A REVERSIBLE SALT-WASTING SYNDROME OF THE NEWBORN AND INFANT

POSSIBLE INFANTILE HYPOALDOSTERONISM

BY

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The suggestion that transient states of primary adrenal hypofunction confined to salt conservation can occur in infancy has been most convincingly supported by Jaudon (1946, 1948). Many of his cases, however, showed varying combinations of hyperpigmentation, hypoglycaemia and acidosis, with some having diminished, and others increased, steroid excretion. On the other hand, in recent reports of infants with transient salt-losing syndrome (Cheek and Perry, 1958; Donnell, Litman and Roldan, 1959; Lelong, Alagille, Phillipe, Gentil and Gabilan, 1960), this has been ascribed to a renal tubular insensitivity to salt-retaining hormones. Raine and Roy (1962), in their discussion of a further example of this condition, consider this explanation unlikely, pointing out that a similar insensitivity to D.C.A. exists in other conditions where a primary renal tubular dysfunction is not likely to be present.

We present a study of two children with manifestations of a salt-losing syndrome within the first month of life. Anorexia and frequent vomiting resulted in a large initial loss of weight and subsequent failure to gain. Constipation and hyperirritability were also present and there was weakness, hypotonia and dehydration with episodes of tachycardia, pallor and collapse, culminating in peripheral circulatory failure. The dependence of these two infants upon a combination of D.C.A. and salt for clinical recovery and electrolyte homeostasis appeared to be specific, but was transient and ended between the first and third years of life. Although many of the features described by Jaudon were not seen in our infants, several of his cases were very similar to ours. In view of the evidence of renal tubular response to D.C.A. or A.C.T.H., as distinct from salt replacement, it appears unlikely that a primary renal defect could underlie the syndrome we

describe. The investigations indicate a fractional adrenocortical insufficiency, possibly confined to aldosterone secretion.

The occurrence in infancy of a reversible hyponatraemic state resulting from adrenocortical dysfunction, whether primary or secondary, has been questioned (Wilkins, 1957). We hope that the investigations undertaken on these two cases will help to substantiate the existence of this syndrome.

Case Reports

Case 1. K.W., a boy, was delivered normally at the Mothers' Hospital, Clapton, on March 14, 1952, after an uneventful pregnancy. He was the first child and there was no consanguinity.

Apart from bilateral webbing of middle and ring fingers, slight oedema of the limbs and eyelids was the only abnormality noted at birth. The birth weight was 9 lb. 6 oz. (4,252 g.) and the initial weight loss appeared large, 14 oz. (397 g.) by the fourth day, although there was then still slight eyelid oedema. Weight loss continued, however, and by the eleventh day he was clearly ill and tube-feeding was necessary. Three days later he was still pale and limp, especially after feeds. Urine examination revealed slight haematuria (red blood cells 10 to 15 per H.P.F.), a trace of albuminuria but no pyuria. The blood urea was 49 mg. per 100 ml. Chloramphenicol was given for six days with apparent response including weight gain, but two days after its withdrawal he again refused feeds sufficiently to compel tube-feeding. Cerebrospinal fluid and stool examinations proved to be normal, but the serum chloride was low (96 mEq/l.). When 25 days of age and weighing only 8½ lb. (3,741 g.) he was transferred to the Queen Elizabeth Hospital for Children, under the care of Dr. Helen M. M. Mackay.

His progress was unaffected by a further course of chloramphenicol. Feeding was slow and vomiting recurred once or twice daily. Each day there were several episodes of violent agitation and screaming, apparently unrelated to feeds or hunger. A sinus

FIG. 1.—Case 1. Male. Progress chart.

tachycardia of 200 per minute, in the absence of crying, was also noted on several occasions. After three weeks, however, he had become relatively subdued and had gained $6\frac{1}{2}$ oz. (191 g.). The microscopic haematuria had, meanwhile, persisted. He was then discharged only to be readmitted 10 days later because of worsening vomiting and constipation, his weight having remained stationary. He continued to take feeds slowly, the vomiting and constipation persisted and no weight progress was made. Mottled cyanosis of his legs was observed and sometimes an ashen-grey facial pallor after crying. Serum electrolyte estimations then revealed very low levels of sodium (117 mEq/l.) and of chloride (86 mEq/l.), and a raised potassium (6.7 mEq/l.), while the urinary chloride ranged between 70 and 100 mEq/l.

Plasma CO_2 combining power was 18.5 mEq/l. There was neither skin nor mucosal hyperpigmentation, nor was there hypertension or hypoglycaemia. The urinary 11-oxysteroid output was normal (0.10 mg./24 hours).

A provisional diagnosis rested between the adrenogenital salt-losing syndrome, or congenital hypoplasia of the zona glomerulosa, the 17-ketosteroid urinary output of 0.35 mg./24 hours excluding the former.

