On the Mechanism of Renal Potassium Wasting in Renal Tubular Acidosis Associated with the Fanconi Syndrome (Type 2 RTA)

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ABSTRACT The mechanism of renal potassium wasting in renal tubular acidosis associated with the Fanconi syndrome (type 2 RTA) was investigated in 10 patients, each of whom had impaired proximal renal tubular reabsorption of bicarbonate as judged from a greater than 15–20% reduction of renal tubular bicarbonate reabsorption ($THCO_3^-$) at normal plasma bicarbonate concentrations. When the plasma bicarbonate concentration ($[HCO_3^-]p$) was experimentally increased to normal levels in three patients with a fractional potassium excretion (C_K/C_{in}) of less than 1.0 during acidosis, C_K/C_{in} and urinary potassium excretion (U_KV/C_{in}) increased strikingly and concurrently with a striking increase in urinary sodium ($U_{Na}V/C_{in}$) and bicarbonate (U_{HCO_3}-V/C_{in}) excretion. When $[HCO_3^-]p$ was increased to normal levels in two patients with a C_K/C_{in} of greater than 1.0 during acidosis and in whom $U_{Na}V/C_{in}$ and U_{HCO_3}-V/C_{in} were already markedly increased, C_K/C_{in} did not increase further. When $[HCO_3^-]p$ was decreased to subnormal levels in a patient given ammonium chloride, U_KV/C_{in}, C_K/C_{in}, and U_{HCO_3}-V/C_{in} decreased concurrently. In the six patients in whom $[HCO_3^-]p$ was maintained at normal levels (oral alkali therapy) for 2 months or longer, C_K/C_{in} was directly related to the urinary excretion rates of sodium and bicarbonate, hence was directly related to the magnitude of reduction of $THCO_3^-$ at normal $[HCO_3^-]p$; C_K/C_{in} was greater than 0.55 in all six patients and greater than 1.0 in four.

In eight patients with classic RTA (type 1 RTA), proximal renal tubular reabsorption of bicarbonate was largely intact as judged from a trivial reduction of $THCO_3^-$ at normal $[HCO_3^-]p$. When $[HCO_3^-]p$ was either increased from subnormal to normal levels, or decreased from normal to subnormal levels, U_{HCO_3}-V/C_{in} remained essentially constant, and U_KV/C_{in} did not change significantly. When correction of acidosis was sustained, U_{HCO_3}-V/C_{in} remained a trivial fraction of that filtered, and C_K/C_{in} was consistently less than 0.55.

These results provide evidence that renal potassium wasting in type 2 RTA is physiologically separable from that in type 1 RTA and in part the result of a reduction in the rate at which the proximal tubule reabsorbs bicarbonate and the distal delivery of supernormal amounts of sodium bicarbonate. With an increased stimulus to distal sodium reabsorption, indicated by the finding of hyperaldosteronism, delivery to the distal nephron of supernormal amounts of sodium with the relatively impermeant bicarbonate anion would be expected to increase intraluminal negativity in the distal nephron, and as a consequence, increase potassium secretion and promote renal potassium wasting.

INTRODUCTION

Renal potassium wasting[1] is a common complication of the clinical syndrome of renal tubular acidosis (RTA) (1–8). Both in patients with so-called classic RTA (type 1 RTA, "distal" or "gradient" RTA) and in patients with RTA associated with the Fanconi syndrome (type 2 RTA, "proximal" or "rate" RTA), it has been inferred that renal potassium wasting is a reversible consequence of the renal acidification defect (1, 4, 8, 9–13). In patients with type 1 RTA, this infer-

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[1] Renal potassium wasting is defined as the continued urinary excretion of more than 40 mEq of potassium daily in the face of potassium depletion of severity sufficient to produce hypokalemia.

ence is based on the observation that correction of systemic acidosis with alkali therapy can lead to a reduction in urinary potassium excretion and correction of hypokalemia (1, 2, 13). In patients with type 2 RTA, this response to corrective alkali therapy has been assumed (12) but apparently never documented (3, 5, 6).

In patients with type 2 RTA, however, the physiologic character of the underlying renal acidification defect suggests the possibility that renal potassium wasting might be augmented rather than corrected by correction of systemic acidosis (14). In these patients, the renal acidification defect is characterized by complete, or nearly complete, renal tubular reabsorption of bicarbonate at subnormal plasma bicarbonate concentrations but by a greater than 15–20% reduction in tubular reabsorption of bicarbonate at normal plasma bicarbonate concentrations, a finding indicating that the rate of bicarbonate reabsorption in the proximal nephron is reduced (15, 16). Accordingly, raising the plasma bicarbonate concentration from subnormal to normal levels has the immediate and sustained effect of swamping the distal nephron with massive amounts of $NaHCO_3$. In the presence of a continued stimulus for sodium reabsorption, the delivery to the distal nephron of such supernormal amounts of $NaHCO_3$ might be expected to increase intraluminal negativity, augment potassium secretion, and thereby promote renal potassium wasting (17–20).

To investigate this possibility and to compare the effects of correction of acidosis on renal potassium wasting in patients with type 1 and 2 RTA, we measured urinary potassium excretion and fractional potassium excretion in the two groups (*a*) at plasma bicarbonate concentrations progressively increased from subnormal to normal levels by intravenous administration of $NaHCO_3$ and (*b*) at normal plasma bicarbonate concentrations sustained for 2 months or longer. The results of these investigations indicate that in type 2 RTA, the physiologic character of renal potassium wasting is distinct from that in type 1 RTA and support the hypothesis that in type 2 RTA renal potassium wasting results in part from the delivery of supernormal amounts of $NaHCO_3$ to the distal nephron.

METHODS

A total of 29 clearance studies were carried out on the following 23 subjects: 8 patients with type 1 RTA; 10 patients with type 2 RTA; and 5 normal subjects.

All studies were performed in the early morning with the patients lying comfortably supine. Breakfast was withheld but free access to water was permitted before and during the studies. Spontaneously voided urine (men, boys) or urine from an indwelling Foley catheter (women, infants) was collected under a layer of mineral oil at 15- to 30-min intervals for immediate determination of pH and carbon dioxide content and for subsequent determination of sodium, potassium, and chloride. At appropriate intervals arterialized blood was drawn from a superficial vein on the back of the hand that had been heated with an electric heating muffler to at least 45°C for more than 60 min for determination of blood pH and carbon dioxide tension and serum sodium and potassium concentrations. Inulin clearance was measured throughout each study period.

