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Effect of mineralocorticoid replacement therapy on renal acid-base homeostasis in adrenalectomized patients

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Effect of mineralocorticoid replacement therapy on renal acid-base homeostasis in adrenalectomized patients. Chronic balance studies were performed in six adrenalectomized patients to investigate the renal and systemic acid-base consequences of mineralocorticoid deficiency in the absence of either glucocorticoid deficiency or parenchymal renal disease. Constant glucocorticoid replacement was provided with dexamethasone, 750 to 875 μg/day, administered orally. Creatinine clearance averaged 98 ± 8 ml/min/1.73 m^2. Following a control period, mineralocorticoid replacement with fludrocortisone (100 to 200 μg/day) was either discontinued ($N = 3$) or initiated ($N = 2$). In an additional patient, mineralocorticoid replacement was initiated and sustained (5 days) by continuous i.v. infusion of aldosterone, at a dose approximating the normal secretion rate (120 μg/day). Net acid excretion (NAE) and plasma total carbon dioxide decreased in each patient in whom mineralocorticoid was discontinued and increased in each patient in whom mineralocorticoid was initiated. The cumulative change in NAE ($\Sigma\Delta$NAE) independent of direction averaged 66 ± 20 mEq ($P < 0.05$) by the fifth experimental day in the six patients, and the corresponding change in plasma total CO_2 averaged 1.2 ± 0.3 mmoles/liter ($P < 0.02$). The magnitude of $\Sigma\Delta$NAE correlated with the basal rate of NAE ($r = 0.87$, $P < 0.05$), which averaged 0.9 ± 0.1 mEq/kg body wt per day. The change in plasma total CO_2 correlated with $\Sigma\Delta$NAE ($r = 0.83$, $P < 0.05$). The changes in NAE correlated positively with the corresponding changes in sodium balance and negatively with the corresponding changes in potassium balance. These findings provide the first evidence that renal acidification is under tonic stimulation by mineralocorticoid at levels not exceeding those in normal subjects ingesting acid-producing diets of normal sodium and potassium content. The extent to which the tonic stimulation of renal acidification is mediated by a direct effect of mineralocorticoid on renal hydrogen ion transport or by an indirect effect dependent on altered renal sodium and/or potassium transport requires further investigation. The findings implicate mineralocorticoid deficiency as a significant renal acidosis-producing condition not dependent on the presence of renal disease or glucocorticoid deficiency, and potentially amplified when endogenous acid production is increased by diet or disease.

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Effet du traitement substitutif par les minéralocorticoïdes sur l'homéostasie rénale acido-basique chez les malades surrénalectomisés. Des bilans ont été réalisés chez six malades surrénalectomisés afin d'étudier les conséquences acido-basiques du déficit en minéralocorticoïdes en l'absence soit de déficit en glucocorticoïdes ou de maladie rénale parenchymateuse. Un remplacement constant des glucocorticoïdes a été réalisé par la dexaméthasone, 750 à 875 μg/jour, par voie orale. La clearance de la créatinine était en moyenne de 98 ± 8 ml/min/l, 73 m^2. Après une période contrôle le remplacement des minéralocorticoïdes par la fludrocortisone (100 à 200 μg/jour) a été soit arrêté ($N = 3$) soit commencé ($N = 2$). Chez un autre malade le remplacement des minéralocorticoïdes a été commencé et prolongé au moyen d'une perfusion intraveineuse d'aldostérone à une dose proche du débit de sécrétion normal (120 μg/jour). L'excrétion nette d'acide (NAE) et le CO_2 total du plasma ont diminué chez tous les malades chez qui les minéralocorticoïdes ont été arrêtés et augmenté chez tous les malades chez lesquels les minéralocorticoïdes ont été commencés. La modification cumulée de NAE ($\Sigma\Delta$NAE), indépendamment du sens, était en moyenne de 66 ± 20 mEq ($P < 0,05$) au cinquième jour expérimental chez les six malades et la modification correspondante de la CO_2 total du plasma était en moyenne de 1,2 ± 0,3 mmoles/litre ($P < 0,02$). L'importance de $\Sigma\Delta$NAE était corrélée avec le débit basal de NAE ($r = 0,87$, $P < 0,05$) qui était en moyenne de 0,9 ± 0,1 mEq/kg de poids corporel par jour. Le modification de la CO_2 total du plasma était corrélé avec $\Sigma\Delta$NAE ($r = 0,83$, $P < 0,05$). Les modifications de NAE étaient corrélées positivement avec les modifications correspondantes du bilan du sodium et négativement avec les modifications du bilan du potassium. Ces constatations apportent pour la première fois la preuve que l'acidification rénale est sous l'influence tonique de la stimulation par les minéralocorticoïdes à des concentrations qui ne dépassent pas celles des sujets normaux qui ingèrent des régimes générateurs d'acide et dont les contenus en sodium et potassium sont normaux. La mesure dans laquelle la stimulation tonique de l'acidification rénale a pour médiateur un effet direct des minéralocorticoïdes sur le transport rénal de l'ion hydrogène ou bien un effet indirect dépendant des modifications du transport du sodium et/ou du potassium nécessite d'autres études. Ces constatations indiquent que le déficit en minéralocorticoïdes est une situation qui détermine une acidose rénale indépendamment de la présence d'une maladie rénale ou d'un déficit en glucocorticoïdes. L'acidose est plus importante quand la production endogène d'acide est augmentée par l'alimentation ou une maladie.

In normal humans, the administration of mineralocorticoid hormones that possess minimal glucocorticoid activity results in agumentation of renal hydrogen ion secretion [1–7]. Acute administration of aldosterone in large amounts to normal subjects results within hours in a decrease in urine pH [3–6] and an increase in net acid excretion [3, 4, 6, 7]. Chronic administration of large amounts of aldosterone results in a sustained increase in plasma bicarbonate concentration and pH indicative of the development of metabolic alkalosis [8].

It has not been established whether mineralocorticoid hormones at normal plasma concentrations modulate renal acidification and systemic acid-base equilibrium in normal adult humans. Aldosterone deficiency has been implicated in the pathogenesis of renal metabolic acidosis in humans with renal diseases [9], but whether renal acidosis occurs in humans with aldosterone deficiency who do not have renal disease has not been conclusively determined. Renal metabolic acidosis has been reported in infants and children with hypoaldosteronism secondary to defects in adrenal steroid biosynthesis (for example, 21 β-hydroxylase deficiency) [10] and in children with inherited renal unresponsiveness to aldosterone (so-called pseudohypoaldosteronism) [11], but critical evaluations of acid-base status after the affected children have reached adulthood have not been reported. In adult patients with Addison's disease or bilateral adrenalectomy, it has been reported that systemic acid-base equilibrium is maintained "normal" without mineralocorticoid replacement therapy, provided that glucocorticoid replacement therapy is adequate, renal function is unimpaired by intrinsic renal disease, and salt intake is liberal or unrestricted [12, 13].

Analysis of the reported data in adrenalectomized patients maintained on glucocorticoid therapy without mineralocorticoid replacement does not compel the conclusion that acid-base equilibrium is decidedly normal [12]. It is possible that plasma bicarbonate concentration is regulated at a significantly lower level during mineralocorticoid deficiency than it is in the mineralocorticoid-replete state, yet the resultant mild degree of metabolic acidosis might remain unrecognized unless plasma bicarbonate is compared in both states inasmuch as interindividual variation in plasma bicarbonate concentration in normal subjects is large [14, 15]. In adult subjects with selective mineralocorticoid deficiency who do not have intrinsic renal disease, there appear to be no reported studies in which systemic acid-base equilibrium and renal acid-base homeostasis have been critically evaluated in the same subjects with and without mineralocorticoid therapy under controlled study conditions, with particular attention to constancy of dietary acid load. The present studies were carried out to further investigate the acid-base effects of selective mineralocorticoid deficiency in such subjects.

