

Renal Bicarbonate Reabsorption and Hydrogen Ion Excretion in Normal Infants *

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Summary. After acute administration of ammonium chloride, infants 1 to 16 months of age were similar to older children in their capacity to acidify their urine. The infants had a higher rate of excretion of titratable acid and a lower rate of excretion of ammonium but were similar in their rate of excretion of total hydrogen ion.

Bicarbonate titrations performed in infants during the first year of life demonstrated a threshold ranging from 21.5 to 22.5 mmoles per L, maximal rate of reabsorption from 2.6 to 2.9 mmoles per 100 ml glomerular filtrate, and marked titration splay. A nephronic frequency distribution curve of the ratio of glomerular filtration rate to tubular reabsorptive capacity demonstrated both heterogeneity and skewing to the right, suggesting the presence of significant numbers of nephrons with low tubular transport capacity relative to filtration rate.

It is suggested that the "physiologic acidosis" of the infant is due neither to a limited renal capacity to excrete hydrogen ion nor to a reduced capacity for reabsorption of bicarbonate, but rather to a low renal plasma bicarbonate threshold. Although the level of the threshold may relate to the kinetics of bicarbonate reabsorption during this period, it appears to be due at least in part to functional and morphologic heterogeneity of nephrons.

Introduction

It is well established that the concentration of bicarbonate in the plasma of normal infants is lower than that observed later in childhood and adult life (1, 2). Although this "physiologic acidosis" is usually attributed to a limited capacity of the kidney to excrete the acid load imposed by diet (2), inadequate data during this period are avail-

able to permit acceptance or rejection of this hypothesis. In subjects in hydrogen ion balance, the concentration of bicarbonate in blood is maintained at a level just below the so-called renal plasma bicarbonate threshold (3). The present investigations were designed 1) to investigate the relationship between renal reabsorption and excretion of bicarbonate and the concentration of bicarbonate in blood of infants during the first year of life, and 2) to compare infants and older children in their responses to administration of ammonium chloride.

Methods

Studies of bicarbonate reabsorption were performed in six infants aged 1 to 12 months (Table II). The response to ammonium chloride was studied in 11 infants aged 1 (3), 2, 3, 4, 5, 6 (2), 8, and 16 months and 10 children aged 7 to 12 years. The older children were hospitalized for minor illnesses or for elective surgery. The latter were studied either before or at least 5 days

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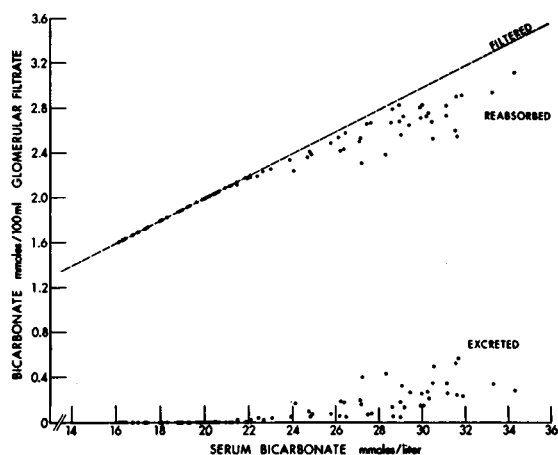


FIG. 1. RATES OF FILTRATION, REABSORPTION, AND URINARY EXCRETION OF BICARBONATE DURING BICARBONATE INFUSION.

after surgery, and no subject undergoing major surgery was included. Subjects with any type of renal disease or nonrenal disorder that might affect water and electrolyte or acid-base metabolism were excluded. All subjects fell within the tenth and seventy-fifth percentiles for height and weight.

The investigations were performed with institutional approval. Informed parental consent was obtained before study.

