Effect of Administered Mineralocorticoids or ACTH in Pregnant Women

ATTENUATION OF KALIURETIC INFLUENCE OF MINERALOCORTICOIDS DURING PREGNANCY

EDWARD N. EHRLICH and MARSHALL D. LINDHEIMER

From the Departments of Medicine and Obstetrics and Gynecology, The University of Chicago, Chicago, Illinois 60637

ABSTRACT The role of augmented aldosterone production in pregnancy is poorly understood. Whereas some consider aldosterone secretion in pregnancy excessive, others suggest that this is a compensatory phenomenon. According to yet another view, mechanisms other than the renin-angiotensin-aldosterone system control sodium homeostasis in pregnancy.

Metabolic balance studies were performed on 14 3rd trimester women. Mineralocorticoid activity was experimentally increased by administering desoxycorticosterone acetate, 9α-fluorocortisol acetate, or ACTH for 4-12 days. Administration of mineralocorticoid or ACTH consistently caused sodium retention. During this mineralocorticoid-induced volume expansion, aldosterone excretion decreased markedly. Natriuresis, which followed discontinuance of the drug, continued while aldosterone excretion, although greatly diminished compared to control values, was greater than that found in normal, nonpregnant individuals. This saline diuresis did not subside until aldosterone excretion returned to its previously high control values. These observations support the concept of the physiological role of increased aldosterone production in pregnancy.

Results further revealed a marked dissociation between antinatriuretic and kaliuretic effects of corticoids. Potassium balance was virtually unaltered during continued mineralocorticoid or ACTH administration, despite initially high or abruptly increased sodium intakes. Finally, mineralocorticoid escape was induced by continued desoxycorticosterone acetate therapy in two male volunteers. Kaliuresis occurred which was subsequently abolished when progresterone was administered. Sodium excretion, however, was virtually unaltered. These data, mimicking results observed in gravidas, suggest that progesterone is an important determinant of potassium homeostasis in pregnant women.

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INTRODUCTION

The role of the strikingly increased secretion of aldosterone during pregnancy (1) has not been clearly defined. In nongravid subjects, the sodium retention induced by continued administration of mineralocorticoids usually subsides within 1 wk, and sodium balance resumes (2-5). After resumption of balance, larger doses of mineralocorticoids do not cause sodium retention. The occurrence of such renal refractoriness has been termed the escape phenomenon. Since earlier studies seemed to demonstrate that administered mineralocorticoids (6, 7) or ACTH (8) did not induce sodium retention in pregnant women, it was suggested that the escape mechanism was already operative and that the increased secretion of aldosterone during pregnancy actually exceeds physiologic requirements. Others proposed that the increased secretion of aldosterone is not excessive but represents a compensatory response required to offset sodium-losing factors associated with pregnancy (1, 9, 10). Another view questions the role of the renin-angiotensin-aldosterone system in pregnancy, and suggests that the accumulation of sodium in the expanding maternal extracellular fluid volume and developing conceptus is dependent upon other sodium-retaining mechanisms (11).

To further clarify the role of augmented aldosterone secretion in electrolyte balance during pregnancy, metabolic balance studies were performed in 14 third trimester

TABLE I

Summary of Individual Experiments

	Intake			Treatment			Cumulative balance			Aldosterone excretion		
	Calories	Na	K	Drug	Daily dosage	Duration	Na	K	ΔWt	Control	Treatment	Recovery
		mEq/day				*days*	*mEq*	*mEq*	*kg*		*μg/24 hr*	
Pregnant women												
V. C.	1783	249	77	DOCA	20–40 mg	8	+232	−25	+1.8	84	30	74
M. H.	1384	163	65	DOCA	20 mg	6	+314	+45	+3.9	19	4	8*
R. T.	1835	229	89	DOCA	20–40 mg	8	+262	−5	+2.0	99	16	96
L. G.	2238	240	85	DOCA	10 mg	7	+230	+3	+0.9	33	18	143‡
B. P.	2078	100	98	DOCA	20 mg	6	+280	−2	+2.0	126	28	131
K. H.	2382	90	63	DOCA	10 mg	8	+222	+8	+1.1	258	166	205
K. D.	1824	93	81	9αFF	0.8–1.6 mg	12	+144	−16	+1.6	202	89	252
S. R.	2335	72	85	9αFF	0.2–0.8 mg	12	+96	+50	+0.5	197	149	233
R. H.	1799	203	98	9αFF	1.0–2.0 mg	8	+271	+5	+1.8	192	19	92*
V. R.	1802	113	84	ACTH	40 U	7	+603	−63	+3.9	76	4	136
P. H.	2243	120	81	ACTH	40 U	6	+263	+15	+1.7	395	100	164
P. D.	2010	20	93	ACTH	40 U	8	+93	−16	+0.5	318	180	246
		138	101	ACTH	40 U	6	+463	−36	+2.9	167	14	—
K. C.	2389	131	100	ACTH	40 U	4	+154	−66	+1.1	111	33	151
P. T.	2174	98	81	ACTH	40 U	4	+352	−59	+2.3	115	12	115
Normal Men												
D. T.	1482	241	67	DOCA	20 mg	6§	+492§	−250§	+1.9§	9.0	0.9	3.1
E. G.	2019	242	90	DOCA	20 mg	7§	+488§	−124§	+2.2§	4.8	1.2	3.4

