EDITORIAL

THE LYME SPIROCHETE: ANOTHER CAUSE OF REITER'S SYNDROME?

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In this issue of *Arthritis and Rheumatism*, Weyand and Goronzy convincingly demonstrate circulating antibodies and proliferative T cell responses to *Borrelia burgdorferi* in 18% of patients with reactive arthritis or Reiter's syndrome (RS) who came from an area of the Federal Republic of Germany where Lyme disease is endemic (1). Antibodies to *B burgdorferi* were found in only 3% each of a well-matched control population and a group of patients with fibromyalgia. Evidence of *Chlamydia trachomatis* infections was found in 29% of the RS cohort, which is similar to findings of other studies (2,3); however, there was little overlap between patients with presumed sexually-acquired reactive arthritis and those with evidence of *B burgdorferi* infection (1 patient only).

The clinical descriptions of these patients, as well as the high incidence of HLA-B27 in this group, strongly support the diagnoses of RS rather than Lyme disease. Although these observations will need to be confirmed in other endemic areas, it appears likely that the spirochete that causes Lyme disease may also trigger a reactive arthritis in the genetically susceptible (HLA-B27 positive) host. Thus, in addition to the previously known gastrointestinal and genitourinary triggers (2), *B burgdorferi* now joins the human immunodeficiency virus (4,5) as another recently recognized infectious agent that must be considered in the patient with RS (Table 1). This very important finding has immediate clinical implications and raises provocative new questions about pathogenetic mechanisms underlying the seronegative spondylarthropathies.

For the physician practicing in a region where *B burgdorferi* is common, patients with suspected or confirmed RS will need careful questioning and examination for stigmata of Lyme disease, as well as screening for spirochetal antibodies (6). Even then, some patients whose disease was triggered by *Borrelia* may not have circulating antibodies, and in such cases where there is a high index of suspicion, T cell blastogenic responses against the organism may need to be confirmed (7). For those found to have *B burgdorferi* infection, appropriate antibiotics should be given (8). Although, as Weyand and Goronzy demonstrated, such treatment is not likely to abrogate the manifestations of reactive disease, the aim would be the prevention of superimposed or subsequent Lyme disease, with its myocardial, neurologic, and articular sequelae (6).

The mechanisms underlying Reiter's syndrome are still poorly understood, but the observations of these authors raise several questions that should be reconciled with several older and more recent discoveries. Reactive arthritis has previously been conceptualized as a probable immune-mediated, sterile inflammatory process occurring distant to a primary infection in the gut or genitourinary tract (2,9). Previous assumptions that local mucosal immunity plays an important role may require reconsideration, since *Borrelia* enters the host via the skin.

Also, inherent to the reactive arthritis hypothesis has been the inability of investigators to demonstrate the initiating microbe in the synovial fluid or

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Table 1. Microorganisms that may trigger reactive arthritis in HLA–B27 positive individuals

Enterobacteriaceae
Shigella flexneri
Salmonella (multiple species)
Yersinia enterocolitica
Yersinia pseudotuberculosis
Campylobacter fetus jejuni
Klebsiella pneumoniae?
Chlamydia
Chlamydia trachomatis
Chlamydia psittaci?
Borrelia
Borrelia burgdorferi?
Viral
Human immunodeficiency virus (predisposing to other infections or immunodeficiency?)

tissue. Although more than 20 years ago *Bedsonia* (now *Chlamydia trachomatis*) were reported in synovial fluid leukocytes in patients with RS (10), other investigators were unable to consistently visualize and recover viable organisms. More recently, both *Chlamydia* (11) and *Yersinia* (9) antigens detected by monoclonal antibodies and/or Western blotting have been identified definitively in synovial tissue from patients, usually HLA–B27 positive, who developed reactive arthritis after each of these infections. Attempts to culture viable organisms from the joints in both instances have been uniformly unsuccessful (9,11). Moreover, in the studies by Granfors et al (9), *Yersinia* antigens were still present in synovial cells from 2 patients with ankylosing spondylitis even after 3 years and 17 years, respectively, of disease. Thus, microbial antigens, but not viable organisms, appear to be present and to persist in joints undergoing a reactive arthritis.

