HEBERDEN SOCIETY

ANNUAL REPORT, 1963

At the Annual General Meeting held on December 6, 1963, the President Dr. G. D. Kersley, was in the Chair.

The Rt. Hon. the Lord Cohen of Birkenhead and Dr. C. B. Heald were unanimously elected as Honorary Members and the President congratulated another member, Sir John Richardson, on his baronetcy.

The following new members were elected:

Ordinary Members (from Associate Members):
Dr. H. Coke, Dr. J. R. Golding, Dr. D. G. Scott, Dr. E. B. D. Hamilton, Dr. M. Carter, Dr. W. G. Wenley, Dr. C. Croft, Mr. G. Platt, Dr. V. L. Steinberg, Dr. C. F. Hawkins.

Associate Members: Dr. J. Cosh, Dr. J. Wanka, Dr. April Kay, Dr. J. M. Bremner, Dr. Page Thomas, Dr. G. Holden, Dr. E. Sever, Dr. E. N. Glick, Dr. K. C. Robinson, Mr. D. R. S. Sweetnam, Dr. D. Felix-Davies, Dr. T. M. Chalmers, Dr. J. Forster, Mr. A. Kates, Dr. F. M. Andrews, Dr. D. J. Ward, Dr. D. A. H. Yates, Dr. D. C. Dumonde.

Overseas Members: Dr. M. G. London, Dr. P. Kaklamani, Dr. K. D. Muirden, Dr. I. Porter, Dr. W. M. O’Brien, Dr. W. A. C. Douglas, Dr. A. I. Grayzel, Dr. B. L. J. Treadwell, Dr. D. Caughey.

The President recorded with regret the deaths of Lord Evans, Mr. W. D. Coltart, and Dr. A. Willcox, who had been active members of the Society and would be greatly missed.

Activities

At the invitation of Dr. A. St. J. Dixon, the first clinical meeting of the year was held on February 8, at St. Stephen’s Hospital (Annals, 22, 279). Papers were presented by Dr. F. Bach (London), Dr. F. B. Gibberd (London), Dr. A. C. Elkin (London), Dr. H. Coke (London), Drs. A. St. J. Dixon (London) and Colin Grant (Buffalo and London), and Dr. D. Caughey and Prof. E. G. L. Bywaters (Taplow).

A particularly valuable symposium on "The Surgery of Rheumatoid Arthritis", held at the Middlesex Hospital Medical School on April 9, was attended by a large number of distinguished orthopaedic guests (Annals, 22, 281). Papers were presented by Dr. A. J. Popert (Manchester), Dr. D. R. Sweetnam (London), Mr. R. Tinning (Edinburgh), Dr. D. L. Savill (Edinburgh), Dr. O. J. Vaughan-Jackson (London), Dr. P. A. Casagrande (New York), Mr. F. W. Holdsworth (Sheffield), Mr. W. A. Law (London), and Mr. A. Kates (London).

A most interesting and enjoyable combined meeting of the Heberden Society and the Netherlands Branch of the International League against Rheumatism was held at the University of Groningen on May 17 and 18. (Annals, 22, 363). Papers were presented by Drs. J. J. de Blécourt, F. Westendorp Boerma, Prof. E. Mandema, and Dr. R. L. E. Nienhuis (Groningen), Drs. F. Westendorp Boerma, A. E. Beute, and E. O. Vorenkamp (Groningen), Drs. J. Chambers, D. Caughey, and Prof. E.G.L. Bywaters (Taplow), Drs. E. Hamilton, B. M. Ansell, and Prof. E. G. L. Bywaters (Taplow), Drs. J. J. Bode, J. J. de Blécourt, and E. O. Vorenkamp (Groningen), Drs. H. O. Nieweg, H. G. D. Bouma, K. deVries, and A. Jansz (Groningen), Dr. J. K. Pameyer (Deventer),

bolic steroids). To help her along this road the patient may be given alcalis, tranquilizers, sedatives, relaxants, and tonics (under the latter heading are included Vitamin B12, liver extracts, phosphates, glutamates, and A.T.P.). Nevertheless, the warning against overdosage with corticosteroids and the contraindications to their use are clear, as is the advice on gold therapy. The paragraph on chloroquine was presumably printed before the complicating retinopathy as such cases are examples of carpal tunnel syndrome and require decompression. The sections on backache, disk sciatias, osteo-arhoses of the knee, hip, and finger joints, on osteomalacias, and on osteoporosis are well worth reading. Those on the techniques of intra-articular and epidural injections are well illustrated. A final chapter on spas (French spas) seems to have been added as an afterthought and a feature which will not appeal to the English reader is 85 pages of thinly disguised advertising of the various proprietary remedies, spas, and braces available. These criticisms excepted, the general impression is that of a useful and authoritative book which, as yet, has no English-language equivalent—and should have.

