ACTH, CORTISONE AND ALLIED SUBJECTS

A Symposium

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PHARMACOLOGY AND PHYSIOLOGICAL ACTION OF ACTH, CORTISONE AND ALLIED SUBSTANCES ON BODY FUNCTION
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INFLUENCE OF ACTH AND CORTISONE ON RHEUMATIC FEVER
(abstract not available)
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Congenital adrenal hyperplasia in females causes pseudohermaphroditism which must be differentiated on the one hand from various types of genetic intersexuality and on the other from virilization due to adrenal tumor. In males it causes macrogenitosomia precox which must be differentiated from other types of sexual precocity and from adrenal tumor. The major manifestations of the disorder are due to the excessive secretion of adrenal androgen which causes progressive virilization throughout embryonic and postnatal life. In some cases there is a defect of electrolyte regulation which may lead to death with Addisonian symptoms or heart block.

Partial adrenalectomy and the administration of estrogens or inert androgens have failed to check the progressive virilization, but cortisone has succeeded in doing so by suppressing the excessive activity of the abnormal adrenals. This effect of cortisone can be accomplished with small doses which do not exceed physiologic requirements, whereas in the treatment of hypersensitivity states and various other conditions large doses of cortisone are required for its pharmacodynamic action.

We have now treated 11 patients continuously for periods of 6 to 17 months without ill effects. It is important to determine in each case the minimum dose required to maintain adequate suppression of the adrenals. This is measured by the level of urinary 17 ketosteroids. In patients over 8 years the ketosteroid excretion should be maintained below 8 mg. per day (preferably 4 to 6 mg. per day) and in young infants at 0.5 to 1.5 mg. per day. This degree of suppression can be brought about rapidly in older children by the administration of 25 to 50 mg. of intramuscular cortisone daily. After suppression is attained, it may be maintained indefinitely in the older children by 25 mg. of intramuscular cortisone daily, or 75 mg. every third day. With oral cortisone 50 to 75 mg. (given in 3 divided doses) are required. Young infants probably require a maintenance dose of 5 to 10 mg. of intramuscular cortisone daily, or 2 or 3 times this amount of oral cortisone.

In 6 female pseudohermaphrodites 8 years and older who were treated there was definite decrease of hirsutism and other signs of virilization. All of them developed breasts and estrinization of the vaginal smears, and 3 have menstruated regularly. With the doses used there have been no changes in carbohydrate metabolism and no other manifestations due to excessive cortisone.

The infants treated have shown no progressive virilization. It is important to follow their rates of growth and osseous development. An excessive amount of cortisone may inhibit growth and development. With proper doses, however, suppression of adrenal androgen may be maintained without inhibiting normal growth and development.

Infants with congenital adrenal hyperplasia who have defective electrolyte regulation must be treated with a high Na intake and/or desoxycorticosterone in addition to cortisone.

It seems probable that cortisone therapy will have to be continued indefinitely. Even after treatment has been continued for as long as a year, the overactivity of the adrenal has returned on withdrawing cortisone. During treatment slight infections and other stresses have caused temporary increases of adrenal activity as measured by the ketogenic excretion.

To reiterate, in order to obtain satisfactory clinical results it is necessary in each case to determine the minimum dose of cortisone required to maintain adequate suppression of the urinary 17 ketosteroids. The maintenance dose of oral cortisone required is 2 or 3 times that of intramuscular cortisone. With proper dosage no abnormal metabolic or toxic effects of cortisone have been encountered.

EXPERIENCES WITH ACTH IN THE TREATMENT OF THE ACUTE PHASE OF RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS

FREDERICK C. BLODI, M.D., ALGERNON B. REESE, M.D., WILLIAM A. SILVERMAN, M.D., AND RICHARD DAY, M.D.

During 1950 a trial of ACTH for 2 or 3 weeks during the acute phase of retrolental fibroplasia in premature infants yielded encouraging results. The number of infants progressing to partial or complete blindness in the hospital where ACTH was used was less than in the hospital where it was not used. During 1951 the treated and untreated infants were in the same nursery and were chosen
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by lot. The treated infants did slightly, though not significantly, worse than the untreated. In the table presented below the results are given for both years combined. Only cases progressing to the stage of distinct peripheral retinal edema are included. The conclusion is that ACTH is not proved to be of benefit in this condition. The treatment schedule followed led directly to 2 deaths, and indirectly to 4 others.