At 9 weeks of age (weight 8 lb. $5\frac{3}{4}$ oz. (3,791 g.)) oral saline administration was initiated with 34 mEq of sodium chloride daily (Fig. 1). Improvement in appetite and weight gain followed, 1 lb. (453 g.) being gained in the first 10 days, but this was maintained only by raising the salt intake to 68 mEq daily. Although vigour improved and he became much more contented, several

episodes of collapse with pallor and dilatation of the pupils were observed, from which he recovered spontaneously with no coincidental hypoglycaemia.

Weight gain slowed down and it became clear that at this level of salt dosage the serum Na concentration could not be sustained above 130 mEq/l., while serum potassium levels still remained between 6.1 mEq/l. and 7.1 mEq/l. Deoxycorticosterone therapy was started on June 14, 1952, when his weight was 10 lb. 1 oz. (4,561 g.). At first, 0.5 mg. i.m. was given daily for three days and then 1.0 mg. i.m. daily when it became possible to lower the salt intake to 34 mEq daily. A remarkable clinical improvement followed, with a weight gain of 2 lb. 4 oz. (1,020 g.) in the subsequent month. The extremities were also noted to have 'become warm for the first time'. Two weeks later the sublingual route was substituted for intramuscular administration of D.C.A. in preparation for his discharge from hospital, 2.0 mg. being given daily in a propylene glycol suspension.

His condition was stabilized on this dosage of D.C.A. with a daily salt supplement of 21 mEq. A temporary reduction of the D.C.A. dosage to 1.5 mg. on one occasion promptly led to anorexia and a conspicuously increased output of urine. By 5 months his weight had reached 13 lb. 11½ oz. (6,223 g.) representing a gain of 27 oz. (765 g.) in the four weeks that had followed the introduction of saline, and a further 58 oz. (1,643 g.) during the seven weeks after the addition of D.C.A.

At 8 months of age his urinary 17-ketosteroid output was 0.4 mg. and 0.74 mg./24 hours. The serum sodium level was still only 134 mEq/l. but the potassium had fallen to 5.6 mEq/l. Both skeletal growth and maturation were then normal, and have remained so since. At 14 months the serum sodium had reached 146 mEq/l., the potassium level was 5.9 mEq/l. and the blood urea 30 mg./100 ml. The 17-ketosteroid output was 0.5 mg./24 hours. At 16 months his general condition was excellent and it was decided to assess the response to A.C.T.H. The results of this test are discussed below. Within two weeks, in the light of consistently sustained normal levels of serum sodium, the D.C.A. dosage was reduced, initially to 1.0 mg. per day. While the weight gain slowed appreciably at this stage, with only 13½ oz. (382 g.) recorded during the next three months, there was no other obvious clinical deterioration, nor did the serum sodium fall below 135 mEq/l. or the serum potassium rise above 5.6 mEq/l. Perhaps over-cautious in this first case, it was not considered worth while risking a further reduction of the D.C.A. dosage until two years later, when it was lowered to 0.66 mg. daily. His steady weight gain was then unaffected, and at intervals of a month the daily dosage was reduced by a further third and finally, at 3½ years of age, was discontinued entirely. One month later, when his serum sodium was 136 mEq/l. and potassium 5.0 mEq/l., saline supplements were also withdrawn. Although his serum sodium declined slightly to 134 mEq/l., his clinical condition and weight remained good.

Five months later, at 4 years of age, he was still a vigorous healthy boy and his blood pressure was 110/70 mm. Hg. An operation for syndactyly (Mr. R. J. V.

Battle) was accomplished without metabolic incident, the pre-operative serum electrolyte levels of sodium 134 mEq/l., potassium 4.7 mEq/l., chloride 106 mEq/l. and CO₂ combining power 20 mEq/l., showing no significant post-operative change. His subsequent general progress has been entirely normal.

Case 2. G.D., a girl, was born after an uneventful full-term gestation on December 6, 1955, weighing 8 lb. 12 oz. (3,967 g.). There was neither consanguinity nor other relevant family history, and the one male sibling is normal.

Breast feeding continued for three weeks, although she showed apathy and exceptional slowness in feeding from the outset. She passed a constipated stool every two to three days. After four weeks her weight was still 10 oz. (283 g.) below that at birth.