Bicarbonate reabsorption. Investigation of bicarbonate reabsorption was performed by the continuous infusion of a solution containing sodium bicarbonate, inulin, and *p*-aminohippurate (PAH). Bicarbonatae, withheld from the initial infusion to permit control collections, was infused at a rate calculated to produce an increase in serum bicarbonate of 2 mmoles per L per hour; when the bicarbonate threshold was reached, as judged by increase in urinary pH to between 6.5 and 7.0, the rate of infusion of bicarbonate was increased by a factor of 1.5 to 2.0 and maintained until serum bicarbonate concentration exceeded 30 mmoles per L for several periods.

Urine collections were made at half-hour intervals, utilizing an indwelling urethral catheter. Urine was collected under mineral oil, and completeness of the collection was assured by manual suprapubic pressure. The initial urine obtained during each study was utilized for urinalysis and culture. Bacteriuria was never demonstrated in these urines or in clean-voided specimens collected serially after catheterization.

Blood samples were obtained anaerobically at the midpoint of each urine collection from an indwelling needle placed in a superficial vein of the arm or hand. Use of a tourniquet was avoided. Blood samples were centrifuged and analyzed anaerobically for pH and CO_2 content.

Response to NH_4Cl . Studies were performed in the renal unit and were begun uniformly between 8 and 9 a.m. The patients remained recumbent during the test,

but were allowed free movement in bed. Breakfast was permitted on the day of the test, and a usual lunch was given at the appropriate time. In order to ensure an adequate and fairly constant rate of urine flow, we administered water throughout the test at the rate of 50 ml per hour per m^2 . In the older subjects urines were collected at hourly intervals by spontaneous voiding. Urine specimens in infants were obtained through indwelling urethral catheters, complete emptying being assured by air washout. Urine specimens were not collected under oil but were examined immediately for pH and titratable acid and were stored for other determinations in air-free containers.

Arterialized capillary blood samples were collected in heparinized tubes for determination of pH, CO_2 tension, (Pco_2), and total CO_2 content. Blood specimens for other determinations were obtained from superficial veins during free flow.

After collection of two 30- to 60-minute control urine samples, control samples of venous and capillary blood were obtained. Ammonium chloride was given by mouth over the course of the next hour; it was taken in gelatin capsules or in water flavored with lemon juice and sugar by the older children and administered by stomach tube as a 5 to 10% solution in the infants.

After administration of the ammonium chloride, five test urine samples, each taken over approximately 60 minutes, were collected. Further blood samples were obtained 3 to 4 hours after the ingestion of ammonium chloride was completed. The dosage of ammonium chloride in infants was 75 mEq per square meter body surface area (equivalent to 3.9 mEq per kg body weight). Children received 150 mEq per square meter (5.4 mEq per kg).

Blood and urine pH were measured at 38°C with a Radiometer pH meter and microelectrode chain. Carbon dioxide content ($t\text{CO}_2$) was determined by the method of Van Slyke and Neill (4), using a Natelson microgasometer. The Pco_2 and bicarbonate concentration were calculated from the Henderson-Hasselbach equation. For serum, values employed for pK^1 and α were 6.10 and 0.0301, respectively. The values for pK^1 were calculated for each urine sample according to the formula $6.33 - 0.5\text{VB}$, where B represents the total cation concentration estimated as the sum of $\text{Na} + \text{K}$, expressed in equivalents per liter (5). Curves of bicarbonate reabsorption and excretion were constructed and plotted according to the method of Pitts, Ayer, and Schiess (6). Corrections were not made for either Donnan equilibrium or transit time between glomerulus and urinary bladder.

