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Research Article

ADJUSTMENT TO ALDOSTERONE OR DESOXYCORTICOSTERONE ACETATE INDUCED SODIUM RETENTION IN PATIENTS WITH ADDISON'S DISEASE*

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Long term administration of aldosterone (1) or desoxycorticosterone acetate (DCA) (2) to normal subjects has been shown, in certain instances, to produce continued renal potassium loss but only transient sodium and chloride retention. This adjustment of the renal response to sodium-retaining adrenal steroids has been termed an "escape" (3) from the expected effects of these compounds, and is seen clinically in the absence of edema with primary aldosteronism. The mechanism of this "escape" from sodium retention, that occurs despite continued excess of steroid sodium-retaining substances, is unknown. Some findings have suggested that the adrenal gland may play a role by producing a substance which either promotes sodium excretion or inhibits the sodium-retaining effect of other hormones.

An adrenal cortical "salt-losing hormone" was postulated by Wilkins and Lewis (4) and Jailer (5) to explain renal salt loss in cases of congenital adrenal hyperplasia. Rosemberg (6) suggested that this might be explained by an aldosterone-inhibiting effect of certain 21-desoxypregnane steroids, and Klein and co-workers (7) reported that partially purified material from urine of patients with congenital adrenal hyperplasia caused increased urinary sodium excretion in rats. Recently, Neher, Meystre and Wettstein (8) reported the isolation of 3α,16α-dihydroxy-pregnan-20-one from patients with the adrenogenital salt-losing syndrome and demonstrated a salt-losing potential of this steroid in adrenalectomized rats. Increased renal sodium excretion has been related to several other steroid compounds as well. Thorn and co-workers (9) reported that patients with Addison's disease who conserved sodium, while receiving 5 mg. of DCA per day, showed an immediate increase in sodium excretion when 100 mg. of cortisone acetate per day was added. Progesterone has been shown by Landau and associates (10, 11) to result in natriuresis in normal subjects and treated patients with Addison's disease, and by Kagawa (12) to block the sodium-retaining effect of DCA in rats. Johnson (13) and Axelrod, Cates, Johnson and Luetscher (14) found that certain 11-oxycorticosteroids and 11-desoxycorticosteroids produced increased sodium excretion in water-loaded, adrenalectomized rats. A synthetic steroid-17-spirolactone, 3-(3-oxo-17β-hydroxy-4-androsten-17α-γ^1)-propionic acid α-lactone, and its 19-"nor" analog, counteract the sodium-retaining properties of DCA and aldosterone, possibly as a competitive inhibitor (15, 16). Neher and co-workers (17) have isolated another compound, 3β,16α-dihydroxy-allopregnan-20-one, from hog adrenals which, under certain biological conditions, also acts as a sodium-excreting factor.

Additional interest in the role of the adrenal gland in the "escape" was stimulated by the reports of severe edema in some patients with Addison's disease treated solely with DCA (18–23), in contrast to the response of normal subjects (1, 2). Also, in canine studies, Kovach and associates (24) reported that adrenalectomy prevented an expected increase in sodium excretion following intracarotid injection of hypertonic sodium chloride.

In the light of these observations, the following study of the "escape" mechanism in patients with Addison's disease given large amounts of aldosterone or DCA was undertaken. The data indicate that an adjustment to aldosterone or DCA

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induced sodium retention may occur in the absence of normal adrenal function.

MATERIAL AND METHODS

The five subjects of this study were three patients with Addison's disease of unknown etiology and two who had been completely adrenalectomized because of Cushing's syndrome with bilateral adrenal hyperplasia. The diagnosis of Addison's disease had been established clinically by low excretion of 17-ketosteroids (25) and 17-hydroxycorticosteroids (26), and by the absence of increased excretion of these steroids during administration of 25 units of adrenocorticotropic hormone (ACTH) intravenously over eight hours for two or three consecutive days. All had been maintained in good health with both cortisone and DCA or fluorohydrocortisone maintenance therapy, and were hospitalized on the Metabolic Ward for purposes of this study.

