ON THE MECHANISM OF ACIDOSIS IN CHRONIC RENAL DISEASE *

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It has been pointed out (1) that, in terms of modern acid-base chemistry, the defects reponsible for the acidosis of renal disease could be: *1*) impaired renal excretion of acid in the form of ammonium and titratable acidity, *2*) loss of bicarbonate (alkali) in the urine due to a failure of renal bicarbonate conservation or *3*) a combination of these two defects.

The two main components of urine responsible for the removal of hydrogen [1] from the body are ammonium and titratable acid. Under the stress of endogenous or exogenous acidosis the normal kidney responds by increasing the excretion of both these moieties, but the increment in ammonium usually far exceeds that in titratable acid. It has long been known that the basal excretion of ammonium is reduced in patients with renal disease, and that the capacity to increase ammonium excretion in response to acidosis is also impaired (2–7). Somewhat less attention has been directed towards the ability of the diseased kidney to excrete titratable acid, although it was demonstrated many years ago that patients with uremic acidosis can elaborate very acid urines (2, 3). In so-called "renal tubular acidosis" it is generally accepted that characteristically this function is lost and that all urines are relatively alkaline (8).

Whether there is any disturbance in bicarbonate reabsorption in renal disease is not clear from available data. With one exception (9) there has been no report of such a defect in patients with uremic acidosis. A recent study of the tubular response to acute bicarbonate loading in such patients has, in fact, led to the conclusion that bicarbonate reabsorption is normal (10). On the other hand, defects in bicarbonate reabsorption have been frequently identified in patients with so-called "renal tubular acidosis" and the Fanconi syndrome (11–13).

No previous attempt has been made to study the sequence of events which occur as patients with renal insufficiency spontaneously become acidotic. The present study has been undertaken in an effort to obtain this information by means of balance studies in patients whose acidosis was initially corrected by administration of alkali. The data to be presented provide some indication of the relative importance of the various renal defects and of their functional relationships. These experiments also appear to throw some light on the mechanisms which allow patients with renal disease to achieve a new steady state of hydrogen ion balance at subnormal plasma bicarbonate concentrations.

METHODS

Balance studies were carried out on five patients. Four of the five (P.D., D.H., H.G. and R.M.) appeared to have chronic glomerulonephritis according to the usual clinical and laboratory criteria; three of these four also had a history of urinary tract infection at some time prior to their study and may also have had chronic pyelonephritis. The fifth patient had a well-documented history of renal tubular acidosis, nephrolithiasis and recurrent urinary tract infections. (For purposes of clarity, this pa-

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[1] The term "hydrogen" as used in this discussion is not restricted to that very small quantity of hydrogen which exists in the free ionized form, but is meant to include hydrogen which has been bound to body buffers.

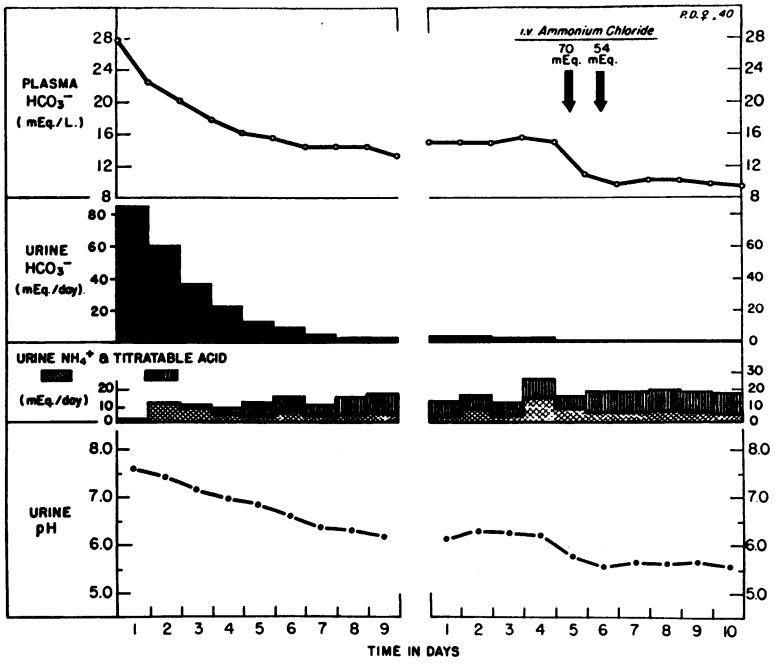

FIG. 1. PLASMA BICARBONATE CONCENTRATION, URINE pH AND DAILY EXCRETION OF BICARBONATE, AMMONIUM AND TITRATABLE ACID IN PATIENT P.D.

Observations began the day after acidosis had been corrected and treatment with alkali had been stopped. The break in the middle of the observations indicates an interruption of seven days. See text for details.

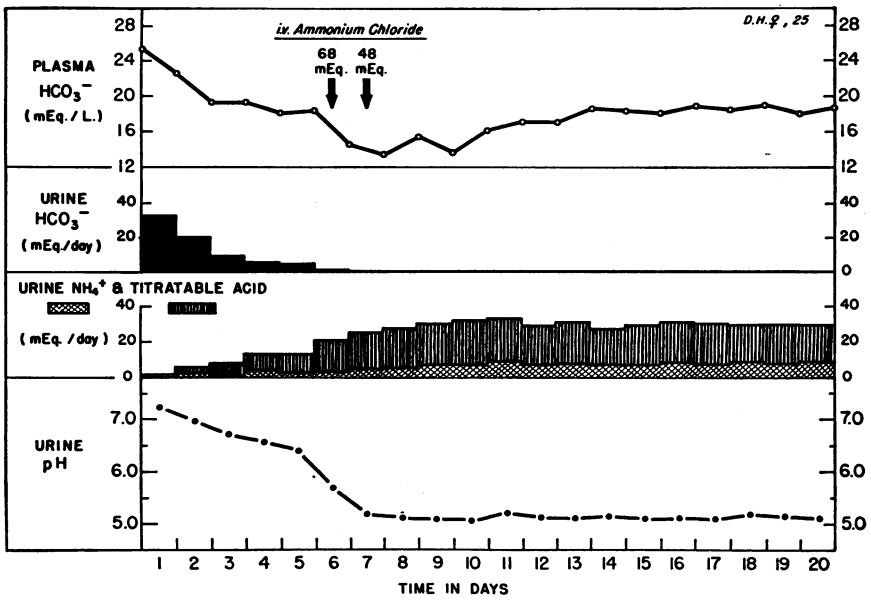

FIG. 2. PLASMA BICARBONATE CONCENTRATION, URINE pH AND DAILY EXCRETION OF BICARBONATE, AMMONIUM AND TITRATABLE ACID IN PATIENT D.H.

