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# The Syndrome of Congenital Adrenocortical Unresponsiveness to ACTH. Report of Six Cases

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*Extract*

Six patients with the syndrome of congenital adrenocortical unresponsiveness to ACTH are reported.

This syndrome is characterized by feeding problems early in life, hypoglycemic episodes and hyperpigmentation of the skin (table I). Blood pressure and levels of electrolytes in serum were normal (table II). PPD and histoplasmin skin tests were negative, while antibodies to adrenal, thyroid, and gastric tissues were undetectable. Urinary excretion of 17-hydroxycorticosteroids and cortisol production rates were low and did not respond to administration of ACTH (table III). While receiving a low sodium diet, the patients were able to conserve sodium (figs. 2, 3 and 4) and to increase the rate of aldosterone secretion (tables IV and V).

In one case, adrenal pathology showed a normal zona glomerulosa with atrophy of the zonae fasciculata and reticularis.

This isolated deficiency in cortisol secretion is not due to a defect in pituitary function or a deficiency of one of the enzymes directly involved in steroid biosynthesis. The most probable pathogenesis is an abnormality at the site (or one of the sites) of ACTH action on cortisol biosynthesis.

*Speculation*

It is probable that some young infants in whom a diagnosis of Addison's disease is made do, in fact, have the syndrome of congenital adrenocortical unresponsiveness to ACTH. Studies of cortisol secretion rates prior to and during ACTH administration and a determination of aldosterone secretion rates while receiving normal and low salt diets will permit differentiation of the two disorders.

## *Introduction*

The present paper is a report of 6 patients who had a low cortisol secretion rate that did not increase during ACTH administration; they had a normal aldosterone secretion rate while receiving a diet normal in sodium content; this increased as expected when the diet was low in sodium.

This clinical entity does not appear to be due to a partial destruction of the adrenal glands with deficiency of cortisol secretion and conservation of normal aldosterone production. Instead, it seems to be related

to an inability of the adrenal cortex to respond to ACTH stimulation. Since the regulation of aldosterone production is not directly controlled by ACTH, while that of cortisol is, the discrepancy between the secretion of glucocorticoids and the electrolyte-regulating factor can be easily understood.

## *Methods*

Total urinary 17-ketosteroids (17-KS) were measured by a modification of the method of CALLOW *et al.* [7] and 17-hydroxycorticosteroids (17-OHCS) by a modification [14] of the method of GLENN and NELSON [9]. The determinations of urinary pregnanediol and pregnanetriol were carried out by the techniques of KLOPPER *et al.* [17] and of BONGIOVANNI and EBERLEIN [6], respectively. The concentrations of cortisol and corticosterone in plasma were determined by the double isotope dilution techniques of PETERSON [22]. The methods of measurement of cortisol [18] and aldosterone [16] secretion rates have been described elsewhere.

For the intravenous ACTH test, 25 mg of ACTH was administered over a 6- to 8-hour period on two successive days. For the intramuscular ACTH test, 10 to 25 mg of ACTH-gel was given every 12 hours for 3 to 12 days (see footnote, table III).

The studies of Na balances and aldosterone secretion rates were carried out while the subjects were in a metabolic research ward. The dietitian in charge of the unit administered the specific diets. The low-sodium diet provided 9 mEq of Na/24 h for 5 or 6 days.

The main clinical findings and the results of the laboratory tests are summarized in tables I to IV. A more detailed description of the cases follows.

*Case No. 1. Caucasian Male*

The pregnancy was full-term and uneventful. Cyanosis lasting approximately one-half hour occurred following circumcision at 48 hours of age. Spitting, poor feeding, slow weight gain, and grayish skin were prominent symptoms until 3 months of age. At that time, the patient became listless, limp, chalk white, and had a low-grade fever following a second DPT injection. Upon arrival at a hospital, he had a seizure. Because of a blood sugar of 15 mg %, glucose and cortisone were given intravenously. Although no diagnosis was made, he was discharged; 20 mg of Meticorten per day was prescribed. On this regimen he showed improved appetite and weight gain. Steroid therapy was slowly decreased and stopped between 17 and 19 months of age. He developed an excessive tan during the summer, which continued into the winter. Excessive skin pigmentation, particularly on the dorsum of the hands and feet, prompted hospitalization. The areolae, mucous membranes, and genitalia were not, however, hyperpigmented. Sexual development, blood pressure, and electrolyte levels in serum were normal for age. Abnormal laboratory findings included low blood sugar levels (44 and 36 mg %) during the fourth and fifth hours of a glucose tolerance test and low levels of 17-OHCS in the urine (0.4–0.7 mg/24 h).

Twenty mg of ACTH administered intravenously for a period of 8 hours and continued thereafter by intramuscular injection for 2 days produced no increase in 17-OHCS excretion. Levels of pregnanetriol in urine and of insulin in serum were normal. At the time of discharge and following a tentative diagnosis of Addison's disease, his regimen included a high protein, low carbohydrate diet with frequent feedings. No medication was prescribed.

One week after discharge, the patient awoke, began shaking, and became limp. Treatment for this acute episode is unknown. Cortisone therapy, 25 mg once a day, was begun and was continued without interruption until the present time. However, there were two separate three-day periods when, through laxness, no medication was given. On both occasions, the patient awoke in the morning, limp and shaking. On both occasions the family doctor administered glucose intravenously, with complete relief of the patient's symptoms.

When referred to our clinic at 4.5 years of age, the height, physical examination, bone age, x-rays of the skull and abdomen were normal. On a diet containing 9 mEq of Na/day, the levels of electrolytes in the serum remained normal, excretion of sodium in the urine decreased to 4.2 mEq/24 h, and aldosterone secretion rose from 137 $\mu$g to 395 $\mu$g/day (table V). Intravenous and intramuscular administration of ACTH (25 mg q 12 hours for 12 days) did not increase steroid excretion (table III). Catecholamine excretion was normal. Cortisone, 12.5 mg every 12 hours, was prescribed and the patient was discharged.