* Abbreviated recovery period.

‡ Na intake reduced during recovery.

§ DOCA treatment period before addition of progesterone.

pregnant women. Mineralocorticoid activity was experimentally increased by continued daily administration of large doses of desoxycorticosterone acetate, 9α-fluorocortisol acetate, or ACTH, and urinary electrolytes and aldosterone excretion were measured. Results demonstrate that pregnant women are, indeed, responsive to the sodium-retaining effects of mineralocorticoids, but are virtually refractory to their kaliuretic action. An explanation for the failure of mineralocorticoids to induce kaliuresis in pregnant women is suggested by experiments performed in normal men in whom kaliureses resulting from desoxycorticosterone were abolished by progesterone administration.

METHODS

Pregnant subjects in this study were normotensive women 16–29 yr of age in their 3rd trimester of pregnancy. They had no evidence of renal or cardiovascular disease. Two normal male volunteers were 24 yr old.

Subjects resided in the metabolic unit of the Clinical Research Center, and were given constant diets. Pregnant subjects received appropriate prenatal vitamin-mineral supplements. When protocols required, supplemental salt was administered in gelatin capsules containing 0.5 g sodium chloride. Subjects were allowed activity ad lib. within the confines of the hospital.

All urine voided during each 24 hr period was measured and samples saved for analysis. Subjects were weighed every morning after voiding. Blood pressure was recorded twice daily. When 24 hr urinary sodium excretion had stabilized, the following medications were administered to the pregnant subjects as indicated in Table I: intramuscular desoxycorticosterone acetate[1] (DOCA),[2] oral 9α-fluorocortisol acetate (9α-FF),[3] or intramuscular ACTH-gel (ACTH).[4] Normal men were given intramuscular progesterone[5] and DOCA as noted below.

24-hr urine collections, or occasionally, 48-hr pooled collections, were analyzed for creatinine, sodium, potassium, aldosterone, and urinary free cortisol, and in some studies urinary chloride was also measured. Sodium determinations were performed on the Technicon Autoanalyzer Flame Photometer[6] using lithium as an internal standard. Chlorides were analyzed by a titrametric method. Urinary aldosterone and free cortisol were measured by modifications of the double isotope derivative technique of Kliman and Peterson. Details of these methods have been published elsewhere (12, 13).

[1] Percorten acetate, Ciba Corp., Summit, N. J.

[2] *Abbreviations used in this paper:* DOCA, desoxycorticosterone acetate; 9α-FF, 9α-fluorocortisol acetate.

[3] Florinef acetate, E. R. Squibb & Sons, New York.

[4] H. P. Acthar gel, Armour Pharmaceutical Co., Chicago, Ill.

[5] Prolutin, Schering Corp., Bloomfield, N. J.

[6] Technicon Co., Inc., Tarrytown, N. Y.

Protocols were approved by the Clinical Investigation Committee and the Clinical Research Center Review Committee. Studies were fully explained to all volunteers and written consent was obtained. In addition, parental consent was obtained in the few instances that subjects were less than legal age. Obstetrical care was provided by faculty members of the Department of Obstetrics and Gynecology (Chicago Lying-In Hospital), who were not investigators in this study.

RESULTS

Studies in pregnant women

Effects of administered mineralocorticoid upon urinary electrolyte and aldosterone excretion. Administration of DOCA or 9α-FF for 6-12 days to normal 3rd trimester pregnant women resulted in decreased urinary sodium excretion in every subject (Table I). The results of a representative study with DOCA are presented graphically in Fig. 1. In this woman, as well as in three others who received DOCA, sodium retention commenced on the 1st day of drug administration and continued throughout the entire treatment period. However, in two

