ACTHAR CONFERENCE*

A conference was held at Harrogate, Yorks., on September 13 and 14, 1951. The following papers were presented. Brief summaries are added of those having a direct bearing on the rheumatic diseases.

First Session: Chairman, Dr. F. T. G. Prunty.

(1) DR. O. JANUS (Manchester) gave a paper entitled The Basic Physiology of ACTH, in which he compared the effect of ACTH and oral cortisone on the eosinophil count; he stated that 25 mg. ACTH had an effect on the eosinophils comparable to that of 10 million T.A.B. intravenously. He mentioned the uncertainty of response to hormone stimulation, quoting one rheumatoid case that was unaffected by ACTH but responded to cortisone, one case unresponsive to both hormones, and a third case that reacted well to ACTH, but showed only a poor response to cortisone. He then proceeded to outline the effect of ACTH on hyperaemia and skin temperature by methods previously published.

(2) DR. A. SLESSOR (Glasgow) discussed The Therapy and Clinical Management of ACTH. He summarized their effects, in suitable dosage, as:

(i) inhibition of fibroblasts;
(ii) inhibition of antigen-antibody reaction;
(iii) increase in capillary resistance;
(iv) increase in resistance to stress.

If excessive doses were given, complications were apt to occur in diabetes, tuberculosis, psychosis, cardiac failure, nephritis, and hyperpiesis.

In addition there might be DOCA, androgenic, and posterior pituitary effects. He showed slides of the many investigations that might be used to control dosage; in the subsequent discussion several speakers pointed out that in the majority of straightforward cases clinical observation, routine testing of the urine for sugar, and possibly occasional potassium estimations, were all that was required, apart from research observation.

(3) DR. J. R. FORBES (Wrexham) spoke on The Gastro-Intestinal Tract, and said that he had confirmed that ACTH produced an increase in uropepsin excretion such as that which occurred in peptic ulceration and was reduced in partial gastrectomy and pernicious anaemia. He had not observed an increase in hydrochloric acid in the stomach. Six cases of perforation or haemorrhage from gastric ulcers had been described in the literature, but in many of these it was doubtful whether ACTH had in fact been the cause.

(4) PROFESSOR F. J. NATTRASS and DR. A. L. LATNER (Newcastle) presented a paper on The Use of ACTH in Asthma.

(5) DR. D. V. HUBBLE (Derby) spoke on The Intravenous Treatment of Acute Dermatomyositis by ACTH. He described in detail a severe case which was at first treated with 12.5 mg. 6-hourly with some improvement, but with persistence of fever. He had then instituted an intravenous drip for 8 hours each day for 10 days with 20 mg. daily, and then for 10 days with 10 mg. daily. At this stage the sedimentation rate and temperature rose. He had then raised the dose to 50 mg., but the patient complained of severe headache, the eosinophil count rose, and the heart dilated, but the electrocardiogram remained normal. On cessation of therapy there was a marked diuresis and the heart began to return to normal dimensions. He felt these phenomena were due to a combination of water retention and possibly sensitization to ACTH.

In the discussion, Dr. Latner suggested that the eosinophil escape might be due to the body running short of some substance produced by the ACTH which was responsible for the eosinopenia. Dr. Sevitt thought that the eosinophil cells themselves might become resistant to ACTH. Dr. Prunty and Dr. Bywaters produced evidence that one batch of ACTH had been below normal strength (said to be one-seventh strength). This was later confirmed by Dr. H. E. Cluxton, the representative of ACTHAR, who said that in America this batch had been recalled.

Commenting on the morning’s papers as a whole, Dr. Cluxton made the following suggestions:

(i) that in using ACTH it was always advisable to restrict salt;
(ii) that what happens in the cell is not always reflected in the blood stream, for possibly the electrocardiogram increase in QT interval and depression of T wave might mean more than a potassium estimation;
(iii) that the therapy was suppressive and must be combined with other treatment;
(iv) that psychoses could be often cured by intravenous potassium chloride;
(v) that in cases of sensitivity it was possible to switch from hog to ox pituitary extract.

Second Session: Chairman, Mr. J. M. Johnston.

(1) DR. DUDLEY HART (London) opened with a paper on Hypo-(Anterior) Pituitarism.

(2) DR. E. G. L. BYWATERS (Taplow) discussed The Effect of ACTH in Rheumatic Fever. He showed how this hormone blanketed symptoms, much as was the case with aspirin, but heart lesions did not seem to be affected. He quoted one case in which pericarditis began while the patient was under full doses of ACTH. Again rheumatic rashes were often not influenced and biopsies of nodules showed little change after ACTH administration.

In a series of 46 cases, divided by random sampling for treatment with ACTH, cortisone, and aspirin, there was little difference in the numbers uncontrolled, in prevention of murmurs, or in the relapse rate. In a series of 79 cases, the only complications were: one case of cellulitis, two of tuberculous infections, two of stomatitis, two of pigmentation, and three of water retention leading to fits. ACTH had a slight influence on the spreading effect of hyaluronidase in rheumatic fever subjects.

Dr. J. D. O. Fearnley stated that as reduction of sedimentation rate and fibrinogen level appeared to run parallel, the effect of a single injection of ACTH on the fibrinogen level in normal students had been measured. It had been shown to cause a reduction.

