inflammatory arthropathy in the region of Lyme, Connecticut [1]. It is now known to be a complex immune-mediated multi-system disorder occurring at any age, in either sex, with onset in summer or early fall. Its clinical hallmark is an early expanding skin lesion, erythema chronicum migrans (ECM), which may be followed weeks to months later by neurologic, cardiac, or joint abnormalities [2–7]. Symptoms may refer to any one of these four systems alone or in combination. Foci of Lyme disease have been found elsewhere along the northeastern coast of the United States, in many other states, in Europe, and in Australia. The disease is caused by a newly recognized spirochete [8–10], and transmitted primarily by the minute tick *Ixodes dammini* or by related ixodid ticks [11–13].

Since our earliest work on Lyme disease, we have always looked beyond it, for possible insights into the onset and development of other inflammatory immune-mediated, "rheumatic" diseases. Here we shall consider for comparison rheumatoid arthritis, the most prevalent example of this constellation of disorders. As a human model for an infectious etiology of rheumatic disease, Lyme disease has distinct advantages, of which some of the more important ones (Table 1) form the core of this discussion.

The seasonal onset, in summer or early fall, provided a synchronized patient population and allowed us to "tool up" for each new outbreak, for whatever study seemed most attractive at the time. The closeness of the Lyme region to our group in New Haven helped make effective a surveillance network. For the epidemiology of
Lyme disease, this seasonal and geographic clustering suggested an infectious etiology, and the presence of adequate numbers of patients allowed a hit-or-miss pattern of affected individuals to be seen in a given season, a pattern compatible with a suspected arthropod-borne vector. Adequate numbers of cases also permitted the recognition of subgroups of Lyme disease and resulted in the appearance of families containing affected and non-affected individuals over as many as three generations—an ideal presentation for immunogenetic analysis.

In the study of Lyme disease, erythema chronicum migrans (ECM) has had many roles. It quickly became the most definitive diagnostic sign [2,7]. From its appearance, and from patient histories, epidemiologic studies, and a long European experience with ECM, we were led backward rather quickly to the tick vector [11–13], now called *Ixodes dammini* [14], and eventually to the causative spirochete [8–10]. Most important for experimental work, erythema chronicum migrans marks the clinical onset of disease, the “zero time” so important for proper retrospective and especially prospective studies [15].

Together with its establishment of clinical onset, erythema chronicum migrans marks a pre-articular phase of Lyme disease. This advantage manifested itself in several ways. It allowed a spectrum of clinical subgroups to be established. At one extreme were those with mild disease, consisting of erythema chronicum migrans that healed without sequelae. At the other extreme were patients with severe disease having subsequent neurologic or chronic joint involvement. We could therefore compare not only affected individuals with controls, but subgroups of patients with each other. Subgroups were found to differ in their humoral immune response [16,17]: those with elevated serum IgM and cryoglobulins containing IgM at the time of ECM were likely to develop subsequent severe disease; those without these findings were not. In other words, the early humoral findings had prognostic significance.

In immunogenetic studies [4,18], severe disease and elevated serum IgM correlated with the presence of the B-cell alloantigen DR2. Rearranged into what would appear to be their proper order, these findings seem to exemplify a situation in which an individual’s immunogenetic make-up determines the variety of his immune response to infection, which in turn determines the clinical expression of disease.

A key question in rheumatoid arthritis is when and how it begins. Without a reliable zero time or pre-articular phase, the diagnosis can only be made when arthritis is well established. In our model, erythema chronicum migrans and the
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known tick vector, *Ixodes dammini*, have provided answers to when and how: infection begins with the tick bite; erythema chronicum migrans appears three to 32 days later; and arthritis, when it occurs, begins weeks (or up to two years) after ECM [7]. The afflicted joint may be pathologically indistinguishable from one affected by rheumatoid arthritis, even to the extent of pannus formation and erosion of cartilage and bone [2,4,6]. Thus, the model demonstrates that this final common pathway of joint pathology—this "rheumatoid" lesion—can occur within a matter of months.