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INFLUENCE OF ACTH AND CORTISONE ON LEUKEMIA

JOHN E. FRANKLIN, M.D.

On the Pediatric Service of Memorial Hospital there have been 44 cases of acute leukemia, from December 1949 to August 1951, which have been treated with ACTH and cortisone. These studies were done under the supervision of Drs. Pearson and Burchenal of the Sloan-Kettering Institute and were undertaken because of the effect of these hormones on lymphoid tissue and producing remissions in leukemia in mice (Lau and Speirs). These cases were all in children ranging between 6 months and 14 years of age. They all fall under the classification of acute leukemia without any further breakdown. Many attempts to establish an accurate classification of leukemia in children were made without success. In the leukemia clinic it is felt that 5% of the patients can readily be classified as myelogenous leukemia, 45% as lymphatic and granulocytic leukemia and the remaining 50% fall into that group diagnosed with difficulty even by expert hematologists. After finding that our hematologist disagreed as to the classification of many of these cases, slides were sent to outstanding hematologists with resulting disagreement among them.

Except where treatment failed, subjective improvement was noted during the first weeks characterized by a sense of well being and improvement in appetite. Most of these children developed a voracious appetite and in the first cases treated 3 and 4 servings at each meal were not unusual. As a result there was a marked and continued increase in their weight. Edema, the result of electrolyte imbalance, developed later. Subsequently, this was controlled by limiting the diet to 1200 to 1600 calories per day with 40 to 60 gm. of protein and a low salt intake. Some of these cases showed an alkalosis, a decrease in potassium and cardiac irregularities. The giving of potassium salts by mouth corrected the potassium deficiency and relieved these secondary symptoms, namely, apathy, lethargy, muscular weakness, paralysis, abdominal distention and cardiac irregularities. Glycosuria was found on occasion in moderate degrees and diabetes developed in one patient requiring treatment and persisting through the remaining course of the disease.

Where treatment was able to be maintained there was usually a slow but gradual development of a Cushings syndrome, manifested by a moon-face, large torso, especially enlargement of the abdomen, thinning of the arms and legs, acne and a sense of general well being. In addition there was a shrinkage in the size of the enlarged lymph nodes, and a decrease in size of the enlarged livers and spleens. Bleeding from the nose, bowel, urinary tract and skin ceased early in those successfully treated. I.V. ACTH, 30 mg. a day, has been very dramatic in controlling bleeding.

Early changes in the hematologic picture occurred during the first week with the WBC starting to return to their normal numbers—if elevated—and with an increase in their maturity. An increase in the number of reticulocytes occurred between the 7th to 14th day, reaching a peak of 10 to 20% during the 2nd and 3rd week of therapy. Platelets increased between the 7th and 21st days.

During the 2nd and 3rd week of treatment there was manifestation of improvement in the bone marrow by an increase in erythropoietic activity. During this time there could be an increased maturity of the myeloid cells and a decrease in percentage of the leukemic cells. In none of the patients was there a complete disappearance of abnormal cells from the bone marrow or peripheral blood.

None of the above reactions interfered with continued treatment. The serious complications which did cause cessation of the treatment were:
1. Pyogenic infections—lowered resistance to infections have previously been noted in Cushing’s syndrome. Skin infection, abscesses, otitis media, tonsillitis and pneumonia were common complications in these cases with acute leukemia and required the constant administration of one of the antibiotics.

2. Hypertension was by far the most serious complication we encountered occurring in 15 patients or 34.9%. Ten of these 15 cases developed cerebral symptoms consisting of headache, stiff neck, listlessness, vomiting, twitchings, convulsions or coma. Most of these patients developed symptoms rapidly and all but 5 lost these slowly following cessation of treatment. One patient was readmitted 16 days after discharge with convulsions, coma and hypertension during which time he had received no treatment with these hormones. The following slide shows us that there was: (a) one patient who died with clinical signs of cerebral hemorrhage; (b) another who had grossly bloody spinal fluid on L.P.; (c) 2 patients where hemorrhage plus softening of the brain were found at autopsy; (d) one patient where autopsy showed cerebral edema; (e) additional case with cerebral symptoms that showed cerebral abscesses on autopsy. These complications occurred on both cortisone and ACTH and developed anywhere between the 2nd and 41st day of treatment. Cortisone was used in 8 and ACTH in 7 cases. Subsequent treatment with cortisone produced a recurrence of the signs in 2 and was without effect in 2 other cases (ACTH produced signs in 5th). In the cases first treated with ACTH cortisone reproduced symptoms in one and had no effect in another case.

