

HEBERDEN SOCIETY

Clinical Meeting.—A meeting was held in the London Hospital Medical School on February 24, 1956.

Drs. E. G. L. Bywaters, B. Ansell, and I. Isdale presented a paper on "Prognosis in Still's Disease as compared with Rheumatoid Arthritis".

In a series of over 200 cases of Still's disease seen at Taplow, the prognosis seems to be better than that in adult rheumatoid arthritis. Because of various factors affecting selection, strict comparison can only be made between cases seen early in the course of their disease. In 84 of these, seen within one year of the onset, the functional state compared originally and after 1, 2, 3, and 4 years shows a general improvement; only three patients failed to get better. A comparison was made with 125 adults, also all seen within a year of the onset of their disease, who formed part of the group being followed over a long-term period with the aid of the Nuffield Foundation. Here the results, although better than in adult cases seen after 1 year from onset, were worse than those found in the early childhood group. After dealing with the factors influencing prognosis and other manifestations of childhood disease, Dr. Bywaters detailed the results of a controlled trial of therapy of Still's disease with cortisone *versus* aspirin, which was being conducted under the auspices of the Medical Research Council and Nuffield Foundation Joint Committee, and has since been published (Ansell, Bywaters, and Isdale, 1956).

Ansell, B. M., Bywaters, E. G. L., and Isdale, I. C. (1956). *Brit. med. J.*, 1, 1075.

Dr. M. Keech presented a Paper on "Further electronmicroscopic observations on the transformation of collagen fibrils into 'elastin'."

The morphological response of both "moth-eaten" fibres (collagenase-treated human-skin collagen from different age-groups) and alkali-produced "elastin" (alkali-treated collagen) to various physical, chemical, and enzymatic agents was described. Most of these agents produce a dramatic conversion into "manufactured" elastic networks together with easily identifiable "moth-eaten" fibre conversion structures.

A striking age-difference in the response of collagenase-treated collagen to heat is demonstrated.

It is believed that "moth-eaten" fibres are intermediate structures, midway between collagen and elastin, and are the electron-microscope equivalent of the refractile fibres described by Cruise (1956).

Cruise, A. J. (1956). *Proc. roy. microscop. Soc.* (in the press).

In the clinical demonstration which followed the following cases were shown:

- (1) SIR RUSSELL BRAIN: Cervical Spondylolisthesis with Cord Compression and Paralysis of the Left Diaphragm.
- (2) MR. H. OSMOND-CLARKE (presented by Mr. G. C. Attenborough): Osteo-arthritis of the Hip located by "Charnley Compression Arthrodesis". This was followed by a discussion on this new operation.
- (3) SIR HORACE EVANS (presented by Dr. J. H. Ross): Polyarthritis, Uveitis, Disseminated Sclerosis, and Sexual Retardation in a Girl aged 17.
- (4) DR. W. S. TEGNER: Generalized Osteopetrosis presenting as Osteo-Arthritis of the Knees.
- (5) DR. R. M. MASON: Alkaptonuria with Ochronosis of Spine and Ears, previously diagnosed as Ankylosing Spondylitis.
- (6) DR. J. H. GLYN: Neuropathic Joints and Rheumatoid Arthritis in a Patient suffering from Syringo-Myelia.

Heberden Round.—This was given on June 1 and 2, by Dr. G. D. Kersley, at The Royal United Hospital, Bath. Fifteen clinical cases were shown and discussed.

Two cases had first appeared under the guise of "rheumatism":

(1) An osteoid osteoma of the thoracic spine commencing at the age of 13, undiagnosed for 5 years, and then cured completely by surgery. There had been localized tenderness, severe pain relieved only by massive doses of aspirin, and no other changes until a small area of absorption became visible in the lamina of the 5th thoracic vertebra.

(2) A case of osteoporosis *circumspecta* in Paget's disease.

Then followed a series of abnormalities of the cervical spine:

(3) Posterior osteophytosis with paraplegia and complete recovery following surgery. Points raised were the short history and good prognosis, the value of trying the Queckenstedt test in full flexion and extension of the neck, and the desirability of doing myelography in this region only when a neurosurgeon was available in case of "contretemps".

(4) Anterior osteophytosis causing the Globus syndrome and (5) marked x-ray osteophytosis with minimal symptoms.

(6) A case of subluxation of C₄-5 with diplegia due to rheumatoid changes and marked improvement after traction and the fitting of a collar. Cervical subluxations seen at the Royal National Hospital during the last 10 years were reviewed: seven had been the result of rheumatoid disease, two of which had succumbed; one which had been due to Neisserian infection, had

made a complete recovery; one due to gout; one due to sarcoma.

