MECHANISMS OF IMPAIRED WATER EXCRETION IN ADRENAL AND PITUITARY INSUFFICIENCY. II. INTERRELATIONSHIPS OF ADRENAL CORTICAL STEROIDS AND ANTIDIURETIC HORMONE IN NORMAL SUBJECTS AND IN DIABETES INSIPIDUS *

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(Submitted for publication March 7, 1960; accepted May 16, 1960)

The impaired water diuresis of adrenal or pituitary insufficiency is completely corrected by the administration of cortisol and other glucocorticoid analogues (1–5). This correction results not from improved renal hemodynamics, altered tubular reabsorption of solutes, or removal of a nonosmotic (volume) stimulus to continued antidiuretic hormone (ADH) release, but probably from a direct effect of the steroid on the diluting segments of the nephrons (2, 6). This interpretation implies that the formation, release and inactivation of ADH are normal in the adrenal-insufficient subject. Most of the available data in humans would tend to confirm this implication (1, 2, 5–14). Others, however, have suggested that glucocorticoids may be either biological antagonists of ADH (15–19) or may improve the impaired water excretion in adrenal and pituitary insufficiency by correcting a defect in the metabolism of ADH (18, 20–22).

In the present investigation, the interrelationship between adrenal glucocorticoids and ADH was evaluated by observing the effect of the steroid on the parameters of water diuresis and antidiuresis. The experiments were designed to answer the following questions. What is the effect of acute and chronic administration of glucocorticoid on: *1*) maximal sustained water diuresis in normals and in patients with diabetes insipidus? *2*) the acute and sustained release of ADH from the neurohypophysis following both osmotic and nonosmotic stimuli? *3*) the rate of inactivation of circulating ADH following inhibition of its release from the neurohypophysis? and *4*) the renal action of endogenous and exogenous ADH? The results indicate that these steroids do not alter the release, inactivation, or action of ADH in normal individuals.

* This investigation was supported (in part) by Research Grant no. A-2972 from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., and by a grant from the Upjohn Company.

METHODS AND MATERIALS

Forty-three experiments were performed on 20 subjects. Sixteen were normal house staff physicians and laboratory technicians, two were patients in the euthyroid phase following I^{131} therapy of thyrotoxicosis, and two were well documented cases of idiopathic diabetes insipidus. All subjects were between the ages of 20 and 40. Each subject served as his own control in paired studies of the effects of exogenous glucocorticoids on water metabolism. The steroids given were cortisol, 150 to 200 mg, or 6-methyl-prednisolone (Medrol), 20 mg. Chronic administration consisted of giving the steroid orally for 4 to 5 days prior to and, in an intravenous drip, during the experiment. "Acute" administration consisted of giving the steroid during the experiment only. In some paired studies the steroid was given during the first study; in others the procedure was reversed.

The technique employed for attaining a maximal sustained water diuresis, the calculation of the parameters of diuresis and antidiuresis, and the chemical procedures used in this laboratory have been described previously (2). When the steroid was administered on the day of an experiment, it was given as a constant intravenous infusion of 20 mg of 6-methyl-prednisolone (3 mg per hour) or 100 mg of cortisol (15 to 20 mg per hour) throughout the experiment.

RESULTS

The effect of acute and chronic steroid administration on the parameters of maximal sustained water diuresis in normal subjects and in patients with diabetes insipidus (Table I)

When the adrenal steroid was given acutely, the control periods of maximal diuresis were com-

TABLE I

Effect of acute and chronic steroid administration on maximal sustained water diuresis *

