HEBERDEN SOCIETY

At a Clinical Meeting held at the Royal National Orthopaedic Hospital, Stanmore, on March 17, 1967, the following papers were presented:

Post Mortem Study of the Hip Joint. P. Byers (London): The right hip joint was removed from 450 cadavers, and 200 of these joints were examined closely and the changes classified in preparation for recording the findings in all the joints. These are to be correlated with age, with radiological changes in the hands and pelvis, and with each other.

Discussion.—Dr. O. Savage (London): I should like to ask two questions. Have you any way of knowing whether these subjects had any symptoms in life and can the changes in the fovea be checked radiologically? It seems to me that this is a new conception, that many patients might present with hip pain in whom the x rays do not permit a firm diagnosis of osteo-arthrosis of the hip. I have always found it very difficult to decide about radiological changes in the region of the fovea. Can you help us?

Dr. Byers: Answering the first question, the clinical records of all these patients are available to us and can be consulted for clinical information, but we have not found this particularly helpful. With regard to the second question, foveal change is perhaps one of the chief appearances both in x rays and in detailed anatomical studies, and I hope that in the future we shall be able to answer this type of question exactly. I think it best to keep my own opinions to myself until I can give a firm answer.

Sir Herbert Seddon (London): Have you yet any evidence of regeneration of cartilage-either of true cartilage or of fibrocartilage?

Dr. Byers: This is a difficult question to answer. On the whole I should say that we have not. This is on the basis of gross examination: we have not yet looked at any histological material.

Prof. J. H. Kellgren (Manchester): I am extremely glad that Dr. Byers is doing this study, because both from our clinical material and from the survey material of Dr. Lawrence we had come to the idea there were certain radiological appearances in the hip that correlated with Heberden's nodes, and were rather different from what one normally regards as the osteo-arthrosis of the degenerative type—the "worn-out" hip that is the main classical problem. We have also observed that these x-ray changes were associated with a ring of osteophytes and possibly some ossification of cartilage, rather fitting in with Dr. Byers' first type of change. Sometimes a striking x-ray picture was associated with very little pain and disability. It seemed to us that there was a possibility of two kinds of degenerative change in the hip—one which is rather common and the other which presents the classical clinical problem. I shall be interested to see what comes out of this radiological/pathological correlation. This is why I was so anxious to get x rays of the hands!

Abnormal Sulphobromophthalein Retention in Gout.* R. Graham, R. V. Haslam, and J. T. Scott (Royal Postgraduate Medical School, Hammersmith).

Comparison of Plasma Cortisol Response to Synovectomy of the Knee in Corticosteroid and Non-corticosteroid Treated Rheumatoid Patients. M. K. Jasani, P. A. Freeman, M. J. Diver, J. A. Boyle, W. W. Buchanan (Glasgow): Understanding of the incidence of suppression and site of involvement of the hypothalamo-pituitary-adrenal (HPA) axis in patients receiving oral corticosteroids has increased recently with the availability of several methods of testing the HPA axis. Plasma 11-hydroxycorticosteroid (11-OHCS) response to the stress of synovectomy of knee was measured in twenty patients with definite rheumatoid arthritis receiving oral corticosteroids, and their range of response was compared with that of twenty non-corticosteroid treated rheumatoid patients matched for age and sex.

The results show that as a group the corticosteroid-treated patients had significantly poorer plasma 11-OHCS responses, and had slightly lower blood pressure responses during surgery.

Nine of the corticosteroid-treated patients with definite HPA axis suppression, as revealed by subnormal response to Synacthen, lysine-vasopressin, and insulin-induced hypoglycaemia tests, had plasma 11-OHCS levels in response to synovectomy which lay below the lower limit of the 95 per cent. confidence limits of plasma 11-OHCS response to the same operation in the control patients; and one patient developed hypotension which required treatment with intravenous hydrocortisone.

The eleven remaining corticosteroid-treated patients had rises in plasma 11-OHCS that lay within the normal range for synovectomy, and none developed hypotension. Six had no detectable suppression of the HPA axis, and five had normal adrenal response to Synacthen but a subnormal response to one or more of the remaining tests. These findings indicate that patients with a subnormal response to Synacthen testing should receive routine corticosteroid cover during and after operation.

The position of the corticosteroid-treated patients who give a normal response to Synacthen testing is still being studied.