The subjects were given constant diets throughout the study. Body weight was determined under standard conditions at the beginning of each metabolic day. Urine was collected and stored at 5° C. Measurements were made of sodium and potassium by flame photometry with an internal standard and of creatinine by the Jaffé reaction following precipitation with Lloyd's reagent.

The aldosterone used in this study was synthetic *d,l*-aldosterone-21-monoacetate which has approximately 50 per cent of the activity of the natural product (kindly provided by Drs. Robert Gaunt and C. H. Sullivan, Ciba Pharmaceutical Products, Inc., Summit, N. J.). The authenticity of this material was tested by paper chromatography before and after enzymatic hydrolysis. Recovery of steroid with the characteristics of aldosterone was consistent with a pure compound with the exception that a small amount of the aldosterone was initially not acetylated. It was administered intramuscularly in sesame oil in divided doses at eight hour intervals. DCA was administered intramuscularly every 12 hours. Vasopressin (Pitressin®) was given to one patient subcutaneously in aqueous suspension every eight hours.

Although endogenous adrenal corticosteroid secretions were not a factor in these studies, cortisone given as maintenance therapy could not be completely eliminated. The studies were designed with variations in cortisone dosage to eliminate its importance to a degree compatible with the health of the subjects.

PROCEDURE AND RESULTS

Study I: Aldosterone with continued cortisone therapy (Figure 1, Table I)

W.D., a 64 year old male, was given 3 mg. of *d,l*-aldosterone monoacetate while being maintained with 50 mg. of cortisone daily. Sodium intake was 174 mEq., chloride, 182 mEq. and potassium,

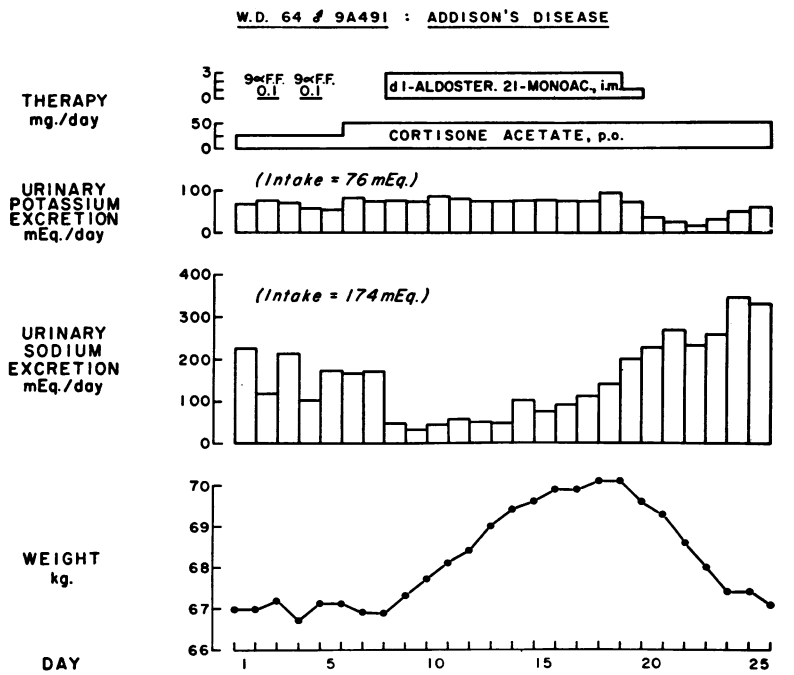

FIG. 1. ALDOSTERONE WITH CONTINUED CORTISONE THERAPY

The "escape" from renal sodium excretion began on the seventh day of aldosterone administration.

TABLE I

Metabolic data on Subject W.D.

