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Aldosterone Secretion Rate in Congenital Adrenal Hyperplasia. A Discussion of the Theories on the Pathogenesis of the Salt-losing Form of the Syndrome *

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The most common form of the congenital adrenal hyperplasia syndrome is caused by an inefficient enzymatic hydroxylation of the adrenal steroids at the 21 position (1-4). The symptoms of this disease can be explained by a deficiency in cortisol secretion resulting in an increased ACTH output and an overproduction of androgens and cortisol precursors by the hyperplastic adrenals (5, 6). About a third of these patients manifest a marked tendency to sodium loss and potassium retention (7). The pathogenesis of this phenomenon has not yet been fully understood, and three major hypotheses have been advanced.

The first was suggested by Crigler, Silverman, and Wilkins (8), who observed an increase in sodium diuresis in patients treated with ACTH (1, 9), as well as a decreasing requirement for desoxycorticosterone acetate (DOCA) when they were treated with cortisone or corticosterone (8). These authors interpreted their results as suggesting the secretion of sodium-losing hormones by the patients' adrenals. Earlier, Darrow (10) had noted that patients with congenital adrenal hyperplasia and salt loss required amounts of DOCA or salt, or both, which were larger than those needed by Addisonian patients. Barnett and

McNamara (11) showed that the electrolyte disturbance in adrenal hyperplasia was different from that observed in patients with Addison's disease. All these findings were interpreted as suggesting the secretion of a salt-losing hormone or of a pattern of steroids conducive to salt loss in congenital adrenal hyperplasia. Several attempts to identify a sodium-losing factor in the patients' urine have failed (12-14).

Another explanation was advanced by Bongiovanni and Eberlein who pointed out that both the salt-losing and the nonsalt-losing forms of congenital adrenal hyperplasia are caused by the same hydroxylation defect in the adrenal glands, the salt-losing form having an almost complete deficiency (15). They suggest that "a minimal amount of hydrocortisone is required for aldosterone to exert its metabolic action in man" (16). The untreated salt-losing patients would produce no cortisol or related corticoids, and therefore, aldosterone could be produced normally but its action would not be manifested. The total lack of cortisol secretion would also explain the need of large amounts of DOCA for the treatment of these patients.

Blizzard, Liddle, Migeon, and Wilkins (17) studied aldosterone excretion in patients with congenital adrenal hyperplasia. They found low to normal aldosterone excretion in salt-losing patients with no increase on salt deprivation. Most of the patients with the nonsalt-losing form had an increased excretion of aldosterone with a further increase on salt deprivation. These findings were interpreted as indicating that the salt loss was due to an inadequate aldosterone production. Furthermore, the high aldosterone excretion in the nonsalt losers led these authors to suggest that a

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"sodium-losing" factor was produced by the adrenals of the patients with adrenal hyperplasia, but that compensation occurred only if aldosterone could be secreted above the normal level. The data mentioned above (17) did not confirm earlier results of Prader, Spahr, and Neher (18), but generally agreed with studies published later by De Graeff and Moolenaar (19) and Mattox, Hayles, Salassa, and Dion (20).

Urinary excretion of aldosterone does not always reflect its secretion rate. The availability of an isotope derivative dilution method for measuring the aldosterone secretion rate rather than its excretion enabled us to reinvestigate this problem in a more appropriate manner.

Bryan, Kliman, and Bartter (21), using a similar method, studied five patients with adrenogenital syndrome of the salt-losing type who were receiving cortisol or prednisolone. The aldosterone secretion rates were extremely low when patients were receiving adequate sodium replacement, and with sodium depletion the secretion rates increased

only slightly. In the present investigation, most of the patients were studied at an early age, before the original adrenal crisis and without any sort of treatment.

Methods

Experimental subjects. Seven patients with the salt-losing form of congenital adrenal hyperplasia and 11 patients with the nonsalt-losing form of the disease were studied.