Subject	Date	Exp.	Urine vol.	Urine conc.	Solute excr.	Free water clearance (C_{H_2O})	Inulin clearance (GFR)	PAH clearance (RPF)	Serum osmol.
			cc/min	*mOsm/kg*	*μOsm/min*	*cc/min*	*cc/min*	*cc/min*	*mOsm/kg*
			Chronic administration (normal subjects)						
1	9/11/58	A†	12.6	67	843	9.5	112	519	274
	9/18/58	B‡	18.4	69	1,266	13.9	110	520	280
2	12/14/57	B	29.4	78	2,293	21.1	173	738	275
	12/26/57	A	23.2	51	1,256	18.7	167	762	276
3	2/7/58	A	22.2	76	1,687	16.2	105		278
	2/21/58	B	22.4	48	850	19.2	100		275
4	4/21/59	B§	20.5	65	1,334	15.7	155	596	277
	4/28/59	A§	19.3	77	1,488	13.9	137	560	276
	5/15/59	B	20.5	44	902	17.2	129	586	271
5	11/21/58	A	13.2	56	739	10.6	90		279
	11/26/58	B	17.0	53	901	13.8	116		282
6	1/12/59	A	19.1	76	1,451	14.0	180	645	285
	1/16/59	B	22.2	60	1,330	17.5	164	695	286
7	2/10/59	A	11.7	78	913	8.5	125	500	282
	2/15/59	B	14.1	74	1,043	10.4	131	642	286
8	3/27/59	B§	21.1	75	1,586	15.7	134	579	290
	4/10/59	A	14.9	61	907	11.7	107	470	289
9	3/13/59	A	14.8	90	1,328	10.2	100	557	290
	3/18/59	B	18.0	72	1,296	13.7	138	565	295
10	8/1/59	B	19.1	41	783	16.4	150	816	291
	8/7/59	A	15.0	44	660	12.7	135	780	291
11	7/7/59	A	13.2	86	1,133	9.8	134	818	285
	7/16/59	B	18.8	52	980	15.3	134	880	275
	7/25/59	B	18.6	41	763	16.0	137	838	288
	9/20/59	A	18.7	58	1,085	14.7	144	881	270
12	7/17/59	B	18.0	61	1,098	14.0	138	799	272
	7/23/59	A	16.8	61	1,027	13.1	173	814	273
			Diabetes insipidus patients						
13	10/7/58	A	16.1	60	960	12.4	110	500	270
	10/12/58	B	24.5	42	1,029	21.0	120	580	287
14	10/31/58	A	16.2	49	795	13.2	160	740	260
	11/5/58	B	30.8	70	2,157	23.0	225	960	277
			Acute administration						
15	12/28/57	A	16.5	38	627	14.3	104		275
	12/28/57	B	18.2	50	910	14.8	100		280
16	11/19/57	A	15.8	88	1,390	10.8	148		280
	11/19/57	B	16.8	88	1,478	11.5	153		280
17	11/5/57	A	17.1	51	872	14.1	137		294
	11/5/57	B	17.5	54	945	14.3	142		295
18	4/15/57	A	16.8	62	1,042	13.3	228	733	298
	4/15/57	B	15.6	61	952	12.3	206	660	292

* All values represent the mean of two or three clearance periods at the height of the diuresis.
† A refers to control experiments (or periods in the acute studies) without steroid administration.
‡ B refers to experiments (or periods) following acute or chronic steroid administration.
§ These subjects received 6-methyl-prednisolone rather than cortisol.

pared with those periods during the 4 hours of continuous steroid infusion. In no instance did an augmentation of the maximal diuresis occur (Subjects 15–18). In contrast, following chronic administration of the steroid, 12 of the 14 subjects demonstrated a significant enhancement of the water diuresis, as measured by all parameters (Subjects 1, 2, 5, 7–11, 13 and 14) or by free water clearance (C_{H_2O}), and minimal osmolality (Subjects 3, 6, and 11–2 [1]). The water diuresis in Subject 4 was not enhanced with 6-methyl-prednisolone, but it was with cortisol. In six subjects (Subjects 2, 5, 8–10 and 14), the increase in renal hemodynamics and/or solute excretion

[1] The "2" represents the second paired experiment done on this patient.