* This paper and the discussion thereon is to be published in the January, 1968, issue of the Annals.
**Discussion.**—Dr. O. Savage (London): I think this was a very brave study, which had to be carried out. You have shown that there was very little difference in the blood pressure response of these groups of patients. You mentioned one patient who had to have intravenous hydrocortisone. Were there any others in this series whom you were worried about after surgery?

Dr. Jasani: No. None of the 20 corticosteroid-treated patients studied, with the exception of the patient already mentioned, developed a systolic blood pressure lower than 90 mm. Hg during or after synovectomy of the knee.

Prof. J. H. Kelly (Manchester): How well were these patients in the immediately post-operative days? In a number of patients with rheumatoid arthritis without adequate steroid cover there is often quite a significant flare and such things as neuropathy in the second, third, or fourth post-operative days. Did you have any impressions of this sort or did the withdrawal of steroids for 24 hours seem to have any specific effect?

Dr. Jasani: These patients had had corticosteroid therapy discontinued for 18 hours pre-operatively. Post-operative side-effects were carefully looked for during the first 48 hours after surgery, and no ill-effects were noted. This could be due to the fact that normal corticosteroid therapy was resumed after the 6-hour blood sample had been taken; we did not want to extend our observations further than this.

Dr. B. M. Ansell (Taplow): Could we have details of the duration of treatment and dosage of corticosteroids in these patients?

Dr. Jasani: The patients who had a sub-normal response to Synacthen had had a much larger dosage as well as much longer duration of therapy than those who had normal responses to all four tests of the HPA axis.

Prof. J. H. Kelly (Manchester): But what sort of dose?

Dr. Jasani: The estimated dose of corticosteroid therapy can best be expressed as grammes of prednisolone. I should explain that none of the patient's had been followed up by us from the initiation of their corticosteroid therapy: they had been referred to us from their general practitioners and were receiving a variety of corticosteroid preparations. The estimated total dose of corticosteroids in grammes of prednisolone for the three groups was as follows:

- Patients with all tests of HPA axis normal—4.4 g. (range 2.0--12.8)
- Patients with a normal synacthen test, but one or more of the other tests of HPT axis abnormal—5.3 g. (range 8.0--22.0)
- Patients with a subnormal synacthen test—15.4 g. (range 3.0--29.0)

**Cultivation of Micro-organisms from Rheumatoid Synovia.** A. G. S. Hill, J. N. McCormick, C. L. Greenbury, C. J. Morris, and J. Kenninagle (Stoke Mandeville): From fifteen of thirty patients with rheumatoid arthritis, diphtheroid organisms were isolated from covenlip tissue culture preparations of synovial fluid cells implanted on blood agar plates. By a similar technique, diphtheroid organisms were recovered from one rheumatoid pleural fluid examined, from each of two cases of psoriasis and arthritis, and from four of six specimens of synovial fluid obtained from patients with osteo-arthritis.

Controls consisted of 45 "subcultures" from unincubated blood agar plates from which diphtheroid organisms were isolated on one occasion and 22 samples of unincoculated tissue culture medium which yielded a diphtheroid contaminant in one instance. Other occasional contaminants were coliform organisms and Gram-positive cocci which occurred as frequently in the controls as in the synovial fluid cultures.

A fluorescein-labelled polyvalent antiserum was prepared against none of the rheumatoid isolates, but in a preliminary investigation no significant staining was observed in sections of rheumatoid synovial biopsies or in cultured synovial fluid cells, although intra-cellular organisms are readily detected by the anti-serum in deliberately infected cell cultures. In view of the negative immuno-fluorescence results and the recovery of diphtheroid organisms from non-rheumatoid control fluids, it is suggested that bacteriological investigations of this kind in rheumatoid arthritis must be interpreted with more caution than optimism.

**Discussion.**—Dr. J. J. R. Duthie (Edinburgh): I should like to congratulate Dr. McCormick and his colleagues on this excellent piece of work, and I am in complete agreement with the caution which they are obviously exercising in the interpretation of these results. I was going to question the use of a fluorescent antiserum raised against the organisms in their extracellular bacterial form on the grounds that it may contain antibodies only to antigens not present in the intracellular form, but Dr. McCormick obviously has this possibility in mind. There is a chance that the use of Gram stain on a fresh impression smear from synovial membrane or on cells recovered from synovial fluid might reveal Gram-positive material. Have you ever seen this?

Dr. McCormick: Not so far. We have seen intracellular Gram-positive material only after the cells have grown in culture for at least 48 hours.