In the patients with the nonsalt-losing form, who were 2 years and eight months to 44 years of age, the criteria for diagnosis were those described by Wilkins (7): increased urinary excretion of 17-ketosteroids (KS) and pregnanetriol, which returned to normal under cortisone therapy, and advanced bone age and height age in the younger patients, pseudohermaphroditism, positive sex chromatin pattern, and progressive masculinization in females, and macrogenitosomia praecox in males. Patients 1, 2, 4, 5, 6, 10, and 11 had never been treated with cortisone. Patients 3, 8, and 9 were studied after 5 to 10 years of continuous cortisone treatment, whereas Patient 7 was studied after stopping treatment for about 6 months. In the patients with the salt-losing form, the criteria for diagnosis were those described by Wilkins (7). The uri-

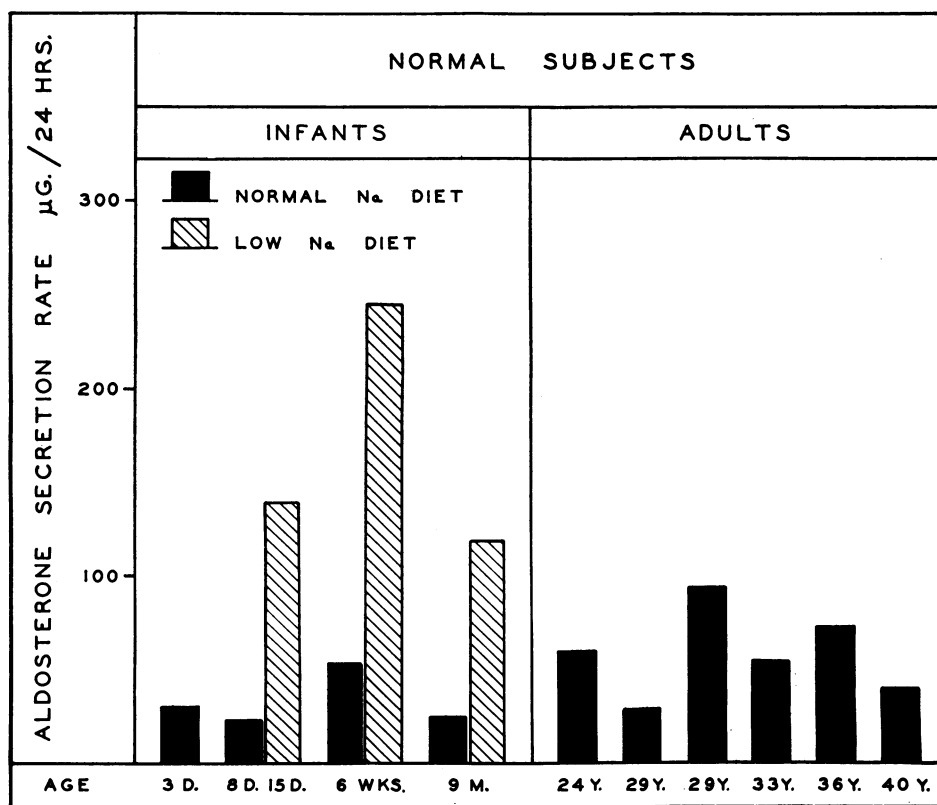


FIG. 1. ALDOSTERONE SECRETION RATE IN NORMAL INFANTS AND ADULTS.