Urinary titratable acid was measured by immediate titration at 25° to pH 7.7, using a Coleman Metrion II pH meter. The end point of 7.7 instead of 7.4 was chosen to correct for temperature. Urinary ammonium was measured by the microdiffusion method of Conway (7). Sodium and potassium were measured utilizing a Perkin-Elmer flame photometer, model 146. Chloride was determined coulometrically using the method of Cotlove, Trantham, and Bowman (8). Creatinine and phosphorus were determined on the Technicon

TABLE I
 Representative study from infant DL*

Time min	Serum				Urine				Inulin clearances ml/min/1.73m ²	PAH clearances ml/min/1.73m ²	Filtered mmoles/100 ml GF	Bicarbonate Excreted mmoles/100 ml GF	Reabsorbed	
	pH	Pco ₂ mm Hg	HCO ₃ ⁻ mmoles/L	Cl	Na	K	V ml/min/ 1.73m ²	pH						HCO ₃ ⁻ μEq/min/1.73m ²
0-35			19.8	101	141	4.95	4.15	5.50	40	26		1.98		1.98
38			Priming inulin (0.14 g) and PAH (0.014 g)											
39			Start infusion of isotonic NaCl containing inulin (6.4 g/L), and PAH (1.3 g/L), at 0.5 ml/min											
36-87	7.29	40	19.7			0.63	5.40	5.40	50	20		1.97		1.97
88			Start infusion of NaHCO ₃ (16.5 g/L), inulin (6.4 g/L), and PAH (1.3 g/L), at 0.5 ml/min											
88-117			19.9			0.80	5.45	5.45	50	19		1.99		1.99
118-149	7.34	37	20.2			0.63	5.33	5.33	45	17		2.02		2.02
150-179	7.34	37	20.6			1.22	5.70	5.70	49	16		2.06		2.06
180-209	7.34	39	21.5			2.76	6.45	6.45	5	15		2.15	0.006	2.15
210-231	7.40	35	22.1	101	143	4.0	1.42	6.92	13			2.21	0.018	2.19
232-254	7.41	36	23.0			1.00	7.36	7.36	29			2.30	0.043	2.26
255	Infusion NaHCO ₃ concentration increased to 33 g/L													
255-279	7.43	34	24.7			1.55	7.63	7.63	76			2.47	0.096	2.38
280-311	7.47	36	26.4			2.87	7.71	7.71	150			2.64	0.178	2.46
312-342	7.42	41	27.2	100	140	4.2	2.08	7.87	124			2.72	0.156	2.56
343-373	7.44	42	29.0			3.03	7.91	7.91	268			2.90	0.326	2.57
374-405	7.44	44	30.5			3.33	8.10	8.10	367			3.05	0.502	2.55
406-437	7.47	43	31.6	96	147	4.05	3.16	8.05	401			3.16	0.532	2.63

 * Abbreviations: Pco₂ = CO₂ tension, V = urine flow rate, TA = titratable acid, PAH = P-aminohippurate, GF = glomerular filtrate.

TABLE II
Bicarbonate threshold and T_m and blood values during bicarbonate infusion

Patient	Age months	C_{in}^* ml/min/ 1.73m ²	HCO_3^- threshold mmoles/L	$HCO_3^-T_m$ mmoles/ 100 ml GF	Pco ₂			Na			K			Cl		
					C†	Th†	Tm†	C	Th	Tm	C	Th	Tm	C	Th	Tm
D.L.	1½	73	22	2.59	42	36.5	44	141	143	147	5.0	4.0	101	101	96	
R.P.	1½	104	22.5	2.82	36	37	42	141	135	138	5.0	4.5	102	99	93	
B.S.	2	92	21.5	2.84	38.5	40	51.5	140	139	143	5.3	5.2	103	100	90	
M.B.	6	124	22	2.87	29	29	35	140	139	141	5.0	3.6	106	100	100	
M.L.	9	128	22	≥2.50	29.5	30.5	36	139	137	140	4.0	3.8	103	97	91	
F.B.	12	68	21.5	2.65	36	37	37	135	138	142	4.0	3.9	101	99	94	
Mean		98	21.9	2.75	35	35	41	139	138	142	4.7	4.2	103	99	94	

* C_{in} = inulin clearance.