A. St. J. Dixon.

The Heberden Round was conducted by Dr. H. F. West who discussed the long-term use of ACTH at the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases, on October 4 and 5 (Annals, 23, 82). Papers were presented by Dr. J. Forster (Southport), Drs. J. T Scott, F. M. McCallum, and V. Holloway (Postgraduate Medical School, London), Dr. A. M. Denman (Postgraduate Medical School, London), Dr. E. Sever (Hammersmith), Mr. C. H. Barnett (St. Thomas’s Hospital Medical School), and Dr. H. F. West (Sheffield).

The Heberden Oration for 1963 was delivered by Prof. J. H. Kellgren on December 6, 1963, at the Wellcome Foundation, London. He took as his subject “The Epidemiological Approach to Rheumatic Diseases” (Annals, 23, 109).

The Annual Dinner was held on December 6, 1963, in the House of Commons. The Society entertained more than thirty doctors and their wives from Belgium in addition to the following distinguished guests: Sir Arthur and Lady Porritt; the Bishop of Bath and Wells and Mrs. Henderson; Sir Bruce Fraser; Sir George Godber; Dr. Bomford, representing the President of the Royal College of Physicians.

The Annual General Meeting, held on December 6 and 7, at the Wellcome Foundation, was attended by a number of Belgian colleagues. The clinical meeting is reported below (p. 243).

Grant-in-Aid

The Society acknowledged with appreciation the renewal of a grant from the Empire Rheumatism Council.

Annals of the Rheumatic Diseases

Full reports of the Society’s activities had appeared regularly in the Annals. The Society was indebted to the Editors for their continued co-operation in furthering the work of the Society.

Library

The Honorary Librarian, Dr. W. S. C. Copeman, reported that the library, now housed in the ancient Hall of the Worshipful Society of Apothecaries by permission of the Faculty of the History of Medicine, was to be moved to the new College of Physicians which was being built in Regent’s Park, when this was completed. By permission of the President the books would be kept separately from the main library of the College, in “The Heberden Room”.

Once again he acknowledged the invaluable help and advice of Dr. F. N. L. Poynter of the Wellcome Historical Medical Library in the cataloguing and maintenance of the books.

The following additions, both by purchase and by gift of members, had been made to the library:


BOERHAAVE, HERMANN. Medical correspondence; containing the various symptoms of chronic distempers... 8vo. London: J. Nourse. 1745.

DAVENPORT, E. W. Davenport’s specific for gout, rheumatic gout and rheumatism. Derby: Richardson and Son [n.d.] Photocopy. 4ll.


LEWIS, P. G. The relief and cure of spinal curvatures. London: John Bale, Sons and Danielsson Ltd. 1897. (Presented by Dr. Malcolm Thompson).

PERCE, ROBERT (1622-1710). Bath memoirs: or observations in three and forty years practice, at the Bath. 8vo. Bristol: H. Hammond. 1697.

SCUDAMORE, SIR CHARLES (1779-1849). A letter to Dr. Chambers... on several important points relating to the nature and proper treatment of the gout. 8vo. London: Longman, etc. 1829. (Presented by Dr. W. S. C. Copeman).


OFFICERS, 1964

President: Prof. E. G. L. Bywaters, F.R.C.P., Postgraduate Medical School of London, Hammersmith Hospital, Ducane Road, London, W.12.


Hon Treasurer: Dr. F. Dudley Hart, F.R.C.P., Westminster Hospital, London, S.W.1.

Senior Hon. Secretary: Dr. G. Loewi, Canadian Red Cross Memorial Hospital, Taplow, Maidenhead, Berks.
Relatives of gouty probands had a higher prevalence of hyperuricaemia than controls and the offspring of both sexes had a higher proportion in Social Classes 1 and 2, though the siblings and parents differed only slightly from the controls. The female relatives did not differ from the controls in respect of obesity or hypertension and none had gout. The male relatives showed a significant increase of gout and a moderate increase of hypertension and obesity over controls.

