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Research Article

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On the Influence of Extracellular Fluid Volume Expansion and of Uremia on Bicarbonate Reabsorption in Man

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ABSTRACT The patterns of bicarbonate reabsorption during increasing plasma concentrations were studied in subjects with a range of glomerular filtration rates (GFR) from 170 to 2 ml/min. In a group of five subjects with GFR values above 30 ml/min, paired bicarbonate titration studies were performed first under conditions which minimized extracellular fluid (ECF) volume expansion, and second under conditions which were conducive to exaggerated expansion of ECF volume. In patients with GFR values below 30 ml/min, a single protocol was employed. Studies also were performed on two patients with far advanced renal disease who were nephrotic and exhibited a sodium-retaining state. When ECF volume expansion was minimized in the nonuremic subjects, values for bicarbonate reabsorption were well in excess of the usually accepted Tm level and over the range of plasma bicarbonate concentrations employed, no evidence of a Tm phenomenon was observed. A similar pattern emerged in the two nephrotic patients despite the presence of uremia. However, with both exaggerated expansion of ECF volume (GFR greater than 30) and in patients with advanced renal disease in the absence of exaggerated ECF volume expansion a tendency towards saturation kinetics for bicarbonate reabsorption was demonstrable. In comparing the minimized with the exaggerated expansion studies, evidence emerged for a decrease in both bicarbonate reabsorption per unit of GFR and the absolute rate of bicarbonate reabsorption. When ECF volume expansion was exaggerated in uremic patients after stable rates of bicarbonate reabsorption had been achieved, a decrease in reabsorption per unit of GFR and in absolute bicarbonate reabsorption occurred. The possible relationship of the factors controlling sodium excretion to the observed patterns of bicarbonate reabsorption is considered in the text.

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INTRODUCTION

It is generally accepted that in normal man the kinetics of bicarbonate reabsorption by the kidney are characterized by an apparent Tm such that a maximum of approximately 2.8 mEq of bicarbonate may be reabsorbed per 100 ml of GFR (1, 2). Moreover, in uremia, Roberts, Randall, Vanamee, and Poppell (3) reported a Tm value for bicarbonate that fell within the normal range. Unfortunately the standard technique for performing a bicarbonate titration experiment involves marked expansion of extracellular fluid (ECF) volume; volume expansion is characteristically associated with a decrease in fractional sodium reabsorption and with an increase in natriuresis per nephron. Furthermore, a decrease in fractional sodium reabsorption and an increase in sodium excretion rate per nephron also are characteristic of the uremic state. On a priori grounds, therefore, the expansion of ECF volume in normal subjects produced by the bicarbonate titration technique and nephron reduction in uremic patients might influence bicarbonate reabsorption through a primary effect on sodium transport; a regulatory and homeostatic change in the patterns of sodium excretion thus could lead to a change in bicarbonate reabsorption that might be fortuitous rather than regulatory or homeostatic. It is of interest in this context that recent studies in the normal rat have shown that when special precautions are taken to minimize ECF volume expansion during the performance of bicarbonate titration studies, no Tm is demonstrable over a wide range of plasma bicarbonate concentrations (4). However, when ECF volume expansion was exaggerated, a definite tendency for bicarbonate reabsorption to become constant was evident (4). Moreover, a transformation in the bicarbonate titration curve similar to

that evoked by volume expansion has been seen in rats subjected to marked reduction in total nephron population (5).

The present studies were performed to reevaluate the patterns of bicarbonate reabsorption in man with particular reference to the influence of extracellular fluid volume expansion and of uremia. In a group of nonuremic subjects, titration studies were performed under conditions of "minimized" and "exaggerated" ECF volume expansion. Titration studies also were performed in a group of patients with moderately to far-advanced bilateral renal disease. In three patients with uremia, the effects of exaggerated ECF volume expansion were measured after the apparent bicarbonate Tm had been reached. Finally, the kinetics of bicarbonate reabsorption were studied in two patients with advanced renal disease who were nephrotic and thus did not exhibit the typical natriuresis per nephron of uremia.

METHODS

A total of 31 studies was performed on 17 subjects. Two were normal adult volunteers, 15 were patients with chronic bilateral renal disease of varying severity. Nine of the patients had chronic glomerulonephritis; four, pyelonephritis; one nephrosclerosis; and one, congenital hypoplastic kidneys. Two of the patients with glomerulonephritis and low glomerular filtration rates were nephrotic at the time of study and their results will be considered separately. The total group studied provided a range of glomerular filtration rates from 170 ml/min to 2 ml/min. In five subjects with GFR values above 30 ml/min, two different protocols were employed in the performance of bicarbonate titration studies. One was designed to minimize ECF volume expansion, the other to allow exaggerated expansion of the ECF. In the nephrotic patients and in the majority of patients with GFR's below 30 ml/min, exaggerated ECF expansion was not induced and only a single standard protocol for bicarbonate infusion was employed. However, in three nonnephrotic patients with low glomerular filtration rates, the effects of ECF expansion were observed on the maximal rate of bicarbonate reabsorption.

In order to decrease plasma bicarbonate concentrations to subnormal levels, from 2 to 8 g of ammonium chloride were given orally for 3–5 days before study in many of the subjects. The dose was prorated on the basis of the GFR and the steady-state plasma bicarbonate concentration. To eliminate mineralocorticoid insufficiency as an indeterminate variable, all subjects received deoxycorticosterone acetate (DOCA), 10 mg intramuscularly, on the morning of study. To avoid potassium depletion during titration studies, supplementary KCl was administered in most instances.

The specific protocols that were employed were as follows.

Subjects with GFR values greater than 30 ml/min

Minimized expansion. Dietary intake of salt was restricted to 1 g/day for 1 wk before study. In some subjects, furosemide (40–120 mg/day) was given orally for several days in order to decrease extracellular fluid volume in advance of the titration studies. This drug was discontinued 48 hr before the studies were performed. If plasma potassium concentrations fell during the period of diuretic administration, supplementary potassium was administered. During a 60–90 min equilibration period and the first three clearance periods, no bicarbonate was infused; the inulin used to maintain constant plasma inulin concentrations was administered in a 5% dextrose and water solution at a rate of 2.5 ml/min. Thereafter the infusion was changed to a 5% sodium bicarbonate solution which was delivered at a rate of 2–2.5 ml/min.

Exaggerated expansion. Dietary intake of salt was maintained between 12 and 16 g/day for 1 wk before study. 9-α-fluorohydrocortisone in a dose of 0.1 mg was administered twice daily during this period. The composition of the infusion during the equilibration period and three control clearance periods was the same as that used in the minimized expansion studies. After the third clearance period the infusion was changed to a 2–2.5% sodium bicarbonate solution which was administered at a rate of 6–12 ml/min.