TABLE I
Aldosterone secretion rates (ASR) in simple virilizing congenital adrenal hyperplasia

Patient	No.	Sex	Age	Na diet		Treatment		ASR	
				days	mEq/day	$\mu\text{g/day}$	$\mu\text{g/day}$		
S.J.	1	F	2 $\frac{8}{12}$		Ad lib.		None	294	
					Ad lib.	7 days	Cortisone	100 im	84
G.	2	F	3		Ad lib.		None	312	
K.M.	3	M	11		Ad lib.	10 yrs	Cortisone	50 p.o.*	113
R.P.	4	M	12	5	100		None		269
				11	100	5 days	Decadron	1.0 p.o.	269
				20	100	16 days	Decadron	1.0 p.o.	47
J.P.	5	F	16	7	85		None		184
				4	9		None		628
				7	85	7 days	Decadron	1.25 p.o.	213
				3	9	10 days	Decadron	1.25 p.o.	511
				3 mos and then 4 days	Ad lib.	3 mos and then 4 days	Cortisone	37.5 p.o.	
			85		Decadron	1.25	73		
J.R.	6	F	17		Ad lib.		None	256	
W.D.	7	M	18		Ad lib.		None	345	
M.D.	8	M	19		Ad lib.	5 yrs	Cortisone	50 p.o.	111
P.D.	9	F	22		Ad lib.	6 yrs	Cortisone	37.5 p.o.	106
B.H.	10	F	24	5	9		None		306
				5	45	5 days	Cortisone	100 im	330
				5	9	10 days	Cortisone	100 im	434
M.H.	11	F	44	2	119		None		350
				5	9		None		600

* Orally.

nary excretion of 17-KS was increased in five of the seven patients (3.6 to 8.6 mg per 24 hours, the normal values in our laboratory being up to 2 mg during the first 3 weeks of life). The two other patients who had urinary 17-KS of 2.6 and 2.7 mg had elevated excretion of urinary pregnanetriol (2.6 and 3.6 mg per 24 hours). The six female patients had ambiguous external genitalia with positive sex chromatin pattern. Two of the patients (no. 12 and 18) had a sibling with diagnosed congenital adrenal hyperplasia of the salt-losing type. They all developed a spontaneous typical adrenal crisis at 7 to 18 days of age except Patient 18, who went into a negative sodium balance only when placed on a low sodium diet, the serum electrolytes becoming abnormal on day 5 of this diet.

The results obtained in patients with congenital adrenal hyperplasia were compared with those found in four normal infants and six normal adults.

Method of measurement of aldosterone secretion rate. A modification of the double isotope derivative dilution method of Kliman and Peterson (22) was used in the present study. Details about the mode of injection of 1,2-H³-d-aldosterone, the urine collection, the purification of the urinary 3-oxo-conjugate of aldosterone, the determination of the specific activity of 1-C¹⁴-acetic anhydride, the radioactivity measurements, and the calculation of the secretion rate have been published elsewhere (23, 24).

Sodium and potassium balances. Patients receiving a known amount of sodium and potassium in their diets

were studied in a metabolic ward. In those cases, sodium and potassium excretion in urine was determined. Sodium and potassium excretion in feces was measured only in the patients with the salt-losing form of the syndrome. In this group of subjects, balance studies were carried out from the time of admission in the hospital until the end of studies of aldosterone secretion. The values mentioned in the text pertain to the balance during the day of study under consideration.

Serum electrolytes were determined routinely.

Results

Normal subjects (Figure 1). In adult subjects, 24 to 40 years of age, the aldosterone secretion rate on an uncontrolled sodium diet ranged from 29 to 95 μg per 24 hours. Four infants, 3 days, 8 days, 6 weeks, and 9 months of age had an aldosterone secretion rate of 32, 22, 54, and 25 μg per 24 hours, respectively, while on a normal sodium diet. The last three infants were placed on a diet containing 3, 6, and 15 mEq of sodium per day. On day 5 of such a diet, the aldosterone secretion rate was 139, 246, and 120 μg per 24 hours, respectively.

