

# The Regulation of Plasma 18-Hydroxy 11-Deoxycorticosterone in Man

G. H. WILLIAMS, L. M. BRALEY, and R. H. UNDERWOOD

*From the Endocrinology-Hypertension Unit, Peter Bent Brigham Hospital,  
and the Department of Medicine, Harvard Medical School,  
Boston, Massachusetts 02115*

**ABSTRACT** 18-hydroxy 11-deoxycorticosterone (18-OH DOC), a weak mineralocorticoid, was estimated by a radioimmunoassay procedure after purification in 49 patients with hypertension and 38 normal control subjects. The sensitivity of the method was 2–4 pg; there was no detectable blank, and the precision was 9–10%. In normal subjects the absolute plasma levels were similar to those of aldosterone. ACTH administration produced a 23-fold increase, and sodium restriction resulted in a 4-fold increase ( $5.4 \pm 0.7$ – $20.5 \pm 3.0$  ng/dl). On the other hand, the plasma levels of 18-OH DOC declined by nearly 50% with upright posture or angiotensin II infusion. During both of these procedures, plasma aldosterone levels significantly increased. Patients with normal and low renin hypertension had similar changes in plasma 18-OH DOC levels with sodium restriction. However, the mean high sodium level in the normal renin essential hypertension group ( $11.6 \pm 1.6$  ng/dl) was significantly greater ( $P < 0.001$ ) than in the control group ( $5.4 \pm 0.7$  ng/dl). In addition, at least 22% and perhaps as high as 37% of the hypertensive subjects had levels greater than the upper limits of normal on a high sodium intake. Differences between the groups were less impressive in the sodium-restricted studies. There were no significant differences in age, duration of hypertension, sodium balance, serum sodium, potassium, or blood urea nitrogen in those patients who had elevated levels of plasma 18-OH DOC. Patients with primary aldosteronism had levels within the normal range on both dietary intake. However, in contrast to the other groups there were no significant changes in the plasma levels with sodium restriction. Thus, a significant number of patients with essential hypertension presumably have an alteration in 18-OH DOC secretion.

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## INTRODUCTION

Péron (1) and Birmingham and Ward (2) reported in 1961 that rat adrenal glands produced 18-hydroxy 11-deoxycorticosterone (18-OH DOC).<sup>1</sup> This steroid was later shown to have weak mineralocorticoid-like activity and to be secreted by human adrenal glands (3–5). Interest in this steroid as a factor producing hypertension increased through the studies of Birmingham et al. (5, 6) who reported elevated 18-OH DOC levels in adrenal regeneration hypertension and of Rapp and Dahl (7) and Dahl et al. (8) who reported differences in the secretion of this steroid in rats genetically susceptible to salt-induced hypertension when compared with rats who were resistant. The data in human hypertension are controversial. Melby et al. (9, 10) reported elevated excretion rates in patients with low renin but not normal renin essential hypertension. On the other hand, Genest et al. (11) and Nowaczynski et al. (12, 13) reported elevated secretory rates in all forms of essential hypertension. The present report describes a radioimmunoassay for the measurement of plasma levels of 18-OH DOC, studies to define its control in normal subjects, and the levels found in plasma of patients with hypertension.

## METHODS

49 patients with essential hypertension, 38 normotensive control subjects, and 18 patients with primary aldosteronism were admitted to The Clinical Research Center of the Peter Bent Brigham Hospital. The normotensive subjects ranged in age from 20 to 60 yr (mean 41 yr), two-thirds were male, four were black. They were taking no drugs and had no evidence of renal, cardiovascular, or endocrine abnormalities on routine screening. Patients with essential hypertension ranged in age from 21 to 62 yr (mean 44 yr), two-thirds were male, eight were black. The criteria for inclusion of patients in the study were: outpatient supine

<sup>1</sup> Abbreviation used in this paper: 18-OH DOC, 18-hydroxy 11-deoxycorticosterone.

diastolic blood pressure greater than 90 mm Hg determined on three different occasions and documented evidence of hypertension for at least 6 mo before the study. In addition, results of the following studies performed to eliminate known secondary cause of hypertension were required to be normal: rapid sequence intravenous pyelogram, creatinine clearance, urine culture, urinalysis, serum electrolytes, and 24-h urine vanillylmandelic acid, metanephrines, 17-hydroxysteroid, and 17-ketosteroid excretory rates. If the upright renin activity in the sodium-depleted state was subnormal, a saline load was given to show that the aldosterone secretory rate was suppressible. No patient had clinical or laboratory evidence for congestive heart failure or malignant hypertension. The 18 patients with primary aldosteronism ranged in age from 26 to 72 yr; 10 were female, and 8 were male. All had plasma aldosterone and aldosterone secretory rates that did not suppress to within the normal range with saline infusion, potassium-wastage with saline loading, and pathologically proven adrenal adenoma at the time of surgery.