Similar studies will be needed to determine whether *B burgdorferi* antigens can be demonstrated in joints with reactive arthritis, especially after antibiotic therapy. Currently, the Lyme spirochete has been demonstrated histologically in only a few synovectomy and synovial fluid specimens from patients with chronic Lyme arthritis and has not yet been cultured from the joints (12). In fact, the most compelling evidence for direct joint infection in Lyme arthritis is a positive response to antibiotic therapy. Even then, genetic factors in the host appear to be contributing to chronic synovitis, since the frequency of HLA–DR4 is increased among individuals who develop persistent arthritis (6).

Any hypothesis about the pathogenesis of reactive arthritis must also take into account its strong association with the class I major histocompatibility complex (MHC) antigen HLA–B27. Approximately three-fourths of patients with RS or reactive arthritis, including those in the study by Weyand and Goronzy, whose disease was associated with *Borrelia* (1), are positive for HLA–B27, and nearly all patients with ankylosing spondylitis are similarly positive (2,13). Moreover, HLA–B27 negative RS patients frequently have immunologically cross-reactive HLA–B7-CREG antigens. Most evidence to date suggests that the HLA–B27 molecule itself, rather than the product of another tightly linked gene, participates in predisposing to disease. Since class I MHC antigens serve to restrict antigen-specific cytotoxic T cell responses, it is generally assumed that an aberrant response of this type initiated by these infections is inherent to the B27 molecule. At least 6 different HLA–B27 subtypes have been identified, and their precise amino acid sequences are now known (13,14). All seem to predispose to spondylarthritis, although correlations between the specific B27 subtypes and the various clinical syndromes, as well as different initiating infections, have not been well studied (13).

The molecular mimicry theory, whereby the class I molecule shares immunologic cross-reactivity with microbial antigens, has received the most support as a mechanism to explain the HLA–B27 association with reactive arthritis. Indeed, cross-reactivity between HLA–B27 and *Yersinia* and *Klebsiella* antigens has been shown using immunologic techniques (13). Moreover, a shared sequence of 6 amino acids between 1 HLA–B27 subtype and the nitrogenase enzyme in *Klebsiella pneumoniae* has been demonstrated by using a computer search of known amino acid sequences (14) (Table 2). A similar sequence, differing by only 1 amino acid, has been determined in

Table 2. Comparisons of amino acid sequences among α1 domains of HLA–B27 subtypes and other B7-CREG antigens and mimicking microbes*

Molecule	Positions	Amino acid sequence
HLA–B27.1	69–78	AKAQTDREDL
HLA–B27.2	69–78	AKAQTDRENL
HLA–B27.3	69–78	AKAQTDRESL
HLA–B7	69–78	AQAQTDRESL
HLA–B40	69–78	TNTQTYRESL
Klebsiella nitrogenase	185–194	NSRQTDREDE
Shigella flexneri plasmid pHS-2	–	VCAQTDRHSL

* Refs. 14,15.

a plasmid found thus far only in arthritogenic strains of *Shigella flexneri* (15) (Table 2). If shared sequences can be found in the other organisms (or plasmids) triggering reactive arthritis, now including *B burgdorferi*, those observations would add compelling evidence that mimicry plays a role in these diseases.

On the other hand, the phylogenetic diversity of the organisms involved has led Weyand and Goronzy to suggest that non–antigen-specific immune responses, which would have to be in some way related to HLA–B27, may be operative in reactive arthritis. If this is the case, then it appears less likely that HLA–B27 itself is directly involved. Instead, another tightly linked gene would need to be found. The genes for tumor necrosis factor (TNF), a potent mediator of inflammation, have recently been mapped close to the HLA–B locus within the MHC. No data have yet been presented, however, suggesting abnormal TNF genes or serum levels in patients with spondylarthropathies. Another genetic system has also recently been discovered within the MHC (16). At least 5 distinct "HLA–B–associated transcripts" map adjacent to the HLA–B and TNF loci. While the functions of these new genes have not yet been reported, they too remain candidates for disease susceptibility.

Epidemiologic studies of reactive arthritis are now needed from other areas endemic for the Lyme spirochete. If the observations of Weyand and Goronzy are reproducible, several clinical and basic research dimensions have been opened. Perhaps there was some truth to Hans Reiter's suggestion that a spirochete caused the disease that now bears his name (17).

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