The relatives of non-gouty hyperuricaemic persons differed from the controls only in respect of a raised prevalence of hyperuricaemia.

When the male gouty relatives were considered alone and divided into hyperuricaemic and normal, it was found that the level of obesity in the hyperuricaemic group was the same as in both groups of probands and fully accounted for the excess in the whole group, and that clinical gout was more common in this group but that hypertension was independent of hyperuricaemia.

The results suggest that obesity is closely associated with hyperuricaemia, but not genetically, and that hypertension is independent of hyperuricaemia, though the significantly higher prevalence among the gouty probands may be related to the much higher levels of serum uric acid found among them.

Gout is more closely linked to gout than to hyperuricaemia as such, while personal success—particularly in business—appears to be a feature of the gouty probands and is not shared by their relatives or by the non-gouty hyperuricaemic persons.

**Discussion.**—Dr. J. H. GLYN (London) Is it possible to produce any information from any of your studies as to the importance of hyperuricaemia in causing renal lesions? I am referring to the clinical problem one sometimes encounters, with patients who have insignificant gout from the rheumatological point of view but have a persistently high serum uric acid, and the problem then arises whether or not to keep them permanently on expensive uricosuric therapy?

Dr. BREMNER: The only thing which has been done in this present study has been to estimate the blood urea in people whose serum uric acid is above 6 mg. In this group four of the probands and two relatives had a raised blood urea. The two relatives who had a raised blood urea were both quite old. Owing to the way in which one works it is not easy to estimate renal function.

G. R. FEARNLEY, R. CHAKRABARTI, and E. D. HOCKING (Gloucester): Effect of Corticosteroid Therapy on Fibrinolysis in Patients with Inflammatory and Non-Inflammatory Conditions. The finding of a greater incidence of low blood fibrinolytic activity among rheumatoid patients than among healthy controls, as judged by a dilute blood clot lysis time longer than 7 hours (see Table) suggested an investigation of the effect of corticosteroid therapy on fibrinolysis. Seventeen in-patients, twelve with inflammatory disease and five with non-inflammatory conditions were studied. Blood fibrinolytic activity was measured daily at 8.30 a.m., fasting; plasma fibrinogen levels and erythrocyte sedimentation rates were estimated frequently. After
control observations for several days, ACTH (6 patients), prednisone (ten patients), and cortisone (one patient) were given, and the observations were continued. Eleven of the twelve patients with inflammatory disease and all of the five patients with non-inflammatory conditions showed a reduction in lysis time, and hence an increase of blood fibrinolytic activity. Although plasma fibrinogen and the erythrocyte sedimentation rate fell in the patients with inflammatory conditions, these parameters were not raised in the patients with non-inflammatory conditions, so that the effect of corticosteroids on fibrinolysis would appear to be primary and specific, rather than secondary to improvement of inflammation. If the effect of corticosteroids on the fibrinolytic activity of blood is reflected in the tissues, it may be a component of the anti-inflammatory action of these drugs, the mechanism of which is largely unknown. Fibrin deposition is both an essential part of inflammation and of healing; persistence of fibrin accompanies chronic inflammation. The fibrinolytic effect of corticosteroids could thus be detrimental in tuberculosis and peptic ulceration, and at the same time beneficial in conditions like rheumatoid arthritis. The Figure illustrates the effect of prednisone on the dilute blood clot lysis time in a woman with rheumatoid arthritis.

**Table**

**BLOOD FIBRINOLYTIC ACTIVITY IN RHEUMATOID ARTHRITIS AND CONTROLS**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Rheumatoid Arthritis</th>
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<td>Sex</td>
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<tr>
<td></td>
<td>Male</td>
<td>Female</td>
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<tr>
<td>Number of Cases</td>
<td>50</td>
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<tr>
<td>Lysis Time (&gt; 7 hrs)</td>
<td>4-5</td>
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**Discussion.**—DR. D. ORLOFF (Brussels): Could you comment on your finding that low fibrinolytic activity was twice as common among the male rheumatoid patients as among the females?