Nonnephrotic patients with GFR values less than 30 ml/min

These patients were maintained on a 4 g salt diet for at least 5 days before study and each was in external salt balance at the time of study with neither evident volume depletion nor edema. The infusion procedure employed in this group of patients was the same as that used in the minimized expansion group.

Nephrotic patients

Two patients with far-advanced renal disease (GFR 7 and 17 ml/min respectively) had marked proteinuria and hypoalbuminemia and both were in positive sodium balance on a 1 g salt diet despite their uremic state. Thus neither of these two patients exhibited the natriuresis per nephron that characterizes the great majority of patients with comparable levels of glomerular filtration rate. Both patients were maintained on a 1 g salt diet for 1 wk before study and both were edematous at the time of the titration studies.

Glomerular filtration rate was measured using a constant infusion of inulin. From 10 to 25 clearance periods were obtained in individual studies and each period varied in duration from 10 to 35 min. Urine was collected using an in-lying Foley catheter. Special precautions were taken to maintain sterility (6). These included the use of an antibiotic ointment for lubricating the catheter and rinsing of the bladder with a neomycin solution at the conclusion of the study. In all subjects, urine cultures were obtained on one or more occasions after the conclusion of each study and in no instance was a positive culture obtained. Urine was collected under oil in acid-washed tubes. Neither water nor air rinses were used in order to avoid introducing changes in the urinary P_{CO_2}, but pressure was applied to the bladder routinely at the end of each collection. Blood was collected from a catheter in the radial artery continuously throughout each clearance period in order to obtain integrated plasma bicarbonate concentrations. The blood was collected into heparinized tubes under mineral oil. Informed consent was obtained from each subject employed in these studies.

Blood and urine pH and P_{CO_2} values were determined immediately after collection of the samples and plasma bicarbonate concentrations were estimated as the study proceeded. In this manner the rate and degree of rise of plasma bicarbonate could be monitored and controlled. Determinations of pH and P_{CO_2} on both blood and urine were made

TABLE I

A Bicarbonate Titration Study on a Normal Volunteer during Minimal ECF Volume Expansion

Clearance period	Time	GFR	Plasma			Urine			HCO_3 reabsorption		HCO_3 excretion		$U_{Na}V$	Filtered Na excreted
			pH	P_{CO_2}	HCO_3	pH	P_{CO_2}	HCO_3						
	min	*ml/min*		*mm Hg*	*mEq/liter*		*mm Hg*	*mEq/liter*	*μEq/min*	*mEq/liter GFR*	*μEq/min*	*mEq/100 GFR*	*μEq/min*	*%*
	Inulin prime and sustain I (5% DW at 2.5 ml/min) started at −85 min													
1	0–19	107.0	7.40	38.3	23.3	6.85	44.0	7.0	2615	24.4	5.26	<0.01	2.2	0.01
2	19–49	117.0	7.39	39.0	22.4	6.91	56.0	10.8	2743	23.5	7.20	<0.01	1.2	0.01
3	49–79	93.0	7.39	38.5	22.5	6.89	53.0	9.0	2191	23.6	8.82	<0.01	1.0	0.01
	Sustain II 5% bicarbonate solution at 2.5 ml/min													
4	79–109	119.0	7.43	38.0	24.4	7.59	62.5	53.2	2946	24.8	96.5	0.08	2.0	0.01
5	109–139	115.0	7.45	39.5	26.6	7.86	72.0	139.0	2926	25.5	284.0	0.25	9.0	0.06
6	139–168	85.5	7.50	39.5	29.8	7.97	85.0	199.0	2298	26.9	382.0	0.45	15.3	0.14
7	168–199	88.0	7.53	38.7	31.0	7.97	82.0	194.0	2430	27.6	440.0	0.50	37.5	0.33
8	199–228	96.5	7.54	41.0	33.2	7.91	97.5	201.0	2880	29.9	490.0	0.51	69.4	0.56
9	228–257	97.0	7.53	43.5	34.5	7.91	100.0	206.0	2997	30.9	513.0	0.53	111.0	0.88
10	257–290	100.0	7.57	41.0	36.6	7.94	101.0	223.0	3195	31.9	645.0	0.45	175.0	1.34
11	290–320	97.0	7.57	41.7	37.2	7.92	103.0	216.0	3110	32.1	680.0	0.70	233.0	1.82

$U_{Na}V$ = sodium excretion rate. Donnan correction (1.05) was applied in calculating the filtered load of bicarbonate.

using an Instrumentation Laboratory Inc. microgas analyzer (model IL 113-SL) and a Medtron pH meter (model 27). Bicarbonate concentrations in urine and plasma were calculated using the Henderson-Hasselbalch equation with a pK′ value of 6.1 and a solubility coefficient of 0.0301 for plasma. For urine, the pK′ value was calculated using the formula $pK' = 6.33 - 0.5\sqrt{B}$, where B represents the sum of Na + K concentrations. An alpha value of 0.0309 for urine was used. Inulin was determined according to the method of Roe, Epstein, and Goldstein (7). Plasma and urine sodium and potassium concentrations were measured with an internally compensated flame photometer.

RESULTS

Subjects with GFR values greater than 30 ml/min. The results of a bicarbonate titration study in a normal subject in whom extracellular fluid volume expansion was minimized are shown in Table I. The plasma bicarbonate concentration was increased progressively from an average value of 22.7 mEq/liter in the three control periods to a maximum value of 37.2 mEq/liter in the final period of study. No tendency for bicarbonate reabsorption to plateau at the usually accepted value of 2.7–2.8 mEq/100 ml of GFR was observed. Indeed, during the final clearance period, the value for bicarbonate reabsorption was 3.21 mEq/100 ml of GFR (32.1 mEq/liter GFR). The same subject was restudied using the protocol for exaggerated expansion of ECF described in the Methods section. The results are shown in Table II. Plasma bicarbonate concentration averaged 18.6

TABLE II

A Bicarbonate Titration Study during Exaggerated ECF Expansion on the Same Subject Depicted in Table I

