abandoned but this change has taken place over the period that you mention. Could some of the improvement of results have been the abandoning of immobilization therapy?

PROF. DEBLÉCOURT Immobilization was not used. We saw in the beginning too many patients treated as cases of tuberculosis or immobilized for other reasons and completely crippled, and initially there was a marked shortage of physiotherapists, but nowadays we have quite a number of very skilled physiotherapists and physiotherapy was much better in the later than in the earlier years.

DR. A. G. S. HILL (*Stoke Mandeville*) Do we all mean the same thing when we talk about peripheral joints and would your figures be different if you separated the intermediate joints of the extremities from the true peripheral joints, *i.e.* those of the hands and feet.

PROF. DE BLÉCOURT The peripheral joints involved were the knees, elbows, ankles, hands, and feet, not the shoulders and hips. The intermediate joints (knees mostly) were more frequently affected than the feet and hands.

DR. J. A. D. ANDERSON (*London*) You carried out a combined retrospective and prospective study over a number of years but gave no indication of the turnover of the population at risk. As you said, identified cases of a serious disease can be followed up because they are likely to continue to attend. Less serious cases may be lost and if the turnover of population of the area is high, could this not affect some of the conclusions about prevalences?

PROF. DE BLÉCOURT I cannot answer this question now. The prevalence of ankylosing spondylitis is estimated at 0.12 in the Netherlands and the turnover rate will certainly influence comparisons, but not, I think, in a very significant way.

DR. J. A. COSH (*Bath*) Did you find any patients with Reiter's syndrome who progressed to spondylitis? I notice that a proportion of your patients in the past decade are still being treated with radiotherapy. Have you any comments on the value and safety of radiotherapy for peripheral joints?

PROF. DEBLÉCOURT Patients with Reiter's disease and spondylitis are not included in this review. But we see quite a few who start with Reiter's disease which develops into something which is very like ankylosing spondylitis. Most of the radiotherapy was given by radiotherapists not from the university hospital. We have no experience in treating peripheral joints with radiotherapy. We now use it only occasionally for a very painful cervical column. To my knowledge we have never treated peripheral joints with radiotherapy in ankylosing spondylitis.

Controlled Trial of Penicillamine in Severe Rheumatoid Arthritis. By J. R. GOLDING, F. M. ANDREWS, VIRGINIA CAMP, A. T. DAY, A. M. FREEMAN, D. N. GOLDING, A. G. S. HILL, W. H. LYLE and A. G. MOWAT (*Oxford*)

A trial of D(—) penicillamine (Distamine) in severe uncontrolled rheumatoid disease has been carried out at five different centres, 105 patients with definite or classical rheumatoid arthritis of at least 2 years' duration and meeting additional criteria of disease severity were admitted. Allocation of patients to penicillamine (52) or

control (53) groups was randomized after stratification by age, sex, and current use of steroids and the trial was double-blind.

Measurements included erythrocyte sedimentation rate, Hb, differential agglutination test, pain, morning stiffness, articular index, grip strength, functional index, well-being, weight, and x-radiology of hands and feet. Results have been analysed to show mean improvement, percentage improvement, and the number and proportion of persons who were much, moderately, or at all improved in the various measurements after 3, 6, and 12 months of treatment.

There were no significant differences in the mean scores for each of these measurements between the two treatment groups at the start of the trial, but there were differences in almost all, with advantage to penicillamine, at the conclusion of the study, the differences being of statistically significant degree for erythrocyte sedimentation rate, Hb, morning stiffness, pain, articular index, function index, and grip strength.

Adverse reactions were more prevalent amongst the penicillamine group during the first 6 months of the trial but not during the second. Sixteen patients in the penicillamine group were withdrawn because of drug intolerance but none because of increasing rheumatoid activity. Nine of the controls withdrew because of increasing rheumatoid activity and one because of drug intolerance. Adverse reactions which led to withdrawal included rash, thrombocytopenia, albuminuria, and gastrointestinal upset. Recovery was invariable. Among the patients given penicillamine who had improved at 12 months, most of that improvement was already evident at 3 months.

The clinicians' opinion whether the trial treatment had been, with respect to the patient's rheumatoid disease, 'successful', 'of doubtful value', or 'of no value' was recorded whether the course was completed or not. Of the patients who completed the course, 71 per cent. of those on penicillamine and 8 per cent. of the controls were judged to have received 'successful' treatment. Similar figures are obtained even when the entire patient population is included.

It is evident that penicillamine is effective in severe and advanced rheumatoid disease. Controlled studies of its use in early disease are now indicated.

Discussion

DR. J. H. GLYN (*London*) What happened in terms of the disease process when you had to withdraw the patients because of toxic effects? Did they all deteriorate again or not?

DR. GOLDING This was very variable. I haven't got sufficient figures to comment on that.

PROF. C. A. KEELE (*London*) What was the dose of penicillamine used?

DR. GOLDING Penicillamine was given as Distamine capsules as follows: 0.2 weeks 1 b.d., from 2.4 weeks 1 q.i.d., 4.6 weeks 2 t.i.d. and so on rising to a maximum of 1.5 g of base. The controls were given dummy capsules.

PROF. C. A. KEELE (*London*) And any other treatment?

DR. GOLDING We did not stop the current treatment in either group. In other words, both the control and the penicillamine groups could have steroids.