$NaHCO_3$ infusion. 10 studies were designed to examine the effect on urinary potassium excretion (U_KV/C_{in}) and fractional potassium excretion (C_K/C_{in}) of progressively increasing the plasma bicarbonate concentration from subnormal to normal levels by intravenous infusion of sodium bicarbonate. The subjects were five patients with type 2 RTA (R. A., R. G., R. Y., G. F., A. M.) and four patients with type 1 RTA (C. V., Le. S., La. S., P. B.) (Table I). When studied, each patient had been in a spontaneous state of mild or moderate systemic acidosis for at least 3 days. In each study plasma bicarbonate was increased by approximately 2 mmoles/liter per hr by the intravenous administration of a 3.75% solution of sodium bicarbonate at rates ranging from 0.25 to 3.8 ml/min. In most studies the rate of infusion remained constant throughout; in some studies on the patients with type 2 RTA, it was necessary to increase the rate of infusion at the higher plasma bicarbonate concentrations.

Sustained correction of acidosis. 17 studies were designed to compare fractional potassium excretion in type 1 and type 2 RTA during prolonged correction of systemic acidosis. The subjects were six patients with type 2 RTA (R. G., M. P., M. H., M. N., E. S., B. L.), six patients with type 1 RTA (C. V., Le. S., B. Mc., N. A., K. E., L. C. S.) (Table I), and five normal subjects ranging in age from 27 to 46 yr. For at least 2 months immediately preceding the studies, normal plasma bicarbonate concentrations (22–26 mmoles/liter) had been maintained in each patient by appropriate alkali therapy (Table I). Two to six consecutive 15- to 30-min urine collections were obtained for determination of fractional potassium excretion. In some studies, urine collections were obtained over a narrow range of normal plasma bicarbonate concentrations (1–3 mmoles/liter) achieved by intravenous infusion of small amounts of sodium bicarbonate.

NH_4Cl loading. In a patient with type 2 RTA (R. A.) and in a patient with type 1 RTA (L. C. S.), paired studies were performed to compare the effect on U_KV/C_{in} and C_K/C_{in} of progressively decreasing the plasma bicarbonate concentration from normal to subnormal levels. The plasma bicarbonate concentration was decreased by oral administration of ammonium chloride; after an initial dose of 6 g (R. A.) or 2 g (L. C. S.), each patient received 5 g in divided doses over the subsequent 2 hr.

Laboratory methods. Laboratory determinations were carried out as described previously (15, 21).

RESULTS

Table I summarizes clinical and physiologic data on the 18 patients with RTA obtained during earlier studies.

$NaHCO_3$ infusion. In base line determinations during acidosis on five patients with type 2 RTA, urinary potassium excretion (U_KV/C_{in}) varied from 0.78 to 7.27 μEq/ml, and fractional potassium excretion (C_K/C_{in}) varied from 0.16 to 2.03 at plasma bicarbonate concentrations ranging from 13.3 to 20.0 mmoles/liter (Table

II, Figs. 1 and 2). Five studies were begun at similar plasma bicarbonate concentrations (16.5–20.0 mmoles/liter); in these, the base line values of U_KV/C_{in} and C_K/C_{in} varied directly with the magnitude of urinary sodium and bicarbonate excretion (Table II). When the plasma bicarbonate concentration was progressively increased from subnormal to normal or near normal levels by intravenous infusion of sodium bicarbonate, U_KV/C_{in} and C_K/C_{in} increased progressively in R. A. (two studies), in G. F., and in A. M., concomitant with a progressive and striking increase in urinary sodium and bicarbonate excretion (Tables II and III, Figs. 1 and 2). In R. G. and R. Y., in whom the base line values of U_KV/C_{in} and C_K/C_{in} were already considerably greater than the maximal values attained in A. M., G. F., and R. A. during sodium bicarbonate infusion, U_KV/C_{in} and C_K/C_{in} did not increase further (Table II, Fig. 1). In R. Y., the only patient with type 2 RTA in whom the serum potassium concentration decreased to levels below 3.0 mEq/liter during sodium bicarbonate infusion, U_KV/C_{in} actually decreased slightly (from 7.27 to 5.02 μEq/ml) but fractional potassium excretion remained essentially constant (2.03–1.85, Table II, Fig. 1). Throughout, as before $NaHCO_3$ infusion, U_KV/C_{in} and C_K/C_{in} varied directly with the magnitude of urinary sodium and bicarbonate excretion (Table II).

In base line determinations during acidosis on four patients with type 1 RTA, U_KV/C_{in} varied from 0.70 to 2.12 μEq/ml, and C_K/C_{in} varied from 0.18 to 0.51 at plasma bicarbonate concentrations ranging from 18.0 to 19.7 mmoles/liter (Fig. 1, Table II). Only in C. V. were the base line values of U_KV/C_{in} and C_K/C_{in} as high as any of those observed in the patients with type 2 RTA (Table II). No correlation was apparent between the base line values of U_KV/C_{in} and C_K/C_{in} and the corresponding values of urinary sodium or bicarbonate (Table II). When the plasma bicarbonate concentration was progressively increased to normal levels by intravenous infusion of sodium bicarbonate, U_KV/C_{in} invariably decreased slightly and C_K/C_{in} either remained constant (P. B., Le. S., La. S.) or tended to decrease (C. V.) (Table II, Figs. 1 and 2).

Sustained correction of acidosis. In six patients with type 2 RTA studied after prolonged correction of systemic acidosis, fractional potassium excretion varied from 0.53 to 3.47 at serum potassium concentrations ranging from 2.5 to 4.5 mEq/liter (Fig. 3). In two patients (M. N., M. P.), C_K/C_{in} was less than 1.0; and in four patients (R. G., E. S., M. H., B. L.), C_K/C_{in} was consistently greater than 1.0 at plasma bicarbonate concentrations ranging from 22 to 26 mmoles/liter. The values of C_K/C_{in} varied directly and nearly linearly with the urinary excretion rates of bicarbonate (Fig. 3) and sodium. In general, C_K/C_{in} varied inversely with the glomerular filtration rate (GFR) (Fig. 4). While a similar inverse relationship between C_K/C_{in} and GFR occurs in chronic renal disease of diverse etiology, the values of C_K/C_{in} in the patients with type 2 RTA were, in comparison, consistently higher at any given GFR (Fig. 4) (27). That the disproportionately greater fractional potassium excretion reflects in fact "renal potassium wasting" in the patients with type 2 RTA is indicated by the presence of frank hypokalemia ($2.5 < K_s < 3.8$) in four of the patients (M. P., M. N., R. G., E. S.) despite the provision of potassium supplements as well as a normal dietary potassium intake. In unpublished balance studies on three of these patients (M. P., R. G., E. S.), the total daily potassium requirement necessary to maintain serum potassium concentrations in the low-normal range exceeded 2 mEq/Kg, even though glomerular filtration rate was reduced.

