HEBERDEN SOCIETY

ANNUAL REPORT, 1951

The Society has again had a most successful year of work. During the year there were five resignations and these vacancies were filled by five admissions. The Executive Committee recommended, and the Annual General Meeting endorsed, the inauguration of Associate Membership to allow admission of members of the profession of junior status, and three associate members were duly admitted; there is, however, still a considerable waiting list for membership. Professor E. C. Kendall, who gave the Heberden Oration in 1951, has been elected an Honorary member of the Society. Dr. J. A. Cronin has succeeded Dr. J. M. Twigg as an ex-officio Hon. Corresponding Member, as the new Chairman of the New Zealand Rheumatism Council.

At a meeting held at the Westminster Hospital, on January 24, Dr. J. H. H. Glyn (for Drs Copeman and Savage) exhibited a film on the therapeutic effects of cortisone, and many cases shown previously were demonstrated again after one year's progress, together with new cases (Annals (1951), 10, 80).

On March 7, at the West London Hospital, a talk was given by Prof. Jiménez Díaz, Professor of Internal Medicine in Madrid University, and Director of the Institute of Medical Research, who showed a film on the effects of nitrogen mustard in rheumatoid arthritis (Annals (1951), 10, 144).

At the Royal Free Hospital, London, N.W.3, on April 6, Dr. Ernest Fletcher discussed the results obtained by the intra-articular injection of cortisone, and illustrated his lecture by a film. Other speakers included Dr. E. G. L. Bywaters, Dr. J. F. Buchan, Mr. Charles Gray, and Mrs. V. David (Annals (1951), 10, 189).

At a General Meeting held the same evening at the Ciba Foundation, 41 Portland Place, W.1, the Presidential Address was delivered by Sir Henry Cohen on "Some observations on the clinical analysis of pain especially in rheumatic disease" (Annals (1951), 10, 221).

On April 11 at the West London Hospital, Prof. J. S. L. Browne, of Montreal, gave a talk on the use of ACTH and cortisone in the rheumatic diseases.

The Heberden Round took place in Edinburgh on May 10, by kind invitation of Prof. L. S. P. Davidson. Cases were demonstrated at the Royal Infirmary, and there was a conducted tour of the Rheumatism Unit, Northern General Hospital. A lecture on William Heberden the elder was given by Dr. Douglas Guthrie (Annals (1951), 10, 217). Short communications were delivered by Prof. G. F. Marrian, Dr. W. R. D. Alexander, Dr. A. G. S. Hill, Dr. B. Cruickshank, Dr. A. P. Meiklejohn, Dr. J. L. Potter, and Dr. R. J. G. Sinclair (Annals (1951), 10, 227).

At a meeting held at the Ciba Foundation on July 27, papers were given by Dr. W. H. Bradley, Drs E. G. L. Bywaters and A. St. J. Dixon, Dr. Fred Wrigley, Dr. D. A. Long,* and Dr. C. J. M. Clark (Annals (1951), 10, 230).

The Heberden Oration for 1951 was delivered by Professor E. C. Kendall on "The Adrenal Cortex and Rheumatoid Arthritis" (Annals (1951), 10, 453). The Old Library at B.M.A. House was filled to capacity and a distinguished audience included Mrs. Rebecca Kendall, Lord Webb-Johnson, Lord Horder, and Dr. A. S. Osborne (American Medical Attaché). Professor Kendall was presented by the President with the Heberden Medal, and the same evening an informal dinner party was given by the President at Claridge's Hotel at which Professor Kendall was guest of honour.

On December 7 and 8 at the Westminster Hospital (see p. 68), papers were given by Dr. M. R. Jeffrey,† Dr. Robert Moore, Prof. N. F. Maclagan, Drs. E. G. L. Bywaters and B. Ansell, and Dr. Bruce Cruickshank;† a symposium on cortisone and ACTH comprised papers by Dr. Norman Ashton, Dr. J. H. Kellgren, Dr. W. S. C. Copeman, Dr. H. F. West, Dr. E. G. L. Bywaters, Dr. G. D. Kersley, and Dr. J. J. R. Duthie.