Methods

The experimental protocol consisted of either discontinuation or institution of replacement mineralocorticoid therapy in six adult adrenalectomized patients studied under metabolic balance conditions. The studies were performed at least 1 year following surgical removal of both adrenal glands for treatment of carcinoma of the breast (patients 1–3), Cushing's syndrome (patients 4 and 6), or primary aldosteronism (patient 5). None of the patients had historical or laboratory evidence of renal disease (Table 1). The studies were carried out in the General Clinical Research Centers at Moffitt Hospital and San Francisco General Hospitals, University of California, San Francisco. The protocols were approved by the Committee on Human Research, and each patient gave informed consent.

The change in mineralocorticoid therapy was made after acid-base and electrolyte balance had been achieved with each patient receiving a constant diet and constant glucocorticoid replacement therapy. Glucocorticoid was provided as dexamethasone (Merck, Sharp and Dohme), 750 μg (patients 1–3, 5, 6) or 875 μg (patient 4), administered orally once daily. During the specified periods of mineralocorticoid replacement therapy (Table 1), mineralocorticoid was provided as fludrocortisone (Squibb), 100 to 200 μg, administered orally once daily (patients 1–5), or *d*-aldosterone (Ciba), 120 μg, administered i.v. by constant infusion over 24 hours each day (patient 6). The daily dose of mineralocorticoid was constant in each patient throughout the specified period.

The conditions of study in each patient are summarized in Table 1. A control period of 4 to 10 days' duration (average, 7 days) was initiated following an equilibration period of variable duration required for achievement of acid-base and electrolyte balance on the specified constant regimen of whole food diet and steroid administration. The entire daily diet was ingested by each patient with the exception of patient 3 in whom dietary noncompliance necessitated termination of study following 3 days of mineralocorticoid discontinuation.

Potassium intake was constant in each study and ranged from 1.0 to 1.6 mEq/kg body wt per day

Table 1. Biochemical data and protocol conditions in adrenalectomized patients without renal disease[a]

Patient no., age (*yr*), sex, wt (*kg*)	Study days	Steroid dose[b] *μg/day*			Intake *mEq/kg/day*		Creatinine clearance *ml/min/1.73 m²*	Urinary aldosterone *μg/day*	Plasma renin activity *ng/ml/hr*	
		Dex	Fludro	Aldo	Sodium	Potassium			Recumbent	Upright
Mineralocorticoid discontinuation studies										
1, 49, F, 67	1–10	750	100	0	1.5	1.3	108	<1	0.4	1.1
	11–18	750	0	0	1.5	1.3		<1	3.3	9.5
	19–21	750	0	0	6.8	1.3		<1	—	2.4
2, 60, F, 63	1–8	750	200	0	1.9	1.6	92	<1	2.9	8.4
	9–22	750	0	0	5.1	1.6		<1	2.4	19.0
3, 54, F, 62	1–5	750	150	0	1.1	1.6	94	<1	1.2	7.6
	6–8	750	0	0	1.1	1.6		<1	—	—
Mineralocorticoid initiation studies										
4, 47, F, 74	1–4	875	0	0	3.0	1.0	70	<1	19.1	—
	5–8	875	150	0	2.0	1.0		—	5.6	8.1
	9–10	875	150	0	3.0	1.0		—	—	—
5, 48, M, 76	1–7	750	0	0	3.1	1.2	95	<1	9.8	26.6
	8–12	750	150	0	1.8	1.2		<1	—	—
6, 47, F, 53	1–5	750	0	0	2.9	1.9	131	<1	9.8	20.5
	6–10	750	0	120	2.9	1.9		11	2.6	5.3

[a] Values of plasma renin activity (in ng/ml/hr) in our laboratory for normal subjects ingesting 1.8 ± 0.3 SD mEq/kg body wt per day dietary sodium were: ages 42 to 62, $N = 9$, PRA 0.1 to 0.6 (supine), 0.9 to 7.9 (upright).

[b] Dex is dexamethasone, Fludro is fludrocortisone, Aldo is aldosterone.

among the subjects (Table 1). Sodium intake was constant during the equilibration and control periods in all studies and ranged from 1.1 to 1.9 mEq/kg/day in the three subjects (patients 1–3) who were receiving mineralocorticoid replacement during these periods, and from 2.9 to 3.1 mEq/kg/day in the three patients (patients 4–6) who were not receiving mineralocorticoid replacement during these periods. In one subject (patient 2), sodium intake was increased simultaneous with discontinuation of mineralocorticoid therapy, in an attempt to minimize negative sodium balance resulting from renal sodium wasting. Sodium intake was also increased in patient 1, but not until an 8-day period of mineralocorticoid deficiency had occurred without change in sodium intake (Table 1). In two patients (patients 4 and 5), sodium intake was decreased simultaneously with institution of mineralocorticoid therapy, in an attempt to minimize positive sodium balance resulting from renal sodium retention. Adjustment of sodium intake was effected without change in composition of foodstuffs by adjustment of the amount of sodium chloride administered as weighed tablets supplementing the diet. Intrinsic diet sodium and potassium content was calculated by a research dietitian from standard food composition tables [16]; previous studies from this laboratory have demonstrated close correspondence between calculated and analyzed estimates of dietary electrolyte composition [17].

Analytical procedures used in this laboratory have previously been described [9]. Urinary aldosterone-18-glucuronide was measured by radioimmunoassay [18]. Statistical analysis was by linear regression and Student's t test [19]. Estimates of variance are reported as ±SEM.

Results

Summary of results in patient no. 1. Figure 1 depicts the results of a representative study of the effect of mineralocorticoid discontinuation. During the control period, the mean value of urinary net acid excretion was 80 mEq/day, and the daily values differed from the mean by no more than 9 mEq/day. On the first day following discontinuation of mineralocorticoid therapy, net acid excretion decreased by 38 mEq from the mean control value. Subsequently, the daily values of net acid excretion remained below control but gradually increased toward control. By day 8, the cumulative reduction in net acid excretion ($\Sigma\Delta NAE$) from the mean control value was 196 mEq. During the final 3 days, net acid excretion returned to control values, and no further cumulative reduction in net acid excretion occurred. This apparent reestablishment of acid-base

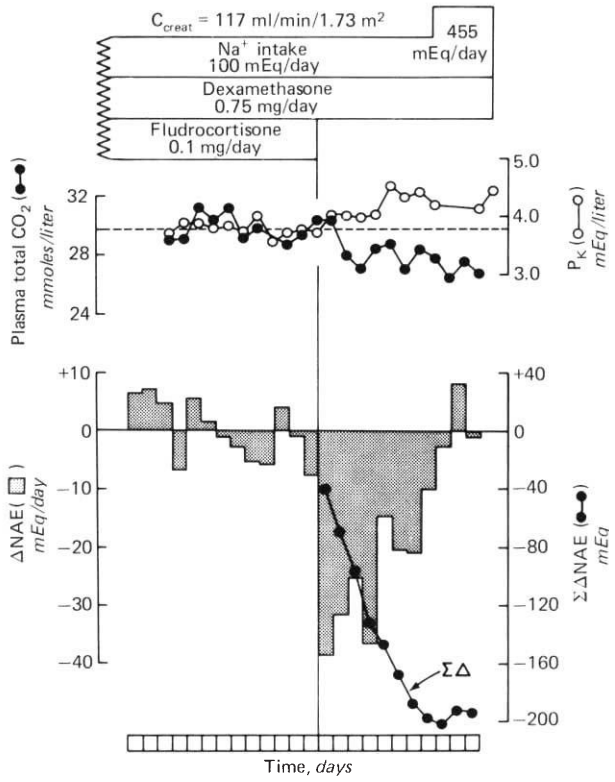

Fig. 1. *Representative study of the effect of discontinuation of mineralocorticoid replacement therapy in an adrenalectomized patient without apparent intrinsic renal disease (patient no. 1).* The *dashed line* in the *upper panel* represents the mean control value of both plasma total carbon dioxide and potassium concentration (P_K). Values of Δ net acid excretion (ΔNAE) represent the difference between the daily net acid and the mean control values. Values of ΣΔ net acid excretion (ΣΔNAE) represent the accumulated sum of the daily values of Δ net acid excretion during the period of mineralocorticoid discontinuation.

balance was temporally associated with a large increase in sodium chloride intake.

