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Research Article

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ABSTRACT In four infants with renal tubular acidosis (RTA), including three with apparently classic RTA and one with Fanconi syndrome (FS), the physiologic character of the renal acidification defect was investigated. In two of the infants with apparently classic RTA, the acidification defect was physiologically separable from that described in both adult patients and children with classic RTA (type 1 RTA) in the following ways. (*a*) The fractional excretion of filtered bicarbonate (C_{HCO_3}/C_{in}) was not trivial but substantial (6–9%), as well as relatively fixed, over a broad range of plasma bicarbonate concentrations (15–26 mmoles/liter). (*b*) This value of C_{HCO_3}/C_{in}, combined with a normal or near normal glomerular filtration rate, translated to renal bicarbonate wasting (RBW). (*c*) RBW at normal plasma bicarbonate concentrations was the major cause of acidosis, and its magnitude was the major determinant of corrective alkali therapy (5–9 mEq/kg per day), just as in the patient with FS, who was found to have type 2 ("proximal") RTA. (*d*) Persistence of RBW at substantially reduced plasma bicarbonate concentrations, which did not occur in FS, accounted for the spontaneous occurrence of severe acidosis and its rapid recurrence after reduction in alkali therapy. (*e*) During severe acidosis the urinary pH was > 7, a finding reported frequently in infants with apparently classic RTA and "alkali-resistant" acidosis but rarely in adult patients with classic RTA. Continued supplements of potassium were required to maintain normokalemia during sustained correction of acidosis with alkali therapy. Yet, in at least two of the three infants with apparently classic RTA, but in distinction from the patient with FS and other patients with type 2 RTA, fractional excretion of filtered potassium decreased when plasma bicarbonate was experimentally increased to normal values. In one of the two infants with apparently classic RTA and RBW, C_{HCO_3}/C_{in} and the therapeutic alkali requirement decreased concomitantly and progressively over 2 yr, but RBW continued. Renal tubular acidosis has persisted in all four patients for at least 3 yr, and in three for 4 years.

INTRODUCTION

Renal tubular acidosis (RTA)[1] is a clinical syndrome of disordered renal acidification characterized biochemically by minimal or no azotemia, hyperchloremic acidosis, inappropriately high urinary pH, bicarbonaturia, and reduced urinary excretion of titratable acid and ammonium (1–13). In "classic" ("distal") RTA, urinary pH is inappropriately high during severe as well as mild degrees of acidosis, persisting urinary excretion of bicarbonate is characteristic (9–12), and the complex dysfunction of the proximal tubule characteristic of Fanconi syndrome is absent. In adult patients with classic RTA, the amount of bicarbonate excreted at both normal and reduced plasma bicarbonate concentrations is a trivial fraction of that filtered, i.e., renal tubular reabsorption of bicarbonate ($THCO_3^-$) is just less than complete (4, 5, 7, 10, 13). "Bicarbonate wasting" has not been reported. In patients with this kind of renal acidification dysfunction, which we have termed type 1 RTA, acidosis results principally from impaired acid excretion.

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[1] *Abbreviations used in this paper:* FS, Fanconi syndrome; RBW, renal bicarbonate wasting; RTA, renal tubular acidosis; TA, titratable acid.

TABLE I

Clinical and Physiological Data in Infants with RTA

Patient, sex, age	Clinical diagnosis	Growth retardation/ corrected with alkali therapy	Rickets	Urine flow*	Glomerular filtration rate	TRP‡	Urinary α-amino nitrogen/ creatinine nitrogen
				ml/24 hr per 1.73 m²	*ml/min per 1.73 m²*	%	*g/g per 24 hr*
Normal values					1–7 wk:§ range 32–83 6 months–1 yr:§ range 52–128		<1.2 infants 0–18 months‖
cRTA (P. B.) F 9 months–3 yr Caucasian	Classic RTA, idiopathic	+/+	Absent	1490 (12 months)	77.5 (10½ months)	85.3 (5.03)	1.24 (13 months)
RBW₁ (V. V.) F 5 months–3½ yr Mexican	Classic RTA, idiopathic	+/+	Absent¶	4567 (13 months)	88.3 (13 months)	89.5 (5.46)	0.81 (13 months)
RBW₂ (T. L.) F 1 wk–2½ yr Chinese	Classic RTA, idiopathic; G-6-P-D deficiency; bilirubin encephalopathy	+/+	Absent	4197 (1 month)	55.0 (1 month)	87.2 (5.7)	0.86 (3 wk)
FS (A. M.)** M 11 months–3 yr Negro	RTA type 2 ("proximal"); Fanconi syndrome; cystinosis	+/0	Marked, improved on vitamin D and alkali Rx	4123 (10 months)	103 (13 months)	61.3 (1.95)	14.7 (13 months)

cRTA, classic renal tubular acidosis; RBW, renal bicarbonate wasting; FS, Fanconi syndrome; TRP, renal tubular reabsorption of inorganic phosphate; G-6-P-D, glucose-6-phosphate dehydrogenase. Initials in parentheses are those of patients' names.

* The mean value of at least three successive 24-hr urine volumes measured when the patients were drinking water ad lib. and systemic acidosis and hypokalemia had been corrected for at least 3 wk.

‡ The mean value from at least three successive 15 to 30-min collection periods at normal plasma bicarbonate concentrations. Numerals in parentheses are the serum concentrations of inorganic phosphate (mg/100 ml) used in calculating TRP.

§ See reference 25.

‖ McSherry, E., A. Sebastian, and R. C. Morris, Jr. Unpublished observations.

¶ Osteopenia, initially present (age 4 months), was not again detectable after alkali therapy had been sustained more than 4 months.

** The only patient in whom glucosuria was detected.

Hence, correction of acidosis is characteristically sustained by an amount of alkali only a fraction more than the normal endogenous production of nonvolatile acid: 1 mEq/kg per day (in adults) (14, 5, 7, 10).

In some children with classic RTA, the disorder of renal acidification may be physiologically indistinguishable from that described in adults (9–12), and 1–3 mEq/kg per day of alkali may be adequate replacement therapy (9, 11). But in many infants with apparently classic RTA, several times this amount of alkali has failed to correct acidosis (2, 15–24), and measurements of $THCO_3^-$ at normal plasma bicarbonate concentrations have been reported in none. In the present study of three infants girls with apparently classic RTA, the renal acidification defect of two was found to be physiologically separable from that described in patients with either type 1 RTA or type 2 ("proximal") RTA (12, 13): $THCO_3^-$ was decreased by a substantial and relatively fixed fraction (6–9%) at plasma bicarbonate concentrations ranging from 26 to 15 mmoles/liter. Bicarbonate wasting was not only the major cause of acidosis in these infants, its persistence at reduced plasma bicarbonate concentrations also accounted for the occurrence of strikingly severe acidosis, both before beginning, and soon after diminishing, corrective alkali therapy. The amount of bicarbonate excreted at normal plasma bicarbonate concentrations was the major determinant of the amount of alkali required to sustain correction of acidosis in these two infants.

METHODS

Four unrelated infants with RTA were studied on the pediatric clinical research ward. Each patient had a history characteristic of RTA. For purposes of clarity, the infants are identified in this paper according to their subsequently determined renal tubular dysfunction: one infant girl with classic renal tubular acidosis without bicarbonate wasting (cRTA), two infant girls with classic renal tubular acidosis and renal bicarbonate wasting (RBW_1, RBW_2), and one infant boy with RTA and the Fanconi syndrome associated with cystinosis (FS). The initials of the patients'

names are given in Table I. 11 adult patients with previously diagnosed classic (type 1) renal tubular acidosis served as a comparative group (8, 13, 26).

Acute studies. All studies were initiated in the morning. In those studies in which intravenous administration of solutions was sustained, the patients were semireclining in an infant seat, urine was collected every 20–30 min from an indwelling Foley catheter, draining under a layer of mineral oil, for immediate determination of pH, carbon dioxide content, ammonium, and titratable acid, and for subsequent determination of sodium, potassium, chloride, and phosphorus. Blood pH and carbon dioxide tension were determined on arterialized blood drawn from a superficial vein on the dorsum of the hand or foot that had been heated with an electric heating muffler to a surface temperature of at least 45° C for more than 60 min. Potassium, sodium, creatinine, and phosphorus concentrations were determined on serum from the arterialized blood. Inulin clearance was measured throughout each study. Breakfast was withheld, but water was offered freely before and during these studies.