DR. FEARNLEY: I do not know how significant this difference may be. The number of patients studied is comparatively small, only eighteen rheumatoid males as compared with 32 females. It might be that a larger number would iron out the difference.

DR. J. H. GLYN (London): Would Dr. Fearney be prepared to speculate on the significance of low fibrinolytic activity in the pathogenesis of rheumatoid arthritis. Recently one has heard Dr. L. E. Glynn implicating an autoimmune response to fibrin as being a possible cause of chronic polyarthritis in animals, and one wonders if this ties up in any way with Dr. Fearney's observations. Also could he tell us what happened to the fibrinolytic activity of those patients who responded clinically to steroids but whose erythrocyte sedimentation rate remained high?

DR. FEARNLEY: In all of these patients with inflammatory conditions plasma fibrinogen levels and erythrocyte sedimentation rates fell with clinical improvement, and the increase in fibrinolytic activity tended to precede these changes.

I am reluctant to speculate, except to say that I believe fibrinolysis is concerned with inflammation. I would emphasize inflammation in general rather than rheumatoid arthritis in particular. If low fibrinolytic activity is concerned in chronic inflammation, rheumatoid arthritis is only one of the relevant conditions.

DR. J. S. LAWRENCE: I find it difficult to see how the effect of corticosteroids on fibrinolysis, which Dr. Fearney has discovered, would explain their beneficial effect in rheumatoid arthritis. If they increase fibrinolysis in the tissues would not this produce peptides which would increase joint swelling?

DR. FEARNLEY: The role of fibrinolysis in inflammation is conjectural rather than clearly understood. This is why I am reluctant to speculate about the significance of our findings. At the same time rheumatoid arthritis is associated with a good deal of fibrin deposition which, in some situations, e.g. tendon sheaths, is responsible for symptoms. Perhaps deposition of fibrin, in one sense a part of healing, may be far from beneficial to joints and tendon sheaths, and anything which aids its removal is helpful. In the days before antibiotics, massive fibrinolysis of the exudate in pneumonia betokened resolution; failure of this to happen resulted in unresolved pneumonia. This may be relevant to chronic inflammation in general.

PROF. E. G. L. BYWATERS (Taplow): I wonder whether Dr. Fearney would like to say something about activators? He suggested that corticosteroids increase the level of activator rather than that of plasminogen.

DR. FEARNLEY: Without going into too much detail, the factor present in normal blood which is responsible for natural fibrinolysis has been separated by Dr. P. T. Flute of King’s College Hospital and shown to be an activator of plasminogen.

Our method of measuring fibrinolysis does not tell us whether the changes we observed resulted from increase in blood activator or from reduction of plasmin inhibitors. We did not measure plasminogen levels, but changes in this parameter are unlikely to be the explanation of our results.

**Figure.**—Blood clot lysis time during prednisone administration.
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F. G. M. Ross (Bristol), and G. D. Kersley (Bath): Tomography of the Small Joints in Arthritis (to be published in full).


Mathew Wilkinson and Brian S. Jones (Bridge of Earn Hospital, Perthshire): Electrophoretic Studies of Synovial Fluid Proteins. (Annals, 23, 22).

V. Wright and W. B. Reed (Leeds): The Link between Reiter’s Syndrome and Psoriatic Arthritis. (Annals, 23, 12).

J. Van Slype and H. Burniat (Antwerp): Neurotoxic Side-effects of Gold Therapy in Rheumatoid Arthritis. Four cases showing toxic effects were described: one died after receiving 30 mg. gold; another showed paresis after a similar dose, with recurrence following another course of injections; another showed polynieuritis during gold therapy, but made a complete recovery after 3 months; the fourth similarly recovered after a biopsy had shown muscle atrophy similar to lateral amyotrophic sclerosis. Attention was drawn to the lack of correlation between the quantity of gold administered and the severity of symptoms.

Discussion.—Dr. O. Savage (London): During the last few years we have heard various discussions of monoarthritis multiplex and its association with steroids. I wonder if we now have to consider another possible cause of peripheral neuritis, and whether clinically these cases show the type of neurological complication that we have seen with corticosteroids, so that these complications may be due to the disease rather than to the treatment?