Day	Body wt.	Urine					Blood			Blood pressure	Therapy		
		Volume	Na	K	Cl	C_{cr}*	Na	K	Cl		Cortisone	F.F.†	Aldosterone‡
	Kg.	*ml./da.*		*mEq./da.*		*ml./min.*		*mEq./L.*		*mm.*		*mg./da.*	
1	67.0	1,740	226	68	207	113	146	4.5	103	116/64	25		
2	67.0	1,220	119	78	145					120/70	25	0.1	
3	67.2	2,110	213	71	222	128	142	4.8	111	124/64	25		
4	66.7	1,250	103	57	136					120/74	25	0.1	
5	67.1	1,880	171	56	188	124	145	4.3	107	124/68	25		
6	67.1	1,400	166	82	178					122/72	50		
7	66.9	2,050	172	75	178	115	140	4.1	107	122/76	50		
8	66.9	960	48	76	103	140	138	3.9	111	118/62	50		3
9	67.3	1,320	32	73	79	121	140	4.1	108	132/72	50		3
10	67.7	1,420	45	86	85	133	141	3.8	113	140/76	50		3
11	68.1	1,360	58	80	106	125	144	4.0	111	164/88	50		3
12	68.4	800	51	75	82	136	146	3.6	109	160/88	50		3
13	69.0	1,020	47	76	97	141	139	3.9	107	144/80	50		3
14	69.4	1,820	101	76	155	132	135	3.9	110	148/80	50		3
15	69.6	1,520	75	77	132	129	134	3.9	109	160/84	50		3
16	69.9	1,160	91	75	132	149	137	3.5	114	164/90	50		3
17	69.9	1,560	111	75	164	130	136	3.8	111	180/90	50		3
18	70.1	2,030	138	114	165	127	143	3.6	113	168/80	50		1
19	70.1	2,120	200	73	205	138	141	3.7	113	170/82	50		
20	69.6	2,140	226	37	214	136	148	3.9	111	160/76	50		
21	69.3	2,200	268	26	260	121	142	3.6	109	158/78	50		
22	68.6	1,680	230	18	213	127	142	3.8	106	148/82	50		
23	68.0	2,020	259	31	240	118	138	4.1	101	150/78	50		
24	67.7	1,900	346	47	270	125	138	3.9	114	154/76	50		
25	67.4	1,780	332	59	297	112	138	3.5	108	140/72	50		

* Corrected to 1.73 M.².
† 9-α-Fluorohydrocortisone.
‡ *d, l*-Aldosterone-21-monoacetate.

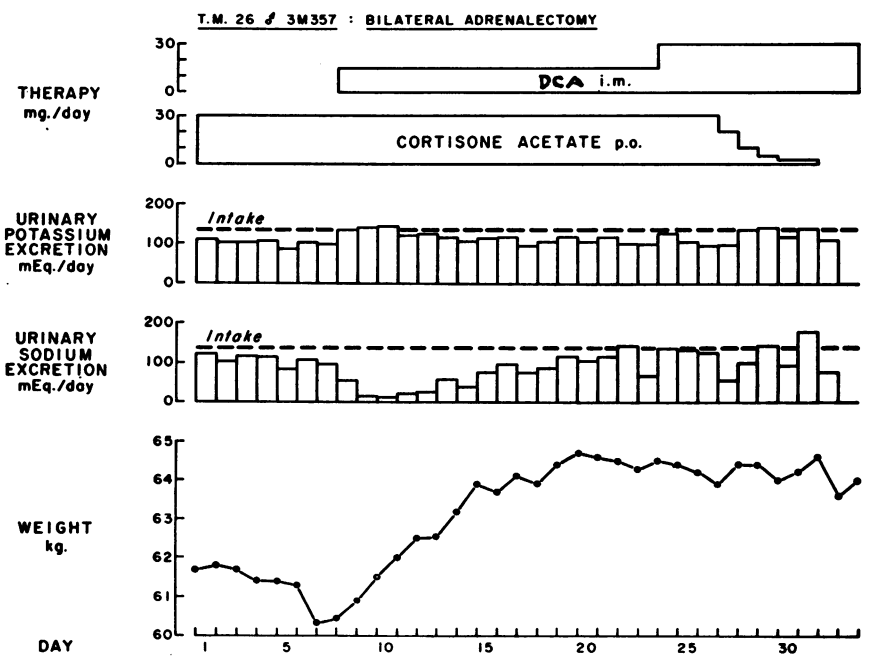

FIG. 2. CORTISONE WITHDRAWAL AFTER THE "ESCAPE" FROM DCA

Urinary sodium excretion was not significantly affected by doubling the amount of DCA administered or by gradual reduction of cortisone.

