An extensive release of this enzyme was noted in 5 out of 11 rheumatoid patients from cells in synovia adjacent to the edges of partially degraded articular and fibrocartilage. There was an equally significant release in 3 out of 5 patients of cathepsin D from many cells in pannus tissue remote from the synovium and overlaying partly degraded articular cartilage.

The extracellular release and presence of this enzyme was particularly striking in synovium bordering partially degraded patella cartilage (3 out of 4 patients). The most common morphologically identifiable and viable cell-type releasing cathepsin D was macrophage-like: all very active tissues contained many such cells, although nonsecreting cells of this type were frequently seen. Only rarely was the release of cathepsin D from chrondrocytes detected, even in partially degraded matrix.

It is suggested that the pathological excessive degradation of proteoglycan in patella and articular cartilage, which was seen only in rheumatoid joints and is particularly marked adjacent to synovium and pannus tissue, may be in part caused by the extracellular activity of cathepsin D and other proteases, resulting from the excessive secretion of these enzymes from cells in synovial and pannus tissues.

Discussion

DR. J. BALL (*Manchester*) I would like to ask whether your antibody will penetrate hyaline cartilage and thus enable you to decide whether there is cathepsin release or not?

DR. POOLE We have done some very careful experimental work with radioactively labelled immunoglobulins to study their penetration into cartilage, and also immunofluorescent studies which have been published (Poole, Barratt, and Fell, 1973). Generally speaking, normal adult cartilage is largely impermeable to IgG antibody, but when the cartilage has been degraded and has lost a certain amount of proteoglycan it becomes significantly permeable to the antibody. Only in these situations is it possible to clearly detect any secretion of cathepsin D from chondrocytes. Our present studies, however, indicate that viable chondrocytes in degraded cartilage are not releasing detectable amounts of cathepsin D. The major contribution to the extracellular pool of cathepsin D appears to be from cells present in the synovium.

DR. M. I. V. JAYSON (*Bristol and Bath*) Did you relate the release of cathepsin D to the detailed histology of the synovium and in particular the amount of lymphocyte infiltration and the amount of surface cell hyperplasia?

DR. POOLE These studies are in progress. All I can say is that there seems to be no evidence to indicate that lymphocytes, polymorphs, or plasma cells are commonly secreting cathepsin D. We have not studied the possible relationship between the release of this enzyme and the actual immunological situation within the synovium, but this is something which we would very much like to look at further.

Reference

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Histocompatibility Antigen (HL-A 27) and Its Relation to Disease. By D. A. BREWERTON, MAEVE CAFFREY, ANNE NICHOLLS, and D. C. O. JAMES (*Westminster Hospital, London*)

In a series of 75 patients with ankylosing spondylitis the histocompatibility antigen HL-A 27 (W 27) was found in 72 patients compared with 3 controls (Caffrey and James, 1973; Brewerton, Caffrey, Hart, James, Nicholls, and Sturrock, 1973a). The same antigen was identified in 32 out of 60 first-degree relatives. W 27 has also been reported in 35 out of 40 patients in an independent investigation (Schlosstein, Terasaki, Bluestone, and Pearson, 1973).

Reiter's disease and nonspecific urethritis have been studied, and HL-A 27 was found in 2 out of 33 controls, 3 out of 33 men with NSU and 25 out of 33 men with Reiter's disease (Brewerton, Caffrey, Nicholls, Walters, Oates, and James, 1973c). This series has now been extended and the first 50 patients with Reiter's disease assessed. HL-A 27 was present in 17 out of 32 patients with peripheral arthropathy alone and in all 18 patients with sacroiliitis or spondylitis.

Preliminary results are available on ulcerative colitis and psoriatic arthropathy. HL-A 27 has been present in 1 out of 21 patients with ulcerative colitis, and in 10 out of 13 patients with spondylitis associated with ulcerative colitis. Other workers have reported a modest association between psoriasis and HL-A 13 and W 17, but not HL-A 27 (Krain, Newcomer, and Terasaki, 1973). So far we have found HL-A 27 in 8 out of 23 patients with psoriatic arthropathy.

HL-A 27 has recently been reported in 20 out of 22 patients with Yersinia arthritis (Aho, Ahvonen, Lassus, Sievers, and Tiilikainen, 1973). This is the first example of an association between HL-A 27, arthropathy and an identified, infective agent.

A study is in progress of acute anterior uveitis as it presents in eye departments. A report of the first 50 patients has been published (Brewerton, Caffrey, Nicholls, Walters, and James, 1973b) and 79 have now been investigated. Associated diseases were present in 24—mostly ankylosing spondylitis, Reiter's diseases and associated disorders of the spine or sacroiliac joints. All of the patients with uveitis and rheumatic disease had HL-A 27. The antigen was not present in 3 men with active urethritis at the same time as their uveitis. 55 patients had no evidence of an associated disease and 17 had HL-A 27. Young women with HL-A 27 may present with acute anterior uveitis and no rheumatic symptoms in their 20s and early 30s, at the same age that men may present with ankylosing spondylitis.

