dosage in all these patients, and were successful in about half of them. We noted an interesting fall in lymphocyte count, comparing the lymphocyte count with the total white cell count at the beginning of treatment and after one year. Whether or not immunosuppressives have any part to play in treatment of rheumatoid arthritis requires further study; we are at the present engaged in a double-blind controlled trial.*

DR. G. D. KERSLEY (*Bath*) In my experience in rheumatoid arthritis, the drug has often had to be stopped on account of side-effects. On the other hand we have had very good results in two cases which previously required a large dosage of steroids to control their disease.

DR. T. BITTER (*Bad Ragaz*) I should like to add one minor comment. The effect on a secondary immune response of a so-called immunosuppressive drug is far from proven. The cytostatic effect is potent and the indications are probably best in highly cellular disease, in which we want to suppress cells. If the cells are sufficiently suppressed, a secondary immune response might appear to be suppressed without actual evidence of an immunosuppression.

***Reference**

MASON, M., CURREY, H. L. F., BARNES, C. G., DUNNE, J. F., HAZLEMAN, B. L., AND STRICKLAND, I. D. (1969). *Brit. med. J.*, 1, 420 (Azathioprine in rheumatoid arthritis).

Effect of Rumalon on Embryonic Cartilage in Culture. By K. T. RAJAN (*Aylesbury*)

Embryonic bones were treated with collagenase which severely depleted the matrix in culture. This effect was reversible and the matrix regenerated when the explants were restored to a normal medium. Paired rudiments treated with the enzymes were subsequently transferred to normal media with and without Rumalon.

Preliminary results suggest that in Rumalon treated explants there was:

(*a*) Englargement of the articular cartilage;

(*b*) Increased metachromasia;

(*c*) Vacuolation of the growth zones.

These changes indicate enhanced function of the chondrocytes; the vacuolation could be due to overstimulation of the cells.

Discussion

DR. G. LOEWI (*Taplow*) As far as I have understood you, the controls without Rumalon had no similar extract added to them; might not the addition of an extract of some other tissue, not related to cartilage, be another interesting control, because it is just possible that you are adding additional nutriments?

DR. RAJAN Another kind of control would be to inactivate the Rumalon and then put it in and watch the result.

DR. SILBERBERG (*St. Louis*) As an experimental pathologist, I should like to put in a word for the animal experiment, which is particularly valuable if the animal develops a disease which is an analogue of the human disease. Mice do develop osteoarthrosis, and we have seen that the course of the development of the disease corresponds closely to that in the human. We have in the past months and years treated mice with small doses of Rumalon subcutaneously and have studied the chondrocytes of the hip joint with the electronmicroscope. The articular chondrocytes of adult mice show a hypertrophy of the cell and an overdevelopment of the cytoplasmic organelles which we interpret as a sign of increased function of the cells as a whole.

A Double-blind Controlled Trial of Rumalon in the Treatment of Painful Osteoarthrosis of the Hip. By A. ST. J. DIXON. G. D. KERSLEY, R. MERCER (*Bath*), M. THOMPSON (*Newcastle*), R. M. MASON, C. BARNES (*London*), and G. WENLEY (*Norwich*), with statistical analysis by E. LEWIS-FANING (*Rhoose, Glam.*)

Rumalon is a bovine bone marrow and cartilage extract which affects the growth and the metabolism of articular cartilage in various experimental animals and procedures. It has been extensively used to treat human osteoarthrosis but seldom under the conditions of a controlled clinical trial. A double-blind, four centre, controlled trial of intramuscular injections of Rumalon (R) in osteoarthrosis of the hip has been completed. 150 patients entered the trial, of whom 75 were randomly allocated to a control group receiving intramuscular injections of a 1 in 10,000 dilution of Rumalon (P). Aloxiprin or paracetamol tablets were given as needed for pain. Injections of R or P were given three times a week for 12 weeks, followed by 12 weeks of observation. For those who accepted, the treatment and observation schedules were repeated to a total of 48 weeks.

At 24 weeks 132 patients remained in the trial. There was no difference between the R and P groups in the doctor's overall estimate of improvement or deterioration, the patient's overall estimate of improvement or deterioration, or in pain at rest, pain on walking, or several measurements of hip function, or in the reasons for premature withdraw from the trial. 36 R and 44 P patients considered they were improved.

At 48 weeks 96 patients remained in the trial. Seven of the indices initially studied were considered to be worth further analysis. Five of these showed no difference between R and P groups, but two, namely pain on movement and pain at rest, showed a significant advantage for R at 48 weeks which was confined to patients with lesser radiological grades (grades 2 and 3) osteoarthrosis.

X rays taken at weeks 0, 24, and 48 showed no difference in rate of deterioration between R and P groups.

Thus Rumalon, in a dosage of 2 ml. intramuscularly given three times a week for 12 weeks for painful osteoarthrosis of the hip was not associated with improvement which was detectable under the conditions of this trial, but when treatment was continued for a total of 24 weeks in patients with lesser radiological grades of osteoarthrosis a significantly higher proportion of those treated with R than those with P reported relief of pain.