A week later she became pyrexial and was admitted with pneumonia to the Queen Elizabeth Hospital for Children, Shadwell, under the care of Dr. J. N. O'Reilly (January 14, 1956). This infection was quickly controlled by penicillin and streptomycin. Transitory microscopic haematuria was noted, as in the previous case, a urine red cell count of 20 per high-power field being recorded on January 16, 1956. Subsequently, her hypotonia, resistance to feeding, vomiting and constipation persisted and although after 2 months of age a slow weight gain began on a full-cream National dried milk feed, it was not until she was 3 months old that she regained her birth weight (Fig. 2). The urine at this stage showed no abnormal features and its specific gravity after thirsting reached 1.027. The blood urea was consistently high, ranging between 80 and 102 mg./100 ml. as were the levels of serum calcium (11.2 to 12.1 mg./100 ml.) and plasma potassium (6.1 mEq/l.), whereas the plasma sodium (120 to 122 mEq/l.) and chloride (91 to 98 mEq/l.) were low. The urinary chloride concentration ranged between 5 and 7 g./l. Radiography of renal and adrenal areas showed no calcification. A tentative diagnosis of hypercalcaemia with associated urea retention and a low plasma sodium due to vomiting led to the introduction at the age of 3½ months of a low calcium milk—'locasol'. During the next two weeks, the weight fluctuated around 9 lb. 7 oz. (4,280 g.) and the vomiting and constipation persisted despite a decline in the serum calcium level to 10.0 mg./100 ml. The blood urea remained high, 87 mg./100 ml., but the plasma sodium level had dropped still further to 119 mEq/l. These results together with the high urinary chloride and raised plasma potassium levels, suggested a primary adrenocortical insufficiency. A normal 17-ketosteroid urinary excretion of 0.16 mg./24 hours excluded the adrenogenital syndrome while the normal ketogenic steroid output of 0.86 mg./24 hours supported the possibility of a selective adrenocortical deficiency confined to salt conservation. A salt supplement of 3.0 g. (51 mEq) daily at once led to definite, although limited, clinical and biochemical improvement (Fig. 2), the serum sodium, for example, never rising above 132 mEq/l.

At 5 months of age she appeared sufficiently well to

FIG. 2.—Case 2. Female. Progress chart.

withstand stress testing by graduated salt depletion (Fig. 2). Unequivocal clinical deterioration ensued, with anorexia and hyperirritability and a weight loss of 8 oz. (226 g.) within six days. The blood pressure fell to 70/45 mm. Hg, the plasma sodium dropping to 120 mEq/l. and chloride to 93 mEq/l., while the urine still showed high concentrations of these ions. Rapid worsening of the dehydration compelled the reintroduction of oral and subcutaneous saline, reinforced this time by 3 mg. of D.C.A. daily. Appetite immediately improved, vomiting ceased and a sharp rise in weight followed. Within a week, however, a slight oedema of the legs led first to a reduction of the D.C.A. dosage to 0.5 mg. daily and a week later to a drop in salt intake to 34 mEq daily. Thereafter, general progress and a normal rate of weight gain proceeded. The blood pressure rose to 100/60 mm. Hg and by 7½ months she weighed 15 lb. (6,803 g.) and was sitting up unsupported. At this stage D.C.A. was withdrawn for a short time during further studies of adrenocortical function, including several tests of the diuretic response to a water load (Fig. 7), and was resumed after the tests, this time in an oral preparation (suspension in propylene glycol) in a dosage of 4.0 mg. daily. At 9½ months of age, weighing 18 lb. (8,164 g.), she was discharged from hospital on this dosage of D.C.A. together with a daily salt supplement of half a teaspoonful.

Satisfactory clinical progress was maintained, and after a further two months she was readmitted for reappraisal of her response to withdrawal of D.C.A. and salt, and to adrenocortical stimulation by A.C.T.H. A healthy happy infant of normal development, she still did not show any hyperpigmentation, her systolic blood pressure was 100 mm. Hg and the blood urea only 24 mg./100 ml. Her bone age by then was in the normal 9 to 12 months' range. Added salt was first omitted from her diet, and then D.C.A. a week later, without any obvious clinical setback following upon either withdrawal. General condition and weight gain remained excellent. Six months later, at 15 months of age, she weighed 24½ lb. (11 kg.). Her urinary excretion of 17-ketosteroids was then 0.26 mg./24 hours, and of 17-ketogenic steroids 2.6 mg./24 hours. It was decided to 'stress-test' her apparent functional recovery of salt conservation by a further period of salt deprivation, this time on the low salt milk, 'edisol'. No significant clinical deterioration was evoked and salt conservation appeared adequate. Her subsequent general progress has remained entirely normal.