At the Annual General Meeting the rules of the Society were altered to make provision for an "Associate Membership" of not more than twenty associates, three or four to be elected annually.

* This paper was reported in full in Annals of the Rheumatic Diseases (1951), 10, 427.
† These papers will appear in full in the June, 1952, issue of the Annals.
over a period of years; the following were accordingly invited to become associate members: Dr. A. St. J. Dixon, Dr. J. H. H. Glyn, and Dr. O. Janus. Rule 5 covers this new status of membership, and Rule 2 was also correspondingly amended. The ordinary membership subscription was increased from three to four guineas as from January 1, 1952. The Executive Committee's recommendation that Rule 4 should be altered to allow for this, in view of the increased cost of the *Annals of the Rheumatic Diseases*, was confirmed.

*This paper will appear in full in this Journal in June, 1952.*

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**ANNUAL GENERAL MEETING, 1951**

The Heberden Society met on December 7 and 8, 1951, in the Westminster Hospital Medical School, London. The President, Professor Sir Henry Cohen, was in the Chair. At the first meeting the following papers were read:

1. *Anaemia of Rheumatoid Arthritis,* by Dr. M. R. Jeffrey (Bath).

2. *Generalized Osteo-Arthritis and Heberden's Nodes,* by Dr. Robert Moore (Manchester).

From a study of 391 cases of osteo-arthritis, it had been possible to define a distinct clinical entity, for which the name "Primary Generalized Osteo-arthritis" is suggested. This group comprised 120 cases, 110 women and ten men. The characteristic feature of the syndrome was involvement of the hand joints, either Heberden's nodes or arthritis of the first carpo-metacarpal joints being present, and it occurred predominantly in the middle-aged, the average age of the women being 52 years, while that of the men was 50 years. There was no accurate association with the menopause.

The pattern of joint involvement was characteristic: Heberden's nodes were present on one or all fingers in most cases, and the first carpo-metacarpal joints were enlarged, deformed, and often partially subluxed, while the proximal interphalangeal joints were enlarged. The spine and hips were often limited in movement, while the knees were enlarged, effusions sometimes being present, and the first tarsometatarsal joints were swollen. The joints tended to go through an initial acute phase of spontaneous onset, during which time they were acutely painful, swollen, and limited in movement, and this pain, especially in the hands, was aggravated by cooling.

*It was reported that the Heberden Medal had been recast to include a likeness of William Heberden the elder, through the generosity of the President, Sir Henry Cohen.*

The President expressed the Society's deep appreciation of the "grant-in-aid" of £100 which had been made annually by the Empire Rheumatism Council; without such a grant the Society would be unable to balance its accounts, and it was much to be hoped that the Empire Rheumatism Council would continue to give this valuable financial support.

3. *Biochemical Abnormalities in Rheumatism,* by Professor N. F. MacLagan (London).

The nature of the biochemical changes seen in patients with rheumatic diseases was discussed. While the advent of ACTH and cortisone had led to much interesting work on the biochemistry of patients treated with these drugs, it appeared to have reduced the interest in changes in untreated patients; these were nevertheless of fundamental interest. A brief review of the changes previously described in the serum proteins, flocculation tests, steroid excretion, and liver function, showed that most of the previous work had failed to differentiate between rheumatoid arthritis and ankylosing spondylitis.

The results were then given of studies on the serum proteins and of flocculation tests on patients at the Westminster Hospital under the care of Dr. Dudley Haslam. These were analysed with particular reference to the difference between rheumatoid arthritis and ankylosing spondylitis. Although the serum globulin results were

*Full details of this work will be published later.*
practically identical in the two diseases, the serum albumin was markedly lower in rheumatoid arthritis while fibrinogen was higher in spondylitis. Among the flocculation tests, the ammonium sulphate and zinc sulphate tests failed to distinguish between the two diseases, but the gold and thymol tests were much more frequently positive in rheumatoid arthritis than in spondylitis.