was of such a magnitude as to contribute significantly to the augmented diuresis. While it is unlikely that the magnitude of the augmentation of the water diuresis in Subject 1 can be explained by the 50 per cent increase in solute excretion, the contribution of the latter cannot be ignored. In the remaining experiments (Subjects 3, 6, 7, 11–1, 11–2 and 13), the increment in free water clearance could not be explained by enhanced renal hemodynamics or solute excretion. The observations in Table I indicate that maximal water diuresis can be enhanced by the chronic administration of glucocorticoids in subjects with clinical as well as physiological diabetes insipidus (maximal sustained water load).

The effect of steroid administration on the acute and chronic release of ADH from the neurohypophysis following osmotic and nonosmotic stimuli (Table II and Figures 1 and 2)

A. Osmotic stimuli. When 400 ml of 5 per cent hypertonic saline was infused into two subjects during a maximal sustained water diuresis, the time of onset and the magnitude of the antidiuresis were not altered by chronic administration of cortisol (Subjects 19 and 20). The pattern of antidiuresis in a paired study is illustrated in Figure 1.

A chronic osmotic stimulus to the release of ADH was produced in two subjects by 24 hours of total restriction of fluid intake and the ingestion of a liquid-free diet. Chronic steroid administration did not lower the maximal urinary osmolality or the magnitude of the negative free water clearance ($T^c_{H_2O}$) following this period of hydropenia (Subjects 21 and 22).

B. Nonosmotic stimuli (Table III and Figures 2 and 3). The results of this group of experiments were difficult to interpret because of the variability of response of the subjects to the nonosmotic stimuli.

1. Inhalation of cigarette smoke during a maximal water diuresis. Nicotine is a strong stimulus to the release of antidiuretic hormone (23) and inhalation of cigarette smoke is a relatively reliable substitute for the parenteral administration of

TABLE II

The effect of chronic adrenal steroid administration on the acute and chronic release of ADH following an osmotic stimulus *

Subject	Date	Exp.	Urine vol.	Urine conc.	Solute excr.	Free water clearance (C_{H_2O})	Inulin clearance (GFR)	PAH clearance (RPF)	Serum osmol.
			cc/min	*mOsm/kg*	*μOsm/min*	*cc/min*	*cc/min*	*cc/min*	*mOsm/kg*
		Hypertonic saline during a maximal water diuresis							
19	12/14/57	B† Control	29.4	78	2,293	21.1	173	736	275
	12/14/57	Hypertonic salt‡	15.0	290	4,350	−0.8	217	878	275
	12/26/57	A§ Control	23.2	51	1,256	18.7	167	762	276
	12/26/57	Hypertonic salt‡	12.0	316	3,792	−1.4	178	800	283
20	7/17/59	B Control	18.0	61	1,098	14.0	138	799	272
	7/17/59	Hypertonic salt‡	1.6	706	1,165	−2.4	164	646	288
	7/24/59	A Control	16.8	61	1,027	13.1	173	814	273
	7/24/59	Hypertonic salt‡	3.0	593	1,791	−3.4	168	754	279
		Maximal antidiuresis following 24 hours of dehydration							
21	9/26/58	A	0.6	849	509	−1.3	150	600	270
	10/2/58	B	0.6	875	525	−1.3	143	562	270
22	1/13/57	A	0.6	1,055	634	−1.5	213		300
	1/15/57	B	0.5	1,065	532	−1.3	212		295

* All values represent the mean of two or three clearance periods at the height of the diuresis and the values from the period of maximal antidiuresis.

† B refers to experiments (or periods) following acute or chronic steroid administration.

‡ 400 ml of 5 per cent saline.

§ A refers to control experiments (or periods in the acute studies) without steroid administration.

