Bacteria and arthritis

Bernard Dixon

"The aetiology of rheumatoid arthritis remains unknown" is the bald verdict of Robert Souhami and John Moxham in their immense, comprehensive, and biblical *Textbook of Medicine*, launched recently by Churchill Livingstone. There follows a very short paragraph headed "Aetiology" with one sentence on the idea that infection is responsible for rheumatoid arthritis and another on the possibility that auto-immunity is to blame. Twelve pages later, not a paragraph but a single sentence tells us that an abnormal response to bacterial infection could be the underlying cause of ankylosing spondylitis.

Over the past 25 years I have amassed an astonishing collection of papers and clippings suggesting that this organism or that—from diphtheroid bacilli to Epstein-Barr virus—was about to be incriminated as the agent of rheumatoid arthritis or ankylosing spondylitis. Indeed, as John Mills commented last year in the *New England Journal of Medicine* (1989;320:245-6), many teeth have been extracted and high colonic irrigations and prolonged courses of antibiotics given in the belief that infection is deeply implicated in the pathogenesis of chronic polyarthritis. Yet despite evidence such as the clear association of infection in the genital tract or bowel with Reiter's syndrome (and of course the arthropathies that can accompany rubella, mumps, and other viral conditions) the issue remains maddeningly confused and certainly unresolved.

Perhaps the next edition of Souhami and Moxham's splendid tome will carry more definitive tidings on exactly what certain micro-organisms are up to in the synovium and synovial fluid of future and current polyarthritis victims. That, at least, is my impression after a review of various strands of evidence compiled over the past six or seven years by Alan Ebringer and colleagues at the Middlesex Hospital and other centres in London. Their original study, carried out under coded conditions and using an indirect Coombs agglutination test, included serum samples from 30 patients with rheumatoid arthritis, 24 active and 28 inactive patients with ankylosing spondylitis, and 41 healthy controls. When compared with each of the other three groups the group with rheumatoid arthritis showed significantly raised antibody titres against *Proteus mirabilis*, whereas the patients with active ankylosing spondylitis had significantly raised titres against *Klebsiella pneumoniae*.

Ebringer and coworkers have now described two more recent investigations. For the first they chose subjects with rheumatoid arthritis who had never been treated with gold; they feared that an allergic response to gold could have accounted for the raised antibodies to *P mirabilis* in the first series. The results parallel those earlier findings, however, and treatment with gold can now be excluded as an explanation for the raised titres. The second study, using the more sophisticated enzyme linked immunosorbent assay (ELISA), again showed significantly higher antibody titres to *P mirabilis* (but not to *Escherichia coli*) in subjects with active rheumatoid arthritis compared with healthy controls. Together with independent corroboration from a survey conducted in Dublin, these findings leave no room for doubt that patients with active rheumatoid arthritis have specific antibodies to *P mirabilis*. These patients do not show raised titres against *K pneumoniae* or *E coli*.

This last finding is both significant and puzzling. When the Middlesex Hospital group first discovered raised titres of *P mirabilis* antibodies in patients with rheumatoid arthritis they wondered whether the organism, acquired from a urinary tract infection, could account for rheumatoid arthritis being four to five times more frequent in women than in men. But the suggestive coincidence with more frequent urinary tract infections in women seems somewhat less meaningful in the light of repeated failures to detect raised titres of other urinary pathogens such as *K pneumoniae* and *E coli*. Moreover, proteus antibody titres in men with active rheumatoid arthritis are raised just as much as those in women with the same condition.

Writing in *Rheumatology International* (1990;9:223-8), Ebringer and colleagues have formulated an enticing hypothesis that could account for these findings and also for one of a series of discoveries made during the last 15 years linking certain inflammatory rheumatic diseases with particular human leucocyte antigens. The most pronounced of these associations is that between ankylosing spondylitis and the B-27 antigen. But there is now a growing interest in another HLA, DR-4, which has proved to be a valuable marker for rheumatoid arthritis. Its incidence in patients with the condition is 50-75% compared with 20-35% in healthy controls. Moreover, there is some evidence for cross reactivity between the DR-4 antigen and proteus.

Like all the best hypotheses, that put forward by Alan Ebringer and his team affords both predictions and specific propositions that are open to experimental or experiential verification or falsification. The idea is as follows. Rheumatoid arthritis is the end stage of repeated episodes of reactive arthritis to proteus, developing predominantly in people positive for DR-4 antigen. The proteus infection occurs in the genito-urinary tract and kidneys. It triggers the production of specific antibodies, some of which are active against DR-4. But human cells expressing DR-4 antigens bind these antibodies. The result, through the production of interleukins and the activation of other immune mechanisms, is a localised inflammatory response.

Thus patients showing inflammatory arthritis and an elevated titre of proteus antibodies are victims of reactive arthritis to proteus. Rheumatoid arthritis may develop, however, following repeated episodes of this condition, especially in a genetically susceptible host—such as one carrying DR-4 antigens. In a parallel analysis, published in *Baillière's Clinical Rheumatology* (1989;3:321-38), Ebringer proposes that ankylosing spondylitis is produced by repeated episodes of reactive arthritis to klebsiella, usually in people positive for B-27 antigens.

Convincing stuff. But this is still evidence at one remove, based on antibody titres and antigenic analysis. What of the bacteria themselves? Clearly, if the Ebringer hypothesis is to be truly vindicated, *P mirabilis* and *K pneumoniae* ought to be present to a greater extent in patients with rheumatoid arthritis and ankylosing spondylitis respectively than in healthy controls. Studies are now in progress, therefore, to identify the sources of the bacterial antigens responsible for inducing the raised antibody titres. Watch this space.

Middlesex HA4 6AW
Bernard Dixon, PHD, science
writer

Br Med J 1990;301:1043