Medications were withheld for a minimum of 2 wk before hospitalization. All subjects were studied in balance on a dietary potassium intake of 100 meq/day and sodium intake of 10 or 200 meq/day. In all patients, at least 5 days were allowed to achieve metabolic balance on the particular dietary intake before plasma levels of 18-OH DOC, aldosterone, and cortisol were obtained. In the patients with essential hypertension, upright plasma renin activities were also determined on the sodium-restricted diet and compared with normal subjects as previously described from this laboratory (14). In the patients with primary aldosteronism a high sodium intake was not used, but samples were obtained the morning after admission on an unrestricted sodium intake.

## Experimental protocol

### STUDIES IN NORMAL SUBJECTS

**Effect of dietary sodium intake.** 20 normal subjects ranging in age from 22 to 58 yr were studied on a 200-meq sodium/100 meq potassium intake. After 5 days on this diet, plasma was obtained at 8 a.m. supine after an overnight fast for aldosterone, 18-OH DOC, and cortisol. These results were compared with those obtained in 18 normotensive subjects (6 being the same on both diets) ranging in age from 20 to 56 yr studied under identical conditions except dietary sodium intake was reduced to 10 meq/day for the 5-6 days before sampling.

**Effect of ACTH infusion.** The effect of ACTH was assessed in 10 subjects studied on a high sodium intake. All studies began at 8 a.m. with the patients in a supine position. Cosyntropin ( $\alpha$ -1-24 synthetic ACTH) was infused at a constant pharmacologic rate of 10 U/h for 60 min. Plasma aldosterone, 18-OH-DOC, and cortisol were obtained at the beginning and at the end of the infusion.

**Effect of upright posture.** In six normal subjects the effect of upright posture was assessed. All patients were in balance on a low sodium intake and supine overnight at the start of the study. They were then ambulated for 3 h, and plasma renin activity, aldosterone, 18-OH DOC, and cortisol were obtained supine and upright.

**Effect of angiotensin II infusion.** 12 subjects were infused with 3 ng/kg per min angiotensin II (Hypertensin, Ciba Pharmaceutical Co., Summit, N. J.) for 30 min. Plasma was obtained before and at the completion of the angiotensin II infusion for determination of aldosterone, 18-

OH DOC, and cortisol. Subjects were studied on an ad lib. dietary intake.

**Individual variation in plasma steroid concentration.** To determine the coefficient of variation of the plasma levels of these three steroids on a fixed dietary intake, several determinations (4-5) in a short time interval on different days were obtained in a group of eight subjects. Four subjects were studied on a 10-meq, and four were evaluated on a 200-meq sodium intake. Samples were obtained between 7 and 8 a.m. on at least 2 days after an overnight fast and with the patients supine.

### STUDIES IN PATIENTS WITH HYPERTENSION

49 patients with essential hypertension were included in this phase of the protocol. 17 of these patients were classified as low, and the rest were classified as normal renin essential hypertension by criteria previously established for this laboratory (14). In 18 subjects in the normal renin group and 9 subjects in the low renin group, the effect of a 5 to 6-day 10 meq sodium intake was assessed. In 18 patients (4 of whom were also studied in the sodium-loaded state) in the normal renin essential hypertension group and 9 in the low renin group, the effect of a 5-day 200 meq sodium intake was determined.

In eight subjects in whom an initial elevated level of 18-OH DOC was found and four in whom the initial level was normal, two to six additional plasma samples for 18-OH DOC were obtained either in the sodium-restricted or the sodium-loaded state.

15 patients with primary aldosteronism also were studied supine on a 10-meq sodium intake. In an additional seven patients, plasma was obtained on an unrestricted sodium intake the morning after admission to the hospital. All studies were approved by the Human Subjects Committee of the Peter Bent Brigham Hospital, and written informed consent was obtained from each subject.

## Laboratory procedures

Daily weight, fluid intake, and urinary output were recorded, and 24-h specimens of urine were collected from 7 a.m. to 7 a.m. Accuracy of collection of urine was checked by daily creatinine determination. Sodium and potassium concentrations in urine were determined by flame photometry utilizing lithium as an internal standard. Upright plasma renin activity was assessed by double antibody radioimmunoassay; plasma aldosterone and cortisol were assessed by radioimmunoassay procedures previously described from this laboratory (15, 16). The plasma 18-OH DOC levels were determined by radioimmunoassay as detailed below. Statistical analysis was performed by Student's *t* test with results expressed as mean  $\pm$  SEM unless otherwise indicated.