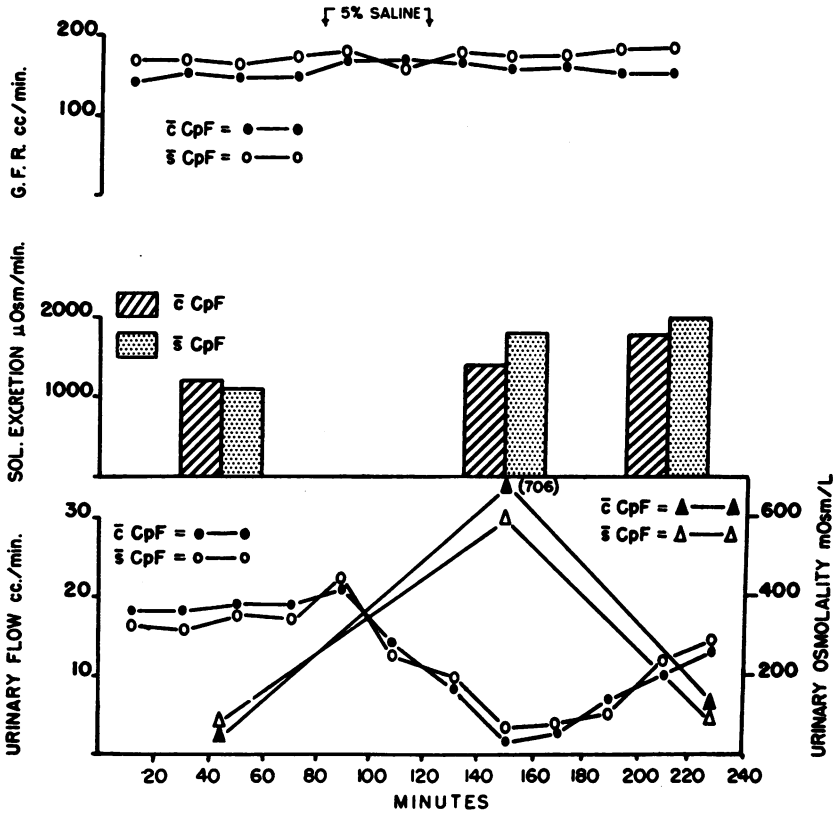

FIG. 1. THE EFFECT OF CORTISOL ADMINISTRATION ON THE ANTIDIURETIC RESPONSE TO AN INFUSION OF 5 PER CENT SALINE DURING A MAXIMAL SUSTAINED WATER DIURESIS (SUBJECT 20). The triangles refer to the osmolality of the urine. The figures in parentheses represent the maximal urinary osmolality.

nicotine tartrate or the pure alkaloid (23).[2] At the height of the sustained water diuresis, therefore, the subjects smoked and inhaled completely four cigarettes over a 10 to 20 minute period. The effect of smoking was subsequently observed for 2.5 hours. In Subjects 23 and 24, smoking caused a pronounced antidiuresis and significant hypertonicity of the urine. The magnitude and pattern of the antidiuresis and the pattern of return to maximal flow of urine was not altered by chronic administration of steroid. This is illustrated in Figure 2 for Subject 24. The marked antidiuretic response to nicotine observed in Subject 25 was not reproduced after 4 days of steroid ingestion. This difference could not be explained by altered renal hemodynamics or solute excretion. Nicotine inhalation without steroid administration caused only a moderate antidiuresis in Subject 26. This antidiuresis was due in part to a significant decrease in solute excretion, renal plasma flow (RPF), and glomerular filtration rate (GFR). When nicotine inhalation was repeated after chronic steroid administration, the antidiuresis was partially (6-methyl-prednisolone 4/21/59) or completely (cortisol 5/15/59) blocked. However, renal hemodynamics and solute excretion changed very little in the experiments done under the influence of the adrenal steroids.

The moderate antidiuresis caused by cigarette smoking in Subject 27 was not altered by chronic steroid administration.