Complete remissions of this disease has not, in our experience, appeared to be obtainable with these hormones. They are usually of short duration and resistance to hormone therapy develops rapidly. Remissions were considered good when there was loss of fever, cessation of bleeding or hemorrhagic tendencies, general well being plus reduction in size of the liver, spleen and lymph nodes. In addition the bone marrow showed an increase in the erythroid elements and there was a marked reduction in the percentage of leukemia cells. A partial remission was considered when the above factors were found with only a partial reduction in the leukemic cells.

In our series of 44 cases there were 17 female and 27 male children between the ages of 6 months and 14 years. Twelve cases had received no previous treatment but the response was similar to the remaining 32 cases that had been treated and had become resistant to various drugs such as 2,6 diaminopurine, A-methopterin, aminopterin, glyoxyhide and urethane. The dosage of ACTH varied between 20 to 100 mg. per day and of cortisone between 50 to 200 mg. per day depending on the age of the patient and response to therapy.

Twenty-four cases or 54.5% showed remissions and there were 20 failures. Fifteen or 60% out of 25 cases treated with cortisone had remissions. Nine or 47.7% out of 19 cases treated with ACTH had remissions. There were 16 good remissions and 8 partial remissions. These lasted from a minimum of 16 days to a maximum of 135 days, averaging 48.3 days. The number of days of treatment in the remissions varied from 8 to 86 days and averaged 26.9 days. The average dose of ACTH was 61.7 mg. and cortisone 130.2 mg. per day.

The partial remissions lasted 6 to 21 days and were treated for a larger period of time and with a greater amount of medication. The average number of days of treatment was 73 (40 days for cortisone and 33 days with ACTH, which averaged 36.5 days), while the average dose was 160.9 mg. of cortisone and 65 mg. per day of ACTH.

In the 20 failures the number of days of treatment averaged 23.1 days with ACTH and 24.4 days with cortisone while the average daily dose was 59.5 mg. of ACTH and 154.4 mg. of cortisone daily.

A summary of these failures show that: (1) 6 cases were treated 8 days or less; (2) one died in cardiac failure in 4 days; (3) one died from a pericardial tap; (4) one had medication stopped following convulsions; (5) 11 were adequately treated.

There were 18 cases treated 2 or more times and a response was obtained in 7 or 38.8%. The average length of these remissions in second courses of treatment was 33.3 days. In all cases but one the hormones had to be given in larger doses and for a longer period of time before a remission was obtained. Many patients who showed an initial response to the treatment failed to show any beneficial response on a second trial and many died while hormone therapy was being administered.

In conclusion these hormones are a useful aid in the treatment of acute leukemias of childhood. ACTH appears to have the more rapid action and is therefore more useful in the acutely ill child. Cortisone, on the other hand, appears to be more effective in our series. Hypertension with cerebral symptoms is a serious complication that must be constantly watched for and treatment discontinued when these signs and symptoms appear. The response to these hormones is as good in the cases
resistant to antifolic antagonists as in untreated cases and it has been found that the antifolic antagonists are just as effective in cases that have become resistant to these hormones. Consequently, our present treatment at Memorial Hospital consists of the use of the antifolic drugs when the diagnosis of acute leukemia is just made until the resistance to these drugs develops. These hormones are saved for a probable relapse when again these patients may respond to the antifolic treatment, with a good chance that a second partial remission can later be obtained with these hormones.

EFFECT OF ACTH IN CHILDREN WITH THE NEPHROTIC SYNDROME
HENRY L. BARNETT, M.D.

It has been demonstrated recently that several agents are capable of inducing abrupt, profuse, and sustained diuresis in children with the nephrotic syndrome. These dramatic events are clinically similar to the diureses which occur spontaneously. At the present time ACTH appears to be the most satisfactory means of inducing such diureses. Diureses occur in about 80% of children given a single course of ACTH. Following such induced diureses, there may be (a) almost immediate reaccumulation of edema, (b) a variable period of clinical remission with later exacerbation or (c) occasionally complete healing. If there is reaccumulation of edema, diuresis may occur with later courses of ACTH. On the other hand, a child who responds to one or two courses may fail to respond subsequently. Finally, failure to respond to the first course does not preclude subsequent responses.

ACTH, in a dosage of 50 mg. per 24 hours given intramuscularly in 4 divided doses for periods ranging from 8 to 12 days, induces diuresis as regularly as in larger doses. However, smaller daily or total dosages given intramuscularly are usually ineffective.