In those studies in which no intravenous solutions were administered (urinary acidification studies only), patients were not catherized, and spontaneously voided urine was collected at timed intervals under a layer of mineral oil, preserved with thymol and refrigerated until pH, carbon dioxide content, ammonium, and titratable acid concentration were determined, usually within 24 hr.

Sodium bicarbonate infusion studies. The relationship between plasma bicarbonate concentration and renal reabsorption and excretion of bicarbonate was examined during intravenous administration of sodium bicarbonate in RBW_1 at 5, 6½, 8, 11, 13, and 26 months of age, in RBW_2 at 4 wk and 2½ yr of age, in cRTA at 10 months of age, and in FS at 10, 14, and 24 months of age. For at least 2 wk before each study in RBW_1, the initial study of RBW_2, and the study of cRTA, appropriate therapy had maintained the plasma bicarbonate concentration at normal levels and the serum potassium concentration at 3.5 mEq/liter or greater. Before the second study of RBW_2, acidosis and hypokalemia had been corrected for only 48 hr. By appropriate adjustment of the amount of alkali administered during the 12 hr period before studies, the initial plasma bicarbonate concentration on the morning of study could be varied over a wide range of normal and subnormal levels. In FS, the plasma bicarbonate concentration was always subnormal on the morning of the study since correction of the patient's acidosis could not be sustained even with the administration of massive amounts (> 20 mEq/kg body weight) of alkali. In each study the plasma bicarbonate concentration was increased by 2–3 mmoles/liter per hr by intravenous administration of a 3.75% solution of sodium bicarbonate at rates varying from 0.3 to 0.8 ml/min. For most studies the rate of infusion remained constant throughout; in some studies of FS it was necessary to increase the rate of infusion at the higher plasma bicarbonate concentrations.

Sodium phosphate infusion. In RBW_1, at 7½ months, correcting alkali and potassium therapy had been administered for 3 months. On the morning of the study, NH_4Cl (0.1 g/kg body weight) was administered orally as a 10% solution over 80 min. 120 min afterward, a 0.15 M sodium phosphate solution (pH 7.4) was administered intravenously at a priming rate of 0.8 ml/min for 6 min and a sustaining rate of 0.5 ml/min for 90 min.

24 hr urine. 24-hr collections of spontaneously voided urine were made on RBW_1, RBW_2, and cRTA, after therapeutic correction of acidosis and hypokalemia[2] had been sustained for at least 2 wk. For small infants, urine collections were made in a metabolic isolette with the baby frocked in and lying on parachute silk. Larger infants wore urine-collecting bags during the day and slept on parachute silk-covered metabolic mattresses at night. Care was taken to ensure that urine emptied promptly into the collection containers. Toilet-trained toddlers (cRTA, 18 months; RBW_1, 20 months; RBW_2, 18 months) were awakened every 2–4 hr during the night for urine collections. Freshly voided urine was collected under mineral oil, preserved with thymol, and immediately refrigerated; carbon dioxide content, pH, titratable acid, and ammonium were determined within 24 hr of the completion of the collection. Blood samples were drawn in the morning before breakfast, at least 4 hr after the last dose of alkali or supplemental potassium.

Laboratory methods. Laboratory determinations were carried out as described previously (8, 13, 27).

Informed consent and special precautions. Both parents of each child studied were informed of the purpose, character, and risks of the studies and specifically that catheterization of the bladder involved a small but finite risk of infection of the urinary tract. The investigators offered to assume continuing responsibility for the management of the child's illness, irrespective of whether the parents gave consent for any of the studies proposed. At the termination of each catheterization, urine collected from the catheter was cultured. During the 48 hr immediately succeeding catheterization, brisk water diuresis was maintained as a prophylaxis against urinary tract infection. Urine was again cultured 48 hr after catheterization. In none of the patients did clinical evidence of pyelonephritis occur or urine cultures become positive.

RESULTS

Bicarbonate studies. In each of the three infants studied with apparently classic RTA (Table I), the general relationship between plasma bicarbonate concentration and the renal reabsorption and excretion of bicarbonate was similar to that described previously in children and adult patients with classic renal tubular acidosis (4, 5, 9, 10): when the plasma bicarbonate concentration was increased from subnormal to normal levels, urinary excretion of bicarbonate ($U_{HCO_3}V/C_{In}$) increased little (RBW_1 and RBW_2) or not at all (cRTA); renal reabsorption of bicarbonate ($THCO_3^-$) increased nearly commensurately with the increase in the filtered load of bicarbonate (Fig. 1). Over a range of plasma bicarbonate concentrations extending from 15.5 to 28.9, the fraction of filtered bicarbonate excreted remained approximately constant. In RBW_1 and RBW_2, however, the reduction in $THCO_3^-$ at normal and subnormal plasma bicarbonate concentrations was *not* trivial as in cRTA and adult patients described with classic RTA (Table II) (5, 10): in the initial studies on RBW_1 (5½ months), RBW_2 (3 wk), and cRTA (10 months), the mean values of the fractional excretion of filtered bicarbonate (C_{HCO_3}/C_{In}) at normal plasma bicarbonate

[2] Serum potassium concentration less than 3.8 mEq/liter.

TABLE II

*Summary of Physiologic Data at Normal Plasma Bicarbonate Concentrations in Infants with RTA**

Patient, study number, age	Plasma HCO_3^-	$U_{HCO_3^-}V$	$\frac{U_{HCO_3^-}V}{C_{in}}$	$\frac{100 \cdot C_{HCO_3^-}}{C_{in}}$	$\frac{100 \cdot V}{C_{in}}$	C_{in}		Serum K	Arterial P_{CO_2}
	mmoles/liter	*μmoles/min*	*μmoles/ml GF*	%		*ml/min*	*ml/min per 1.73 m²*	*mEq/liter*	*mm Hg*
cRTA									
Study 1	20.2	6.1	0.34	1.7	2.5	17.9	77.5	4.4	35
10 months	±1.2	±3.0	±0.15	±0.8	±2.1	±3.5	±15.2		
RBW_1									
Study 1	20.6	10.8	1.57	7.6	13.3	7.2	56.6	4.8	33
5½ months	±1.6	±1.4	±0.29	±1.3	±4.0	±0.5	±3.9		
Study 3	21.5	18.1	1.45	6.5	16.6	12.8	73.9	3.6	37
8 months	±0.7	±4.6	±0.26	±1.1	±5.4	±1.0	±5.8		
Study 5	20.9	22.4	1.09	5.2	12.9	20.4	88.3	4.4	39
13 months	±1.4	±4.4	±0.17	±0.7	±4.4	±1.1	±4.8		
Study 8	20.0	26.3	0.83	4.0	9.1	31.3	100.2	4.1	41
26½ months	±1.4	±5.6	±0.12	±0.5	±3.4	±3.1	±9.9		
RBW_2									
Study 1	20.5	8.6	1.41	6.8	18.0	7.0	55.0	4.3	36
1 month	±0.8	±6.1	±0.83	±3.5	±12.8	±3.7	±29.1		
Study 2	25.2	29.9	1.15	4.6	10.6	26.1	87.0	4.3	41
28½ months	±0.7	±4.2	±0.14	±0.6	±3.5	±3.1	±10.4		
FS									
24 months	22.4	57.3	2.68	12.0	9.7	21.1	84.9	3.4	37
	±0.7	±14.8	±0.54	±2.4	±5.0	±2.0	±8.0		
Classic RTA	23.5	38.2	0.66	2.8	7.5	63.0	77.5	4.1	38
(11 adult patients)	±0.75	±19.1	±0.38	±1.6	±4.4	±19	±25	±0.3	±3

Results of significance tests‡		*P* value less than						
RBW_1-(1)§: RBW_1-(5)	NS	0.01	0.01	0.01	0.01	0.01	0.01
(1): (8)	NS	0.01	0.01	0.01	NS	0.01	0.01
(3) (8)	0.05	0.05	0.01	0.01	0.05	0.01	0.01
(5): (8)	NS	NS	0.01	0.01	NS	0.01	0.05
(1): cRTA (1)	NS	0.01	0.01	0.01	0.01	0.01	0.01
(8): (1)	NS	0.01	0.01	0.01	0.01	0.01	0.01
RBW_2 (1): (1)	NS	NS	0.01	0.01	0.05	0.01	NS

$U_{HCO_3^-}V$, urinary excretion rate of bicarbonate; C_{in}, inulin clearance; $\frac{C_{HCO_3^-}}{C_{in}}$, the fraction of filtered bicarbonate excreted; V, urinary flow; P_{CO_2}, carbon dioxide tension; GF, glomerular filtrate; NS, not significant.