2. Venous congestion of the lower extremities. Another nonosmotic stimulus to the release of ADH (24) was achieved by producing venous

[2] Although it was realized that the injection of nicotine would give the most consistent results, initial trials with parenteral administration produced such severe side reactions that it was considered inadvisable to continue this mode of administration.

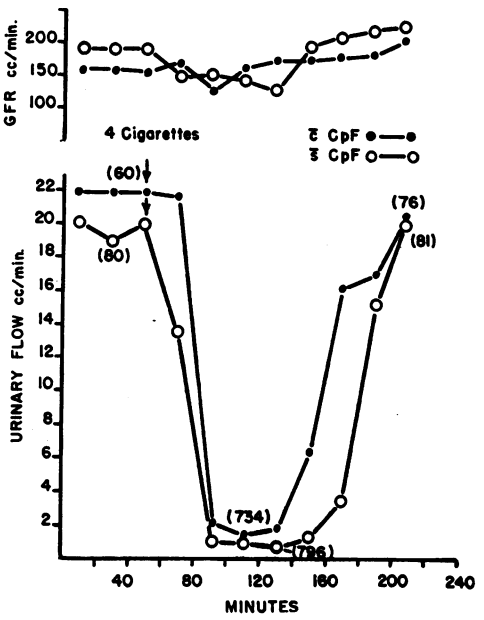

FIG. 2. THE EFFECT OF CORTISOL ADMINISTRATION ON THE ANTIDIURETIC RESPONSE TO CIGARETTE SMOKING DURING A MAXIMAL SUSTAINED WATER DIURESIS. The figures in parentheses represent the urinary osmolality.

obstruction of the lower extremities for 40 minutes by placing sphygmomanometer cuffs high on both thighs. Venous congestion was initiated after a sustained maximal diuresis had been achieved. The effects of congestion were observed for 2.5 to 3 hours. The moderate antidiuresis induced by cuffing in Subjects 28 and 29 was unaffected by chronic steroid administration (Figure 3). Venous congestion in Subject 30 markedly inhibited the water diuresis, and it appeared that administration of steroid on 7/16/59 and 7/25/59 "blocked" the effect of cuffing. However, when the experiment was repeated *without steroids* (9/20/59), venous congestion did not cause a significant antidiuresis (Table III). The effect of venous congestion upon water diuresis was thus not clearly altered by chronic administration of glucocorticoid.

Despite the variability in the release of ADH following these nonosmotic stimuli, the results do not suggest that the steroids significantly or regularly altered the responses.

The effect of steroid administration on the rate of inactivation of circulating ADH

The pattern of development of a maximal water diuresis and its subsequent disappearance was followed in two subjects. The intravenous infusion of 2.5 per cent glucose was stopped after two or three periods of maximal flow were obtained. Both subjects showed a comparable pattern of response. This is illustrated in Figure 4 for one of the subjects. It is evident that chronic steroid