Observations began the day after acidosis had been corrected and treatment with alkali had been stopped.

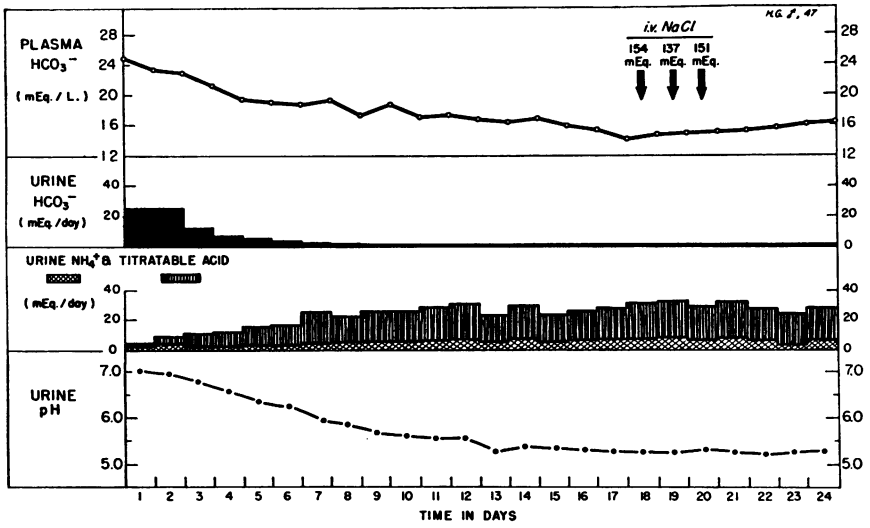

FIG. 3. PLASMA BICARBONATE CONCENTRATION, URINE pH AND DAILY EXCRETION OF BICARBONATE, AMMONIUM AND TITRATABLE ACID IN PATIENT H.G.

Observations began the day after acidosis had been corrected and treatment with alkali had been stopped.

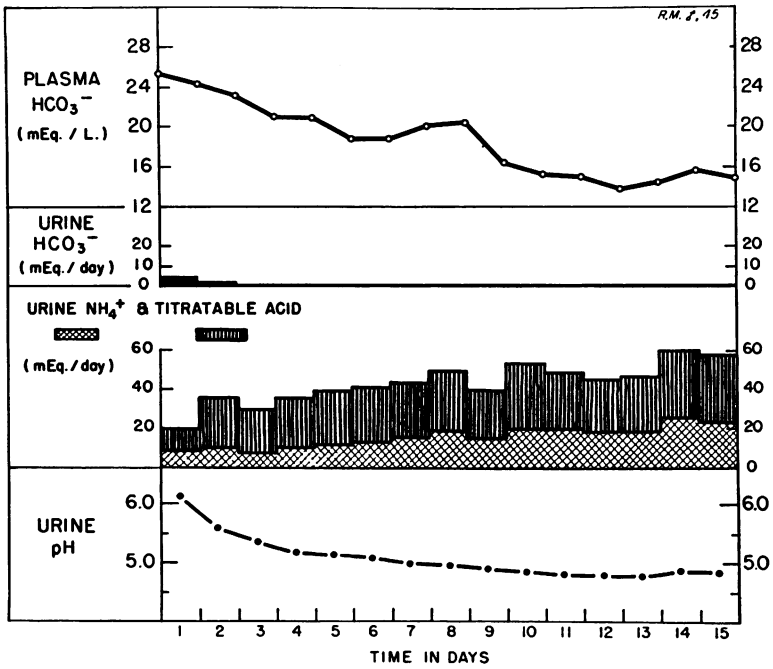

FIG. 4. PLASMA BICARBONATE CONCENTRATION, URINE pH AND DAILY EXCRETION OF BICARBONATE, AMMONIUM AND TITRATABLE ACID IN PATIENT R.M.

Observations began the day after acidosis had been corrected and treatment with alkali had been stopped.

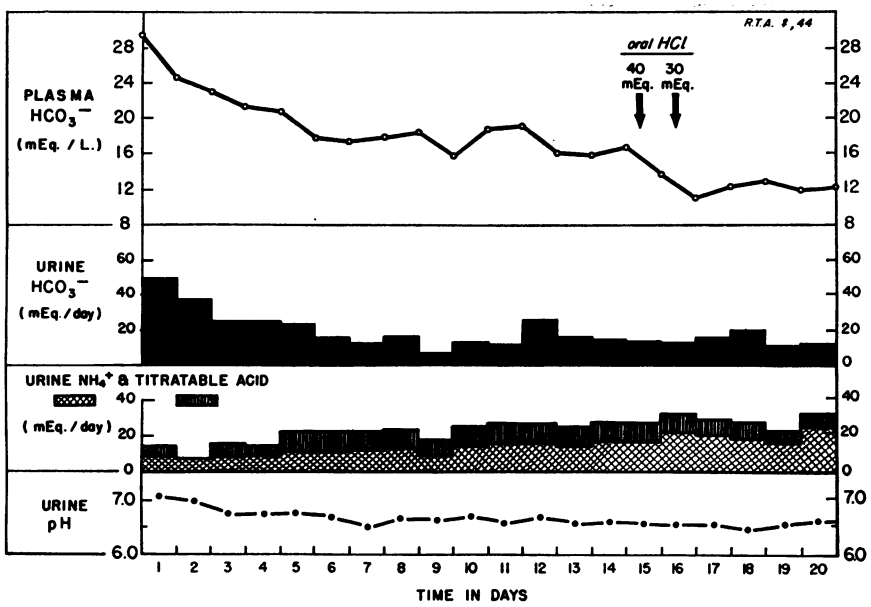

FIG. 5. PLASMA BICARBONATE CONCENTRATION, URINE pH AND DAILY EXCRETION OF BICARBONATE, AMMONIUM AND TITRATABLE ACID IN PATIENT R.T.A.

Observations began the day after acidosis had been corrected and treatment with alkali had been stopped.

TABLE I

Electrolyte balances: Patient P. D.