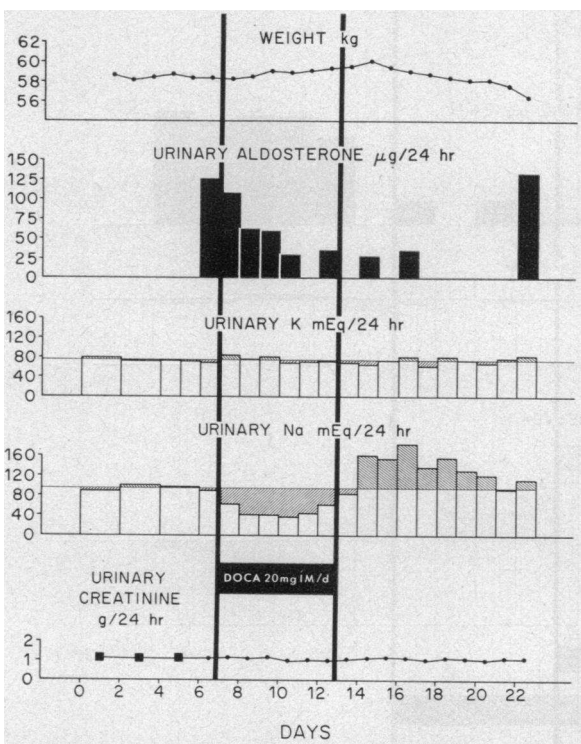

FIGURE 1 Effect of intramuscular administration of DOCA for 6 days to B. P., a normal 23 yr old pregnant woman. Heavy vertical lines delineate treatment period. Horizontal base lines for urinary sodium and potassium are arithmetic average of pretreatment values. Wider bars or squares denote excretion rates per 24 hr in 48-hr urine collections. All other excretion rates determined in 24-hr urine collections. This scheme is followed in subsequent figures.

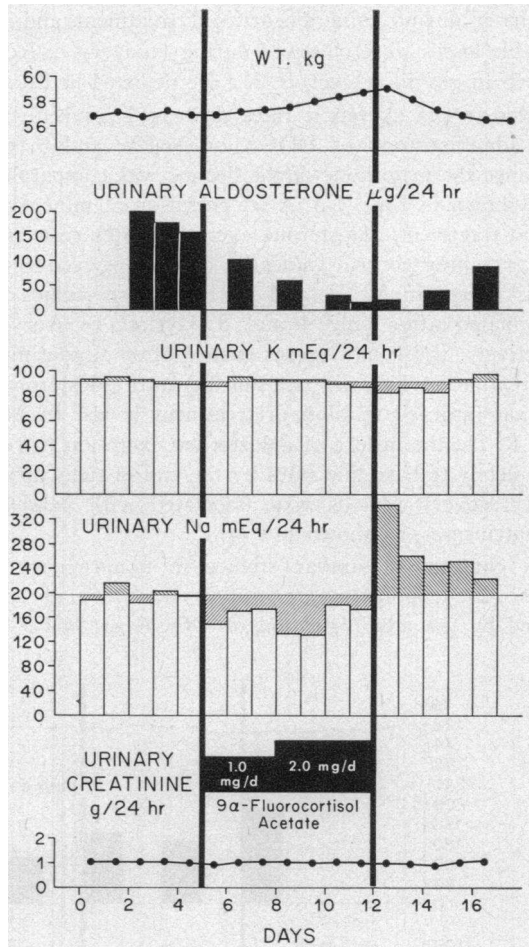

FIGURE 2 Effect of oral administration of 9α-FF for 7 days to R. H., a normal 30 yr old pregnant woman.

of the six DOCA-treated women, V. C. and R. T., urinary sodium excretion returned to the base line rate on the 5th treatment day. In four other subjects, sodium excretion was still below the base line rate when DOCA administration was stopped after 6-8 days of treatment, as shown in Fig. 1. Urinary chloride excretion, measured daily in V. C. and R. T., was decreased to the same extent as sodium excretion by DOCA administration.

Treatment with 9α-FF was initiated with low or modest dosages which were increased at 4-6 day intervals. Sodium retention occurred in every instance. The decrement in sodium excretion was not sustained for more than 4 days by any dosage schedule. However, each increase in drug dosage resulted in more sodium being retained. In one subject, S. R. (Table I), whose control aldosterone excretion rate was 197 μg/24 hr, a dosage of only 0.2 mg daily resulted in appreciable sodium retention. Increases in body weight of 0.9–3.9 kg

occurred during mineralocorticoid treatment and comparable losses were observed during recovery. Effects of 9α-FF in gravid subject, R. H., are depicted in Fig. 2.