In the six patients with type 1 RTA studied after prolonged correction of acidosis, fractional potassium excretion varied from 0.17 to 0.39 at serum potassium concentrations ranging from 3.5 to 4.2 mEq/liter (Fig. 3). No correlation was apparent between C_K/C_{in} and urinary sodium excretion ($U_{Na}V/C_{in}$) or between C_K/C_{in} and urinary bicarbonate excretion (U_{HCO_3}-V/C_{in}). An inverse relationship between fractional potassium excretion and GFR was not apparent (Fig. 4). The following values of C_K/C_{in} were essentially the same as those observed in five normal subjects: 0.10–0.33 (mean 0.22) at normal plasma bicarbonate concentrations and serum potassium concentrations ranging from 4.1 to 4.6 mEq/liter.

NH_4Cl loading studies. When the plasma bicarbonate concentration was progressively decreased from 22.8 to 12.9 mmoles/liter in a patient with type 2 RTA (R. A.), U_KV/C_{in} and C_K/C_{in} decreased progressively from 3.46 to 1.75 μEq/ml and 0.82 to 0.42, respectively, concomitant with a progressive decrease in U_{HCO_3}-V/C_{in} from 4.59 to 0.68 μmoles/ml and an increase in urinary chloride excretion ($U_{Cl}V/C_{in}$) from 1.56 to 3.10 μEq/ml (Table IV). The greatest reduction in U_KV/C_{in}, C_K/C_{in}, and U_{HCO_3}-V/C_{in} occurred as the plasma bicarbonate concentration decreased to 16.6 mmoles/liter. In contrast, when the plasma bicarbonate concentration was progressively decreased from 22.8 to 16.7 mmoles/liter in a patient with type 1 RTA (L. C. S.), U_KV/C_{in}, C_K/C_{in}, U_{HCO_3}-V/C_{in}, and U_{Cl}-V/C_{in} remained essentially constant (Table IV). No significant change in urinary sodium excretion occurred in either study.

Urinary aldosterone. Table V summarizes the daily urinary excretion rates of aldosterone in six of the patients with RTA associated with the Fanconi syndrome. The urine collections were obtained during prolonged correction of the patients' acidosis and when sodium intake had been normal or supernormal for at

TABLE I

Clinical and Physiologic Data in Patients with Renal Tubular Acidosis (RTA)

Patient, age (yr), sex	Clinical diagnosis	C_{in}	Urinary acidification*			$THCO_3^-$ (Plasma $[HCO_3^-]$ 22–24 mmoles/liter)	Alkali requirement‡	Urinary excretion		
			U_{pH}min (CO_2)	$U_{TA}V_{max}$	$U_{NH_4}V_{max}$			α-Amino N	α-Amino N/creatinine N	Glucose
		ml/min per 1.73 m²		*μEq/min*		*mmoles/100 ml GF*	*mmoles/kg per 24 hr*	*mg/24 hr*	*g/g*	
Normal values										
Adult subjects			<5.31	>25.0	>39.0			50–150		
Children (a)			<5.60	>13.9	>45.7				0.30–0.62	
(b)			<5.90	>31	>27					
Infants			4.90	62 ±4.9	57 ±4.3					
Renal tubular acidosis associated with the Fanconi syndrome (type 2 RTA)										
M. P. 63 M	Multiple myeloma	74.3	5.83 (14.0)	18.3	68.7	2.0	3–4	333		0
R. A. 58 F	Sjogren's syndrome	30.7	6.81 (12.2)	7.6	6.4	1.6	3–4	366		0
R. G. 20 M	Idiopathic Fanconi syndrome	22.3	5.24 (15.3)	35.0	20.8	1.6	3	640		+
R. Y. 9 M	Cystinosis	23.7	5.0 (10)	—	—	1.3	10		1.69	+
B. L. 8 M	Cystinosis	21.5	6.67 (18.8)	23.2	17.3	1.5	5–6		1.8–2.6	0
M. H. 8 M	Idiopathic type 2 RTA	34.7	5.93 (17.5)	28.9	35.9	2.0	4		0.3	0
M. N. 7 M	Lowe's syndrome	83.0	5.83 (18.1)	33.8	49.5	1.7	7–8		4.9	+
E. S. 5 M	Cystinosis	36.4	5.29 (13.3)	70.3	75.0	1.9	6		1.3	+
G. F. 4 F	Idiopathic Fanconi syndrome	122	5.04 (21.0)	47.3	70.4	2.0	4		0.7–1.3	0
A. M. 1½ M	Cystinosis	92.0	5.13 (13.3)	62.0	56.0	2.0	20		13.9–15.3	+
Classic renal tubular acidosis (type 1 RTA)										
N. A. 56 F	Sjogren's syndrome	55.0	6.68 (17.2)	22.0	11.2	2.24	1	59.5		0
C. V. 51 F	Idiopathic RTA, nephrocalcinosis	48.8	6.48 (13)	12.9	28.1	2.36	1–1½	89.6		0
Le. S. 38 F	Familial RTA, nephrocalcinosis	71.9	6.59 (15.5)	14.3	59.1	2.29	1–1½	132		0
B. Mc. 32 F	Idiopathic hypergammaglobulinemia, nephrocalcinosis	45.0	6.80 (17)	13.0	14.0	2.36	<1	76.0		0
K. E. 22 F	Lupoid hepatitis, nephrocalcinosis	82.1	7.10 (20.1)	4.3	16.4		1	67		0

TABLE I—(*Continued*)

Patient, age (yr), sex	Clinical diagnosis	C_{in}	Urinary acidification* U_{pH}min (CO_2)	$U_{TA}V_{max}$	$U_{NH_4}V_{max}$	$THCO_3^-$ (Plasma $[HCO_3^-]$ 22–24 mmoles/liter)	Alkali requirement‡	Urinary excretion α-Amino N	α-Amino N/creatinine N	Glucose
		ml/min per 1.73 m²		*μEq/min*		*mmoles/100 ml GF*	*mmoles/kg per 24 hr*	*mg/24 hr*	*g/g*	
Li. S. 19 F	Familial RTA, nephrocalcinosis	89.3	6.79 (16.5)	7.7	23.1	2.32	2–3	78		0
La. S. 14 M	Familial RTA	85.7	6.17 (17.5)	26.9	62.2	2.29	<1		0.42–0.44	0
P. B. 1 F	Idiopathic RTA	86.8	7.13 (11.4)	—	63.9	2.18	2–3		0.7–1.6	0

C_{in}, inulin clearance; U_{pH}min, minimal urinary pH (numerals in parentheses indicate lowest measured serum CO_2 content in mmoles/liter); $U_{TA}V_{max}$ and $U_{NH_4}V_{max}$, maximal rates of excretion of titratable acid and ammonium, respectively (values in infants and children were corrected to a standard body surface area of 1.73 m²); $THCO_3^-$, tubular reabsorption of bicarbonate (values in infants, children, and adults were determined at plasma bicarbonate concentrations of 22, 23, and 24 mmoles/liter, respectively); GF, glomerular filtrate.