76 mEq. daily. Prior to the administration of aldosterone, sodium retention alternated with increased sodium excretion as the result of 0.1 mg. of 9-α-fluorohydrocortisone given every other day. When aldosterone was administered, sodium excretion promptly diminished and remained between 32 and 58 mEq. per day for six days, accompanied by rapid weight gain. Chloride retention also occurred. Following a weight increase of 2.5 Kg., sodium chloride excretion gradually increased and the rate of weight gain diminished despite continued aldosterone administration. A moderate elevation of blood pressure persisted during the period of increased weight. After omission of aldosterone, there was potassium retention, increased sodium and chloride excretion and a loss of weight. There were no significant variations in endogenous creatinine clearance.

Study II: Cortisone withdrawal after "escape" from DCA (Figure 2, Table II)

In this study, the mineralocorticoid was increased and the glucocorticoid decreased after the "escape" from sodium chloride retention had occurred. T.M., a bilaterally adrenalectomized male, 26 years of age, received 136 mEq. of sodium, 145 mEq. of chloride and 138 mEq. of potassium daily. Maintenance hydrocortisone, 30 mg. daily, was given initially. During the first seven days of DCA administration, sodium excretion was 12 to 56 mEq. per day and there was a weight gain of 3.5 Kg. Thereafter, sodium excretion was as great as before DCA and there was no further consistent weight gain. The daily excretion of sodium following the "escape" was not significantly affected by doubling the amount of DCA

TABLE II

Metabolic data on Subject T.M.

Day	Body wt.	Urine					Blood			Blood pressure	Therapy	
		Volume	Na	K	Cl	C_{cr}*	Na	K	Cl		DCA	Cortisone
	Kg.	*ml./da.*		*mEq./da.*		*ml./min.*		*mEq./L.*		*mm.*		*mg./da.*
1	61.7	1,850	121	110	134					122/80		30
2	61.8	1,280	102	102	115	107	140	5.0	108	124/80		30
3	61.7	2,000	118	102	126					120/80		30
4	61.4	1,700	117	105	132	117	143	4.9	106	124/70		30
5	61.4	1,330	83	87	106					118/80		30
6	61.3	1,940	108	101	121	124	138	4.9	104	110/60		30
7	60.3	1,540	96	99	115					120/72		30
8	60.5	2,080	55	133	74					112/80	15	30
9	60.9	1,080	14	140	30	136	139	5.1	105	116/74	15	30
10	61.5	1,260	12	141	29					114/65	15	30
11	62.0	1,420	21	120	56	115	136	4.5	109	100/60	15	30
12	62.5	1,400	26	122	63					92/56	15	30
13	62.6	1,380	58	113	99	146	135	3.9	110	110/60	15	30
14	63.4	1,140	40	104	52					130/70	15	30
15	63.9	1,440	77	112	82	123	139	4.1	111	120/60	15	30
16	63.7	1,240	96	113	117					110/60	15	30
17	64.1	1,120	76	92	92					126/72	15	30
18	63.9	1,300	86	103	100	125	144	4.4	109	132/80	15	30
19	64.4	1,400	115	116	132					124/80	15	30
20	64.7	1,260	104	104	130	136	141	4.0	107	140/90	15	30
21	64.6	1,560	115	115	128					134/90	15	30
22	64.5	1,590	142	99	160	134	142	4.4	108	130/84	15	30
23	64.3	1,180	69	98	82					127/74	15	30
24	64.5	1,360	136	123	147					140/92	30	30
25	64.4	1,560	132	102	162	120	144	3.9	105	142/94	30	30
26	64.2	1,640	123	92	138					136/84	30	30
27	64.9	980	54	93	82	141	138	3.8	106	140/80	30	20
28	64.4	1,600	100	131	123	138	141	3.8	109	142/84	30	10
29	64.4	1,980	143	138	161	116	134	3.9	105	138/80	30	5
30	64.0	1,300	52	92	68	128	147	4.3	110	122/80	30	2.5
31	64.2	1,400	92	115	103					130/76	30	2.5
32	64.6	2,400	178	137	152					144/80	30	2.5
33	63.6	1,620	85	107	99	139	135	3.8	108	120/74	30	
34	64.0	1,460	93	111	117	124	139	3.6	108	132/68	30	