These results supported clinical impressions as to the essential difference between the two conditions.

(4) Difficulties in the Assay of ACTH Potency, by Dr. E. G. L. Bywaters (Taplow and London), and Dr. Barbara Ansell. (Read by Dr. Ansell.)

Differences between batches of pituitary corticotrophin found by various animal assay methods are not always congruent and may not be entirely relevant to antirheumatic potency. It was thought desirable to check the potency of various corticotrophin batches judging primarily by their clinical effects, and the results according to various methods of testing are presented. Seven different batches were tested on each of seven cases. It was found that the intramuscular route was not quite as informative as the intravenous one, although thrombosis of veins was troublesome with the latter. Furthermore, some patients might become resistant, and in others symptoms might disappear; it was important, therefore, to retest the initial batch at the end of the testing period. It was better in general to separate periods of treatment by periods without treatment, and the optimum length of both of these periods was discussed. The dosage should be small enough not to mask minor differences in potency.

The criteria of hormone action used were the clinical yardsticks of joint range, pain, walking time, strength, temperature, etc. Eosinophil counts and 17-ketosteroid estimations were of little value. Despite these various difficulties it was possible to classify the seven batches tested into three categories: good, fairly good, and poor.

(5) Need for Caution in the Interpretation of Serial Tissue Biopsies,† by Dr. Bruce Cruickshank (Edinburgh).

The President expressed the gratitude of the Society to the authors of these valuable papers, which had been presented most concisely with due regard to the rules of presentation.

After Friday's session Members adjourned to the Royal College of Physicians for the Annual Dinner.

After the Annual General Meeting on December 8, the President, Professor Sir Henry Cohen, being in the Chair, a Symposium on ACTH and Cortisone was given, and the following short papers were read:

* This paper will appear in full in this Journal in June, 1952.

effect of cortisone upon the factors which normally stimulate their activity. Since these stimuli were themselves imperfectly understood, much research work might be required before it was possible to point to the first link in the chain of events which led to the cortisone effect.

**Discussion.**—Dr. J. J. R. Duthie said that he had been interested in the subject from the point of view of capillary permeability changes. He suggested that the action of cortisone had not necessarily been localized: it might be directed upon some mechanism which induced the changes observed, rather than acting directly.

Dr. E. G. L. Bywaters thought that some idea of the mechanism concerned might be gained by observing the time taken by cortisone to produce the changes and how long it took to pre-treat in order to get the ciliary permeability changes. Did the effect come about rapidly?

Dr. W. S. C. Copeman asked how the amount given experimentally to the rabbit—he thought Dr. Ashton had mentioned 2.5 mg.—compared with the dosage given to the human being. He took it that it would have to be arranged on a dosage-bodyweight basis. Was the term “capillary fragility” interchangeable with “capillary permeability” as Dr. Ashton had seemed to suggest?

Dr. Ashton replied that the effect of cortisone was fairly rapid—a matter of a few hours—but that the full effect would take some days. With regard to the relation of quantities used in the rabbit to those used therapeutically in man, he thought this should not be evaluated on a bodyweight basis. The quantity they gave was roughly related to the therapeutic doses used in man as calculated on the basis of eye size.

The President asked whether Dr. Ashton had carried out any metabolic investigations on these rabbits.

Dr. Ashton replied that he had not done so.

The President suggested that it might have been discovered that change through other mechanisms was responsible.

(2) Individual responsiveness to ACTH and Cortisone, by Mr. J. H. Kellgren (Manchester).

The eosinopenic response to single doses of ACTH and cortisone has been studied extensively in four normal male subjects. As judged by this test the responsiveness of the four subjects differed greatly.*

The response to single doses of 50 mg. cortisone by mouth and 25 mg. ACTH intramuscularly had been studied in fourteen patients with rheumatoid disease, using the degree of eosinopenia, and changes in grip and joint tenderness as a measure of response. Wide individual variations in responsiveness were observed. Five patients responded well to both ACTH and cortisone, four to cortisone only, one to ACTH only, and four to neither hormone.