† C, Th, and Tm refer to values during the control period, at the threshold, and during maximal rate of reabsorption, respectively.

Autoanalyzer, using modifications of standard methods. Inulin was determined by a modification of the method of Schreiner (9). *p*-Aminohippurate was measured by a modification of the method of Smith and co-workers (10). Statistical comparisons were performed by means of Student's *t* test according to Snedecor (11).

Results

Bicarbonate reabsorption. Data from a representative study are given in Table I. The data from all studies are plotted in Figure 1, in which rates of reabsorption and excretion of bicarbonate, expressed as millimoles per 100 ml glomerular fil-

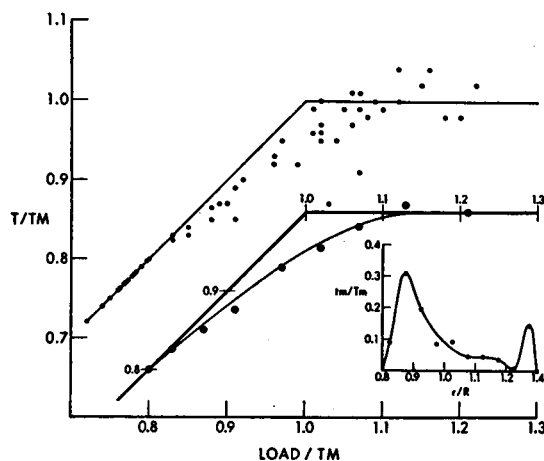


FIG. 2. MASS PLOT, MEAN CURVE, AND FREQUENCY DISTRIBUTION CURVE FOR THE DATA SHOWN IN FIGURE 1. The terms T/T_m and $load/T_m$ refer to individual rates of bicarbonate reabsorption and filtration, respectively, divided by the corresponding maximal rate of transport. This treatment allows data from all infants to be included in the same plot. A mass plot of data from all observations is presented in the upper graph. Mean curve of the data, shown in the lower graph, was derived by averaging the data in blocks of $\Delta load/T_m = 0.05$, the smooth curve being drawn by inspection. The frequency distribution curve, shown in the insert, was drawn according to the method of Smith (12). The rate of bicarbonate reabsorption in saturated nephrons, expressed as a fraction of the maximal rate of reabsorption for both kidneys, is given by the ratio tm/T_m . This ratio, therefore, serves as an index of the fraction of the total nephron population. r/R is the ratio of glomerulotubular balance of groups of nephrons (r , calculated as the ratio of their glomerular filtration rate to their maximal rate of bicarbonate reabsorption) to the mean value for glomerulotubular balance of the total nephron population (R). The frequency distribution curve, therefore, represents the per cent of the total nephron population with particular levels of glomerulotubular balance, related to the mean value for the two kidneys.

TABLE III
 Blood and urine values before and 3 to 5 hours after administration of NH_4Cl *

	Blood					Urine					$\mu\text{moles}/\text{min}/1.73\text{m}^2$	
	pH	tCO ₂	Pco ₂	pH	TA	NH ₄ ⁺	U _H ⁺ V	NH ₄ ⁺ per 100 ml Ccr	P			
Before NH₄Cl												
Infants												
Mean	7.34†	20.0†	37†	5.32†	53†	32	85†					54†
SE	0.009	0.28	0.4	0.084	4.9	3.3	7.0					5.8
n	10	9	9	11	11	11	11					11
Children												
Mean	7.41	25.2	39	6.25	15	25	28					20
SE	0.013	0.50	0.9	0.185	2.4	3.2	10.2					2.3
n	10	10	10	10	10	10	10					10
After NH₄Cl												
Infants												
Mean	7.31	17.1	34†	4.90	62†	57†	119	68				60
SE	0.012	0.43	1.1	0.033	4.9	4.3	9.2	5.7				4.9
n	11	10	10	11	11	11	11	10				11
Children												
Mean	7.29	18.5	37	4.87	50	80	130	65				47
SE	0.010	0.66	0.6	0.056	3.1	3.7	4.5	5.7				4.2
n	10	10	10	10	10	10	10	10				10

* Abbreviations: U_H⁺V = rate of H⁺ excretion, C_{Cr} = creatinine clearance.

