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.

DR. SCOTT What happens to haemoglobin levels at the time of puberty and menopause? I should think this is a much less likely cause. The changes produced by stilboestrol are very striking, and a hormonal mechanism of this kind could well explain the sex difference in urate levels, though of course this suggestion does not preclude other contributory factors.

References

- Acheson, R. M., and O'Brien, W. M. (1966) *Lancet*, 2, 777
 Mikkelsen, W. M., Dodge, H. J., and Valkenburg, H. (1965) *Amer. J. Med.*, 39, 242
 Scott, J. T., and Pollard, A. C. (1970) *Ann. rheum. Dis.*, 29, 397
 Wolfson, W. Q., Hunt, H. D., Levine, R., Guterman, H. S., Cohn, C., Rosenberg, E. F., Huddleston, B., and Kadota, K. (1949) *J. clin. Endocr.*, 9, 149

Experimentally-induced Osteoarthritis in the Dog. By M. J. POND (*University of Glasgow Veterinary School*) and G. NUKI (*The Centre for Rheumatic Diseases, Glasgow*)

The development of animal models of arthritis has figured in many investigations into the pathogenesis of connective tissue disease. Some experimentally induced forms of inflammatory arthritis are widely accepted as models for rheumatoid arthritis, but there is at present no adequate animal model of osteoarthritis.

Hind limb lameness in the dog commonly results from rupture of the anterior (cranial) cruciate ligament in the stifle (knee) joint and, if the subsequent instability is not surgically corrected, a high percentage of dogs develop degenerative joint changes.

The anterior cruciate ligament in one stifle joint of each of ten dogs was ruptured using a new closed technique and the opposite joint served as the control. The dogs were killed at various times between 1 and 26 weeks after rupture of the ligament and the radiological and pathological features suggest that this may be a model which closely simulates clinical osteoarthritis.

A large number of investigations were performed at regular intervals before the dogs were killed and a detailed examination was made of all the joint tissues obtained. *post mortem*.

The progression of the experimentally-induced condition follows a very similar course to that of the naturally occurring instability and the final gross pathology is that of an osteoarthritis.

The histological appearance of the articular cartilage varied from normal in the dog killed one week after surgery to gross fibrillation extending into the depth of the tissue in those killed at a longer interval after ligament rupture. In a number of areas that do not show gross fibrillation, an abnormality is seen in the more superficial zones. In these specimens the superficial layers of tangentially arranged cells are absent and so are the chondrocytes in the region immediately beneath the superficial layers. Early fibrillation is seen in some of these 'acellular zones'.

Articular cartilage from areas adjacent to those showing 'acellular zones', when examined under the scanning electron microscope, shows flaking and peeling of the normal surface membrane with exposure of collagen fibre bundles. In more severely damaged areas, gross fibrillation is seen on the articular surface and on the fractured specimens.

Discussion

PROF. D. L. GARDNER (Belfast) Dr. Pond and his colleagues are not wholly accurate in stating that no other models exist for the reproduction of osteoarthritis. Division of the sciatic nerve in the dog, the injection of papain into synovial joints, and other techniques have been used in the past. Nevertheless, he has elucidated something of the early changes in one experimental disease. What causes the loss of superficial glycosaminoglycan? What are the changes in the chondrocytes? What relationship do these bear to the human disease?

DR. POND There were few models that satisfied our criteria, though we knew that there had been many attempts. We have planned a more detailed assessment of the biochemical abnormalities in the articular cartilage in these areas and a more detailed investigation of the chondrocytes which we hope will perhaps help to answer your query, but in this pilot study we did not reach those depths.

PROF. V. WRIGHT (Leeds) This is a very interesting model. The only thing that worries me about it is that severing the cruciate ligament causes a pretty acute synovitis. That is one reason presumably why the dog cannot walk on its leg for about a fortnight. I wonder therefore how much one can extrapolate from this model.

DR. POND There certainly is a very marked inflammatory response in the synovial membrane for the first 48 hours, which decreases markedly thereafter, and there was very little evidence of an acute synovial inflammation even at one week.

DR. J. H. GLYN (London) The nearest clinical analogue of a grossly unstable weightbearing joint is that seen after poliomyelitis. I was very struck in the course of a study carried out a few years ago (Glyn, Sutherland, Walker, and Young, 1966) by how little osteoarthritis these unstable and recurrently traumatized joints developed over the years. I tried to encourage some veterinarian colleagues to carry out nerve-section experiments in dogs, but I was told that they would not work satisfactorily because such quadrupeds would not take any weight on their paretic joints. Therefore, they would not be expected to develop osteoarthritis. Did your dogs distribute their weight normally after you sectioned their anterior cruciate ligaments and do you attribute the changes you found entirely to weight bearing?

DR. POND Most of them will take weight 2 weeks after induction of the disability.

DR. J. H. GLYN (London) Would you agree despite this that your experimental model could not be used for nerve-section experiments in order to determine any possible protective effect of such a procedure?

DR. POND Certainly most of our patients when they have had any traumatic injury or experimental induction of nerve trauma just tend to drag their limb around and don't bear weight at all.

MR. A. R. TAYLOR (Stoke Mandeville) We often see changes in the femoral condyles at removal of torn menisci. You did not make it clear whether the changes you saw in the femoral condyle occurred irrespective of damage to the menisci?