Dr. J. S. Lawrence (Manchester): I was interested to note that in three cases, when the toxic features appeared, the erythrocyte sedimentation rate became normal and the rheumatoid factor disappeared from the serum. I have only seen one case of neurotoxicity and this also came on after the disease had become quiescent. I would like to suggest that perhaps toxicity is not the real explanation of this. The occurrence is more likely to be due to some antigenic complex being formed between gold and substances in the tissue, a sensitivity phenomenon. You said the dose was often quite small and this would be against intoxication with gold.

Prof. J. Michéz (Brussels): I should like to ask Dr. Van Slype if he has not observed the same thing in patients with tuberculosis treated with gold? Is there a special sensitivity in rheumatoid arthritis patients or is it common for all patients given gold treatment?

Dr. Van Slype: 35 years ago, when the same treatment was applied to tuberculosis, the same toxic effects were described.

M. Ruelle and J. L. Dupuis (La Louvière): Relationship between Acetabular Protrusion and Rheumatic Disease of the Hip Joint. Acetabular protrusion is often secondary to inflammatory arthritis of the hip joint, appearing in the course of rheumatoid arthritis. The protrusion is directed upwards and inwards. This abnormality is nearly always complicated by osteo-arthritis; in 924 cases of degenerative joint disease involving the hip joint, 20 per cent. developed protrusion.

The radiological signs include condensation and thickening of the acetabulum, producing a characteristically dense shell, and osteophytes around the head of the femur. The joint stiffens in flexion.

H. Lefin (Liége): Interphalangeal Arthropathy in Hemiplegia of Long Duration. In forty patients with hemiplegia (3 months to 43 years duration), the interphalangeal joints were investigated for passive and active movements, joint skin and muscle atrophy, pain on pressure, and skin temperature. Oscilometric indices were measured at the arm. All measurements were compared with the unaffected side.

The following conclusions were drawn:

After a phase of early arthropathy lasting 3 to 4 months (stiffness; paresis; swelling; pain; heat; hyperphagia), all phenomena with the exception of paresis in patients affected by stiffness for more than 4 years, spontaneously regress during the first year and some of them are reversed.

After 2 or 3 years, during which any joint stiffness disappears, one half of the patients—mostly males with left hemiplegia—progressively develop stiffness again. Decrease in flexion of distal joints appears first, followed by reduction in flexion-extension of proximal joints, and some symptoms of early arthropathy. The other half of the patients do not develop stiffness or other symptoms.

X-ray examination has demonstrated that atrophy does not involve bone (apart from slight decalcification) except in patients with Heberden’s nodes, in whom bone diameters are larger on the non-paralysed side.

C. M. Lapière (Liége): Collagen Metabolism during Tissue Remodelling. Growth and development of vertebrate animals require removal and replacement of structural elements for remodelling of tissues.

Working on this hypothesis with J. Gross, the behaviour of collagen during the change in organ shape in metamorphosing tadpoles was investigated from the point of view of metabolic modification of the collagen, using isotope labelling and salt fractionation.

Reduction in the non-extractable fraction and increase in extractable fractions of the collagen occur in both tissues when remodelling of these organs is induced by thyroxin treatment of the animals. Increased synthesis of collagen occurs in the thickening body skin and little change in synthesis per unit volume of tail skin.

Consideration of the different relationships between the amount and the concentration of incorporated labelled precursor in the different collagen fractions in the untreated and treated tissues points to a schematic pathway.
for explaining the migration of the newly-synthesized collagen among isolated fractions of the collagen.

After synthesis in the fibroblast, the collagen is first located in one insoluble fraction from which two different pathways could be followed. A short pathway leads directly to a neutral salt extractable fraction; a long one involves the passage through different pools of insoluble and acid-extractable fractions before reaching another salt-extractable fraction. Enzymatic breakdown of the collagen proceeds from the mixed neutral salt-extractable fraction without distinguishing between various molecular species.

Steady-state connective tissues are characterized by the large prevalence of the short metabolic pathway, and remodelling tissues by an increasing importance of the long pathway.

Discussion.—Dr. G. Loewi (Taplow): Could I ask whether you are proposing an extra-cellular pathway, and if so, is it an enzymatic one? Also is there any sign of a labelled precursor?