† Significantly different from children (p < 0.001).

‡ Significantly different from children (p ≤ 0.05).

trate (GF), are plotted against serum bicarbonate concentration in millimoles per liter. The diagonal line in the figure represents the rate of filtration of bicarbonate in millimoles per 100 ml GF. As shown in the Figure, urinary excretion of bicarbonate remained essentially zero until serum concentrations exceeded 22 mmoles per L; thereafter, bicarbonate appeared in the urine in significant amounts (more than 0.01 to 0.02 mmoles per 100 ml GF, and increasing rapidly), defining the renal plasma threshold. The maximal rate of tubular reabsorption of bicarbonate (T_m) ranged from 2.6 to 2.9 mmoles per 100 ml GF. In individual studies (with the exception of ML), rates of reabsorption were constant during the last two or three periods, despite increasing concentrations of bicarbonate in blood. Nevertheless, it is possible that greater rates of reabsorption of bicarbonate might have been observed had blood bicarbonate concentration been raised to higher levels. The term T_m is used, therefore, to indicate the maximal rate observed; if actual values of T_m in infants are greater, interpretation of the data would not be changed.

Individual and mean values for bicarbonate threshold and T_m , P_{CO_2} , and concentrations of sodium, potassium, and chloride in serum during the test are given in Table II.

In Figure 2 the ratio of reabsorbed bicarbonate to T_m is plotted as a function of the ratio of filtered bicarbonate to T_m . Both individual points from each infant as well as the mean response of the group are shown. If all nephrons functioned identically and if filtered bicarbonate were totally reabsorbed until the T_m was reached, points would fall along the theoretical curve. However, a marked deviation from the theoretical line or "titration splay" is apparent.

Response to ammonium chloride. Measurements obtained in infants and children in blood and urine samples obtained before and 3 to 5 hours after administration of ammonium chloride are shown in Table III.

During the control period the mean pH and tCO_2 in the infants of 7.34 and 20.0, respectively, demonstrate the physiologic acidosis expected at this age. Their strongly acid urine and high rates of excretion of hydrogen ion before administration of ammonium chloride should be noted. The dose of ammonium chloride in each subject

was adequate to depress blood tCO_2 well below threshold levels.

Three to 4 hours after completion of administration of ammonium chloride, blood pH and tCO_2 were similar in both groups. No significant differences were observed in urinary pH or total excretion of hydrogen ion. Titratable acid in the infants was higher than in the children due to the greater rate of excretion of phosphate in the former group. Although the rate of excretion of ammonium was greater in the children, similar values were obtained when a comparison was made of excretion per 100 ml creatinine clearance.

Discussion

Bicarbonate reabsorption. Tudvad, McNamara, and Barnett (13) performed tests of bicarbonate reabsorption and excretion in premature infants ranging in age from 8 to 37 days. The renal threshold for bicarbonate ranging from 22 to 24 mmoles per L in those infants is close to the range of 21.5 to 22.5 reported here in premature and full-term infants during the remainder of the first year of life. However, the maximal rate of reabsorption of bicarbonate of 2.5 to 2.6 mmoles per 100 ml GF during the first month of life is lower than the range of 2.6 to 2.9 mmoles per 100 ml GF observed in the present study. The threshold observed in the young premature infant persists, apparently, throughout at least most of the first year of life, whereas the maximal rate of reabsorption appears to increase more rapidly than the threshold.