Clearance period	Time	GFR	Plasma			Urine			HCO_3 reabsorption		HCO_3 excretion		$U_{Na}V$	Filtered Na excreted
			pH	P_{CO_2}	HCO_3	pH	P_{CO_2}	HCO_3						
	min	*ml/min*		*mm Hg*	*mEq/liter*		*mm Hg*	*mEq/liter*	*μEq/min*	*mEq/liter GFR*	*μEq/min*	*mEq/100 GFR*	*μEq/min*	*%*
	Inulin prime and sustain I (5% DW at 2.5 ml/min) started at −60 min													
1	0–40	160	7.44	28.2	18.5	4.40	33	0.002	3105	19.4	0.00	<0.01	287	1.38
2	40–60	184	7.43	29.0	18.7	4.50	27	0.002	3450	19.6	0.01	<0.01	347	1.44
3	60–82	168	7.43	29.2	18.7	4.58	27	0.002	3300	19.6	0.02	<0.01	294	1.35
	Sustain II 2.5% bicarbonate solution at 8 ml/min													
4	82–113	161	7.44	29.5	19.5	5.25	28.5	0.9	3287	20.4	13	<0.01	320	1.49
5	113–140	125	7.52	31.5	24.8	7.38	42.0	18.7	3190	25.5	70	0.06	471	2.82
6	140–169	144	7.52	33.3	26.4	7.70	53.0	66.6	3740	25.9	250	0.17	598	3.08
7	169–201	139	7.54	31.8	26.2	7.70	60.3	76.5	3563	25.6	257	0.15	580	3.09
8	201–230	144	7.56	31.5	27.4	7.74	60.0	83.5	3846	26.7	304	0.18	624	3.23
9	230–259	141	7.58	33.2	30.5	7.80	64.0	103.0	4125	29.2	395	0.23	665	3.50
10	259–290	143	7.59	32.5	30.0	7.88	73.0	142.0	3885	27.2	615	0.43	820	4.24
11	290–318	146	7.61	33.7	33.0	7.91	76.0	157.0	4215	28.9	845	0.58	1049	5.30
12	318–399	155	7.62	35.5	35.1	7.90	79.0	158.0	4775	30.6	925	0.60	1170	5.56

mEq/liter during the three control periods. Levels were elevated thereafter in a progressive manner to a final value of 35.1 mEq/liter during the 12th clearance period. Bicarbonate reabsorption averaged 19.5 mEq/liter GFR during the control periods. Values then increased to 29.2 mEq/liter GFR in the 9th clearance period but a tendency for stabilization was observed during the final four clearance periods when plasma bicarbonate concentrations ranged from 30.5 to 35.1 mEq/liter. It is of interest that even in the presence of exaggerated expansion of ECF and with GFR markedly increased in relation to the initial study, values for reabsorption approximated 30 mEq/liter GFR rather than 27 to 28 mEq/liter GFR.

With minimized expansion (Table I) sodium excretion was negligible during the control periods, reflecting the prior regimen of sodium deprivation and diuretic administration, and the maximum rate of sodium excretion observed was 233 μEq/min (1.82% of the filtered sodium) during the final clearance period when the bicarbonate excretion was 680 μEq/min. In the second study with exaggerated expansion of ECF volume (Table II) sodium excretion rate averaged 309 μEq/min during the control clearance periods and the values increased progressively thereafter to a maximum rate of 1170 μEq/min (5.56% of the filtered sodium). Due to the greater GFR in the second study, the absolute rates of reabsorption of both bicarbonate and sodium were higher during exaggerated than minimized expansion.

The results in the second normal subject are presented in Table III and IV. With minimized expansion of ECF (Table III) plasma bicarbonate concentrations were increased from a control value of 20.4 mEq/liter to a peak value of 32.7 mEq/liter. Bicarbonate reabsorption increased throughout the study showing no evidence of stabilization at a constant level and at the peak plasma bicarbonate concentration, the value for reabsorption was 30.7 mEq/liter GFR. During exaggerated expansion of ECF volume (Table IV) the plasma bicarbonate concentration was increased from the control value of 15.4 mEq/liter to a maximum value of 35.6 mEq/liter. Bicarbonate reabsorption stabilized between a range of 26.1 and 27.5 mEq/liter GFR during the last seven clearance periods corresponding to a plasma bicarbonate concentration range of 28.9–35.6 mEq/liter. Sodium excretion patterns also differed markedly in the two studies. With minimized ECF volume expansion the maximal rate of sodium excretion observed at the peak plasma bicarbonate concentration was 239 μEq/min or 1.23% of the filtered sodium. At the same plasma bicarbonate concentration in the presence of exaggerated expansion (period 16), the comparable values were 709 μEq/min and 4.45% of the filtered sodium excreted. The average value for glomerular filtration rate was greater during the exaggerated expansion than the minimized expansion study; however, above a plasma bicarbonate concentration of 28 mEq/liter the difference disappeared and, in fact, values were higher in the minimized expansion study. Consequently, the absolute rate of bicarbonate reabsorption (as well as the rate of reabsorption per unit of GFR) was greater in the minimized expansion study.

TABLE III

A Bicarbonate Titration Study on a Normal Volunteer during Minimal ECF Volume Expansion

Clearance period	Time	GFR	Plasma			Urine			HCO_3 reabsorption		HCO_3 excretion		$U_{Na}V$	Filtered Na excreted
			pH	P_{CO_2}	HCO_3	pH	P_{CO_2}	HCO_3						
	min	*ml/min*		*mm Hg*	*mEq/liter*		*mm Hg*	*mEq/liter*	*μEq/min*	*mEq/liter GFR*	*μEq/min*	*mEq/100 GFR*	*μEq/min*	%
	Inulin prime and sustain I (5% D/W at 2.5 ml/min) started at −90 min													
1	0–29	94.5	7.37	36.6	20.6	5.30	38.0	0.15	2045	21.6	0.08	<0.01	2.4	0.02
2	29–55	92.3	7.38	35.6	20.4	5.40	36.8	0.19	1975	21.4	0.12	<0.01	2.8	0.02
3	55–81	94.1	7.37	35.7	20.2	5.40	36.5	0.18	1998	21.2	0.11	<0.01	2.1	0.02
	Sustain II 5% bicarbonate solution at 2.5 ml/min													
4	81–111	114	7.39	35.2	20.7	5.35	35.7	0.16	2465	21.7	0.11	<0.01	2.6	0.02
5	111–137	108	7.41	36.1	22.1	5.31	35.7	0.15	2500	23.2	0.11	<0.01	3.3	0.02
6	137–163	116	7.43	37.7	24.1	6.80	72.5	10.5	2920	25.2	10.3	<0.01	5.9	0.04
7	163–190	112	7.44	35.7	23.8	7.39	66.2	38.6	2759	24.7	41.0	0.04	11.5	0.08
8	190–217	107	7.44	37.5	24.7	7.65	63.0	68.2	2656	24.9	84.5	0.08	19.8	0.14
9	217–248	106	7.47	37.8	26.6	7.87	68.0	123.4	2784	26.3	181.0	0.17	41.7	0.30
10	248–275	115	7.48	37.9	27.2	7.93	68.7	145.2	3068	26.7	214.0	0.19	48.5	0.30
11	275–298	130	7.48	39.7	28.7	7.92	73.0	153.0	3694	28.5	216.0	0.17	51.5	0.30
12	298–331	120	7.48	40.2	29.3	7.93	77.0	161.0	3412	28.4	283.0	0.24	95.5	0.60
13	331–360	130	7.51	40.2	31.2	8.02	83.7	222.0	3796	29.3	449.0	0.35	151.7	0.87
14	360–392	125	7.50	39.1	29.2	7.99	83.7	209.0	3475	27.9	410.0	0.33	155.0	0.92
15	392–422	127	7.51	40.0	31.0	8.01	86.7	226.0	3714	29.3	436.0	0.34	159.0	0.94
16	422–456	138	7.52	41.5	32.7	8.00	83.0	199.0	4245	30.7	475.0	0.35	239.0	1.23