Seventeen patients with rheumatoid diseases were given standard 3-day courses of ACTH—25 mg. 6-hourly, and cortisone 50 mg. 6-hourly with a 4-day interval between courses, the same batch of ACTH and cortisone being used throughout. Response was measured in terms of eosinopenia, alteration in grip, joint tenderness, range of joint movement, and overall function. Four patients responded fully to both hormones. Four patients responded partially to both hormones. Four patients responded either fully or partially to cortisone and not at all to ACTH. One patient responded fully to ACTH and only partially to cortisone. Four patients showed no significant response to either hormone in the dosage used.

On withdrawal of the hormones, most patients returned rapidly to their pre-treatment condition, but three remained improved for considerable periods after both hormones. Five patients showed a temporary deterioration so that their condition was worse than before treatment. In general, withdrawal deterioration followed absence of response.

**Discussion.**—Dr. G. D. Kersley said that this work was interesting in that it brought out the absence of correlation of the eosinophil response and the clinical response. He had had two quite outstanding cases where there was a good eosinophil response but poor clinical response to ACTH, though one reacted to cortisone.

Professor L. S. P. Davidson spoke of similar difficulties in treating cases of haemolytic anaemia.

Mr. Kellgren said, in reply, that the question of responsiveness to either, or both, or neither, of the agents from a practical point of view was rather important. Although it was by no means certain that a single test dose was conclusive, if one had eosinophil and subjective and clinical response in the rheumatic diseases, one could get a rough idea of what the outcome of a prolonged course would be. If ACTH evoked no response to the test dose and cortisone some response, then the latter was the drug to use and vice versa. This was something very well worth considering when one was thinking of employing either of these substances in a case whatever.

(3) Cortisone and ACTH in the Treatment of Rheumatoid Arthritis, by Dr. W. S. C. Copeman (London).

It was fairly generally agreed that rheumatoid arthritis presented the most clear-cut indications for such therapy at this stage. Cortisone and ACTH seemed to have arrived in a bigger way in rheumatology than in any other branch of medicine. He proposed to talk only on the results found personally in a comparatively small series of cases which his group had been following for just under a year.

In assessing the effects of these drugs, it was essential that the patients must be co-operative, of stable personality, and good witnesses, as so much depended on their own account of their condition. Cases selected were those which seemed to be potentially reversible or sufficiently so to allow the patient to return to work. This last practical consideration was the most important one. He did not find the length of history of the lesion...
was important; it was not necessarily the earliest case that gave the best results.

Of twenty cases, seventeen had got back to a comfortable life and all the men were at work. Several of the women had returned to full work, and others to light housework with occasional full work. In only one case had treatment been stopped on account of side-effects, and after an interval further treatment had been possible. Only minor side-effects were noted; moderate rounding of the face, not uncommonly abscesses at the site of injection, and occasional oedema on high doses.

Progress was judged by assessing spontaneous pain, joint tenderness, grip test, functional test, and subjective assessment. He had not aimed at completely suppressing all the signs of the disease and this was fully explained to the patients beforehand. The aim was to get them back to work on the minimum effective dose.

Discussion.—PROF. L. S. P. DAVIDSON asked how many patients Dr. Copeman had treated with cortisone over a period of 6 months.

PROFESSOR S. J. HARTFALL asked whether intercurrent disease was a problem in patients on prolonged cortisone therapy.

Dr. Copeman replied that, as regards the length of treatment, one patient had had cortisone for 3 months, one for 4 months, two for 5 months, three for 6 months, two for 7 months, four for 8 months, and one for 10 months. This last was a patient who had just died from cerebral haemorrhage. She had been at work the day before her death, and was found dead in bed next morning. He doubted whether that death could be attributed to cortisone. He did not know about intercurrent diseases. It was hoped to study this question in the next period of investigation, but concerning diabetes, they had produced one case which had been reported by Dr. Bishop and Dr. Glyn in the Section of Endocrinology of the Royal Society of Medicine the previous week. He believed that this was the only case so far recorded of permanent diabetes.