Day	Body wgt.	Intake					Urine									
		H_2O	Na	K	Cl	N	Vol.	pH	HCO_3	T. A.	NH_4	Na	K	Cl	P	N
	Kg.	*ml./ day*	*mEq./ day*	*mEq./ day*	*mEq./ day*	*Gm./ day*	*ml.*		*mEq./ day*	*mEq./ day*	*mEq./ day*	*mEq./ day*	*mEq./ day*	*mEq./ day*	*mM/ day*	*Gm./ day*
							First study									
1	64.78	2,000	9	50	13	8.2	2,170	7.56	85	0	2	138	53	27	20	7.4
2	64.23	2,000	9	50	13	8.2	2,568	7.45	60	0	12	112	63	26	23	8.7
3	63.71	2,000	9	50	13	8.2	2,247	7.15	36	2	9	68	62	17	21	8.1
4	63.26	2,000	9	50	13	8.2	2,206	7.00	22	4	5	46	60	12	20	8.2
5	63.00	2,000	9	50	13	8.2	2,213	6.80	13	8	4	40	55	14	20	8.2
6	62.73	2,000	9	50	13	8.2	2,267	6.60	9	10	6	35	55	13	22	8.8
7	62.21	2,000	9	50	13	8.2	2,074	6.35	5	7	4	29	51	13	20	8.7
8	62.00	2,000	9	50	13	8.2	1,870	6.30	3	11	5	24	47	11	18	8.2
9	62.03	2,000	9	50	13	8.2	2,248	6.25	3	12	6	30	52	15	19	9.2
10	61.57															
							Second study									
1	61.29	2,000	9	50	13	8.2	1,745	6.10	4	9	4	49	24	37	10	5.4
2	61.38	2,000	9	50	13	8.2	2,075	6.25	4	9	8	43	28	31	11	5.8
3	61.11	2,000	9	50	13	8.2	2,097	6.25	3	8	4	38	30	27	11	5.7
4	60.87	2,000	9	50	13	8.2	2,140	6.20	3	11	15	36	33	25	13	6.0
5*	60.78	2,000	9	50	83	9.2	2,135	5.75	1	8	8	34	37	31	12	6.7
6†	60.38	2,000	9	50	67	9.0	1,683	5.55	1	13	6	23	34	26	10	5.6
7	60.60	2,000	9	50	13	8.2	2,001	5.60	1	13	6	27	38	31	12	6.2
8	60.47	2,000	9	50	13	8.2	2,123	5.60	1	13	7	30	39	33	12	6.6
9	60.17	2,000	9	50	13	8.2	1,788	5.60	1	13	6	23	36	25	12	6.1
10	60.03	2,000	9	50	13	8.2	1,825	5.55	1	13	5	25	35	26	13	6.4
11	59.63															

* 70 mm. NH_4Cl administered intravenously.
† 54 mm. NH_4Cl administered intravenously.

TABLE I—*Continued*

Day	Body wgt.	Stool Na	Stool K	Stool Cl	Stool N	Plasma pH	Plasma HCO_3	Plasma Na	Plasma K	Plasma Cl	Plasma P	Plasma Creat.
	Kg.	*mEq./day*	*mEq./day*	*mEq./day*	*Gm./day*		*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg. %*	*mg. %*
						First study						
1	64.78	1	12	2	1.1	7.46	27.9	143		95		10.8
2	64.23	1	12	2	1.1	7.33	22.6	140	5.2	97		
3	63.71	1	12	2	1.1	7.32	20.3	136	5.1	97		
4	63.26	1	12	2	1.1	7.30	17.9	138	5.2	97		
5	63.00	1	12	2	1.1	7.29	16.3	135	5.1	98		
6	62.73	1	12	2	1.1	7.29	15.7	135	4.8	97		
7	62.21	1	12	2	1.1	7.22	14.6	140	4.6	98		9.2
8	62.00	1	12	2	1.1	7.29	14.6	133	4.7	96	12.0	
9	62.03	1	12	2	1.1	7.25	14.7	143	4.9	92		
10	61.57					7.23	13.3	133	4.7	100		
						Second study						
1	61.29	1	10	2	1.1	7.25	15.0	139	3.7	106	7.8	8.3
2	61.38	1	10	2	1.1	7.26	15.0	142	4.3	105		
3	61.11	1	10	2	1.1	7.29	14.9	137	4.0	103	7.1	
4	60.87	1	10	2	1.1	7.28	15.6	141	4.3	102		
5*	60.78	1	10	2	1.1	7.26	15.1	138	4.4	103	5.7	
6†	60.38	1	10	2	1.1	7.20	11.0	140	4.7	108		
7	60.60	1	10	2	1.1	7.15	9.8	138	5.3	110	8.4	9.5
8	60.47	1	10	2	1.1	7.16	10.1	133	5.0	110		
9	60.17	1	10	2	1.1	7.19	10.1	135	5.0	111		
10	60.03	1	10	2	1.1	7.17	9.7	131	5.3			
11	59.63					7.16	9.4	131	4.6	103	8.9	

tient will be referred to as R.T.A.) Prior to study, all patients demonstrated a persistently low plasma bicarbonate concentration, ranging between 13 and 18 mEq. per L. At the time of study none of the patients had active infection except R.T.A. She was continuously maintained on 1 Gm. of chloramphenicol during the experimental period and usually had bacterial counts of less than 1,000 colonies per ml. in clean voided urine specimens.

Plan of study. Before starting the balance study, plasma bicarbonate was raised to between 25 and 29 mEq. per L. over a two to three day period by the administration of sodium bicarbonate intravenously and by mouth. Bicarbonate administration was then stopped and the patient placed on a constant weighed diet. In four experiments the sodium content of the diet was low (7 to 12 mEq. per day), and in the fifth (R.M.) it was normal.

TABLE II

Electrolyte balances: Patient R. M.