* Corrected to 1.73 M.^{2}.

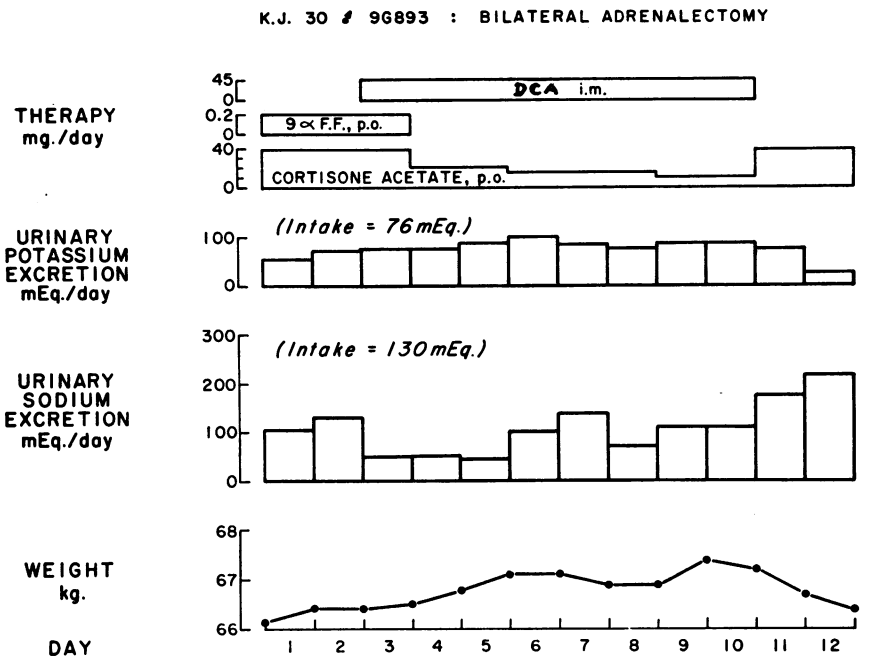

FIG. 3. CORTISONE WITHDRAWAL DURING "ESCAPE" FROM DCA

administered to 30 mg. daily, by gradual reduction of hydrocortisone, nor by total omission of hydrocortisone for one day. Endogenous creatinine clearance and urine volume were not significantly affected by the withdrawal of hydrocortisone. The observations could not be continued, however, due to a rapid decrease in the subject's sense of well-being when hydrocortisone was withdrawn.