When he was readmitted at 5.7 years of age, he reportedly had been well and had been taking cortisone regularly. Following cessation of cortisone medication, 25 mg of ACTH given intramuscularly every 12 hours for 15 days, did not affect steroid excretion. On the 15th day of ACTH administration, exploration of the adrenals was performed. Immediately prior to anesthesia, cortisone was administered intramuscularly and cortisol by intravenous injection. At surgery, the adrenals were so small that an attempt to take a biopsy resulted in total unilateral adrenalectomy (fig. 1). Following a rapid recovery and while receiving a low sodium diet, 9 mEq/day, Na content of urine fell normally, indicating the ability of the remaining adrenal to secrete aldosterone in quantities sufficient to

*Table I.* Abnormal clinical findings in patients with the syndrome of adrenal unresponsiveness to ACTH

| Patient No. | Sex | Early feeding problem | Hypoglycemia[1] | | | Skin hyperpigmentation[4] | Sibs |
|---|---|---|---|---|---|---|---|
| | | | Clinical | Laboratory | | | |
| | | | | Low FBS[2] | During GTT[3] | | |
| 1. | M | yes | yes (0.3 yr) | 15 mg (0.3 yr) | yes | yes (0.3 yr) | 5 healthy sibs<br>1 sister died at 24 h<br>1 brother died at 1.6 yr<br>hyperpigmentation<br>adrenal lipid depletion |
| 2. | M | yes | yes (0.7 and 0.8 yr) | 19 mg (0.8 yr) | yes | yes (0.3 yr) | sib of patient No. 3 |
| 3. | M | yes | no | no | no | no (10 wks) | sib of patient No. 2 |
| 4. | M | yes | yes (2 and 2.3 yrs) | no | yes[5] | no (2.3 yrs) | 1 brother died at 0.3 yr<br>solitary, afebrile convulsion; trema; excessive sweating |
| 5. | M | yes | no | no | no | yes (0.1 yr) | 1 healthy brother<br>1 brother died at 1.5 yr<br>'underdeveloped adrenals' |
| 6. | M | no | no | no | no | yes (0.2 yr) | 5 healthy sibs |

[1] Age at time of episode is given in parentheses.
[2] Fasting blood sugar.
[3] Six-hour oral glucose tolerance test.
[4] Numbers in parentheses: age when noted, patient Nos. 1, 2, 5, and 6; age when treatment started, patient Nos. 3 and 4.
[5] Patient exhibited insulin sensitivity during insulin tolerance test.

prevent sodium loss (table IV). At the time of discharge, the regimen consisted of 12.5 mg of cortisone every 12 hours. The family doctor was advised to increase the cortisone therapy during stress conditions. Subsequently, the patient has been well, developing normally, and when last seen at the age of 10 years, was asymptomatic.

*Case No. 2. Caucasian Male*

Poor feeding, some vomiting without diarrhea, and chronic crying occurred from birth in this male child. A diagnosis of colic was made at 4 months of age, but treatment with antispasmodic drugs was ineffective, as were many formula changes. At 5 or 6 months of age, a generalized increase in pigmentation was noted. At 7 months of age, when first seen by Dr. J. D. Stull, Olney, Illinois, pigmentation was marked. The infant's height was normal, but his weight was below average. Two weeks later, an apparent episode of hypoglycemia occurred. At 7 a.m., the infant was found cold, clammy, and drowsy, but recuperated shortly thereafter following feeding. A glucose tolerance test and levels of electrolytes in serum were normal. One month later, a tonic-clonic seizure occurred in association with high fever. Hypertonicity, profuse sweating, and clamminess of the skin were noted. Blood pressure, cerebrospinal fluid, and levels of electrolytes in serum were normal. The glucose level in blood was 43 mg/100 ml.

Fasting levels of glucose on subsequent days were 47, 19, 80, 77 and 95 mg/100 ml. Chest and abdominal x-rays, PPD, and histoplasmin skin tests were unremarkable. The administration of ACTH both intramuscularly and intravenously failed to stimulate the excretion of 17-OHCS (table III). Cortisol, 2.5 mg twice daily, was prescribed for Addison's disease. The child was not fond of extra salt or salty foods.

At 3.1 years of age, when evaluated in our clinic, the height and bone ages were 2.2 and 2.5 years, respectively. The general examination, blood pressure, hematologic studies, urinalysis, x-rays of the skull, chest, and abdomen, and pigmentation were normal.

Dexamethasone, 0.125 mg every 6 hours, was substituted for cortisol. Neither 17-KS nor 17-OHCS was detectable in the urine after 15 mg of ACTH gel was given intramuscularly every 12 hours for 8 days. At that time, levels of cortisol and corticosterone in plasma at 8 a.m. were 1.2 and 0 $\mu$g/100 ml, respectively. Consumption of a diet providing 9 mEq of Na/day for 5 days did not affect levels of electrolytes in serum, and sodium was conserved normally (fig. 2). At the time of discharge, 15 mg of cortisol daily was prescribed, and the patient has done well for the past 6 years.

*Case No. 3. Caucasian Male*

Both prenatal and birth history were unremarkable. During the newborn period, symptoms identical to those of the older sibling (Case No. 2) appeared. Blood pressure, levels of electrolytes in serum, chest x-ray, and skin tests were unremarkable. Addison's disease was suspected because of failure to detect 17-OHCS in the urine (table III). Five mg of cortisol to be taken twice daily was prescribed. At one year of age, the dose was increased to 15 mg/day. No hyperpigmentation was noted.