Day	Body wgt.	Intake H_2O	Intake Na	Intake K	Intake Cl	Intake N	Urine Vol.	Urine pH	Urine HCO_3	Urine T.A.	Urine NH_4	Urine Na	Urine K	Urine Cl	Urine P	Urine N
	Kg.	*ml./day*	*mEq./day*	*mEq./day*	*mEq./day*	*Gm./day*	*ml.*		*mEq./day*	*mEq./day*	*mEq./day*	*mEq./day*	*mEq./day*	*mEq./day*	*mM/day*	*Gm./day*
1		2,480	52	65	55	14	2,840	6.10	4	11	9	191	64	122	22	15.9
2	72.32	2,480	52	65	55	14	2,140	5.60	1	26	10	115	67	69	19	13.1
3	72.13	1,980	52	65	55	14	1,680	5.35	1	22	8	60	61	47	16	10.6
4	72.39	2,480	52	65	55	14	1,960	5.15	1	25	11	71	75	45	20	12.7
5	72.58	2,480	52	65	55	14	2,150	5.10	1	28	12	71	80	47	21	13.3
6	72.36	2,480	52	65	55	14	2,180	5.05	1	28	14	65	72	41	20	12.6
7	72.27	2,480	52	65	55	14	2,530	4.95	1	28	16	68	78	48	23	14.4
8	71.88	2,480	52	65	55	14	2,520	4.95	1	30	19	62	76	43	24	13.9
9	71.69	2,480	52	65	55	14	1,820	4.90	1	24	16	41	58	31	17	10.6
10	71.20	2,480	52	65	55	14	2,650	4.85	1	34	20	56	74	45	23	14.0
11	70.99	2,480	86	65	89	14	2,195	4.80	1	29	20	42	70	35	20	12.7
12	71.13	2,480	153	65	156	14	2,088	4.80	1	27	19	59	61	52	19	11.9
13	71.46	2,680	153	65	156	14	2,188	4.80	1	28	19	77	61	70	18	12.5
14	71.63	2,480	153	65	156	14	2,840	4.85	1	35	25	127	81	116	25	17.6
15	71.43	2,480	149*	63*	137*	14	2,580	4.85	1	34	24	134	67	121	20	15.5
16	70.53															

* Intake figures corrected for rejected diet.

TABLE II—*Continued*

Day	Body wgt.	Stool				Plasma						
		Na	K	Cl	N	pH	HCO_3	Na	K	Cl	P	Creat.
	Kg.	*mEq./ day*	*mEq./ day*	*mEq./ day*	*Gm./ day*		*mEq./ L.*	*mEq./ L.*	*mEq./ L.*	*mEq./ L.*	*mg. %*	*mg. %*
1		3	9	4	1.1	7.51	25.7	146	4.4			
2	72.32	3	9	4	1.1	7.40	24.3	146	4.5	99	8.2	
3	72.13	3	9	4	1.1	7.31	23.1	144	4.4	96	8.8	
4	72.39	3	9	4	1.1	7.33	21.2	140	4.6	96	9.4	
5	72.58	3	9	4	1.1	7.33	20.8	137	4.3	96	9.5	9.8
6	72.36	3	9	4	1.1	7.32	18.9	145	4.4	97	9.9	
7	72.27	3	9	4	1.1	7.26	18.8	137	4.2	97	9.8	
8	71.88	3	9	4	1.1	7.32	20.0	136	4.2	95	10.3	
9	71.69	3	9	4	1.1	7.31	20.5	136	4.2	96	10.4	
10	71.20	3	9	4	1.1	7.32	16.3	136	3.9	93	10.7	12.6
11	70.99	3	9	4	1.1	7.29	15.2	136	4.0	95	9.8	
12	71.13	3	9	4	1.1	7.28	14.9	139	4.0	97	9.9	
13	71.46	3	9	4	1.1	7.25	13.8	139	4.1	101	9.9	11.1
14	71.63	3	9	4	1.1	7.25	14.5	141	4.2	102	9.5	
15	71.43	3	9	4	1.1	7.29	15.7	140	4.2	103	8.4	
16	70.53	3	9	4	1.1	7.26	14.7	140	4.2	104	8.5	

In all other respects the diet was normal in composition. Balances were corrected for vomitus and rejected foods, which were always analyzed. In some instances ammonium chloride or hydrochloric acid was given for two days during the latter part of the study. In two patients supplementary salt was given for several days. Water intake was set at a level selected by the patients and maintained constant thereafter. Urines were placed under oil and refrigerated immediately after voiding. Saturated thymol and chloroform was used as a preservative.

The analytic procedures and the methods used in calculation of results, as well as other details of the balance technique, have been described in a previous paper (14).

RESULTS

Figures 1 to 5 show plasma bicarbonate concentration and the acid-base composition of the urine in all five patients. The complete balance data for Patients P.D., R.M. and R.T.A. are presented in Tables I to III.

Plasma composition

Bicarbonate and pH. During the first few days plasma bicarbonate concentration fell relatively rapidly in all patients to levels between 15 and 20 mEq. per L. In three (P.D., D.H. and R.T.A.) the plasma concentration appeared to reach a plateau within a week, while in two (H.G. and R.M.) there was a further slow decline of about 5 mEq. per L. over the next seven to 10 days.

Administration of HCl or NH_4Cl (P.D., D.H. and R.T.A.) over a two day period was followed by a fall in plasma bicarbonate of 5 to 6 mEq. per L. to final levels of between 10 and 13 mEq. per L. In two of the three patients (P.D. and R.T.A.) plasma bicarbonate concentrations remained at the new low level. In the third patient (D.H.) there was a rise of approximately 6 mEq. per L. over the next six days, restoring the plasma bicarbonate concentration to the level which had obtained prior to the administration of ammonium chloride. As shown in Tables I to III, plasma pH tended to fall as plasma bicarbonate concentration was reduced.

Sodium, potassium, chloride and phosphorus. Serum sodium, potassium, chloride and phosphorus concentrations showed only minor changes during the course of the study in four of the patients. In the fifth (R.T.A.), there was a gradual fall in sodium concentration from an initial value of 146 mEq. per L. to final levels of 124 mEq. per L., but chloride, potassium and phosphorus did not change significantly (Table III).

Plasma creatinine. Plasma creatinine concentration was elevated to between 8 to 13 mg. per cent in P.D., D.H., H.G. and R.M. There was no significant change during the course of each study. In R.T.A. plasma creatinine concentration was 1 mg. per cent at the beginning, and 0.9 mg. per cent at the end of the study.

Urine composition

Bicarbonate excretion. Four out of five subjects (Figures 1 to 3 and 5) showed significant urinary excretion of bicarbonate at a time when plasma bicarbonate levels were below 25 mEq.

per L. As plasma bicarbonate fell progressively, there was a stepwise reduction in bicarbonate excretion with the result that within five to seven days bicarbonate had virtually disappeared from the urine in all patients except R.T.A.

The cumulative bicarbonate loss during this phase of rapid excretion was approximately 260 mEq. in P.D., and approximately 75 mEq. in H.G. and D.H.

Patient R.T.A. continued to excrete significant amounts of bicarbonate in her urine (averaging 10 to 20 mEq. per day) throughout the entire study. There was no reduction in bicarbonate excretion following the administration of hydrochloric acid.