* Renal acidification response to existent or NH_4Cl-induced acidosis; procedure of Wrong and Davies (22). Normal values for adults were established in a previous study (23); normal values for children and infants, corrected to 1.73 m², were derived by measurements (a) on the last day of a 3–5 day period of NH_4Cl-induced acidosis in children aged 1–16 yr (24), and (b) after a single oral dose of NH_4Cl (75 mEq/m²) in children aged 4–13 yr (25) and in infants (26) (values in infants are mean ±SE).

‡ Total daily alkali requirement (administered orally in divided doses) necessary to maintain plasma bicarbonate concentration in the range of 22–26 mmoles/liter (adults, children) or 21–24 mmoles/liter (infants).

least 2 wk. Except in M. P., who was potassium depleted when the urine collection was obtained, the urinary excretion rates of aldosterone were supernormal (normal values: 4–17 μg/24 hr).

DISCUSSION

According to current views (16, 28), the syndrome of renal tubular acidosis can reflect two physiologically distinct disorders of renal acidification. In patients with so-called classic RTA (type 1 RTA, "distal" or "gradient" RTA), the urinary pH remains inappropriately high during mild as well as severe degrees of acidosis and persisting bicarbonaturia is characteristic. The amount of bicarbonate excreted, however, remains a trivial fraction of that filtered both at subnormal and at normal plasma bicarbonate concentrations, a finding which indicates no substantial reduction in the rate at which the proximal (or distal) nephron reabsorbs bicarbonate (4, 9). In contrast, in patients with RTA associated with the Fanconi syndrome (type 2 RTA, "proximal" or "rate" RTA), the amount of bicarbonate excreted at normal plasma bicarbonate concentrations is more than 15% of that filtered, indicating that the rate of reabsorption of bicarbonate in the proximal nephron is reduced (15, 16). Prototypically in patients with type 2 RTA, the urinary pH is inappropriately high, and bicarbonaturia occurs only during mild or moderate degrees of acidosis; during more severe degrees of acidosis, bicarbonaturia disappears and the urinary pH decreases to normal minima (15, 28, 29).

The results of the present study provide evidence that renal potassium wasting in type 2 RTA is physiologically separable from that in type 1 RTA and in part the result of a reduction in the rate at which the proximal nephron reabsorbs bicarbonate and the consequent delivery to the distal nephron of supernormal amounts of $NaHCO_3$. In each of the 10 patients studied with type 2 RTA, bicarbonate reabsorption in the proximal nephron was almost certainly impaired, since at normal plasma bicarbonate concentrations renal bicarbonate reabsorption was invariably reduced by more than 15% (Table I). In four studies on three patients with type 2 RTA, urinary potassium excretion (U_KV) and fractional potassium excretion (C_K/C_{in}) increased strikingly when the plasma bicarbonate concentration was progressively increased from subnormal to normal or near normal levels by intravenous infusion of $NaHCO_3$. As would have been predicted from the physiological character of the renal acidification defect in these patients, urinary sodium and bicarbonate excretion also increased strikingly and concomitantly. In the two patients in whom fractional potassium excretion did not increase when the plasma bicarbonate concentration was increased to normal levels, the base line values of fractional potassium excretion during acidosis were already considerably greater than the maximal values observed in the other three patients

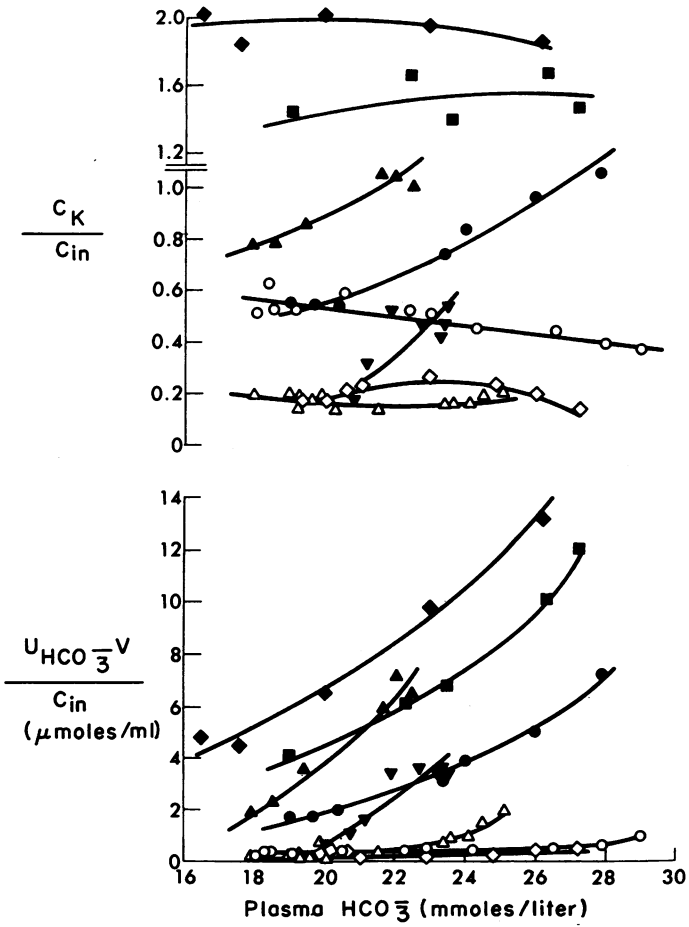

FIGURE 1 Effect of experimentally increasing plasma bicarbonate concentration (intravenous administration of sodium bicarbonate) on fractional potassium excretion and urinary bicarbonate excretion in four patients with renal tubular acidosis associated with the Fanconi syndrome (closed symbols) and in three patients with classic renal tubular acidosis (open symbols). ●, ▲, R. A.; ■, R. G.; ◆, R. Y.; ▼, G. F.; ○, C. V.; ◇, La. S.; △, Le. S.