Discussion

DR. E. B. D. HAMILTON (*London*) We have carried out a controlled double-blind trial on the knee in 107 patients, at five centres, and over a period of 6 months.

As you might expect, we did not get a decisive answer after 6 months. Like Dr. Dixon we found a very striking placebo response after 3 months. 84 per cent. of the patients on placebo were improved at 3 months and over 50 per cent. at 6 months. There are two other points I should like to make. As in Dr. Dixon's trial no physical treatment was to be given to our patients unless absolutely necessary; but when the results were analysed, ten patients in the placebo group had had additional physical treatment, whereas only two in the Rumalon treated group had this treatment. The other point is that, unlike the hip trial, at the end of 6 months there was a definite trend in all the radiological parameters in favour of Rumalon; in one of these parameters, the reduction in the medial joint space approached a significant level. 5 per cent. of the Rumalon treated patients (with Grade 2 or 3 osteoarthrosis) showed deterioration at 6 months and 25 per cent. of the placebo group showed deterioration. The *x* rays were read independently by three observers and are now going to be re-read by Dr. Popert and Dr. Golding.

DR. J. H. GLYN (*London*) If you want to get the Rumalon into the joint cartilage, why don't you put it there directly instead of giving it systemically? The cartilage presumably does not receive the Rumalon in high concentrations and it would seem more logical to inject directly into the joint. Has this been done? Could the difference in concentration explain the difference between the experimental results and the clinical results?

DR. DIXON I am not aware of any experiments with local injections. I do not think that you can assume that the conditions for the nutrition of chondrocytes in fairly advanced destructive osteoarthrosis are the same as in the normal cartilage. It may well be that the nutrition from the subchondral vascular supply is far more important.

DR. A. J. POPERT (*Droitwich*) When we consider the results of any therapeutic trial it is important to have clearly in mind what information it is possible for that trial to produce. When a disease has run its full course it seems naïve to expect that any method of treatment should have any effect at all. I think that we should have learnt, by this time, that patients in advanced stages of a disease are best excluded from a therapeutic trial. Secondly, the duration of an experiment should bear some relation to the natural history of the complaint. In a disease with a life history extending perhaps over 20 to 50 years it would seem to me incredible that any treatment given over a period of weeks or months could produce any noticeable effect. Trials of this nature should be conducted over a long period of time, and preferably on patients in an early rather than an advanced stage of the disease. Finally, although I have not assessed patients in this trial, I have seen some of them from time to time. In an osteoarthritic knee with fairly advanced changes, crepitus is a striking physical sign; never yet have I seen crepitus, once present in an osteoarthritic knee, disappear. In two of the patients in this trial, however, whether they received the active substance or not, this sign has disappeared. One further patient I know, with severe rheumatoid arthritis and secondary osteoarthritis in the knees, was treated by her physician with Rumalon. She chanced to be referred to me later; I asked her whether it had helped her, and she said 'It did nothing to my knees, but it straightened out my fingers beautifully'.

Stiffness of the Knee in Normal and Osteoarthrosic Subjects. By R. GODDARD, D. DOWSON, M. D. LONGFIELD, and V. WRIGHT (*Leeds*)

Part of the programme of the Bioengineering Group for the Study of Human Joints has been devoted to characterizing stiffness of the knee. Studies on the metacarpophalangeal joint have been extended to measure quantitatively and qualitatively the stiffness of a weight-bearing joint.

The apparatus imposes a sinusoidal motion on the knee at various amplitudes and frequencies of rotation. The torque resisting this motion was measured and related to rotational displacement. Physiological variations in stiffness of the knee were measured in relation to sex, age, and body temperature. Joints with osteoarthrosis were studied, and in particular the characteristic phenomenon of 'articular gelling' was investigated.

Discussion

DR. J. A. MATHEWS I should like to ask whether, as the knee is a weight-bearing joint, an attempt was made to measure stiffness in the knee joint when it was in a weight-bearing condition?

DR. GODDARD We are aware of this problem of weight-bearing and we can see no other means at present of loading the joint physiologically and measuring it. In fact the only loading present was the slight load imposed by the weight of the thigh, and at present this is the only loading condition we are investigating.

DR. H. L. F. CURREY (*London*) May I ask whether the changes were recorded at different body temperatures? Might they be due to altered viscosity of the synovial fluid, for example, or perhaps to altered physical properties of the subcutaneous fat around the joints?

DR. GODDARD In the temperature investigations the major changes were in the elastic range of stiffness; changes in the viscous effect were negligible as far as we could tell.

Radioisotope Studies of Rheumatoid Knees before and after Synovectomy. By A. KAY, A. KATES, E. N. COOMES, C. B. CAMERON, and E. CHANDLER (*London*)

Ten patients with rheumatoid arthritis and knee involvement about to undergo synovectomy were studied to assess the amount of synovial tissue left at operation and the extent to which the synovium regenerated over the subsequent year.

In each patient the knee was scanned after the introduction of 50-70/μci of Au^{198} colloid, first 2 days before