Nonsalt-losing form of congenital adrenal hyperplasia (Table I). Seven untreated patients (Cases

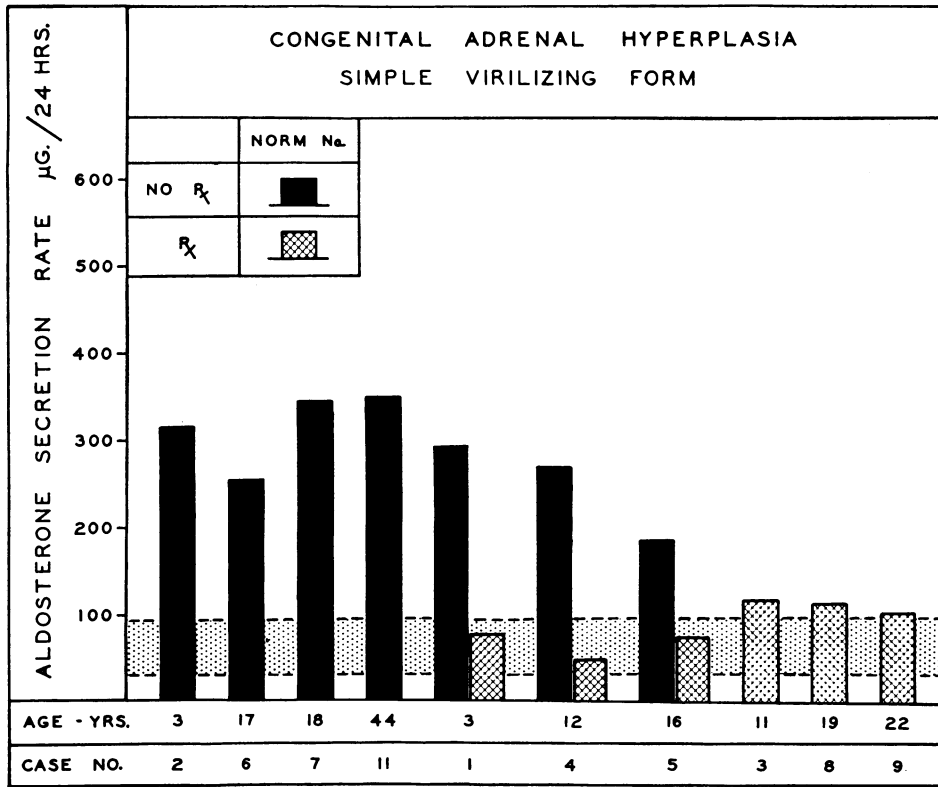


FIG. 2. ALDOSTERONE SECRETION RATE IN TEN PATIENTS WITH THE SIMPLE VIRILIZING FORM OF CONGENITAL ADRENAL HYPERPLASIA. All the patients presented in this Figure were on a normal sodium diet, and they were either untreated or had been treated for at least 7 days (the shaded area represents the range of variation of aldosterone secretion rate in six normal adults on a normal sodium diet). When patients were untreated, the secretion rates were greater than normal, whereas they came to the normal range after a week of treatment.

2, 6, 7, 11, 1, 4, and 5 of Figure 2) had aldosterone secretion rates ranging from 184 to 350 μg per 24 hours while on a regular sodium diet. These values are definitively higher than those found in our normal subjects.

In two untreated patients (Cases 5 and 11) aldosterone secretion rate was measured while on a 9-mEq sodium diet and was found to be increased further.

The effect of treatment (cortisone or dexamethasone) on aldosterone secretion rate was determined in several patients (Figure 2). In Patients 4 and 5 the determination was made after 5 and 7 days of treatment, respectively, and the values remained high. The determinations were repeated after 16 days and 3 months of therapy, respectively, and the values were found to be within the range for normal adult subjects. Patient 1 had a normal level after 7 days of treatment. In three

other patients (no. 3, 8, and 9), who had been treated continuously for 5 to 10 years, the values were also in the normal adult range. It would appear that more than a week of treatment may be required for the aldosterone secretion rates to reverse to normal values.