TABLE IV

A Bicarbonate Titration Study during Exaggerated ECF Expansion in the Same Subject Depicted in Table III

Clearance period	Time	GFR	Plasma			Urine			HCO_3 reabsorption		HCO_3 excretion		$U_{Na}V$	Filtered Na excreted
			pH	P_{CO_2}	HCO_3	pH	P_{CO_2}	HCO_3						
	min	*ml/min*		*mm Hg*	*mEq/liter*		*mm Hg*	*mEq/liter*	*μEq/min*	*mEq/liter GFR*	*μEq/min*	*mEq/100 GFR*	*μEq/min*	%
	Inulin prime and sustain I (5% D/W at 2.5 ml/min) started at −64 min													
1	0–21	114	7.32	30.5	15.2	4.78	29.4	0.003	1810	15.9	0.01	<0.01	416	2.78
2	21–41	107	7.33	30.1	15.3	4.72	29.1	0.003	1720	16.0	0.02	<0.01	354	2.50
3	41–61	113	7.32	31.4	15.7	4.80	31.0	0.004	1855	16.5	0.02	<0.01	325	2.21
	Sustain II 2% bicarbonate solution at 12 ml/min													
4	61–91	122	7.33	32.4	16.1	4.80	32.7	0.004	2055	16.9	0.01	<0.01	266	1.66
5	91–120	132	7.38	33.7	19.4	4.81	33.0	0.005	2680	20.4	0.02	<0.01	397	2.29
6	120–150	122	7.40	34.7	20.8	4.80	32.7	0.005	2670	21.8	0.02	<0.01	352	2.18
7	150–180	122	7.43	34.9	22.5	6.10	50.5	1.37	2874	23.5	6.45	<0.01	284	1.74
8	180–210	130	7.45	35.2	24.0	7.25	59.1	24.6	3178	24.2	91.7	0.07	314	1.77
9	210–240	121	7.49	35.3	26.3	7.64	68.0	72.5	3116	25.7	234.0	0.19	357	2.21
10	240–270	136	7.50	36.0	27.2	7.82	79.5	133.0	3463	25.4	417.0	0.31	404	2.22
11	270–300	125	7.51	37.1	28.9	7.86	82.2	149.0	3271	26.1	519.0	0.42	474	2.80
12	300–330	130	7.53	37.5	30.4	7.89	82.0	157.0	3551	27.4	589.0	0.46	510	2.94
13	330–360	132	7.51	37.2	29.0	7.91	75.3	152.0	3446	26.2	564.0	0.43	462	2.62
14	360–390	131	7.53	35.7	29.0	7.91	83.5	171.0	3380	25.8	610.0	0.47	480	2.73
15	390–420	113	7.54	37.5	30.8	7.94	84.5	187.5	3022	26.7	638.0	0.56	505	3.34
16	420–450	117	7.56	37.5	32.8	7.91	85.5	171.0	3200	27.3	840.0	0.72	709	4.45
17	450–480	125	7.59	38.7	35.6	7.89	95.5	186.0	3450	27.5	1232.0	0.99	1172	6.82

Similar paired studies were performed on three patients with bilateral renal disease. Glomerular filtration rates for these patients averaged 133 ml/min (this patient had clinical and histologic evidence of chronic glomerulonephritis despite the high GFR), 80 ml/min. (bilateral pyelonephritis), and 37 ml/min (bilateral pyelonephritis). In the minimized expansion studies, plasma bicarbonate levels were elevated to peak values of 39.3, 29.8, and 36.5 mEq/liter respectively. But in none of the patients was a Tm observed. However when volume expansion was exaggerated the titration curves were different in each instance and reabsorption tended to stabilize at values of 35.2, 28.2, and 28.2 mEq/liter. The two titration curves for the patient with a GFR of 37 ml/min are shown in Fig. 1.

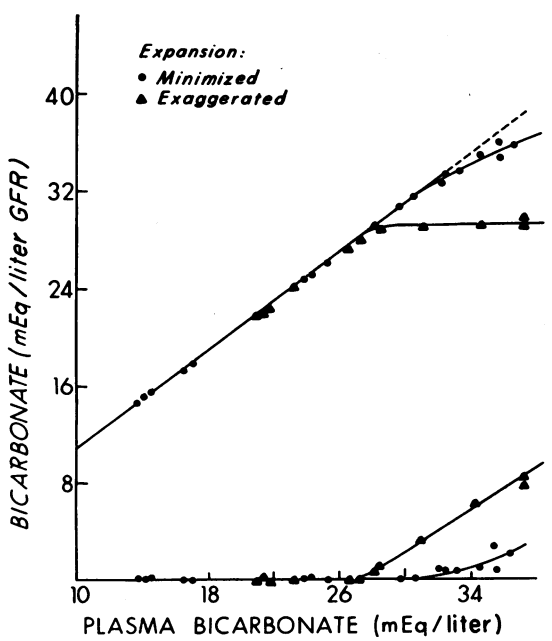

FIGURE 1 Bircarbonate titration curves obtained from a patient with a GFR of 37 ml/min studied under conditions of minimized and exaggerated expansion of ECF volume. The two upper curves depict bicarbonate reabsorption, the bottom curves bicarbonate excretion.

