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CORTISONE AND A.C.T.H. IN TREATMENT OF NON-RHEUMATIC CONDITIONS

BY

G. M. ABER, M.B., Ch.B.
Registrar

AND

G. N. CHANDLER, B.M., M.R.C.P.
Senior Registrar

S. J. HARTFALL, M.D., B.Sc., F.R.C.P.
Professor of Clinical Medicine

(From the Department of Clinical Medicine, University of Leeds, and the General Infirmary at Leeds)

Since cortisone and A.C.T.H. were made available in this country in 1951, 78 patients have been treated with these drugs at the General Infirmary at Leeds. In no case has the decision to start the treatment rested on conditions other than therapeutic indication, so that our experience, though fairly broadly based, has been gained more from individual needs than from research interest.

In non-rheumatic conditions the results obtained seem valuable enough to allow of an interim report on our conclusions. Patients in this group have been submitted to treatment not only where it was felt that cortisone or A.C.T.H. offered the best hope of improvement, but also in an attempt to elucidate their various and varying effects in disease processes. Due weight has been afforded these aims in the allocation of cortisone or A.C.T.H. for individual patient treatment, applications for the drugs being submitted to the cortisone committee at the infirmary, one of us (S. J. H.) acting as secretary to this panel.

This report summarizes the results and experience gained in the non-rheumatic diseases. Fourteen patients have been observed with disorders of the blood and blood-forming organs; 16 patients have been treated for disease or dysfunction of the endocrine glands; and in a third, miscellaneous, group the effect of treatment has been studied in two patients with cirrhosis and portal hypertension, in two patients presenting a nephrotic syndrome, and in nine patients suffering from asthma.

No attempt has been made to review the literature, since this is thought to fall outside the scope and intention of a report which deals, in the main, with the routine treatment of problems common to a general teaching hospital.

DISEASES OF THE BLOOD

Acute Acquired Haemolytic Anaemia

Four children, whose ages ranged from 6 months to 8 years, were admitted to hospital during a period of 16 days in March, 1952, suffering from acute acquired haemolytic anaemia. Because of the poor response of three of them to blood transfusions a trial was given to the use of A.C.T.H., and the results have been reported elsewhere in greater detail (Rose and Nabarro, 1953).

Clinical Presentation.—All described a short febrile illness characterized by lethargy, irritability, increasing pallor, breathlessness, and haemoglobinuria; two showed moderate icterus, one of these also demonstrating enlargement of the spleen, liver, and lymph nodes. They were acutely ill, and in no case were any specific aetiological factors evident.

Haematology.—The findings in the peripheral blood were of a severe haemolytic process without evidence of leukaemia. The sternal marrow in the two patients on whom this examination was performed showed only normoblastic hyperplasia. The direct Race–Coombs test was positive on admission in two patients and eventually positive in three.

Treatment.—Three of the children required the protection of A.C.T.H. or cortisone. The fourth responded to a single blood transfusion given on the seventh day after admission, and she remained in good health despite persisting hepato-splenomegaly. Of the three treated with hormones, a girl aged 3 who had relapsed rapidly after each of three transfusions responded to a course of A.C.T.H. given over a period of five weeks, begun at an initial dosage of 50 mg. daily intramuscularly and gradually reduced after three weeks. A second child, a boy aged 8, was given A.C.T.H. because of severe relapse after several transfusions. He responded well to a dosage of 100 mg. daily continued for two weeks, gradually reduced in a " steppage " procedure in the next three weeks, but he relapsed when A.C.T.H. was discontinued. After further transfusion, splenectomy was performed without apparent effect. A second course of A.C.T.H. (100–75 mg. daily) was given, to which he again responded. In the seventeenth week after admission cortisone was substituted for A.C.T.H. A final attempt at drug withdrawal resulted in brisk haemolysis and he still required 75 mg. of cortisone daily, nearly 60 weeks after the beginning of his illness and the start of treatment. His general health remained excellent, though " mooning " of the face was clearly evident. In this case the direct Race–Coombs test, previously positive, became negative during the thirteenth week of treatment whilst he was receiving A.C.T.H., though later it reverted with cortisone.

The third patient to come under treatment, a female child of 6 months, was given A.C.T.H. after a preliminary trial of transfusion. Relapse followed withdrawal

of the drug, which had been given at a dosage of 25 mg. daily, and splenectomy was undertaken during a second course of A.C.T.H. Relapse again occurred when the drug was discontinued. A third course of A.C.T.H., later changed to cortisone, was continued in gradually diminishing dosage for a further period of 14 weeks, and no ill effects have attended its final withdrawal, 28 weeks after the onset. The direct Race–Coombs test, positive at the outset, is now only weakly so.

Comment.—In this small group, one child responded after one transfusion, and another after transfusion and A.C.T.H. The other two were given intensive hormone therapy, and both were submitted to splenectomy. The relatively large requirements of A.C.T.H. made it difficult to achieve haematological response and clinical control without the production of side-effects. Undue gain in weight, mooning of the face, and glycosuria were recorded, but without biochemical or electrocardiographic evidence of electrolyte disturbance. Splenectomy proved of little benefit in the two children who relapsed after withdrawal of the drug, the operation being undertaken because of the large requirements of A.C.T.H. and the long duration of the illness. Of these two children, one appeared to recover after splenectomy performed under the protection of a second course of A.C.T.H., but relapsed on withdrawal of the drug, subsequently responding to intramuscular cortisone. The other child was operated on during a relapse, but failed to improve, the haemolytic process being ultimately controlled with cortisone. Rose and Nabarro conclude that the underlying abnormal antibody reaction can be controlled by sufficiently large doses of hormone, yet cortisone and A.C.T.H. cannot be said to displace transfusion and splenectomy in the treatment of the individual patient, both remaining as important therapeutic adjuvants.

Aplastic and Hypoplastic Anaemia

Two patients with marrow aplasia have received A.C.T.H. A man aged 27 with Hodgkin's disease, confirmed by gland biopsy, was given a long period of treatment with oral nitrogen mustard (R48), for the supply of which we are indebted to Professor Haddow. After nine months a persistent anaemia required frequent correction by blood transfusion. It seemed likely that treatment had conditioned marrow aplasia, for the anaemia was associated with thrombocytopenia and profound neutropenia. Marrow puncture gave no diagnostic information. Accordingly a trial of A.C.T.H. was made: the dosage was 100 mg. daily, reduced after eight days to 75 mg. daily. The drug was continued for 20 days (total 1.7 g.). The blood count at the start of treatment showed: Hb, 72%; W.B.C., 900 per c.mm. (60% neutrophils); and platelets, 40,000 per c.mm. No improvement occurred in the peripheral blood as a result of treatment. In the ensuing months the interval between transfusions has lengthened and the white-cell and platelet count has gradually returned to normal.