Laboratory Methods

Sodium and potassium were estimated on heparinized plasma or urine by the flame photometer, chloride by the colorimetric method of Sendroy (1939, 1942) and

TABLE 1
CASE 2: SALT DEPLETION TEST AT 5 MONTHS

	Haematocrit (ml./100 ml.)	Blood Urea (mg./100 ml.)	Plasma Electrolyte (mEq/l.)			Urinary Electrolyte (mEq/l.)			Urinary Concentration Urea (mg./100 ml.)
			Na	K	Cl	Na	K	Cl	
Day 1	40	71	133	5.3	105	—	—	—	1,840
Day 6	44	56	120	5.1	92	80	78	62	

the plasma carbon dioxide capacity by the manometric method of Van Slyke and Neill (1924). Calcium was determined by the method of Sobel and Sobel (1939). For urinary 17-ketosteroids the method recommended by the M.R.C. Committee on Clinical Endocrinology (1951) was used. In Case 1 a modification of the method of Sprechler (1950), based on that of Sobel and Heard (1946), was employed for the urinary determination of 11-17 oxycorticosteroids. The method of Norymberski (Norymberski, Stubbs and West, 1953; Appleby, Gibson, Norymberski and Stubbs, 1955) was used for the estimation of 17-ketogenic steroids in Case 2. Aldosterone in urine was estimated by the procedure described by Rinsler and Rigby (1957).

Investigations and Results

A. Urinary Excretion of Sodium and Chloride. Urinary chloride concentrations on qualitative testing ranged between 3 and 5 g./l. in Case 1, between 5 and 7 g./l. in Case 2, both during phases of vomiting and in the absence of saline supplements. The 24-hour urinary excretion levels before introducing salt therapy are illustrated by one specimen collected in Case 1 when 3 months old. This revealed a sodium concentration of 58 mEq/l., although plasma levels of sodium and chloride were only 113 and 84 mEq/l. respectively.

B. Effects of Salt Deprivation. The first salt deprivation test in Case 2 was undertaken when she was 5 months, merely by lowering the daily salt intake of 1.5 g. to 0.4 g. for six days, the fluid intake being maintained at between 800 and 1,000 ml. per day. The plasma sodium concentration fell to 120 mEq/l. at a time when the concentration in a nine-hour night specimen of urine was 80 mEq/l. Table 1 summarizes the biochemical findings on days 1 and 6 of the test. Clinically, hypotonia and hyperirritability had soon reappeared, with dehydration worsening on the last two days, the blood pressure falling to 70/45 mm. Hg, necessitating the administration of both salt (2 g. in 24 hours) and D.C.A. (3.0 mg. intramuscularly). Dehydration was relieved and the clinical improvement was striking within the next 24 hours.

At the age of 15 months, a more stringent test of salt conservation was undertaken three months

after treatment with D.C.A. and salt supplements had been discontinued. A low-salt milk, 'edosoil', was administered for eight days, analysis of each feed proving that the total sodium intake was between 55 to 65 mg. per day. Urine was collected for 24 hours before salt restriction began, and for the following eight days. Much improved and apparently normal conservation is indicated by the results shown in Fig. 3. The daily excretion of sodium, for example, fell from 21 mEq to 1 mEq by the eighth day, while the plasma sodium fell from 140 to 130 mEq/l. Although the infant remained clinically well, there was a weight loss of 20 oz. (567 g.) during the two days of salt restriction.

C. Effects of Salt and D.C.A. Supplementation.

In both Cases 1 and 2 (Figs. 1 and 2) a rise in the plasma sodium and a small weight gain followed an increase in sodium intake, but the response to intramuscular D.C.A. was more dramatic, a normal plasma electrolyte pattern being rapidly achieved and considerable weight gain sustained.

D. The Effects of Corticotrophin Administration.

In Case 1 this investigation was carried out when the infant was 16 months old and taking 2.0 mg. D.C.A. and 1.25 g. added salt daily. Plasma electrolytes were estimated and 24-hour urine collections made on the two days preceding, on days 2 and 3 of the three days of intramuscular corticotrophin administration (7.5 mg. A.C.T.H. Organon six-hourly), and on two days shortly after corticotrophin administration had ceased. Urinary excretion of sodium, potassium, 17-ketosteroids and 17-hydroxycorticoids, was determined for each 24-hour specimen. The results are summarized in Table 2 and Fig. 4, a significant fall in urinary sodium during corticotrophic stimulation coinciding with a rise in urinary potassium output. The maximum reduction in the urinary Na/K ratio was greater than 50% of the baseline value (Nabarro, 1954). The plasma sodium rose concurrently from 135 to 141 mEq/l., falling again to 134 mEq/l. two days after corticotrophin administration ended.

A similar test was carried out on Case 2 at the age of 7 months. On this occasion D.C.A. was

FIG. 3.—Case 2. Second salt depletion test at age of 15 months.