(4) Cortisone and ACTH in the Treatment of Ankylosing Spondylitis, by DR. H. F. WEST (Sheffield).

It appeared to be generally assumed that cortisone and ACTH affected rheumatoid arthritis and ankylosing spondylitis alike. The treatment of both might be considered under the headings of stiffness, pain, and deformity. ACTH and cortisone rapidly abolished the stiffness and allowed correction of that part of the deformity due to the presence of inflammatory exudate and the existence of muscle spasm. The pain may be subdivided into:

(i) spontaneous and aggressive;
(ii) that appearing during non-weightbearing movement and
(iii) that occasioned by weightbearing (i.e. the forcible rubbing together of two eroded bone surfaces).

In both diseases (i) is relieved and (iii) little affected. The difference between the diseases is apparent when (ii) is studied. A stage must come in an ankylosing joint when callus bridges the gap. At this stage movement of the joint will be painful and no relief will be expected from ACTH or cortisone. This state of affairs has been seen recently in a girl with fulminating ankylosing spondylitis. One hip, which was more advanced than the other, remained very painful on attempted movement, while the other became pain free. Such a state of affairs is not seen in rheumatoid joints treated with ACTH or cortisone. Thus it may be necessary in some cases of ankylosing spondylitis to reduce the dose in order to facilitate bony union.

Reference was made to other patients with hip involvement in ankylosing spondylitis who had remained free (on continuous therapy) for periods up to 15 months.

Discussion.—PROFESSOR S. J. HARTFALL described one case satisfactorily treated with ACTH and cortisone.

Mr. J. H. KELLOGREN said that one of the most useful points about cortisone was the quieting effect which it had on certain pain mechanisms. He thought they ought to take into account a little more deeply the mechanism by which pain was produced, and he gave on the blackboard a demonstration of the factors involved.

Dr. F. DUDLEY HART described six cases of ankylosing spondylitis treated with cortisone or ACTH. The response was usually satisfactory but wore off very rapidly, unlike the beneficial effect obtained by deep x-ray therapy.

(5) Cortisone and ACTH in the Treatment of Still's Disease, by DR. E. G. L. BYWATERS (Taplow).

Still's disease was essentially rheumatoid arthritis occurring in children: so-called "specific" features (rash, fever, cervical spondylitis, and pericarditis) were seen from time to time in adults. Out of 92 children treated in the last 3 years, 29 had been treated with cortisone or corticotrophin. Results were very similar to those in adults; the dosage was the same as in adults except for extremely small children. Even large dosage (up to 500 mg. a day) was followed by a relapse within a week or so of stopping treatment. Complications were few in cases treated for up to 6 weeks. Amyloid did not seem to be affected within this time period. These substances controlled the symptoms in most cases, but relapse always occurred within a short time of stopping treatment.

(6) Cortisone and ACTH in the Treatment of Gout, by DR. G. D. KERSLEY (Bath).

Little had been written on this subject since the early days when Wolfson and others showed that an acute attack of gout could be cured within a few hours by ACTH, but that there was usually a severe attack within 4 to 5 days of stopping this, unless colchicine was given in large doses. He had explained this by suggesting that the trigger factors of gout acted as stresses, producing
a low level of circulating corticoids, which in a susceptible person brought on an acute attack. Again, in the low corticoid phase following cessation of ACTH therapy, a severe attack followed. He had stated that there was a low 17-ketosteroid excretion in gout, which in view of the reverse of an androgen deficiency—its usual onset coinciding with the incidence of familial hyperuricaemia, in males after puberty, and in females after the menopause—suggested to him an abnormal androgen metabolism in gout.

There had been surprisingly little evidence so far to substantiate or refute this suggestion. Random observations made in the laboratory at Bath on nine men with gout, gave an average reading of 11·2 mg. 24 hrs. and in two women 6·1 mg. 24 hrs., as compared with 13·4 mg. for ten male rheumatoids and 10·7 for eight female rheumatoids.

It had been attempted to use the ACTH withdrawal attack as a test for gout, but even when combined with a ketogenic diet it was found to be unreliable.