A retired policeman aged 64 had been anaemic for three years. Marrow examination at the onset in 1949 demonstrated notable reduction in the formation of erythrocytes, though the marrow was not aplastic. The diagnosis of hypersplenism was considered, but splenectomy in 1950 failed to establish a clinical cure, and since operation he had been kept alive by blood transfusions. A course of A.C.T.H., 100 mg. daily for eight days, was without effect on the anaemia and no reticulocytosis was observed. No decrease in the frequency of subsequent transfusions followed this course of treatment, which was held responsible for the recognition, three months later, of diabetes mellitus, requiring insulin. He died six months later at home, and no post-mortem examination was possible.

Comment.—In the first patient the restoration of a normal blood count was seemingly uninfluenced by A.C.T.H., the subsequent haematological improvement being more in keeping with the experience of Matthews (1950) though occurring rather less promptly, which probably reflected on the large amount of R48 previously given. In the year of observation following the course of A.C.T.H. there has been no progression of the Hodgkin's disease, which appears entirely quiescent. In the case of idiopathic aplastic anaemia A.C.T.H. had no effect on the blood condition, diabetes mellitus developing three months later as a complication of treatment.

Agranulocytosis

A patient with agranulocytosis consequent on thiouracil treatment of thyrotoxicosis was admitted as an emergency. A blood count showed 1,200 leucocytes per c.mm., with 4% neutrophils; and marrow examination demonstrated severe hypoplasia of the myeloid series. A.C.T.H., 25 mg. six-hourly, produced prompt symptomatic and haematological improvement, with myeloid hyperplasia evident at a second marrow examination on the fourth day of treatment, the peripheral blood at this time showing 70% of polymorphs in a total white-cell count of 2,900 per c.mm. Restoration to normality was complete by the seventh day, and there seemed little doubt that A.C.T.H. was the agent responsible for the swift reversal of this profound neutropenia.

A housewife aged 57 had been found to be granulocytopenic two years previously. Apart from a course of sulphonamides, given prior to recognition of the condition, no cause was evident. Treatment with haematinics had been without effect and she was subject to recurrent coliform urinary infections. The total white-cell count averaged 2,000 per c.mm., with neutrophils 10–20%. Marrow examination demonstrated a failure of maturation of the cells of the myeloid series in a quiescent marrow. Seven intravenous infusions of A.C.T.H., each of 20 mg. in 1 litre of normal saline, were given on alternate days without significant change in the peripheral white-cell count, and a seven-day course of A.C.T.H. by intramuscular injection (total 900 mg.) was similarly ineffective. Her progress has been followed for 18 months. Her health remains good, though still liable to interruption by urinary tract infection, and on one occasion by a large gluteal abscess of spontaneous origin from which *Bact. coli* was cultured. The added complication of a mild diabetes mellitus, recognized six months after the course of A.C.T.H., has been well controlled by dietary restriction of carbohydrates.

The third patient in this group, a man aged 51, first came under treatment for a left-upper-lobe pneumonia which gradually resolved with antibiotic therapy. Granulocytopenia was observed at this time, the bone marrow showing granulocytopoiesis to be arrested at the stage of transition from myeloblasts to myelocytes, the more mature forms showing heavy toxic stippling. The erythroid elements were hyperplastic in response to a moderately severe anaemia. The anaemia was corrected by blood transfusion, and the patient returned to work. His condition slowly deteriorated, with irregular pyrexia and progressive fall in the neutrophils to 7% of a leucocyte count of 2,400 per c.mm. A.C.T.H., 100 mg. daily for 16 days, caused some improvement, the white-cell count after treatment being 3,300 per c.mm., with 64% neutrophils. The diagnosis in this case remained obscure, the haematological findings being compatible with a chronic agranulocytosis or progressive marrow aplasia. Further investigation was prevented by the development of psychotic traits, the patient taking his own discharge and dying a month later at home. The possibility of tuberculosis was suggested by a chest *x*-ray examination within a month of death, which showed a diffuse mottling throughout the lung fields.

Comment.—Of three patients with agranulocytosis, an excellent response to A.C.T.H. occurred in the one in whom thiouracil was the agent responsible for the acute development of serious neutropenia. A.C.T.H. was entirely

without effect in a second case of agranulocytosis of idiopathic origin and two years' duration, and led to the later development of diabetes. In a third patient, A.C.T.H. produced a temporary improvement in the white-cell count where the cause of the granulocytopenia remained obscure.

Thrombocytopenic Purpura

Cortisone has been used in two cases. A man aged 65, with a lifelong bleeding tendency and several previous admissions for thrombocytopenia, was readmitted because of persistent epistaxis, with a platelet count of 100,000 per c.mm. and a bleeding-time of 12 minutes. Cortisone, 100 mg. daily intramuscularly, was given for five days without significant haematological response, though the bleeding stopped on the second day of treatment.

The second patient, a woman aged 39, developed thrombocytopenic purpura after a course of sodium aurothiomalate given for disseminated lupus erythematosus. The platelet count averaged 80,000 per c.mm., sternal marrow biopsy showing no evidence of aplasia or leukaemia, the megakaryocytes being normal in number and form. The spleen was not palpable. Splenectomy was done without persisting effect on the platelet count and bleeding continued, requiring frequent transfusion. Treatment with A.C.T.H., 100 mg. daily for three days followed by 50 mg. daily for two weeks, coincided with clinical improvement, and bleeding ceased shortly after the drug was discontinued, the platelet count showing little significant change. Since this time two further episodes of bleeding and purpura have necessitated her readmission, but her general condition has steadily improved and she is now well. The lupus erythematosus is quiescent.