at normal plasma bicarbonate concentrations, and the base line values of urinary sodium and bicarbonate excretion were more than twice the base line values in these three patients. In the one patient in whom the plasma bicarbonate concentration was acutely decreased by the administration of ammonium chloride, U_KV and C_K/C_{in} decreased concurrently with a decrease in urinary bicarbonate excretion. In six patients in whom correction of acidosis was sustained for 2 months or longer, fractional potassium excretion was consistently greater than 0.55, usually greater than 1.0, and varied directly with the urinary excretion rates of both sodium and bicarbonate, hence varied directly with the magnitude of reduction in tubular reabsorption of sodium and bicarbonate. It might be argued that the fractional excretion rates of potassium were high in these patients because their glomerular filtration rates were reduced, but in each patient in whom GFR was reduced, fractional potassium excretion was disproportionately high relative to the degree of reduction of glomerular filtration rate, despite the occurrence in some cases of hypokalemia.

These characteristics of urinary potassium excretion in patients with type 2 RTA can be explained in part as a consequence of increased intraluminal negativity in the distal nephron resulting from the combination of an increased distal delivery of sodium with the relatively impermeant bicarbonate anion and an increased stimulus for renal sodium reabsorption. In the rat, under a variety of metabolic conditions that increase potassium excretion, including the administration of a poorly perme-

ant anion (sulfate) in a sodium-deficient state and the inhibition of carbonic anhydrase (dichlorphenamide), the degree of intraluminal negativity in the distal nephron is a critical determinant of the net rate of potassium secretion in the distal nephron and, as a consequence, of urinary potassium excretion (18–20). In rats stimulated to reabsorb sodium avidly, increasing the delivery of sodium and bicarbonate to the distal nephron results in a substantial increase in intraluminal negativity (17). In the patients with type 2 RTA, the stimulus for renal sodium reabsorption was undoubtedly increased since, in the six patients in whom urinary aldosterone was measured, it was either increased (five patients) or effectively increased relative to the degree of potassium depletion (one patient) (30, 31).

In the two patients with type 2 RTA in whom C_K/C_{in} was greater than 1.5, the finding that urinary excretion of potassium did not increase further when acidosis was corrected does not indicate that the delivery of abnormally large amounts of $NaHCO_3$ to the distal nephron was not an important determinant of their renal potassium wasting. Because of the marked impairment of renal bicarbonate reabsorption in these two patients, urinary sodium and bicarbonate excretion during acidosis was already greatly increased. Hence, the maximal potassium secretory response of the distal nephron may have already been elicited.

In the patient with type 2 RTA in whom the plasma bicarbonate concentration was decreased by the administration of ammonium chloride, the finding that urinary sodium excretion did not decrease as urinary potassium excretion decreased does not indicate that the initially high urinary excretion rates of potassium were not the result of increased distal delivery of $NaHCO_3$. Since in this study the reduction in urinary excretion of bicarbonate was accompanied by an increase in urinary excretion of chloride, it can be inferred that the delivery of HCO_3^- and Cl^- to the distal nephron decreased and increased, respectively. For a given delivery of sodium to the distal nephron and a given stimulus for renal sodium reabsorption, the combination of an increased distal delivery of the highly permeant anion, chloride, and a

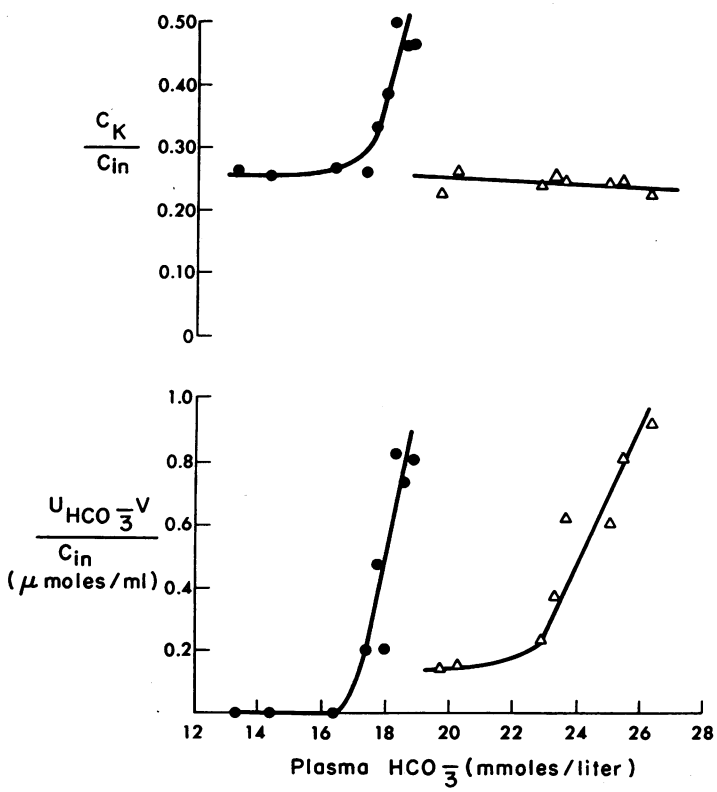

FIGURE 2 Effect of experimentally increasing plasma bicarbonate concentration (intravenous administration of sodium bicarbonate) on fractional potassium excretion and urinary bicarbonate excretion in an infant with renal tubular acidosis associated with the Fanconi syndrome (A. M., closed symbols) and in an infant with classic renal tubular acidosis (P. B., open symbols).