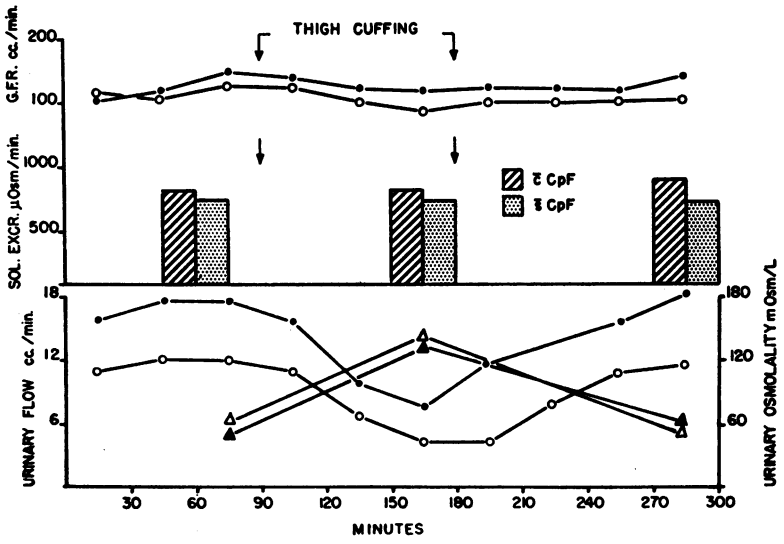

FIG. 3. THE EFFECT OF CORTISOL ADMINISTRATION ON THE ANTIDIURETIC RESPONSE TO VENOUS CONGESTION OF THE LOWER EXTREMITIES DURING A MAXIMAL SUSTAINED WATER DIURESIS. The open circles and triangles represent the control study; the closed, the study with steroid administration.

TABLE III

The effect of chronic adrenal steroid administration on the acute release of ADH following a nonosmotic stimulus *

Subject	Date	Exp.	Urine vol.	Urine conc.	Solute excr.	Free water clearance (C_{H_2O})	Inulin clearance (GFR)	PAH clearance (RPF)	Serum osmol.
			cc/min	*mOsm/kg*	*μOsm/min*	*cc/min*	*cc/min*	*cc/min*	*mOsm/kg*
			Cigarette smoking						
23	3/27/59	B† Control	21.1	75	1,586	15.7	134	579	290
	3/27/59	Nicotine	1.8	580	1,050	−1.9	148	599	278
	4/10/59	A‡ Control	14.9	61	907	11.7	107	470	289
	4/10/59	Nicotine	1.4	700	987	−2.1	108	481	279
24	1/12/59	A Control	19.1	76	1,451	14.0	180	645	285
	1/12/59	Nicotine	1.2	796	946	−2.2	175	672	283
	1/16/59	B Control	22.2	60	1,330	17.5	164	695	286
	1/16/59	Nicotine	1.2	734	888	−1.8	158	603	289
25	3/13/59	A Control	14.8	90	1,328	10.2	100	557	290
	3/13/59	Nicotine	1.3	589	760	−1.4	102	455	289
	3/18/59	B Control	18.0	72	1,296	13.7	138	565	295
	3/18/59	Nicotine	8.1	122	988	4.7	138	407	287
26	4/21/59	B§ Control	20.5	65	1,334	15.7	155	596	277
	4/21/59	Nicotine	9.6	101	975	6.1	141	507	275
	4/28/59	A Control	19.3	77	1,488	13.9	137	560	276
	4/28/59	Nicotine	4.2	156	645	1.9	116	445	274
	5/15/59	B Control	20.5	44	902	17.2	129	586	271
	5/15/59	Nicotine	19.6	47	921	16.3	126	531	273
27	2/10/59	A Control	11.7	78	913	8.5	125	500	282
	2/10/59	Nicotine	6.9	142	970	3.4	122	523	282
	2/15/59	B Control	14.1	74	1,043	10.4	131	642	286
	2/15/59	Nicotine	6.8	168	1,142	2.8	136	658	284
			Venous congestion of lower extremities						
28	9/11/58	A Control	12.6	67	843	9.5	112	519	274
	9/11/58	Cuffing	4.6	123	563	2.5	100	400	279
	9/18/58	B Control	18.4	69	1,266	13.9	110	520	280
	9/18/58	Cuffing	8.5	108	927	5.4	137	770	296
29	8/1/59	B Control	19.1	41	783	16.4	150	816	291
	8/1/59	Cuffing	4.6	113	523	2.9	123	653	296
	8/7/59	A Control	15.0	44	660	12.7	135	780	291
	8/7/59	Cuffing	7.4	56	414	6.0	130	690	291
30	7/7/59	A Control	13.2	86	1,133	9.8	134	818	285
	7/7/59	Cuffing	1.8	416	761	−0.8	155	778	285
	7/16/59	B Control	18.8	52	980	15.3	134	880	275
	7/16/59	Cuffing	11.9	61	726	9.6	135	773	285
	7/25/59	B Control	18.6	41	763	16.0	137	838	288
	7/25/59	Cuffing	15.4	42	645	13.1	135	885	288
	9/20/59	A Control	18.7	58	1,085	14.7	144	881	270
	9/20/59	Cuffing	15.8	60	948	12.3	151	770	270