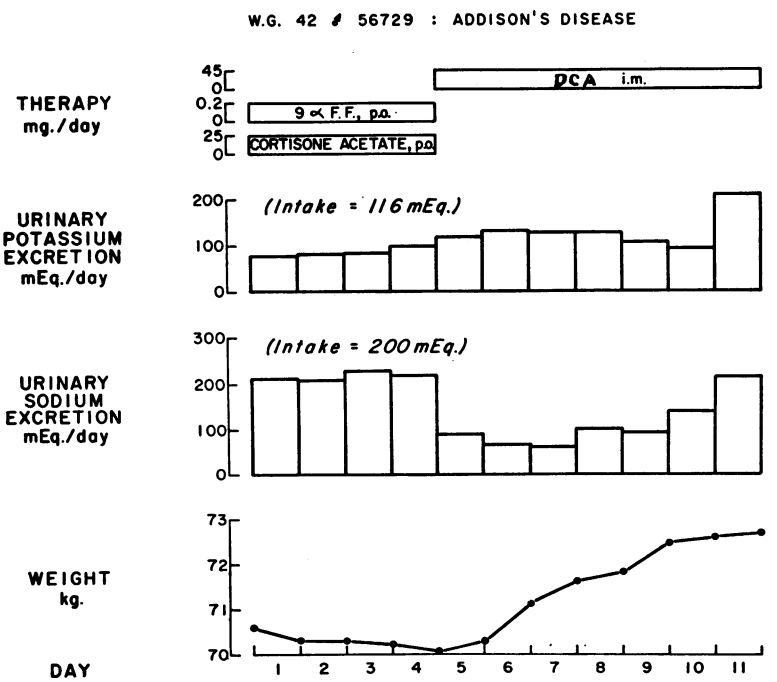

FIG. 4. DCA DURING COMPLETE CORTISONE WITHDRAWAL

The "escape" was conclusive on the sixth and seventh day of DCA administration.

Study III: Cortisone withdrawal during "escape" from DCA (Figure 3)

Another bilaterally adrenalectomized male, age 30, was given 45 mg. of DCA daily for nine days while cortisone was gradually diminished from 37.5 to 10 mg. daily. Sodium intake was 130 mEq. and potassium, 76 mEq. daily. Sodium excretion fell to 49 mEq. on the first day of DCA given in conjunction with 0.2 mg. of 9-α-fluorohydrocortisone, the maintenance level of mineralocorticoid in this case. On the fourth and fifth days of DCA, when only 15 mg. of cortisone was being given, sodium excretion increased to 100 and 137 mEq. per day. Thereafter a cyclic pattern of sodium excretion, previously seen during the "escape," continued despite further reduction of the cortisone dosage to 10 mg. per day. It is noteworthy that the "escape" occurred in this case after a weight gain of only 0.7 Kg. as compared to a weight gain of 2.5 to 3.0 Kg., as seen in normal subjects (1) and the other patients in this study. A probable explanation for this finding is that excess body sodium and water were already present when DCA was first given, due to daily use of 0.2 mg. of 9-α-fluorohydrocortisone as maintenance therapy. This explanation is supported by other studies which showed that the sodium-retaining effects of 9-α-fluorohydrocortisone were inversely related to the initial exchangeable sodium in patients with Addison's disease (27). Moreover, it has been observed that patients with Addison's disease, who are depleted of salt and water, gain weight in excess of 3 Kg. before achieving sodium balance when given large amounts of DCA.

Study IV: DCA during complete cortisone withdrawal (Figure 4)

Cortisone was completely withdrawn while the patient with Addison's disease, age 42, was given 45 mg. of DCA daily. Previous maintenance therapy had been cortisone, 25 mg. and 9-α-fluorohydrocortisone, 0.2 mg. daily. The diet in this study provided 200 mEq. of sodium and 116 mEq. of potassium per day. Sodium excretion was lowest, 62 mEq., on the third day of DCA administration and the "escape" was definite on the sixth day, after a weight gain of 2.3 Kg., when 142 mEq. of sodium was excreted. On the last day of DCA, 214 mEq. of sodium was excreted.