Urine pH. Urine pH fell progressively in all patients except R.T.A. as metabolic acidosis became more severe. Final pH values of 4.8 to 5.5 were attained in P.D., D.H., H.G. and R.M. The most abrupt fall in urine pH followed the administration of ammonium chloride to P.D. and D.H.

R.T.A., despite the administration of hydrochloric acid and a drop of plasma bicarbonate to 12 mEq. per L., achieved a minimal urine pH of only 6.5.

Titratable acid. In all patients excretion of titratable acid increased progressively during the initial five to 10 days of the study. The maximum value ranged between 11 to 34 mEq. per day with an average of 18 mEq. per day. In all patients except R.T.A., titratable acid accounted for approximately two-thirds of the total acid excretion throughout the period of study.

The administration of ammonium chloride produced a significant increase in titratable acid excretion in Patient D.H., with a rise from 11 to 29 mEq. per day as urine pH fell from 6.4 to 5.0. In P.D., a fall in urine pH from 6.2 to 5.6 was unaccompanied by a significant change in titratable acid. In R.T.A., whose urine pH was unaffected by acid administration, titratable acid excretion remained constant.

Ammonium excretion. All patients showed a marked limitation of ammonium excretion during the spontaneous development of acidosis, and following the administration of acid. The maximum ammonium excretions observed ranged from

TABLE III

Electrolyte balances: Patient R. T. A.

Day	Body wgt.	Intake					Urine									
		H_2O	Na	K	Cl	N	Vol.	pH	HCO_3	T.A.	NH_4	Na	K	Cl	P	N
	Kg.	*ml./day*	*mEq./day*	*mEq./day*	*mEq./day*	*Gm./day*	*ml.*		*mEq./day*	*mEq./day*	*mEq./day*	*mEq./day*	*mEq./day*	*mEq./day*	*mM/day*	*Gm./day*
1	42.82	5,720	7	47	10	6.2	5,765	7.05	50	6	9	108	31	37	17	6.9
2	42.15	5,720	7	47	10	6.2	5,530	6.95	38	0	8	87	37	33	18	7.7
3	41.54	5,720	7	47	10	6.2	5,605	6.75	25	7	9	57	35	25	15	6.7
4	41.05	5,720	7	47	10	6.2	5,375	6.70	25	5	10	41	46	18	18	7.0
5	41.03	5,720	7	47	10	6.2	5,500	6.75	24	11	12	33	49	15	21	7.2
6	40.69	5,720	7	47	10	6.2	4,960	6.70	16	11	12	24	51	14	21	6.9
7	40.83	5,720	7	47	10	6.2	4,940	6.50	13	10	13	16	51	11	18	6.9
8	40.93	5,720	7	47	10	6.2	5,720	6.65	17	10	14	17	55	11	21	7.7
9*	40.33	3,245	6†	32†	9†	5.2†	2,308	6.60	7	8	10	9	38	7	15	5.3
10	40.00	4,940	7	47	10	6.2	4,300	6.70	13	11	15	11	51	9	20	7.7
11	40.14	5,720	7	47	10	6.2	5,000	6.55	12	11	16	12	51	8	20	7.5
12	40.35	5,720	7	47	10	6.2	5,600	6.70	26	11	16	17	52	9	19	7.6
13	39.90	5,720	7	47	10	6.2	4,970	6.60	16	11	15	11	50	7	17	7.0
14	40.02	5,720	7	47	10	6.2	5,260	6.60	15	11	17	11	51	6	18	7.4
15‡	39.90	5,720	7	47	50	6.2	5,350	6.60	14	11	17	11	53	7	20	7.5
16§	39.51	5,720	7	47	40	6.2	5,400	6.55	13	11	22	10	49	9	19	7.0
17	39.14	5,720	7	47	10	6.2	4,940	6.55	16	9	21	9	51	10	18	6.9
18	39.20	5,720	7	47	10	6.2	5,300	6.50	20	9	19	8	49	7	19	7.4
19	38.93	5,720	7	47	10	6.2	4,720	6.55	11	7	16	8	45	8	16	6.8
20	39.31	5,720	7	47	10	6.2	5,130	6.65	12	8	25	9	50	9	19	7.7
21	39.13															

* On this day patient vomited 2 L. of fluid containing 4 mEq. of Na, 12 mEq. of K, 28 mEq. of Cl, and 2 Gm. of nitrogen.

† Intake figures corrected for rejected diet.

‡ 40 mEq. HCl given in drinking water.

§ 30 mEq. HCl given in drinking water.

TABLE III—*Continued*

Day	Body wgt.	Stool				Plasma						
		Na	K	Cl	N	pH	HCO_3	Na	K	Cl	P	Creat.
	Kg.	*mEq./day*	*mEq./day*	*mEq./day*	*Gm./day*		*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg. %*	*mg. %*
1	42.82	1	2	1	0.4	7.41	29.3	146	3.4	105	2.6	1.0
2	42.15	1	2	1	0.4	7.39	24.9					
3	41.54	1	2	1	0.4	7.40	23.2	143	3.8	111	3.2	
4	41.05	1	2	1	0.4	7.31	21.7					
5	41.03	1	2	1	0.4	7.32	21.2					
6	40.69	1	2	1	0.2	7.32	18.0	139	3.9	110	4.2	
7	40.83	1	2	1	0.2	7.32	17.7					
8	40.93	1	2	1	0.2	7.33	18.2	133	4.4	104	3.9	
9*	40.33	1	2	1	0.2	7.32	18.6					
10	40.00	1	2	1	0.2	7.31	15.9	134	5.2	104		
11	40.14	1	2	1	0.2			130	3.8	101	3.5	
12	40.35	1	2	1	0.2	7.32	19.3					
13	39.90	1	2	1	0.2	7.27	16.2	129	3.4	100	4.1	
14	40.02	1	2	1	0.2	7.35	16.0	129	3.7	100	3.4	
15‡	39.90	1	2	1	0.2	7.30	16.8	127	3.7	100		
16§	39.51	1	2	1	0.2	7.32	13.9	127	3.7	101		
17	39.14	1	2	1	0.2	7.26	11.2	128	3.7	104	3.5	
18	39.20	1	2	1	0.2	7.25	12.3	126	3.4	108	3.4	
19	38.93	1	2	1	0.2	7.28	13.0	126	3.5	108	3.4	
20	39.31	1	2	1	0.2	7.25	11.9	124	3.7	105	3.4	
21	39.13					7.30	12.2	124	3.5	105		0.9

8 to 25 mEq. per day, the average being 12 mEq. per day. In all patients except P.D., there was a slight tendency for ammonium excretion to increase as the urine pH fell.