The reduction in ΣΔNAE following mineralocorticoid discontinuation was accounted for in part by an increase in urinary bicarbonate ($\Sigma\Delta HCO_3^-$, +61 mEq) and in part by decreases in urinary titratable acid (ΣΔTA, −49 mEq) and ammonium ($\Sigma\Delta NH_4^+$, −86 mEq).

In association with the observed reduction in net acid excretion, a small but significant reduction occurred in venous plasma total carbon dioxide (Δ plasma total CO_2, −1.7 mmoles/liter; plasma total CO_2 control vs. days 5-8, 29.8 ± 0.3 vs. 28.1 ± 0.4 mmoles/liter, $P < 0.02$) (Fig. 1, Table 2). There was no tendency for the reduced values of plasma total CO_2 to return toward control throughout the 11-day period of mineralocorticoid discontinuation. Arterialized blood hydrogen ion concentration increased slightly (Table 2). No significant change occurred in plasma anion gap.

In the control period, mean urinary potassium excretion was 70 ± 1 mEq/day; the daily values differed from the mean by no more than 7 mEq/day. During the first 4 days following mineralocorticoid discontinuation, daily potassium excretion decreased from the mean control value by 12 to 18 mEq. Thereafter, potassium excretion returned to values virtually identical to control. This apparent reestablishment of balance occurred prior to the large increase in sodium chloride intake that was initiated on the 9th day following mineralocorticoid discontinuation. The cumulative retention of urinary potassium was 74 mEq, and was associated with a sustained significant increase in plasma potassium concentration (3.8 ± 0.0 vs. 4.3 ± 0.1 mEq/liter, $P < 0.001$, control vs. days 5-8).

Following mineralocorticoid discontinuation, a significant increase in urinary sodium and chloride excretion occurred ($\Sigma\Delta Na^+$, +609 mEq; $\Sigma\Delta Cl^-$, +396 mEq; day 8), accompanied by a significant reduction in plasma sodium and chloride concentration (P_{Na}, 139 ± 1 vs. 133 ± 2 mEq/liter, $P < 0.005$; P_{Cl}, 104 ± 0.4 vs. 99 ± 0.8 mEq/liter, $P < 0.001$). Plasma renin activity was within normal limits with respect to posture and dietary sodium prior to mineralocorticoid discontinuation, and increased to supernormal values following mineralocorticoid discontinuation (Table 1). In response to a large increase in sodium intake (days 9-11 of mineralocorticoid discontinuation), urinary sodium increased to approximate intake, and plasma sodium concentration (136 mEq/liter) and renin activity (2.4 ng/ml/hr, upright) returned toward control (day 11).

Summary of results for entire group: (a) Acid-base changes. Within 24 hours of discontinuing mineralocorticoid replacement in each patient (patients 1-3), urine pH increased, and the urinary excretion rates of titratable acid, ammonium, and net acid decreased (Fig. 2). Conversely, within 24 hours of initiating mineralocorticoid replacement in each patient (patients 4-6), urine pH decreased, and the excretion rates of titratable acid, ammonium, and net acid increased (Fig. 2). Because the directional change in each of these indexes of urine acid-base composition was indicative of a positive effect of mineralocorticoid on acidification in every patient, the magnitude of the change in each index was used without regard for sign for purposes of statistical testing. Averaging the absolute values of the differences between mineralocorticoid-replete and -de-

Table 2. Acid-base effects of discontinuation or initiation of mineralocorticoid replacement therapy in glucocorticoid-replete adrenalectomized patients without intrinsic renal disease

Patient no.	Mineralocorticoid dose	Venous plasma total CO_2 *mmoles/liter*	Δ Plasma total CO_2[a] *mmoles/liter* Day 5	Δ Plasma total CO_2[a] *mmoles/liter* Days 4–5	Δ Arterialized blood $[H^+]$ *nEq/liter*	Initial net acid excretion *mEq/day*	Cumulative change in net acid *mEq*	Cumulative change in Na^+ balance[b] *mEq*
		Mineralocorticoid discontinuation studies[c]						
1	Fludrocortisone 100 μg/day	29.8 ± 0.3				80.3 ± 1.8		
	Discontinued							
	day 1						− 38	
	day 3						− 94	
	day 5	28.7	−1.1	−1.2	+1.7		−145	−400
2	Fludrocortisone 200 μg/day	29.6 ± 0.4				63.1 ± 2.0		
	Discontinued							
	day 1						− 10	
	day 3						− 30	
	day 5	29.0	−0.6	−0.5			− 57	− 16
3	Fludrocortisone 150 μg/day	29.6 ± 0.4				37.2 ± 1.4		
	day 1						− 23	
	day 3	28.9	−0.7	−1.3			− 41	−230
		Mineralocorticoid institution studies[d]						
4	Mineralocorticoid—none	26.9 ± 0.3				55.3 ± 0.7		
	Initiate fludrocortisone 150 μg/day							
	day 1						+ 10	
	day 3						+ 38	
	day 5	27.6	+0.7	+1.2	−1.8		+ 42	+229
5	Mineralocorticoid—none	28.1 ± 0.2				63.6 ± 1.0		
	Initiate fludrocortisone 150 μg/day							
	day 1						+ 3	
	day 3						+ 19	
	day 5	29.3	+1.2	+0.8	−0.9		+ 47	+ 13
6	Mineralocorticoid—none	23.8 ± 0.4				41.6 ± 2.1		
	Initiate aldosterone 120 μg/day							
	day 1						+ 13	
	day 3						+ 26	
	day 5	26.4	+2.6	+2.4	−7.1		+ 37	+456
	Combined groups[e] ($N = 6$)						ΣΔNAE	
	Mean of absolute values of Δ and ΣΔ		1.2 ± 0.3 $P < 0.02$ (day 5)	1.2 ± 0.3 $P < 0.01$ (days 4–5)			day 1, 16 ± 5, $P < 0.05$ day 3, 41 ± 11, $P < 0.02$ day 5, 66 ± 20, $P < 0.05$	

[a] In patient no. 3, data for days 3 and 2 to 3 are used owing to dietary noncompliance after day 3; in patients no. 2 and 6, data for days 5 and 6 are used instead of days 4 and 5 because day 4 blood specimens were not drawn.

[b] Cumulative change in sodium balance is the accumulated daily external balance calculated solely from changes in urinary excretion relative to intake.

[c] Values during mineralocorticoid therapy are steady-state values prior to discontinuation of mineralocorticoid therapy.

[d] Values prior to mineralocorticoid initiation are steady-state values.

[e] Δ Plasma total CO_2 and ΣΔNAE represent the average of their absolute values for the two groups of patients combined; P values indicate the probability of a significant difference from zero.

prived states in the six patients, we found the changes in urine pH and excretion of titratable acid, ammonium, and net acid to be statistically significant: $\Delta pH = 0.31 \pm 0.02$, $P < 0.001$; $\Delta TA = 7 \pm 3$ mEq/day, $P < 0.005$; $\Delta NH_4^+ = 5 \pm 2$ mEq/day, $P < 0.05$; $\Delta NAE = 16 \pm 5$ mEq/day, $P < 0.05$.

