localized osteochondritis. Is there any similarity between these lesions and those that occur in young people without ankylosing spondylitis?

DR. CAWLEY Although we have no examples of the histology of osteochondritic lesions in non-spondylitics, Schmorl (1959) showed these lesions to consist of a herniation of the disc into the vertebral body. Radiologically and pathologically both our localized lesions and spinal osteochondritis probably represent such discal herniation.

PROF. E. G. L. BYWATERS (*Hammersmith and Taplow*) I agree with much that you have said about the clinical and therapeutic aspects—for instance, that these cases are best treated by immobilization. While some instances of disc collapse in ankylosing spondylitis may be triggered by trauma, in others it often occurs insidiously, and we have seen a few at autopsy. I demonstrated one of these at the Annual General Meeting of this Society in 1968; we thought then that these disc lesions were similar to the anterior discitis of Romanus lesions. If there is a traumatic element, we think that this acts on a pre-existing pathological lesion, which we think is an inflammatory discitis. In the spine of a boy with a 4-year history, x rays show an inflammatory granulomatous discitis at two sites between three vertebrae which we think is similar to the inflammatory lesions that I demonstrated in 1968 in the anterior and posterior margins of the disc and also in the sacroiliac joints. The present x-ray slide shows depressed cartilage, obviously due to pressure, and the granulomatous disc replacement. We think that this lesion occurs in this particular position because of junctional reactions between cartilage and blood vessels at the small gaps which are sometimes seen in the basal calcified cartilage and bone layer of the epiphysis. Movement can certainly contribute to such lesions and we showed, also in 1968, that the new bone formation responsible for the radiological appearances of the Romanus lesions, similar to the new bone formation around these disc lesions, occurs specifically at moveable segments in an otherwise immovable spine. I do not equate movement with trauma and I do not emphasize trauma in the genesis of these lesions. I think the major factor is inflammation.

DR. D. L. GARDNER (*London*) You did not state at the time that the biopsies in your four cases were taken in the course of the disease. This will make a great difference in interpretation.

DR. CAWLEY I am much interested in Prof. Bywater's comments and slides. We have looked *post mortem* for evidence of active anterior spondylitis coexisting with destructive lesions, and have found none; nor have we found any published reports to substantiate such a relationship. We cannot claim to have proved that destructive lesions never follow an inflammatory process, but in the cases we have studied trauma seems to be dominant and we have found no evidence of inflammatory spondylitis as the initiating event.

In reply to Dr. Gardner, these patients presented several months after the change in symptoms which seems to be an important event in the evolution of these lesions, and pathological material was therefore obtained

either at surgery or *post mortem*. To be absolutely sure of the earliest changes, one would need to have both pathological and radiological evidence at the time of the onset of the lesion and this would obviously be very difficult to obtain.

Reference

SCHMORL, G., and JUNGHANS, H. (1959) 'The Human Spine in Health and Disease', trans. S. P. Wilks and L. S. Goin. Grune and Stratton, New York and London.

Development of Antibodies during Long-term Therapy with Tetracosactrin (Synthetic 1-24 ACTH) in Rheumatoid Arthritis. By D. GLASS (*Clinical Research Division, Kennedy Institute of Rheumatology and West London Hospital*), G. NUKI (*Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow*), and J. R. DALY (*Department of Chemical Pathology, Charing Cross Hospital Medical School*) This paper and the discussion thereon will be published in full in the *Annals* in November, 1971.

Cell-mediated Immunity to Micro-organisms in Rheumatoid Arthritis. By R. N. MAINI, I. T. MCGRATH, A. S. RUSSELL, and D. C. DUMONDE (*Divisions of Clinical Research and Immunology, Kennedy Institute of Rheumatology*)

Inappropriate cellular immune responses to extrinsic antigens may play a pathogenetic role in rheumatoid disease. To investigate this field, the cellular responses of lymphocyte transformation and cell migration inhibition were defined in relation to known infections (*e.g.* varicella, tubercle, leishmania, rubella) accompanied by clinical hypersensitivity states. Against this background we report the occurrence of cellular hypersensitivity to certain micro-organisms (diphtheroids, mycoplasma) that have been associated with rheumatoid arthritis.

Discussion

DR. J. BROSTOFF (*London*) We have obtained different results, but I think that the two sets are not comparable in that the antigens used were different. Our antigen is sonicated mycoplasma membrane, well washed in the ultracentrifuge, and devoid of cell contents and culture medium. Yours is whole sonicated organism. It is well known that the immunological specificity of the mycoplasma rests in the membrane alone, the cytoplasm being strongly cross-reacting. It is perhaps not surprising, therefore, that you are able to show inhibition of migration in normal subjects and also a cross-reaction with *M. gallisepticum*.

Our own results show a good discrimination between patients with rheumatoid arthritis and those with osteoarthritis or normal controls: in fact, the two latter groups rarely showed any inhibition. We have so far tested very few gouty subjects and the numbers are still too small for valid conclusions to be drawn. There is little evidence to support your last point that rheumatoid arthritics carry these organisms as commensals because of obvious diminution of delayed hypersensitivity; in fact, these patients give normal PHA responses and show positive skin tests to a range of antigens.