Cortisone had also been used in the treatment of severe tophaceous gout. One extremely severe case, over the period of 10 years, had gradually lost toes and fingers because the tophi had become so large. He had discharging sinuses on fingers, elbow, and feet. At the end of 3 weeks’ treatment with 100 mg. cortison per day, the tophi were appreciably less tense, and slightly smaller, and the discharge had decreased, whereas, up till that time they had steadily but slowly increased.

There was no appreciable effect on the plasma uric acid, but the sedimentation rate fell a little.

To summarize—the effects of ACTH and cortisone in gout do, to some extent, bear out Selye’s theories. ACTH is of practical value in cutting short a severe attack of gout, and cortisone may be of use in the comparatively rare cases of “malignant” tophaceous gout.


Dr. Duthie said that he had been fortunate in being able to visit the U.S.A. for 3 months under the auspices of the World Health Organization. He had visited most of the main centres in the East, and Middle West. One of the main objects of his trip was to meet those clinicians who had gained experience in the therapeutic use of ACTH and cortisone on a long-term basis, and to ascertain their present views on the value of these hormones in the treatment of the chronic rheumatic diseases. As one would expect, a considerable divergence of opinion had been found and he proposed to confine himself to a brief review of the main trends.

Preparations.—Oral cortisone had largely replaced parenteral cortisone and ACTH in long-term administration for obvious reasons. Its action was more rapid, and divided doses gave a smoother effect, but the speed of absorption on an empty stomach may cause undue stimulation, jitteriness, and inability to concentrate, so it was best taken after food.

Dosage.—Many clinicians had abandoned the high initial loading doses used in the early days—300-2000 mg.—not entirely because of the greater danger of side-effects, but because patients who had experienced complete suppression found it difficult to accept even a partial return of symptoms when the dose was cut to a safer level, especially when the initial euphoria was followed by mental depression. One disadvantage of oral cortisone in this type of case was that dosage was more difficult to control on an out-patient basis. In the U.S.A. it was possible to buy cortisone without prescription—at a price—and patients might supplement their official supply. The method currently adopted was to start with 50-75 mg. daily and to adjust the dose up or down as required during the first few weeks of treatment. Complete suppression of symptoms was not aimed at, and the dose was stabilized when a useful degree of relief had been attained. This method had the advantage that, when it became obvious that the maintenance dose was going to be too high for safety, the medicine could be stopped before any harm had been done. Requirements in the individual varied, and the disease not infrequently “broke through.” Such an event might be heralded by a rise in blood sedimentation rate or eosinophils—or it might happen without clinical flare-up.

The consensus of opinion to date was that about one-third of patients started on cortisone could be fairly well controlled with a dose (50-75 mg.) which caused no serious side-effects. Further experience might lower this figure, as the incidence of undesirable effects tended to increase as time went on.

Side-Effects.—Side-effects of greater or lesser significance occurred in about 50 per cent. of cases. Some were serious, some not, but the persistence of even minor effects—acne, obesity, mild oedema, mental depression, headaches, dizziness, tachycardia, blurring of vision, disturbances of menstruation, nervousness, increased in hair growth, etc.—might so disturb the patient that he voluntarily requested the drug to be stopped.

More serious effects were the masking of signs of intercurrent infections or surgical emergencies (appendicitis, perforation of the gut), activation of latent tuberculosis, haemorrhages from the gut, appearance or activation of peptic ulcers, perforation of existing ulcer, fractures of the long-bones, collapse of vertebrae, bodies, thrombo-phlebitis with embolic complications, major psychosis, and coronary infarction. Complications of this type were commoner amongst women, and in the older age groups.

