THE aetiology of rheumatoid arthritis remains unknown, though much is known about the immunopathogenic mechanisms involved in joint destruction [1]. Although a systemic disease, it primarily attacks synovial joints. The synovial membrane becomes an organized lymphoid tissue suggesting a chronic hypersensitivity reaction to an exogenous or self antigen [2]. The primary site of joint destruction is the articular cartilage, and yet it may also be the tissue responsible for driving the immune response as, once it is destroyed, the synovitis usually subsides within that joint. This suggests that inciting exogenous antigens or autoantigens may be sequestered within the cartilage framework.

The concept that autoimmunity plays a pathogenic role in RA was initially voiced following the discovery of serum antiglobulins [3]. However, it was many years later that Steffen [4] first proposed autoimmunity to collagen as a possible pathogenic mechanism for RA. Since then, our knowledge of the biochemistry of the collagens has expanded widely, and immunological techniques have advanced, yet much confusion has arisen over the frequency and significance of this autoimmunity in human disease. The purpose of this editorial is to give a personalized and, I hope, balanced view of this field in which I have been involved for 12 years.

Articular cartilage is a complex organized structure with chondrocytes synthesizing an extracellular matrix of proteoglycan gel held in a collagen framework. The major component is collagen, comprising 70% of the dry weight. Currently, there are at least 11 well-defined types of collagen, five of which are found in cartilage [5]. Type II collagen (85%) is the major component, with types IX (5%) and XI (10%) forming minor constituents of the total collagenous content. Type VI collagen is a trace component (1–2%) and type V, if found, is in similar quantities.

The structure of collagen is also important from an immunological and arthritogenic viewpoint. The native molecule is composed of three individual α-chains wound in a triple helix with short telopeptide regions at its ends [6]. Heat denaturation at 45°C causes uncoiling of the helix to produce the individual α-chains and revealing new antigenic determinants. In animal studies, only native types II and XI collagen are arthritogenic [5,7] and immunization with the native or denatured molecule produces antibody largely reactive with the immunogen [8]. Thus there are large numbers of potential collagenous autoantigens within cartilage, and it is important that all biochemical preparations are meticulous. This was emphasized by a study suggesting that immune complexes bind to type II collagen [9], though the binding material was eventually identified as the pepsin employed in its isolation from cartilage [10].

Immunological methodology has improved over the last two decades with solid-phase radioimmunoassays (RIA) and more recently enzyme-linked immnosorbent assays (ELISA) replacing the less sensitive passive haemagglutination and semiquantitative immunofluorescent assays. Although the RIA and ELISA for collagen antibodies are not subject to interference by non-antibody proteins [11], they are highly sensitive techniques. This has the drawback that the calculation of the normal range and upper limit of normal in a healthy population is critical and often anomalously low. Many patients with inflammatory or immunological diseases have a polyclonal rise in gammaglobulin and may appear in a solid phase assay to have mildly elevated antibody levels to the antigen under test in these assay systems. No allowance is usually made for this, which has been the major source of confusion in calculating the incidence of this autoantibody.

In view of the above biochemical and immunological problems, more standardization of assays between different laboratories [12] with known positive and negative controls will be necessary in order to bring meaning to the chaos created. In the late 1970s and early 1980s, a high incidence of serum antibodies to native type II collagen in RA and other inflammatory
arthritis was described [13-16]. These results can be largely faulted by the problems indicated above. The true incidence of this autoantibody is probably nearer 10-12% in RA [17], though its incidence in other arthritides cannot be calculated as numbers in these groups remain low. There is no doubt that serum autoantibody specific for native type II collagen is found in a few patients with psoriatic arthritis [15; personal observation], juvenile chronic arthritis [18; personal observation], systemic lupus erythematosus (SLE) [16,19], generalized osteoarthritis [19; personal observation], Paget's disease [19], relapsing polychondritis (RP) [20] and lepromatous leprosy (LL) [19]. Thus this autoantibody is most frequently associated with approximately 10% of patients with RA but can occasionally occur in other diseases.

Most of these conditions involve joint disease as even in LL a rheumatoid-like arthritis has been described [21]. The data on Paget's disease indicate that some patients had osteoarthritis [19]. The recent report of autoantibodies to the collagen-like portion of Clq in SLE [22] which could cross-react with collagen is interesting and again emphasizes the complexity of this area. It is obvious from the varied joint diseases described that not all patients with antibodies to native type II collagen have an erosive arthritis, but it is likely that they all have some cartilage destruction. Relapsing polychondritis affects various cartilaginous tissues, and this autoantibody is found in most untreated patients with early active disease, but is rarely described in treated and late disease [20]. It is interesting that auricular lesions were noted in studies on native type II collagen-induced arthritis in rats [23] but extra-articular cartilaginous lesions are not seen in RA patients with the autoantibody.

The question of the specificity and significance of this autoantibody for RA should therefore be questioned. The fact that it occurs in other forms of arthritis could indicate that it is a secondary phenomenon induced following the exposure of the native molecule to the immune system after initiation of cartilage destruction by another primary event. This would parallel animal studies, where the spontaneous occurrence of this autoantibody has not been described. However, immunization of rodents with native type II collagen can induce the production of specific antibody and arthritis in the presence of specific immune response genes of the major histocompatibility complex (RT1 in rats and H2 in mice) [24,25]. In RA, there is evidence that immune response genes (HLA-DR3, and/or DR7) are also linked with the persistence of this autoantibody [26], whereas it will only appear temporarily in early disease if these immune response genes are absent (e.g. HLA-DR4 positive RA) [27].