In three of the five sets of paired studies, values for GFR and plasma bicarbonate concentrations were closely comparable during minimized expansion and exaggerated expansion of ECF in three or more consecutive clearance periods. Thus the opportunity exists to examine absolute values for bicarbonate reabsorption at the same filtered load of bicarbonate in the same subjects under different conditions of volume expansion. The data are shown in Table V. In subject 2, six consecutive clearance periods obtained during minimized expansion are compared with eight consecutive periods obtained during exaggerated expansion. GFR averaged 128 vs. 126 ml/min respectively in the two studies. Plasma bicarbonate concentrations averaged 30.4 vs. 30.5 mEq/liter. Filtered load of bicarbonate ranged from 3695 to 4720 μEq/min (mean 4101) in the minimized expansion study and from 3660 to 4680 (mean 4024) in the exaggerated expansion study. Absolute bicarbonate reabsorption aver-

TABLE V

Values for GFR, Plasma Bicarbonate Concentrations, Bicarbonate Reabsorption, and Excretion in the Same Subjects during Minimized vs. Exaggerated Expansion of ECF Volume

	Minimized expansion					Exaggerated expansion				
	GFR	Plasma HCO_3	Filtered load HCO_3	Bicarbonate excretion	Bicarbonate reabsorption	GFR	Plasma HCO_3	Filtered load HCO_3	Bicarbonate excretion	Bicarbonate reabsorption
	ml/min	*mEq/liter*	*μEq/min*	*μEq/min*	*μEq/min*	*ml/min*	*mEq/liter*	*μEq/min*	*μEq/min*	*μEq/min*
Subject 2										
	130	28.7	3910	216	3694	136	27.2	3880	417	3463
	120	29.3	3695	283	3412	125	28.9	3790	519	3271
	130	31.2	4245	449	3796	130	30.4	4140	589	3551
	125	29.2	3885	410	3475	132	29.0	4010	564	3446
	127	31.0	4150	436	3714	131	29.0	3990	610	3380
	138	32.7	4720	475	4245	113	30.8	3660	638	3022
						117	32.8	4040	840	3200
						125	35.6	4680	1232	3448
Mean	128	30.4	4101	378	3723	126	30.5	4024	676	3348
Subject 3										
	38.6	29.7	1203	1	1202	42.5	28.2	1260	19	1241
	40.5	32.3	1374	1	1373	38.1	28.3	1132	34	1098
	39.8	30.6	1277	2	1275	40.6	31.0	1322	131	1191
	35.2	33.2	1226	26	1200	41.8	34.4	1509	274	1235
	35.7	32.1	1204	34	1170	42.4	37.4	1665	376	1289
	38.6	35.7	1449	36	1413					
	38.0	34.6	1379	43	1336					
	35.4	36.5	1358	85	1273					
	42.6	35.4	1584	138	1446					
Mean	38.3	33.3	1340	41	1299	41.1	31.9	1378	167	1211
Subject 4										
	152	29.4	4700	57	4644	160	29.4	4990	451	4539
	152	30.3	4840	174	4666	176	30.7	5680	469	5211
	163	30.9	5290	268	5022	143	32.5	4880	734	4146
	149	33.3	5210	310	4900					
Mean	154	31.0	5010	202	4808	160	30.9	5184	551	4633

Using the *t* test (method of set comparison) there is no significant difference between the filtered loads of bicarbonate in minimized vs. exaggerated expansion in any of the three subjects. However bicarbonate excretion is significantly greater ($0.05 > P > 0.02$) during exaggerated expansion in all three subjects.

In each of the three subjects values for GFR and plasma bicarbonate concentration were closely comparable during three or more consecutive periods.

aged 3723 μEq/min (range 3412–4245) in the minimized expansion study; the comparable value during exaggerated expansion was 3348 μEq/min (range 3022–3463). In subject 3, GFR averaged 38.3 ml/min during minimized expansion and 41.1 ml/min during exaggerated expansion. The mean value for the filtered load of bicarbonate was slightly higher during exaggerated expansion, but the absolute value for bicarbonate reabsorption was 1214 μEq/min during exaggerated expansion and 1299 μEq/min during minimized expansion. In subject 4, GFR averaged 154 ml/min during minimized expansion and 160 ml/min during exaggerated expansion. The filtered load of bicarbonate averaged 174 μEq/min less during minimized than exaggerated expansion whereas the mean value for bicarbonate reabsorption was 175 μEq/min less during exaggerated expansion.

Patients with advanced renal disease. In patients with advanced renal disease a single standard protocol was employed. The patients were not salt deprived before study and the infusion rate for bicarbonate was the same as that used in the minimized expansion studies already described. Fig. 2 depicts the results of a

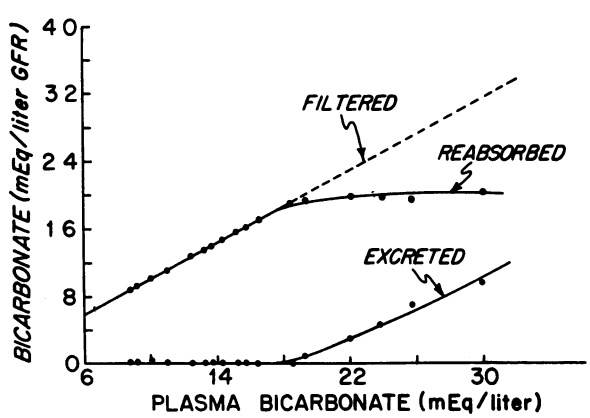

FIGURE 2 Bicarbonate titration curve in a patient with far advanced bilateral renal disease and a glomerular filtration rate of 2 ml/min.

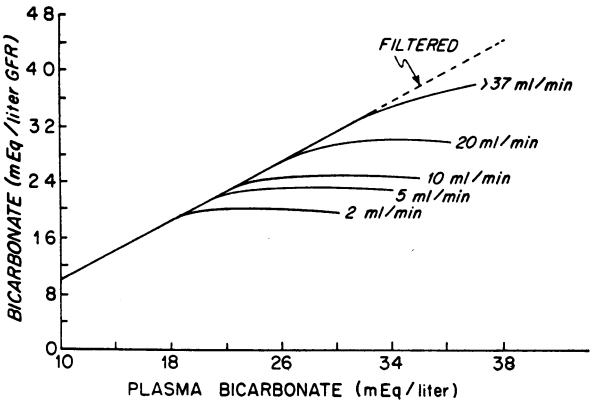

FIGURE 3 Representative bicarbonate titration curves for patients with GFR's ranging from 170 to 2 ml/min. The curve labeled greater than 37 ml/min is a mean titration curve for five subjects. The other curves are single titration curves but are representative of other patient's with GFR's in the same range.

titration study in a patient with far-advanced chronic glomerulonephritis and a GFR of 2 ml/min. Bicarbonate was excreted into the urine at a plasma bicarbonate concentration of 18 mEq/liter and reabsorption stabilized at a value of 19 mEq/liter GFR. In Fig. 3 a summary is presented of representative titration curves obtained in patients with advanced renal disease at different levels of GFR. With a GFR of 37 ml/min or greater, no apparent Tm was demonstrable when ECF volume expansion was minimized. In the patients with GFR's of 20 ml/min or lower an apparent Tm was observed and the lower the value for GFR, the lower the value for the Tm.