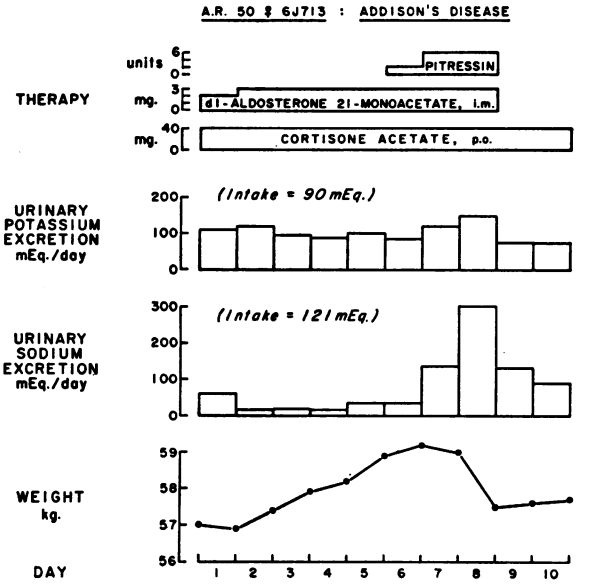

FIG. 5. PITRESSIN® DURING ALDOSTERONE AND CORTISONE ADMINISTRATION

Marked natriuresis and diuresis occurred when Pitressin® was given after five days of aldosterone administration.

Study V: Pitressin® during aldosterone and cortisone therapy (Figure 5)

A 54 year old woman with Addison's disease, while receiving 40 mg. of cortisone and 3 mg. of *d,l*-aldosterone acetate daily, was given aqueous Pitressin®. Sodium intake was 121 mEq. and potassium, 90 mEq. per day. Following a weight gain of 2 Kg., marked natriureses of 134 and 301 mEq. and diuresis occurred on the second and third days of Pitressin® administration despite continued aldosterone. It may be noted that neither weight gain nor water retention was apparent during the 24 hour periods of Pitressin® administration.

DISCUSSION

It was previously shown, in normal subjects receiving 3 to 6 mg. of *d,l*-aldosterone-21-monoacetate daily, that sodium and water retention ceased following weight gain of approximately 3 Kg. (1). Since the responses of the patients with Addison's disease in this study appear similar to

those seen in the normal subjects, it is unlikely that secretion of an adrenal cortical "sodium-excreting" hormone is responsible for the return to sodium balance which occurs during continued administration of sodium-retaining steroid.

Whether the "escape" phenomenon would occur or continue in all patients with Addison's disease treated solely with aldosterone or DCA cannot be determined from this study. Diminution or withdrawal of glucocorticoid therapy in three of the studies did not indicate that the "escape" depends on cortisone but the period of withdrawal from cortisone was not prolonged. Reports describing treatment of patients with Addison's disease with DCA alone indicate that many gained not more than 2 to 4 Kg. and did not become severely edematous despite administration of up to 40 mg. of DCA daily combined with large sodium chloride intake (28–32). However, several cases of massive edema and congestive heart failure have been attributed to DCA therapy (18–23). The number of complicating factors which may have prevailed make the interpretation of these cases difficult. Pre-existing cardiac or renal disease may have been present in some (19, 21, 23), and others were severely ill due to adrenal insufficiency. In this respect, it should be noted that continued sodium retention is not the normal response to a mineralocorticoid, and that patients with congestive heart failure, cirrhosis with ascites, or nephrosis, respond differently from normal subjects (33). These patients show virtually complete sodium retention, continuous weight gain without an "escape" and urinary potassium excretion not in excess of intake. Patients with pre-existing abnormal sodium retention and edema, or patients with low cardiac or hepatic reserve with a tendency to edema formation, would not be expected to "escape" from the sodium-retaining effects of aldosterone or other mineralocorticoids. It may be possible that severe, untreated glucocorticoid deficiency would result in abnormal renal function and continued sodium chloride retention during treatment with a mineralocorticoid. This is not to say, however, that an adrenal hormone is directly responsible for the "escape" phenomenon.

SUMMARY

Five patients with Addison's disease, in two due to bilateral adrenalectomy, received large amounts of aldosterone or desoxycorticosterone acetate while on constant diets. Glucocorticoid therapy was varied in the different patients as follows. It was held constant, gradually reduced after the "escape" from sodium retention, gradually reduced before and during the "escape," and completely omitted. In one study, Pitressin® was given with aldosterone. In each of these patients with Addison's disease, sodium chloride retention was transient and apparently was not acutely affected by change in glucocorticoid therapy. It is concluded that an adrenal cortical "sodium-excreting" hormone is not responsible for the "escape" from sodium retention that occurs despite continued administration of sodium-retaining hormone.

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