* Mean ±SD of three or more successive values.

‡ Student's *t* test.

§ Numbers in parentheses refer to patient study number.

concentrations were, respectively, 7.6 ±1.3, 6.8 ±3.5, and 1.7 ±0.8%. These reductions in $THCO_3^-$ of 7.6 and 6.8% in RBW_1 and RBW_2 would amount to the urinary excretion of 124 and 97 mEq of bicarbonate/day, respectively, in adult patients (surface area, 1.73 m^2) with glomerular filtration rates per unit body surface area like those observed in the infants; such rates of bicarbonate excretion are much greater than those observed in adult patients with classic RTA (Table III) (5, 10). By contrast, in cRTA, the reduction of $THCO_3^-$ of 1.7% would correspond to a urinary excretion rate of bicarbonate of only 33.7 mEq/day, a magnitude of bicarbonaturia characteristic of classic RTA in adult patients (Table III).

TABLE III

Comparison of Urinary Bicarbonate Excretion at Normal Plasma Bicarbonate Concentrations Achieved Experimentally and Sustained Therapeutically in Infants with RTA

Patient, age, body weight	During acute $NaHCO_3$ infusion study					During sustained correction of acidosis with oral alkali therapy				
	Plasma $[HCO_3^-]$	$U_{HCO_3^-}V$*	$U_{HCO_3^-}V$‡		$U^{Net}_{Base}V$‡	$U^{Net}_{Base}V$	$U_{HCO_3^-}V$		Bicarbonate intake	Plasma $[HCO_3^-]$
	mmoles/liter	*μEq/min*	*mmoles/ 24 hr per 1.73 m²*	*mmoles/ 24 hr per kgBW*	*mmoles/ 24 hr per kgBW*	*mmoles/ 24 hr per kgBW*	*mmoles/24 hr per kgBW*	*mmoles/24 hr per 1.73 m²*	*mmoles/24 hr per kgBW*	*mmoles/ liter*
RBW_1										
8 months 5.9 kg	20.8–22.4	18.1	150.4	4.4	3.6	4.4	4.6, 5.1	150, 164	5–8	19.5–20.1
13 months 8.5 kg	19.01–22.71	22.4	139.7	3.8	2.4	2.1	2.8, 2.9	106, 108	3–4	24.1–27.7§
37 months 13.7 kg	19.3–22.2	26.3	121.2	3.0	2.4	—	2.6, 2.9, 2.7	103, 111, 105	4.4	23.4–25.1§
44 months 15.7 kg						3.1¶	3.2‖	125‖	5.4	23.3–25.8
RBW_2										
4 wk 3.6 kg	20.1–22.73	8.6	96.9	3.4	2.1	1.7	2.9, 2.4	69, 65	5–7	20.8–22.6§
28 months 10.8 kg	24.6–25.1	31.5	151.1	4.2	3.6	—	5.9, 7.9	172, 221	10	21.9–24.8§
cRTA										
10½ months 7.5 kg	19.9–22.9	5.4	33.7	1.0	0.54	0.6	0.9, 1.2	30, 37	1.5	20.4–21.5
Classic RTA (11 adult patients)	23.05 ±0.8	38.2 ±19	66.0 ±32	1.03 ±0.54	0.61 ±0.87	0.46 ±0.5	0.73 ±0.3	43.9 ±17	1.4 ±0.4	26.5§ ±1.8

$U_{HCO_3^-}V$, urinary bicarbonate excretion; BW, body weight.

* Mean of three or more values from successive urine collections obtained over the range of plasma bicarbonate concentrations indicated.

‡ Calculated from the mean value of urinary bicarbonate ($U_{HCO_3^-}V$) or net base ($U_{Net\ Base}V$) excretion, assuming a constant rate of excretion for 24 hr. Net base excretion = the urinary excretion rate of bicarbonate minus the sum of the urinary excretion rates of titratable acid and ammonium.

§ Serum CO_2 content.

‖ Mean of six successive values.

In each of six studies performed on RBW_1 between the ages of 5 and 26 months, the general relationship between renal bicarbonate reabsorption (or excretion) and the plasma bicarbonate concentration remained unchanged over the entire range of plasma bicarbonate concentrations studied (Fig. 1, Table IV). In the four studies performed during the 1st yr of life (Fig. 1), the values of $THCO_3^-$ at any given plasma bicarbonate concentration did not change significantly ($P < 0.05$) even though the studies were carried out at plasma bicarbonate concentrations of widely varying initial values and subsequent ranges of increase (Fig. 1). During the subsequent 2 yr of life, the magnitude of impairment in renal bicarbonate reabsorption at subnormal and normal plasma bicarbonate concentrations decreased progressively (Table II). At normal plasma bicarbonate concentrations, $U_{HCO_3^-}V/C_{In}$ decreased from 0.157 to 0.083 mEq/100 ml glomerular filtrate (GF), and $C_{HCO_3^-}/C_{In}$ from 7.6 to 4.0% (Table II). Accordingly, the magnitude of the reduction in $THCO_3^-$ at normal plasma bicarbonate concentrations decreased by nearly 50% over a 21 month period. The reduction of $U_{HCO_3^-}V/C_{In}$ and $C_{HCO_3^-}/C_{In}$ was not associated with a reduction in the absolute rate of urinary bicarbonate excretion ($U_{HCO_3^-}V$) as the patient became older. Rather, $U_{HCO_3^-}V$ increased progressively, but a rate less than the rate at which glomerular filtration rate (GFR) increased (Table II). Despite progressively increasing renal bicarbonate reabsorption in RBW_1, $C_{HCO_3^-}/C_{In}$, as well as $U_{HCO_3^-}V/C_{In}$ and $U_{HCO_3^-}V$, remained significantly greater than in cRTA (Table II).

In RBW_2, $C_{HCO_3^-}/C_{In}$ and $U_{HCO_3^-}V/C_{In}$ also decreased with time, but remained significantly greater than in cRTA (Table II).

In cRTA, RBW_1, and RBW_2, 24-hr urinary excretion rates of bicarbonate, extrapolated from results of the bicarbonate infusion studies at normal plasma bicarbonate concentrations, approximated the actual 24-hr urinary excretion rates of bicarbonate observed during sustained correction of the patients' acidosis with oral alkali therapy (Table III). As the patients became older, the correspondence between extrapolated and measured rate of bicarbonaturia held, both in RBW_1 and RBW_2. The extrapolated and measured values of 24 hr net base ex-

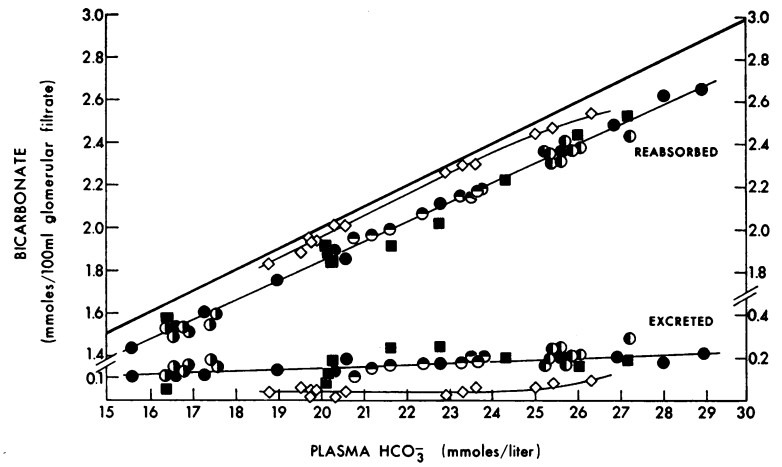

FIGURE 1 Relationship between plasma concentration, renal tubular reabsorption, and urinary excretion of bicarbonate ($[HCO_3^-]_p$, $THCO_3^-$, and $U_{HCO_3^-}V$, respectively) during the 1st yr of life in three infants with apparently classic renal tubular acidosis: RBW_1 (circles: ●, 5½ months; ◐, 6 months; ◓, 8 months; ◑, 11 months); RBW_2 (squares), cRTA (diamonds). Heavy diagonal line: filtered load of HCO_3^-.