TABLE II

*Summary of Results of Sodium Bicarbonate Infusion Studies**

Patient	Plasma HCO_3^-	Serum K	$\frac{U_KV}{C_{in}}$	$\frac{C_K}{C_{in}}$	$\frac{U_{Na}V}{C_{in}}$	$\frac{UHCO_3^-V}{C_{in}}$
	mmoles/liter	*mEq/liter*	*μEq/ml*		*μEq/ml*	*μmoles/ml*
Type 2 RTA						
A. M.	13.3	3.5	0.92	0.26	1.38	0
	18.9	3.0	1.39	0.46	2.57	0.80
G. F.	20.0	4.8	0.78	0.16	1.82	0.41
	23.5	4.1	2.20	0.54	4.50	3.39
R. A.$_1$	19.0	4.3	2.30	0.54	3.12	1.65
	27.9	3.5	3.67	1.04	7.22	7.30
R. A.$_2$	17.9	4.4	3.43	0.78	3.89	1.94
	22.5	4.3	4.43	1.03	8.37	7.09
R. G.	19.0	3.9	5.53	1.45	8.28	4.10
	27.2	3.7	5.38	1.44	18.2	12.0
R. Y.	16.5	3.6	7.27	2.03	19.5	4.80
	26.2	2.7	5.02	1.85	29.7	13.2
Type 1 RTA						
P. B.	19.7	3.4	0.75	0.22	0.72	0.14
	26.3	2.8	0.62	0.22	2.96	0.92
La. S.	19.3	3.9	0.70	0.18	2.77	0.07
	27.2	3.5	0.58	0.16	2.45	0.58
Le. S.	18.1	4.0	0.78	0.20	2.22	0.24
	25.1	3.5	0.76	0.22	4.65	1.96
C. V.	18.0	4.1	2.12	0.51	2.46	0.28
	28.9	3.0	1.17	0.38	6.42	0.88

C_{in}, inulin clearance; C_K, potassium clearance; U_KV, $U_{Na}V$, and U_{HCO_3}-V, urinary excretion rates of potassium, sodium, and bicarbonate, respectively.

* For each patient, the initial and final values obtained during $NaHCO_3$ infusion are shown as vertical pairs.

TABLE III

Representative Study of the Effect of Intravenous Bicarbonate Infusion on Urinary Potassium Excretion in a Patient with Renal Tubular Acidosis Associated with the Fanconi Syndrome (Type 2 RTA) (R. A.)

Time	Urine					$\frac{U_{HCO_3}-V}{C_{in}}$	$\frac{U_KV}{C_{in}}$	$\frac{C_K}{C_{in}}$	C_{in}	Arterial			Serum	
	Flow	Na	K	HCO_3^-	pH					HCO_3^-	P_{CO_2}	pH	K	Na
	ml/min	*μEq/min*		*μmoles/min*		*μmoles/ml*	*μEq/ml*		*ml/min*	*mmoles/liter*	*mm Hg*		*mEq/liter*	
Priming infusion: 25 ml of 10% inulin over 5 min period intravenously. Constant infusion 1: 5% inulin at 0.191 ml/min intravenously at 0 time.														
151–174	5.61	83.0	61.1	44.0	7.04	1.65	2.30	0.535	26.6	17.9	35.9	7.319	4.3	141
174–191	5.65	71.6	50.9	37.3	7.01	1.66	2.27	0.531	22.4	18.8	36.7	7.332	4.3	137
Constant infusion 2: 3.75% sodium bicarbonate at 3.82 ml/min intravenously.														
191–218	5.75	81.6	57.0	55.2	7.09	1.93	1.99	0.481	28.6	20.4	35.8	7.379	4.1	138
218–244	3.00	82.1	63.9	68.4	7.46	3.08	2.88	0.725	22.2	23.4	38.5	7.405	4.0	138
244–263	4.25	137.2	100.8	124.2	7.57	3.87	3.14	0.828	32.1	24.3	38.0	7.428	3.8	139
263–291	3.39	135.7	88.8	127.9	7.65	4.98	3.46	0.939	25.7	27.2	40.4	7.450	3.7	141
291–315	4.55	210.0	106.9	222.2	7.71	7.30	3.67	1.04	29.1	28.6	40.6	7.470	3.5	141

C_{in}, inulin clearance; U_{HCO_3}-V and U_KV, urinary excretion rates of bicarbonate and potassium, respectively; C_K, potassium clearance; P_{CO_2}, carbon dioxide tension.

decreased distal delivery of the relatively impermeant anion, bicarbonate, would be expected to reduce intraluminal negativity in the distal nephron and the stimulus for potassium secretion and excretion (17–20). The importance of the anion accompanying sodium as a determinant of potassium excretion was specifically examined by Bank and Schwartz (32). In dogs stimulated to conserve sodium avidly, a constant intravenous infusion of sodium phosphate was abruptly replaced by a constant infusion of sodium chloride. Potassium excretion first increased as sodium and phosphate excretion increased. When, however, the infusion of sodium phosphate was replaced by that of sodium chloride, potassium excretion decreased as phosphate excretion decreased and chloride excretion increased, despite a further increase in the rate of sodium excretion.

The results of the present investigation do not exclude the possibility that in patients with type 2 RTA, renal potassium wasting results in part from impaired proximal tubular reabsorption of potassium. The finding in some patients, however, that C_K/C_{in} was greater than 1.5 indicates that even complete suppression of potassium reabsorption in the proximal nephron would not have been sufficient to account for the degree of renal potassium wasting (18, 19).