Aldosterone excretion rates decreased markedly during administration of DOCA or 9α-FF, and in every instance the magnitude of the decline was comparable to that shown in Figs. 1-3. After cessation of mineralocorticoid treatment, aldosterone excretion rates rose gradually, reaching control values by the end of recovery periods except in M. H. and R. H., whose studies were terminated after only 4 and 5 days of recovery, respectively. Brisk natriureses ensued after discontinuance of treatment which did not subside until aldosterone excretion returned to high pretreatment levels. In M. H. and R. H., the failure of aldosterone excretion to return completely to base line rates by the end of their abbreviated recovery periods was associated with persistence of natriureses, as shown in Fig. 2.

In contrast to similar studies in nonpregnant subjects (2-5), potassium excretion was virtually unaffected by the administration of DOCA or 9α-FF. The greatest cumulative losses were only 25 and 16 mEq occurring in V. C. and K. D. during 8 and 10 days of treatment with up to 40 mg of DOCA or 1.6 mg of 9α-FF daily. In one subject, K. D., sodium intake was abruptly increased from 93 to 195 mEq daily, and although a major portion of this increment was retained during the first 48 hr, no increase in potassium excretion occurred (Fig. 3).

Effects of ACTH administration upon urinary electrolytes and aldosterone excretion. Six studies were performed with ACTH in five pregnant women. ACTH administration resulted in positive sodium balance in every study (Table I). Cumulative sodium retention resulting from ACTH administration in three of the subjects was greater than in any of the women treated with DOCA or 9α-FF. One ACTH-treated subject, V. R. (Fig. 4), retained 603 mEq of sodium, and two others, P. D. and P. T. (Table I), retained 463 and 352 mEq, respectively.

Aldosterone excretion rates increased transiently after the initiation of ACTH injections, but then declined pro-

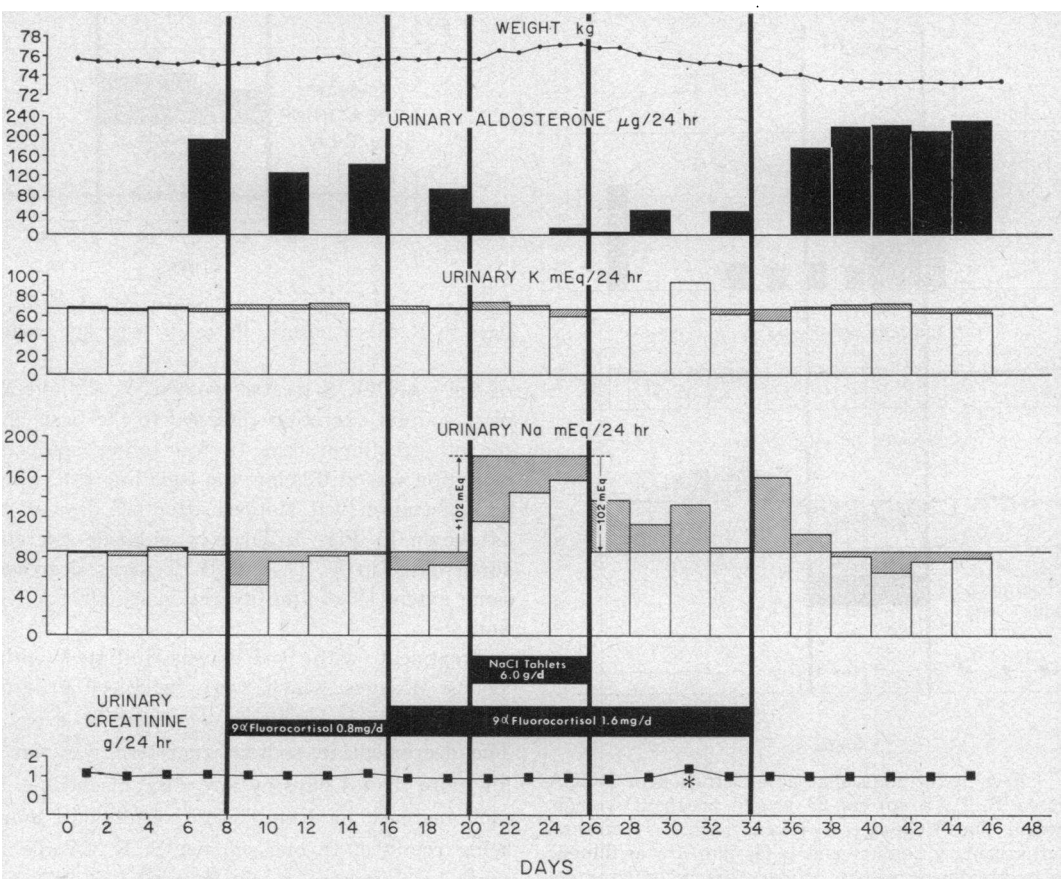

FIGURE 3 Effect of increased salt ingested during oral administration of 9α-FF in K. D., a 19 yr old normal pregnant woman. Asterisk indicates high 24 hr urinary creatinine excretion suggesting collection error.

gressively with continued treatment soon falling far below control values (Fig. 4). Generally, the degree of lowering of aldosterone excretion rates tended to correlate with the quantity of sodium retained. In P. D. aldosterone excretion was reduced to a much lower level by the same ACTH dosage during a study in which daily sodium intake was 138 mEq than during a similar study with sodium intake of 20 mEq. ACTH administration resulted in marked increments in urinary free cortisol excretion; the magnitude of these responses was similar to that shown in Fig. 4.