If the hormone had to be withdrawn for any reason, relapse was the rule sooner or later, and usually sooner. Although it had recently been claimed that long remissions had followed the use of very high doses—500 mg. daily for 14-30 days—yet all patients had eventually
Withdrawal Syndrome.—In a proportion of cases, very distressing symptoms appeared when cortisone was stopped—the post-cortisone withdrawal syndrome. These patients complained of profound weakness, exhaustion, anorexia, mental depression, and generalized aching pain and stiffness. Their symptoms, which were relieved by sleep or rest, made worse by movement, and not controlled by previously effective doses of analgesics, were not wholly due to adrenal suppression, for they persisted when tests showed the cortex to be normally active, but they might arise from a relative deficiency of adrenal steroids in tissues conditioned to an abnormally high level. This suggested that in a proportion of cases cortisone might become a drug of addiction. The combination of the withdrawal syndrome with relapse in the arthritis produce a very distressing state of affairs. A very rare, but perhaps significant, complication of cortisone withdrawal had been the appearance, in several cases of rheumatoid arthritis, of the signs and symptoms of disseminated lupus, or of peri-arteritis nodosa. Dr. Duthie had personally seen three patients in which this occurred—all rheumatoids of some years’ standing.

Mode of Action.—Intensive research had not yet revealed the mode of action of the adrenal steroids, but it was now generally accepted that the anti-inflammatory effect was non-specific and could be dissociated from the known effects on the metabolism of carbohydrate, fat, and protein.

Present Position.—Experience during the last two years had led the majority of physicians to adopt a much more conservative attitude to the use of cortisone or ACTH as a long-term method of treatment. It was no longer regarded as a substitute, but rather as an ancillary to other methods of treatment. In most clinics, orthodox methods, including gold, splints, and physiotherapy, were tried for several months first. Only those cases who continued to run a downhill course were considered, and cortisone was only used to augment the effect of standard treatment.

Complete suppression of symptoms was no longer aimed at. Early cases where damage was minimal were preferred, but in severely crippled cases the drug might be used to facilitate the application of other methods—manipulation, surgical operation, and corrective exercises—in the hope that the gain might be consolidated and cortisone then withdrawn. Orthopaedic surgeons felt that its use in this way had been a valuable contribution to treatment. There was no evidence that cortisone altered favourably the natural course of the disease. It was even possible that the increased activity allowed by suppression of inflammation may, in the continued presence of the unknown tissue irritant, lead to an increase in joint damage. Radiological progression of the disease without return of symptoms had been noted in cases receiving cortisone. At least an increase in the secondary osteo-arthritic changes in the affected joints put to excessive use under cortisone cover must be anticipated. Long-term follow-up of those cases would be of the greatest interest and importance.

The combination of cortisone with other substances, such as gold, insulin, and testosterone, had not been very encouraging, although it had been reported that PABA enhanced the effect of cortisone and allowed a substantial lowering of the dose. Different methods of administration—interrupted courses, low maintenance with booster doses, combination with ACTH—had not been very helpful in lowering the incidence of side-effects or preventing relapse on withdrawal. Cortisone was now available in a form which could be given intravenously, and it had been hoped that more prolonged effects might follow administration by this route, but such had not proved to be the case. The therapeutic effect was good, but not sustained. Intravenous ACTH had proved to be an economical method of producing maximum adrenal stimulation, 20-50 mg, being given by slow drip over 8-12 hours. Here again, hopes that more prolonged remission of symptoms might follow had not been fulfilled.

Intra-Articular Cortisone.—Diminution of pain and swelling had followed the intra-articular injection of 25-50 mg. cortisone acetate. Unfortunately, repeated injections appeared to have an irritating effect and symptoms recurred. Compound F, now available in limited quantities in America, was well tolerated, and repeated injections could be given without untoward effects. The beneficial effect lasted for 4-5 days on an average, and this method of treatment might prove of real value, especially in patients crippled by pain and swelling in one or both knees. No systemic effects were produced, and a weekly injection had proved adequate in most cases.

ACTH had largely been replaced by oral cortisone in long-term treatment, although its use was probably more physiological, and there was much less danger of severe withdrawal symptoms. A reliable long-acting preparation had not yet become available, but Armstrong hoped to produce one soon. The development of abscesses at injection sites was one serious complication liable to occur in out-patients. Astwood in Boston had produced highly purified preparations, and 1 mg given in three divided doses had been sufficient to maintain good control in cases of rheumatoid arthritis. Side-effects were the same, but salt and water retention might be more troublesome. Variation in the potency of commercial preparations had caused a good deal of trouble, in Great Britain as well as in America.

