two out of 91 probands showed bilateral sacroiliitis alone without spondylitis?

DR. MACRAE Yes.

PROF. E. G. L. BYWATERS (*Taplow*) Isn't this rather low? Or perhaps I should ask Dr. Lawrence?

DR. LAWRENCE I wonder whether your method of assessing the ankylosing spondylitis criteria may have played a part? Taking flexion only as the criterion for limitation would include many people with disc disorders.

DR. MACRAE. I think this can be explained on the basis of our epidemiological technique. To my knowledge this is the first time that the New York Diagnostic Criteria have been used in an epidemiological survey. It may be that these criteria are too sensitive. We shall find out when more surveys have been done.

Some Observations on Culturing Human Cartilage and Joints. By K. T. RAJAN, ANNE HOPKINS, and ALAN HILL (*Oxford Regional Rheumatic Diseases Research Centre, Stoke Mandeville Hospital, Aylesbury*)

The technique of culturing limb bone rudiments has for the first time been extended to human tissue. Digits obtained from abortions were maintained in BGJ 5 medium supplemented with fetal calf serum for 12 days. Photomicrographs indicate that articular and epiphyseal cartilage survived for the maximum culture period. Preliminary observations on the development of joints have been made. The system offers potentialities for future studies of human disease.

Discussion

DR. K. M. BACKHOUSE (*London*) You mentioned a cartilaginous bar and you showed the beginnings of the joint. Did you in fact take these fingers before the joint formed or afterwards? Thinking back to Sokoloff, he showed an inter-relationship between muscle activity and joint formation. Does this come into your investigation?

DR. RAJAN In the earliest fetuses—about 10 weeks—you could just see where the future joint cavity was going to form. But in all the older fetuses the joints had already formed. The role of muscle activity in the formation of joints has been suggested by Murray in Australia and by Sokoloff. This is disproved by my experiments because there was no movement at all and we found that especially in the later fetuses which we allowed to grow for 12 days there was no evidence of ankylosis or disappearance of the joint cavity.

DR. J. H. GLYN (*London*) Would Dr. Rajan consider that he has a possible experimental model which could be employed to throw light on the alleged clinical risks of repeated intra-articular corticosteroid injection, in relation to destruction of the joint cartilage? Such an objective method of evaluating the effect of steroids on mucopolysaccharides would seem to be particularly desirable in view of Salter's experimental work on rabbit knee joints.

DR. RAJAN Preliminary work has shown that high doses of steroids in culture can produce osteoporosis. This can also be produced by using high doses of vitamin A, and we hope by using this carefully controlled condition to be able to develop a dose titration, from which you could say that from such and such a dose you get osteoporosis.

PROF. E. G. L. BYWATERS (*Taplow*) This is a very nice technique with obviously a great future. I was rather surprised that you said cartilage was so pernickety in its growth requirements. Some 30 odd years ago we were able to culture rabbit cartilage in glucose bicarbonate Ringer's solution for 10 days; the metabolic curve showed that there was some falling off but there was good glycolysis right up to the end of the 10 days. Is this difference between animal and human cartilage one of vitamin C requirement?

DR. RAJAN I started growing mouse cartilage, which is comparable to rabbit cartilage, and I subsequently changed to human cartilage. Regarding the question whether human tissue responds differently to biological substances, such as vitamins A and C and hydrocortisone, I have found that adding 10 i.u./ml. vitamin A to post-fetal mouse bones produced loss of metachromasia, diminution of the growth zone, and other effects that have been described by Fell and Mellanby. Adding the same dose to human rudiments, there was complete necrosis. When I added 3 i.u./ml. (one third of the dose necessary to produce the hypervitaminotic effect on mouse cartilage), I was able to obtain a comparable result. Thus one-third of the dose necessary to produce hypervitaminosis on mouse cartilage was sufficient for the human tissue. Our experiments in screening drugs in animals may in the long run not be suitable when we try to extrapolate to human tissue.

Do Oral Corticosteroids cause Osteoporosis in Rheumatoid Arthritis? By W. W. BUCHANAN, B. M. SAMUELS, M. K. JASANI, J. A. ANDERSON, W. M. O'BRIEN, J. A. BOYLE, G. NUKI, and I. T. BOYLE (*The Centre for Rheumatic Diseases and the University Department of Medicine, Royal Infirmary, Glasgow, and the Department of Preventive Medicine, University of Virginia School of Medicine, Charlottesville, Virginia, U.S.A.*).

A technique of multiple regression and covariance analysis has been performed to correct for differences in the many factors, such as age, duration and severity of disease, years since the menopause, and oral corticosteroid therapy, which could influence the development of osteoporosis in rheumatoid arthritis. The analysis showed that oral corticosteroids do cause osteoporosis when given in low doses to rheumatoid patients; a year of therapy causes as much osteoporosis as 5 years of ageing, and 2 years of therapy does as much damage as an increase of one in *x*-ray class.