In the patients with type 1 RTA, delivery of super-

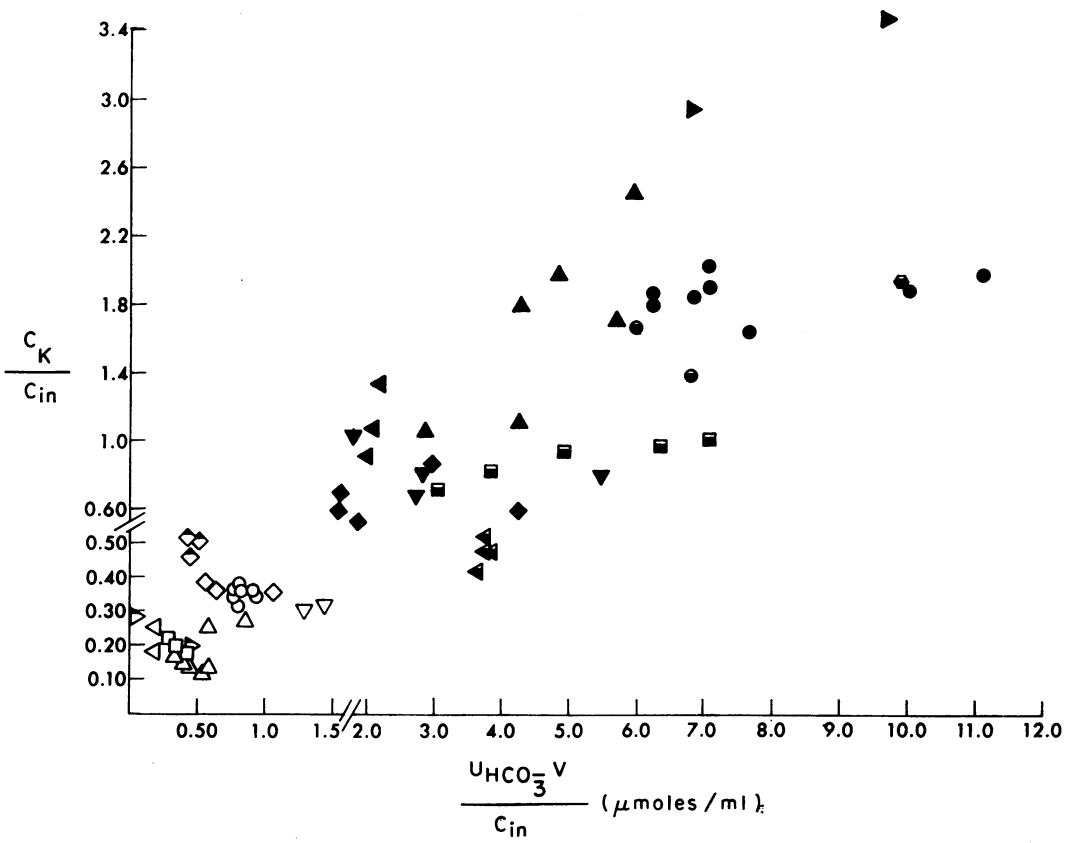

FIGURE 3 Relationship between fractional potassium excretion (C_K/C_{in}) and urinary bicarbonate excretion (U_{HCO_3}-V/C_{in}) in patients with renal tubular acidosis associated with the Fanconi syndrome (closed and three-quarter closed symbols) and in patients with classic renal tubular acidosis (open and three-quarter open symbols) in whom the plasma bicarbonate concentration was maintained at normal levels (22–26 mmoles/liter) for more than 2 months (closed and open symbols) or was rapidly increased to normal levels (intravenous administration of sodium bicarbonate) (three-quarter closed and three-quarter open symbols; data from Fig. 1). Like geometric symbols represent measurements made in a single patient. The near overlap of U_{HCO_3}-V/C_{in} in patients represented by ◆ and ▽ reflects the fact that in ◆ $THCO_3^-$ was the least reduced of the Fanconi group and U_{HCO_3}-V/C_{in} was measured at the lowest normal plasma bicarbonate concentrations (22.2 mmoles/liter) while in ▽ $THCO_3^-$ was the most reduced of the classic RTA group and U_{HCO_3}-V/C_{in} was measured at the highest normal plasma bicarbonate concentrations (25.5 mmoles/liter).

TABLE IV

Effect of Ammonium Chloride Administration on Urinary Potassium and Bicarbonate Excretion in a Patient with Renal Tubular Acidosis Associated with the Fanconi Syndrome (Type 2 RTA) (R. A.) and in a Patient with Classic RTA (Type 1 RTA) (L. C. S.)

Time	Urine						$\frac{U_{HCO_3}-V}{C_{in}}$	$\frac{U_{Cl}V}{C_{in}}$	$\frac{U_KV}{C_{in}}$	$\frac{C_K}{C_{in}}$	C_{in}	Arterial			Serum		
	Flow	Na	K	Cl	HCO_3^-	pH						HCO_3^-	P_{CO_2}	pH	K	Na	Cl
	ml/min		*μEq/min*		*μmoles/min*		*μmoles/ml*		*μEq/ml*		*ml/min*	*mmoles/liter*	*mm Hg*		*mEq/liter*		
Type 2 RTA (R. A.)																	
Priming infusion: 25 ml of 10% inulin over 5 min period intravenously.																	
Constant infusion 1: 5% inulin at 0.191 ml/min intravenously.																	
Ammonium chloride, 6.0 g, orally at 0 time.																	
0–30	2.27	104.0	70.5	48.0	93.6	7.60	4.59	2.35	3.46	0.815	20.4	22.6	38.9	7.384	4.2	140	
30–43	1.65	62.6	69.5	33.4	44.0	7.45	2.06	1.56	3.25	0.777	21.4						
43–63*	2.35	87.7	70.8	50.2	46.9	7.29	1.72	1.85	2.60	0.636	27.2	18.7	37.2	7.323	4.1	140	117
63–97*	2.97	112.0	64.5	60.6	53.1	7.28	1.88	2.15	2.29	0.573	28.2	16.6	34.1	7.308	4.0	140	116
97–115*	3.50	117.5	75.0	63.0	56.1	7.26	1.67	1.88	2.23	0.571	33.6						
115–129*	2.86	89.5	56.4	51.5	38.1	7.19	1.45	1.96	2.14	0.546	26.3						
129–145*	2.94	88.0	53.5	54.4	29.8	7.10	1.16	2.12	2.08	0.524	25.7	14.9	33.7	7.268	4.0	138	116
145–159	2.78	83.6	45.4	56.4	23.5	7.01	1.01	2.41	1.94	0.486	23.4						
159–175	3.00	93.9	46.2	72.8	18.8	6.93	0.73	2.83	1.80	0.447	25.7						121
175–190	3.00	96.3	43.3	78.8	18.6	6.91	0.72	3.05	1.76	0.430	25.8	13.5	32.2	7.241	4.0	136	
190–206	2.72	90.3	40.5	71.9	15.7	6.89	0.68	3.10	1.75	0.422	23.2						
207																	
Type 1 RTA (L. C. S.)																	
Priming infusion: 18 ml of 10% inulin over 5 min period intravenously.																	
Constant infusion 1: 10% inulin at 0.191 ml/min intravenously.																	
Ammonium chloride, 2.0 gm, orally at 0 time.																	
0–20	2.25	33.4	54.2	24.8	26.1	7.30	0.69	0.64	1.42	0.386	38.2	22.8	39.0	7.388	3.7	147	109
20–40*	2.80	45.5	69.4	35.8	38.9	7.32	0.64	0.50	1.15	0.307	60.3						
40–60	1.20	35.7	53.5	14.5	23.6	7.44	0.35	0.21	0.80	0.210	66.5	20.1	36.9	7.358	3.8	142	109
60–80	3.40	42.8	73.8	29.2	34.2	7.21	0.54	0.46	1.15	0.303	63.6	19.8	36.9	7.351	3.8	143	
80–100	6.75	41.9	63.5	27.0	31.5	6.98	0.59	0.50	1.18	0.311	53.4						
100–120*	7.95	39.8	55.7	23.9	41.1	6.87	0.78	0.45	1.06	0.279	52.5	19.3	36.9	7.340	3.8		
120–140	6.65	35.9	51.2	26.6	34.4	6.88	0.77	0.59	1.14	0.300	44.8						
140–160*	4.95	36.1	52.0	13.6	35.8	6.98	0.68	0.26	0.98	0.258	52.8	17.9	36.7	7.310	3.8	139	
160–180	2.75	31.1	50.0	23.4	25.4	7.19	0.52	0.47	1.01	0.266	49.0						
180–200*	1.55	31.9	52.1	29.5	28.9	7.47	0.55	0.56	0.99	0.261	52.4	18.3	35.9	7.329	3.8		
200–220*	1.50	33.0	56.7	30.0	30.6	7.49	0.66	0.64	1.22	0.321	46.3						
220–240	2.45	40.4	72.7	34.3	41.4	7.42	0.65	0.53	1.13	0.297	63.9	17.2	34.5	7.320	3.8	137	
240–260	4.10	35.3	61.9	28.7	38.9	7.23	0.73	0.54	1.16	0.305	53.1						
260–280	3.56	32.4	55.2	28.5	34.8	7.22	0.69	0.56	1.09	0.287	50.4	17.2	34.9	7.313	3.8		
280–300	7.26	48.6	81.3	28.6	44.6	7.06	0.62	0.60	1.15	0.297	71.6	16.7	35.1	7.300	3.8	135	116