### Plasma 18-OH DOC assay

**Materials.** [1,2-<sup>3</sup>H]18-OH DOC (Amersham/Searle Corp., Arlington Heights, Ill.) was submitted to paper chromatography in a Bush V solvent system before utilization. The specific activity of this material was estimated at 29 Ci/mmol by radioimmunoassay. Nonradioactive 18-OH DOC was purchased from Steraloids, Inc. (Pawling, N. Y.) and had a melting point of 166-168°C.

**Preparation of 18-OH DOC lactone antisera.** The 18-OH DOC conjugate was synthesized by techniques previously described (17). In brief, 18-OH DOC was oxidized to the lactone, purified, and the oxime derivative was synthesized and conjugated to bovine serum albumin by the mixed

TABLE I  
*Percent Cross-Reaction on a Weight-to-Weight Basis of 18-OH DOC Lactone  
Antibody with Other Steroids*

18-OH DOC lactone	100	Aldosterone	<0.01
18-OH corticosterone lactone	61	ISO aldosterone	<0.01
Aldosterone lactone	0.3	Cortisone	<0.01
18-OH DOC	0.5	Cortisol	<0.01
18-OH corticosterone	0.13	17-OH progesterone	<0.01
Testosterone	0.1	Corticosterone etio acid	<0.01
11-Deoxycorticosterone	0.05	ISO Aldosterone etio acid	<0.01
Progesterone	0.03	Cortisol etio acid	<0.01
Corticosterone	0.02	Cortisone etio acid	<0.01
11-Deoxycorticosterone etio acid	0.02		

anhydride procedure (18). The conjugate was mixed with Freund's complete adjuvant, and two sheep were immunized by injecting this material intradermally and subcutaneously at multiple sites above the four shanks.

**Assay procedure.** The assay procedure is similar to that previously described for plasma aldosterone, corticosterone, and cortisol, except for the use of a different chromatography system (16). In brief, 1,500 dpm of tritiated 18-OH DOC were added to 2 ml of plasma as an internal indicator, and the plasma was extracted with methylene chloride. The organic phase was taken to dryness and oxidized with periodic acid solution overnight at 25°C. The oxidized solution was then extracted with methylene chloride and chromatographed in a P1 solvent system (cyclohexane: benzene: methanol: water: : 500: 200: 500: 100). The radioimmunoassay procedure itself was identical to that previously described for aldosterone lactone (19).

## RESULTS

**Characterization of 18-OH DOC radioimmunoassay.** The antiserum used for the assay had a titer of 1/

300,000. The specificity of the assay was assessed by determining the sensitivity, the cross-reaction with other steroids, and the blank value. The sensitivity of the assay whether defined by the formula:  $(4V2)/(\sqrt{KS\sqrt{T}})$  (where  $K$  = the equilibrium constant,  $S$  = specific activity of tracer,  $V$  = reaction mixture volume, and  $T$  = counting time) (20) or as twice the SD of the zero point (21) was 2–4 pg.  $K$  was  $9.2 \times 10^{10}$  liters/mol.

In 16 studies 2-ml aliquots of water and in five studies 2 ml of adrenalectomized plasma were processed through the entire method. In all 21 experiments levels of 18-OH DOC lactone were less than the sensitivity of the method, i.e., less than 4 pg/reaction tube.

The cross-reactions with other steroids as shown in Table I were calculated on a weight-to-weight basis from the amount of standard 18-OH DOC lactone and the amount of other steroids that produced a 40%

TABLE II  
*Response of Plasma Aldosterone, 18-OH DOC, and Cortisol to Sodium Restriction and Loading in  
Normal Subjects and Patients with Essential Hypertension or Primary Aldosteronism  
(Mean  $\pm$  SEM)*

	No. of subjects	Plasma			Urine	
		Aldosterone	18-OH DOC	Cortisol	Sodium	Potassium
		ng/dl	ng/dl	μg/dl	meq/24 h	
Normal subjects						
10 meq Na	18	22.3 $\pm$ 3.8	20.5 $\pm$ 3.0	14 $\pm$ 1	12 $\pm$ 2	84 $\pm$ 6
200 meq Na	20	6.5 $\pm$ 0.8	5.4 $\pm$ 0.7	14 $\pm$ 1	184 $\pm$ 14	86 $\pm$ 4
Essential hypertension						
Normal Renin						
10 meq Na	18	26.2 $\pm$ 3.4	30.9 $\pm$ 6.2	14 $\pm$ 1	8 $\pm$ 1	79 $\pm$ 6
200 meq Na	18	6.2 $\pm$ 0.8	11.6 $\pm$ 1.6	15 $\pm$ 1	176 $\pm$ 16	86 $\pm$ 8
Low Renin						
10 meq Na	9	28.5 $\pm$ 5.9	14.7 $\pm$ 2.0	12 $\pm$ 1	14 $\pm$ 2	82 $\pm$ 6
200 meq Na	9	8.8 $\pm$ 0.6	5.7 $\pm$ 1.6	12 $\pm$ 1	194 $\pm$ 18	80 $\pm$ 8
Primary aldosteronism						
10 meq Na	15	39 $\pm$ 9	9.1 $\pm$ 1.0	14 $\pm$ 2	14 $\pm$ 2	76 $\pm$ 4
Ad lib.	7	36.5 $\pm$ 13.8	9.9 $\pm$ 3.1	14 $\pm$ 2	120 $\pm$ 12	78 $\pm$ 8