TABLE 2
CASE 1: A.C.T.H. TEST AT AGE OF 16 MONTHS

Day	Cortico- trophin (mg.)	24-hr. Out- put of Urine (ml.)	24-hr. Out- put of 17-Keto- steroids (mg.)	24-hr. Out- put of 11-17-Oxy- steroids (Reducing)	Urinary Sodium		Urinary Potassium		Urinary Na ⁺ :K ⁺ Ratio
					Concen- tration (mEq/l.)	24-hr. Output (mEq)	Concen- tration (mEq/l.)	24-hr. Output (mEq)	
1	—	260	0.94	—	110.0	28.4	48.0	12.4	2.3
2	—	215	0.82	0.107	136.0	29.2	71.0	15.2	1.9
3	30	—	—	—	—	—	—	—	—
4	30	198	2.16	—	64.0	12.7	116.0	23.0	0.55
5	30	192	5.25	0.124	83.0	15.9	48.0	9.2	1.7
6	—	—	—	—	—	—	—	—	—
7	—	—	—	—	—	—	—	—	—
8	—	330	0.87	—	119.0	39.1	57.0	19.0	2.1
9	—	260	1.17	0.11	114.0	29.6	90.0	23.4	1.3

FIG. 4.—Case 1. A.C.T.H. test at age of 16 months.

discontinued five days before the test. A daily intake of 83 mEq of salt and 1,100 ml. water was maintained throughout, urine was collected for two consecutive 24-hour periods before corticotrophin was administered, 25 mg. 'actar' gel (Armour) intramuscularly daily for three days, and for the ensuing four days, plasma electrolyte and urea levels being measured during the control period and on the first and fourth days of the test. Urinary excretion of sodium, potassium, 17-ketosteroids and 17-ketogenic steroids was determined for each 24-hour period. The results are summarized in Table 3 and Fig. 5, the urinary sodium concentration and absolute output falling during the first two days of corticotrophic stimulation.

The second test was carried out on Case 2 at the age of 12 months, the daily salt supplementation of 2.4 g. and the oral D.C.A. dose of 4.0 mg. daily being omitted in turn, and she was left on a standardized daily intake of 0.6 g. (26 mEq) sodium and 1.4 g. (36 mEq) potassium. The results are shown in Table 4 and Fig. 6, the urinary sodium concentration and output again falling during the period of corticotrophin administration.

E. Influence of D.C.A. and Cortisone on Water Diuresis. A series of water load tests was performed on Case 2 when the patient was 8 months old and poor salt-conserving power could still be demonstrated. The first was done while she was still having 0.5 mg. D.C.A. intramuscularly and 2 g. (34 mEq) of added salt daily, the second test three days after the D.C.A. had been withdrawn, and the third test on the following day and nine hours after giving 30 mg. cortisone intramuscularly. Normal feeding was continued up to and including the 10 p.m. feed on the night preceding the test. A water 'load' of 20 ml. per kg. was given at 10 a.m. and urine was collected via an indwelling catheter at 30-minute intervals for four hours. The results

FIG. 5.—Case 2. A.C.T.H. test at age of 7 months.

are shown in Figs. 7 to 9. While the four-hour diuresis was within the normal range in all tests, over 90% of the water load, there were interesting differences in the total output and in the rate of flow in the first two hours. In the first test, under the influence of D.C.A. the total urinary output already exceeded the water load in the first two hours (105%). When off D.C.A. in the second

FIG. 6.—Case 2. A.C.T.H. test at age of 12 months.

test, however, the proportion of water load excreted in the first two hours was only 40%.

With a few reservations, an excretion of less than 50% of the water load within four hours of its administration characterizes adrenocortical insufficiency in adults (Soffer and Gabrilove, 1952) and an apparently normal diuretic response can be restored by the preliminary administration of cortisone (Oleesky and Stanbury, 1951; Garrod and Burston, 1952). This also has been demonstrated by one of us (Russell, 1952) by the use of an indwelling

TABLE 3
CASE 2: A.C.T.H. TEST 1 AT 7 MONTHS

Day	Cortico- trophin (mg.)	24-hr. Out- put of Urine (ml.)	24-hr. Out- put of 17-Keto- steroids (mg.)	24-hr. Out- put of 17-Keto- genic Steroids (mg.)	Urinary Sodium		Urinary Potassium		Urinary Na+ : K + Ratio
					Concen- tration (mEq/l.)	24-hr. Output (mEq)	Concen- tration (mEq/l.)	24-hr. Output (mEq)	
1	—	610	0.1	0.2	98.0	60	31.3	19.0	3.1
2	—	680	0.1	0.2	101	69	32.3	21.9	3.2
3	25	605	0.1	0.6	63.5	38.5	25.4	15.4	2.5
4	25	558	0.3	1.0	75.0	42.0	24.6	13.9	3.12
5	25	665	0.1	0.7	106.1	70.5	23.0	15.4	4.6
6	—	720	Nil	0.5	101.7	73.5	34.2	24.6	2.98