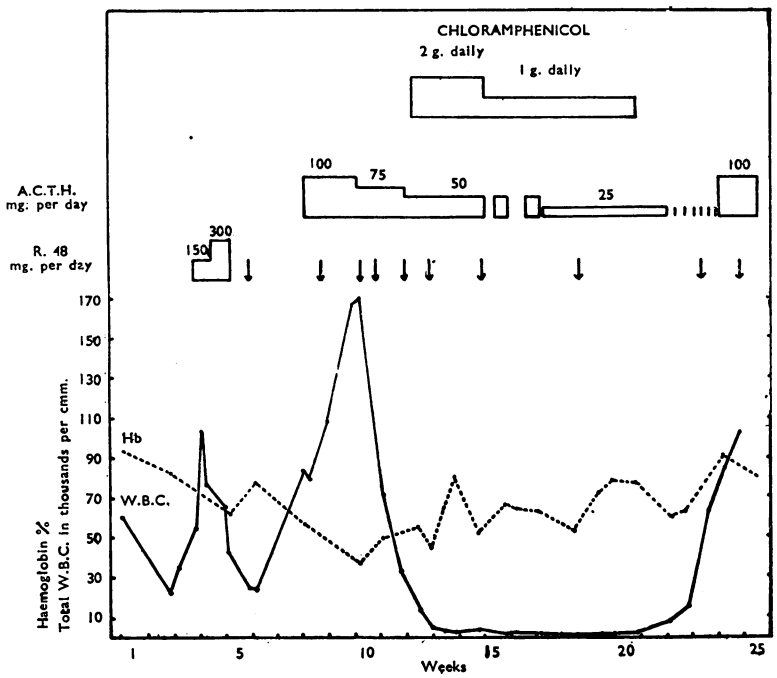

FIG. 1.—Effect of A.C.T.H. in a patient with subacute myelogenous leukaemia. Arrows indicate blood transfusions.

Comment.—In both patients clinical improvement coincided with the administration of cortisone or A.C.T.H., unaccompanied by significant haematological response.

Leukaemia

Three patients with leukaemia have been treated with A.C.T.H. The first of these, a woman aged 42, presented in an acute termination of a myeloid leukaemia with the unusual feature of extensive glandular enlargement. Three weeks previously she had completed a course of deep *x*-ray therapy. Blood examination showed 51% neutrophils, 22% metamyelocytes, and 27% myelocytes in a total white-cell count of 48,000 per c.mm. A.C.T.H. was given at a dosage of 100 mg. daily for seven days, without clinical improvement or haematological response, the peripheral blood demonstrating an increasing number of less-differentiated cells in a higher total count. Her death from cerebral haemorrhage followed shortly on the withdrawal of A.C.T.H.

Our second patient, a man aged 30, had subacute myeloid leukaemia and the clinical appearance of so-called "pseudoscurvy." A course of R48 was discontinued on the development of skin purpura and A.C.T.H. introduced in an attempt to influence the extreme dysphagia occasioned by infiltration and oedema of the oropharynx. Symptomatic relief was rapid and striking, regression of swelling and clearing of ulceration from the mouth being associated with control of fever and a sensation of well-being that bordered on the euphoric. The total white-cell count initially increased, but later it progressively and rapidly declined to leucopenic levels, averaging 1,500–2,500 per c.mm., with neutrophils about 40–60% and lymphocytes 60–40%; immature white cells disappeared from the peripheral blood (Fig. 1). The dosage of A.C.T.H. was gradually reduced, but attempts to discontinue it entirely were met by a prompt return of fever with local and general deterioration. It appeared probable that A.C.T.H. was the agent responsible for the temporary control of the leukaemic process, though the concomitant employment of chloramphenicol may well have contributed to marrow depression—an effect reported in this country by Hawkins and Lederer (1952) and by Wolman (1952). In the fifteenth week of treatment with A.C.T.H., and some nine days after chloramphenicol had been discontinued, the peripheral blood demonstrated a return of leukaemic features, with the reappearance of primitive white cells. Thereafter deterioration was rapid, jaundice preceding death.

The third patient, a boy aged 16 with acute myeloid leukaemia, received five daily transfusions each of 25 mg. of A.C.T.H. in 1 litre of normal saline. The total white-cell count fell from 140,000 to 13,000 per c.mm. in this period, but the proportion of primitive cells remained unchanged. The later administration of folic acid antagonists clouded estimation of the therapeutic effect, but no remission followed, and the boy has since died.

Comment.—We have had no experience of the effect of cortisone and A.C.T.H. in the acute leukaemias of childhood, in which favourable results have been reported. In this small group of older patients with myeloid leukaemias the discouraging response to treatment has been in keeping with that generally recorded.

ENDOCRINE DISEASES

Exophthalmic Ophthalmoplegia

Our original report (Chandler and Hartfall, 1952) concerned the treatment with cortisone and A.C.T.H. of five patients (Cases 1–5) with this condition. Since then four more patients have been treated, without dietary regulation of sodium.

Case 6.—A woman aged 70 developed thyrotoxicosis in January, 1951. Treatment with thiouracil led to general improvement, but proptosis and chemosis became more pronounced, though unaccompanied by ophthalmoplegia. She was admitted in March, 1952, and given A.C.T.H., 100 mg. daily for 21 days, without change in the ocular condi-

tion, either subjective or objective. Her thyrotoxicosis showed no signs of settling and she was given a treatment dose of I^{131} in June, 1952. Control of thyrotoxicosis has been associated with a slow improvement in the eye signs.

Case 7.—A woman aged 25 underwent partial thyroidectomy for primary thyrotoxicosis in April, 1951. There was some post-operative increase in exophthalmos, and on admission in May, 1952, the exophthalmometer readings were R. 23 mm., L. 22½ mm. Gross nystagmus, hysterical in pattern, prevented measurement of duction movements. There was no diplopia. She gave the impression of considerable anxiety without evidence of thyrotoxicosis (B.M.R. +20%). Treatment with cortisone by mouth, 25 mg. six-hourly, was started on May 30 and continued to June 19. There was some slight subjective improvement and a minimal decrease in proptosis (R. 21 mm., L. 22½ mm. on June 19). The dosage was reduced to 50 mg. daily on July 2 and then to 25 mg. daily on July 7, and was finally discontinued after another three weeks. No further change was observed, the readings of exophthalmos in November being R. 21 mm. and L. 22 mm. The patient claims continued symptomatic relief.