The well-defined zero time and pre-articular phase also allowed us to trace the immunologic evolution of Lyme disease, long before an etiologic agent had been identified. By the time erythema chronicum migrans appears, almost all patients have abnormal serum Clq-binding activity, a measure of circulating immune complexes [19,20]. The abnormal binding persists in patients with subsequent nerve or heart involvement, but usually disappears within three months among those with only subsequent arthritis. In the synovial fluid of affected joints, however, abnormal binding is uniformly present, and always to a greater extent than in the circulation. (Again, in rheumatoid arthritis, it is not until this apparently late date in the natural history of the disorder that we arrive upon the scene.) And adjacent to that fluid is proliferative synovium often replete with lymphocytes and plasma cells that, as in rheumatoid arthritis [21], are presumably capable of producing immunoglobulin locally. Thus our model seems to portray an initially disseminated, immune-mediated inflammatory disorder that in some patients becomes localized and propagated in joints.

The next major advantage of this human model is its responsiveness to antibiotics, and particularly to penicillin. Our initial experience with oral antibiotics did not confirm European suggestions that penicillin or tetracycline cures erythema chronicum migrans, a lesion that often resolves promptly even without treatment. As the number of patients increased (again, the advantage of adequate numbers), it became clear that these drugs do shorten the duration of ECM and prevent or attenuate subsequent disease [22,23]. The clear implication, since confirmed [9], was that a penicillin- (and tetracycline)-sensitive agent is often still present at this stage of the illness.

This finding ruled out a viral etiology, and narrowed the possible contenders to a list on which some kind of spirochete was most likely. It also provided a general method of approaching the question whether the host is still harboring a live causative agent at a given stage of disease: if penicillin cures the disease, then the agent was there. (Note that only this positive result is decisive; failure to cure is more ambiguous.) And penicillin in particular can be used in high parenteral dosage with relative impunity. Indeed, we have now cured Lyme meningitis with penicillin [24] (and the causative agent has been cultured from cerebrospinal fluid [9]). We are well aware of the rheumatologic implications of a disorder (Lyme meningitis) formerly treated with high-dose corticosteroids tapered over months [3], now cured by high-dose penicillin in days [22]. Formerly, we suppressed the host's response to an agent that is immunostimulatory but otherwise apparently rather unaggressive; now (with antibiotics) we address the agent directly.

We are currently evaluating the effect of high-dose penicillin on established Lyme arthritis. The question whether a persistent infectious agent is necessary for continued disease activity (versus the persistence of antigenic degradation products; the periodic rechallenge of ultimately injurious immunologic memory cells; or the trig-
gating of true self-perpetuating autoimmunity) is of central importance in a number of immune-mediated disorders.\textsuperscript{1}

The final major advantage of this model is its known causative agent, the \textit{I. dammini} spirochete. Specific antigen is what every rheumatologist dreams of having at his disposal; a whole organism is even better. It opens up entirely new areas of endeavor; for example, diagnosis through the use of specific antibody \textsuperscript{[8–10]}; localization of the organism \textsuperscript{[25,27]} (or parts of it, or cross-reacting components) in tissues; the antigen-specific immunology of the disease; the establishment of prevalence in vectors \textsuperscript{[8–10]}, and of true attack rates in human and animal hosts; and the development of animal models.

In summary, as a model for an infectious etiology of rheumatic disease (Table 1), Lyme disease, a human, immune-mediated inflammatory disorder, has intrinsic advantages which, taken together, are unique. We suspect that this model will continue to be useful in helping us to consider the possible evolution of other rheumatic problems whose developmental signposts are less prominent or lacking.

\textsuperscript{1}Note added in proof: Since this paper was written, we have presented evidence that Lyme arthritis may be treated successfully with high-dose parenteral penicillin \textsuperscript{[26]}. Moreover, spirochetes have been found in synovial lesions of Lyme arthritis \textsuperscript{[27]}.

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