After discontinuance of ACTH, suppression of aldosterone excretion rates persisted and was accompanied by intense natriureses which did not abate until aldosterone excretion was restored to high levels noted before treatment. Quantities of sodium lost during recovery periods exceeded amounts retained during ACTH treatment in all subjects (Table I). In V. R. (Fig. 4), sodium loss during recovery was 921 mEq compared to 603 mEq retained during ACTH administration.

ACTH administration resulted in negligible changes in urinary potassium excretion in three of the studies and in the other three slight increases occurred. Maximum urinary loss was 66 mEq in K. C., and in V. R. there was a slight irregular rise in urinary potassium excretion resulting in a net loss of 63 mEq.

Studies in normal men: effect of progesterone upon DOCA-induced kaliuresis

The intramuscular administration of DOCA 20 mg/day to two normal young men resulted in sodium retention followed by the occurrence of escape on the 5th day. Kaliureses commenced on the 1st day of treatment and were sustained up to the time that progesterone was given (Figs. 5 and 6). While continuing administration of DOCA, the addition of intramuscular progesterone 50 mg twice a day resulted in decreased urinary potassium excretion. In D. T. (Fig. 6) urinary potassium excretion was reduced to the base line rate, and in E. G. (Fig. 5) it fell below the base line average. When progesterone administration was stopped after 6 days, the kaliureses promptly resumed in both subjects. During treatment with progesterone, urinary sodium excretion in D. T. did not change appreciably, but was irregularly increased in E. G. However, in both subjects, sodium excretion fell after discontinuing progesterone. When DOCA was finally stopped, a marked natriuresis ensued accompanied by decreased urinary potassium excretion.

DISCUSSION

In earlier reports, it was claimed that administration of DOCA (6), aldosterone (7), or ACTH (8) to pregnant women had no effect upon urinary sodium excretion. Since such unresponsiveness occurs in patients with primary aldosteronism (14) and in normal persons during

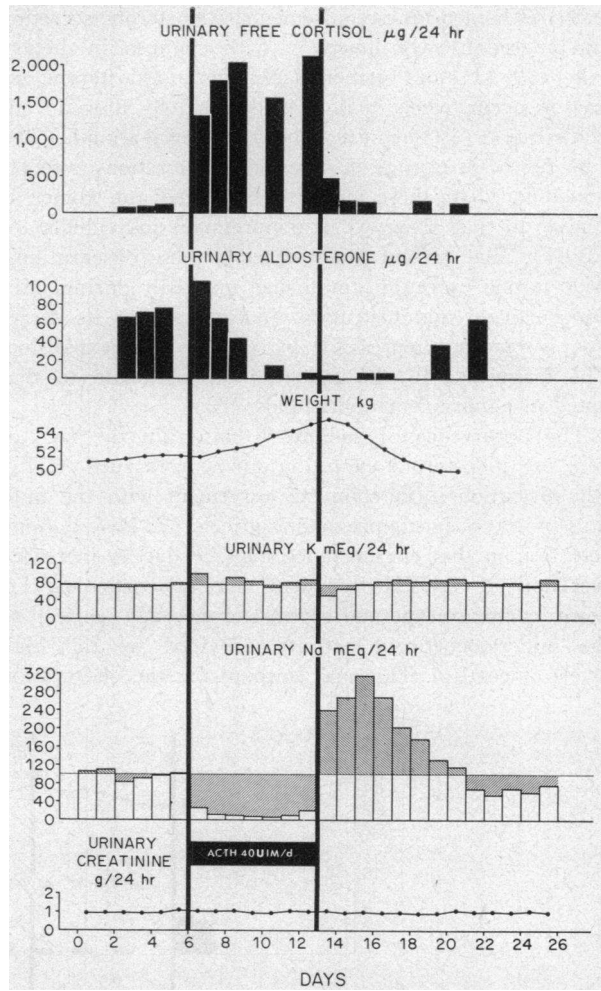

FIGURE 4 Effect of intramuscular administration of ACTH for 7 days to V. R., a 29 yr old normal pregnant woman.