At normal and subnormal $[HCO_3^-]_p$, $THCO_3^-$ in RBW_1 and RBW_2 is significantly less than in cRTA. Regression lines of $THCO_3^-$ on $[HCO_3^-]_p$: RBW_1 (composite data of all studies), $THCO_3^- = 0.092\ [HCO_3^-]_p + 0.01$, $r = 0.98$, $P < 0.01$; RBW_2, $THCO_3^- = 0.09\ [HCO_3^-]_p + 0.13$, $r = 0.98$, $P < 0.01$; cRTA ($[HCO_3^-]_p < 24$ mmoles/liter), $THCO_3^- = 0.1\ [HCO_3^-]_p - 0.07$, $r = 0.99$, $P < 0.01$. The slopes of the regression lines are not significantly different. But, at $[HCO_3^-]_p = 20$ mmoles/liter, the intercepts of the regression lines for RBW_1 (1.84) and RBW_2 (1.87) differ significantly from that for cRTA (1.97) ($P < 0.05$); the intercept for RBW_1, however, is not significantly different from that for RBW_2. In RBW_1, the relationship between $THCO_3^-$ and $[HCO_3^-]_p$ is not affected by the $[HCO_3^-]_p$ at which the measurements of $THCO_3^-$ were initiated or by the range of increase in $[HCO_3^-]_p$ over which $THCO_3^-$ was measured in a single study. In RBW_1, the values of $THCO_3^-$ in separate studies are not significantly different at $[HCO_3^-]_p = 16.5$, 22, and 25.5 mmoles/liter ($P < 0.05$).

In RBW_1 and RBW_2, $U_{HCO_3^-}V$ varied directly with $[HCO_3^-]_p$, although increasing only slightly with increasing $[HCO_3^-]_p$. Regression lines of $U_{HCO_3^-}V/C_{in}$ on $[HCO_3^-]_p$: RBW_1 (composite data of all studies), $U_{HCO_3^-}V/C_{in} = 0.123\ [HCO_3^-]_p - 2.65$, $r = 0.56$, $P < 0.01$; RBW_2, $U_{HCO_3^-}V/C_{in} = 0.034\ [HCO_3^-]_p - 0.55$, $r = 0.79$, $P < 0.05$; cRTA ($[HCO_3^-]_p < 24$ mmoles/liter), $U_{HCO_3^-}V/C_{in} = -0.002\ [HCO_3^-]_p + 0.07$, $r = 0.20$ (not significant). The slopes of the lines for RBW_1 and RBW_2 are significantly different from zero ($P < 0.001$); the slope of the line for cRTA is not.

cretion ($U_{HCO_3^-}V - U_{NH_4^+}V - U_{TA}V$) were also similar. In RBW_1 and RBW_2, net base excretion varied from 60 to 90% of the bicarbonate excretion rate (Table III). The sum of net base excretion and the assumed production rate of endogenous nonvolatile acid in infants (1–3 mmoles/kg body weight per 24 hr) approximated the oral bicarbonate requirement in RBW_1 and cRTA, but underestimated it somewhat in RBW_2. This sum can be regarded as a minimal estimate of the amount of bicarbonate required to sustain correction of acidosis, if there is no large extrarenal loss of bicarbonate.

Relationship between urine flow and bicarbonate excretion. In the initial studies of $THCO_3^-$ at normal and subnormal plasma bicarbonate concentrations in RBW_1 and RBW_2 and in the one study on cRTA, urinary bicarbonate excretion ($U_{HCO_3^-}V/C_{in}$) varied directly with urine flow (Figs. 2 and 3). Because $U_{HCO_3^-}V$ varied inversely with urine osmolality,[8] the flow dependence of bicarbonaturia in these patients appears related to water diuresis, the magnitude of which presumably fluctuated

[8] The sum of urinary sodium and potassium concentrations [$U_{(Na+K)}$] for the composite data of RBW_1 in the 1st yr of life showed a significant negative linear correlation with urine flow (V/C_{in}): $U_{(Na+K)} = -1.66\ V/C_{in} + 51.2$, $r = 0.75$, $P < 0.01$. Whenever measured, urinary osmolality varied inversely with flow.

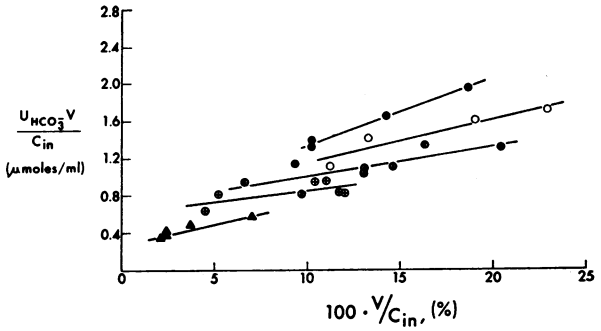

FIGURE 2 The relationship between urinary bicarbonate excretion ($U_{HCO_3^-}V/C_{in}$) and urinary flow (V/C_{in}) at normal plasma bicarbonate concentrations (19–23 mmoles/liter) in two infants with RTA: (RBW_1: ●, 5½ months; ○, 8 months; Φ, 13 months; ⊗, 26½ months) and (cRTA: ▲, 10 months).

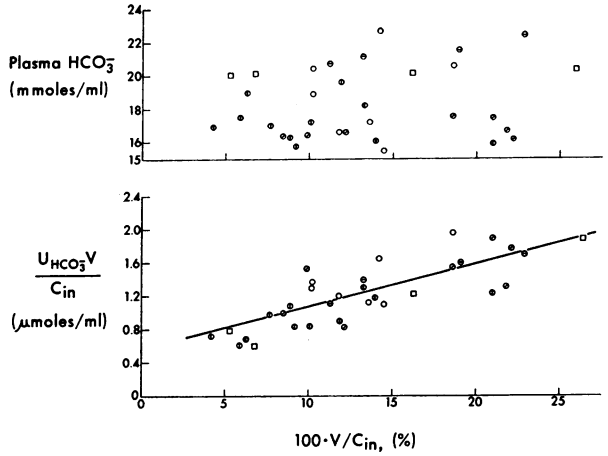

FIGURE 3 Relationship between urinary bicarbonate excretion and urine flow (lower figure), and between plasma bicarbonate concentration and urine flow (upper figure) at subnormal and normal plasma bicarbonate concentrations (15–23 mmoles/liter) during the 1st yr of life, in RBW_1 (○, 5½ months; Φ, 7½ months; ⊖, 8 months; ⊘, 11 months) and in RBW_2 (□, 1 month). In both infants the relationship between bicarbonate excretion and urine flow has a positive linear correlation (RBW_1: $r = 0.78$, $P < 0.01$; RBW_2: $r = 0.98$, $P < 0.05$). Plasma bicarbonate concentration and urine flow are not significantly correlated.

because the patients drank water freely but intermittently during the studies. Fractional bicarbonate excretion and net base excretion also varied directly with urine flow.

In the earliest studies on RBW_1 and RBW_2, urine flow generally exceeded 10% of the glomerular filtration rate and the effect of increasing flow on bicarbonate excretion was striking (Fig. 2). In study 1 on RBW_1, for example, an increase in V/C_{in} from 0.10 to 0.20 was associated with an increase in $U_{HCO_3^-}V/C_{in}$ of approximately 6 μmoles/ml GF, an increase of bicarbonate excretion equal to 3% of the filtered bicarbonate load. In cRTA, by contrast, urine flow ranged from 2 to 7% of GFR, and within this range $U_{CHO_3^-}V/C_{in}$ changed < 0.5 μmole/ml GF. The greater bicarbonate excretion in RBW_1 and RBW_2, however, could not be related solely to greater urine flows. At similar urine flows, urinary excretion of bicarbonate was greater in RBW_1 and RBW_2 than in cRTA, irrespective of age (Fig. 2, Table II). Moreover, in later studies of RBW_1 bicarbonate excretion varied little with flow, but remained significantly greater than in cRTA.