Discussion

DR. D. A. BREWERTON (*London*) It seems to be suggested that local factors did not make the metacarpal index unreliable, and I must admit that this surprises me. I should have thought that the severity of local disease activity, local deformities, tendon disease, and so on would have had an enormous effect on local osteoporosis. This might not be well reflected in the radio-

graphic changes, which give only a crude measure of what is going on in a hand. As the metacarpals are surrounded by local problems, the choice of the metacarpal index worries me; and I do not see how mathematical corrections based on radiographic abnormalities reliably overcome this difficulty.

DR. BUCHANAN We have made it clear that local factors do indeed contribute, in the sense that the severity of the arthritis generally contributes to the degree of osteoporosis and this was essentially a group study. There may be an isolated case in which only one wrist and one hand were involved. This would throw the calculation out, but in general rheumatoid arthritis is a polyarticular disease and I do not think that local factors will make much difference to results. In any case the femoral index gives exactly the same results as this metacarpal index, but I take your point that in isolated cases these local factors would be important.

DR. P. J. L. HOLT (*London*) Everyone concentrates on corticosteroids in the production of osteoporosis. What about the other anti-inflammatory agents? Aspirin, for instance, has a marked effect on bone turnover. Have you studied this as well, or taken it into account?

DR. BUCHANAN No we have not studied this, but I agree that it would be worth taking into account. There are probably other factors involved and these regression equations could be made to tell you the magnitude of any other such possible factors. One should not underrate the difficulty of obtaining an accurate history of drug consumption.

DR. A. J. POPERT (*Worcester*) You will correct me if I am wrong, but the average age of your group who did not receive steroids was 47·7, whereas the age of the group who did was about 52·9. Now the average age at the menopause in women in this country is about 47, so that your treated group in fact were all about 5 years post-menopausal relative to the untreated group. If, as you say, each year past the menopause doubles the rate at which osteoporosis develops, this would give a weighting of about 10 years to the treated groups and I myself would doubt whether you have entirely proved your point.

DR. BUCHANAN Differences in age between the treated and untreated group are taken into account in the analysis of covariance. This is why we did it. The regression equation was worked out separately on each of the groups, making corrections for each of the factors considered in order to exclude any weighting due to these factors.

MR. A. KATES (*London*) Have you taken into account the *x*-ray changes associated with disuse atrophy as opposed to osteoporosis?

DR. BUCHANAN No we have not, but I think it would be rather important to do so.

DR. M. A. CHAMBERLAIN (*Middlesex Hospital*) I wonder if you have related the dose of prednisolone to osteoporosis. Does it relate in a linear fashion? Does 5 mg. have half the effect of 10 mg. or is there a logarithmic variation?

DR. BUCHANAN We have not done this because obviously it is very difficult to find out precisely what a patient has taken over a number of years. What we did was to exclude from the study patients who took large doses of prednisolone, *i.e.* 15 or 20 mg., and we tried to pick out those who had taken 10 mg. or less and were kept on a constant low dose of corticosteroid therapy. Within that 5 to 10 mg. range we do not, however, know what the relationship is. It would be a very difficult thing to discover and would require a prospective study.

DR. B. MCCONKEY (*Birmingham*) I should like to comment first on the choice of the metacarpal index. When we looked into this some years ago, with patients who had rheumatoid disease and others who had not, we often found quite severe osteoporosis of the spine when the metacarpal bones were apparently normal. My other comment is about patients with rheumatoid disease who develop obvious osteoporosis of the spine. The time at which they developed this after the beginning of treatment was very variable and there appeared to be a group who developed it fairly soon. These patients are not distinguished by age, sex, duration or severity of disease, or the use of other drugs as far as we could tell. I wonder if you have any comments on that?

DR. BUCHANAN As I have said, we have not studied the spine, but I suspect that if you study a group such as this you will find a reasonable correlation between the metacarpal index and any other index of osteoporosis. There will perhaps be the isolated case with osteoporosis of the metacarpals, but the question is how often did you observe this? What percentage of patients actually showed this? If it was 1 per cent. it wouldn't concern me in this particularly analysis, but if it was 50 per cent. then it would be very serious.

DR. B. MCCONKEY (*Birmingham*) I cannot give you the figures, but the percentage was big enough for the two radiologists who were looking at the *x* rays with me to give this up as a method at the time.

DR. BUCHANAN And this was in rheumatoid patients?

DR. B. MCCONKEY (*Birmingham*) In patients with rheumatoid arthritis and in people with senile osteoporosis of undetermined cause.

DR. B. A. MYLES (*Chertsey*) Am I right in thinking that you have assumed that the difference in the two groups, having allowed for the five or six parameters that you have excluded, is all due to corticosteroids?

DR. BUCHANAN Yes.

DR. MYLES (*Chertsey*) You have not considered that any other factors would be involved? Do you assume that, having made these exclusions, the rest of the difference is entirely due to corticosteroids?

DR. BUCHANAN There are probably many factors involved in the present study, such as aspirin and so forth, that have not been taken into consideration. This gives you a crude index as to how great a part steroids will play, but there is still a residuum which incorporates these other factors.