Dr. Duthie: That is our experience too. It may be the third or fourth subculture before colonies of the organisms develop on solid media. I may add that we have isolated organisms from the joints of another six patients since our first report. We have not as yet seen anything grow in our control material, which includes another six fluids from osteo-arthritis joints.

**Rheumatoid-like Arthritis produced by Streptolysin S and by Streptococcal L-Forms.** J. Cook (Stannmore): Chronic arthritis was produced in rabbits by the intra-articular injection of streptolysin S and streptococcal L-form. Various changes were seen in these two different forms of arthritis: The mechanism of their production was discussed.

**Proteases involved in the Breakdown of Cartilage in vitro.** Y. Ali (Stannmore): An attempt was made to study the endogenous enzymes in cartilage which are capable of degrading the matrix autocatalytically under suitable conditions. There was evidence of the presence of a proteolytic enzyme in cartilage which is capable of releasing 50 per cent. of the chondromucoprotein in the matrix within 24 hours at pH5. The properties of this cathepsin-like enzyme, its mode of activation, its inhibition by specific inhibitors, and its presence in cartilage from various sources were discussed.
Pathogenesis of Rheumatoid-like Arthritis. C. Lack (Stanmore): Histological changes in synovial tissue resembling those seen in rheumatoid arthritis were produced by a variety of agents. Caragheenin, heterologous fibrin, streptolysin S, streptococci, and streptococcal L-forms were injected into the joint cavity in single or multiple doses and evoked the same sequence of change—hyperplasia of lining cells, round cell infiltration, peri-vascular cuffing, "lymphoid follicles", pannus, and cartilage erosion. The time sequence of these changes were related to a hypothetical auto-immune mechanism and to fibroplasia.

Discussion.—Dr. K. T. Rajan (Stoke Mandeville): Dr. Cook mentioned that, in animals pre-treated with chloroquine, there were still the changes of chronic synovitis. Have you any data on the production of arthritis in animals treated with steroids?

Dr. Cook: No. We did not pre-treat any animals with steroids.

Dr. K. T. Rajan (Stoke Mandeville): I should like to ask Dr. Ali about the pH measurement being around 5. Would not the usual figure in vivo be around 7?

Dr. Ali: Yes. I emphasized that this work was done in vitro. We do not know the conditions in vivo and we still need a lot of evidence about it.

Prof. E. G. L. Bywaters (Taplow): Can Dr. Cook say anything more about the role of endotoxin and has she tried the effect of tetracycline in the L-form model, particularly with a view to the prevention of fibrosis, at which stage the lesion is reversible.

Dr. Cook: No, we have not tried tetracycline, but it would be interesting to do this because in theory it should stop the whole process. I think Dr. Lack had better answer the question about endotoxin.

Dr. Lack: Hollingworth has put forward the view that endotoxin may well have "leached off" the dead streptococci during the production of the streptolysin S. How much you can attribute these changes to streptolysin S, the endotoxin, or some unknown toxin, does not seem to me to matter very much. We recognize these toxins because we have been accustomed to recognizing them.

Dr. Cook: It does not contain streptolysin S and does not appear to have an antigen.

Dr. D. J. Ward (Oswestry): Can Dr. Cook say how long it takes for the chloroquine to stabilize the lyosomes?

Dr. Cook: I believe it takes about 48 hours, but we gave them all several days before we began injections (daily during the whole time), and then gave a large dose on the day of injection.

Dr. McCormick: We are arranging to have these cells examined with the electron microscope, and this may tell us whether or not the intracellular organisms have a membrane. I do not think they can be either mycoplasmatic or bacterial L-forms, since I understand that these would not be Gram-positive. One cannot be sure, however, that the intracellular granular forms are not derived from L-forms as an intermediate stage in the evolution of the mature rod-shaped organisms.

Demonstrations were presented by Dr. C. Lack and the late Dr. A. MacPherson.

A Symposium was held on the Physiology of Bone, to which the following speakers contributed:

Dr. D. A. Brewerton (Stanmore): Introduction.

The Late Dr. A. MacPherson (Stanmore): Haemodynamics of Bone.

Dr. K. PiekarSKI (Cambridge): Mechanical Properties of Cortical Bone.

Mr. A. Catterall and Mr. T. L. Bowen (Stanmore): Electrical Properties of Bone.

Dr. P. Byers (London): Nerve Supply of Bone.