In RBW_2, the progressive decrease in the mean values of $U_{HCO_3^-}V/C_{in}$ that occurred with age could not be related solely to decreasing mean values of V/C_{in}: $U_{HCO_3^-}V$ decreased even when V/C_{in} did not (Table II). Moreover, at any given V/C_{in}, over a wide range of values, $U_{HCO_3^-}V/C_{in}$ appeared to decrease progressively with age (Fig. 2). The progressive reduction in $U_{HCO_3^-}$ at any V/C_{in} (Fig. 4), which accounted for the progressive reduction in $U_{HCO_3^-}V/C_{in}$ at any V/C_{in}, can be related to a progressive reduction of urinary pH at any V/C_{in} (Fig. 4) but not to a change in the relationship between urinary pH and bicarbonate concentration;

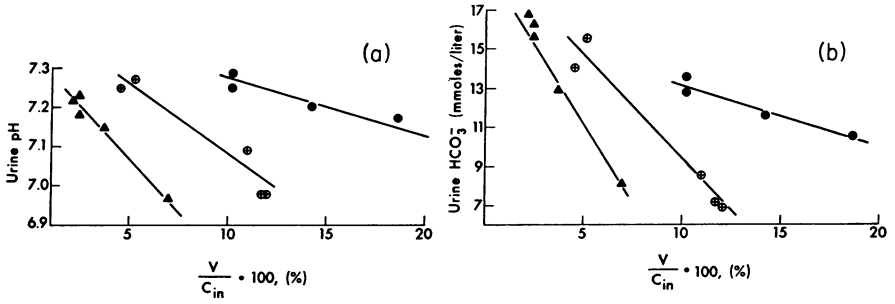

FIGURE 4 Relationship between urine pH and urine flow (*a*) and between urine bicarbonate concentration and urine flow (*b*) in RBW_1 (●, 5½ months; ○, 26 months) and in cRTA (▲, 10 months). The reduction in mean $U_{HCO_3^-}V/C_{in}$ and $C_{HCO_3^-}/C_{in}$ as RBW_1 became older (see Table II) was not a consequence solely of an increase in mean C_{in} or a decrease in mean urine flow: at any given flow, $U_{HCO_3^-}$ decreased.

TABLE IV

A Representative Study of the Effect of Sodium Bicarbonate Infusion in an Infant

Time	Urine						C_{in}	$\frac{U_{HCO_3}V}{C_{in}}$
	Flow (V)	Na^+	K^+	Cl^-	HCO_3	pH		
min	*ml/min*		*μEq/min*		*μmoles/min*		*ml/min*	*μmoles/ml*
Priming infusion: 9 ml of 10% inulin over 5 min period intravenously. Constant infusion I: 10% inulin at 0.123 ml/min intravenously.								
0–84	1.8	11.5	11.5	7.2	15.0	7.10		
84–98	2.4	15.8	12.2	8.5	20.1	7.11	18.1	1.11
98–125	1.0	15.6	18.7	12.7	17.2	7.33	22.1	0.78
125–142	2.7	22.9	18.8	17.0	22.0	7.09	20.6	1.07
Constant infusion II: 3.75% $NaHCO_3$ solution at 0.392 ml/min intravenously.								
142–150	2.8	22.0	16.5	17.6	22.1	7.12	21.1	1.04
150–162	1.9	18.2	15.3	13.0	15.9	7.15	19.8	0.81
162–177	1.2	18.6	16.8	15.6	17.1	7.29	18.1	0.94
177–197	2.0	28.3	20.5	19.0	23.7	7.23	21.0	1.13
197–209	3.1	30.8	15.4	15.4	26.5	7.06	20.3	1.31
209–221	3.6	32.3	14.3	13.6	29.1	7.06	22.0	1.33
221–232	3.0	30.0	12.0	12.9	22.6	7.07	20.5	1.10
232–249	1.8	27.8	11.7	15.6	19.4	7.31	20.4	0.95
249–261	2.0	33.0	12.0	17.6	23.0	7.27	19.5	1.18
261–278	2.2	40.2	14.5	23.0	28.5	7.34	22.0	1.30
278–294	2.1	26.8	7.2	14.7	18.8	7.16	14.7	1.28
294–301	5.8	75.2	17.4	34.7	49.5	7.18	38.5	1.29
301–314	2.5	34.5	8.6	16.5	21.6	7.17	19.9	1.09
314–324	2.1	30.8	8.2	12.3	20.3	7.24	19.0	1.07
324–331	3.7	52.0	13.0	18.2	37.1	7.18	29.9	1.24
331–338	2.9	37.2	8.6	12.6	24.3	7.16	22.5	1.08

C_{in}, inulin clearance; $U_{HCO_3}V$, urinary excretion rate of bicarbonate; $THCO_3^-$, tubular reabsorption of bicarbonate; C_{HCO_3}, bicarbonate clearance; P_{CO_2}, CO_2 tension; GF, glomerular filtrate.

urinary carbon dioxide tension for any pH remained the same.

Acid excretion during acidosis. In RBW_1, RBW_2, and cRTA, urinary pH was inappropriately high during moderate as well as severe degrees of metabolic acidosis (Table V). During the 1st yr of life, the lowest urinary pH observed in any of the infant girls was 6.91 (RBW_1, age 7 months). The minimal values of urinary pH and bicarbonate concentration in RBW_1 were consistently and significantly higher than those in cRTA when compared at similar urine flows during similar degrees of acidosis (acute ammonium chloride administration) and when the patients were approximately the same age (Fig. 5). With the exception of the initial value of urinary ammonium excretion in RBW_1, obtained after prolonged acidosis and potassium depletion, the rates of excretion of urinary ammonium and titratable acid during acidosis were subnormal in each of the infants (Table V) (compared with rates observed during experimentally induced acidosis in normal infants or during spontaneously occurring acidosis in the infant with Fanconi syndrome). Bicarbonaturia occurred during acidosis in each infant. But in RBW_1 and RBW_2, in striking contrast to cRTA and adult patients with classic RTA, the rate of urinary excretion of bicarbonate exceeded the sum of the rates of excretion of titratable acid and ammonium, i.e. in RBW_1 and RBW_2 net acid excretion was negative, or net amounts of base (bicarbonate) were excreted (Table V).

Potassium clearance studies. During acidosis, urinary potassium excretion (U_KV/C_{in}) and the fraction of filtered potassium excreted (C_K/C_{in}) was greater in RBW_1 than in FS at similar concentrations of serum potassium (Fig. 6). When the plasma bicarbonate concentration was increased from subnormal to normal levels, however, U_KV/C_{in} and C_K/C_{in} decreased strikingly in RBW_1, but increased in FS. At normal plasma bicarbonate concentrations in RBW_1, the values of

with Apparently Classic RTA and Bicarbonate Wasting (RBW_1, Study 5)

$THCO_3^-$	$\frac{C_{HCO_3}}{C_{in}}$	$\frac{V}{C_{in}}$	Arterial			Serum		
			HCO_3^-	P_{CO_2}	pH	K^+	Na^+	Cl^-
mmoles/ 100 ml GF	%	%	*mmoles/ liter*	*mm Hg*			*mEq/liter*	
						4.4	140	106
1.85	6.5	13.4	19.56	38.0	7.333			
1.69	4.4	4.7	17.90	37.0	7.306			
1.79	5.6	13.0	19.34	38.1	7.327	4.0	138	108
1.85	5.3	13.0						
1.90	4.1	9.7	19.84	38.1	7.338	3.9	138	107
1.95	4.6	6.6						
2.02	5.3	9.3	21.37	40.3	7.346			
2.06	6.0	15.2						
2.09	6.0	16.3						
2.16	4.8	14.6	22.59	40.4	7.369	3.7	137	105
2.24	4.0	8.8	23.71	42.3	7.370	4.6	139	104
2.28	4.9	10.2						
2.32	5.3	10.2						
2.39	5.1	14.0	25.06	42.7	7.390	3.3	141	92
2.40	5.1	15.0						
2.44	4.3	12.4	25.45	41.5	7.409	3.0	139	
2.52	4.1	10.8						
2.57	4.6	12.4	26.92	42.8	7.420	2.9	140	
2.63	3.9	12.7						

U_KV/C_{in} and C_K/C_{in} were less than those in FS at any plasma bicarbonate concentration. In FS, the *increase* in urinary potassium excretion was associated with a concurrent, marked *increase* in urinary bicarbonate excretion, while in RBW_1, the *decrease* in urinary potassium excretion was associated with essentially no change in urinary bicarbonate excretion (Fig. 1). The relationship between urinary potassium excretion and plasma bicarbonate concentration in RBW_1 was similar to that observed in patients with type 1 RTA, including cRTA (13). Although the rate of excretion of urinary potassium in RBW_1 decreased with correction of acidosis, it remained inappropriately high (> 20% of the filtered load of potassium), given the presence of hypokalemia (Fig. 6). This finding accords with the observation in RBW_1 that maintenance of normokalemia required continued administration of supplemental potassium despite sustained correction of acidosis with sodium bicarbonate.