In Patient 10, it was possible to determine the aldosterone secretion rate only under the three following experimental conditions: no treatment and low sodium diet, treatment for 5 days and normal sodium diet, treatment for 10 days and low sodium diet. The lack of control value on no treatment and normal sodium diet, as well as the unfortunate timing of the studies during treatment, make interpretation of the data in this patient difficult.

Salt-losing form of congenital adrenal hyperplasia (Table II and Figure 3). In five patients (nos. 12, 13, 14, 16, and 18) aldosterone secretion rates were determined before any therapy. Pa-

TABLE II
Aldosterone secretion rate in salt-losing virilizing congenital adrenal hyperplasia

Patient	No.	Sex	Age	Na diet	Treatment	ASR	Age at time of first spontaneous crisis
			<i>days</i>	<i>mEq/24 hours</i>		<i>µg/24 hours</i>	<i>days</i>
L.A.B.	12	F	4	Regular (5.5)	None	15	7
G.	13	F	5	Regular (5.5)	None	8.5	8
S.E.	14	F	6	Regular (7.5)	None	4.0	9
			8	Regular (8.8)	None	11.0	
J.A.F.	15	F	13	Regular (15)	None	7.0	11
			15	Regular (10)	None	9.0	
C.R.	16	F	7	Regular (8)	None	29.0	10-11
			23	Regular (11.5)	None for 3 days	18	
R.H.	17	M	5 $\frac{8}{12}$ yrs	Regular (-)	None for 14 days	22	18
J.W.	18	F	5	Regular (8.0)	None	64	Treatment started before crisis
			9	Day 4 low (2.4 to 4.4)	None	61	

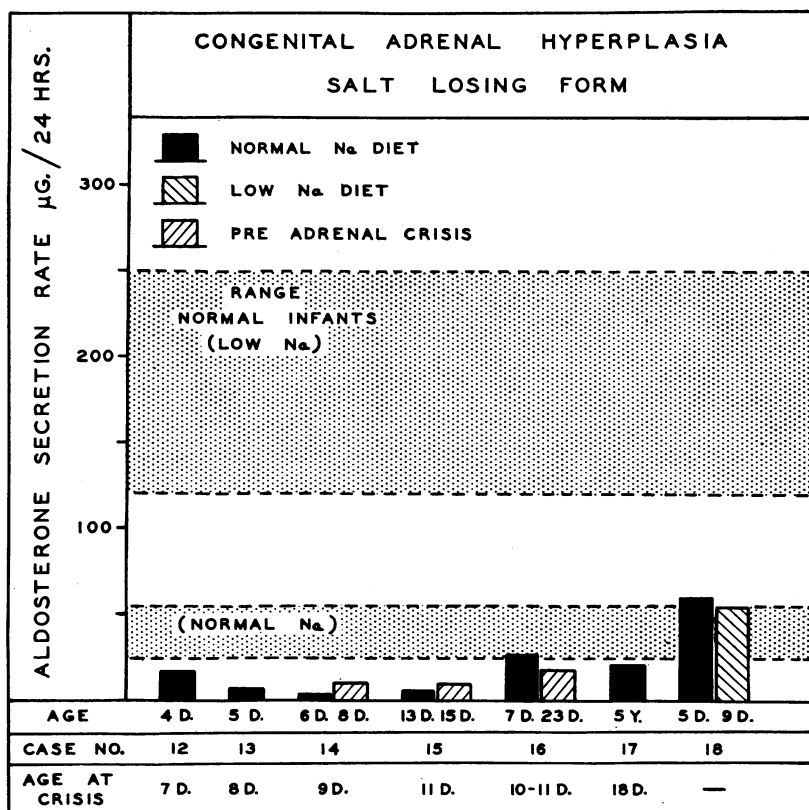


FIG. 3. ALDOSTERONE SECRETION RATE IN PATIENTS WITH THE SALT-LOSING FORM OF CONGENITAL ADRENAL HYPERPLASIA. The seven patients presented in this figure had no therapy and were receiving a normal sodium diet at the time of the study. A second study was carried out on Patients 14, 15, and 16 just before an adrenal crisis and on Patient 18 when on a low sodium diet. The patients are arranged according to the severity of their salt-losing tendency as determined by their age at the time of the first spontaneous adrenal crisis; Patient 18 did not go into crisis even when put on a low sodium diet for 4 days.

tient 15 had received only an intravenous NaCl infusion, and Patient 17 had been treated for 5 years and 8 months before withdrawal of therapy for 2 weeks.