TABLE 4
CASE 2: A.C.T.H. TEST 2 AT 12 MONTHS

Day	Cortico- trophin (mg.)	24-hr. Out- put of Urine (ml.)	24-hr. Out- put of 17-Keto- Steroids (mg.)	24-hr. Out- put of 17-Keto- genic Steroids (mg.)	Urinary Sodium		Urinary Potassium		Urinary Na+ : K + Ratio
					Concen- tration (mEq/l.)	24-hr. Output (mEq)	Concen- tration (mEq/l.)	24-hr. Output (mEq)	
1	—	268	0.23	2.4	51	13.5	125	33.6	0.41
2	35	268	0.40	4.9	27	7.2	119	32.1	0.22
3	35	325	0.19	4.7	37.9	12.3	84.5	27.4	0.44
4	50	400	0.40	7.0	44.5	17.8	77.3	30.9	0.59
5	—	610	0.09	2.7	51	31.3	54.6	33.4	0.93

FIG. 7.—Case 2. Water load test (20 ml./kg.) at age of 8 months, while on D.C.A. and added salt.

FIG. 8.—Case 2. Water load test (20 ml./kg.) at age of 8 months, 3 days after withdrawal of D.C.A.

Fig. 9.—Case 2. Water load test (20/ml. kg.) at age of 8 months, after cortisone (30 mg. i.m.).

catheter for urine collection in children 1 to 2 years old with either primary or secondary adrenocortical insufficiency (Table 5). Although it has often been stated that D.C.A. has no influence upon diuretic function, both Moehlig and Jaffe (1942) and Sirek and Best (1952) have demonstrated that it diminishes renal tubular responsiveness to antidiuretic hormone (A.D.H.) as does cortisone. Further, Morel (1951)

has shown that the restoration of diuretic capacity by cortisone in adrenocortical insufficiency is incomplete without D.C.A. so that the effect of D.C.A. in giving a more complete diuretic response in Case 2 suggests a mineralo-corticoid deficiency despite the relatively normal four-hour diuretic response.

F. Urinary Corticosteroid Output

17-ketosteroids. In each case, the basal urinary excretion of 17-ketosteroids and their response to corticotrophic stimulation appeared to be normal (Ferrazzini, Borth and Mach, 1952; Sprechler and Vesterdahl, 1953). In Case 1, there was a fivefold increase, and in Case 2 a threefold increment in urinary 17-ketosteroid output.

Glucocorticoid Excretion. In Case 1 the daily output of formaldehydogenic corticoids rose from 0.107 mg. per 24 hours to only 0.124 mg. per 24 hours after the administration of corticotrophin. Although this increase might not be considered significant, there was a concurrent fivefold increase in 17-ketosteroid output, and it is possible that the preparation used was predominantly of 17-ketosteroid rather than glucocorticoid stimulatory material (Bayliss and Steinbeck, 1954). Read, Venning and Ripstein (1950) have shown that the increase of glucocorticoid urinary output following the administration of corticotrophin during the second week of life may be no more than 0.22 mg. to 0.33 mg. per 24 hours from a basal level of 0.04 mg. to 0.14 mg. per 24 hours. They concluded that on the basis of body weight or surface area these increments were equivalent to the adult response.

In Case 2, however, the responses were more clear-cut. At 7 months the increment of ketogenic steroids was 0.8 mg. per 24 hours and five months later it was 4.6 mg. per 24 hours. These higher levels, both basal and following corticotrophin adminis-

TABLE 5
RESULTS OF WATER LOAD COMPONENT AND OF PROCEDURE II (ROBINSON-POWER-KEPLER)
IN CHILDHOOD: 1-2-YEAR SERIES (RUSSELL, 1952)

	I Diuresis After Water Load (20 ml./kg.)		II Kepler Factor
	Overall Night/Day Test	Percentage Load Excreted in 4 hrs.	
Normals (10)	Negative	Mean: 84	Mean: 246
Adrenocortical Insufficiency:			
A. Primary			
Adrenocortical atrophy (bilateral) 3 tests	Positive	All <40	31, 29 and 32
Adrenogenital salt losers: 6 cases	Positive	43	28
B. Secondary 2 cases (2 tests each)			
Case 1	Positive	8 and 32	31.0 and 26.5
Case 2	Positive	37 and 31	26 and 29

tration, may derive from the different methods of estimation used (Norymberski *et al.*, 1953).

Aldosterone. In Case 2 the urinary excretion of aldosterone was estimated twice; on the first occasion aldosterone was not detected in a 24-hour specimen of the urine five days after the conclusion of the second salt deprivation test when the patient was 15 months old, apparently clinically well and on a normal diet, having neither salt supplement nor D.C.A. For the second estimation, three months later, a 48-hour specimen of urine was used, the amount excreted being just below 1 μ g. per 24 hours.

G. Other Investigations. Absolute eosinophil counts, when performed as preliminaries to corticotrophin administration, proved to be low in both infants. In Case 1 these were zero and 7 per c.mm. and in Case 2 they ranged between 14 and 33 per c.mm. A glucose tolerance test undertaken on Case 2 at 6 months of age, while still having D.C.A. and salt, was normal.

