The findings indicate that the phagocytic activity of inflammatory macrophages and polymorphs is increased in untreated RA and may be suppressed below non-rheumatoid control levels by prednisolone or gold therapy. They also suggest that the coverslip technique may be a useful means of assessing the efficacy of anti-inflammatory drugs and the response of individual patients to treatment with gold and prednisolone.

Effects of Gold and Prednisolone on Inflammation and Phagocytosis in the Rat. By B. VERNON-ROBERTS and J. D. JESSOP (*The London Hospital and University Hospital of Wales*)

It is widely recognized that, unlike corticosteroids, gold salts must be administered for some length of time before any diminution of inflammatory activity can be clinically detected in joints exhibiting active inflammation in rheumatoid disease. In view of this apparent difference in the mechanisms whereby gold salts and corticosteroids suppress inflammation in man, we have carried out studies, in rats, of the effects of both anti-inflammatory agents on the cellular and fluid phases of the inflammatory response and on the phagocytic activity of macrophages and polymorphs migrating into inflamed areas.

After 14 days of treatment with various doses of sodium aurothiomalate ('Myocrisin') or prednisolone, the fluid and cellular phases of the inflammatory response were quantitatively assessed by a cotton pellet implantation technique (Nicol, Quantock, and Vernon-Roberts, 1967) and phagocytosis was measured by assessing the percentages of carbon-containing macrophages and polymorphs among the inflammatory cells adhering to the glass 24 hours after the application of carbon-coated coverslips to abraded areas of skin. The results showed that:

- (1) Gold salts and prednisolone both suppress the fluid and cellular phases of inflammation, and reduce the numbers of macrophages and polymorphs containing endocytosed carbon
- (2) Prednisolone is more effective than gold salts in suppressing inflammation and phagocytic activity
- (3) The amounts of fluid and cellular exudate and the percentages of carbon-containing cells exhibit a linear dose-response relationship with the daily dose of prednisolone and the total dose of gold.

Using the carbon-coated coverslip technique, phagocytic activity was assessed at intervals after a single injection of sodium aurothiomalate (5 mg.) or prednisolone (1 mg.). The results showed that:

- (1) Phagocytosis was suppressed during the first 24 hours after the injection of prednisolone, but thereafter did not differ significantly from control levels, whereas
- (2) Although phagocytosis was not significantly reduced until 48 hours after the injection of sodium aurothiomalate, it was maximally depressed from 6 to 10 days after injection, and did not return to the control level until 24 days after injection.

In rats injected with ^{198}Au -sodium aurothiomalate, light microscope autoradiography revealed the label

located within macrophages situated at inflammatory sites and elsewhere in the body; electron microscope autoradiography revealed the label located to the plasma membranes, lysosomes, nuclear envelopes, and mitochondria of macrophages.

It is concluded that, although gold salts are effective suppressants of inflammation and inflammatory cell activity, they differ from prednisolone in that they are less potent, take longer to exert their effects, and exhibit a different type of dose-response relationship. The fact that gold localizes to many different regions within the macrophage suggests that gold salts may affect a variety of cellular functions.

Discussion

DR. A. K. THOULD (*Cornwall*) Was there any difference in the response of macrophages or polymorphs in patients who subsequently developed gold sensitivity?

DR. JESSOP We only had one patient who developed serious haematological complications and there was no difference in her scores.

DR. VERNON-ROBERTS I have not presented the results of the differential counts in these patients, but a high proportion of patients on gold treatment showed a significant increase in eosinophil counts in inflammatory exudates, although they did not show blood eosinophilia.

DR. W. W. BUCHANAN (*Glasgow*) You expressed the number of cells which contained carbon particles as a percentage of the macrophages or polymorphs, but was the total number of these cells always the same? Did you always count three hundred macrophages and three hundred polymorphs?

DR. VERNON-ROBERTS Yes, we did.

DR. W. W. BUCHANAN And was the total number of polymorphs in the window constant?

DR. VERNON-ROBERTS We used the pellet technique in the rat because in the exudate on cover slips there are millions of cells and it is not possible to assess the number. I must add that the colloidal carbon used has a diameter of about 300 Å; it is therefore not possible to see individual particles by light microscopy but most of the cells from the cover slip exudates do in fact contain carbon by electron microscopy. There must be an aggregate of at least three hundred of these particles in order to see them with a light microscope and therefore the suppression or elevation of phagocytosis is a relative, not an absolute, term.

DR. A. J. PALFREY (*London*) It seems to me that, particularly in the pellet count, there is a change in proportion of the polymorphs to monocytes. Did you notice the same thing in the exudates under the cover glasses?

DR. VERNON-ROBERTS No, there was not a significant change in the differential count.

DR. R. N. MAINI (*London*) In the untreated rheumatoid patients, was there any correlation between disease activity and your count, and did you study the effect of

steroids on any other patients than rheumatoids using this technique?