These human and animal studies suggest a key role for class II molecules in the development of this autoimmunity. It has been postulated in organ-specific autoimmunity that epithelial cells that normally do not express class II molecules can be induced to express them by lymphokines secreted in the initial inflammatory process [28,29]. Once expressed, tissue-specific self molecules that are not normally immunogenic may be presented as immunogenic, and autoimmunity to the self molecule may result. A similar hypothesis involving the interaction of exposed native type II collagen with specific class II molecules on immune cells in the synovial membrane activated by lymphokines [30] could result in the development of autoimmunity to this molecule.

Is there evidence therefore that this autoimmunity has pathogenic relevance in RA? There is good indirect evidence that it does. Trentham and his colleagues [5] first described the induction of a polyarthritis in rats following immunization with native type II collagen. Since then, many studies have established that the autoantibody plays a role in the induction of the arthritis by complement binding and activation [31-33] and is capable of transferring the arthritis to non-immunized animals [33,34]. More recent work has shown that this arthritis can be induced in a non-human primate by a similar immunization regimen [35].

The autoantibody is synthesized by plasma cells in synovial membrane [36], is found in synovial fluid where it is capable of forming immune complexes [16,37,38], and is capable of binding to cartilage in vitro [12]. Wooley et al. [39] showed that the IgG subfraction from the serum of a patient with seronegative RA but high levels of serum antibody levels to native type II collagen could bind to cartilage and induce synovitis when injected into mice. Recent work has established that the main IgG antibody subclasses produced are the complement binding IgG1 and IgG3 [40,41], indicating that the autoantibody could perpetuate joint inflammation by intra-articular complement activation.

Although this autoantibody has been found as early as 2 months after onset of symptoms in RA (personal observations), published data have failed to show definite correlations with any
clinical, investigative, immunological or radiological parameters in RA except immunogenetic studies. When taken at a single time point, there is no direct correlation with measures of disease activity such as ESR [12,26]. However, longitudinal studies in individual patients have shown a correlation in some patients [42], especially when IgG1 and IgG3 subclasses are measured. These studies confirm that autoimmunity to native type II collagen can remain at high and varying levels over long periods of time.

Autoimmunity to denatured type II collagen is undoubtedly commoner (approximately 25%) than to its native molecule in RA [17]. However, this appears to be far less specific for RA and joint disease, as it is found in other arthritides and inflammatory conditions [16,19] though it can be synthesized in the synovial membrane [43]. It is interesting that one study has found an association with HLA-DR4 in RA [44] and another group had previously found cellular immunity to denatured collagen in both RA and normal controls who were HLA-DR4 positive [45]. The difficulty of cross-reactivity with other denatured collagens probably accounts for the presence of these antibodies in non-articular inflammatory diseases. Further studies searching for an antibody to specific type II collagen peptides using more sophisticated immunological techniques may prove very rewarding especially if it is shown to be associated with HLA-DR4.

Published data on cell-mediated immunity to collagen are sparse [15,45-47] and probably irrelevant as all have been carried out on peripheral blood lymphocytes. Reactivity to denatured collagens was more frequent than to the native molecule and was not restricted to RA. However, as with organ-specific autoimmunity, the activated and committed lymphocytes are largely compartmentalized to the target organ [28]. Studies on lymphocytes isolated from synovial tissue and fluid are therefore needed before valid data on cell-mediated immunity to type II collagen can be interpreted.

The nature of autoimmunity to cartilage collagens is complex and intriguing. The modern story is in its infancy and the application of further immunological techniques (e.g. Western blotting, monoclonal antibodies) will help to elucidate its role in arthritis. There are a wealth of autoantibodies in the connective tissue diseases, yet here we have an autoantibody with a pathogenic role in laboratory animals. The evidence points towards such a pathogenic role in chronic inflammatory arthritis, but it is likely to be only one of many mechanisms in RA. Its relatively low incidence and lack of specificity for RA makes its routine measurement in patients seem unattractive and unrewarding unless we can conclusively show, as seems likely, that it has prognostic significance in being associated with more severe joint destruction. It is also currently the most relevant measurable autoantibody against joint tissue, so may prove a further useful immunological marker in assessing new therapeutic regimens against joint destruction.

R. B. CLAGUE

Department of Rheumatology, Withington Hospital, Manchester M20 8LR, and Devonshire Royal Hospital, Buxton, Derbyshire, UK.

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Imagine, if you will, the following unlikely situation. You have been invited to attend a meeting on 'Medical Advances' at 6 pm in a nearby hotel. You have a busy rheumatology out-patient clinic that afternoon and arrive tired, breathless and a little late. As you sit down, Bill is talking about AIDS—again. Your mind drifts back to the clinic . . . if only we understood more about arthritis . . . if only I knew how to help poor Mrs. Smith . . . .

'Thank you for coming Dr. Goodguy.' The mention of your name by the Chairman jolts you out of the clinic.

'I am sure you all know Paul Goodguy, our local arthritis expert. I have asked him to come along to help discuss advances in arthritis and rheumatism. Paul is going to talk about the scientific advances being made in this field. Carol is from the Unintelligible Biophysics Department at Ivory Tower University—I'm sure you all recognize her from the television. . . . Paul.'

Your mind races. Carol Who? What advances?

You shuffle a few papers and make a nervous beginning. 'Well, umh, thank you Chairman, arthritis is certainly a major health problem in other . . . .

PAUL AND CAROL: A TALE OF TWO DISCIPLINES