Other rheumatoid syndromes:

(7) Severe rheumatoid arthritis of the wrists and hands for 20 years with complete absence of pain, marked disorganization, but no neurological lesion.

(8) An "episodic" rheumatoid, who for 9 years had had attacks in the knees only, always occurring at 12-day intervals and lasting 2 days. The sedimentation rate had always been normal, there were no x-ray changes except a little osteoporosis, symptoms were only controlled by gold or synovectomy, and typical rheumatoid pathology had twice been demonstrated on biopsy. Intermittent hydrarthrosis, palindromic rheumatism, and allergy were discussed.

(9) A case of allergic arthritis resembling rheumatoid arthritis was shown, with cure following removal from the diet of coffee and fish.

Of thirteen cases of rheumatoid arthritis and asthma, the asthma and rheumatoid symptoms had alternated in seven, had seemed to correspond in two, and had had no relationship in four.

Dr. Kersley then took up a previous challenge that rheumatoid arthritis and gout were very rarely associated together, and showed three cases (10, 11, 12) in which both probably coexisted. Of 69 cases of gout, seventeen had also shown definite rheumatoid features; of this seventeen, fourteen were males.

A very severe case of tophaceous gout (13) was then demonstrated, with x-ray findings ranging over 10 years. The D.A.T. was negative.

In twenty cases of uncomplicated gout reviewed, the D.A.T. had been normal in every case. In ten of the gout+rheumatoid arthritis group, seven D.A.T.s were positive.

A challenge was then thrown out as to the value of a normal plasma uric acid in excluding a diagnosis of gout, and a case (14) was shown in whom the plasma uric acid had been estimated 57 times, all values being under 6 mg. per cent. In ten out of 55 cases of gout, normal plasma uric acid values had been a common feature before Benemid or large doses of salicylate had been used.

Finally (15) a case showing one of the "collagenoses" was on view for favour of diagnosis.

The following papers were given:

Animal Experiments with Radio-Active Gold, by Dr. M. R. Jeffrey (*Bath*).

Gold is still widely used in treating rheumatoid disease. Very little is known of its distribution or effects within the human body. The radio-isotope ^{198}Au (half-life 185 days) offers the possibility of information on the long-term distribution and excretion of gold. Preliminary results of animal experiments, undertaken before human use is considered, are reported.

Up to one month after injection, the pattern of distribution is similar in healthy rats, guinea-pigs, and rabbits. Up to 30 per cent. of the dose remains at the injection site and the kidneys concentrate much more activity than any other tissue. Roughly one-third of the

dose is excreted in a month. When inflammation is produced by the granuloma pouch technique of Selye, gold is more rapidly mobilized, only about 2 per cent. of the dose remaining at the injection site after a month. All tissues contain a larger amount and the rate of excretion is doubled.

Studies of the distribution at longer intervals after injection and of the finer details of distribution, using autoradiography, are proceeding.

In Vitro Metabolic Studies of Synovial Membrane, by Dr. D. P. Page Thomas and Mr. J. T. Dingle (*Bath*).

Synovial tissue from traumatic cases was shown to have a very low oxygen uptake, but a comparatively higher rate of aerobic and anaerobic glycolysis. There was a marked inhibition of glycolysis under aerobic conditions.

Rheumatoid synovia were classified into three types depending upon their proliferative state. All classes showed much greater metabolic activity than the synovia of traumatic aetiology. The metabolic activity of the rheumatoid synovia varied with their proliferative state, the most actively metabolizing tissues being found where the proliferative state was most intense. These rheumatoid synovia had a high degree of aerobic glycolysis. The lower oxidative metabolism displayed by the less proliferative rheumatoid synovia was not thought to be due to a diminution of enzymes or co-factors as the various enzyme systems of the tricarboxylic acid cycle were capable of stimulation by the addition of appropriate substrates. The *in vitro* effect of hydrocortisone at levels within the usual intra-articular therapeutic range was shown to inhibit aerobic glycolysis and oxidate metabolism to a marked degree. The percentage inhibition was greatest where synovial proliferation was most marked.

Excretion of 17-Ketosteroids in Gout, by Dr. E. R. Cook (*Bath*).

The abnormally low 17-ketosteroid output said to occur in gouty patients is being re-investigated by the determination of total and fractionated urinary 17-ketosteroids. The patients selected were free from renal complications to avoid the false low values reported to occur from urines containing protein.