continued administration of large doses of mineralocorticoids (2-5), it was suggested that pregnant women have escaped from the sodium-retaining effect of *excessively* secreted aldosterone. This suggestion was supported by the observation that the glomerular filtration rate and maternal extracellular fluid volume are increased during pregnancy (15), since excessive mineralocorticoids produce similar changes in nonpregnant individuals (14, 16-18). However, in contrast to the renal refractoriness previously noted by others, the present data obtained during carefully controlled metabolic studies clearly demonstrate that pregnant women are responsive to the sodium-retaining action of administered mineralocorticoids or ACTH. In every instance, experimentally-induced increases in mineralocorticoid activity resulted in substantial sodium retention.

Aldosterone excretion, although markedly increased in pregnancy, responds normally to physiologic stimuli, which would not occur if the secretion of aldosterone

exceeded homeostatic requirements. Aldosterone secretion and excretion vary inversely with changes in dietary salt (1, 9, 13), and further increments in aldosterone excretion occur when volume is depleted by diuretic administration (19) or in response to postural stimuli (20). The degree of change in aldosterone excretion or secretion induced by these maneuvers in pregnant women is similar to that observed in nonpregnant individuals (9, 13, 21). The present study extends these observations. Aldosterone excretion diminished markedly during mineralocorticoid administration, indicating that its secretion is readily suppressible by volume hyperexpansion. The magnitude of the fall was proportionate to that noted in nonpregnant individuals (22).

The occurrence of sodium retention in the face of very low aldosterone excretion during continued ACTH administration is in complete agreement with the findings of others in nonpregnant subjects (23-26). Sodium retention in this circumstance may be due to increased secretion of ACTH-dependent mineralocorticoids, i.e. desoxycorticosterone and corticosterone (25), as well as the mineralocorticoid activity provided by the high levels of cortisol. This may account for the observation that greater quantities of sodium were retained during ACTH administration in three of the pregnant women than in any of those receiving DOCA or 9α-FF. Aldosterone does not play an important role during continued ACTH administration, since its secretion is only transiently increased initially and then declines progressively while sodium retention persists (23-26). The relationship of the sodium retention to the depression of aldosterone production has not been clearly defined, but studies in nongravid subjects suggest that the fall in aldosterone secretion is due to a direct intra-adrenal effect of ACTH, rather than to suppression by ACTH-induced sodium retention (25, 26). However, in the present study, there was good correlation between the quantity of sodium retained and the extent to which aldosterone excretion decreased. This relationship is particularly evident in the sequential experiments performed with high and low salt intake in P. D. (Table I).

Diminished aldosterone excretion persisted for up to 8 days after discontinuance of mineralocorticoid or ACTH administration. It is noteworthy that the ensuing natriureses continued during the recovery periods while aldosterone excretion rates, although greatly diminished