Case 8.—This patient was a woman aged 50. The onset of bilateral proptosis four years previously antedated by nearly two years the clinical recognition of thyrotoxicosis. Thiouracil treatment was instituted in January, 1951, but was discontinued after five months because of leucopenia. Since this date there has been little change, either in thyroid status or in the severity of the eye signs. In August exophthalmos measured R. 22½ mm. and L. 23½ mm. There was no oedema either of lids or of conjunctivae, and the ocular movements were full. The patient was euthyroid as judged by B.M.R. and radio-iodine studies. A course of cortisone, 100 mg. daily by mouth to a total of 2 g., was entirely without effect on the eye signs, and a subsequent trial of A.C.T.H. was likewise ineffective.

Case 9.—A man aged 54 was admitted on October 19, 1952, with a short history of progressive exophthalmos, first noted in the left eye four months previously. Diplopia was experienced on upward movement, and, concomitantly with the ocular disturbance, increasing irritability and weight loss suggested a mild thyrotoxicosis, confirmed by B.M.R. (+40%) and radio-iodine studies. Examination revealed rigid proptosis (R. 24 mm., L. 27 mm.), with chemosis and conjunctival prolapse. There was gross limitation of upward movement in both eyes with paresis of left inferior oblique and left superior rectus. A course of A.C.T.H. to a total of 2 g. (100 mg. daily for 20 days) was undertaken. During the period of observation and treatment the ophthalmoplegia and area of diplopia increased, later measurement of proptosis showing R. 26 mm. and L. 28 mm.—a small deterioration.

Comment

In summary, six patients showed no improvement, yet three responded well and one dramatically. This conflict of response is reflected in the publications of other investigators, some of whom (Lederer and Hambresin, 1950; Cole, 1951) reported conspicuously favourable results.

The reasons for this remarkable disparity are not immediately obvious, though some preliminary and necessarily tentative conclusions appear to be justified.

1. Our best results were obtained with A.C.T.H. in patients whose exophthalmos was of recent origin or had suddenly and rapidly progressed. It is possible that the greater effectiveness of A.C.T.H. may be the result of the stimulation of mineral corticoid secretion and consequent local withdrawal of fluid from the orbital tissues (Campbell, 1952). Such an effect could be expected in exophthalmos of recent development only before fibrotic changes have occurred in the ocular muscles and tissues. We have previously had experience of the ability of these steroid hormones to promote a saline diuresis in certain oedematous states (notably the nephrotic syndrome), and our original investigation was framed so as to relate the sodium balance of patients, with exophthalmos to the effect of treatment.

2. Those patients in whom exophthalmos and thyrotoxicosis coexist form a group of particular therapeutic difficulty. Though a treatment dose of I^{131} may prove a less drastic insult to the thyroid-pituitary relationship than partial thyroidectomy, yet in our series the control of thyrotoxicosis was the most notable feature of the treatment of two patients (Cases 1 and 5) in whom this coexisted with exophthalmos and ophthalmoplegia. This suppressive effect of the adrenal steroid hormones on thyroid function is in accord with the experience of Hill *et al.* (1950), who obtained good results in three out of six patients with uncomplicated Graves's disease. However, two patients in our series (Cases 6 and 9) showing the combination of thyrotoxicosis and exophthalmic ophthalmoplegia obtained no benefit from A.C.T.H.

3. Our experience with cortisone in patients showing exophthalmos unaccompanied by ocular muscle weakness has been entirely disappointing (Cases 6, 7, and 8), and no benefit from treatment has been observed. These patients showed only an overfilling of the orbit, presumably the effect of excess of fat.

4. Another consideration, that of dietary restriction of sodium which was enforced in our original series (Cases 2–5), cannot be discounted as a factor responsible for clinical improvement, bearing in mind the belief that oedema of the orbital tissues plays a part, at least, in the production of exophthalmos.

Simmonds's Disease

A.C.T.H. has been used in the treatment of three women with panhypopituitarism. On inquiry all gave histories typical of this disorder, dating their illness to a previous childbirth which had been attended by severe post-partum haemorrhage, following which lactation had never been established and the periods had failed to return. They had lost in energy, appetite, and variably in weight, one patient in particular presenting the picture of pituitary cachexia originally described by Simmonds (1914). Her slow deterioration over the years had been interrupted by infrequent attacks of drowsiness and coma. One such attack was observed in hospital, the patient lapsing into semi-coma with markedly cold extremities, immersion in a hot bath producing a striking but temporary improvement.

Clinical examination showed, in each, the changes of severe pituitary insufficiency. One patient was notable for the absence of mental change, preserving a bright though facile cheerfulness, in striking contrast to her physical enfeeblement. Of the others, one was deaf and apathetic, the other confused and hallucinated. The details of investigation before and during treatment are recorded in the accompanying Table. The Thorn test was normal in all, and hypoglycaemic unresponsiveness was observed in the two patients (Cases 2 and 3) in whom this investigation was made.

Treatment was by A.C.T.H. alone, and led to an improvement which was considerable in all, and dramatic in one (Case 2). It was appreciated by the patients, who without exception spoke of a feeling of strength and health, which had been absent for many years. The mental condition returned to normal in the two patients (Cases 1 and 2) in whom the symptoms of confusion and hallucination had predominated. Increase in appetite was universal, though gain in weight was not remarkable, averaging 8 lb. (3.6 kg.). All mentioned their new-found freedom from cold.

Concomitant anaemia, of normochromic type, which existed in Cases 1 and 3, did not respond to A.C.T.H., either alone or in combination with haematinics, and blood transfusion was required in Case 3 to correct the deterioration in this respect, the Hb having fallen to 49%.