Complications of ACTH administration in children with the nephrotic syndrome include: 1. metabolic disturbances: hypotonicity of the extracellular fluid accompanied by low serum potassium, alkalosis, and tetany may occur. The potassium content of the diet should be increased in an attempt to prevent this complication. 2. Infections: The administration of ACTH may mask signs of the serious infections which are so common in these children. Prophylactic antibiotic therapy is given routinely during ACTH administration. 3. Cardiovascular complications: Progressive elevation of blood pressure or increase in a pre-existing hypertension may require cessation of ACTH administration. 4. Hyperadrenocorticism: During short courses of treatment physical and metabolic signs of Cushing's disease usually do not appear. However, they may be seen if children are treated longer than 14 days or when repeated courses are given at short intervals. These changes disappear following cessation of ACTH administration.

There is no evidence that changes which accompany or follow diureses induced by ACTH differ in any respect from those accompanying spontaneous or other types of induced diuresis. The demonstration that proteinuria and hyperlipemia are decreased and filtration rate may be increased after diureses leads us to attach more than symptomatic importance to these events and to believe they should be induced. However, on the principle that hormonal therapy should not be given unless clearly indicated, we believe patients should be given a chance to have a spontaneous diuresis before receiving ACTH. Our present practice is to withhold ACTH for 6 to 8 weeks after the onset of the disease or of an exacerbation. If a spontaneous diuresis has not occurred by this time, and particularly if reduced renal clearances are found, we advise giving ACTH.

It is obviously difficult to evaluate the true importance of agents such as ACTH. Although at present it must be doubted that the eventual course of the nephrotic syndrome is altered by the administration of ACTH, the ability to induce sustained diureses followed by variable periods of remission permits at least symptomatic benefit and has facilitated important observations hitherto not practicable. It can be hoped that such observations will lead to greater understanding of the mechanisms of the disease.
Five infants and children, 2 boys and 3 girls, suffering from atopic dermatitis and varying in age from 6 months to 14 years were treated with ACTH or cortisone. All responded favorably to treatment but relapsed when this was discontinued. In no case did the skin ever return completely to normal but the improvement was highly satisfactory both from the standpoint of appearance and relief of pruritis. The skin could be cleared sufficiently so that direct testing could be done which in every instance corroborated the results of previous passive transfer tests. There were 2 instances in which the treatment was accompanied by complications. A 2 year old girl, who also had minimal pulmonary stenosis, the only symptom of which was a murmur, developed hypertension which disappeared when the dose of ACTH was reduced. A 1½ year old boy developed mild but typical nephrosis during the second week of treatment with ACTH. This suggests that ACTH, which is often employed satisfactorily for producing diuresis in nephrosis, probably has no influence on the etiologic factors in this disease. One adolescent girl with a severe mental depression caused by the disfiguration of eczema responded very well to cortisone treatment both as regards the psychosis and the eczema. All patients, except the boy with nephrosis, gradually improved under orthodox management after the hormone therapy was discontinued. A 2½ per cent cortisone ointment was found ineffective in the local treatment of eczema. The rebound phenomenon, i.e., recurrence of the eczema in a more severe form after cessation of therapy, was not observed.

There were 8 children with intractable perennial asthma, 2 boys and 6 girls, ranging in age from 19 months to 14 years. In 2 asthma had started at the ages of 3 and 4 months, respectively. All cleared under ACTH or cortisone therapy with remissions varying from 24 hours to 3 months. Occasionally these patients had relapses of sufficient severity as to require second and third courses of ACTH or cortisone. Three were continued at home on ambulatory therapy. One girl, after 76 days of ambulatory therapy, developed a typical Cushing's syndrome which disappeared in the course of 3 months after hormone therapy was discontinued.

There were 4 additional children, all under 5 years of age, who had frequent severe asthmatic attacks at home, not bad enough to require hospitalization often, but severe enough to require frequent injections of epinephrine. These children were carried along on occasional ambulatory courses of ACTH. One of these, a 3 year old, has done very well on a dose of 5 mg. daily.

So far as is known at present, both ACTH and cortisone produce the same effects in eczema and asthma. We used ACTH more often than cortisone because it was less expensive and more readily available. These drugs should be used only when the disease is severe enough to cause symptoms imperatively demanding relief which the patient has been unable to secure from any other form of therapy.
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JEROME W. CONN
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