* All values represent the mean of two or three clearance periods at the height of the diuresis and the values from the period of maximal antidiuresis.
† B refers to experiments (or periods) following acute or chronic steroid administration.
‡ A refers to control experiments (or period in the acute studies) without steroid administration.
§ This subject received 6-methyl-prednisolone rather than cortisol.

administration did not alter the characteristics of the water diuresis curve.

Two subjects received an infusion of the same lot of Pitressin (vasopressin, 200 mU per hour) at the height of the water diuresis. When maximal antidiuresis was achieved, the infusion of vasopressin was stopped and the return toward a maximal diuresis was observed. Both subjects showed a comparable response. This is illustrated for one subject in Figure 5. Chronic steroid administration did not alter the pattern of response to exogenous vasopressin. Similarly, the curve of urinary flow following release of endogenous ADH was not affected by the steroids (Figure 2). It is apparent from these experiments that the rate of "inactivation" of exogenous or endogenous ADH was not modified by prior ingestion of adrenocortical steroids.

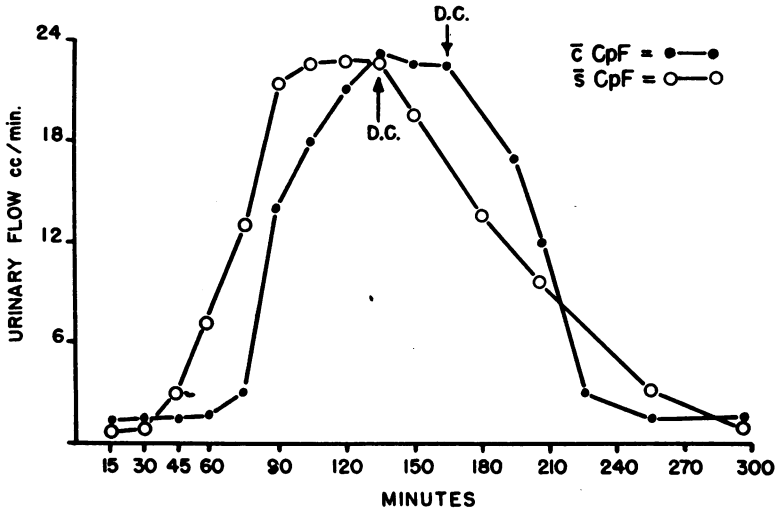

FIG. 4. THE EFFECT OF CORTISOL ADMINISTRATION ON THE PATTERN OF DEVELOPMENT AND DISAPPEARANCE OF A MAXIMAL WATER DIURESIS. "D.C." indicates the time when the sustained water infusion was discontinued.

The effect of steroid administration on the renal responsiveness to endogenous or exogenous ADH

If the glucocorticoids directly inhibited the action of antidiuretic hormone on the renal tubule, their administration should have caused a consistent reduction in the maximal antidiuretic response to endogenous or exogenous ADH. This was not observed in any of the experiments. However, it must be stated that the experiments as performed do not indicate whether the *minimal* dose of ADH necessary to produce an antidiuretic response is altered by steroid administration.