C_{in}, inulin clearance; $U_{HCO_3}-V$ and U_KV, urinary excretion rates of bicarbonate and potassium, respectively; C_K, potassium clearance; P_{CO_2}, carbon dioxide tension.
* Ammonium chloride, 1.0 g, administered orally.

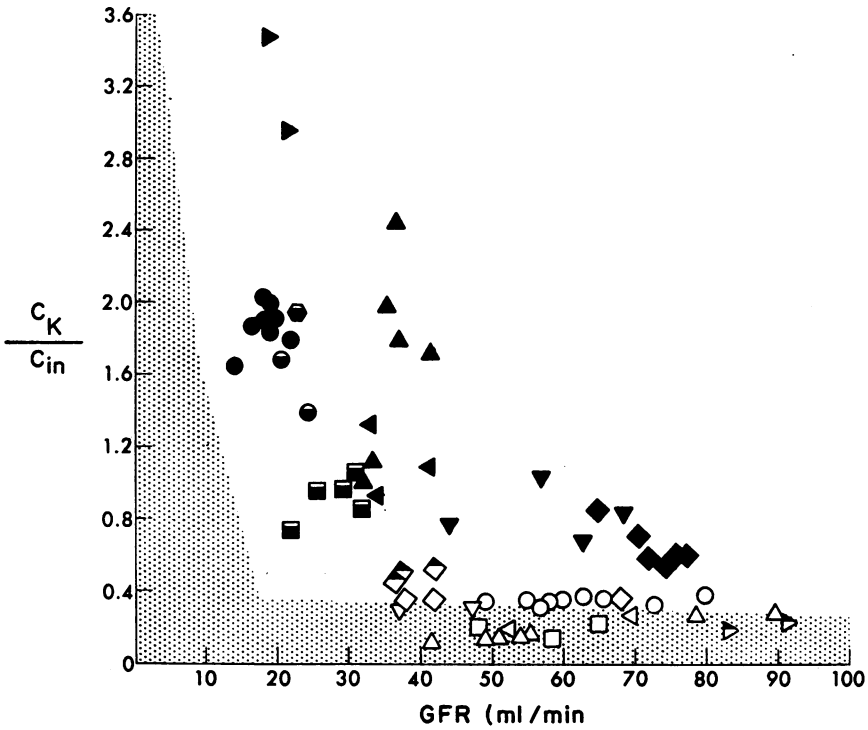

FIGURE 4 Relationship between fractional potassium excretion (C_K/C_{in}) and glomerular filtration rate (GFR) in patients with renal tubular acidosis associated with the Fanconi syndrome (closed and three-quarter closed symbols), in patients with classic renal tubular acidosis (open and three-quarter open symbols), and in patients with chronic renal insufficiency of diverse etiology (shaded area) (27). See Fig. 3 for explanation of symbols.

normal amounts of $NaHCO_3$ to the distal nephron could not be supported as a cause of renal potassium wasting. In each of the eight patients studied, the rate of bicarbonate reabsorption in the proximal nephron could not have been substantially reduced since tubular reabsorption of bicarbonate at normal plasma bicarbonate concentrations was nearly complete (Table I). In the four patients with type 1 RTA in whom the plasma bicarbonate concentration was progressively increased from subnormal to normal levels by intravenous infusion of $NaHCO_3$, U_KV and C_K/C_{in} remained essentially constant or decreased. As would have been predicted from the physiological character of the renal acidification defect in these patients, urinary bicarbonate excretion also remained essentially constant until normal or supernormal plasma bicarbonate concentrations were reached. In the one patient in whom the plasma bicarbonate concentration was rapidly decreased by the administration of ammonium chloride, U_KV and C_K/C_{in} remained essentially constant, as did urinary sodium and bicarbonate excretion. In the six patients with type 1 RTA maintained at normal plasma bicarbonate concentrations for 2 months or longer, fractional potassium excretion was consistently less than 0.55 and did not correlate with the urinary excretion rates of either sodium or bicarbonate.

In patients with type 2 RTA but not in patients with type 1 RTA, the results of the present studies permit the prediction that renal potassium wasting will occur invariably and even worsen when systemic acidosis is corrected with alkali therapy. Conceivably, during pro-

TABLE V

Urinary Aldosterone in Patients with Renal Tubular Acidosis Associated with the Fanconi Syndrome (Type 2 RTA)

Patient	Urinary aldosterone*	Sodium intake*	Serum potassium
	μg/24 hr	*mEq/24 hr*	*mEq/liter*
R. A.	39.3	95	4.5
M. P.	9.1	>100	3.7
R. G.	30.5	85	4.1
M. H.*	159.4	>200	3.8
A. M.*	105.9	157	4.5
E. S.*	148.6	275	3.6

* Values in children aged <12 yr corrected to 1.73 m^2.

longed $NaHCO_3$ therapy, the severity of renal potassium wasting in some patients might diminish as a consequence of a reduction in aldosterone secretion. But in three patients in whom serial measurements of urinary aldosterone were made, hyperaldosteronism persisted despite sustained correction of acidosis with alkali therapy and despite normal or supernormal sodium intake and no measured reduction of plasma volume (unpublished observations).

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