Proteus—is it a likely aetiological factor in chronic polyarthritis?

The hypothesis that infection with Proteus is associated with rheumatoid arthritis (RA), whereas ankylosing spondylitis is related to Klebsiella infection, is at first sight enormously attractive. It is simple to grasp, requires no talent for remembering complex cascades of CD numbers and interleukins and, if true, could point to new diagnostic and therapeutic possibilities. The question is to what extent there is experimental support for an idea which was first put forward nearly 10 years ago. Two papers in the current issue of the journal report findings relevant to the postulated RA-Proteus connection, and prompt an assessment of the present state of this half of the hypothesis.

Underlying the hypothesis is the simple observation that RA patients, particularly those with active disease, have somewhat higher titres of antibodies to Proteus than controls. Although initial observations suffered from a lack of age matched controls, the later study of slides pairs reported by Deighton et al. was free of such criticism. In all cases the increase in antibody levels was significant but not especially striking—a difference of one or two dilutions in mean titre, and a great deal of overlap. Antibodies of IgM, IgG and IgA subclass have all been reported, although one study failed to demonstrate an increase in Proteus antibodies when only IgA was examined.

What could these observations mean? Obviously they could point to a greater incidence of Proteus infection in the RA group, but studies examining this point are in conflict. Other work has been directed to looking for links between immune responses to Proteus and the development of RA. One idea receiving particular attention is the possible cross reactivity of antibodies to Proteus with those HLA antigens which confer susceptibility to RA. There are several difficulties with this concept: the titres of antibodies are not strikingly different in disease and controls, so that it is hard to envisage that the disease is dependent on such small and variable differences in antibody titre; also, there is little reason to believe that RA is driven by pathogenic antibodies. Molecular mimicry of the kind suggested also fails to explain the distinctive tissue distribution of RA (as HLA-DR molecules are expressed on all antigen presenting cells throughout the body). Nevertheless, in pursuit of this idea diverse pieces of information have turned up (table). Can these pieces be fitted together into some kind of picture, or are they in fact from different jigsaw puzzles?

Let us examine first the similarity in amino acid sequence between the third hypervariable region of RA associated major histocompatibility complex alleles (e.g. DRB1*0401, 0404, 0101) and Proteus mirabilis haemolysin; the sequences in questions are EQR (or K) RAA and ESRRAL, respectively. Not surprisingly, given their degree of similarity, the ESRRAL peptide can be modelled in a conformation similar to that taken up by the HLA-DR peptide in an intact DR molecule (paper in this issue by Wilson et al.). Its structure within the haemolysin is unknown, but would need to be similar if the haemolysin is really the bacterial antigen responsible for inducing cross reactive antibodies. RA patients had higher titres of antibodies to the haemolysin peptide than did controls (though, again, age matching was conspicuously absent), so in theory these antibodies should also react with the HLA-DR peptide. Indeed, they should be absorbed out by reaction with either intact haemolysin or HLA-DR.

Likewise, if the haemolysin is the crucial antigen accounting for the higher titres of antibodies to whole Proteus bacteria, this reactivity should be abolished by absorption of sera with peptides or haemolysin. Furthermore, the activity of DR4 sera against Proteus, or indeed the same cross reactivity shown by rabbit anti-DR4 antisera, should be abolished by absorption with specific peptide. None of these points has been established, making it difficult to be confident of any relationship between the various findings. Indeed, although ESRRAL is also found in Serratia haemolysin, RA patients did not have increased antibody to this organism. Unless the haemolysin is in some way masked in Serratia, this result raises the possibility that the antibodies to whole Proteus bacteria and to the ESRRAL peptide are in fact unrelated. Similar arguments apply to the results reported on antibodies to

### Relationships between Proteus antigens and molecules relevant to RA pathogenesis

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<tr>
<td>Antisera from rabbits immunised with DR4 lymphocytes cross react with Proteus</td>
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<td>DR4-specific sera bind to Proteus</td>
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<td>Proteus haemolysin shares a short stretch of amino acids with DR4 subtypes associated with RA</td>
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<tr>
<td>RA patients have antibodies to the peptide common to DR4 and Proteus haemolysin</td>
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<td>Proteus urease shares a short sequence of amino acids with the a2 chain of type XI collagen</td>
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the Proteus urease which happens to have a short sequence of homology with the α2 chain of type XI collagen.

A striking feature of the first reports of increased antibodies to Proteus was the relationship with disease activity, particularly as judged by measurement of C reactive protein (CRP). The changes in Proteus antibody titres in the patients treated with vegetarian diet reported in the paper in this issue by Kjeldsen-Kragh et al are in line with these previous findings, as the diet treated patients also had a significant change in CRP. However, if RA really represents recurrent episodes of Proteus induced reactive arthritis, a relationship of this kind would not be predicted; antibodies to infectious agents normally persist for substantial periods after the resolution of the inflammatory response and do not closely follow fluctuations in disease activity. Indeed, in a recent paper Proteus antibodies failed to correlate with other measures of disease activity.8

A reasonable summary of current findings might be as follows: some aspect of active rheumatoid inflammation boosts the titre of antibodies having the ability to bind to whole Proteus organisms. The target Proteus antigen(s) recognised by these antibodies are unknown, and how they might be involved in disease pathogenesis remains obscure. Intriguing relationships between Proteus antigens and self proteins relevant to RA pathogenesis have been discovered by computer, but the biological meaning of these similarities is also unclear. Perhaps the idea can best be characterised using the Sellars and Yeatman designation of the Cavaliers—‘Wrong but Wromantic’.10 By the same criteria our more conventional ideas of RA pathogenesis (cytokines, CD numbers, etc) may have to be classed with the Roundheads—‘Right but Repulsive’.

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