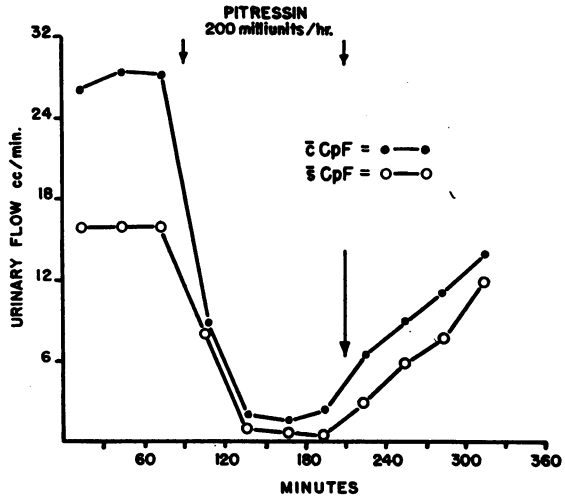

FIG. 5. THE EFFECT OF CORTISOL ADMINISTRATION ON THE ANTIDIURETIC RESPONSE TO AN INTRAVENOUS INFUSION OF VASOPRESSIN (200 mU PER HOUR).

DISCUSSION

A physiological "antagonism" or interaction between the glucocorticoids of the adrenal cortex and the neurohypophyseal system and its hormone (ADH) has frequently been proposed (15–22); namely, excessive amounts of adrenal steroids appear to block the release of ADH from the neurohypophysis (16–18, 20), while deficiency of these cortical hormones enhances its release (19, 20, 22), delays its inactivation (19, 21), or increases the renal tubular sensitivity to its action (20). The majority of these studies have been performed in normal or adrenalectomized rats (19–21) and for the most part have not been confirmed in humans with primary or secondary adrenal insufficiency (2, 5, 7, 10, 11, 13, 14).

In the present study an attempt was made to demonstrate in normal subjects an interaction between glucocorticoids and the metabolism of ADH at three levels. These were: *1*) the release of ADH from the neurohypophysis; *2*) the inactivation of circulating ADH; and *3*) its action on the renal tubule. As part of this study, it seemed essential to demonstrate whether adrenal steroids could alter maximal water diuresis in the absence of circulating ADH (physiological or clinical diabetes insipidus). It was shown that this aug-

mentation could occur without a change in renal hemodynamics or solute excretion, thus confirming the observations of Raisz, McNeely, Saxon and Rosenbaum (9) and those of Vesin (25). These results should be supplemented by those showing that adrenal steroids can markedly improve the impaired water diuresis in patients (7–12, 14) and in animals (26) with combined anterior and posterior pituitary insufficiency. One can then conclude that augmentation of water diuresis in the above circumstances certainly is not due to an alteration of the metabolism of ADH.

Because of the variability in response to venous congestion and inhalation of cigarette smoke, these results were not as conclusive as the others. However, they did not indicate a consistent effect of the glucocorticoids on the nonosmotic release of ADH. It is reasonable to conclude that chronic steroid administration to the normal subjects of the present study did not modify the secretion (release), "inactivation," or action of antidiuretic hormone.[3]

SUMMARY AND CONCLUSIONS

1. The interrelationships of adrenal steroids and antidiuretic hormone (ADH) were evaluated in normal subjects.

2. Chronic steroid administration significantly augmented the maximal water diuresis of normal subjects and patients with diabetes insipidus. Although this augmentation was frequently accompanied by increased renal hemodynamics and/or solute excretion, it may occur without a significant change in these parameters.

3. No evidence was obtained to indicate that the release, inactivation, or renal tubular action of ADH was affected by prior steroid administration.

4. In normal human subjects, an antagonism between ADH and adrenal glucocorticoids could not be demonstrated.

[3] The results of the present study are somewhat at variance with those of Dingman, Thorn and Despointes (16–18). They stated that acute or chronic steroid administration raised the threshold of response of the neurohypophysis to the nonosmotic stimulus, nicotine, and that the correction of the impaired water metabolism in adrenal insufficiency and the augmentation of water diuresis in the normal subject was due to an effect of adrenal steroids on the neurohypophyseal system. We are unable to evaluate their findings, since two of the reports appeared only in abstract form (16, 17) and one was a review article without original data (18).

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