Effect of intravenous administration of sodium phosphate. In RBW_1, the urinary pH during acute NH_4Cl-induced acidosis (after prolonged correction of acidosis) was little affected by intravenous administration of a neutral isotonic solution of sodium phosphate. During the base line period (200 min), oral administration of NH_4Cl resulted in a progressive decrease in arterial pH (from 7.37 to 7.33) and in plasma bicarbonate concentration (from 19.6 to 15.9 mmoles/liter) and a modest decrease in urinary pH (from 7.39 to 6.91). During the subsequent infusion of sodium phosphate (100 min), the arterial pH and plasma bicarbonate concentration remained unchanged, the plasma phosphate concentration increased progressively from 5.4 to 14.2 mg/100 ml, the urine pH decreased slightly from 6.91 to 6.76, and the urinary carbon dioxide tension increased from 37 to 55 mm Hg. The urinary excretion of phosphate increased strikingly and that of titratable acid (TA) appropriately, but the excretion rates of bi-

TABLE V

Urinary Acidification during Metabolic Acidosis in Infants with RTA

Patient, age		Arterial blood pH	Arterial blood P_{CO_2}	Plasma $[HCO_3^-]$‡	Urine* pH	Urine* TA	Urine* NH_4^+	Urine* HCO_3^-	Net acid§	$(V/C_{in})\cdot 100$	C_{in}
			mm Hg	*mmoles/liter*		*μmoles/min per 1.73 m²*				%	*ml/min per 1.73 m²*
Normal values‖					4.90 ±0.03	62 ±4.9	57 ±4.3				
Classic RTA											
Type 1											
cRTA	11 months¶	—	—	(15.9)	7.13	—	17.2	14.0	>3.2	1	84.9
	22 months**	7.18	28.8	10.4	6.62	8.0	19.1	4.7	22.4	—	—
Renal bicarbonate wasting (in apparently classic RTA)											
RBW_1	4½ months¶	—	—	(8.7)	7.22	11.5	87.8	131.9	−32.6	—	—
	5 months¶	7.30	31.8	15.2	7.04	—	26.3	71.7	—	15	64.4
	7 months**	7.34	30.5	15.9	6.91	19.9	23.3	97.5	−54.3	21	79.9
	17 months¶	7.28	33.0	15.0	7.71	7.8	34.5	82.6	−40.3	16	68.4
	41 months**	7.24	36.6	15.2	7.13	1.0	12.0	46.1	−33.1	5	80.4
RBW_2	8 days¶	7.06	24.0	6.6	7‡‡	—	—	—	—	—	—
	14 days¶	7.20	35.0	13.3	7.0–7.5‡‡	—	—	—	—	—	—
	30 days¶	7.35	33.5	17.8	6.96	5.0	24.0	57.2	−28.2	21	38.7
RTA associated with Fanconi syndrome (type 2 RTA, "proximal")											
FS	10 months**	—	—	(13.0)	5.13	58.6	53.6	0	111.8	—	—
	13 months¶	7.30	27.6	13.3	5.19	—	—	0	—	7	118.1

TA, titratable acid; NH_4^+, ammonium; V, urine flow, C_{in}, inulin clearance.

* Values of pH are the minimal ones observed; values for TA and NH_4^+, the maximal ones observed.

‡ Values in parentheses indicate carbon dioxide content of venous serum.

§ Net acid excretion = the sum of the excretion rates of titratable acid and ammonium minus the excretion rate of bicarbonate.

‖ Normal values of urinary pH, TA, and NH_4^+ were derived from measurements made after a single oral dose of NH_4Cl, 75 mEq/m² (28).

¶ Spontaneously occurring acidosis.

** Ammonium chloride-induced acidosis.

‡‡ Nitrazine paper.

carbonate and ammonium were unchanged from those observed immediately before phosphate was administered.

DISCUSSION

In normal children and adults, the renal acidification process maintains plasma bicarbonate at normal concentrations by reabsorbing all filtered bicarbonate and excreting acid in an amount equal to the amount of nonvolatile acid produced endogenously, approximately 1 mEq/kg of body weight per day in adults (29, 14) and 1–2 mEq in infants and young children (30). Both the reabsorption of bicarbonate and the excretion of acid appear to be mediated by a single operation of the renal tubule: the exchange of reabsorbed Na^+ for secreted H^+. At normal concentrations of plasma bicarbonate and under normal physiologic conditions, the proximal tubule reclaims 85–90% of filtered bicarbonate (31, 32), hence accounts for the great preponderance of hydrogen ion secreted by the renal tubule. In the distal nephron the hydrogen ion secretory process titrates the residual 10–15% of filtered bicarbonate as the pH of the luminal fluid decreases to values less than about 6.2. The distal nephron, by its ability to generate steep lumen-peritubular H^+ gradients, can reduce the urinary pH to values of 5 or so and titrate the urinary buffers such that the combined rates of excretion of titratable acid and ammonium equal that of the endogenous production of nonvolatile acid (14). The sum of the rates of excretion of titratable acid and ammonium, minus the normally negligible excretion rate of bicarbonate, has been termed "net acid excretion" (1): when the rate of excretion of bicarbonate exceeds that of the sum of titratable acid and ammonium, "net base excretion" can be said to occur.

In adult patients with classic ("distal") RTA, the observation that $THCO_3^-$ is just less than complete at normal as well as subnormal plasma bicarbonate concentrations (4, 5, 7–13) permits the inference that reabsorption of bicarbonate in the proximal tubule is not substantially reduced, identifies the disorder as type 1 RTA (Fig. 7), and indicates that impaired renal acid excretion need not be associated with renal "bicarbonate wasting" (5, 7, 10, 12). At normal and reduced concentrations of plasma bicarbonate, renal "bicarbonate wasting" can be said to occur when net base excretion exceeds the rate at which nonvolatile acid is produced endogenously. So defined, bicarbonate wasting is quantitatively more important in the causation of acidosis

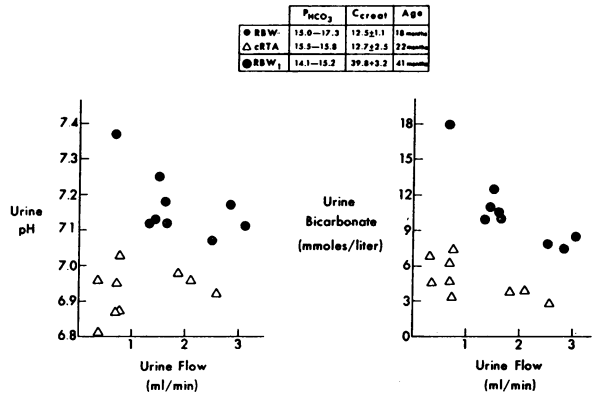

FIGURE 5 Comparison of urinary pH and bicarbonate concentration at similar urine flows during acidosis (ammonium chloride administration) in RBW_1 and cRTA. The values of pH and bicarbonate concentration are higher in RBW_1 at ages both younger and older than that at which cRTA was studied.

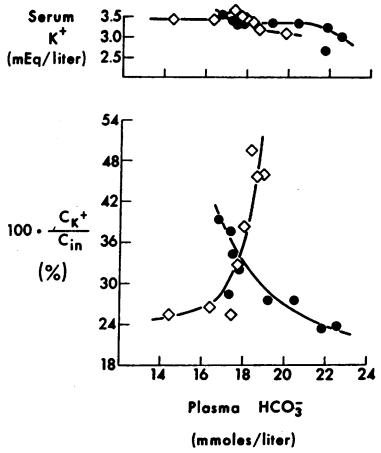

FIGURE 6 Effect of experimentally increasing plasma bicarbonate concentration (intravenous administration of sodium bicarbonate) on urinary potassium excretion in the patient with apparently classic renal tubular acidosis with bicarbonate wasting (RBW_1, closed symbols) and in the patient with renal tubular acidosis associated with the Fanconi syndrome (FS, open symbols).

than impaired acid excretion per se (which predictably attends bicarbonate wasting because of the inappropriately high urinary pH at which bicarbonate wasting occurs). Impaired acid excretion per se can be a factor in the causation of acidosis only to the extent that the endogenously produced nonvolatile acid titrates body buffers, including plasma bicarbonate, a relatively minor, slowly developing loss of base compared with that which can result from a substantial reduction in renal bicarbonate reabsorption.[4] Accordingly, patients with RTA and renal bicarbonate wasting will require more alkali to sustain correction of acidosis than patients with RTA and no bicarbonate wasting, the difference in alkali requirement reflecting the magnitude of bicarbonate wasting at normal plasma concentrations of bicarbonate.