Urinary excretion of 17-ketosteroids increased in all patients, particularly during the early weeks of treatment, but this was not maintained and perhaps was related to the reduction in dose of A.C.T.H. Examination of the fluid balance was remarkable for the demonstration, prior to the inception of A.C.T.H. therapy, of the small intake of water on which these patients were able to exist, the 24-hour urinary volume averaging 400–600 ml. The low level of sodium, which was a feature of the plasma chemistry of Cases 1 and 2, returned to normal and remained so under the influence of A.C.T.H. Serial E.C.G. recordings showed a parallel improvement. These patients have now returned home. Their maintenance requirements are being met by a single weekly injection of "acthar gel" 40 mg., on which

Effect of A.C.T.H. in Three Patients with Simmonds's Disease

Case	Age	Duration of History	Days from Start of A.C.T.H	Hb %	B.M.R.	Blood Cholesterol (mg./100 ml.)	Blood Na (mg./100 ml.)	Blood K (mg./100 ml.)	17-Ks in mg./24 Hours	Fasting Blood Sugar (mg./100 ml.)	A.C.T.H. Dosage	Response
1	63	25 yrs.	0 7 20 25	84 67 	−28%	268 140	280 345 333	19·6 17·1 17·8	0·8 5·0 1·9	60 80	25 mg. I.M. b.d. 25 ,, ,, ,, 25 ,, daily 25 ,, alt. days	Excellent. Discharged home on 25th day of treatment. Maintenance requirements, acthar gel 40 units weekly
2	58	32 yrs.	0 25 47 160	91 90 	−50%	240 180 250	270 325 330	15·7 18·8 17 18	2·3 4·0 3·8 2·1	80 130	25 ,, b.d. 25 ,, daily 25 ,, alt. days 25 ,, ,, ,,	Excellent. Severely confused and hallucinated on admission. Mental condition now normal. Returned home on 51st day of treatment and is managing all housework. Continuing as an out-patient on acthar gel 40 units weekly
3	42	18 yrs.	0 18	64 49	−7%	130	332 315	21·5 16·5	1·2 3·1	70	25 ,, q.d.s. 25 ,, b.d.	Good. Previously bed-ridden is now taking an active part in her household duties. On acthar gel 40 units weekly as an out-patient

17-Ks = Urinary 17-ketosteroid excretion.

improvement has been steadily sustained: all are leading active useful lives, managing their homes in a way previously impossible of fulfilment.

No toxic effects have been observed in this series, the appearance of oedema of feet and legs during the initial period of treatment responding to moderate salt restriction and the later reduction in A.C.T.H. dosage.

Comment.—The effect of A.C.T.H. in severe pituitary insufficiency has been studied in three patients, with a benefit from treatment so remarkable as to leave no room for doubt. In one patient (Case 2), almost moribund on admission, the effect was life-saving. They are now restored to useful domestic activity, though the glandular deficiency is such that continued maintenance treatment seems necessary.

Adrenal Hyperplasia

Cortisone has been given to four patients. Two were young women showing the syndrome of adrenal virilism, and two were children presenting as pseudo-hermaphrodites.

Adrenal Virilism

A woman aged 22 had noted rapid gain in weight and irregular menstruation for six months. Examination revealed moderate hirsutism, mooning of the face, and gross acne of the chest and back. The blood pressure was normal. The urinary excretion of 17-ketosteroids varied between 28 and 34 mg. per 24 hours, and the test for dehydroisoandrosterone was negative. Perirenal air insufflation and aortograms were thought to exclude an adrenal tumour. Total right adrenalectomy was without benefit or appreciable effect on 17-ketosteroid excretion. Two months later, left hemi-adrenalectomy was carried out under the protection of cortisone, 200 mg. being given on the day before operation, the drug being carried into the immediate post-operative period in gradually diminishing dosage. There resulted a very definite improvement in hirsuties, and the urinary excretion of 17-ketosteroids declined to an average of 6 mg. per 24 hours. Within two months, however, symptoms returned in their old severity, 17-ketosteroid excretion increasing to 15 mg. per 24 hours, and a third operation of left subtotal adrenalectomy was undertaken, the adrenal remnant being some one and half times the size of the normal gland. Five-sixths of this was removed, again under the cover of cortisone, which was given at a dosage of 50 mg. daily for two days before and for seven days after operation. The adrenal tissue removed at these successive procedures showed no histological abnormality. The further progress of this patient has been reasonably satisfactory, though a tendency to hirsutism remains.

The second patient, a woman aged 25, had been raised as a boy until the age of 9, when a large clitoris was removed. The mother noted hirsuties at this time. Menstruation later occurred only under the influence of oestrogens. She presented with typical virilism, a strong beard requiring shaving twice daily. There was no evidence in the skin or face of basophilism, and the B.P. was 190/120. Urinary excretion of 17-ketosteroids was 26.5 mg. per 24 hours. An aortogram demonstrated enlargement of both adrenal glands without evidence of tumour. Excretion of 17-ketosteroids increased to a maximum of 108 mg. per 24 hours during a period of in-patient observation. Total right adrenalectomy was followed by a course of cortisone, 50 mg. daily for 34 days, during which 17-ketosteroid excretion fell to normal, the hirsuties greatly improving. Left subtotal adrenalectomy was done five months later under the protection of a second course of cortisone, but within two months of this operation a mild Addisonian syndrome developed, with weakness, vomiting, and pigmentation. She improved with deoxycortone acetate and salt therapy, cortisone being withheld as her condition suggested functional activity of the adrenal remnant. The histological appearances were those of simple cortical hyperplasia.

Comment.—Surgical removal of hyperplastic adrenal tissue and cortisone therapy have effected a small improvement in two patients with virilism; in neither did the results appear commensurate with the risks involved, though the time of observation had admittedly been short.

Pseudo-hermaphroditism

An infant of 3 weeks presented with persistent vomiting and perineal hypospadias. The diagnosis of female pseudo-hermaphroditism was confirmed by a raised urinary 17-ketosteroid excretion of 8.2 mg. per 24 hours (normal less than 1 mg.) and the infant's inability to retain salt. Despite vomiting, the urinary excretion of salt averaged 2 g. daily on an intake of less than 0.5 g. a day. The blood sodium was 228 mg. per 100 ml., chloride 430 mg. per 100 ml., and potassium 25 mg. per 100 ml. The infant was given extra saline equivalent to 2–3 g. of salt a day, with cortisone 5 mg. intramuscularly daily. The 24-hour excretion of 17-ketosteroids fell rapidly to an average of 1–1.5 mg., but the child remained ill and miserable, passing loose offensive stools; analysis of a 24-hour specimen showing 47% of total fatty matter with trypsin present down to a dilution of 1:100. A loose cough was uninfluenced by a course of aureomycin. After four weeks, deoxycortone acetate, 2 mg. daily, was introduced and cortisone continued at a dosage of 5 mg. intramuscularly twice weekly, with some clinical improvement and restoration of the blood sodium and chloride levels to normal. The improvement was short-lived, the child dying from bronchopneumonia in the eighteenth week. At necropsy the suprarenal glands were greatly enlarged (each weighing 10.4 g.) and showed a pale hyperplastic cortex. Histological examination revealed fibrocystic disease of the pancreas.