Patient 12 had an aldosterone secretion of 15 μg per day on day 4 of life, when the serum electrolytes were normal (sodium, 146; potassium, 4.4; chloride, 105; CO_2 , 18.3).

Patient 13 had a sodium balance of -2 mEq per day and a potassium balance of $+5.8$ mEq with serum sodium equaling 142 mEq per L and potassium equaling 5.5 mEq per L when the aldosterone secretion rate was 8.5 μg on day 5 of life. She had a spontaneous crisis at 8 days of age.

Patient 14 had a sodium balance of -6 mEq per day and a potassium balance of $+3.4$ mEq per day with serum sodium equaling 143 mEq per L and potassium equaling 5.4 mEq per L when the aldosterone secretion rate was 4 μg on day 6 of life. On day 8, the sodium and potassium balances were similar, but serum electrolytes were sodium = 136 mEq per L and potassium = 6.9 mEq per L, and there was a definite deterioration of the clinical condition. The aldosterone secretion then was 11 μg , and acute adrenal crisis occurred at the end of this test.

Patient 15, at age 10 days, had a negative sodium balance (-5.1 mEq per day) with serum sodium equaling 134 and potassium equaling 8.2 mEq per L. The next day iv NaCl was administered bringing the serum sodium to 141 mEq per L and potassium to 7.1 mEq per L. The iv NaCl administration was tapered and stopped on day 13. On that day the sodium balance was -5.95 mEq and the potassium balance $+1.3$ mEq. The serum sodium and potassium were 138 and 6.5 mEq per L, and the aldosterone secretion rate was 7 μg . On day 15, when the electrolytes were similar but the clinical condition was deteriorating rapidly, the aldosterone secretion rate was 9 μg . The patient went into acute crisis as the test was terminated.

Patient 16 was doing well at 7 days of age on a regular formula and no treatment (serum sodium, 141, potassium, 8.1 mEq per L). The aldosterone secretion rate was 29 μg at that time. Three days later, the serum sodium had fallen to 125 mEq per L, whereas the other blood chemistries were potassium, 7.6 mEq per L; chloride, 112; CO_2 , 12; and blood urea nitrogen, 27 mg per 100 ml. The patient was found to have *Escherichia coli* (100,000

colonies per ml) in the urine culture and required treatment with iv NaCl and Solu-Cortef, im DOCA, and Chloromycetin. At 20 days of age the patient was much improved, and all therapy was stopped. Three days later, at age 23 days, the aldosterone secretion rate was 18 μg with serum sodium equaling 129 mEq per L and potassium equaling 6.5 mEq per L.

Patient 17 had various episodes of dehydration at 18 days and 6 and 7 months of age. He received intermittent treatment with DOCA, cortisone, and added salt, but could do fairly well for 2 to 4 weeks without any treatment. At 8 months his urinary 17-KS (3.5 to 5.3 mg per 24 hours) and pregnanetriol (2.9 mg per 24 hours) were found to be elevated. It was decided that the patient had a definite but mild, salt-losing tendency. Two 125-mg DOCA pellets were implanted and 2 g of salt was added daily to the diet along with the administration of 25 mg im cortisone every third day. Later in life, the therapy was changed to oral cortisone, 0.05 to 0.25 mg of Florinef, and salt ad libitum. At 21 months, a spinal cord lipoma at $\text{C}_2\text{-T}_4$ was partially removed. At 3 years, the tumor recurred, and a second partial removal was carried out. At about 4 years, the patient developed asthmatic attacks. At 5 years and 8 months of age, treatment was stopped for 14 days before the determination of the aldosterone secretion rate, which was found to be 22 μg . The serum electrolytes at that time were normal.