In patients with type 2 RTA ("proximal" RTA), including the infant with Fanconi syndrome of the present study (FS), the identifying observation that $THCO_3^-$ at normal plasma bicarbonate concentration is reduced by 15% (and is at an apparent maximum ($T_mHCO_3^-$)) (Fig. 7) not only implicates the acidification process of the proximal tubule (10, 12, 13), but also translates to bicarbonate wasting and "alkali-resistant" acidosis (10, 12, 13), defined here arbitrarily as acidosis requiring for its sustained correction alkali therapy in amounts greater than 3 mEq/kg per day. Conceivably, a defect of the acidification process of the proximal tubule could account for the alkali resistance of some infants who appear to have classic RTA. In a few adult patients with RTA in whom $THCO_3^-$ at normal plasma bicarbonate concentrations has been reduced by more than 15%, urinary pH has remained inappropriately high despite severe degrees of acidosis, and $THCO_3^-$ has been just less than complete over a broad range of reduced plasma bicarbonate concentrations (12, 13). In such a hybrid of types 2 and 1 RTA, the acidification process in both proximal and distal tubules is presumably impaired (12, 13). But such a hybrid has been

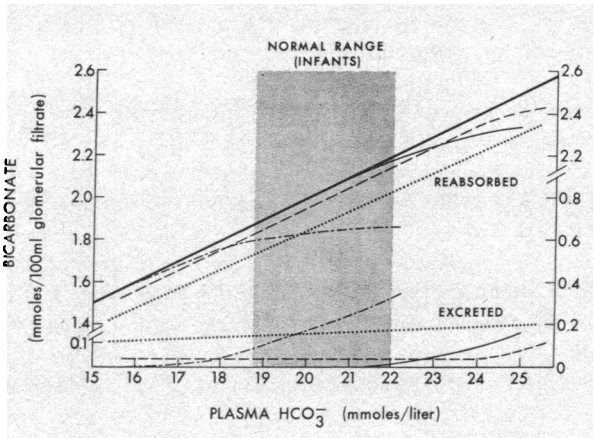

FIGURE 7 The physiologic spectrum of renal tubular acidosis in infants. Relation between plasma concentration, renal tubular reabsorption, and urinary excretion of bicarbonate in infants with renal tubular acidosis: type 1, classic RTA (— — —, cRTA); type 2, "rate" or "proximal" RTA (- — - —, FS); type 3, "bicarbonate-wasting" apparently classic RTA (· · · ·, RBW_1 and RBW_2). Minimal values of renal bicarbonate reabsorption and maximal values of urinary bicarbonate excretion for normal infants are represented by the solid curves (28). The range of normal plasma bicarbonate concentrations (the mean ±SD) (shaded portion) in infants 3–12 months of age is derived from data of Albert and Winters (30)

[4] This assumes no supernormal endogenous production of nonvolatile acid as could occur in diabetic ketoacidosis or lactic acidosis.

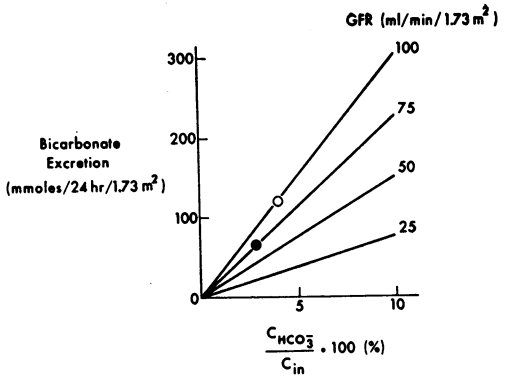

FIGURE 8 Comparison of the predicted rates of urinary bicarbonate excretion (in mmoles/24 hr/1.73 m²) at any given fractional excretion of filtered bicarbonate in patients with different glomerular filtration rates (25–100 ml/min). The effect of a small difference in fractional bicarbonate excretion on daily urinary loss of bicarbonate is magnified by higher glomerular filtration rates: the predicted 24 hr bicarbonate excretion with a 4.0% fractional bicarbonate excretion and GFR of 100.2 ml/min (○, data on RBW_1, 26 months) is nearly twice that with 2.8% and 77.5 ml/min (●, data on 11 adult patients with classic RTA) (see Table II).

described only in adult patients with the complex dysfunction of the proximal tubule characteristic of the Fanconi syndrome. In all infants and very young children described wit type 2 RTA, with and without the Fanconi syndrome, the acidification process of the distal nephron cannot be implicated (9, 10, 13): during moderately severe degrees of acidosis, urinary pH has been appropriately reduced, acid excretion not reduced, and $THCO_3^-$ perforce complete.

In the present study of three infants with apparently classic RTA, the finding in two (RBW_1 and RBW_2) that fractional excretion of filtered bicarbonate (C_{HCO_3}/C_{in}) was 6–9% at plasma bicarbonate concentrations ranging from 26 to 15 mEq/liter (Fig. 1, Table II) identifies a disorder of renal acidification different from that of either type 1 RTA (cRTA) or type 2 RTA (FS) (Figs. 1 and 7). Although the value of C_{HCO_3}/C_{in} of 6–9% at normal plasma bicarbonate concentrations is less than that required to implicate the acidification process of the proximal tubule (10, 12), the lesser value combined with the normal or near normal glomerular filtration rate of RBW_1 and RBW_2 translates to renal bicarbonate wasting (Figs. 1 and 8 and Tables II and III). Accordingly, in RBW_1 and RBW_2, just as in FS with type 2 RTA, renal bicarbonate wasting at normal plasma bicarbonate concentrations accounts for the occurrence of acidosis. In patients with type 2 RTA, however, the severity of acidosis is frequently self limiting and not extreme because renal bicarbonate reabsorption is characteristically complete during mild to moderate degrees of acidosis, and acid excretion brisk (Table V) (9–13). By contrast, in RBW_1 and RBW_2, the spontaneous occurrence of severe acidosis (Fig. 9) and its rapid recurrence after reducing corrective alkali therapy could have been predicted because bicarbonate wasting persisted during moderately severe acidosis (Table V, Fig. 1). It is apparent that in patients with RTA, the finding that urinary pH remains inappropriately high during severe metabolic acidosis does not permit one to predict the absence of bicarbonate wasting, as has been contended (9, 11), even when type 2 RTA can be excluded. In RBW_1 and RBW_2 the finding that urinary pH was consistently greater than 7 during severe metabolic acidosis in fact signifies the persistence of bicarbonate wasting, whereas in patients with type 1 RTA and no bicarbonate wasting urinary pH is predictably less than 7 during severe acidosis and usually less than 7 during the moderate degrees of acidosis characteristic of these patients before their treatment with alkali (Fig. 9).

The physiological characteristics of RBW_1 and RBW_2 were anticipated by a triad of findings often described years ago in infants with apparently classic RTA, but unexplained by a renal acidification defect not characterized by renal bicarbonate wasting at both reduced and normal plasma bicarbonate concentrations: (*a*) spontaneous acidosis of striking severity as indicated by values of serum CO_2 content of less than 13 mmoles/liter (Fig. 9); (*b*) during severe acidosis, values of urinary pH of 7 or more (Fig. 9); (*c*) "alkali-resistant" acidosis indicated by corrective alkali requirements ranging from 4 to 25 mEq/kg per day (2, 15–22, 24). In some infants with apparently classic RTA, acidosis of striking severity and alkali resistance could result in part from intestinal loss of bicarbonate. Although no published evidence supports this possibility, precedents exist for defects of specific transport systems common to gut and kidney (54). In RBW_2, such a dual defect of bicarbonate transport might explain why the amount of alkali required to sustain correction of acidosis was substantially more than the sum of net base excretion and assumed production of endogenous acid.