Following day 1 and throughout the subsequent period of observation, the cumulative change in net acid excretion (ΣΔNAE) remained negative in each patient in whom mineralocorticoid replacement was discontinued and remained positive in each patient in whom mineralocorticoid replacement was instituted (Table 2). Combining the results in the two groups and averaging the absolute values, we found the cumulative change in net acid excretion (ΣΔNAE) to be 41 ± 11 mEq ($P < 0.02$) by day 3 following the experimental maneuver. By day 5, ΣΔNAE was 66 ± 20 mEq, $P < 0.05$. A significant positive correlation was observed between the magnitude of the cumulative change in NAE (ΣΔNAE) in each patient and the corresponding mean value of NAE measured prior to discontinuation or initiation of therapy ($r = 0.85$, $P < 0.05$; day 5) (Fig. 3).

The findings in the patient who had the longest period of mineralocorticoid deprivation (patient no. 2, 14 days) are shown in Fig. 4. Throughout the pro-

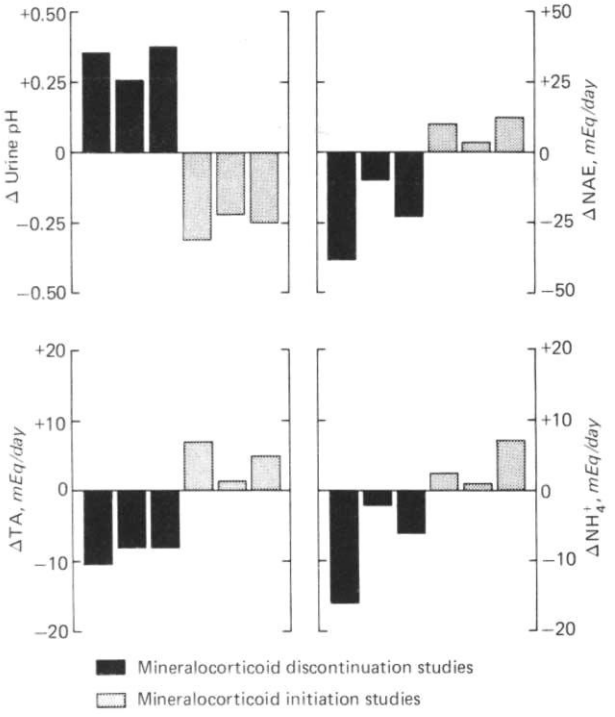

Fig. 2. *Effect of discontinuation or initiation or mineralocorticoid replacement therapy on urine pH and the excretion rates of titratable acid (TA), ammonium, and net acid (NAE) in six adrenalectomized patients without apparent intrinsic renal disease.* Values represent change from mean control value on the first day following discontinuation or initiation of mineralocorticoid.

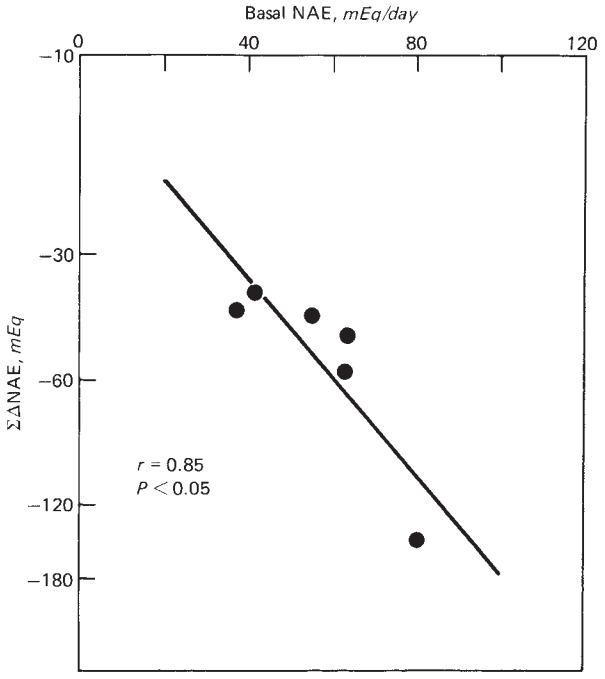

Fig. 3. *Relation between cumulative change in net acid excretion (ΣΔNAE) and the initial rate of net acid excretion prior to discontinuation or initiation of mineralocorticoid replacement therapy in six adrenalectomized patients without renal disease.* Because the directional change in net acid excretion in every patient was indicative of a negative effect of mineralocorticoid deficiency on acidification regardless of the order of the two experimental periods, ΣΔNAE was plotted as a decrement in each case. The magnitude of ΣΔNAE was used without regard for sign for purposes of regression analysis. Values plotted represent the 5th experimental day except for patient no. 3 in whom only 3 days of experimental observation were obtained.

longed period of observation, net acid excretion remained below control. There was no tendency for the cumulative reduction in net acid excretion that occurred during the first half of the mineralocorticoid deprivation period to be counterbalanced by an increase in net acid excretion to values exceeding control during the second half of the mineralocorticoid deprivation period. Elimination of hydrogen ion retained initially following mineralocorticoid withdrawal also was not observed during the course of prolonged mineralocorticoid deprivation in patient no. 1 (11 days), in whom net acid excretion returned to control, but not to values exceeding control, during the final period of observation (Fig. 1). The period of observation in the remaining patients was of insufficient duration to provide information concerning long-term (> 14 days) renal acid-base effects of mineralocorticoid deficiency.

Venous plasma total CO_2 decreased in each patient following mineralocorticoid withdrawal and increased in each patient following mineralocorticoid institution (Table 2, Fig. 5). For the two groups of patients combined, the absolute value of the change in plasma total CO_2 averaged 1.2 ± 0.3 mEq/liter ($P < 0.02$) by day 5 following discontinuation or institution of mineralocorticoid therapy. These changes did not reflect primary changes in the respiratory component of systemic acid-base equilibrium as judged from the observed directional change in blood hydrogen ion concentration in four patients in whom measurements of arterialized blood pH were obtained. A significant positive correlation was observed between the change in plasma total carbon dioxide and the corresponding cumulative change in net acid excretion in the six patients: Δ plasma total $CO_2 = 0.015 \cdot \Sigma\Delta NAE + 0.64$, $r = 0.83$, $P < 0.05$ (day 5) (Fig. 5).

(b) *Relation of acid-base changes to changes in sodium balance.* The observed changes in both NAE and plasma total CO_2 correlated positively with the corresponding changes in sodium balance calculated from the change in sodium excretion relative to intake: $\Sigma\Delta NAE = -21.3 + 0.20 \cdot \Sigma\Delta Na^+$ balance, $r = 0.82$, $P < 0.05$; Δ plasma total $CO_2 = 0.31 + 0.004 \cdot \Sigma\Delta Na^+$ balance, $r = 0.90$, $P < 0.05$ (day 5) (Fig. 6). The relation between changes in net acid excretion and sodium balance was further evaluated in one patient