There is also overwhelming evidence for immune complexes in the joint in the form of cryoprecipitates, diminished complement level, and polymorph inclusions, so that if delayed hypersensitivity is present it may be

only the stimulus to a pathogenetic mechanism which is partly immune complex and partly cell-mediated hypersensitivity.

DR. MAINI Of course, we were fully aware of your results and we were glad to have chosen gouty patients as one of our control groups. The gouty patients in this study had often had recurrent attacks of arthritis, but there is nothing to suggest that they had anything other than gout; certainly they did not have rheumatoid arthritis. Our results show very clearly that, if one compares rheumatoid with non-rheumatoid subjects, using any of the three mycoplasma strains, there is a statistically significant difference in hypersensitivity *in vitro*. If one compares rheumatoid arthritics with healthy individuals, the difference is very striking—it is only with gouty controls that the difference is not so impressive and there is this apparent anomaly. We shall have to look into this further.

The second point was the interesting finding with *M. gallisepticum* which is not found in man and is a chicken mycoplasma.

Thirdly, I did not say that delayed hypersensitivity to diphtheroids and mycoplasma was suppressed in rheumatoid disease. If anything, these organisms may act as adjuvants for some autoimmune responses. If there is a 'rheumatoid virus', its persistence may indeed represent a selective failure of immune surveillance, whereas adjuvant and inflammatory responses to other organisms, such as mycoplasma or diphtheroids, may underline the results we get. Of course viruses are known to induce immunodepression, particularly a selective suppression of some cellular immune responses. We have recently studied patients with shingles, whose lymphocytes transform to PHA and PPD but not to the varicella virus antigen.

DR. P. J. L. HOLT (*Hammersmith*) Many circulating peripheral blood lymphocytes in active rheumatoid disease are already stimulated and the spontaneous DNA synthesis (*e.g.* during the first 2 hours) is often very high. Thus it may be that, instead of testing a response to mycoplasma or other known antigen *in vitro*, the response you are measuring is at least in part the result of previous activation *in vitro* and has nothing to do with whether you add mycoplasma, etc., or not. Thus, without eliminating this spontaneous activity, it is impossible to ascribe these results to mycoplasma, etc. The relevant controls are difficult to design, but you might find similar results in, say, Hodgkin's disease where spontaneous activity can be high.

DR. MAINI We also have considerable experience in lymphocyte transformation in rheumatoid arthritis. We find the lymphocyte transformation test very difficult to standardize, and that the patients studied must also be carefully controlled, so that they have not received, *e.g.*, steroids or gold, which might be immunosuppressants. We do not agree with your findings. We find that the spontaneous lymphocyte transformation in rheumatoid arthritis is, if anything, suppressed.

DR. D. A. RAJAPAKSE (*Hammersmith and Taplow*) We have obtained entirely different results using the macrophage migration inhibition test. We tested rheumatoid arthritics to assess cellular hypersensitivity to *Mycoplasma fermentans* membrane preparations. With guinea-pig macrophages and human lymphocytes, no cellular immunity as demonstrated. We tested six patients, and only one showed migration inhibition. The absence of cellular immunity was also supported by a lymphocyte transformation test using the same antigen. Therefore these two tests seemed to show no evidence of cellular immunity to *Mycoplasma fermentans* membrane antigen in rheumatoid arthritics. The macrophage migration inhibition method used by us was first tried on tubercular patients and subsequently in the study of rheumatic fever using streptococcal cell wall antigen. We have screened fifty different antigens successfully by this method. Besides, neither the macrophage migration inhibition test nor the lymphocyte transformation method measures adjuvant activity—they measure cellular immunity.

DR. MAINI I cannot comment on your findings or your interpretations. Your technique, of course, is quite different and perhaps the dose of antigen you used was not the right one.

Plasma Lipid Levels and Platelet Adhesiveness in Gout. By L. G. DARLINGTON, S. SHAW, and J. T. SCOTT (*Charing Cross Hospital and Kennedy Institute of Rheumatology*) Plasma lipid levels were investigated in a group of 27 adult patients with gout and in 27 closely matched controls. No subject had any known predisposing cause for hyperlipidaemia.

No significant difference in plasma cholesterol levels was found between the two groups, but significant increases in both phospholipid and glyceride values and a highly significant increase in unesterified fatty acid levels were observed in the gouty patients.

The results were analysed to find whether factors, such as obesity, smoking, heavy alcohol intake, hypertension, drug treatment, social class, occupation, or blood group, affected the values obtained. The only significant effect on the lipids was a possible marginal one of obesity on plasma unesterified fatty acids.

The complex inter-relationships between the lipid results were investigated in detail.

In addition, correlation was sought between plasma lipids, and plasma and urinary uric acid values. No significant correlation was found in the gouty patients between plasma uric acid and plasma lipid levels, or between urinary uric acid and plasma cholesterol or unesterified fatty acid levels, but between urinary uric acid and plasma glycerides a marginally significant correlation was noted and between urinary uric acid and plasma phospholipids a highly significant correlation was observed.

A full analysis was made of relationships between haemoglobin values and plasma and urinary uric acid and plasma lipid levels.

Blood group distribution was investigated in both gouty patients and controls and, while gouty subjects showed ABO and Rhesus distributions, the controls showed an unexpected relative deficit of Rhesus-negative subjects.