In Patient 18, at 5 days of age, the sodium balance was -0.46 mEq, and the potassium balance $+2.11$ mEq, whereas the serum electrolytes were sodium, 138 mEq per L; potassium, 6.1 mEq per L; chlorides, 105; and CO_2 , 21. On that day the aldosterone secretion rate was 64 μg . For the next 4 days the patient was placed on a 2.4- to 4.4-mEq sodium diet, and on day 4 of this regimen the sodium balance was -2.6 mEq and the potassium balance $+0.25$ mEq with serum sodium equaling 130 mEq per L, potassium equaling 5.1 mEq per L, chlorides equaling 90, and CO_2 equaling 20. The patient showed no signs of dehydration except for a 90-g weight loss. At that time, the aldosterone secretion rate was 61 μg showing no change in secretion despite a 50% decrease in sodium intake and a slightly negative sodium balance. The next day the serum sodium and potassium were 128 and 7.0 mEq per L, respectively, and im

DOCA was administered. This case probably represents an intermediate state between nonsalt losers and frank salt losers.

Discussion

In previous studies on aldosterone excretion in patients with congenital adrenal hyperplasia (17–20), conclusions were drawn on the assumption that aldosterone excretion is proportional to its secretion. This assumption is not always valid (25), but it seems to be generally justified in congenital adrenal hyperplasia. It must be noted, however, that the studies of aldosterone excretion were not always clear-cut because of the limitations of the methods used. On the other hand, the present work on aldosterone secretion gives a clearer picture of the relationship between the symptoms of the adrenogenital syndrome and the rate of production of aldosterone.

Aldosterone secretion rate in normal infants.

The secretion rate of cortisol in man was found to be directly related to the body surface area (26, 27). Cortisol secretion in normal infants over 5 days of age and adults up to 48 years is 12.0 ± 2.0 mg per m² per 24 hours. The actual secretion rate of cortisol thus increases with age from an average of 3.1 mg per 24 hours in infants to an average of 19.2 mg per 24 hours in adults. However, the secretion rate of aldosterone does not seem to follow the same pattern since we could not demonstrate a relation between aldosterone secretion rate and age. We have found the aldosterone secretion rate of infants and adults to be in the same range. Presently, the only other report of values in children is by Bryan, Kliman, and Bartter (21), who studied two normal subjects, aged 4 months and 2 years, and found their aldosterone secretion rate to be 112 and 26 μ g per 24 hours, respectively.

These findings could have been surmised from the fact that the dosage of DOCA required by young Addisonian and congenital adrenal hyperplasia patients is at least equal to, and sometimes greater than, that required by adult patients. In addition, the dosage of salt-retaining steroid required by young patients with these conditions does not increase with age (7).

Aldosterone secretion rate in patients with the nonsalt-losing form of congenital adrenal hyperplasia. In all our untreated patients, the aldosterone secretion rate was above the normal range.

We have found similar values in patients with clinical signs of hyperaldosteronism (28), yet none of the patients with the nonsalt-losing form showed clinical manifestations of the syndrome of primary hyperaldosteronism. An antagonistic factor would appear to counteract the sodium-retaining and potassium-losing effects of the increased amounts of aldosterone secreted by these patients.

Treatment with cortisone or Decadron lowered the values in Patients 1, 4, and 5. Three other patients (Cases 3, 8, and 9) on long-term treatment also had a normal rate (Figure 2). Yet the lowering of the aldosterone secretion was not accompanied by any disturbance of serum electrolytes. It must be assumed, therefore, that the secretion of the antagonistic factor was lowered at the same time as that of aldosterone. Indeed, the increased production of this factor could be the primary cause for a compensatory increase in the aldosterone secretion, and its lowering by treatment could be the mechanism by which aldosterone secretion decreased to normal.