Discussion

Salt Wasting in Presence of Hyponatraemia. An increase of sodium reabsorption by the renal tubules is normally effective in preventing hyponatraemia even when there are large extrarenal losses of sodium as well as a low intake. This mechanism is profoundly influenced by adrenocortical steroids, probably by directly modifying the permeability of renal tubular cells, and will fail in adrenocortical insufficiency resulting in urinary sodium wastage despite hyponatraemia.

Poor salt conservation was demonstrated in our cases at an early stage by high urinary sodium and chloride excretion despite the severe chloride losses accompanying persistent vomiting, and in the face of consistently low plasma sodium levels (between 113 and 135 mEq/l.). When stress was first applied in Case 2 by lowering the supplementary salt intake to 0.4 g. (7 mEq) daily, urinary sodium and chloride excretion remained high despite a rapid fall in their plasma levels. The urinary sodium concentration of 80 mEq/l. (and urinary tonicity calculated as 623 mOsm/l.) coincided with a plasma sodium of 120 mEq/l. with an osmolality of 275 mOsm/l. Clinical deterioration accompanied these biochemical changes. Although the tonicity of the plasma was low there was severe dehydration culminating in peripheral failure, which was readily reversed by making up the salt deficit and preventing further salt depletion by treatment with both D.C.A. and salt.

When at 15 months of age clinical recovery appeared well established, a still more stringent

salt deprivation test (Fig. 3), involving a restriction of total sodium intake to between 55 and 65 mg. (2.5-3 mEq) daily, confirmed the recovery or perhaps the maturation of normal salt-conserving mechanisms. No clinical deterioration ensued and the sodium output fell from 21 mEq per 24 hours to 2.5 mEq by the fifth day, and to 1 mEq by the ninth day, when the plasma sodium level was 130 mEq/l. The plasma sodium was not depressed below the lower limit of normal until the seventh day of salt deprivation.

Renal Tubular Function. It appears unlikely that the failure of salt conservation resulted from a primary defect of the renal tubules. Thus azotaemia was rapidly eliminated by overcoming the sodium depletion and dehydration, and acidosis did not occur. Both the ability to concentrate and to dilute urine were normal. Moreover, the administration of D.C.A. promptly effected salt retention; and during the second day of corticotrophic stimulation a reduction in urinary excretion of sodium coincided with a rise in its plasma level. Both these effects suggest a normal capacity of the renal tubules to respond to adrenal steroids.

Selective Adrenal Dysfunction. A selective reversible insufficiency of adrenocortical mineralo-corticoid function, whether primary or secondary, appears best to fit the findings in our cases. No evidence was found to suggest insufficiency of other adrenocortical function. There was neither skin nor mucosal hyperpigmentation. Significant hypotension developed only during salt deprivation. There was no hypoglycaemia and eosinopenia was consistent. Urinary 17-keto and 17-ketogenic steroid excretion was also normal with a normal response to A.C.T.H.

In favour of fractional mineralo-corticoid insufficiency was the normal diuretic response in Case 2 after D.C.A. withdrawal at 7 months of age. This pointed to an adequate secretion of endogenous cortisone-like substances. It is interesting to note that the diuresis was enhanced when D.C.A. was given, which is consistent with the observation of Morel (1951) that the correction of impaired diuresis by cortisone in panhypo-adrenocorticism is incomplete without D.C.A., suggesting that fully normal diuresis is dependent upon both groups of adrenocortical steroids. Furthermore, correction to normal plasma levels of sodium and potassium appeared more dependent on D.C.A. than on salt supplementation alone. Response to a graduated increase in the salt supplement was limited both clinically and biochemically, especially in Case 1,

but improvement in both respects was marked and immediate when small doses of D.C.A. were added, indicating either a specific need for, or a relative or absolute deficiency of, an analogous mineralo-corticoid factor.

Although the salt-retaining effect of A.C.T.H. in the two infants was in agreement with that found in normal infants over 2 to 3 months of age (Klein, 1951), the concurrent reduction in the Na : K ratio in Case 1 or in the first test of Case 2 was less than 50%. If the criteria suggested by Nabarro (1954) are applicable to infants, this result would imply some selective adrenocortical insufficiency of electrolyte regulation. In the second test in Case 2, the fall in the urinary Na : K ratio exceeded 50%, and, on the same basis, this would imply a normal adrenocortical function, agreeing with the clinical and biochemical recovery.

Finally, the 24-hour output of aldosterone was zero in Case 2 five days after a period of severe salt depletion when one might expect it to have been increased and three months later with the infant on a normal diet, it was still less than 1 μ g./24 hours, i.e. much lower than the normal range reported by Blizzard, Liddle, Migeon and Wilkins (1959).