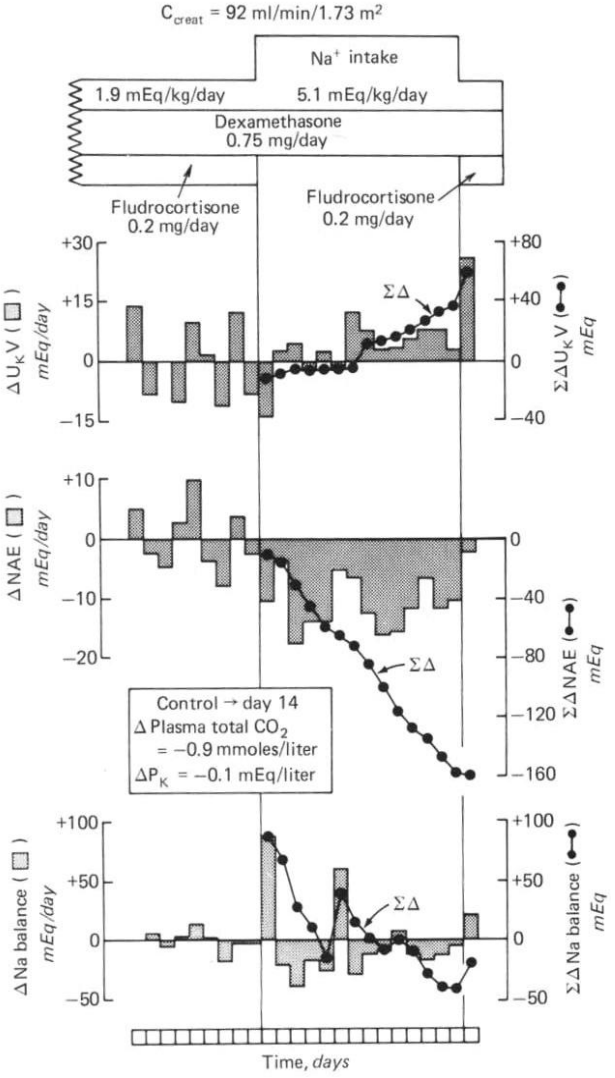

Fig. 4. *Effect of a prolonged period (14 days) of mineralocorticoid discontinuation in an adrenalectomized patient without intrinsic renal disease (patient no. 2) in whom dietary sodium chloride was increased simultaneous with discontinuation of mineralocorticoid in an attempt to prevent negative sodium balance.* Values of Δ excretion represent the differences between the daily excretion values and the corresponding mean control values. Values of ΣΔ excretion represent the accumulated sum of the daily values of Δ excretion during the period of mineralocorticoid discontinuation. Values of Δ sodium balance were calculated from the changes in urinary sodium excretion relative to intake.

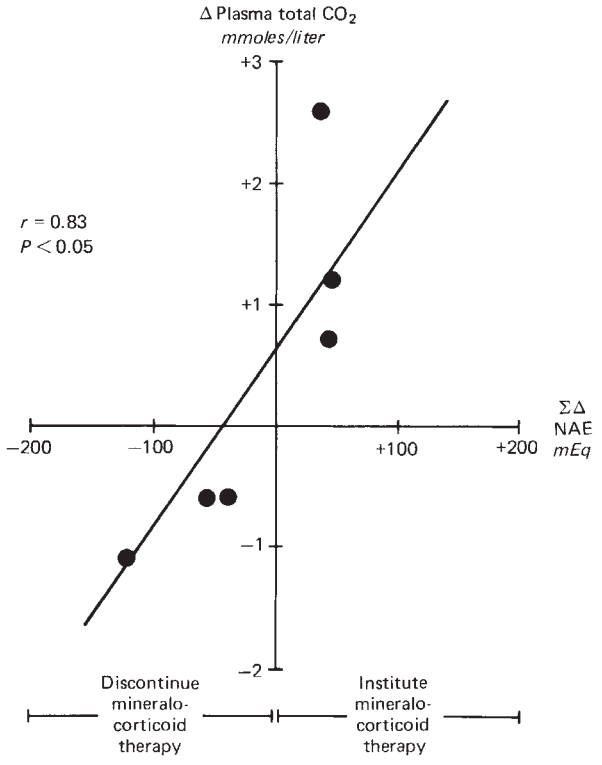

Fig. 5. *Relation between change in plasma carbon dioxide content and the cumulative change in urinary net acid excretion (ΣΔNAE, mEq) following the first 5 days of discontinuation or initiation of mineralocorticoid replacement therapy in six adrenalectomized patients without apparent intrinsic renal disease.* In one patient (patient no. 3) the duration of study was only 3 days.

in whom mineralocorticoid therapy was discontinued for a period of 14 days, throughout which period sodium chloride intake was greatly increased in an attempt to prevent negative sodium balance (Fig. 4). During most of the period of mineralocorticoid deprivation, the cumulative sodium balance was either positive or near zero, yet net acid excretion remained below control such that the decrement from control (ΣΔNAE) accumulated progressively at a nearly constant rate (Fig. 4).

(c) *Relation of acid-base changes to changes in potassium balance.* The effect of institution or discontinuation of mineralocorticoid therapy on net acid excretion in relation to changes in potassium metabolism for the entire group is shown in Fig. 7. During the first 3 days, a significant negative correlation was observed between changes in daily net acid excretion and the corresponding cumulative changes in potassium balance as calculated from the change in urinary potassium excretion relative to intake. Similarly, a significant negative correlation was observed between the changes in daily net acid excretion and the corresponding changes in plasma potassium concentration. With chronicity of mineralocorticoid discontinuation, these correlations may not persist, as is evidenced by the finding in patient 2 of a persisting reduction in net acid excretion in association with delayed reversal of the initially observed retention of urinary potassium (Fig. 4).

Discussion

The findings in the present study indicate that discontinuation of mineralocorticoid replacement therapy in adrenalectomized patients maintained on

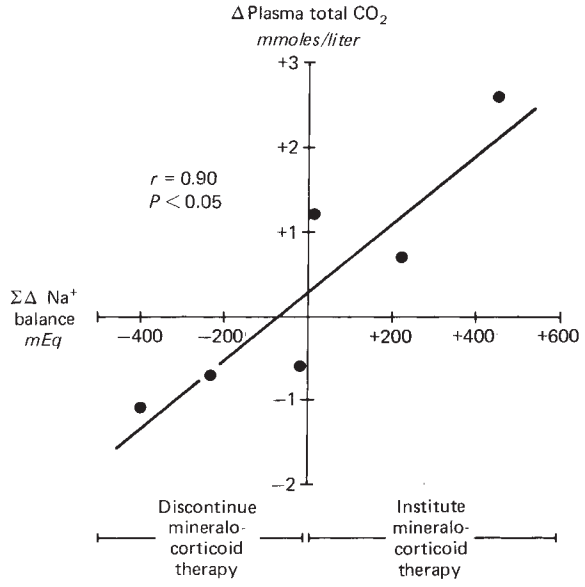

Fig. 6. *Relation between change in plasma carbon dioxide content and the cumulative change in sodium balance ($\Sigma\Delta Na^+$ balance, mEq) following the first 5 days of discontinuation or initiation of mineralocorticoid replacement therapy in six adrenalectomized patients without apparent intrinsic renal disease.* The changes in sodium balance were calculated from the changes in urinary sodium excretion relative to intake. In one patient (patient no. 3), the duration of study was only 3 days.

glucocorticoid replacement leads to a reduction in net acid excretion and plasma bicarbonate concentration, and that initiation of therapy leads to the opposite effect. These results provide the first evidence in adult humans without kidney disease that mineralocorticoid at levels not exceeding those observed in normal subjects critically modulates renal acid-base homeostasis and thereby contributes to maintenance of normal systemic acid-base equilibrium under conditions of normal dietary sodium and potassium and acid load.

Interpretation of the present results as reflecting an acid-base effect of normal or low levels of mineralocorticoid is based in part on the estimated aldosterone potency-equivalence of the synthetic mineralocorticoid steroid, fludrocortisone, and the magnitude of the resultant mineralocorticoid effect of the fludrocortisone administered as reflected by plasma renin activity and plasma sodium and potassium concentration. Fludrocortisone is estimated to have nearly identical mineralocorticoid potency as aldosterone [20–24]. The commonly used replacement dose of fludrocortisone in patients with Addison's disease (50 to 150 μg/day) [20, 21, 25, 26] is nearly identical to the secretion rate of aldosterone observed in normal subjects on a liberal sodium intake (60 to 168 μg/day, ± 2 SD) [27]. In the dose range of fludrocortisone used in the present study, plasma renin activity was normal or slightly increased and substantially lower than that observed when mineralocorticoid was withheld (Table 1).[1] Plasma renin activity provides an index of "effective" extracellular fluid volume and therefore of the adequacy of mineralocorticoid replacement [26, 28].