The nonsalt-losing patients can further increase their aldosterone secretion when placed on a low sodium diet, enabling them to maintain their electrolyte homeostasis.

Aldosterone secretion rate in patients with the salt-losing form of congenital adrenal hyperplasia.

The rates in the untreated patients with the salt-losing form of the disease varied from very low to normal values, being lower in the patients with the greater salt-losing tendency, and increasing towards normal in those with the milder form of the disease. An inability to conserve sodium in the unstressed state could be expected in the patients with low aldosterone secretion rates but not in those with normal rates, unless an antagonistic factor counteracts the effects of aldosterone.

The salt-losing patients differ from the nonsalt-losing patients by their inability to increase their aldosterone secretion rate when depleted of sodium. Indeed, this inability is probably the cause of their salt-losing tendency.

Theory. A deficiency of 21-hydroxylation has been reported in both the nonsalt-losing and the salt-losing forms of congenital adrenal hyperplasia (1–4). Cortisol and aldosterone, the two biologically significant steroids secreted by the human adrenal cortex, require 21-hydroxylation for their biosynthesis. Since cortisol secretion is normally

many times greater than that of aldosterone, a limited 21-hydroxylation deficiency might lower the production of the former without affecting the secretion of the latter. The 21-hydroxylation deficiency is more marked in the salt-losing patients (15) although never complete (26).

An increased production of various cortisol precursors is a constant feature of congenital adrenal hyperplasia. Two of these precursors, progesterone (29-31) and 17 α -hydroxy-progesterone (32), are aldosterone antagonists, capable of bringing about negative sodium balance in patients with impaired aldosterone production. Other intermediates may well have a similar effect. The nonsalt-losing patients have a relatively milder 21-hydroxylase defect and are therefore able to compensate for these antagonists by an increased secretion of aldosterone. However, in patients with a more severe deficiency, aldosterone production is also affected. Whenever these patients are unable to secrete enough aldosterone to maintain sodium homeostasis they become salt losers. It would appear that the nonsalt-losing and the salt-losing forms of congenital adrenal hyperplasia are not two different entities but rather one entity with a full spectrum of variation of the degree of severity.

The treatment with glucocorticoids of patients with congenital adrenal hyperplasia lowers the secretion of the cortisol precursors (7), which are aldosterone antagonists. A decreased secretion of the aldosterone antagonists will bring about a decreased aldosterone secretion in the nonsalt-losing patients. In the mild salt losers, cortisone treatment alone can sometimes control the electrolyte disturbances (7). One could theorize that these subjects (such as our Patient 18) have an aldosterone secretion rate in the normal range when untreated. Treatment with cortisone, by lowering the secretion of the antagonists, would enable these patients to achieve sodium homeostasis. In patients with an almost complete 21-hydroxylase deficiency, aldosterone secretion is insufficient even when the production of antagonists is lowered by treatment. These patients require additional treatment with mineralocorticoids.

Summary

Aldosterone secretion rates were measured in patients with congenital adrenal hyperplasia. In

patients with the nonsalt-losing form the aldosterone secretion rates were above the normal range and could be further increased by a low sodium diet. Treatment with glucocorticoids brought the aldosterone secretion to the normal range. In patients with the salt-losing form of the syndrome, aldosterone secretion rates were below the normal range in the severe cases and normal in the milder cases. However, there was no increase on low sodium diet.

The salt-losing phenomenon in congenital adrenal hyperplasia appears to be brought about by a combination of overproduction of aldosterone antagonists and decreased ability to synthesize aldosterone. The nonsalt losers have a mild enzymatic deficiency and are able to secrete enough aldosterone to compensate for antagonistic factors.

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