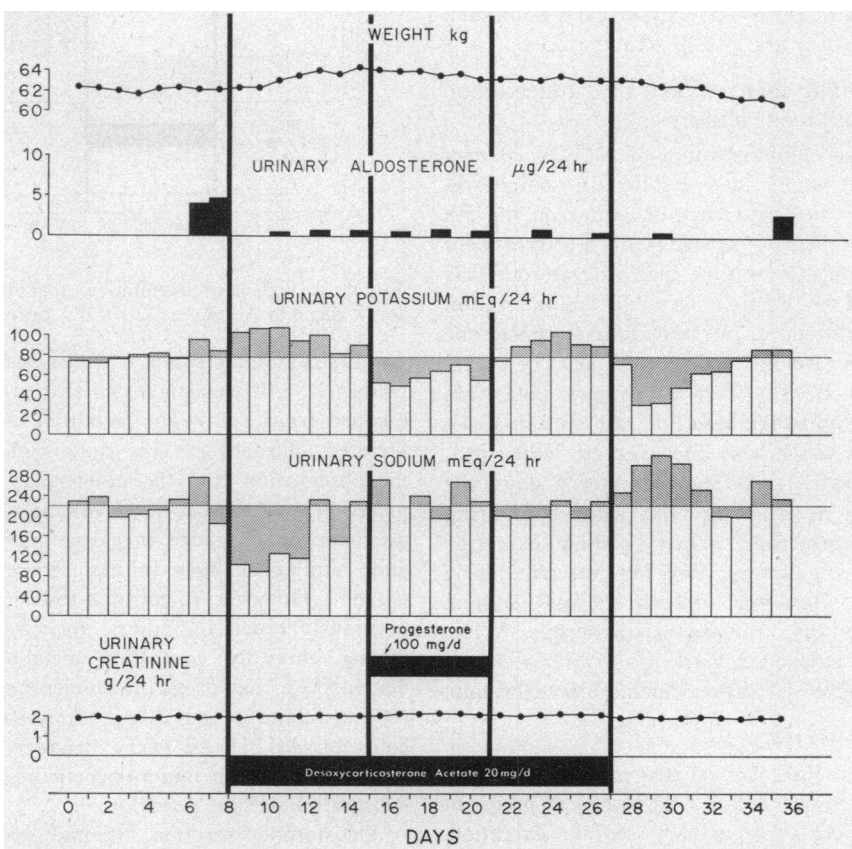

FIGURE 5 Effect of intramuscular progesterone administered to E. G., a 24 yr old normal man during continued treatment with intramuscular DOCA.

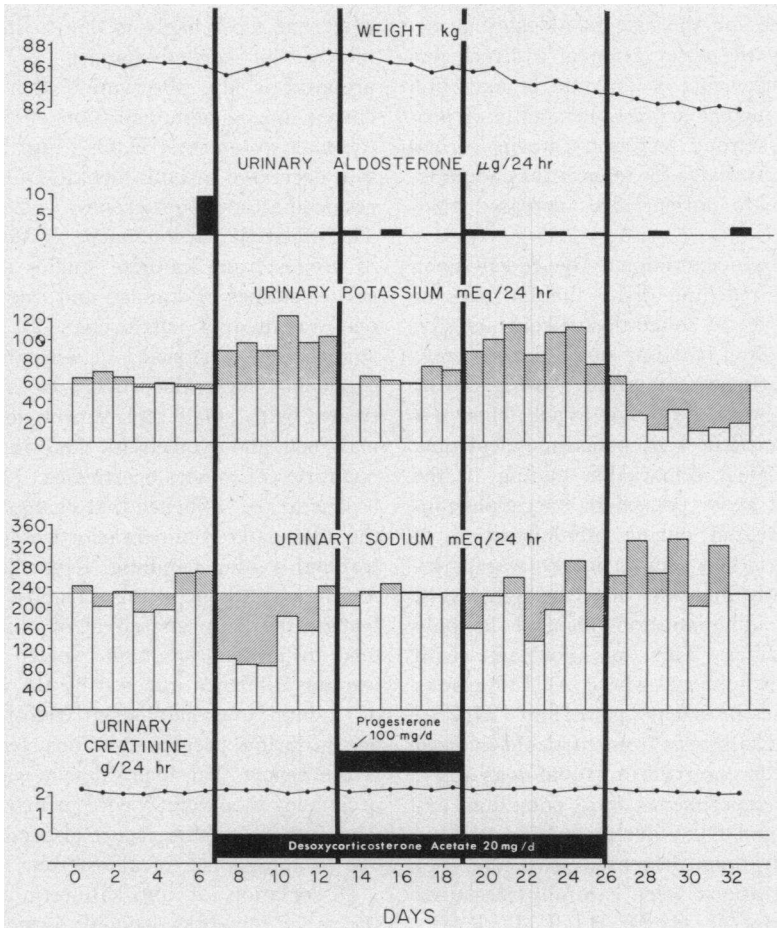

FIGURE 6 Effect of intramuscular progesterone administered to D. T., a 24 yr old normal man, during continued treatment with intramuscular DOCA.

compared to control values, were above normal nongravid levels. Sodium losses during recovery did not abate until aldosterone excretion rose to pretreatment rates (Figs. 1-4). In a previously reported study, aldosterone excretion was inhibited without concomitant volume expansion in pregnant women by heparinoid administration (10). Not only did the resultant natriuresis persist after cessation of heparinoid treatment until aldosterone excretion rates returned to the very high values characteristic of pregnancy, but also during treatment, the inhibition of aldosterone secretion resulted in profound sodium losses which commenced while the aldosterone excretion rates were still above nonpregnant values.

These observations provide strong evidence that increased aldosterone secretion is required in order to maintain sodium balance in pregnant women, and accordingly, it can also be assumed that during pregnancy, there are potent factors opposing the sodium-retaining effects of aldosterone. Since aldosterone secretion in pregnant women responds normally to physiologic stimuli, it can be concluded that its increased secretion is not excessive, but reflects a physiologic response to threatened sodium depletion.