The 17-ketosteroid excretion of nineteen cases of gout, with a mean age of 53 ± 10 years was 10.9 ± 3.7 mg./24 hrs. Chromatographic analysis of the ketosteroids from fourteen of these patients with a mean age of 49 years showed the usual wide variations in pattern between individuals, the mean values being dehydroandrosterone 21 per cent. (range 7-44 per cent.), androsterone 33 per cent. (range 15-44), etiocholanolone 37 per cent. (range 20-57), and 11-oxy-17-ketosteroids 8 per cent. (range 5-13). The androsterone etiocholanolone ratio was 0.9 (range 0.4-2.0).

These figures do not suggest an abnormal 17-ketosteroid excretion in gout, but it must be emphasized that this is a preliminary account of work which is not yet complete.

Peripheral Vascular Studies in Early Rheumatoid Arthritis, by Dr. J. H. Peacock (*Bristol*).

Eleven cases of early generalized rheumatoid arthritis were investigated. Arteriograms performed by puncture of the brachial artery showed no evidence of arterial obstruction in the digital blood vessels. Peripheral nerve blocks of the ulnar, median, and radial nerves confirmed the ability of the blood vessels of the hands to undergo full vasodilatation. Skin temperature studies of the fingers and toes were performed simultaneously with hand and forearm blood flows at a constant room temperature of $20 \pm 0.5^\circ \text{C}$. The hand blood flows were measured in a water-filled thermostatically controlled venous occlusion plethysmograph through an entire local temperature range of $18-42^\circ \text{C}$. The patterns of blood flow obtained were compared with normal standard controls, Raynaud's disease, and acrocyanosis.

The effects of aspirin, intravenous hydrocortisone, phenyl-butazone, and a peripheral vaso-dilator ("Dibenziline") were compared. The degree of vasodilatation induced and improvement of clinical symptoms that resulted were tabulated.

The hand blood flows in five of eleven cases were found to be much higher than those obtained in normal controls. Two cases only were found to have a degree of peripheral vascular ischaemia normally seen in Raynaud's disease. In four cases the blood flows were in the normal or lower normal range.

Vasodilatation induced by the use of Dibenziline was not found to be effective in relieving the symptoms and signs of the rheumatic process.

In some cases a discrepancy between the skin temperatures and blood flows was observed. As the forearm blood flows were found to be in the normal range and no inflammatory process was present in the joints of the hands when the observations were made, this discrepancy appeared to be due to the presence of an arteriovenous shunt. It appeared possible that the relationship normally seen between blood flow and skin temperatures may not apply in this particular condition—further studies are proceeding.

It was seen that the pattern of blood flow in rheumatoid arthritis is infinitely variable, non-specific in character, and possibly linked to stages in the metabolic or endocrine changes associated with the disease process. The sympathetic nervous system is not primarily involved in this condition.

Functional Focus of Human Mechanics and its Significance in Arthritis, by Mr. Norman Capener (*Exeter*).

In dealing with the joints situated around the centre of gravity within the pelvis of the standing person, the speaker developed the theme of Saunders, Inman, and Eberhart (1953) upon the determinants of normal human gait. These authors had shown how the control of the centre of gravity in its passage through space, was economically effected by the rotation and tilting of the pelvis aided by the movements of the hip and knee joints. The speaker dwelt upon the associated movements of the lumbar spine and emphasized the effects of the contrary

thrusts exerted from below against the thrusts exerted from above in all dynamic activities of freely-standing people, as in walking, running, and, in particular, with the association of swinging movements of the arms, as in labourers, or in sportsmen such as cricketers and golfers. These thrusts were materially altered by disease or by fixation of joints. Human body mechanics was dominated by the compelling necessity of maintaining the centre of gravity in equilibrium. We should think more of this and of the complexity of the associated joint movement and muscular control, and less of the simpler problems of static weight bearing. Furthermore we should cease to think of the clinical problems of the lumbo-sacral and hip joints as single entities. These joints comprised a compound articulation, limitation of function in one element of which was bound sooner or later to affect adversely the function in each of the other elements. The paper was illustrated by drawings after Leonardo da Vinci, from newspaper photographs of contemporary sports contests, and from the author's own work upon the lumbo-sacral spine and hip joints, together with an articulated model in metal.

Saunders, J. B. de C. M., Inman, V. T., and Eberhart, H. D. (1953). *J. Bone Jt Surg.*, 35A, 543.

The Antigenicity of Synovial Tissue, by Drs. D. G. Scott and A. G. S. Hill (*Stoke-Mandeville, Bucks*).

The immuno-histological method of Coons was used to study the distribution of antigenically active components of human synovial membrane and of human glomeruli.