The maximal rate of reabsorption of 2.6 to 2.9 mmoles per 100 ml GF observed here in infants is virtually identical with the range of 2.6 to 3.0 observed by Pitts and co-workers (6) in adults. However, subjects in the latter investigation received NH_4Cl before study, had higher levels of P_{CO_2} in blood during the study, and had their blood bicarbonate increased to much higher levels than in the study in infants. Although these differences limit precise comparison of the results of the two investigations, any effect of the different conditions in adults would be to increase the level of their T_m . Therefore, it can be concluded that the T_m in infants is at least as high as in the mature subject.

It is of interest to relate these functional data to the observations of Fetterman, Shuplock,

Philipp, and Gregg (14) on morphologic development of the kidney. Using microdissection techniques, these authors made measurements of glomerular surface area and proximal tubular volume of isolated nephrons from the kidneys of children varying in age at time of death from birth to 18 years. In comparison to the child of several years of age, the newborn infant demonstrated higher values for and a greater degree of heterogeneity in the ratio of glomerular surface area to proximal tubular volume. The heterogeneity demonstrated in the infant with regard to morphologic glomerulotubular balance suggests the possibility of corresponding functional heterogeneity. Nephrons with relatively low glomerular surface area, and, therefore, possibly low glomerular filtration rate (GFR) relative to tubular size, might be expected to saturate their reabsorptive capacity and to excrete filtered bicarbonate only when the plasma bicarbonate concentration reached high levels. More importantly, nephrons with a relatively large glomerular surface area (and GFR) might excrete bicarbonate at relatively low plasma levels, tending to lower the bicarbonate threshold.

Support of this formulation can be found in the construction presented in the insert of Figure 2, calculated according to the method of Smith (12), in which a frequency distribution curve of the ratio of glomerular filtration rate to maximal rate of bicarbonate reabsorption for groups of nephrons (r) is compared with the mean value for both kidneys (R). This method, applied previously only to examination of glucose reabsorption, provides a graphic presentation of the glomerulotubular balance of groups of nephrons compared to the mean value for glomerulotubular balance for both kidneys as a unit. The marked skewing to the right and the wide dispersion of r/R values should be noted. It is perhaps of significance that this distribution of functional glomerulotubular balance is almost identical to the distribution of the ratio of glomerular surface area to proximal tubular volume found by Fetterman and associates in infants at term (14). However, their histogram of nephrons from the kidneys of infants $3\frac{1}{2}$ to 5 months of age resembled the adult pattern, indicating that anatomical heterogeneity per se may explain only part of the functional heterogeneity which may persist throughout the first year of life.

As pointed out by Rieselbach and associates

(15) with regard to data obtained during glucose titration studies, splay in the titration curve of patients with renal disease may relate to alterations in the kinetics of the enzyme reactions underlying transport mechanisms, as well as to functional heterogeneity. Thus, an alternative explanation of the low threshold and marked splay observed in the infants is a possible difference in the kinetics of bicarbonate reabsorption during this period. However, it is difficult to explain the findings shown in the frequency distribution curve on this basis.

Other factors may modify the renal bicarbonate threshold and thus the concentration of bicarbonate in blood. In the studies of Tudvad and associates (13), adequate activity of carbonic anhydrase was suggested by the response observed to administration of a carbonic anhydrase inhibitor. Nothing in either that investigation or the present study suggested disturbances in extracellular volume or in potassium balance. The values for blood P_{CO_2} in the infants reported here, however, as well as in other normal infants, are lower than those observed in older children or adults. Since a direct relationship has been demonstrated between blood P_{CO_2} and bicarbonate reabsorption (16–18), the possible effects of hypocapnia on the bicarbonate threshold and the maximal rate of reabsorption must be considered. However, in contrast to subjects with respiratory alkalosis, in whom hypocapnia is primary and the renal reabsorption of bicarbonate is depressed secondarily, these infants show marked splay of their reabsorption curve with no apparent lowering of the T_m . Moreover, no correlation was present between blood P_{CO_2} and threshold or maximal rate of reabsorption. It appears likely, therefore, that the hypocapnia observed in infants is a consequence and not a cause of their low blood bicarbonate concentration.