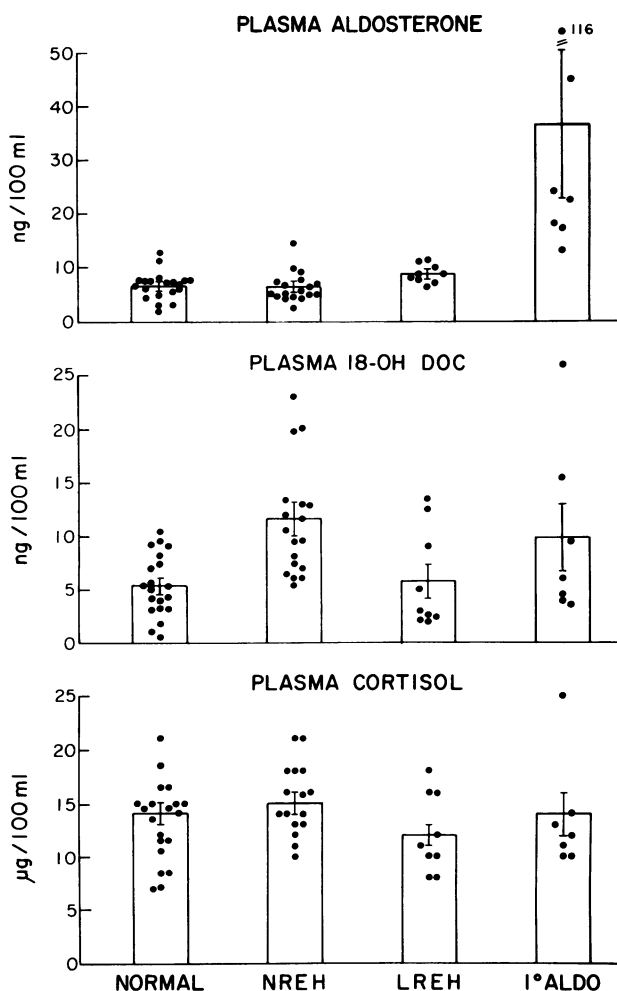


FIGURE 1 Individual and mean  $\pm$  SEM plasma levels of aldosterone, 18-OH DOC, and cortisol in 20 normal controls, 18 patients with normal and 9 patients with low renin essential hypertension and 7 patients with primary aldosteronism in balance on a 200 meq Na/100 meq K intake. All samples obtained supine at 8 a.m.

decrease in the zero point binding of tritiated 18-OH DOC lactone with its antibody. The antibody used in the present study exhibits a large cross-reaction with 18-hydroxycorticosterone lactone (61%) and slight cross-reactions with aldosterone lactone, 18-OH DOC, and 18-hydroxycorticosterone. All the other steroids exhibited less than 0.01% cross-reaction.

**Precision and accuracy.** 10 aliquots from one and 4 aliquots from a second plasma pool were assayed for 18-OH DOC lactone. The mean value for the first plasma pool was  $2.7 \pm 3.0$  ng/100 ml (SD) with a coefficient of variation of 10%, and the mean value for the second pool was  $4.3 \pm 0.4$  ng/100 ml (SD) with a coefficient of variation of 9%. Thus, the precision of this particular assay is similar to that described for most

steroid radioimmunoassays. The accuracy was assessed by the extent of recovery of standard 18-OH DOC added to water, normal pooled plasma, or adrenalectomized plasma. Either 0.25, 0.50, or 2.5 ng of steroid was added to 2 ml of water or plasma. There was excellent agreement between the amount of steroid added and the amount recovered with the slope of the regression relationship being 0.99, the *F*-ratio 1553, and a *P* < 0.001.