Estimation of the aldosterone potency-equivalence of fludrocortisone is not the only basis for interpretation of these results as reflecting the renal acid-base effect of normal mineralocorticoid levels. In one mineralocorticoid-deprived adrenalectomized subject (patient no. 6), an increase in net acid excretion and plasma bicarbonate concentration occurred when mineralocorticoid replacement was effected by constant infusion of the major naturally occurring mineralocorticoid hormone, aldosterone. The amount of aldosterone administered (120 μg/day) approximated that ordinarily secreted in normal subjects at comparable levels of dietary sodium and potassium [27]. This amount of aldosterone did not provide over-replacement inasmuch as plasma renin activity was not reduced to subnormal levels (Table 1).

It might be argued that the present results do not establish whether the level of mineralocorticoid that provides the observed tonic stimulation of renal acidification is in the "physiologic" range inasmuch as the observed renal acidosis-producing effect of mineralocorticoid deficiency was evidenced during the state of presumed complete mineralocorticoid lack. Conceivably, a fully expressed tonic stimulation of acidification is provided with mineralocorticoid at low levels only a small fraction of normal, whereas at higher levels within the "physiologic" range small deviations in mineralocorticoid level may have little effect on acidification. Nevertheless, the present results establish that renal acidification is under tonic stimulation by mineralocorticoid at levels that do not exceed those observed in normal subjects ingesting diets of normal sodium and potassium content. Furthermore, the results permit the inference that under conditions of normal dietary acid loads neither glucocorticoid deficiency nor renal disease are prerequisites for expression of the renal acidosis-producing effect of mineralocorticoid deficiency.

[1] One subject required a fludrocortisone replacement dose of 200 μg per day to prevent postural hypotension and marked hyperreninemia; such a fludrocortisone requirement is not unprecedented among patients with Addison's disease [25, 26].

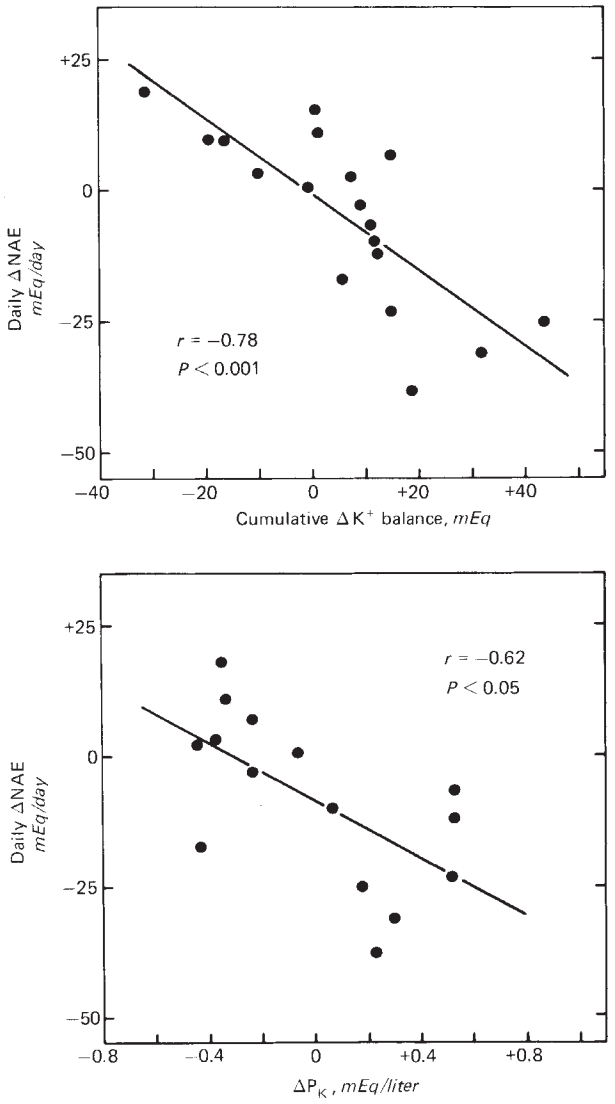

Fig. 7. *Relation between daily Δ net acid excretion (ΔNAE) and the cumulative change in potassium balance* (upper panel) *and the change in plasma potassium concentration* (lower panel) *following discontinuation or institution of mineralocorticoid replacement therapy (days 1–3) in six adrenalectomized patients without apparent intrinsic renal disease.* Values of Δ excretion, balance, and concentration represent the difference between the daily values of excretion, balance, and concentration, respectively, and the corresponding mean control values. The changes in potassium balance were calculated from the changes in urinary potassium excretion relative to intake; values of cumulative Δ potassium balance represent the accumulated sum of the daily values of Δ potassium balance during the period of mineralocorticoid discontinuation.

The magnitude of the changes in plasma total carbon dioxide (0.6 to 2.6 mmoles/liter) that occurred in response to discontinuation or initiation of mineralocorticoid therapy indicates a relatively small tonic effect of mineralocorticoid on systemic acid-base equilibrium. The magnitude of the decrement in plasma bicarbonate concentration resulting from lack of mineralocorticoid activity in the present subjects is similar to the magnitude of the increment (1 to 3 mEq/liter) observed in normal subjects during prolonged administration of superphysiologic amounts of aldosterone [8]. Taken together, these results indicate that within the range from zero to superphysiologic levels of aldosterone, there exists an aldosterone-dependent range of variation of plasma bicarbonate concentration of approximately 5 mEq/liter in normal subjects eating normal diets.

In these studies the change in plasma carbon dioxide content following discontinuation or initiation of mineralocorticoid replacement correlated positively with the cumulative change in net acid excretion (Fig. 5). Further, the change in net acid excretion correlated with the control rate of net acid excretion (Fig. 3). Taken together, these findings suggest that the severity of the renal acidosis-producing effect of mineralocorticoid deficiency is greatest in those individuals with the largest endogenous acid loads, given that steady-state net acid excretion normally reflects the rate of endogenous acid production [29, 30]. These considerations raise the possibility that the modulating role of physiologic levels of aldosterone would become critical in clinical conditions in which endogenous acid production is abnormally high, for example, lactic acidosis, diarrhea. Plasma aldosterone concentration is characteristically increased in acute diabetic ketoacidosis [31], and aldosterone secretion in normal subjects ordinarily increases when the systemic acid load is increased by exogenous acid loading [32–34]. Further studies are required to elucidate the role of aldosterone in the defense of systemic acid-base equilibrium in clinical states of increased acid production, and to investigate the mechanism whereby aldosterone secretion is increased in response to exogenous acid loading [35].

The potential deleterious effects of a small but lifelong reduction in plasma bicarbonate concentration requires consideration. A persisting reduction in plasma bicarbonate concentration of even 1 to 2 mEq/liter cannot be dismissed as benign because the metabolic consequences of chronic metabolic acidosis remain to be completely defined and are probably not inconsequential [36–47]. In considering the possible deleterious effects of chronic metabolic acidosis, we might make a distinction between acidemia and acid retention by the kidney. In patients with familial proximal renal tubular acidosis, it has been reported that a progressively accumulating positive hydrogen ion balance does not oc-

cur owing to the excretion of net acid at normal rates in the steady-state, yet negative calcium balance and metabolic bone disease common in other states of chronic metabolic acidosis are not present despite persisting acidemia [48]. Whether the absence of a progressively accumulating positive acid balance lessens the risk of acidosis-related derangements of metabolism is not known. The present studies were not designed to investigate the relationship between chronicity of mineralocorticoid deficiency and acid balance.