(3) DR. G. D. KERSLEY and DR. L. MANDEL (Bath) gave a paper on The Comparative Effects of Hypoglycaemia with ACTH and Cortisone in Rheumatoid Arthritis, with an Investigation of Two Cases completely Resistant to ACTH.

Twenty-two cases had been treated with a daily dosage of 60 mg. cortisone or 30 mg. ACTH and later hypoglycaemia, and then with hypoglycaemia and cortisone or ACTH. It was felt that hyperglycaemia probably stimulated the pituitary, and produced a clinical
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effect equivalent to 40 mg. ACTH. Seventeen of the 22 cases showed the best clinical result with the combined treatment.

Two cases completely clinically resistant to ACTH up to a dose of 400 mg. in a day were described. Neither responded to 100 mg. ACTH intravenously, and one did not respond to 500 mg. cortisone, though in the other the cortisone appeared to act satisfactorily. Neither case appeared to suffer from adrenal insufficiency, and the Thorn and Keppler tests were normal. Some metabolic observations were recorded.

As there was complete absence of correlation between clinical response and the Thorn test, it was suggested that the fraction of ACTH responsible for the remission obtained in the majority of cases of rheumatoid arthritis was distinct from that causing the reduction in circulating eosinophils of the blood. This seemed to accord with the recent work of Young on the ascorbic acid depleting fraction and adrenal weight increasing fraction of ACTH.

Dr. J. J. R. Duthie doubted whether hypoglycaemia acted directly on the anterior pituitary. Dr. Long suggested that the failure of the two cases to respond to ACTH might be due to ascorbic acid or thyroxin deficiency.

Third Session: Chairman, Dr. W. S. C. Copeman.

(1) Professor L. J. Witts (Oxford) discussed The Effect of ACTH on Blood Diseases, saying that the results had not been dramatic.

In the subsequent discussion several speakers said they were not impressed with the effect of ACTH or cortisone on the anaemia of rheumatoid arthritis.

(2) Dr. J. J. R. Duthie and Dr. H. N. Robson (Edinburgh) presented a paper on The Relationship between Capillary Resistance and Adreno-Cortical Activity. They showed a series of slides demonstrating a parallel response in increase in capillary resistance, eosinopenia and clinical benefit with both ACTH and cortisone, although more slowly with the latter, and a fall in resistance with 20 mg. desoxycorticosterone acetate (DOCA). In a case of Simmond's disease, the capillary resistance increased with a small dose of either insulin (4 units) or adrenaline, more quickly than it did with ACTH (25 mg.). With progesterone, testosterone, oestrone, or pregnenolone, there was no change either in capillary resistance or in eosinophil response. They felt that estimation of increase in capillary resistance was an easy and quick method of estimating glucocorticoid effect. The apparatus used was as previously described, but must have a satisfactory exhausting mechanism, lighting, and lens.

Fourth Session: Chairman, Professor F. J. Nattrass.

(1) Dr. W. Wolman (Manchester) gave a paper on The Function of the Adrenal Glands in the Newborn. He said that this subject had been studied by means of the eosinopenic response to ACTH in 24 full-term and twelve premature infants. Sixteen of the full-term infants and eight of the prematures had a normal adrenal response, as shown by 50 per cent. fall in eosinophils on the first day. Of the remainder, all but two had a normal response on the second day. The smallest child responded on the third day, whereas the child of a diabetic mother responded only on the seventh day. These results suggested that though in the first days of life the adrenal cortex is histologically immature, its function is normal in most full-term and premature babies on the first day of life.
(2) DR. W. S. C. COPEMAN and DR. OSWALD SAVAGE (London) gave a paper on Rheumatoid Arthritis. They reported that every case studied had responded with measurable clinical improvement, but that the lowest dose at which initial improvement had occurred was 120 mg. ACTH a day, given in four intramuscular injections. The lowest maintenance dose achieved was 40 mg./24 hrs, also in four injections, and any lowering of the number of injections had resulted in relapse at this dosage. The best method of judging the dose requirements in this disease was by a careful clinical assessment using a combination of measurements of pain, tenderness, and function. These were particularly important when judging the required maintenance dose. Using such tests it was shown that an intravenous dose of 20 mg. in an 8-hour drip gave a clinical response equal to 200 mg. by intramuscular injections. After intravenous ACTH the improvement had lasted for an average of 4 days. It had been found impossible to correlate the clinical response with pathological and biochemical changes such as a fall in eosinophils and sedimentation rate and a rise in 17-ketosteroids and corticoids; often a much higher dosage was required to obtain these changes than to achieve a clinical response. It had been found impossible to predict what dose a patient would require for either initial or maintenance dosage.

(3) DR. H. E. CLUXTON (Chicago) spoke on Recent Concepts in the Use of ACTH and Cortisone. He reviewed recent work in America with these substances, and suggested that ACTH should be used to stimulate the suprarenal when cortisone was withdrawn. During routine long-term therapy with either substance a low salt diet and the addition of 3 g. potassium a day was advisable. There was no doubt that intravenous administration resulted in a great saving of material and was becoming a feasible proposition in certain cases. Eosinophil counts were now being done only as a preliminary to treatment.