At 2 years of age, he presented at our clinic for evaluation. Both height and bone ages were 18 months. Skull, chest, and abdominal x-rays were negative. Dexamethasone, 0.125 mg every 8 hours, was substituted for cortisol therapy. Ten milligrams of ACTH gel, administered every 12 hours for 8 days, did not result in any detectable urinary steroid excretion. Response to a diet containing 9 mEq of Na/day was normal (fig. 3). For the subsequent six years, he has done well while receiving 10 mg of cortisol per day.

*Case No. 4. Caucasian Male*

The prenatal history was unremarkable. Labor was induced at 39 weeks of gestation and the birth weight was 2.16 kg; however, the infant did well. The history was uneventful until an unexplained episode of lethargy occurred at 23 months of age. Skull and chest x-rays and cerebrospinal fluid were normal. No treatment was administered. At 26 months of age, during a second similar episode, levels of glucose in cerebrospinal fluid and blood were 20 and 56 mg/100 ml respectively. Orange juice and intravenously administered glucose relieved the symptoms.

At 2.3 years of age, the height age and bone age were 3 years. No hyperpigmentation was present. Levels of electrolytes in serum were normal. Glucose levels in blood obtained after fasting varied between 45 and 80 mg/100 ml. After a fast of 19 hours duration, the glucose level was 15 mg/100 ml. No leucine sensitivity was demonstrable. After 10 mg of ACTH gel had been given every 12 hours for 7 days, levels of 17-OHCS in urine were essentially undetectable (table III). After receiving a low sodium diet (9 mEq/24 h), the aldosterone secretion rate was normal (450 $\mu$g/24 h) and the levels of electrolytes in serum were normal. During the past 3 years, he has done well while receiving 2.5 mg of prednisone at bedtime.

*Case No. 5. Caucasian Male*

Following a normal pregnancy and delivery, this male infant fed poorly, vomited chronically, and was excessively pigmented, especially over the hands and wrists. A craving for salt and a dislike for bright lights were noted by the parents.

At 3 years of age, hyperpigmentation and chronic vomiting prompted hospitalization. The height age was advanced (4.5 years), the weight was normal for age, and the skin was deeply pigmented, particularly over the knuckles and gums. The general examination, sexual development, blood pressure, levels of electrolytes in serum, hematologic studies, urinalysis, and x-rays of the skull, chest, and abdomen were normal. Neither 10 mg of ACTH gel administered intramuscularly every 12 hours for 3 days nor methapyrapone, 250 mg, given every 4 hours for 24 hours on a separate occasion, had any effect on the urinary excretion of 17-OHCS. The cortisol secretion rate, corrected for surface area, was below normal (table III). While receiving a low sodium diet (9 mEq/day), the urinary excretion of sodium was 4.1 and 4.8 mEq/24 h on the 4th and 5th day respectively. At that time, the aldosterone secretion rate was 160 $\mu$g/24 h.

Three months after receiving 12.5 mg of cortisone three times a day, the skin became much lighter in color and the child was more active. He has received 30 mg of cortisone daily for the past 3 years and is doing well.

*Case No. 6. Caucasian Male*

At 2 months of age, hyperpigmentation of the skin was noted, but no other signs or symptoms were present until asthmatic bronchitis, marked hyperpyrexia, and a convulsion occurred at 6 months of age. During the second year of life, growth was normal, but three mild

*Table II.* Important normal clinical findings in patients with the syndrome of adrenal unresponsiveness to ACTH

| Patient[1] No. | Blood pressure | values in serum mEq/l Na | K | Height age | Bone age | Skin tests: PPD histoplasmine | Serum antibodies against adrenal or thyroid[2] |
|---|---|---|---|---|---|---|---|
| 1. (0.3 yr) | 100/50 | 140 | 4.9 | – | – | negative | negative (4.5 yrs) |
| 2. (0.8 yr) | 110/60 | 140 | 5.5 | 0.7 yr | – | negative | negative (3.1 yrs) |
| 3. (0.2 yr) | 80/ | 145 | 5.8 | 0.1 yr | – | negative | negative (2 yrs) |
| 4. (2.3 yrs) | 110/60 | 138 | 5.2 | 3 yrs | 3 yrs | negative | negative (2.3 yrs) |
| 5. (3 yrs) | 105/55 | 137 | 4.6 | 4 yrs | 3.5 yrs | negative | negative (3 yrs) |
| 6. (2.2 yrs) | 100/60 | 136 | 4.4 | 3 yrs | 2.5 yrs | negative | negative (2.2 yrs) |

[1] Numbers in parentheses, age at which observations were made.
[2] Numbers in parentheses, age at which tests were performed.