The relationship of this finding to pathogenesis is unknown. It is possible that the inheritance of HL-A 27, or some closely related immune response, renders a small proportion of the population peculiarly susceptible to the effects of a variety of infective agents.

Discussion

DR. R. D. STURROCK (*Glasgow*) These results are very interesting. We confirm the findings of HL-A 27 in spondylitis, but using serum AJ we have found that in 50% of our patients who have HL-A 27 they also have associated AJ antigen. Now AJ was first suggested by Dr. Sandberg

in Copenhagen (Suejaard, Staub Nielsen, Ryder, Kissmeyer-Neilsen, Sandberg, Lindholm, and Thorsby, 1972) as may be associated with a new segregant series at the second locus closely associated with the second locus antigens, and this does raise the possibility that the HL-A picture may not be quite as straightforward as we thought. We have also looked at patients with Still's disease and we found that 24% of these had W 27 and 6 out of the 7 patients involved were male. All these patients had sacroiliiitis, so it does seem to suggest that HL-A 27 may be a marker of sacroiliitis rather than associated with any particular disease syndrome.

DR. BREWERTON I agree that the serological findings are complex, and that it is not only a question of the presence of HL-A 27. It may be wrong to regard HL-A 27 as a marker of sacroiliitis. We have seen several adults with peripheral arthropathy alone, or acute anterior uveitis without evidence of any rheumatic disease. HL-A 27 may prove not to be relatively specific for the spine and sacroiliac joints.

DR. A. ST. J. DIXON (*Bath*) These clinical manifestations do not all appear at once. A follow-up may give you further information.

DR. A. M. DENMAN (*Northwick Park*) I wonder if you have tried incubating lymphocytes which lack this antigen with serum from patients with this group of diseases, perhaps after treating the cells with papain or other enzymes and then retyped them to exclude the rather remote possibility that this is a serum antigen which is picked up by circulating lymphocytes?

DR. BREWERTON We have not done this experiment, but I hope we will.

PROF. V. WRIGHT (*Leeds*) It is a very interesting and good study. I missed the spouse figures for your various groups. Secondly would you like to comment further about Reiter's disease because that is the one thing that does not fit too well into the story. Is your figure of over 50% positives in patients with long standing or acute Reiter's syndrome? The third question is to ask if you have any data on colitic arthritis without sacroiliitis?

DR. BREWERTON We have not studied the spouses specifically. This will be done when we conduct a more thorough family study. In our article on Reiter's disease in the *Lancet* and in subsequent figures, we divided those with peripheral arthropathy alone into those seen during their initial acute attacks, those that had had the disease for less than 5 years, and those who had had it for more than 5 years (with a mean of 13 years). The proportion in each group who had HL-A 27 was the same. This seemed to apply whether the duration of disease was 2 weeks or 25 years. We are studying colitic arthritis without sacroiliitis, but we have not yet seen enough to present the results.

DR. T. R. LITTLER (*Liverpool*) One point I would like to make is that I occasionally find some difficulty in making up my mind between an incomplete Reiter's disease clinically and the psoriatic with sacroiliitis and arthropathy. Am I correct in assuming that if your Reiter's and ankylosing spondylitics are HL-A 27 positive and psoriatics are HL-A 18 positive would this new test help from the clinical point of view in differentiating between the two when these occasional problems of differential diagnosis arise?

DR. BREWERTON I cannot give a direct answer because we have excluded from our investigations patients with these overlap phenomena. At present this test is complicated, and I doubt whether it will prove to be a practical way of distinguishing Reiter's disease and psoriatic arthropathy. Anyway, I suspect that we may soon be thinking in terms of a series of underlying processes, overlapping in different proportions, rather than psoriasis with spondylitis and Reiter's disease with spondylitis as two completely separate entities.

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Lymphocyte Subpopulations in Rheumatoid Arthritis and Systemic Lupus Erythematosus. By M. POPOVIC, J. MUNRO, P. DAVIES, and P. J. L. HOLT (*Royal Postgraduate Medical School, London*)

Direct immunofluorescence and audioradiography for surface antigen receptors on lymphocytes and spontaneous rosette formation using untreated sheep red cells have been used to detect subpopulations of 'B' and 'T' lymphocytes, respectively, in peripheral blood. 12 patients with systemic lupus erythematosus, 22 rheumatoid arthritic, and 11 osteoarthrotic patients have been examined. Other tests of lymphocyte function such as transformation with phythohaemagglutin and 'spontaneous' transformation have been performed and the results compared with clinical status and following treatment.

Increased proportions of 'B' cells were only found in rheumatoid arthritis 35% (range 21–53%), the controls' levels being 24% (16–34%). A decrease in 'T' cells was found in both rheumatoid arthritis, mean 19% (range 8–34%) and systemic lupus erythematosus, mean 10% (range 3–32%), our normal values being 32% (range 7–42%). All these results were highly significant ($P < 0.001$).

Rosette formation of normal lymphocytes was shown to be impaired by sera from patients with systemic lupus erythematosus, this impairment being reversed when the systemic lupus erythematous sera was replaced with normal human sera. Both increased spontaneous transformation and impaired rosette formation were related to disease activity and, using DNA antibodies as a marker, returned to normal with successful treatment.