Recent investigations have indicated a physiological basis for the possible occurrence of a fractional adrenocortical dysfunction. Thus production of aldosterone and hydrocortisone has been shown to be to some extent independent, first by the failure of steroids, which suppress the release of corticotrophin, to affect the secretion of aldosterone (Venning, Dyrenfurth and Beck, 1956) and secondly by the rise in aldosterone output without apparent influence upon cortisone secretion in response to salt restriction (Liddle, Duncan and Bartter, 1956).

Possible Diencephalic Involvement. The underlying adrenocortical defect could be a hypoplasia, immaturity or suppression of the zona glomerulosa, which has been shown (Ayres, Garrod, Tait and Tait, 1958) to be the site of aldosterone production in man. This might be primary or secondary to dysfunction at hypothalamo-hypophyseal or other diencephalic levels. Farrell (1959) has adduced some experimental evidence for the existence of a diencephalic hormone, 'glomerulotrophin', specifically able to activate the zona glomerulosa. That diencephalic-hypophyseal levels might in our cases be the seats of primary dysfunction is suggested by the prompt response to adrenocorticotrophic stimulation with reduction in the salt excretion coinciding with a rise in plasma sodium in all three tests.

The Mechanism of Recovery. There are several possible ways in which recovery may have taken

place. First the initial salt-retaining effects of corticotrophin in our infants suggest that the adrenal cortex was able to compensate by the synthesis of large enough amounts of corticosteroids other than aldosterone to bring about overall salt retention. Such a salt-retaining response could, for example, result from an enhanced secretion of hydrocortisone or cortisone or both, as suggested especially by the sharp increase in urinary ketogenic steroids in Case 2, or even from an increased output of the more potent sodium-retaining steroid, 11-dehydrocorticosterone. Thus Skanse and Hökfelt (1958) found that a low sodium diet in an adult said to show pure hypoaldosteronism provoked a striking rise in the secretion of cortisone and hydrocortisone without any aldosterone excretion. Overproduction of other corticosteroids would, however, be unlikely to compensate precisely for the effect of aldosterone, so that the electrolyte adjustments in these infants might well be incomplete or distorted. The subnormal depression of the Na : K excretion ratio coinciding with the salt-retaining effects in the first A.C.T.H. test of Case 2 might be accounted for in this way.

Secondly, the recent illustration (Giroud, Saffron, Schally, Stachenko and Venning, 1956; Giroud, Stachenko and Riletta, 1958) of the powers of regeneration of the adrenal cortex suggests an alternative explanation of the recovery from adrenocortical dysfunction during infancy. After removing one adrenal in male rats, they enucleated the other and observed its regeneration from capsular tissue. Corticosterone secretion increased progressively to a peak by 30 days, by which time the cortex had regenerated. The restoration of aldosterone secretion proved to be a much slower process and was still subnormal at the end of this period. A similar mechanism could account for recovery in our cases.

Finally, our cases show some similarity to infants with the adrenogenital salt-losing syndrome who also demonstrate an apparent reversibility of their salt-losing state. Since the latter condition is known to be due to a primary enzymatic defect, it is therefore possible that in our cases the defect may be an enzymatic one, and the mechanism of recovery may also be similar. Whatever this may be, it is essential to preserve their metabolic equilibrium meanwhile with the aid of salt and D.C.A.

Summary and Conclusions

Two children are presented in whom a salt-wasting syndrome was manifest from birth, although spontaneously reversible when tided over their first year or so with the help of D.C.A. and salt supplementation.

Their salt depletion was reflected clinically in anorexia and vomiting, with arrest of weight gain until treated. Hyperirritability was conspicuous, and increasing hypotonia, dehydration and episodes of collapse and pallor culminated in peripheral circulatory failure.

In both cases there was hyponatraemia and hyperkalaemia similar to that found in panhypoadrenocorticism or adrenogenital salt-losing, although both lacked other specific criteria of either disorder.

Restoration of apparent clinical and biochemical normality depended upon supplementation with both D.C.A. and salt. Until full functional recovery or compensation is established, withdrawal of either promptly leads to relapse.

It is suggested that a primary renal tubular defect is unlikely because of the disappearance of azotaemia when the dehydration and the sodium deficit were corrected; the normal ability to concentrate urine and to undergo diuresis; and of the normal salt-retaining response to corticotrophin or desoxycorticosterone.

Adrenocortical function other than the mineralocorticoid effect appeared to be normal both by clinical examination and laboratory investigation. A fractional adrenocortical insufficiency confined to its mineralo-corticoid activity, whether primary or secondary, is postulated. This may reflect a temporary insufficiency of aldosterone synthesis, a pure hypoaldosteronism of infancy, which could be secondary to a temporary upset, or delayed maturation of a presiding diencephalic integration.

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