**Effect of dietary sodium intake in normal subjects.** The mean data for the 20 normal subjects studied on the high sodium and the 18 normal subjects on the sodium-restricted intakes are given in Table II. The individual values are shown in Figs. 1 and 2 for plasma levels of

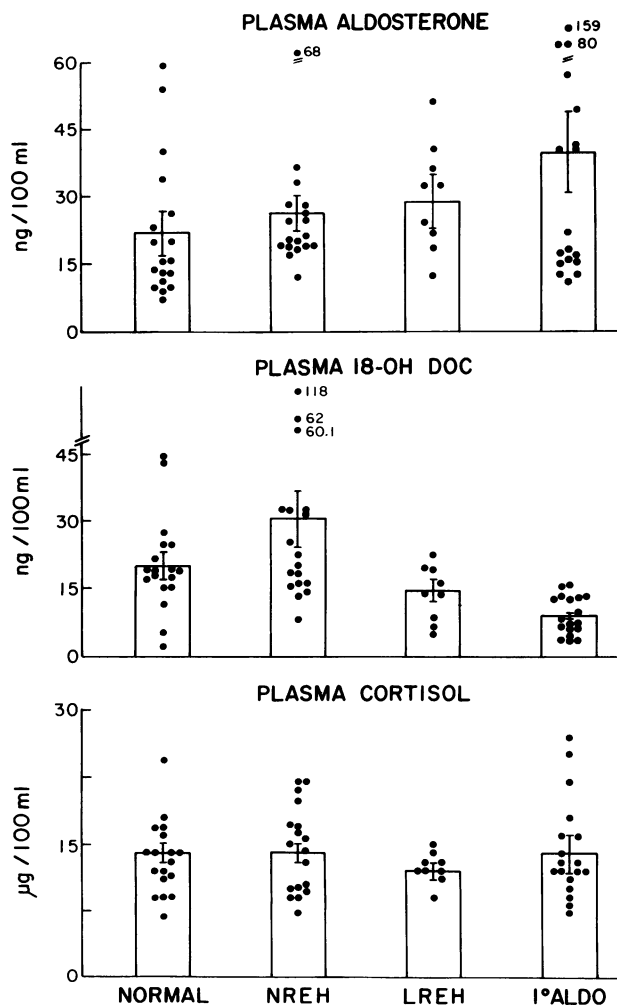


FIGURE 2 Individual and mean  $\pm$  SEM plasma levels of aldosteronism, 18-OH-DOC, and cortisol in 18 normal subjects, 18 patients with normal renin and 9 patients with low renin essential hypertension and 15 patients with primary aldosteronism in balance on a 10 meq Na/100 meq K intake. All samples obtained supine at 8 a.m. The scale is different from that used in Fig. 1.

aldosterone, 18-OH DOC, and cortisol. Plasma levels of aldosterone and 18-OH DOC were quite similar and correlated closely with each other when the low and high sodium data were pooled ( $r = 0.74$ ;  $P < 0.001$ ). In contrast, there was no significant correlation between the plasma levels of cortisol and the other two steroids. Sodium restriction significantly increased the plasma levels of aldosterone and 18-OH DOC ( $P < 0.001$ ). Cortisol levels, however, did not change significantly with sodium restriction.

*Coefficient of variation of steroid levels.* Repeat plasma samples were obtained in four subjects on a 200-meq sodium intake to assess the coefficient of variation of the plasma levels. Four or five samples were obtained on 2 consecutive days while in balance between

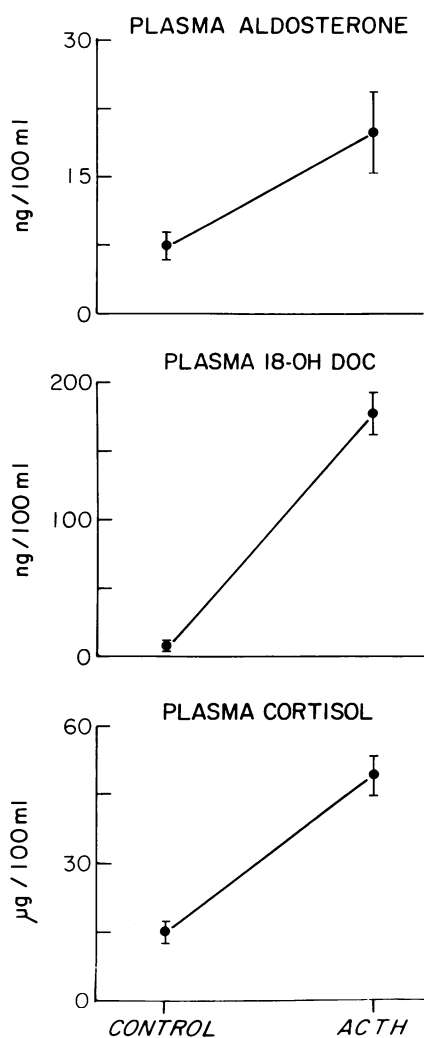


FIGURE 3 Effect of ACTH infusion (10 U/h for 1 h) on plasma aldosterone, 18-OH-DOC, and cortisol levels in 10 normal subjects on a 200-meq Na/100 meq K intake (mean  $\pm$  SEM).