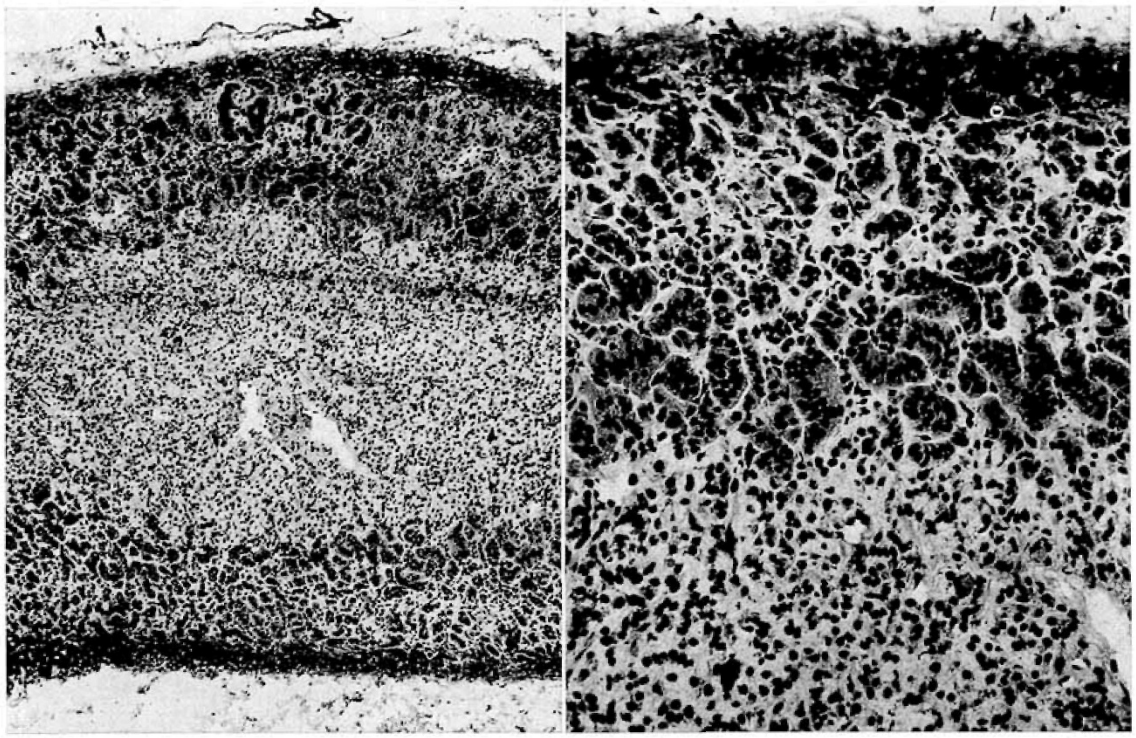

*Fig. 1.* Microscopic aspect of the adrenal gland of patient No. 1. *On the left* is a full section of the gland showing the atrophic cortex (×75). *On the right* is a ×200 enlargement of the gland. The capsule is on the top of the picture, the upper left represents the cortex and the lower half the medulla.

*Table III.* Urinary and plasma steroids in patients with the syndrome of adrenal unresponsiveness to ACTH

| Patient No. | Age at time of studies Years | Basal | | | | | Intravenous injection of ACTH | | Intramuscular injection of ACTH-gel[9] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Urine | | | | CPR[5] mg/m²/24 h | Urine | | Urine | | Plasma μg/100 ml | |
| | | mg/24 h | | | mg/m²/24 h | | 17-KS[1] mg/24 h | 17-OHCS[4] mg/m²/24 h | 17-KS[1] mg/24 h | 17-OHCS[4] mg/m²/24 h | F[6] | B[7] |
| | | 17-KS[1] | 'Triol[2] | 'Diol[3] | 17-OHCS[4] | | | | | | | |
| 1. | 4.10[8] | 0.7 | 0.6 | 0 | 0.2 | – | 0.3 | 0.3 | 0.2 | 0.4 | 2.0 | 0.1 |
| 2. | 0.8 | 0.1 | – | – | 0.5 | – | 0.1 | 1.7 | 0.1 | 0.5 | 1.2 | 0 |
| 3. | 0.2 | 0.1 | – | – | 1.4 | – | 0.0 | 0.0 | 0.9 | 3.2 | 4.5 | 0.2 |
| 4. | 2.3 | – | 0.6 | 0.2 | 0.17 | 2.5 | – | – | 0.4 | 1.5 | 3.0 | 0.3 |
| 5. | 3.0 | 1.6 | 0.7 | 0.1 | 0.9 | 2.3 | – | – | 1.1 | 0.3 | – | – |
| 6. | 2.2 | 0.3 | 0.1 | 0 | 0.2 | 1.0 | – | – | 0.4 | 0.5 | 1.5 | 0.4 |

*Note to table III*

[1] 17-ketosteroids
[2] Pregnanetriol
[3] Pregnanediol
[4] 17-hydroxycorticosteroids
[5] Cortisol production rate
[6] Cortisol
[7] Corticosterone
[8] Data obtained 4 months after stopping cortisone therapy.
[9] Daily dosage × duration in days:
Patient No. 1, 50 mg × 12;
Patient No. 2, 30 mg × 5;
Patient No. 3, 20 mg × 4;
Patient No. 4, 40 mg × 7;
Patient No. 5, 40 mg × 3;
Patient No. 6, 40 mg × 4.

*Table IV.* Aldosterone secretion rates in patients with the syndrome of adrenal unresponsiveness to ACTH

| Patient No. | Age in years at time of testing | Treatment at time of testing | Aldosterone secretion rate μg/24 h | |
|---|---|---|---|---|
| | | | Normal Na diet | Low Na diet (9 mEq/24 h) |
| 1. | 4.8 | none for 4 months | 137 | 395 |
| | 4.9 | after unilateral adrenalectomy | 128 | 291 |
| 4. | 2.3 | none | – | 450 |
| 5. | 3 | none | – | 180 |
| 6. | 2.2 | none | – | 212 |

*Table V.* Levels of electrolytes in serum and urine while patient No. 1 was receiving a normal and a low-salt diet

| Date 1963 | Na intake mEq/24 h | Blood pressure mm Hg | Pulse | Serum | | | | | Urine | | Aldosterone µg/24 h | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | SUN[1] | $CO_2$ | Na | K | Cl | vol. | Na | Urinary excretion rate | Secret. |
| | | | | mg/100 ml | mEq/l | | | | ml/24 h | mEq/24 h | | |
| 3–25 | 50 | 110/50 | | 15 | 27.6 | 145 | 5.3 | 104 | 390 | 49.9 | | |
| 3–26 | 50 | 110/60 | 80 | | | | | | 530 | 41.3 | 4 | 137 |
| 3–27 | 9 | | | | | 150 | 4.9 | 105 | | | | |
| 3–28 | 9 | 120/60 | 90 | | | | | | 440 | 14.1 | | |
| 3–29 | 9 | | | | | | | | 540 | 11.9 | | |
| 3–30 | 9 | 110/60 | 80 | | 31.8 | 144 | 5.4 | 104 | 450 | 5.8 | | |
| 3–31 | 9 | | 80 | 27 | 28.4 | 146 | 5.2 | 105 | 385 | 4.2 | 10 | 395 |