In RBW_1 and RBW_2 the flow dependence of bicarbonate excretion demonstrated in their earliest studies suggest the possibility that polyuria might have exaggerated their daily renal loss of bicarbonate during the 1st yr of life. During this time in RBW_1 pitressin-resistant hyposthenuria was demonstrated and urine flow was repeatedly observed to be brisk, despite severe dehydration. To the extent that the patient's observed potassium depletion during early infancy contributed to her polyuria, potassium depletion could conceivably have amplified bicarbonate wasting. Some years ago, McCrory suggested the possibility that potassium deple-

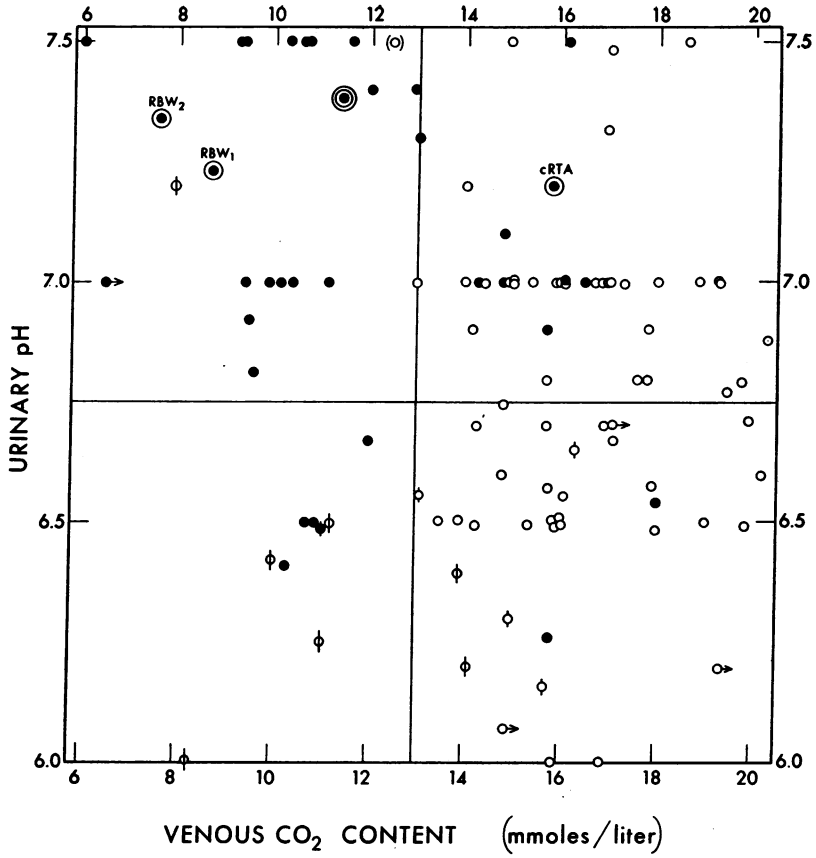

FIGURE 9 The relationship between urinary pH and serum CO_2 content in untreated infants (closed circles) (15, 16, 20, 23, 24, 33), children and adults (open circles) (5, 6, 8, 9, 24, 34–53)[5] with idiopathic or familial, apparently classic renal tubular acidosis. When serum CO_2 content was not available, plasma bicarbonate concentration was used (indicated on symbol by horizontal arrow). A single pair of values is shown for all but six adult patients, in each of whom an additional value of urinary pH is plotted at values of serum CO_2 content experimentally reduced to <15 mmoles/liter by administration of NH_4Cl (ϕ). (These additional values are plotted because of the paucity of data available on adult patients at lower values of CO_2 content.) In those patients in whom no value of urinary pH is available during spontaneously occurring acidosis, a single value during NH_4Cl-induced is plotted (ϕ or ϕ). Closed circle within two circles denotes values for what appears to be the index case of bicarbonate-wasting, classic RTA (16). The single open circle in parentheses denotes values in a patient in whom RTA was diagnosed after treatment with sulfathiazole (36).

tion might increase the "renal tubular bicarbonate leak" of some children with RTA (55).

With the exception of the magnitude of bicarbonaturia, the physiological character of the renal tubular dysfunction in RBW_1 and RBW_2 is like that of type 1 RTA: (*a*) the pH of the urine remains inappropriately high, and bicarbonaturia persists, despite severe degrees of acidosis (11, 12); (*b*) when the plasma bicarbonate concentration is progressively increased from subnormal to normal levels, renal bicarbonate reabsorption increases nearly commensurately with the increase in filtered bicarbonate load (4, 5); (*c*) during water diuresis, the rate of excretion of urinary bicarbonate varies directly with urine flow (7); (*d*) during diuresis of intravenously administered sodium phosphate (as a neutral isotonic solution), the pH of the urine changes little, but the rate of excretion of titratable acid increases in direct proportion to the rate of excretion of urinary phosphate (5); (*e*) urinary potassium excretion and fractional excretion of filtered

[5] Morris, R. C., Jr. Unpublished observations.

potassium decrease when the plasma bicarbonate concentration is increased from subnormal to normal levels (1, 13). In adult patients with RTA and trivial bicarbonaturia, identical physiologic characteristics have been explained as a consequence of an inability of the distal segments of the nephron to generate or maintain appropriately steep lumen-peritubular hydrogen ion gradients (5, 7). Such a defect could also account for a substantial reduction of $THCO_3^-$ in patients with otherwise typical type 1 RTA if in these patients, as in RBW_1 and RBW_2, minimal urinary pH were greater than 7.0 and urine flow were high. In patients with type 1 RTA, a greater than usual fractional excretion of filtered bicarbonate could then be only the physicochemical consequence of simultaneous, marked impairments in both the ability of the renal tubule to generate steep lumen-peritubular H^+ gradients and to concentrate the urine. RBW_1 and RBW_2 may exemplify such a kind of bicarbonate-wasting RTA.

Because of functional immaturity of the proximal nephron in early infancy or because proximal tubular function was frankly impaired, renal bicarbonate wasting in RBW_1 and RBW_2 could have been augmented by the delivery to the distal nephron of a relatively large fraction of the filtered bicarbonate load. But, since the rate of excretion of bicarbonate was little affected by large changes in filtered bicarbonate load (Fig. 1), such reduction of fractional bicarbonate reabsorption in the proximal nephron would seem unlikely to account entirely for the bicarbonate wasting of these patients, unless the amount of bicarbonate escaping reabsorption proximally were little affected by changes in the filtered load of bicarbonate; i.e., unless the leak of bicarbonate from the proximal nephron were relatively fixed (7, 56). If one assumes that the change in urinary bicarbonate excretion noted over the subnormal-to-normal range of plasma bicarbonate concentrations studied in RBW_1 (approximately 0.05 mmoles/100 ml of glomerular filtrate [Fig. 1]) was entirely due to changes in the filtered load of bicarbonate, bicharbonate rejected from the proximal nephron at normal plasma bicarbonate concentrations could have accounted for the excretion of as much as 2.5% of the filtered bicarbonate load (Table II), some 30% of the over-all fractional bicarbonate excretion observed in the early studies on RBW_1 (Table II). But, as stated, excretion of some portion of the proximal tubular rejectate of bicarbonate need not reflect increased rejection of bicarbonate from the proximal nephron, however affected by changes in filtered bicarbonate load, but only a failure of distal tubular reclamation of bicarbonate.

In RBW_1, renal bicarbonate reabsorption increased progressivly with age, as evidenced by progressive reductions in both fractional bicarbonate excretion (C_{HCO} / C_{In}) and daily bicarbonate excretion ($U_{HCO_3}V$ per unit body weight or body surface area) at normal plasma bicarbonate concentrations (Tables II and III). The basis of this improvement was not defined by the present studies. Since a substantial part of the bicarbonate loss during early infancy may have resulted from the proximal rejection of an abnormally large fraction of the filtered bicarbonate load, the decrease in fractional bicarbonate excretion with age could have been due in part to a reduction in fractional bicarbonate delivery to the distal nephron, a consequence either of maturation of normal proximal tubular function or of amelioration of defective proximal bicarbonate reabsorption, or of both. Part of the decrease in fractional bicarbonate excretion could have resulted from an increased ability of the distal nephron to generate or maintain steep lumen-peritubular H^+ gradients (6): during severe acidosis (i.e. at low filtered bicarbonate loads) urinary pH decreased with age (when the values are compared at similar low urine flows) (Fig. 7). With age, a given degree of water diuresis at normal plasma bicarbonate concentrations induced a greater magnitude of reduction in urinary pH and bicarbonate concentration. Both of these findings can be explained by improvement of the acidification process of either the proximal or the distal nephron, or of both.

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