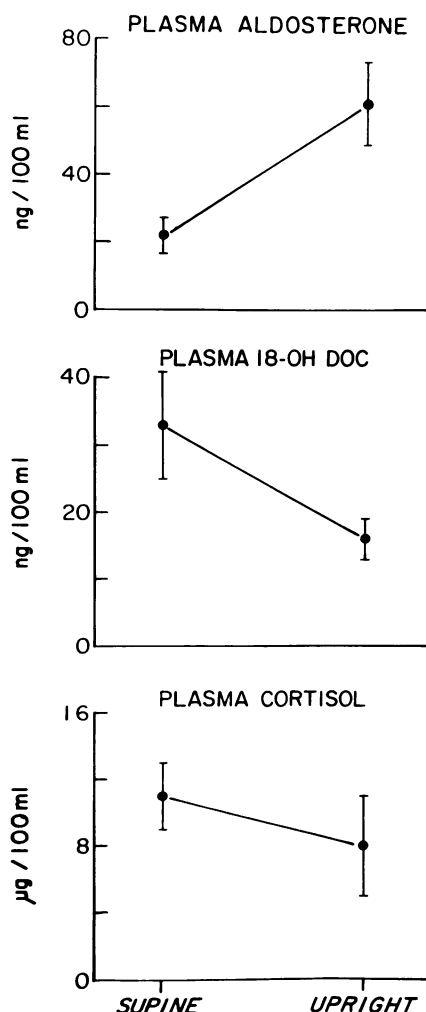


FIGURE 4 Effect of 3 h of upright activity on the plasma levels of aldosterone, 18-OH DOC, and cortisol in six normal subjects in balance on a 10-meq Na/100 meq K diet (mean  $\pm$  SEM).

7 and 8 a.m. The coefficient of variation of the 18-OH DOC levels was  $18 \pm 4\%$  (SD); for aldosterone  $20 \pm 3\%$  (SD); for cortisol  $16 \pm 3\%$  (SD). In subjects on the 10-meq sodium intake the coefficients of variation were  $39 \pm 15\%$  (SD) for 18-OH DOC,  $33 \pm 11\%$  (SD) for aldosterone, and  $15 \pm 7\%$  (SD) for cortisol.

*Stimulatory procedures in normal subjects.* The effect of ACTH administration was observed in 10 normal subjects studied on a high sodium intake. Results are presented in Fig. 3. The mean aldosterone levels rose from  $7.6 \pm 1.7$  to  $21.5 \pm 4.7$  ng/dl, while the 18-OH DOC levels rose from  $7.5 \pm 1.3$  to  $179 \pm 15$  ng/dl. Cortisol levels rose from  $14.9 \pm 1.2$  to  $49.3 \pm 3.9$  µg/100 ml.

The effects of acute upright posture were assessed in six subjects. The results are shown in Fig. 4. Plasma renin activity rose from  $4.2 \pm 0.8$  to  $8.6 \pm 1.2$  ng/ml per dl,

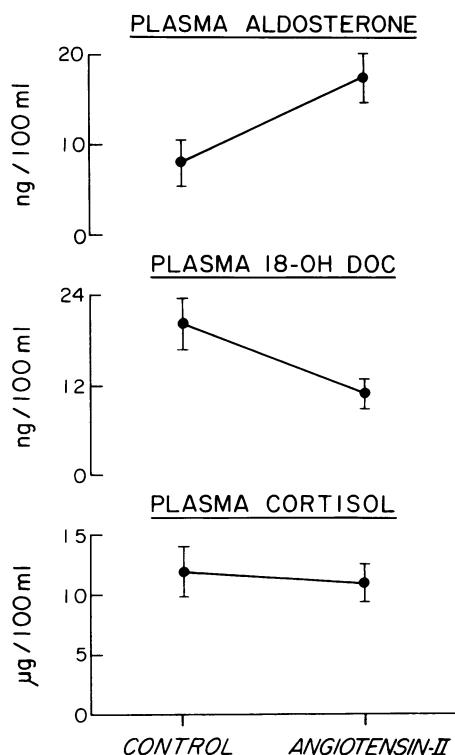


FIGURE 5 Effect of a 30-min infusion of angiotensin II (3 ng/kg per min) on plasma aldosterone, 18-OH DOC, and cortisol levels in 12 normal subjects on an ad lib. sodium and potassium intake (mean±SEM).

while 18-OH DOC levels fell from  $33 \pm 8$  to  $16 \pm 3$  ng/dl; cortisol levels also fell from  $11 \pm 2$  to  $8 \pm 3$  μg/dl. Thus, in this study, 18-OH DOC and aldosterone levels were dissociated from each other.