[1] Serum urea nitrogen

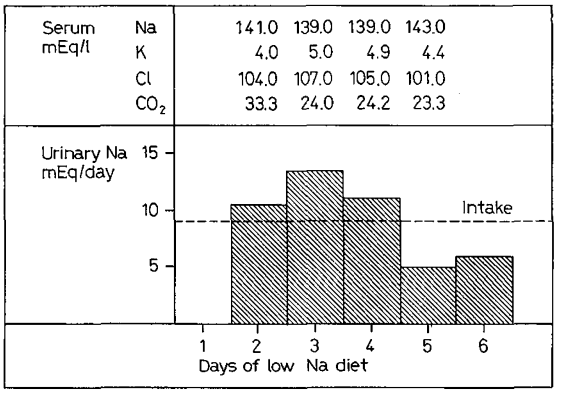


*Fig. 2.* Effects of a low Na diet on electrolytes in serum and Na in urine of patient No. 2.

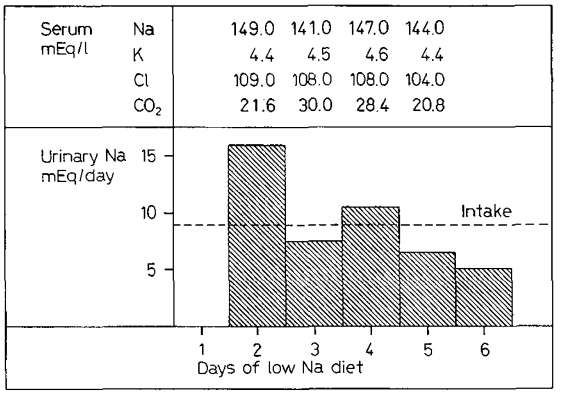


*Fig. 3.* Effects of a low Na diet on electrolytes in serum and Na in urine of patient No. 3.

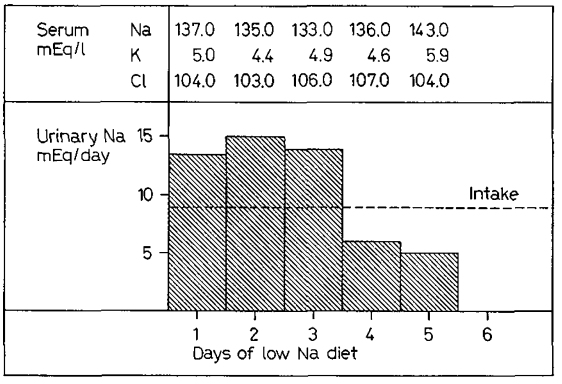


*Fig. 4.* Effects of a low Na diet on electrolytes in serum and Na in urine of patient No. 6.

seizures occurred in association with upper respiratory infections.

Because of hyperpigmentation, which was most marked at the areas normally subjected to friction of the body, the child was seen by us at 2.2 years of age. The physical examination was otherwise normal. An electroencephalogram was also normal. The hematological studies, urinalysis, levels of electrolytes, PBI and BEI in serum, several determinations of glucose in blood, and leucine and tolbutamide tests were all normal. In 4 hours, 76 % of a water load was excreted. Cortisol production rate was very low (table III). Excretion of 17-OHCS in urine remained low following intramuscular administration of ACTH gel every 12 hours for 4 days (table III). While receiving a low sodium diet (9 mEq/day), the sodium excretion in urine fell to 6 and 5 mEq/24 h on days 4 and 5, respectively (fig. 4), and the aldosterone secretory rate was normal (212 $\mu$g/24 h). The child has been maintained on cortisol medication and has done well.

When a maternal uncle of this patient was 12 years of age, a diagnosis of Addison's disease was made by Dr. Robert Klein. Mineralocorticoid and glucocorticoid deficiencies of the uncle were demonstrated again when he was 26 years old.

### *Principal Aspects of the Syndrome of Congenital Adrenocortical Unresponsiveness to ACTH*

Based on the six cases reported in the present paper, the main symptoms of the syndrome can be summarized as follows:

*Early Feeding Problems*

Feeding problems appeared early in life and were characterized by chronic spitting or vomiting, generally poor appetite, and, in some cases, a poor weight gain. One of our patients (No. 6) did not show any of these symptoms.

*Hypoglycemic Episodes*

Hypoglycemic seizures in patients Nos. 1 and 2 were documented. Patient No. 3, the younger sibling of patient No. 2, never had hypoglycemia. But, because of his feeding problems, and as a result of the study of his urinary steroid excretion, treatment with steroids was started at 10 weeks of age. Patient No. 4 had episodes of lethargy but no hypoglycemia; however, abnormal and symptomatic hypoglycemia was observed during an insulin tolerance test. No hypoglycemia was demonstrated in patients Nos. 5 and 6. It would appear, therefore, that hypoglycemic episodes are characteristic of the syndrome, but they are not a constant finding (table I).

*Hyperpigmentation of the Skin*

This symptom was observed in 4 of the 6 patients (table I). Early treatment of patient No. 2 probably obviated hyperpigmentation. On the other hand, patient No. 4 had normal skin coloration at 2.3 years of age.

*Important Normal Clinical Findings*

In five of the six cases, pregnancy was uneventful; the edema noted during pregnancy by the mother of patient No. 6 is probably of no significance insofar as the syndrome is concerned. Labor was spontaneous in five cases and, in case No. 4, was induced at 39 weeks of gestation. Delivery was uneventful in all cases. In term infants, birth weights were normal; the low weight of patient No. 4 may probably be related to prematurity.