DR. F. DUDLEY HART (London) This interesting compound definitely does produce therapeutic benefit. The side-effects are the problem. Would Dr. Golding say that these side-effects all recover and, if you re-start reappear to disappear again on stopping? How long do you go on doing this? How often do you think it is safe to re-start?

DR. GOLDING This is a question of cardinal importance. Our conclusions are as follows: if a patient develops albuminuria, thrombocytopenia, or rash we withdraw the drug and wait until the side-effect has completely gone. We then very cautiously re-introduce penicillamine, but if the same side-effect returns we regard that as a final warning and do not give the patient the drug under any circumstance in the future. All patients recovered.

PROF. V. WRIGHT (Leeds) I am very much interested in the functional index that Dr. Golding referred to, because if we don't have a cure, in the final analysis it is the function that is all important. What intrigued me was how one obtained standardization between five units doing occupational therapy assessment?

DR. GOLDING The functional index worked out as follows. Patients were asked to perform 64 simple tasks, either at home or outside, and they were scored according to whether they could do it easily, with difficulty, or not at all. We did not find that standardization between the five groups was a problem. It needs improving but we are reasonably well satisfied.

DR. J. T. SCOTT (London) There was an overall fall in titre of rheumatoid factor. Was there a correlation between this and clinical improvement in individual patients?

DR. GOLDING Not particularly.

DR. B. MCCONKEY (Birmingham) Do these results mean that quite a lot of patients did fairly well or that a small number of patients did very well? Can you give me some idea of the proportions?

DR. GOLDING There was a very wide spectrum between those who did extremely well and those who did moderately well. All grades of improvement are shown.

DR. H. L. F. CURREY (London) If this drug is effective in rheumatoid arthritis a lot of interest obviously attaches to its mode of action. We have looked at this in the laboratory and I should like to report very briefly if I may some work of Dr. Liyanage. We gave rats D-penicillamine by mouth in courses lasting up to 21 days and in doses up to over ten times the human dose (doses which exceeded the rat LD₅₀) and we were able to show absolutely no suppression whatsoever of adjuvant arthritis or indeed of conventional minimum response or of nonspecific inflammatory responses in these rodents. This is in striking contrast to results obtained in the same model using drugs such as azathioprine and cyclophosphamide where one can quite easily suppress the disease by doses comparable to those used clinically in treating rheumatoid arthritis. So this would suggest that, if this drug is effective in rheumatoid arthritis and if the rodent model has any relevance to this, penicillamine works in a different manner from the so-called immunosuppressive drugs.

DR. I. A. JAFFE (U.S.A.) In response to your question about the titres, that is exactly what we reported initially. That is to say there is a latent period after treatment has begun, before the titre drops. We agree completely with

your statement about animal models and it is gratifying that penicillamine works in man and not in animals. But quite seriously, and worthy of emphasis with respect to mechanism, is that the drug is not cytotoxic. It is not an immunosuppressant in that sense of the word, and I think we must keep a completely open mind with respect to its mechanism of action in a disease of which the aetiology is unknown.

Effect of Stilboestrol on Levels of Uric Acid in Plasma and Urine. By A. NICHOLLS, M. L. SNAITH, H. YABLONSKY, and J. T. SCOTT (*West London Hospital and Kennedy Institute of Rheumatology*)

It is well known that plasma levels of urate in adult women under the age of the menopause are about 1.0 mg./100 ml. lower than those of men (Mikkelsen, Dodge, and Valkenburg, 1965). Renal clearance of urate tends to be higher in women than in men (Wolfson, Hunt, Levine, Guterman, Cohn, Rosenberg, Huddleston, and Kadota, 1949; Scott and Pollard, 1970). It is possible that this sex difference is mediated by hormonal influences and the present study examines the effect of long-term administration of stilboestrol on plasma and urinary urate.

The study was carried out on 22 adult trans-sexual men (courtesy Dr. John Randell, D.P.M.) who were to undergo psychotherapy and hormone therapy. Basal 24-hour urate and creatinine clearances were estimated with the subjects taking a low-purine diet, after which treatment was started with stilboestrol in a daily dose of 10 to 30 mg. After treatment had continued for a mean of 10 weeks, the subjects again took a low-purine diet and clearances were repeated.

Plasma urate fell in fifteen of the 22 subjects, the mean overall fall being 0.7 mg./100 ml., a significant decrease ($P < 0.01$). Urinary urate rose in seventeen of twenty subjects, the mean rise being 115 mg./24 hrs, again significant ($P < 0.01$). Mean urate clearance rose correspondingly while the hormone was being taken, creatinine clearance remaining unchanged.

The results show clearly that stilboestrol enhances the excretion of urate and lowers the plasma level. It is suggested that such a hormonal factor is the cause of the difference in plasma urate levels found between the sexes.

Discussion

DR. R. GRAHAME (London) Have you had the opportunity of studying the effect of androgens in female transvestites?

DR. SCOTT Only in one, with rather doubtful results. Most of these patients are men and there are various difficulties in studying women with this condition. We are now moving on to use animals, which may give us the opportunity of investigating the interplay of these hormones in a way which would not be possible with humans.

DR. J. S. LAWRENCE (Manchester) Do you feel that this action of stilboestrol is the whole explanation of the sex difference in serum uric acid level? Acheson and O'Brien (1966) have shown a relationship of serum uric acid to haemoglobin levels. This would suggest that the sex difference in uric acid is due to difference in turn-over of blood cells.