The response of these three steroids to the administration of angiotensin II was assessed in 12 normal subjects on an ad lib. sodium intake. The results are shown in Fig. 5. After a 30-min infusion of angiotensin II at a dose of 3 ng/kg per min, plasma aldosterone levels rose from  $10 \pm 2$  to  $18 \pm 3$  ng/dl, while 18-OH DOC levels fell from  $18 \pm 3$  to  $11 \pm 2$  ng/ml. Cortisol levels did not change significantly from  $12 \pm 2$  to  $11 \pm 3$ . The increase in plasma aldosterone levels and the decline in plasma 18-OH DOC levels were significant ( $P < 0.01$ ).

**Studies in patients with hypertension.** In the patients with normal or low renin essential hypertension, the plasma levels of corticoid and aldosterone were not significantly different than those found in normotensive individuals when dietary sodium is considered (Table II, Figs. 1 and 2). In contrast, there were significant differences in the plasma levels of 18-OH DOC. The 18-OH DOC levels in patients with normal renin essential hypertension on the high sodium intake were significantly greater than normotensive subjects on a similar sodium intake ( $t = 3.25$ ,  $P < 0.001$ ) (Table II).

The mean 18-OH DOC level in the low renin group was not significantly different than the normal controls. However, 2 of the 9 subjects with low renin hypertension as well as 8 of the 18 subjects with normal renin hypertension had plasma 18-OH DOC levels greater than any normal subject (Fig. 1). In contrast, the mean 18-OH DOC levels in patients with either normal or low renin essential hypertension on a low sodium intake were not significantly different than normal controls although they were borderline, significantly different from each other ( $t = 2.18$ ,  $P < 0.05$ ). None of the patients in the low renin group and only 3 of the 18 patients in the normal renin group, all of whom had elevated high salt levels, had values outside the normal range on a sodium-restricted intake (Fig. 2).

8 of the 10 patients with essential hypertension who had an initial level of 18-OH DOC outside the normal range, i.e., greater than 10 ng/dl on the high sodium intake, had repeat determinations performed on several different occasions supine between 7 and 8 a.m. on either a sodium-restricted and/or a sodium-loaded intake. If more than two specimens were obtained, sampling occurred on at least two different days (Table III). Six out of the eight subjects had all and the other two had the majority of values determined while on a high sodium intake outside the normal range. On the other hand, on a low sodium intake, one subject had both values, two had one-half the values, and three none of the values outside the normal range. Four of the normal renin essential hypertensive patients with initial values of 18-OH DOC within the normal range on the high sodium intake also had two or three additional determinations. They were all within the normal range.

TABLE III  
Frequency of Elevated 18-OH DOC Levels in Patients with Essential Hypertension who had an Initial Value Outside the Normal Range

Patient no.	Number of samples	Number with elevated 18-OH-DOC levels	Low salt elevated	High salt elevated
			%	%
1	5	3	0	100
2	7	7	100	100
3	6	5	50	100
4	6	4	—	67
5	3	2	0	100
6	3	3	—	100
7	4	3	50	100
8	5	3	0	75

All samples obtained supine after an overnight fast between 7 and 8 a.m. Elevated low salt levels were greater than 45 ng/dl, high salt greater than 10 ng/dl.

A variety of biochemical and epidemiologic parameters were compared in those patients with normal and those with elevated 18-OH DOC levels. There were no significant differences in age, duration or level of hypertension, serum sodium, potassium or creatinine, sodium-loaded or restricted plasma aldosterone or cortisol, or secondary effects of the hypertension, e.g., retinopathy or cardiac hypertrophy whether the entire group of patients with elevated 18-OH DOC levels or only the subgroup of six with repetitive elevations was used. The only differences, although not statistically significant, was the lower frequency of suppressed renin activity in the elevated 18-OH DOC subgroup (18 vs. 35%).

The data on the patients with primary aldosteronism are summarized in Table II and in Figs. 1 and 2. Plasma cortisol levels in this group of patients were not significantly different from any of the other groups on the sodium-loaded diet but were significantly less than the normal renin essential hypertension group with sodium restriction ( $P < 0.01$ ). In contrast to the other three groups, the plasma levels of aldosterone and 18-OH DOC in the patients with primary aldosteronism were not significantly altered by dietary sodium restriction.

## DISCUSSION

A disturbance of volume or sodium homeostasis has been suggested as an important factor in producing or maintaining an elevated blood pressure. Approximately 25% of patients with essential hypertension have suppressed renin activity (14, 22–25), and some investigators have suggested that these patients are volume-expanded (22, 26, 27). Since increased secretion of aldosterone is found in only a small fraction of these patients, secretion of other mineralocorticoid-like steroids has been assessed. The steroid that has been most extensively evaluated is 18-OH DOC.

Most studies so far have suggested that this steroid is predominantly under the control of ACTH (9). The present study confirms the importance of ACTH in the control of this steroid and suggests that it may be more responsive than cortisol to ACTH.