Phosphorus. Phosphorus excretion in the entire group ranged from 10 to 24 mM per day. In the course of any single study, there was no significant change in phosphorus excretion either during the spontaneous development of acidosis or after administration of acid or sodium chloride.

Sodium excretion. Figure 6 shows the daily urinary sodium excretion for Patients P.D., D.H., H.G. and R.T.A., all of whom had a sodium intake of 7 to 12 mEq. per day. The level of the cross-hatched area at the bottom represents the average sodium intake of 9 mEq. per day. It is apparent that initially sodium excretion significantly exceeded intake but decreased rapidly towards intake values within the first week. However, in two subjects, P.D. and H.G., there was a continued excretion of sodium in excess of intake. The irregular line connecting Days 9 and 10 in P.D. signifies the actual passage of seven days during which time the balance study was interrupted because of vomiting. The patient was given approximately 100 mEq. of extra sodium each day during this interval, but was put back on an intake of 9 mEq. of sodium when the balance was resumed. It is clear, however, that in P.D., as well as in H.G., renal conservation of sodium was defective. In the other two subjects, sodium excretion slowly dropped to levels virtually equal to the intake. Stool sodium losses were negligible, but in view of the unmeasured skin losses of sodium, a continued urinary excretion of even 8 to 10 mEq. per day probably represented a net negative balance. Furthermore, during this period serum sodium in R.T.A. had fallen to 124 mEq. per L. (Table III).

R.M., whose sodium intake was 52 mEq. per day during the first 10 days of study, had a slight but persistent excess of sodium in his urine during the last few days of this period. When supplementary salt was given in the latter part of the study, the sodium balance became positive.

Chloride. Urinary chloride excretion exceeded intake during the first five to seven days after the patients were placed on a low-salt diet, but subsequently excretion and intake were virtually equal. R.M., whose chloride intake was 55 mEq. per day during most of his study, also excreted chloride in amounts approximately equal to his dietary intake.

Following administration of HCl or NH_4Cl (P.D., D.H. and R.T.A.) there was no increase in chloride excretion despite a rise in serum chloride concentration to between 108 and 111 mEq. per L.

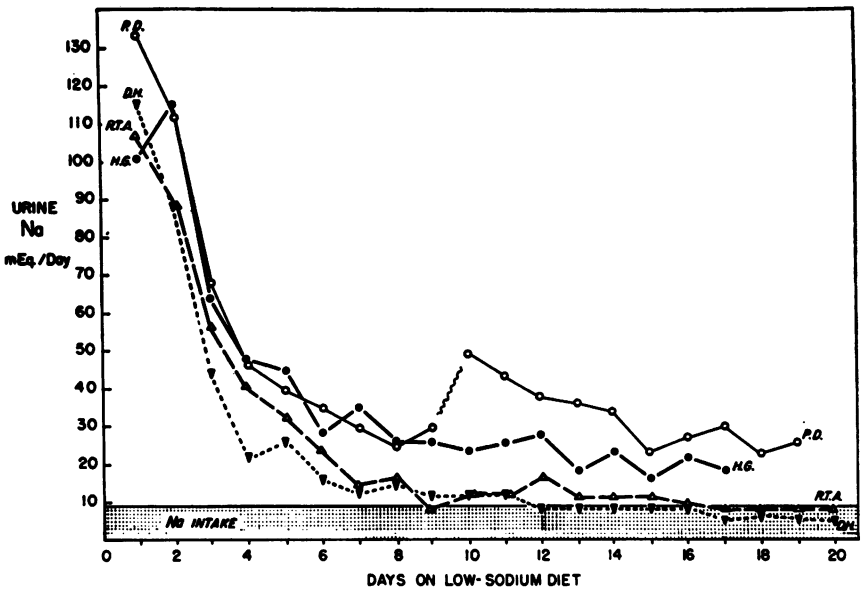

FIG. 6. DAILY EXCRETION OF SODIUM IN FOUR PATIENTS WITH RENAL DISEASE AND ACIDOSIS, THREE WITH UREMIA AND ONE (R.T.A.) WITH RENAL TUBULAR ACIDOSIS

The observations began the day after acidosis had been corrected and treatment with sodium bicarbonate had been stopped. The height of the cross-hatched area at the bottom indicates the average sodium intake of the four patients (range, 7 to 12 mEq. per day). The irregular line joining Days 9 and 10 for Patient P.D. indicates an interruption of seven days (see text).

Potassium. Patients P.D. (second study), D.H., H.G. and R.T.A. excreted potassium in amounts approximately equal to their intake, and there was little or no cumulative negative potassium balance during the course of study. R.M. and P.D. (first study) showed a urinary excretion of potassium consistently greater than intake, and cumulative negative potassium balances of 194 and 147 mEq., respectively. When potassium balance was corrected (N × 2.7 mEq.) for the small negative nitrogen balance observed in each of these two subjects, the cumulative balance values were 180 and 116 mEq., respectively.

Stool electrolytes. Stool electrolyte content for the group as a whole was as follows: sodium, 1 to 3 mEq. per day; potassium, 2 to 12 mEq. per day; chloride, 1 to 4 mEq. per day.

DISCUSSION

The defect in bicarbonate conservation found in three of the four patients with uremic acidosis is noteworthy, in view of the scant attention accorded this problem in the past. It is recognized that patients with renal tubular acidosis and the Fanconi syndrome may show an inappropriate excretion of bicarbonate at subnormal plasma concentrations (11–13), and a similar defect has recently been described in the tubular nephropathy associated with Wilson's disease (15). However, this has been considered an abnormality confined essentially to the tubular nephropathies. Only one patient with uremia has been reported who seemed to waste bicarbonate (9), and Roberts, Randall, Vanamee and Poppell found no evidence of impaired reabsorption of bicarbonate in chronic renal insufficiency (10) when they acutely loaded such patients with alkali.

The difference between the present observations and those of most previous workers can probably be accounted for by several factors. In the first place, since patients with degenerative renal disease and bicarbonate-wasting may elaborate an acid urine virtually free of bicarbonate when the plasma bicarbonate is at or below the new

threshold level, the existence of the defect could readily be overlooked. Bicarbonate-wasting would not be evident unless such patients were receiving alkali. Secondly, it seems likely that many patients with uremia and acidosis do *not* have a bicarbonate-wasting defect. Of the group of four patients with uremic acidosis reported here in detail, all but R.M were found to have some significant degree of bicarbonate-wasting. However, of an additional group of eight acidotic, uremic patients studied without complete balances, only two were found to excrete significant quantities of bicarbonate after plasma levels had dropped below 24 mEq. per L. (16). Thus, of a total of 12 patients, bicarbonate-wasting was found in only five, and it is clear that the defect is often absent in uremic acidosis.