Globulin fractions prepared from the sera of rabbits immunised with isolated human renal glomeruli or with human synovial membrane were conjugated with fluorescein. Unfixed sections of healthy human organs and tissues were examined under the fluorescence microscope after exposure to one or other of the conjugates. In each case the resulting green fluorescence was shown to be specific by its failure to appear if the section had been pre-treated with unlabelled antiserum before "staining" with the corresponding conjugate. The distribution of specific fluorescence produced by the one conjugate was compared with that produced by the other. Cross inhibition experiments in which sections were pre-treated with antiglomerulus globulin before exposure to conjugated antisyndromia globulin (and *vice versa*) were performed to compare the antibody content of the two antisera.

The results of the experiments indicated that reticulin and basement membrane are antigenically distinct. The renal glomerulus was shown to possess both antigens while only the reticulin antigen was demonstrated in the synovial membrane and only the basement membrane antigen was found in the media of muscular arteries.

It was suggested that a study of the distribution of reticulin and basement membrane throughout the body might help towards an understanding of the significance of the sites of the lesions in the diffuse mesenchymal diseases.

Laboratory Tests in the Control of Steroid Therapy in Rheumatoid Arthritis, by Dr. J. H. Glyn (*London*).

The absence of and the need for objective criteria for controlling steroid therapy was stressed.

Certain laboratory estimations were applied to this problem in eight cases of rheumatoid arthritis undergoing treatment with cortisone or hydrocortisone. Serial estimations were performed throughout treatment and compared to this clinical finding.

The tests were chosen for their simplicity so that they might be used continually if they proved useful. Most of them were non-specific "acute-phase" serological reactions.

It was hoped that they would also prove helpful in distinguishing a true remission of the disease from cortisone suppression, also in the problem of case selection and the "screening" of new "anti-rheumatic" drugs.

The results indicated that the tests could broadly be divided into two groups of which the serum hexosamine, the Winzler mucoproteins, and the total protein-bound polysaccharides are the most obstinate and therefore the most reliable indices of underlying disease activity. By contrast, tests such as the "C-reactive protein" are excessively sensitive, but seem to reflect the day-to-day variations more accurately and rapidly.

In general these tests did not prove sufficiently reliable to recommend them for routine clinical application.

The relationship of the hexosamine, mucoproteins, and polysaccharides to each other and to the primary disorder of the ground substance was discussed in some detail.

Sensitized Sheep Cell Test in Rheumatoid Arthritis, by Drs. Rowland Alexander and Lynda Roy (*Edinburgh*).

The Coons fluorescent-protein technique was used in

an attempt to demonstrate transfer of protein from rheumatoid serum to sensitized sheep erythrocytes. The experiments were unsuccessful, but examination of other haemagglutinating systems showed that erythrocytes agglutinated by fluorescein-conjugated antibody were rendered fluorescent only when the antibody had been prepared against whole erythrocytes.

It was suggested that the factor in rheumatoid serum responsible for enhanced agglutination of sensitized sheep erythrocytes was active in very small amounts, and preliminary results of experiments with fractions of serum prepared in the ultracentrifuge supported this contention.

FUTURE ARRANGEMENTS

Clinical Meeting, on October 19, at 4.30 p.m., at the Wellcome Foundation.

Heberden Oration, 1955, on "Research and the Rheumatic Diseases", by Dr. Walter Bauer, on October 19, at 8.30 p.m., at the Royal Society of Medicine.

Heberden Oration, 1956, on "The Connective Tissue System", by Prof. R. E. Tunbridge, on December 14, at 5 p.m., at the Wellcome Foundation.

Annual Dinner, 1956, on December 14, at 7.45 for 8 p.m., at the Apothecaries Hall, Blackfriars Lane, Queen Victoria Street, E.C.1.

Annual General Meeting, 1956, on December 15, at 9.30 a.m. at the Wellcome Foundation.

Clinical Meeting, on December 15, at 10 a.m. as above.

AMERICAN RHEUMATISM ASSOCIATION

The Annual Meeting was held on June 8 and 9, 1956, at Chicago, Ill., under the presidency of Dr. Charles L. Short. The scientific sessions included a panel discussion on Gout, and also one on "A Teaching Collection of Lantern Slides illustrating the Pathology of Arthritis and Rheumatism", the work of a Sub-committee of the Arthritis and Rheumatism Foundation. The A.R.A. Committee

on Diagnostic Criteria presented a Report on Criteria for Rheumatoid Arthritis. Part of the programme was arranged in collaboration with the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. A full account of the proceedings with summaries of the papers and discussions thereon will be published in the December issue of the *Annals*.



Heberden Society

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