Dr. Lapierre: The extracellular collagen undergoes changes which might be controlled by enzymes. The only enzyme that we have isolated is the collagenase involved in the lysis of the collagen in these tissues. Regarding your second question, the precursor proline is used by the fibroblast and hydroxylated to form the hydroxyproline of the collagen which we did not try to isolate as such.

Dr. G. Loewi (Taplow): What is the optimum temperature for these reactions in the tadpole?

Dr. Lapierre: One can study all these metabolic pathways at 25° C. The processes are slower and therefore easier to study in the tadpole than in mammals.

Dr. D. Orloff (Brussels): Do you happen to have some of your studies on tadpoles at higher temperatures? For instance to see whether the insoluble collagen pool would be higher?

Dr. Lapierre: No, we have not done this. I do not think the temperature could be increased. The maximum temperature of these tadpoles is about 30° C. Above this temperature these animals would not normally live.

Dr. J. Ball (Manchester): I do not have any practical experience. However, the recent studies of atrophy in tissue have been notable in pointing out that such a situation should not lead to a decrease in metabolic activity but rather to an increase. Would you say that this is true for the tail of the tadpole? Does this suggest that there is in fact during the removal stage an accretion of soluble collagen?

Dr. Lapierre: I did not have time to show all the patterns we obtained; but if you look at the amount of label per unit size, you will see that an increased amount of collagen is produced in remodelling tissues.

Prof. J. H. Kelgren (Manchester): This is a very interesting demonstration of these pathways and I should like to ask whether, in talking about an insoluble collagen pool, we are not perhaps using "pool" in the wrong sense? The insoluble collagen has a fibrous framework which has been remodelled; and if you divide those two pathways, at one point new collagen is laid down and old collagen removed. It seems to me that you have two activities going on. When you remove tissue and homogenize it, it gets mixed up. One wonders whether, in the intact animal, there is one cycle going on in one place and another in another.

Dr. Lapierre: There can be two meanings for the word "pool" according to its use in a biochemical or histological sense. These pools could be inhomogenous because they contain two kinds of elements closely mixed together or because they proceed from different loci undergoing dissimilar changes. Autorhonoradiography will answer this question.

Prof. E. G. L. Bywaters (Taplow): I do not see what is wrong with an insoluble pool. After all, in a liquid pool in a field, some things are being put in at one place and taken out at another. The word "pool" has acquired a general significance, transcending its liquid origin.

D. J. Ward, E. J. Holborow, and G. D. Johnson (Taplow): Clinical Significance of the Antinuclear Factor Test in Rheumatoid Arthritis. Previous work has shown that the A.N.F. test is positive in some cases of rheumatoid arthritis. The present study was undertaken to investigate the incidence and clinical significance of this finding in a group of 260 adult patients with rheumatoid arthritis (classical or definite A.R.A. classification). Of the patients studied, 23 per cent. had a positive test on one or more occasions and the remainder were negative throughout. The tests were repeated in more than half the patients.

A positive result did not appear to bear any relation to age and duration of disease, nor to the presence of erosions. Kerato-conjunctivitis sicca, Felty's syndrome, splenomegaly, vascular lesions, and infections were more frequent in patients with a positive test. These findings were compared with the incidence in patients having a negative A.N.F. test.

A. J. Popert, E. Grayzel, D. Longson, and A. H. Gowenlock (Manchester): Excretion of Cortisol in Patients with Rheumatic and Other Diseases. Treatment with corticosteroids for active inflammatory connective tissue diseases may not cause the side-effects expected with similar treatment in patients with degenerative joint disease. The therapeutic effectiveness of a given dose varies from patient to patient, and it has been suggested that the metabolism of corticosteroids may differ from normal in connective tissue diseases; previous investigations have proved inconclusive, however. In this investigation the urinary excretion of free cortisol after its oral administration has been compared in patients with connective tissue diseases and in controls.

Three groups of patients were given 100 mg. cortisol by mouth daily for 3 days, and the free cortisol excreted during the third day was estimated. Mean free cortisol excretion was five times higher in nine control patients (190 μg.) than in ten patients with active connective tissue disease (37 μg.). Three patients with quiescent disease (two being hypercorticoid) gave values in the control
range (mean 169 µg.). In a woman with systemic lupus erythematosus receiving 100-200 mg. hydrocortisone daily, the free cortisol excretion was low (46-63 µg.) while the disease was highly active. Clinical and laboratory evidence of improvement was closely reflected by the cortisol excretion, which rose to 146 µg. after 12 weeks although the patient had not become hypercorticol.