Angiotensin has been shown not to alter significantly the plasma levels of 18-OH DOC in adrenal venous effluent (9). The data obtained in the present study would support this conclusion and would further raise the possibility that angiotensin infusion significantly decreases the plasma levels of 18-OH DOC. In the 12 normal subjects infused with angiotensin II, all showed a significant decrement in the plasma levels of 18-OH DOC after a 30-min infusion. This occurred at a time when there were no significant changes in plasma cortisol levels and significant increments in plasma aldosterone occurred. Further indirect support is obtained from the upright posture study where the plasma levels of 18-OH

DOC fell in parallel with plasma cortisol at a time when aldosterone levels were increasing. Thus, these results would suggest that 18-OH DOC is primarily regulated by ACTH; however, angiotensin may also influence its production by either inhibiting its secretion or increasing its rate of degradation.

The present investigation shows that sodium intake significantly alters the plasma levels of 18-OH DOC. The plasma levels of this steroid parallel the response of plasma aldosterone to sodium restriction in both the normotensive and hypertensive groups. These changes in plasma concentration may reflect alterations in either secretion or clearance rate of the steroid. There are no published data on the effect of sodium intake on the metabolic clearance rate of 18-OH DOC. However, there is a remarkable similarity between aldosterone and 18-OH DOC secretion. In the present study the plasma levels of the two steroids were nearly the same. Moreover, other investigators have reported quantitatively similar secretion and excretion rates (9–12). Thus, it is probable that their metabolic clearance rates are the same. Since it is known that sodium intake does not influence the metabolic clearance rate of aldosterone (28, 29), it would seem improbable that it would have such a drastic effect on the metabolic clearance rate of 18-OH DOC. Thus, we would conclude that the increased plasma levels are probably a reflection of increased secretion, a conclusion supported by the findings in three patients reported by Kuchel et al. (30). Since acute infusion of angiotensin II does not increase 18-OH DOC levels, the mechanism by which sodium restriction increases the plasma levels and presumably secretion of 18-OH DOC is not clear.

The plasma levels of 18-OH DOC in sodium-loaded hypertensive patients are greater than in normal controls. The frequency of this abnormality varied from 25 to 45% and within the limits of the small numbers evaluated occurred with approximately equal frequency in patients with low renin and normal renin essential hypertension. These findings would be in general agreement with the data reported by Nowaczynski et al. (12, 13) for secretory rates of this steroid in various hypertensive groups. The results in the patients with normal renin essential hypertension do not agree with the excretory data reported by Melby et al. (9, 10). These discrepancies may in part reflect different patient populations, different methodologies, or different experimental conditions under which samples were obtained. For example, the present study measured instantaneous levels of the steroids while the previous studies reported 24-h excretory or secretory patterns. Thus, the circadian and interdiem fluctuations in the plasma levels of 18-OH DOC may account for some of the differences. The coefficient of variation of its levels in repetitive samples

obtained on consecutive days was between 15 and 20% similar to that for cortisol and aldosterone in this and previous studies (31). Sodium restriction increased the coefficient of variation for aldosterone and 18-OH DOC but not cortisol. Thus, using plasma rather than excretory values to assess 18-OH DOC secretion may actually decrease the probability of observing significant differences in group means because of the increased randomness of the individual levels. This may be the explanation for the contrasting results in the sodium-loaded vs. sodium-restricted subjects. On the other hand, it would be an unlikely explanation for the discrepancy between the present and some of the previous studies using excretory values.

The possibility of significant short-term fluctuations in plasma levels does raise a question concerning the validity of defining an abnormal state from a single value. Thus, only the six hypertensive subjects who consistently had elevated levels could be classified as definitely abnormal. In all probability, this is a conservative estimate of increased 18-OH DOC secretion in patients with essential hypertension.

Another possible reason for the difference in the results between the present and the two previous studies could relate to the metabolism of 18-OH DOC in patients with hypertension. Nowaczynski et al. (12) have suggested that patients with hypertension have a change in the metabolism of aldosterone. If such a change also occurred in 18-OH DOC, then excretory data may not reflect secretory rates or plasma levels. Alternatively, since there is no information available on the dietary intake of the subjects reported by Melby, a variable sodium intake might obscure any differences between the subgroups.

Finally, there could be a methodologic error in the radioimmunoassay procedure used in the present study. None was found after extensive evaluation of the assay. Moreover, the conclusions from the present study are similar to that made by Nowaczynski et al. (12, 13) using totally different methodology.

The reason for the elevated 18-OH DOC levels in these patients is not clear. As noted earlier, there were no significant differences in a number of biochemical and epidemiologic factors in those subjects who consistently had elevated levels of 18-OH DOC and the rest of the hypertensive patients evaluated. One subject had low renin hypertension, and the others had normal renin essential hypertension.

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