Several known factors in pregnancy promote sodium loss and consequently could elicit a compensatory rise in aldosterone secretion. The glomerular filtration rate (GFR) is increased 50% during pregnancy (15), and even if glomerulotubular balance were maintained in the proximal nephron, there would still be an increment in the amount of sodium presenting to more distal tubular sites where aldosterone stimulates sodium reabsorption. However, the sodium-retaining action of aldosterone at certain of these sites is competetively inhibited by progesterone (27), which is secreted in large amounts during pregnancy. Thus, increased secretion of aldosterone would be required in pregnancy to offset the threatened sodium loss imposed by the convergent effects of the increased GFR and the aldosterone-inhibiting effects of progesterone. That pro-

gesterone is responsible for the rise in aldosterone secretion is supported by the observation of a direct correlation between measurements of the rate of excretion of pregnanediol, the principal urinary metabolite of progesterone and the aldosterone secretion rate in normal pregnant women (28), and also by reports that administration of progesterone to normal men increased aldosterone secretion (29).

Since urinary potassium excretion is dependent upon the amount of sodium reaching distal tubular sites as well as the existing level of mineralocorticoid activity, the changes in renal sodium handling noted during pregnancy should lead to urinary potassium wasting. However, normal pregnant women are not hypokalemic nor do they exhibit other evidences of potassium depletion. On the contrary, the most remarkable finding in the present study was that renal potassium excretion consistently was not increased during administration of mineralocorticoids even when sodium intake was maintained at or was abruptly increased to very high levels. Furthermore, ACTH administration resulted in only slight, transient kaliureses. This too, contrasts with findings in nonpregnant subjects where ACTH results in more marked increases in urinary potassium (24, 25). A similar dissociation of kaliuresis from corticoid-induced sodium retention has been observed in gravid dogs (11). However, in these dog experiments, fecal potassium excretion was enhanced by DOCA administration and serum potassium concentrations decreased markedly. Serum potassium concentrations were carefully measured in studies in six subjects (V. C., M. H., R. T., R. H., P. D., K. D.). Values decreased slightly (4.08-3.91 mEq/liter), which may have been related to the increased extracellular fluid volume; fecal potassium was not measured. Slight urinary potassium retention occurred after discontinuing treatment, perhaps reflecting recovery of antecedent fecal losses or cumulative urinary losses which were too small to be appreciated in individual 24-hr collections.

One possible explanation for the absence of kaliuresis noted in pregnant women is that the administered mineralocorticoids resulted mainly in enhanced distal tubular secretion of hydrogen ions rather than potassium ions. This possibility cannot be ruled out with certainty since urinary ammonium excretion and titratable acidity were not measured, although it is extremely unlikely in view of the observation that urinary chloride excretion was decreased to the same extent as sodium excretion during the administration of DOCA.

The abolition of DOCA-induced kaliuresis in the normal men by the administration of progesterone suggests that endogenously-secreted progesterone is responsible for the failure of administered mineralocorticoids to induce kaliureses in pregnant women. This effect of progesterone most likely is due to its capacity to act as a mineralocorticoid antagonist (27). Consistent with this proposal is the observation that slight natiuresis occurred during administration of progesterone to one of the male volunteers, E. G. (Fig. 5), and sodium excretion decreased in both men as DOCA-induced kaliureses resumed after progesterone was stopped (Figs. 5 and 6). The apparent predominance of the anti-kaliuretic effect of progesterone in these studies differs from results of earlier studies by Landau and Lugibihl where progesterone was mainly natriuretic (27, 30). However, their studies were performed in normal subjects receiving no exogenous mineralocorticoid or in Addisonian patients treated with small replacement doses, whereas the normal men and women in this study received excessive quantities of mineralocorticoids. These differences might be due to the influence that changes in volume status, or the administered mineralocorticoids might have upon intrarenal sodium handling. Regardless of the explanation for these differences, this capacity of progesterone to attenuate the kaliuretic effect of mineralocorticoids would tend to protect pregnant women from the potassium-wasting influence imposed by the increased filtered load of sodium and heightened aldosterone activity which occur during pregnancy. Consistent with this proposal is the report that hypokalemia was ameliorated during pregnancy in a woman with primary aldosteronism (31). The authors of this report also concluded that this was due to antagonism of aldosterone by progesterone.

Dissociation of anti-kaliuretic and sodium-retaining effects of mineralocorticoids is consistent with current concepts of distal tubular function. Micropuncture and microperfusion studies performed on single nephrons indicate that potassium secretion is not stoichiometrically coupled to active inward sodium transport by an ion-exchange process (32, 33). Indeed, such studies have shown that the distal convoluted tubule is the main site for potassium secretion, whereas lowest sodium concentrations are achieved in the collecting duct. Furthermore, aldosterone is no longer believed to act at a single distal tubular site, but may also enhance sodium reabsorption in the ascending loop of Henle (34-36), a site where potassium secretion does not occur.

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