DR. VERNON-ROBERTS We intended to carry out a further investigation on patients before and during therapy to evaluate them clinically by one of the recognized indices. We did not carry this out in the investigation presented, but Dr. Jessop made a clinical assessment of disease activity and we found a significant correlation between this and the phagocytic scores of macrophages in the untreated patients with rheumatoid arthritis, which gives us encouragement to continue this investigation. Regarding your second point, we had a few patients not included in this series who had polymyalgia rheumatica and were on steroids. They exhibited marked depression compared to our control group.

DR. A. G. MOWAT (*Oxford*) These are two very nice papers, but I wonder if you have not confused yourselves by this simple 'skin window' technique? There are four or five stages to this inflammatory process: these include changes in the vessel wall, migration of cells through the vessel wall, chemotaxis of the cells, and finally phagocytosis. Your method measures only phagocytosis. In rheumatoid arthritis there are important vascular changes and a serious defect in chemotaxis of the cells has been demonstrated (Mowat and Baum, 1971).

DR. VERNON-ROBERTS We have qualified our statements and have made it clear that all these factors operate in inflammation. In using these techniques we cannot distinguish which aspects of the inflammatory response these compounds were inhibiting. We know, for example, that prednisolone inhibits every stage from the release of monocytes from the bone marrow pool to the phagocytic activity of the migrant cells. One does not know much about the mechanism of action of gold, but we are going to carry out further experiments on animals to study the production of monocytes, their emigration, chemotaxis, and so on. We think that the very significant difference between the rheumatoid and control groups and the results in our patients on gold and steroid therapy suggest that this relatively crude test may provide useful information on response to treatment.

Reference

- Mowat, A. G., and Baum, J. (1971) *J. clin. Invest.*, 50, 2541 (Chemotaxis of polymorphonuclear leukocytes from patients with rheumatoid arthritis)
 Nicol, T., Quantock, D. C., and Vernon-Roberts, B. (1967) in 'Reticulo-endothelial System and Atherosclerosis', pp. 221. Plenum Press, New York

Joint Hypermobility—Asset or Liability? A Study of Joint Mobility in Ballet Dancers. By R. GRAHAME and the late Miss J. M. JENKINS* (*Guy's Hospital*) This paper was published in the *Annals* (1972), 31, 109.

Discussion

DR. J. A. D. ANDERSON (*London*) Have you considered using applicants rejected by the Royal School of Ballet as alternative controls for your study?

* We regret to announce that Miss J. M. Jenkins died on March 15, 1972.

DR. GRAHAME It was difficult enough to examine the ballet students, let alone the rejects!

PROF. E. G. L. BYWATERS (*Taplow*) Did any of your ballet students in training show, or give a history of, joint effusions, and do you think that these could be avoided by adequate muscular control?

DR. GRAHAME Surprisingly few of these girls—they were only 17 years old—had had trouble of this nature, but a lot of older patients whom I have seen with generalized hypermobility do have this problem and in these cases I do believe that attention to the musculature, and particularly quadriceps drill, in relation to the knee joint, is of great value in preventing this complication.

DR. J. H. GLYN (*London*) Dr. Grahame has persuaded us that hypermobility is indeed an asset to a 17-year-old ballet student. Does he know what happens to these hypermobile joints eventually? Presumably there must have been long-term studies on the incidence of degenerative and other arthritic diseases as such girls mature. The first metatarsophalangeal joint would seem to be an obvious joint worthy of such a simple prospective study.

DR. GRAHAME I don't think there are much data on this subject, but perhaps this would be the appropriate time to mention that we have now set up at Guy's a clinic that will study the consequences of joint hypermobility as seen in ballet dancers. Perhaps in 20 years time we may be able to look into this.

DR. J. B. MILLARD (*Clacton*) May I ask Dr. Grahame to carry on with this type of research, because osteoarthritis of the hips is a great problem, and my impression is that people with hypermobile hips, like the Chinese and the people from the far East, do not get osteoarthritic hips. It is important to find out why.

Total Hip Replacement using the Charnley Prosthesis in Inflammatory Joint Disease. By J. HARRIS, C. D. R. LIGHTOWLER, and R. C. TODD (*The London Hospital*)

Between August, 1966, and December, 1970, 73 Charnley low-friction arthroplasties were performed in 55 patients with inflammatory joint disease. The main indication for surgery was severe pain in a hip which was the site of extensive destructive change. There were 54 operations performed for rheumatoid arthritis, twelve for ankylosing spondylitis, psoriatic arthropathy (3), Still's disease (3), and Behçet's syndrome (1).

44 patients were reviewed in a clinic and five replied to a questionnaire. Three are dead and three are lost to follow-up. 65 operations were therefore reviewed (59 in the clinic and six by questionnaire).

Before total hip replacement, 95 per cent. of the hips were severely painful, and postoperatively 88 per cent. were virtually pain-free. In those patients who attended for follow-up (excluding four in whom the prosthesis had been removed) movement had increased by at least one grade (d'Aubigné and Postel, 1954) in 89 per cent. There was at least 60° of flexion in 89 per cent. of hips.