None of the patients showed symptoms of deficient secretion of salt-retaining hormones, blood pressures and serum electrolytes being normal. The PPD and histoplasmin skin tests were negative in all six patients. Antibodies to adrenal, thyroid, and gastric tissues were undetectable in the serum of the patients. It is of interest to note that one-third of patients with isolated idiopathic Addison's disease have been found to have antiadrenal antibodies [5].

*Somatic Growth*

Patients Nos. 4, 5 and 6, who received therapy only after 2 years of age, had normal bone and height ages. Patient No. 4 had questionable hypoglycemia while the other two patients did not present any hypoglycemic episodes. As a corollary, it is possible that patients Nos. 1 and 2, who had documented hypoglycemic seizures, would have shown growth retardation if treatment had not been administered early in life.

*Steroid Studies*

Cortisol production rate was determined prior to administering any glucocorticoid therapy in patients Nos. 2, 4, 5 and 6. When corrected for body surface area, values (table III) were well below the levels characteristic of normal subjects (4 months to 20 years of age) who have a mean and standard deviation of $12.1 \pm 2.9$ mg/m$^2$/24 h [15]. Levels of 17-OHCS in urine were also low, when compared with the mean and standard deviation in 180 normal subjects (3.1 mg/m$^2$/24 h) [20]. The low values of patient No. 1 could be related to treatment. This seems unlikely, however, since cortisone administration had been stopped for four months before testing. The low levels in patient No. 3 may have reflected a developmental delay in enzymes other than those directly related to adrenal steroidogenesis, but data on this point is unavailable. Notwithstanding, parenteral administration of ACTH

to these two patients, as well as to the other four, would have been expected to markedly increase plasma levels of cortisol and urinary excretion of 17-OHCS (table III).

All six patients were able to conserve sodium while receiving a low-salt diet (figs. 2–4, table V) and, under this condition, to increase their aldosterone secretion rate (table IV) as do normal children [28].

### *Pathology*

After intramuscular administration of ACTH for seven days, a surgical exploration was carried out on patient No. 1. No adrenal tumor was observed and both adrenal glands were found to be extremely small in size. An attempt to obtain a biopsy resulted in total left adrenalectomy. The net weight of tissue removed was 170 mg (fig. 1). One pathologist noted: 'Atrophic adrenal cortex. The cells look like a zona glomerulosa with atrophic zona fasciculata-reticularis.' The conclusions of another member of the department of pathology were very similar: 'It does resemble a gland that is not under pituitary stimulation.' Dr. G.H. Klinck, Armed Forces Institute of Pathology, was consulted independently and stated: 'Well-developed glomerulosa, possibly some atrophic fasciculata and no discernible reticularis—extensive adrenocortical atrophy.' It must be noted that there was no specific lesion, no calcification, and no lymphocytic infiltration, in contrast to the changes often observed in the adrenal gland of patients with Addison's disease.

*In vitro* and *in vivo* studies have established that aldosterone is secreted only by the zona glomerulosa and cortisol uniquely by the zona fasciculata-reticularis, whereas corticosterone is secreted by both [1, 2, 8, 26]. Therefore, the adrenal histology in patient No. 1 is consistent with the secretion of aldosterone and the deficient secretion of cortisol.

### *Pathogenesis*

In the adrenogenital syndrome, a congenital deficiency of one of the enzymes necessary for the biosynthesis of cortisol (21-hydroxylase, 11-hydroxylase, 3$\beta$-hydroxysteroid dehydrogenase, or enzymes necessary for the formation of pregnenolone) results in an increased secretion of ACTH, which in turn produces adrenal hyperplasia with specific patterns of steroid secretion and a specific clinical picture [29]. More recently, a 17-hydroxylase deficiency has also been reported [3, 10]. In contrast, the symptoms observed in our patients and their steroid patterns are entirely different. In addition, the adrenocortical atrophy demonstrated histologically in the gland of patient No. 1 contrasts with the adrenocortical hyperplasia characteristic of the adrenogenital syndrome.

Hypopituitarism can also be associated with hypoadrenocorticism and is related to deficient secretion of ACTH. Administration of ACTH to such patients, however, results in a normal increment in cortisol output. After cessation of prolonged glucocorticoid therapy, there is often partial hypoadrenocorticism but, in our experience, administration of ACTH by intramuscular injection for 7 days restores cortisol secretion. Although few cases of isolated ACTH deficiency have been reported, most patients with hypopituitarism present a deficiency of several trophic hormones, particularly growth hormone. The 6 patients reported in this study had normal growth and no evidence of hypothyroidism.

Addison's disease is due to a progressive destruction of the adrenal cortex. Tuberculosis and histoplasmosis can be the cause of such destruction. At present, however, the large majority of the cases must be classified as idiopathic. BLIZZARD *et al.* [5] have reported that among 67 patients with Addison's disease alone, 31 % (21 patients) had antiadrenal antibodies in their serum, while 51 patients presented adrenal insufficiency along with an associated disorder (thyroid disease, hypoparathyroidism, diabetes, pernicious anemia, moniliasis). Of this total group of 118 patients with Addison's disease, 75 (64 %) had either an associated disorder or antibodies against a glandular structure (adrenal, thyroid, parathyroid, parietal cells). In our six patients, negative skin tests for tuberculosis and histoplasmosis and the absence of the type of antibodies mentioned above are evidence that they did not have typical Addison's disease. Furthermore, patients with Addison's disease present not only with a deficiency of cortisol secretion but also of aldosterone secretion.

Despite differences of opinion concerning the site of action of ACTH [11, 12, 19, 24], the activating effect of ACTH on steroidogenesis is due, in final analysis, to an increased availability of NADPH which is necessary for various hydroxylation steps (fig. 5). Although levels of ACTH in plasma were not determined in this study, hyperpigmentation of the skin suggests, in analogy with Addison's disease, that our patients had elevated concentrations of ACTH as well as of MSH in plasma. Furthermore, administration of ACTH did not result in increased secretion of cortisol. If all our patients had shown adrenal pathology similar to that of patient No. 1 (i.e., normal zona glomerulosa, unstimulated zonae fasciculata, and reticularis), the possibility exists that the cells of the fasciculata-reticularis lacked the ability to respond to ACTH.