The second patient, first seen aged 3 years 3 months, had hitherto been reared as a boy. He was of slender build with girlish facies, showing a perineal hypospadias flanked on either side by gonadal sacs containing no testes. Over these sacs and the top of the phallus there was a quantity of black hair, suggesting a masculinizing process in a female.

This was confirmed by hormone estimations on the urine: 17-ketosteroids, 16.6 mg. per 24 hours; dehydroisoandrosterone, negative; follicle-stimulating hormone, 17 units. These results suggested bilateral diffuse hypertrophy of the adrenal cortex, though the amount of follicle-stimulating hormone, not usually present at this age, raised the possibility of primary pituitary dysfunction. The patient's bone age was between 5 and 6 years. Laparotomy a year later demonstrated female internal organs, biopsy from the right ovary showing normal ovarian tissue.

Cortisone therapy was started in July, 1952, the child being then almost 5 years old. The dosage was 50 mg. daily for three weeks, reduced to 25 mg. daily for a further four weeks, thereafter continued at 75 mg. and 100 mg. twice weekly. The 24-hour excretion of 17-ketosteroids, which had averaged 18–19 mg. per 24 hours prior to cortisone therapy, was controlled in the succeeding months at 4–6 mg. per 24 hours. Little objective change has so far occurred, but the child is well and happy, conforming easily to feminine outlook.

MISCELLANEOUS CONDITIONS

Cirrhosis with Portal Hypertension

Our experience of the treatment of this syndrome with A.C.T.H. has been limited to two patients in whom hepatic fibrosis had occasioned portal hypertension with frequent episodes of gastro-intestinal bleeding. Previous reports (Bongiovanni and Eisenmenger, 1951) of the effect of A.C.T.H. in cirrhotic subjects have stressed the risk to those patients whose liver function is seriously impaired. In others, certain benefit seems to have attended treatment, though evidence of the specific nature of the response is lacking.

A man aged 35 developed cirrhosis consequent on homologous serum jaundice. Three attacks of haematemesis at six-monthly intervals brought him under our observation, when, in addition to the finding of splenomegaly, extensive oesophageal varices were visible on barium examination and confirmed at oesophagoscopy. Measurement of oesophageal varix pressure (Mr. Allison) showed an excess over systemic venous pressure of 140 mm. H_2O. A course of A.C.T.H. was given over 39 days of study (total 2.5 g.). Day-to-day variation in dosage was determined by the patient's response, particularly in relation to fluid and salt retention and also by the levels of blood sugar. Fluid retention was easily induced—far more readily than has been our experience in other conditions with similar dosage. The details of treatment and investigation are shown in Fig. 2. Serial estimations of plasma chemistry showed a progressive and sustained improvement in liver function with final return to normality. Direct measurement of portal hypertension gave equivocal results. By the fifth week of treatment the pressures in the portal and systemic systems were equal, but this second measurement coincided in time with the period of maximum fluid retention and systemic venous pressure was notably raised. Six months later, measurement showed that the difference in pressure between the two systems was as before treatment. Treatment occasioned some improvement in general health, and in the eight months since A.C.T.H. was discontinued the improvement, both clinical and biochemical, has persisted without recurrence of bleeding.

A man aged 36 had survived numerous attacks of haematemesis and melaena as well as the operations of splenectomy and oesophageal devascularization, both without benefit. This patient suffered a recurrence of bleeding whilst under treatment, and has recently reported a further attack of melaena. A.C.T.H. has contributed nothing to this man's rehabilitation.

Comment.—This small experience suggests that A.C.T.H. has no certain place in the present admittedly unsatisfactory attack on the problem of portal hypertension, though it may remain a valuable therapeutic adjuvant in the treatment of cirrhosis.

Nephrotic Syndrome

We have had experience of the paradoxical diuretic power of these drugs in two patients whose presentation conformed to that described by Ellis (1942) as type II nephritis.

A woman aged 48 developed the characteristic triad of oedema, albuminuria, and hypoproteinaemia following on the employment of sodium aurothiomalate for a polyarthritis of rheumatoid type. Yet the time interval of nearly 12 months was such that the aetiological role of gold was of questionable significance. This patient received cortisone at a dosage of 100 mg. intramuscularly daily for six weeks (total 4.3 g.) and by the fourth week of treatment had lost 20 lb. (9.1 kg.) and was clear of oedema. Proteinuria declined from 7–8 g. per litre to an average of 1–2 g. per litre, yet no change in the level and ratio of plasma proteins accompanied this clinical improvement. She slowly relapsed after cortisone had been discontinued, oedema reaccumulating, uninfluenced by a 10-day course of A.C.T.H. (1.1 g.) and a final short course of cortisone, though she never became so waterlogged as on admission. Renal function was unchanged as judged by clearance tests, and the patient was normotensive throughout.

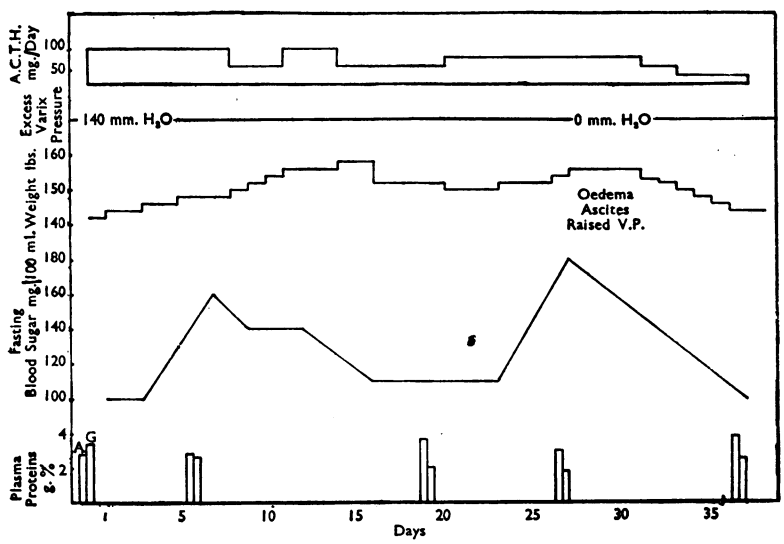

FIG. 2.—Effect of A.C.T.H. on a patient with hepatic cirrhosis and portal hypertension. Note initial rapid increase in weight, with equalization of portal and systemic venous pressures at a time of maximum fluid retention, and improvement in the levels and ratio of plasma proteins.