The results provide evidence for an alteration of cortisol metabolism in active inflammatory connective tissue disease.

**Discussion.**—**Prof. E. G. L. Bywaters (Taplow):** We have noticed this phenomenon of sudden mooning over many years, particularly in lupus erythematosus when large doses of steroids are given; one may have patients running along on 100-200 mg. prednisone per day over many weeks or months and then, as the disease, I suppose spontaneously, goes into remission, suddenly they blow up with mooning. I think this is a good clinical example.

**Dr. Popert:** I am quite confident that in the next 2 weeks she will do this.

**Dr. B. M. Ansell (Taplow):** Have you any labelling studies showing the actual turnover rates in these patients?

**Dr. Popert:** No.

**Dr. W. A. Bourne (Hove):** It was said some years ago that patients with blood disease tolerated steroids much better than the average patient or the normal, so that would of course be in keeping with this. The other point is that I find rather a lot of patients who do not improve on developing mooning. I take it this is a different mechanism?

**Dr. Popert:** I think it is. I was careful to point out that this patient only started treatment at this time, while she was in hospital on a full conservative regime. I think that when patients are physically active a new element is introduced.

**Dr. J. S. Lawrence (Manchester):** A rather similar problem arose many years ago with gold. Patients with very active rheumatoid arthritis tolerated rather larger doses of gold than those with less active disease. When tagged gold was used, it was found that it went rather more into active joints than into the other joints. Gold is entirely bound to protein in the serum and it seems possible that it is sieved through damaged capillaries and reaches a higher level in these joints. It is possible that the same thing is happening with cortisol.

**Dr. Popert:** I think this is possible, because this is probably where the cortisol is metabolized which may account for part of the answer.

**Prof. J. H. Kellgren (Manchester):** The data are very scanty as yet, but the estimation of free urinary hydrocortisone does seem to supply a method of assessing a patient's steroid requirements. The ordinary clinical method, where you give a dose and hope for the best, and go on pushing it up until you get a suppression effect on the disease, is all right up to a point, but you may be very far out in your original estimate and take a long time to arrive at the dose you require. The next problem is the reduction of disease activity which leads to the rapid development of hypercorticism on what was originally a satisfactory dose. The difficulty is that one is always a few weeks behind, because the signs of hypercorticism come on not in a day but in weeks, and the disappearance of hypercorticism also takes a little time.

**Prof. E. G. L. Bywaters (Taplow):** May I enquire about the ‘kinky hair’? The explanation most women give of kinky hair is that they have had their hair done at the hairdressers and that since coming into hospital it has got rather bad and wants re-doing. You do not think this kinky hair was due to manipulation by the hairdresser some time ago, and that since she had been in hospital she had not had time to get it done again? Falling out and regeneration occurs in lupus but with little change in the quality of the hair.

**Dr. Popert:** This patient was too ill to go to the hairdressers before coming into hospital but had had it done since she started to improve. I agree that hair falls out in lupus, but I think Prof. Kellgren has observed for some time that it is often crinkly as well.

**H. van Caubenberg (Liège), N. Lisin, and R. Leclercq (Brussels):** The Phlogistic Action of Kallidin and its Inhibition. Local injections of Kallidin into the back paw of a rat in increasing dose produced oedema proportional to the dose. Various anti-inflammatory substances were used to reduce the phlogistic action of Kallidin. Salicylate and cortisone proved most effective.

**Discussion.**—**Dr. A. St. J. Dixon (Kensington):** The most interesting result would seem to be the way in which the addition of strontium and ascorbate to phenylbutazone increased its action in inhibiting Kallidin oedema. Does Dr. Lisin think this was an action of ascorbic acid or strontium or what?

**Dr. Lisin:** I do not know. We did not study the separate actions of strontium and ascorbate.

**Dr. F. Dudley Hart (Westminster Hospital):** read a short paper on Recent Rheumatism Cures sent in from all parts of the world. He commented that these varied from seaweed incorporated into the couch on which the patient rested to one of the oldest of all, acupuncture. Antirheumatic underwear was also in fashion. Seldom was it evident, however, from what disease the patient suffered, and many “cures” were probably due to natural remission.