In an attempt to clarify this problem, slices (15 to 20 mg) of the adrenal of patient No. 1 were pre-in-

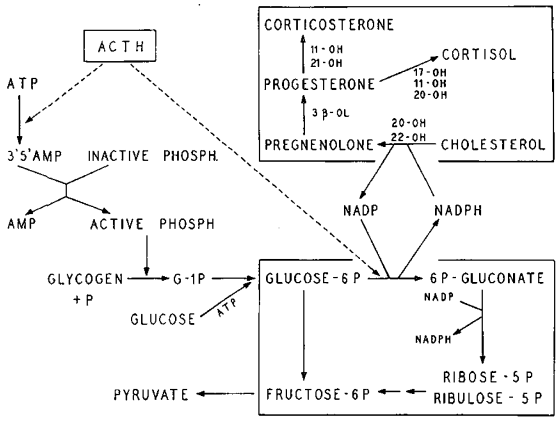


*Fig. 5.* Possible sites of action of ACTH in steroidogenesis [11, 12, 19, 24].

*Table VI.*
*In vitro* study of the steroid production by the adrenal gland of patient No. 1

| Additions (per gram tissue) | Steroid production (μg/g tissue)[1] | | |
|---|---|---|---|
| | F[2] | B[3] | F:B |
| None | 4.4 | 12.5 | 0.35 |
| 22 I.U. ACTH | 4.9 | 14.4 | 0.34 |
| 200 μM 3'5' AMP | 3.3 | 109.6 | 0.03 |

[1] Incubation for 1 hour at 37°
[2] Cortisol
[3] Corticosterone

cubated in 2 ml of Krebs-Henseleit bicarbonate buffer with a 10 mM glucose concentration for 1 hour at 37°, after which time they were incubated with 2 ml of fresh solution for 1 hour at 37°. Some of the flasks received an addition of either ACTH or 3',5'-adenosine monophosphate. 1,2-$^3$H-cortisol and 1.2-$^3$H-corticosterone (specific activity: 15 C per mMole) were added to the incubation mixture. Following extraction with $CHCl_3$ and paper chromatography (Bush B5), the areas of the chromatograms corresponding to cortisol and corticosterone were eluted. Each eluate was acetylated with $^{14}$C-acetic anhydride (specific activity: 20 mC per mMole) and the products were chromatographed on paper using two different solvent systems (cyclohexane: dioxane: methanol: water (360: 160: 330 : 80), and cyclohexane: dioxane: methanol: water (360: 360: 180: 90). The cortisol and corticosterone acetate eluates were oxidized with chromic acid to cortisone acetate and compound A acetate, respectively. Following two further chromatographic steps on paper (benzene: heptane: methanol: water (166: 330: 400: 100) and *heptane: methanol: water* (500: 425: 75), the eluates were counted and the amounts of cortisol and corticosterone present in the original slices were calculated and corrected for recovery. When no addition was made, the amount of corticosterone was greater than that of cortisol with an F: B ratio of 0.35 (table VI). This result is in contrast with the F: B ratio of 10–15 that was obtained using normal adrenal tissue and confirms the *in vivo* findings. The addition of ACTH had no effect on cortisol output, and this finding is consistent with the *in vivo* unresponsiveness to ACTH. The failure to synthesize corticosterone after incubation with ACTH may be explained by the fact that this steroid is produced by cells of the zona glomerulosa in response to angiotensin, rather than to ACTH [4, 23]. The addition of 3',5'-adenosine monophosphate produced no change in cortisol production, but did produce a marked increase in corticosterone. Outer slices (mainly glomerulosa) of beef adrenals have been shown to increase output of aldosterone and corticosterone when 3',5'-adenosine monophosphate is added to the incubation media [13]. In our experiments, the increase in corticosterone can therefore be considered as a direct effect of 3',5'-adenosine monophosphate on the zona glomerulosa. Failure to increase cortisol synthesis suggests that the defect in the fasciculata reticularis of patient No. 1 was probably not at the level of the cyclase enzyme.

### *Cases in the Literature*

In 1959, SHEPARD *et al.* [25] reported two sisters with hyperpigmentation, weakness, and convulsions. One was studied at 30 months of age by postmortem examination; the most striking finding was adrenocortical atrophy. Only occasional lumps of cortical cells remained in the zona glomerulosa, while cells of the zonae fasciculata and reticularis were absent. The other sister was studied at $3^5/_{12}$ years of age. She was found to have low levels of corticoids in blood, which did not increase during ACTH administration, but she was able to sustain a sodium-free diet without changes in blood pressure or levels of electrolytes in serum, and with an increase in aldosterone secretion. Through the courtesy of Drs. Vincent Kelley and Rogelio Ruvalcaba, we were able to restudy this patient in 1965 at the age of 12 years. During the interval, the only notable incident was an attempt in 1963, when the patient was 10 years old, to wean her from steroid very gradually over a long period of time. Shortly

after therapy was discontinued, she developed marked symptoms of hypoglycemia and treatment was promptly resumed. For this reason, the patient was maintained on 0.75 mg of dexamethasone throughout the 16 days of the 1965 study. During a control period, levels of 17-OHCS and 17-KS were 0.3 mg and 1 mg/24 h, respectively. On a diet containing 40 mEq of Na, aldosterone secretion was 201 $\mu$g/24 h. After consuming a diet containing only 3–4 mEq of Na for five days, levels of electrolytes in serum were normal (in mEq/l: Na = 138, K = 4.1, Cl = 99, $CO_2$ = 25) and aldosterone secretion was 274 $\mu$g/24 h. ACTH gel (25 mg intramuscularly, every 12 hours) was administered for 7 days and on the 7th day, daily urinary output of 17-OHCS was 0.4 and of 17-KS was 1 mg. This girl, and probably her sibling, would appear, therefore, to represent the syndrome of adrenal unresponsiveness to ACTH.