The relationship between the fractional excretion of sodium and bicarbonate reabsorption in the group of 12 uremic patients is shown in Fig. 4. The figure was constructed by averaging all values in each patient for bicarbonate reabsorption and fractional sodium excretion at plasma bicarbonate concentrations between 28 and 31 mEq/liter. It is evident that the greater the rate of fractional sodium excretion, the lower the value for bicarbonate reabsorption.

The effects of acute ECF volume expansion on the bicarbonate Tm in uremic patients. In three uremic patients, ECF volume was expanded after bicarbonate reabsorption had stabilized at an apparent Tm level. The results in each of the three patients were qualitatively similar and the detailed value for one of the three patients are shown in Table VI. GFR in this patient averaged 10.5 ml/min during the three control clearance periods. Values for plasma bicarbonate concentrations were increased from a control level of 15.7 mEq/liter to a peak level of approximately 34.9 mEq/liter. Bicarbonate reabsorption stabilized at approximately 25 mEq/liter GFR. With the superimposition of acute ECF volume expansion, values for reabsorption fell precipitously to a final value of 19.8 mEq/liter GFR. Of interest is the fact that GFR and the filtered load of bicarbonate increased markedly during the period of acute expansion. Yet absolute rates of bicarbonate excretion failed to increase proportionately; indeed in comparing the last four periods of the standard titration procedure with the four periods in which acute volume expansion was superimposed, GFR increased from 12.5 to 13.4 ml/min and the filtered load of bicarbonate increased from 350 to 455 μEq/min, but the absolute rate of bicarbonate reabsorption decreased from 307 to 277 μEq/min.

Nephrotic patients. GFR values in the two nephrotic patients averaged 7 and 17 ml/min. Both were in positive sodium balance on a 1 g salt intake. The detailed results in the patient with the lower GFR are shown in Table VII. Plasma bicarbonate concentrations were increased from a mean value of 17.6 mEq/liter during the three control periods to a maximum value of 34.5 mEq/liter during the 17th clearance period. Bicarbonate excretion in the urine remained at negligible levels until the plasma bicarbonate concentration approached 30 mEq/liter and at the highest plasma level observed, bicarbonate excretion rate was under 10 μEq/min (0.12 mEq/100 ml GFR). Bicarbonate reabsorption increased from an average value of 18.5 mEq/liter GFR in the control periods to a peak value in excess of 35 mEq/liter GFR during the final two clearance periods. Thus, bicarbonate reabsorption was essentially complete throughout the entire study despite the existence of far-advanced renal disease and chemi-

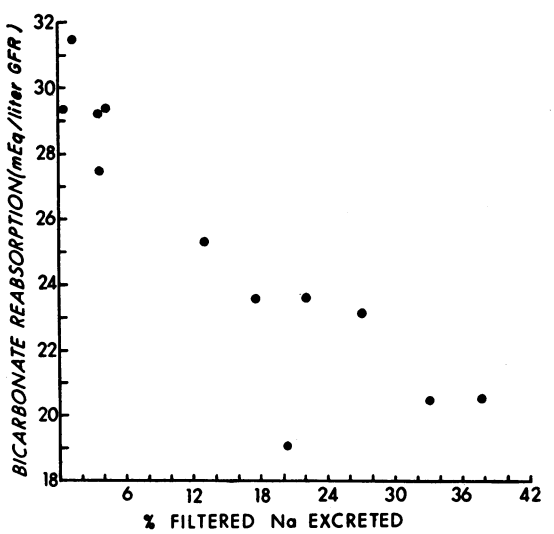

FIGURE 4 Comparison of bicarbonate reabsorption with fractional sodium excretion in the 12 uremic patients. In each patient all values for bicarbonate reabsorption and fractional sodium excretion were averaged at plasma bicarbonate concentrations between 28 and 31 mEq/liter.

TABLE VI

The Effects of Exaggerated ECF Volume Expansion on Bicarbonate Reabsorption after an Apparent Tm had been Reached in a Uremic Patient

Clearance period	GFR	P_{HCO_3}	F.L. HCO_3	$U_{HCO_3}V$	$U_{Na}V$	Filtered Na excreted	$\frac{T_{HCO_3}}{GFR}$	T_{HCO_3}
	ml/min	*mEq/liter*	*μEq/min*	*μEq/min*	*μEq/min*	%	*mEq/liter GFR*	*μEq/min*
	Inulin prime and sustain I (5% D/W at 2.5 ml/min) started at −85 min							
1	10.2	16.6	177.5	0.654	81.5	6.4	17.3	176.9
2	10.2	15.4	165.0	0.675	112.0	8.8	16.1	164.3
3	11.0	15.0	173.5	0.813	155.0	11.5	15.7	172.7
	Sustain II 5% bicarbonate solution at 2.5 ml/min							
4	11.5	16.6	200	1.3	149	10.5	17.3	198.7
5	12.3	18.5	239	3.3	199	12.9	19.1	235.7
6	12.9	21.4	290	4.4	173	10.5	22.1	285.7
7	11.3	22.6	268	8.5	162	11.1	22.9	259.5
8	12.9	24.0	326	17.8	189	11.2	23.8	308
9	11.9	25.5	319	24.8	177	11.2	24.7	294
10	11.9	27.5	344	45.6	212	13.2	25.0	298
11	13.3	29.4	410	84.0	279	15.3	24.5	326
	Sustain III 4% bicarbonate solution in isotonic saline at 6 ml/min							
12	11.5	29.7	358	96.6	315	19.7	22.7	261
13	12.2	31.4	403	147.0	375	22.0	21.0	256
14	15.4	32.7	529	224.0	572	26.1	19.8	305
15	14.4	34.9	530	245.0	569	27.1	19.8	285

TABLE VII

A Bicarbonate Tritration Study in a Patient with Chronic Glomerulonephritis and the Nephrotic Syndrome