Excretion of acid. Previous studies have indicated major limitations in urinary acidification and excretion of hydrogen ion in infants during the first few days of life (19). It has been assumed generally that the same limitations apply to infants throughout the entire first year. However, very few data are available during this period (20–22). In the present study infants aged 1 to 16 months demonstrated no limitation in urinary acidification; mean urinary pH after administration of am-

monium chloride was as low as in the older children.

All infants in the present study were fed cow's milk formulas, providing a high daily intake of phosphate with a high rate of urinary excretion. Therefore, it is not surprising that the rate of excretion of titratable acid was higher in the infants than in the older children (23).

The mean rate of excretion of ammonium in the infants was significantly less than in the children. When the relatively low glomerular filtration rates of the infants are taken into consideration, however, it appears likely that no qualitative difference is present in the renal mechanism for production of ammonia, but rather that the lower rate of excretion is related to renal size or tubular mass (19).

The rate of excretion of total hydrogen ion in the infants was not significantly different from that observed in the children, the higher rate of excretion of titratable acid in the younger age group balancing their lower rate of ammonium excretion.

Physiologic acidosis of the infant. The finding of lower values for blood pH and bicarbonate during the first year or two of life usually is attributed to an imbalance between the endogenous rate of production of metabolic hydrogen ion and the ability of the kidney to excrete that hydrogen ion (2). Although this type of imbalance does exist in subjects with renal insufficiency and those with distal renal tubular acidosis, it is associated with a positive balance of hydrogen ion (24), an unlikely circumstance to be found in a healthy growing subject. Furthermore, if the capacity to excrete hydrogen ion were the limiting factor, one would expect a difference in blood pH and total CO₂ in infants fed high or low protein diets. Neither the data of Fomon, Harris, and Jensen (25) nor data from our own laboratory (26) have demonstrated such differences. Finally, the results of administration of ammonium chloride in the present study demonstrate that, at least beyond the first few weeks of life, the capacity of the infant to excrete hydrogen ion is similar to that of older children.

In subjects in hydrogen ion balance, the renal threshold for bicarbonate regulates its concentration in plasma, which normally remains at a level somewhat below the threshold, with almost total

reabsorption of filtered bicarbonate (3). Increase of plasma bicarbonate above the threshold, due to acute ingestion or infusion of bicarbonate, is followed by incomplete reabsorption of filtered bicarbonate and renal excretion, with subsequent reduction of plasma and interstitial concentrations to levels below the threshold, at which point reabsorption of filtered bicarbonate is complete, excretion ceases, and a steady state is again reached. Conversely, reduction of plasma bicarbonate concentration below the threshold leads to complete reabsorption of filtered bicarbonate, net excretion of hydrogen ion by the kidney, leading toward restoration of the previous bicarbonate concentration in blood.

In their study of infants between the ages of 3 months and 2 years, Albert and Winters (2) found the CO₂ content of arterialized capillary blood to be 21.1 ± 1.9 mmoles per L (mean \pm SD). These data are in excellent agreement with the values that would be anticipated on the basis of the present observations on bicarbonate threshold.

After investigating bicarbonate reabsorption in infants, Tudvad and associates (13) concluded that "in healthy premature infants the maximal rate of reabsorption of bicarbonate is such that, in the absence of other factors, concentrations of bicarbonate in serum would be stabilized at values of 24 to 26 mEq per L. Consequently, the physiologic acidosis of the premature infant cannot be explained on the basis of renal immaturity involving bicarbonate reabsorption." However, these authors did not consider that it is the level of the threshold and not the maximal rate of reabsorption of bicarbonate that determines its concentration in plasma. Therefore, even though reabsorptive capacity during the first year of life greatly exceeds the rate of reabsorption observed at the bicarbonate threshold, low threshold values result in low plasma concentrations.

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