Our second patient, a girl of 15 years, came under observation in March, 1951, when for two months she had noticed swelling of the feet and legs, unaccompanied by haematuria. She was found to have gross albuminuria and a B.P. of 180/120. Since this time, oedema had fluctuated but never remitted. Renal function was adequate; the plasma chemistry demonstrated reversal of the albumin/globulin ratio. In March, 1952, no improvement having followed the adoption of orthodox dietary measures, A.C.T.H. was started at a dosage of 25 mg. intramuscularly six-hourly and continued for 17 days (total 1.7 g.), the patient being placed on a diet providing a constant daily intake of sodium. During the administration of A.C.T.H. she gained weight steadily, oedema sensibly increasing in a period of negative sodium balance (Fig. 3). Cessation of A.C.T.H. was followed by a profound saline diuresis over 10 days, when the patient lost 15 lb. (6.8 kg.) in weight, oedema clearing entirely. Albuminuria

diminished slightly and the level of blood cholesterol fell from 350 to 170 mg. per 100 ml. This patient's progress has been observed for 12 months, and neither increase in weight nor return of oedema has occurred. Hypertension remains unaltered, and renal function is adequate. No significant change was noted in the level of plasma proteins during the time of in-patient observation, but in the succeeding months the trend of the plasma chemistry has shown an encouraging progress to normality.

Comment.—Two patients with a nephrotic syndrome have been treated with cortisone and A.C.T.H. The first patient went into remission whilst under treatment with cortisone, decrease in albuminuria and diuresis occurring simultaneously. Partial relapse followed the withdrawal of cortisone. In a second patient, treated with A.C.T.H., the diuresis was observed immediately after withdrawal of the drug and continued for 10 days. In this case the remission induced by treatment has lasted for 12 months. It seems clear from these observations that A.C.T.H. and cortisone are capable of exerting profound effects on electrolyte metabolism. More doubtful, however, is the possibility that the underlying disease process has been radically altered. This favourable response to cortisone and A.C.T.H. compares with other clinical reports of the effect of induced malaria (Gairdner, 1952), and the natural remissions sometimes observed following measles, for these may well represent the common results of adrenal activation by stress. Whatever the precise mechanism, these effects of the adrenal steroids in nephrotic disease provide interesting problems in fundamental physiology.

Asthma

The dramatic relief afforded to patients with bronchial asthma, and particularly those in status asthmaticus, by cortisone and A.C.T.H. is generally known. We have had the opportunity of observing their effects in nine patients, all of them subjects of severe chronic asthma, for whom emergency hospital admission had been requested after the usual remedies had failed.

Three women in their fifties obtained rapid relief from a single intravenous infusion of normal saline to which 20 mg. of A.C.T.H. had been added. These drips were allowed to run for 12 hours, when symptomatic benefit was such that treatment could confidently be continued by more orthodox means.

A woman aged 45, admitted desperately ill in intractable status asthmaticus, did not respond to A.C.T.H. by intravenous infusion and died on the second day. Post-mortem examination demonstrated almost solid plugging of the air passages by thick mucoid material, a mechanical obstruction to respiration which only bronchoscopic aspiration might have relieved.

Two patients have been treated with cortisone by inhalation, 5 mg. of the standard preparation being made up into 2 ml. with normal saline and administered at two-hourly intervals. The response of both lacked the dramatic quality attending the use of intravenous A.C.T.H., but was judged by the patients themselves to provide more rapid and lasting improvement than they had obtained in previous attacks of similar severity.

Two patients have received cortisone by intramuscular injection. A housewife aged 59 derived no benefit from 100 mg. of drug given daily for five days. The other, a woman of 25 in status asthmaticus, made an excellent response to 50 mg. given thrice weekly for five doses, treatment being continued at 50 mg. twice weekly for a further fortnight. The remission in this patient lasted until her return home one week later.

Though not directly touching on the therapy of the asthmatic attack, cortisone has been used in a case of allergic asthma in which orthodox desensitization had been abandoned because of the production of severe asthma. It was found possible to complete desensitization under the protection of cortisone, 25 mg. twice weekly, and since its completion the patient, a man aged 40, has remained free of attacks.

Comment.—We have confirmed the beneficial effects of cortisone and A.C.T.H. in seven of nine patients with severe bronchial asthma. The intravenous infusion of A.C.T.H. in normal saline seems to offer the best prospect of rapid symptomatic relief, and, together with the topical administration of cortisone by inhalation, allows of considerable economy in prescribing. The remissions induced by these forms of treatment average one to two months, probably differing little from the duration of freedom afforded by the more usual forms of treatment.

Summary

The effect of cortisone and A.C.T.H. in non-rheumatic diseases has been studied in 43 patients.

Fourteen patients with disorders of the blood have been observed. A favourable response occurred in three children with acute acquired haemolytic anaemia, and in thrombocytopenic purpura apparent clinical benefit resulted in the two patients treated. No effects were produced in aplastic anaemia, though one patient with acute agranulocytosis from thiouracil made a good response. The effect of A.C.T.H. in leukaemia was at best temporary. This small experience suggests that, apart from acquired haemolytic anaemia and some cases of purpura, cortisone and A.C.T.H. have little place in the treatment of blood disorders.

Sixteen patients with disorders of endocrine function have been studied. Of nine patients with exophthalmic ophthalmoplegia, only three responded well, the best results being obtained with A.C.T.H. in those examples of recent onset or rapid progression. Three patients with Simmonds's disease have made a dramatic and sustained improvement on A.C.T.H. Two patients showing the virilizing effects of adrenal hyperplasia have been