The mechanism whereby mineralocorticoid deficiency caused a reduction in net acid excretion in the present studies was not specifically investigated. Conceivably, the predominant pathogenetic factor is the reduction in renal sodium reabsorption that results from mineralocorticoid deficiency. Sodium depletion is a potential acidosis-producing factor by virtue of its effect to diminish delivery of sodium to the distal nephron. Pre-existing sodium depletion limits the acid excretory response to mineralocorticoid administration [1, 49]. In the present studies, the changes in net acid excretion correlated positively with the corresponding cumulative changes in sodium balance, as calculated from the changes in urinary excretion relative to intake. These findings are consistent with the hypothesis that the changes in net acid excretion are secondary, at least in part, to the alterations in sodium transport that result from the change in mineralocorticoid therapy. In one study of mineralocorticoid discontinuation, however, net acid excretion and plasma bicarbonate concentration decreased even when sodium depletion was prevented by adjustment of intake (Table 2, Fig. 4). Conversely, in one study in which mineralocorticoid was initiated, net acid excretion and plasma bicarbonate concentration increased even when sodium retention was prevented (Table 2). Hence, the tonic effect of mineralocorticoid on renal acidification may not be mediated solely through modulation of sodium balance. The reduction in net acid excretion that occurs in mineralocorticoid-deficient dogs [50] is not dependent on the depletion of sodium induced by mineralocorticoid deficiency [51], but this does not appear to be the case in rats [52], and remains to be tested in humans.

Further studies are required to assess the role of altered sodium chloride balance in mediating the renal acid-base response to mineralocorticoid deficiency in humans. Even though negative sodium balance and consequent reduced distal nephron sodium delivery are prevented during mineralocorticoid deficiency by appropriate increase in sodium chloride intake, reduced rates of sodium reabsorption in the distal nephron persist and might compel a persisting reduction in distal hydrogen ion secretion [53–56]. In mammalian species, the existence of a sodium-dependent mineralocorticoid-stimulated distal acidification process is consistent with the results of clearance and micropuncture studies that relate urinary acidification to distal sodium supply, anion absorbability, and mineralocorticoid activity [57, 58]. Nevertheless, a sodium transport-mediated acidification process has not been identified in the mammalian distal nephron [59].

Hyperkalemia secondary to potassium retention is another potential acidosis-producing consequence of mineralocorticoid deficiency. Potassium loading diminishes renal ammonia production [60] and net renal bicarbonate reabsorptive capacity [61] in the mammalian kidney. Evidence has been adduced that hyperkalemia is a significant acidosis-producing factor in patients with hypoaldosteronism secondary to chronic renal disease and associated impaired renin secretion [62]. The role of potassium in the present studies was not specifically investigated. For the group as a whole, the changes in daily net acid excretion were observed to correlate negatively with the corresponding cumulative changes in potassium balance calculated from the changes in urinary excretion relative to intake (Fig. 7). A similar negative correlation between the changes in net acid excretion and plasma potassium concentration was observed (Fig. 7). These findings are consistent with the hypothesis that the changes in net acid excretion are secondary, at least in part, to the alterations in potassium transport that result from the change in mineralocorticoid therapy. Further studies are needed to assess the influence of potassium balance inasmuch as, with chronicity of mineralocorticoid discontinuation in one patient, a persisting reduction in net acid excretion was observed despite elimination of the retained potassium that occurred initially (Fig. 4).

Whatever the mechanism whereby mineralocorticoid hormones modulate renal acidification, the findings in this study provide the first evidence that renal acidification is under tonic stimulation by mineralocorticoid at levels not exceeding those that prevail in normal subjects ingesting acid-producing diets of normal sodium and potassium content. The findings implicate mineralocorticoid deficiency as a significant renal acidosis-producing condition not dependent on the presence of intrinsic renal disease or glucocorticoid deficiency, and potentially ampli-

fied when endogenous acid production is increased by diet or disease.

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References

1. RELMAN AS, SCHWARTZ WB: The effect of DOCA on electrolyte balance in normal man and its relation to sodium chloride intake. *Yale J Biol Med* 24:540–558, 1952
2. LIDDLE GW: Aldosterone antagonists. *Arch Intern Med* 102:998–1004, 1958
3. MILLS JN, THOMAS S, WILLIAMSON KS: The acute effect of hydrocortisone, deoxycorticosterone and aldosterone upon the excretion of sodium, potassium and acid by the human kidney. *J Physiol* 151:312–331, 1960
4. MILLS JN, THOMAS S, WILLIAMSON KS: The effects of intravenous aldosterone and hydrocortisone on the urinary electrolytes of the recumbent human subject. *J Physiol* 156:415–423, 1961
5. SONNENBLICK EH, CANNON PJ, LARAGH JH: The nature of the action of intravenous aldosterone: Evidence for a role of the hormone in urinary dilution. *J Clin Invest* 40:903–913, 1961
6. CRABBE J, THORN GW: Effets de l'aldosterone sur la fonction renale de l'homme normal. *Rev Franc Etudes Clin Biol* 9:729–735, 1964
7. LEMANN J JR, PIERING WF, LENNON EJ: Studies of the acute effects of aldosterone and cortisol on the interrelationship between renal sodium, calcium and magnesium excretion in normal man. *Nephron* 7:117–130, 1970
8. KASSIRER JP, LONDON AM, GOLDMAN DM, SCHWARTZ WB: On the pathogenesis of metabolic alkalosis in hyperaldosteronism. *Am J Med* 49:306–315, 1970
9. SEBASTIAN A, SCHAMBELAN M, LINDENFELD S, MORRIS RC JR: Amelioration of metabolic acidosis with fludrocortisone therapy in hyporeninemic hypoaldosteronism. *N Engl J Med* 297:576–583, 1977
10. OETLIKER OH, ZURBRUGG RP: Renal tubular acidosis in salt-losing syndrome of congenital adrenal hyperplasia (CAH). *J Clin Endocrinol Metab* 31:447–450, 1970
11. ROSLER A, RABINOWITZ D, THEODOR R, RAMIREZ LC, ULICK S: The nature of the defect in a salt-wasting disorder in Jews of Iran. *J Clin Endocrinol Metab* 44:279–291, 1977
12. PEREZ GO, OSTER JR, VAAMONDE CA: Renal acidification in patients with mineralocorticoid deficiency. *Nephron* 17:461–473, 1976
13. HILLS AG, ZINTEL HA, PARSONS DW: Observations of human adrenal cortical deficiency: With special reference to replacement therapy with cortisone. *Am J Med* 21:358–379, 1956
14. ALTMAN PL, DITTMER DS: *Blood and Other Body Fluids*. Bethesda, Federation of American Societies for Experimental Biology, 1961
15. Normal Laboratory Values. *N Engl J Med* 298:34–45, 1978
16. WATT BK, MERRILL AL: In Composition of Foods. Raw. Processed. Prepared. Consumer and Food Economics Research Division Agricultural Research Service, United States Department of Agriculture, Washington, D.C., (Revised) 1963
17. SEBASTIAN A, MCSHERRY E, MORRIS RC JR: Impaired renal conservation of sodium and chloride during sustained correction of systemic acidosis in patients with type 1, classic renal tubular acidosis. *J Clin Invest* 58:454–469, 1976
18. SEALEY JE, LARAGH JH: Measurement of urinary aldosterone excretion in man, in *Hypertension Manual*, edited by LARAGH JH, New York, Yorke Medical Books, 1974, pp 641–654
19. SNEDICOR GW, COCHRAN WG: *Statistical Methods* (6th ed.). Ames, Iowa State University Press, 1967
20. LIDDLE GW, MELMON KL: The adrenals, in *Textbook of Endocrinology* (5th ed.), edited by WILLIAMS RH, Philadelphia, WB Saunders Company, 1974, pp 233–283
21. HAYNES RC JR, LARNER J: Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of adrenocortical steroid biosynthesis, in *The Pharmacological Basis of Therapeutics* (5th ed.), edited by GOODMAN LS, GILMAN A, New York, McMillan Company, 1975, pp 1478–1485
22. GOLDFIEN A, LAIDLAW JC, HAYDAR NA, RENOLD AE, THORN GW: Fluorohydrocortisone and chlorohydrocortisone, highly potent derivatives of compound F. *N Engl J Med* 252:415–421, 1955
23. THORN GW, SHEPPARD RH, MORSE WI, REDDY WJ, BEIGELMAN PM, RENOLD AE: Comparative action of aldosterone and 9-alpha-fluorohydrocortisone in man. *Ann NY Acad Sci* 61:609–619, 1955
24. THORN GW, RENOLD AE, MORSE WI, GOLDFIEN A, REDDY WJ: Highly potent adrenal cortical steroids structure and biologic activity. *Ann Intern Med* 43:979–1000, 1955
25. KNOWLTON AI: Addison's disease: A review of its clinical course and management, in *The Human Adrenal Cortex*, edited by CHRISTY NP, New York, Harper and Row, 1971, pp 329–358
26. OELKERS W, L'AGE M: Control of mineralocorticoid substitution in Addison's disease by plasma renin measurement. *Klin Wochenschr* 54:607–612, 1976