STEMPFEL and ENGEL [27] reported in 1960 what was thought to be a congenital, familial syndrome of adrenocortical insufficency without hypoaldosteronism. When the family moved to West Virginia, the patient was referred to our clinic. In 1965, at the age of 9.8 years, the patient was studied while receiving 0.5 mg of dexamethasone per day. After 10 days of treatment with ACTH gel (25 mg every 12 hours by intramuscular injection) the cortisol secretion rate was 1.5 mg and the corticosterone secretion rate was 0.5 mg/24 h. On a diet with normal amounts of sodium, the aldosterone secretion rate was 41 $\mu$g, but on the 5th day of a low Na regimen (9 mEq/day), the aldosterone secretion remained 45 $\mu$g/24 h. In addition, the sodium balance was negative and the level of K in serum went from 3.9 to 5.2 mEq/l and that of Na from 152 to 132 mEq/l. An episode of vomiting occurred at the end of the low sodium period. Therapy (oral cortisone 5 mg twice a day) was resumed, and the patient did well, requiring slightly increased amounts of salt in his food. While in Europe a year later, however, the patient developed manifest adrenal insufficiency with serum levels of Na at 117 mEq/l, and Dr. Andrea Prader in Zurich instituted therapy with DOC-trimethylacetate (25 mg every 3 weeks by intramuscular injection) and cortisone (15 mg daily by mouth). This patient, therefore, presented with Addison's disease rather than with the syndrome described in this paper.

In a family of 5 children, WILLIAMS and FREEMAN [30] observed that one boy and two girls had adrenal dysfunction affecting predominantly the glucocorticoid and not the mineralocorticoid mechanism. The excretion of 17-OHCS of these three children did not respond to the administration of ACTH. In one child, aldosterone excretion was reported as normal, which in itself is not very significant, and all children conserved sodium when on a low-salt diet. It is probable that these three patients had an isolated cortisol deficiency.

It is certain that some patients, who early in life develop hyperpigmentation, hypoglycemic episodes, deficient cortisol secretion without electrolyte disturbances, and have siblings with a similar syndrome, have been called examples of Addison's disease. Instead, they probably have the syndrome of adrenal unresponsiveness to ACTH. Nevertheless, in view of the absence of results from critical tests, such as measurement of aldosterone secretion and study of the Na and K balances during regular and low-salt diets, it is difficult to critically review the medical literature.

### *Genetic Aspects of the Syndrome*

In five of the six patients (Nos. 1 to 5), feeding problems occurred early in life. Patients Nos. 1 and 2 had hypoglycemic seizures at 3 and 7 months of age, respectively. Hyperpigmentation of the skin appeared at the age of 2 or 3 months. The appearance of symptoms so early in life suggests strongly that the syndrome is congenital.

Patients Nos. 2 and 3 were brothers and had no other siblings. Patient No. 1 had two healthy brothers and three normal sisters (table I); there was a history of two abortions early in pregnancy, and one sister had died at 24 hours of age of unknown causes; another brother who died at 18 months of age of viral pneumonia also had hyperpigmentation of the skin early in life. At autopsy, the adrenal glands were reported to be small and to show 'lipid depletion'. Patient No. 4 had a brother who died at 3 months of age during a solitary afebrile convulsion and was described as showing excessive sweating and tremors. One of the two brothers of patient No. 5 was healthy, while the other one died at 17 months of age of 'undetermined cause'; findings were nonspecific, but the pathologist noted that the 'adrenal glands were underdeveloped'. The three brothers and two sisters of patient No. 6 are all healthy.

Although the evidence is more circumstantial than factual, there is a suggestion that three of our patients each had one brother who died of the syndrome. This circumstantial evidence and the fact that two of the patients were brothers strongly suggest a genetic origin of the syndrome. If the syndrome is genetic and since our patients had normal parents, it is a recessive disorder. Because all six patients were males and the three siblings who presumably had the syndrome were also males, an X-linked mode of inheritance is suggested. There was no evidence, however, in any of the families indicating that a maternal uncle might also have had the syndrome. Furthermore, among the five patients in the literature [25, 30] who probably had this syndrome, there were four girls and one boy.

*Summary*

The cases of six patients with congenital adrenal unresponsiveness to ACTH are reported. The syndrome is characterized by feeding problems, hypoglycemic episodes, and skin hyperpigmentation occurring early in life; the cortisol secretion rates and urinary excretion of 17-hydroxycorticosteroids are low and do not respond to the administration of ACTH; the tolerance to salt deprivation is normal and is accompanied by a normal increase of aldosterone secretion rates.

In one patient, the adrenal glands were found to be extremely small in size with a normal zona glomerula and atrophic zonae fasciculata and reticularis. *In vitro* incubations of adrenal tissue from this patient resulted in a production of cortisol and corticosterone in a ratio of 0.35 (normal adrenal tissue treated similarly had a cortisol:corticosterone ratio of 10–15); addition of ACTH to the media was without effect, whereas addition of 3′,5′-adenosine monophosphate resulted in a marked increase in corticosterone production with no changes in cortisol production. These results and the clinical data suggest that the syndrome is due to an abnormality of the ACTH-dependent system which activates cortisol secretion by the cells of the zonae fasciculata and reticularis of the adrenal gland.

There is good evidence that the syndrome is congenital and is due to a recessive autosomal mutation expressed clinically only in subjects who are homozygous for the mutant gene.

At least five children (from two families) whose cases have been reported in the literature probably had the syndrome.

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