In the acute studies of Roberts and associates (10) mentioned above, difficulties inherent in the accurate measurement of very low filtration rates may have introduced methodologic uncertainties which would make the calculation of bicarbonate reabsorption subject to significant error. Finally, as will be pointed out below, it is possible that in acidotic patients with bicarbonate-wasting, loading with bicarbonate may of itself raise the apparent threshold and may, therefore, give higher values than those observed during acidosis.

The present study does not elucidate the mechanism leading to defective conservation of bicarbonate, but a possible explanation may be suggested. Renal disease may reduce carbonic anhydrase activity in tubular cells to the point at which the enzymatic reaction becomes the rate-limiting step in the process of reabsorption (17). The situation may be comparable to that which occurs when carbonic anhydrase is partially inhibited by chronic administration of acetazoleamide (18, 19). Under these conditions, plasma bicarbonate level falls until a new balance is attained between available enzyme activity and the filtered load of bicarbonate. However, it has been shown in acute studies (17) that the rate of reabsorption during partial inhibition of carbonic anhydrase is a direct curvilinear function of the plasma bicarbonate level, possibly reflecting a Michaelis-Menten relationship between enzyme activity and substrate concentration (17). Thus, in the experiments of Roberts and co-workers (10) loading with bicarbonate might well have accelerated the rate of reabsorption and masked a lowered renal threshold.

The bicarbonate-wasting defect apparently plays a dual role in the genesis of the acidosis in these uremic patients. The excretion of bicarbonate in the urine, in the first place, represents a direct loss of alkali from body fluids and so leads to acidosis. In P.D., in whom the defect was severe, a total of approximately 260 mEq. of alkali was excreted in the first seven days, prior to establishment of acid-base equilibrium. Distributed through a volume estimated as 40 per cent of total body weight, such an alkali deficit would be expected to lower plasma bicarbonate by approximately 10 mEq. per L. Since the observed drop in plasma level during this time was 13 mEq. per L., it is clear that in this patient loss of bicarbonate in the urine contributed the major share in the development of acidosis. Similar calculations for Patients D.H. and H.G., in whom cumulative losses of bicarbonate were approximately 75 mEq., indicate that excretion of alkali probably accounted for approximately half of the observed fall in plasma bicarbonate.

Bicarbonate-wasting, however, has another important influence on the genesis of uremic acidosis. Impairment of bicarbonate reabsorption would result in persistence of an alkaline fluid in the distal part of the nephron where ammonium and titratable acid normally appear. Thus, in addition to producing alkali loss, bicarbonate-wasting, by limiting the output of ammonium and titratable acid, contributes to acidosis by reducing the renal excretion of hydrogen. It is to be noted, in each of the first three figures, that acid excretion was suppressed during the early bicarbonate-wasting phase of each balance. In R.M. (Table II and Figure 4) there was essentially no bicarbonate loss and hence no direct contribution by this factor to the development of acidosis. However, as will be pointed out below, he, as well as all the other uremic patients, showed an abnormal lag in acidification of the urine which contributed to the delay in achieving acid-base equilibrium.

That patients with uremia and acidosis can ultimately acidify their urine had been noted by earlier workers (2, 3) and has recently been confirmed (20). In the present group minimal pH

values of 4.8 to 5.5 eventually were achieved. Since the major urinary buffer is phosphate (pK' approximately 6.8), it follows that in urines of this acidity excretion of titratable acid must be nearly maximal. It would appear, however, that uremic patients require a more severe degree of acidosis to achieve this level of urine acidity than do normal subjects given ammonium chloride. In all the uremic patients, the lowest urine pH was achieved only after plasma bicarbonate levels had been depressed, spontaneously or with acid loads, to concentrations of 10 to 15 mEq. per L. (In the bicarbonate-wasting patients minimal urine pH did not develop until plasma levels were below those at which overt wasting had ceased.) By contrast, normal subjects loaded with NH_4Cl produce urine of comparable acidity when their plasma bicarbonate concentrations are in the range of 20 to 25 mEq. per L. (4, 21, 22).

A delay in acidification of the urine was apparently the major factor preventing Patient R.M. from initially excreting the maximal ammonia and titratable acid of which he was capable. The cumulative deficiency in the net excretion of acid (ammonia plus titratable acid) during the first 13 days of his balance (Figure 4), as compared to the average acid excretion on the last two days, amounted to 257 mEq. This is approximately two-thirds of the total amount calculated to be necessary to produce the observed drop in plasma bicarbonate during the first 13 days. Inefficiency in the acidifying process, with consequent delays in achievement of maximal excretion of titratable acid and ammonia, may well have been largely responsible for the development of acidosis in the other uremic patients who did not have any overt bicarbonate-wasting defect.

It should be emphasized, however, that all uremic patients appear to have an underlying defect in ammonium excretion, an abnormality which has long been recognized (2–7). Despite the progressive acidity of the blood and urine in these patients, excretion of ammonium rose only slightly. The present data emphasize the fact that this defect in ammonium excretion cannot be attributed to an unfavorable pH gradient for the accumulation of ammonium in the distal tubule. While the reduction in ammonium excretion may be the result of specific tubular dysfunction, it is equally possible that it is simply the consequence of the loss of tubular mass or of a critical reduction in tubular blood supply which limits the availability of substrate or the removal of by-products.

As a result of the impairment of ammonium excretion, this moiety constitutes only a third or less of the total acid excretion in the four patients with uremia (Figures 1 to 4). In normal subjects, by contrast, ammonium is usually one and one-half to two times the excretion of titratable acid, and in severe metabolic acidosis, ordinarily constitutes more than three-quarters of the total acid excretion.