Conclusion.—Opinion in America regarding the value of these hormones in long-term treatment of the chronic rheumatic diseases could be summarized as follows: Some believed that the benefits were so much greater than those following all other forms of treatment that their
use was fully justified, even on out-patients with the minimum of laboratory control. At the other extreme were those who thought the risks of long-term administration so great in most patients that it should never be advised. The majority of clinicians thought long-term therapy might be justifiable, if combined with orthodox methods in patients running a progressive downhill course. Short-term administration for a specific purpose (to cover manipulation or operation or to facilitate correction of deformities by other methods) was considered of real value. Intra-articular injection had only had a limited trial, but justified further study. The first enthusiasm had been replaced by a more cautious and conservative attitude. A tremendous amount of research into the hormones’ mode of action was going on, but so far with little success. It was to be hoped that the experience gained in America would be fully utilized in planning therapeutic trials and research in Great Britain when cortisone and ACTH became cheaper and more plentiful, as they undoubtedly would in the not too distant future.

The President, in closing, said he did not intend to summarize what had been, in effect, a summary of the different aspects of ACTH and cortisone in the treatment of rheumatic disease. He had only to say how very much indebted the Society was to those who had made such admirable contributions. Much original work had been presented that morning and they looked forward with great interest to its completion.

For this instructive session with its experiences so freely related he expressed deep gratitude on behalf of the Executive.

SYMPOSIUM ON THE SUPRARENAL CORTEX

COLSTON RESEARCH SOCIETY, UNIVERSITY OF BRISTOL

The fifth symposium arranged by the Colston Society will be held from March 31 to April 4, 1952, at the University of Bristol. The subject will be the Suprarenal Cortex, and the eighteen following papers will be presented:

1. Preparation and Assay of ACTH, by Dr. C. H. Li, University of California, U.S.A.
2. Physical and Chemical Properties of ACTH, by Professor F. G. Young, Cambridge University.
4. Suprarenal Cortex. The Structural Background, by Professor J. M. Yoffey, University of Bristol.
5. Nature of Adrenal Cortical Secretion, by Professor F. Verzar, University of Basel, Switzerland.
6. Control of Secretory Activity of the Suprarenal Cortex, with special reference to the Isolated Preparation, by Dr. Marthe Vogt, University of Edinburgh.
7. Suprarenal Cortex and the Gonads, by Professor S. Zuckerman, University of Birmingham.
8. Metabolism of Adreno-Cortical Steroids, by Professor G. F. Marrian, University of Birmingham.
9. Role of the Adrenal Glands in Infection and Intoxication, by Dr. Harry J. Robinson, Merck Institute, Rahway, U.S.A.
10. Adrenal Steroids and Personality Disorders, by Dr. Hudson Hoagland, Worcester Foundation, Shrewsbury, Mass., U.S.A.
11. Changes in Suprarenal Cortex Function in Shock and Hormone Treatments, by Dr. R. E. Hemphill, Bristol Mental Hospital.
12. Suprarenal Cortex Activity in the Endocrine equilibrium of Humans, by Dr. M. Reiss, Bristol Mental Hospital.
13. ACTH, Steroid Hormones, and Tissue Changes, by Professor G. R. Cameron, University College Hospital Medical School, London.
15. Influence of the Suprarenal Cortex on Mineral and Water Metabolism, by Professor H. Helle, University of Bristol.
16. Surgery of the Suprarenal Gland with special reference to the Cortex, by Mr. L. R. Broster, Charing Cross Hospital, London.
17. Clinical Applications of ACTH and Steroid Hormones, by Professor E. B. Astwood, Tafts College Medical School, Boston, Mass., U.S.A.
18. Clinical Responses as illustrated by the Rheumatic Diseases, by Dr. G. D. Kersley, Royal National Hospital for Rheumatic Diseases, Bath.

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