Clearance period	Time	GFR	Plasma			Urine			HCO_3 reabsorption		HCO_3 excretion		$U_{Na}V$	Filtered Na excreted
			pH	P_{CO_2}	HCO_3	pH	P_{CO_2}	HCO_3						
	min	*ml/min*		*mm Hg*	*mEq/liter*		*mm Hg*	*mEq/liter*	*μEq/min*	*mEq/liter GFR*	*μEq/min*	*mEq/100 GFR*	*μEq/min*	%
	Inulin prime and sustain I (5% D/W 2.5 ml/min) started at −84 min													
1	0–57	6.80	7.36	30.3	16.7	4.80	34.1	0.039	119	17.5	0.05	<0.01	15.0	1.83
2	57–82	7.45	7.37	31.2	18.5	4.75	32.2	0.034	145	19.4	0.04	<0.01	15.0	1.56
3	82–109	8.52	7.32	34.7	17.7	4.80	29.7	0.035	159	18.6	0.05	<0.01	23.7	2.18
	Sustain II 5% bicarbonate solution at 2 ml/min													
4	109–142	7.40	7.34	34.8	18.3	4.80	32.7	0.039	142	19.2	0.05	<0.01	20.0	2.11
5	142–171	6.84	7.38	35.5	20.4	4.90	34.0	0.050	146	21.4	0.07	<0.01	17.7	2.03
6	171–205	6.73	7.43	34.6	22.0	4.90	33.0	0.049	156	23.1	0.06	<0.01	15.5	1.78
7	205–234	8.10	7.47	34.5	24.1	4.90	36.0	0.053	203	25.3	0.07	<0.01	14.8	1.43
8	234–254	8.55	7.44	33.6	22.3	5.05	34.9	0.073	226	23.4	0.09	<0.01	14.3	1.26
9	254–274	8.47	7.51	30.5	23.7	5.00	33.6	0.063	211	24.9	0.07	<0.01	13.6	1.24
10	274–305	7.60	7.49	36.0	26.8	5.00	34.6	0.065	214	28.1	0.07	<0.01	12.5	1.24
11	305–338	7.55	7.49	36.2	26.5	5.10	33.7	0.079	211	27.8	0.09	<0.01	13.7	1.33
12	338–367	7.79	7.55	34.5	29.4	5.19	35.5	0.103	241	30.9	0.12	<0.01	13.2	1.24
13	367–398	7.50	7.54	35.5	29.7	5.31	37.6	0.144	234	31.2	0.18	<0.01	14.0	1.40
14	398–435	5.91	7.58	34.6	31.0	5.80	40.7	0.484	192	32.5	0.54	<0.01	14.4	1.77
15	435–465	8.85	7.52	41.2	32.3	6.30	43.1	1.650	298	33.6	2.17	0.03	18.4	1.57
16	465–494	6.57	7.50	41.7	31.4	6.51	45.5	2.780	214	32.5	3.36	0.05	16.9	2.01
17	494–525	6.16	7.58	38.4	34.5	6.70	48.1	4.600	219	35.4	5.53	0.09	20.4	2.44
18	525–559	8.17	7.57	38.4	34.4	6.95	49.0	8.300	286	35.1	9.65	0.12	21.0	1.89

cal manifestations of uremia. The bicarbonate titration curve for this study is shown in Fig. 5.

In the second patient with the nephrotic syndrome, bicarbonate reabsorption was studied over a plasma bicarbonate range of 20.5–33.6 mEq/liter. Values for reabsorption showed no tendency to stabilize, rising from 21.8 mEq/liter GFR during the control periods to 34.2 mEq/liter GFR at the peak level of plasma bicarbonate.

DISCUSSION

The traditional interpretation of the kinetics of renal bicarbonate reabsorption has been strongly influenced by studies using the bicarbonate titration technique. The prototype of the titration curve that has been recorded for normal man is shown in the triangles in Fig. 1. As the plasma bicarbonate concentration is increased progressively, bicarbonate is completely reabsorbed until plasma levels approximate 26 mEq/liter. At this concentration, which is the so-called bicarbonate threshold, bicarbonate begins to enter the urine. As plasma levels are increased further, the rate of reabsorption tends to become constant such that approximately 2.8 mEq of bicarbonate are reabsorbed per 100 ml of glomerular filtrate (28 mEq/liter GFR). This apparent maximum velocity of reabsorption has been accepted for many years as the normal Tm for bicarbonate. However, there are reasons to suspect that the classic titration curve may be influenced by the condition of the titration experiment, which of necessity involves marked expansion of the extracellular fluid volume. Volume expansion is known to diminish fractional sodium reabsorption in the proximal tubule (8, 9) and thus to influence the setting of glomerulotubular balance for sodium. On a priori grounds, volume expansion might be expected to influence sodium-hydrogen exchange in the proximal tubules as well as sodium reabsorbed with chloride; thus the status of extracellular fluid volume could also influence the setting of glomerulotubular balance for bicarbonate. Recent observations by Purkerson, Lubowitz, White, and Bricker, in the rat, lend support to the latter possibility (4). When the bicarbonate titration procedure was modified so as to minimize ECF volume expansion, no Tm could be demonstrated in normal rats in which plasma bicarbonate concentrations were elevated to levels as high as 60 mEq/liter. However, when volume expansion was exaggerated, a clear tendency for reabsorption to plateau was observed and the threshold for bicarbonate excretion was decreased. ECF volume expansion also has been shown to decrease bicarbonate reabsorption in individual superficial nephrons of the rat (10).

A second state characterized by increased fractional sodium excretion and natriuresis per nephron is nephron

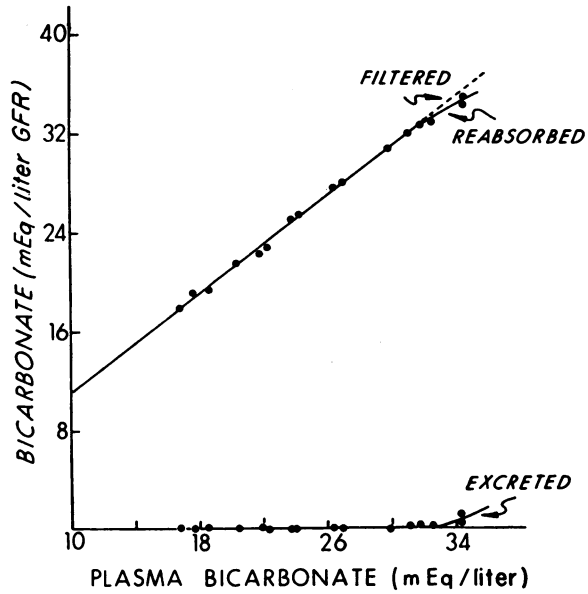

FIGURE 5 Bicarbonate titration curve in a nephrotic patient with chronic glomerulonephritis and a GFR of 7 ml/min.