With the development of acidosis and reduction of urine pH to relatively low levels, it can be assumed that the uremic patients are excreting acid at close to their maximal rates. It is clear that under these circumstances they are at the mercy of whatever additional exogenous or endogenous acid loads may be imposed. Thus, for example, when the plasma bicarbonate level was acutely reduced from 15 to 10 mEq. per L. in P.D. (Figure 1) acid excretion did not rise significantly and bicarbonate concentration remained fixed at this new low level for the next four days. Actually, as shown in Table I and Figure 1, there was a further reduction in urine pH (from 6.20 to 5.55) but, because the control pH was already well below the pK' of phosphate, the increment in titratable acid was negligible. In Patient D.H. (Figure 2), it is not clear whether urine pH and plasma bicarbonate had reached their spontaneous minima prior to administration of the ammonium chloride load. However, in this case a reduction in urine pH from 6.5 to 5.2 was enough to permit a small, though appreciable, increase in excretion of titratable acid and ammonium. This produced a slow restitution of plasma bicarbonate level to its preloading concentration. The response, though ultimately effective, was clearly less than normal. Had still more acid been superimposed upon the rather modest load administered, it is quite likely that no further renal adjustments would have been possible, since the urine was now almost maximally acid.

Are these patients in acid-base equilibrium when their plasma bicarbonate concentrations have stabilized at lower than normal levels?

Since there is no method of computing the total hydrogen ion load, it is difficult to be certain whether renal acid excretion actually accounted for total hydrogen production. It is possible that slow, continuous titration of bone buffers as a result of a reduction in extracellular pH may have contributed to the stabilization of the plasma bicarbonate concentration. This appears to be the case in patients with renal tubular acidosis where there is much evidence to suggest the continuous gradual dissolution of bone salts (23), but whether this also occurs in uremic acidosis has not been clearly established. Analysis of bone in adults dying of uremia has so far failed to indicate significant changes in cation content (24), despite the fact that osteomalacia and demineralization of bone are occasionally quite apparent in chronic uremia (25). The role of bone buffers in the stabilization of extracellular pH in uremic acidosis therefore remains to be elucidated.

The observations on the patient with renal tubular acidosis (R.T.A., Figure 5 and Table III) have been reserved for separate consideration because the tubular defects in this condition appear to be characteristic and in part distinguishable from those found in patients with uremic acidosis. Previous workers have noted that in renal tubular acidosis there is a defect in acidification of the urine (8) as well as a tendency to waste significant amounts of bicarbonate at subnormal plasma concentrations (11–13). These two defects are well illustrated in Patient R.T.A., who excreted a total of 162 mEq. of bicarbonate during the first five days of the study, as her plasma level fell from 29 to 18 mEq. per L. Thereafter she continued to excrete an average of 15 mEq. per day and her urine pH never dropped below 6.5, even when the plasma bicarbonate was further depressed to 12 mEq. per L. by oral administration of HCl. In another adult with typical renal tubular acidosis and nephrocalcinosis similar observations have been made, but without benefit of balance studies (16). In this latter patient a total of 68 mEq. of bicarbonate was excreted over three days as the plasma level fell from 26 mEq. per L. to 16 mEq. per L. following withdrawal of alkali. Thereafter, with the plasma level remaining steady, this patient continued to excrete approximately 10 mEq. of bicarbonate per day in a urine of pH 6.4 to 6.7.

Although excretion of titratable acid was low, both patients were able to excrete normal amounts of ammonium relative to urine pH (13, 20). This pattern contrasts with that found in uremic acidosis where, under the proper stimulus, maximal excretion of titratable acid will occur, but ammonium excretion is persistently low. In both types of renal disease, however, bicarbonate-wasting may be a significant factor in the genesis of the acidosis. Thus, while the exact defects in these two disorders may vary, their general nature is the same, and consists essentially of a disturbance in acid (hydrogen) excretion or bicarbonate reabsorption, or both. Since these are entirely tubular functions, both types of acidosis should properly be considered as "tubular" in origin. A possible explanation for the difference in plasma anion pattern between uremic acidosis and renal tubular acidosis has been presented elsewhere (1).

Since reabsorption of bicarbonate is thought to involve sodium-hydrogen exchange, it is of interest to consider how the renal conservation of sodium in these patients might be related to their renal handling of bicarbonate. It is reasonable to assume that a part of the initial excretion of sodium during the first few days of sodium and bicarbonate withdrawal was directly linked with the bicarbonate-wasting (Figure 6). In Patients D.H. and R.T.A. sodium excretion dropped to very low values as the bicarbonate-wasting phase ended. In P.D. and H.G., however, significant wasting of sodium continued long after bicarbonate had virtually disappeared from the urine. It is therefore apparent that sodium-wasting does not require simultaneous loss of bicarbonate.

SUMMARY

In an effort to define the mechanisms responsible for the development of acidosis in patients with chronic renal failure, balance studies have been carried out in four patients with uremic acidosis and in one with renal tubular acidosis. Each study began with the restoration of the plasma bicarbonate concentration to normal by administration of sodium bicarbonate. Thereafter, no alkali was given and the patients were allowed to develop acidosis spontaneously. In

some cases challenging loads of acid were administered after the patients had reached subnormal but steady plasma bicarbonate concentrations.

During the phase of developing acidosis, three of the four patients with uremia were found to excrete significant quantities of bicarbonate in their urine even after plasma levels had fallen well below normal. Bicarbonate excretion virtually ceased only when plasma concentration had reached 15 to 20 mEq. per L. This loss of alkali in the urine accounted for most of the initial rapid reduction in plasma level in one patient, and approximately half of the drop in the other two. The bicarbonate-wasting defect was not present in the fourth uremic subject nor in the majority of other uremic patients studied less completely.

The other factor apparently responsible for the development of acidosis was a suppression of the excretion of ammonium and titratable acid, which appeared to be due in part to the relative alkalinity of the urine during the bicarbonate-wasting phase. There was, in addition, a delay in the acidification of the urine which occurred even when bicarbonate-wasting was absent or had ceased. However, each of the uremic patients, when severely acidotic, was ultimately able to lower urine pH below 5.5 and therefore to excrete nearly maximal amounts of titratable acid. Even in the most acid urines ammonium excretion increased only slightly. Most of the renal excretion of acid responsible for the maintenance of a low but steady plasma bicarbonate level was therefore accounted for by titratable acid. Two of these patients were unable to excrete any significant part of additional challenging loads of acid since titratable acid and ammonium were already nearly maximal.

The patient with renal tubular acidosis not only wasted bicarbonate in the urine, but also continued to excrete an alkaline urine even at low plasma bicarbonate levels. In this patient, ammonium excretion was not significantly reduced relative to urine pH and therefore accounted for most of the excretion of hydrogen in the steady state.

It is concluded that in patients with acidosis due to renal disease, defects in the tubular reabsorption of alkali or in tubular excretion of hydrogen, or both, are at fault. The relative importance of these disorders may vary, but in general terms, all renal acidosis is "tubular" acidosis.

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