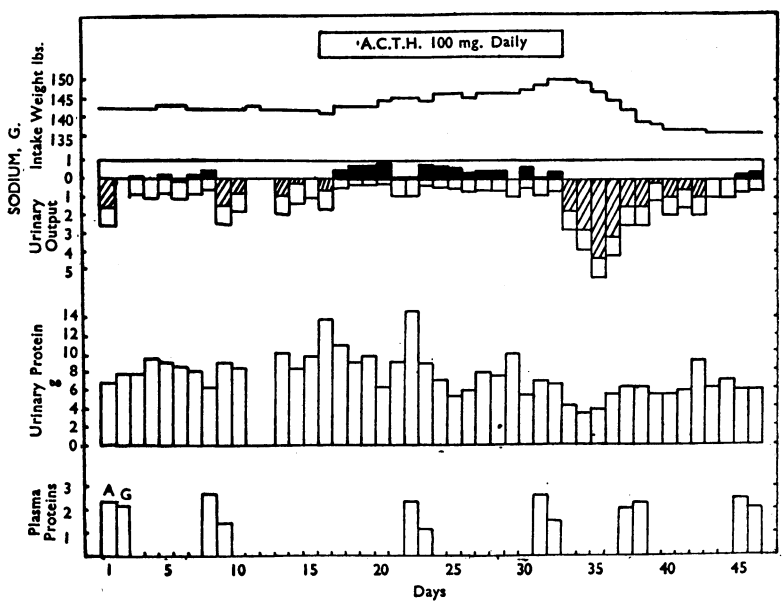

FIG. 3.—Effect of A.C.T.H. in a patient with nephrotic syndrome. Black areas, positive sodium balance; hatched areas, negative sodium balance. Note rapid loss of weight and saline diuresis when A.C.T.H. was discontinued. The levels and ratio of plasma proteins show no persisting improvement.

treated by adrenalectomy and cortisone : in neither did the results obtained appear to justify the risks involved. 17-ketosteroid excretion was controlled in two pseudo-hermaphrodites by the use of cortisone.

The beneficial effect of cortisone and A.C.T.H. in asthma has been confirmed. The use of A.C.T.H. by intravenous drip and of cortisone by inhalation usually brought prompt improvement and was an important economy in prescribing. In two patients with nephrosis a considerable diuresis attended treatment, and in one of them the remission obtained has lasted more than a year. There is no evidence that A.C.T.H. influences portal hypertension accompanying cirrhosis, though apparent clinical benefit occurred in one patient.

We are grateful to the physicians and surgeons of the General Infirmary at Leeds and the Hospital Cortisone Committee, who have allowed us to publish details of patients under their care. We are indebted to the Medical Research Council for the cortisone used in the treatment of exophthalmic ophthalmoplegia and to Armour Laboratories for a supply of acthar gel.

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DEVELOPMENTAL DYSARTHRIA

BY

MURIEL MORLEY, B.Sc., F.C.S.T.

DONALD COURT, M.D., M.R.C.P.

AND

HENRY MILLER, M.D., F.R.C.P., D.P.M.

(From the Children's Department, Royal Victoria Infirmary, Newcastle-upon-Tyne, and the Department of Child Health, Durham University)

In 1950 we advocated a simple classification of speech disorders in childhood (Miller and Morley, 1950). This had grown naturally from our work and was conceived within the framework of accepted neurological terminology. The five broad categories of deafness, defective articulation or dysarthria, retarded development of language or dysphasia, dyslalia, and stammering, with their main subdivisions, are presented again, as follows :

Disorders from Deafness
1. Congenital nerve deafness:
   (*a*) Severe for all frequencies.
   (*b*) Partial, or high-frequency deafness.
2. Acquired nerve deafness.

Dysarthria
1. Due to local anatomical lesions of the speech organs.
2. Dysarthria with neurological signs of cerebral disease or maldevelopment.
3. Dysarthria unassociated with abnormal neurological signs elsewhere.

Dysphasia
1. Mainly expressive dysphasia.
2. Mainly receptive dysphasia:
   (*a*) Dyslexia.
   (*b*) ? Congenital auditory imperception.
3. Delayed development of speech or global dysphasia.

Dyslalia
Transient defects of consonant substitution and omission.

Stammering.

Continuing experience has confirmed the value of this classification in assessing the prognosis and designing the treatment of the individual child. In the past two years we have given particular attention to the problem of dysarthria, which is, to us, slow and clumsy articulation arising from dysfunction of the muscles used in speech. The association with cerebral palsy in all its forms is well known. A group of children, however, presented with dysarthria as the only disorder without detectable neurological abnormality in any other part of the body. It is this isolated form of dysarthria which is the subject of this paper. The literature on the subject is scanty, but suggests that the condition is uncommon. As we have studied 18 affected children over a period of four years we realize that it occurs more often than we suspected, and should be more widely recognized. We shall first describe four children whose cases illustrate the clinical patterns we have seen, and then consider the nature of the condition and its differentiation from other forms of defective articulation.

Clinical Patterns in Developmental Dysarthria

Case 1 : Dysarthria with Clumsy Movements of Lips, Tongue, and Palate.—This boy is now 7 years 9 months old. He is the second child in the family, was born before the arrival of the nurse, and weighed 12 lb. 10 oz. (5.7 kg.). He breathed and cried immediately after birth, was sucessfully breast-fed for seven months, and was walking on his first birthday. Words were first used between 12 and 18 months and sentences from 2 years onwards. On his first visit at the age of 5 his mother complained that "he dribbled when he was excited, sucked instead of chewing his food, and could not talk properly." Though rather nervous, he co-operated well and his I.Q. on the Drever Collins scale was 111. No abnormality could be found in the nervous system except that speech was slow and clumsy, the tongue bunched and writhed on lateral movement, and the palate moved to the right. During speech the lips, tongue, and soft palate moved in an awkward and uncoordinated fashion. Two years after the beginning of treatment he could repeat all consonant sounds except "s," and speech was intelligible when spoken slowly, though some final consonants were still omitted. Although it may be some years before he speaks easily, and still longer before speech is satisfactory under stress, it seems likely that this boy will eventually achieve normal speech.

Case 2 : Dysarthria with Clumsy Movement of the Soft Palate.—This 15-year-old girl is the second of four children. There is a history of language delay in her father until the age of 7 and of an unspecified speech difficulty in a cousin persisting into adult life. She was born normally and weighed 11 lb. 4 oz. (5.1 kg.). Her mother does not remember the child's early years very clearly, but she did not take the breast or bottle well and was slow in gaining weight. She was walking just before her first birthday. She was almost completely silent until 2, and then words came slowly. When first seen at 11 years she was a pleasant sensible girl with no evident disease of the nervous system apart from a tight soft palate which bunched up in the centre but did not contract at the sides. There was no sign of a submucous cleft. Speech was nasal in character. Consonants were weak or were omitted, and attempts to coordinate the use of vowels and consonants produced a