reduction with a decreased GFR. Indeed, in advanced renal disease the maintenance of sodium balance on an average salt intake requires the excretion of a substantially greater fraction of filtered sodium than is encountered in saline diuresis in subjects with normal renal function (11). It is of interest, therefore, that reduction of the nephron population by approximately 75% in rats initiated alterations in the bicarbonate titration curve comparable to those observed after exaggerated expansion of ECF (5). Furthermore, micropuncture studies have shown that nephron reduction in the rat leads to marked inhibition of fractional bicarbonate reabsorption in individual superficial nephrons of the rat.[1]

The present studies were performed to examine the influence of both extracellular fluid volume expansion and uremia on bicarbonate reabsorption in man. Patients were studied with a range of glomerular filtration rates from 170 ml/min to 2 ml/min. The normal subjects and the patients with renal disease in whom GFR was greater than 30 ml/min fell into one group. When ECF volume expansion was minimized by salt deprivation and diuretic administration in advance of the titration study and by the infusion of the minimum amount of sodium bicarbonate consistent with the desired elevation of plasma bicarbonate concentrations during the study, no definite Tm for bicarbonate was observed. In four of these five subjects the excretion

[1] Lubowitz, H., M. L. Purkerson, and N. S. Bricker. 1969. A micropuncture study of the effect of nephron reduction on proximal tubular bicarbonate reabsorption in the rat. In press.

rate of sodium during the control clearance periods was less than 0.1% of the filtered load.

In the same group of subjects, exaggerated expansion of ECF led to an alteration in the patterns of bicarbonate reabsorption. In comparison to the minimized expansion studies, the threshold for bicarbonate excretion was lower and there was a tendency for bicarbonate reabsorption to stabilize below 30 mEq/liter of GFR. These subjects exhibited a moderate degree of natriuresis before the onset of the bicarbonate infusion and the natriuresis became quite marked during the course of the studies.

The patients with glomerular filtration rates of 20 ml/min or less resembled the exaggerated expansion group although ECF volume expansion was not exaggerated. However, in order to maintain sodium balance at a GFR of 20 ml/min on a 4 g salt intake, approximately 2% of the filtered sodium must be excreted and the lower the GFR the greater must this percentage be (e.g. at a GFR of 5 ml/min, approximately 10% of the filtered sodium must be excreted). It is of interest, therefore, that the patients with the more markedly reduced levels of GFR and the higher fractional sodium excretion rates reabsorbed bicarbonate in a manner qualitatively similar to the subjects with higher GFR's subjected to exaggerated expansion of ECF volume. It also is of interest that the lower the level of GFR, and thus the greater the rate of fractional sodium excretion, the more striking was the alteration of bicarbonate reabsorption (see Fig. 4). Finally, when acute volume expansion was induced in uremic patients with stable values for bicarbonate reabsorption per unit of GFR, fractional sodium excretion increased markedly, the apparent Tm for bicarbonate was perturbed, and bicarbonate reabsorptive rates, both per unit of GFR and in absolute terms, diminished.

Additional evidence relating fractional sodium reabsorption to the patterns of bicarbonate reabsorption emerges from the studies on the two nephrotic patients. These two subjects, despite very low glomerular filtration rates, were edema formers and thus did not exhibit the natriuresis per nephron which is characteristic of patients with their levels of GFR. Of considerable interest is the fact that their bicarbonate titration curves were strikingly different from other patients with uremia, resembling those for the nonuremic subjects studied during minimized ECF volume expansion. Indeed, the titration curves in the two uremic nephrotic patients exhibited the highest slope for bicarbonate reabsorption per unit of GFR vs. plasma bicarbonate concentration of all the subjects studied.

Several possible conclusions emerge from these studies.

(*a*) The "normal" Tm for bicarbonate in man may actually represent an inhibited rate of bicarbonate reabsorption imposed by volume expansion attendant upon the standard titration protocol.

(*b*) Intrinsic renal disease per se does not appear to depress bicarbonate reabsorption per unit of GFR in the residual nephrons. The evidence for this is found in the titration curves of patients with GFR levels of over 30 ml/min during minimized ECF volume expansion and in the two uremic patients who were nephrotic. In both groups, bicarbonate reabsorption increased over the entire range of plasma bicarbonate levels employed and threshold values were higher than the usually accepted normal.

(*c*) The intensity of natriuretic forces appears to influence the character of the bicarbonate titration curve. In both of the nephrotic uremic patients and in four of the five subjects studied during minimized expansion, fractional sodium excretion tended to remain below 2% even at the highest plasma bicarbonate concentrations obtained. On the other hand, in the presence of exaggerated ECF expansion and in the non-nephrotic uremic patients peak values for fractional sodium excretion ranged from 5% to 40%. Moreover, the higher the fractional sodium excretion rate, the lower was the apparent Tm for bicarbonate. Finally, when the uremic patients with stable rates of bicarbonate reabsorption were subjected to acute volume expansion, natriuresis increased strikingly and bicarbonate reabsorption decreased correspondingly.

Thus bicarbonate reabsorption appears to be influenced by the concurrent activity of the factors controlling sodium excretion. In all probability, therefore, the factors that modulate sodium reabsorption in the proximal convoluted tubule must have a secondary influence on bicarbonate reabsorption whether the latter occurs in consequence of sodium-hydrogen exchange or the reabsorption of bicarbonate as an ion.

One final possibility must be considered in explanation for the present data. Both volume expansion and nephron reduction may be attended by an increase in GFR per nephron especially in the superficial nephrons (12, 13). The effects of either acute or chronic hyperfiltration on the kinetics of bicarbonate reabsorption remain to be established and although the experimental induction of hyperfiltration both in normal dogs (14) and uremic man (11) does not influence fractional sodium excretion, the possibility was considered that the decrease in bicarbonate reabsorption expressed per unit of GFR seen with exaggerated ECF volume expansion was secondary to an increase in GFR per nephron rather than to inhibition of bicarbonate reabsorption. However, the opportunity to compare absolute rates of bicarbonate reabsorption at comparable levels of GFR

and comparable plasma bicarbonate concentrations existed in three of the subjects studied during both minimized and exaggerated expansion. The data presented in Table V suggest that the exaggerated expansion was accompanied not only by a decrease in fractional bicarbonate reabsorption but by a decrease in absolute bicarbonate reabsorption. The same phenomenon was observed in the uremic patients in whom ECF volume expansion was exaggerated after an apparent Tm for bicarbonate had been reached (Table VI). Thus volume expansion does appear to inhibit tubular reabsorption of bicarbonate.

ACKNOWLEDGMENTS

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