27. BIGLIERI EG, SLATON PE, SCHAMBELAN M, KRONFIELD SJ: Hypermineralocorticoidism. *Am J Med* 45:170–175, 1968
28. LIPTON HL, TAN SY, NOTH R, MULROW PJ, GENEL M: Usefulness of plasma renin activity to monitor mineralocorticoid replacement in salt-losing congenital adrenal hyperplasia, in *Congenital Adrenal Hyperplasia,* edited by LEE PA, PLOTNICK LP, KOWARSKI AA, MIGEON CJ, Baltimore, University Park Press, 1977, pp 127–139
29. RELMAN AS, LENNON EJ, LEMANN J JR: Endogenous production of fixed acid and the measurement of the net balance of acid in normal subjects. *J Clin Invest* 40:1621–1630, 1961
30. LENNON EJ, LEMANN J JR, LITZOW JR: The effects of diet and stool composition on the net external acid balance of normal subjects. *J Clin Invest* 45:1601–1607, 1966
31. CHRISTLIEB AR, ASSAL JP, KATSILAMBROS N, WILLIAMS GH, KOZAK GP, SUZUKI T: Plasma renin activity and blood volume in uncontrolled diabetes: Ketoacidosis, a state of secondary aldosteronism. *Diabetes* 24:190–193, 1975
32. PEREZ GO, OSTER JR, VAAMONDE CA, KATZ FH: Effect of NH_4Cl on plasma aldosterone, cortisol and renin activity in supine man. *J Clin Endocrinol Metab* 45:762–767, 1977
33. KISCH ES, DLUHY RG, WILLIAMS GH: Regulation of renin release by calcium and ammonium ions in normal man. *J Clin Endocrinol Metab* 43:1343–1350, 1976
34. SCHAMBELAN M, SEBASTIAN A: Adrenocortical hormone response to metabolic acidosis in normal man (abst). *Clin Res* 25:301A, 1977
35. MAHNENSMITH R, THIER SO, COOKE R, BROADUS A, DEFRONZO RA: Effect of acute metabolic acidemia on renal electrolyte transport in man. *Metabolism* 28:831–842, 1979
36. RELMAN AS: Metabolic consequences of acid-base disorders. *Kidney Int* 1:347–359, 1972
37. LENNON EJ: Metabolic acidosis: A factor in the pathogenesis of azotemic osteodystrophy? *Arch Intern Med* 124:557–562, 1969
38. MITCHELL JH, WILDENTHAL K, JOHNSON RL JR: The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney Int* 1:375–389, 1972
39. MCSHERRY E, MORRIS RC JR: Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. *J Clin Invest* 61:509–527, 1978
40. COE FL, FIRPO JJ: Evidence for mild reversible hyperparathyroidism in distal renal tubular acidosis. *Arch Intern Med* 135:1485–1489, 1975
41. LEE DBN, DRINKARD JP, GONICK HC, COULSON WF, CRACCHIOLO A: Pathogenesis of renal calculi in distal renal tubular acidosis: Possible role of parathyroid hormone. *Clin Orthopaed* 121:234–242, 1976
42. COE FL, FIRPO JJ JR, HOLLANDSWORTH DL, SEGIL L, CANTERBURY JM, REISS E: Effect of acute and chronic metabolic acidosis on serum immunoreactive parathyroid hormone in man. *Kidney Int* 8:262–273, 1975
43. WACHMAN A, BERNSTEIN DS: Parathyroid hormone in metabolic acidosis: Its role in pH homeostasis. *Clin Orthopaed Related Res* 69:252–263, 1970
44. BECK N, WEBSTER SK: Effects of acute metabolic acidosis on parathyroid hormone action and calcium mobilization. *Am J Physiol* 230:127–131, 1976
45. BARZEL US, JOWSEY J: The effects of chronic acid and alkali administration on bone turnover in adult rats. *Clin Sci* 36:517–524, 1969
46. BURNELL JM: Changes in bone sodium and carbonate in metabolic acidosis and alkalosis in the dog. *J Clin Invest* 50:327–331, 1971
47. LEE SW, RUSSELL J, AVIOLI LV: 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol: Conversion impaired by systemic metabolic acidosis. *Science* 195:994–996, 1977
48. LEMANN J JR, WILZ DR, BRENES LG: Acid, calcium and phosphorous balances in proximal renal tubular acidosis. *Kidney Int* 10:561, 1976
49. COHEN JJ, LYONS H, HARRINGTON JT, SCHWARTZ WB: Total correction by DOCA of HCL-induced chronic metabolic acidosis. *Clin Res* 21:681, 1973
50. HULTER HN, ILNICKI LP, HARBOTTLE JA, SEBASTIAN A: Impaired renal H^+ secretion and NH_3 production in mineralocorticoid-deficient glucocorticoid replete dogs. *Am J Physiol* 232:F136–F146, 1977
51. HULTER HN, LICHT JH, GLYNN RD, SEBASTIAN A: Renal acidosis in mineralocorticoid deficiency is not dependent on NaCl depletion or hyperkalemia. *An J Physiol* 236:F283–F294, 1979
52. DITELLA PJ, SODHI B, MCCREARY J, ARRUDA JAL, KURTZMAN NA: Mechanism of the metabolic acidosis of selective mineralocorticoid deficiency. *Kidney Int* 14:466–477, 1978
53. GROSS JB, KOKKO JP: Effects of aldosterone and potassium-sparing diuretics on electrical potential differences across the distal nephron. *J Clin Invest* 59:82–89, 1977
54. O'NEIL RG, HELMAN SI: Transport characteristics of renal collecting tubules: Influences of DOCA and diet. *Am J Physiol* 233:F544–F558, 1977
55. ZIEGLER TW, FANESTIL DD, LUDENS JH: Influence of transepithelial potential difference on acidification in the toad urinary bladder. *Kidney Int* 10:279–286, 1976
56. AL-AWQATI Q, MUELLER A, STEINMETZ PR: Transport of H^+ against electrochemical gradients in turtle urinary bladder. *Am J Physiol* 233:F502–F508, 1977
57. SCHWARTZ WB, JENSON RL, RELMAN AS: Acidification of the urine and increased ammonium excretion without change in acid-base equilibrium: Sodium reabsorption as a stimulus to the acidifying process. *J Clin Invest* 34:673–680, 1955
58. CLAPP JR, RECTOR FC JR, SELDIN DW: Effect of unreabsorbed anions on proximal and distal transtubular potentials in rats. *Am J Physiol* 202:781–786, 1962
59. MCKINNEY TD, BURG MB: Bicarbonate absorption by rabbit cortical collecting tubules in vitro. *Am J Physiol* 234:F141–F145, 1978
60. TANNEN RL, WEDELL E, MOORE R: Renal adaption to a high potassium intake: The role of hydrogen ion. *J Clin Invest* 52:2089–2101, 1973
61. KURTZMAN NA, WHITE MG, ROGERS PW: The effect of potassium and extracellular volume on renal bicarbonate reabsorption. *Metabolism* 22:481–492, 1973
62. SZYLMAN P, BETTER OS, CHAIMOWITZ C, ROSLER A: Role of hyperkalemia in the metabolic acidosis of isolated hypoaldosteronism. *N Engl J Med* 294:361–365, 1976