MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

APRIL 13, 1967

RENAL ACIDOSIS

Case 1. [redacted]

This 42 year old [redacted] man was well until [redacted] of 1965 when he developed a flu-like illness for which he was treated by "penicillin shots". He failed to improve and became progressively weaker, this culminating in his admission to the [redacted] in [redacted] 1966. At that time the patient stated he had been vomiting and had lost about 70 lbs. of weight. He also gave a history of polydypsia, polyuria and nocturia. He was found to be profoundly weak, hypokalemic (serum K^+ = 1.0 mEq/L) and acidotic. The diagnosis of renal tubular acidosis was made and the patient was treated with Shohl's solution and potassium chloride.

He was readmitted to [redacted] in [redacted] 1966 because of pain in the left flank that radiated anteriorly and downward to the left thigh. An extensive work-up at that hospital and at the [redacted] failed to reveal any urinary stones. There was no history of hematuria. The patient was admitted to [redacted] in [redacted] 1966 for further work-up.

PAST HISTORY:

An episode of G. I. bleeding while in the service. Hearing loss in the right ear which he attributed to artillery fire.

PHYSICAL EXAMINATION:

Ht. 5'6", Wt. 147 lbs., B. P. 126/88, P. 76, R. 16.

Except for diminished hearing in the right ear, the physical examination was unremarkable.

LABORATORY FINDINGS:

Hb. 13.3 gm %, WBC 4800/cu mm, Urinalysis: pH 7.0, Sp. Gr. 1.013, Trace Protein, Negative sugar and acetone, 0-4, RBC/HPF, 0-5 WBC/HPF, occasional granular casts. BUN 18 mg %, creatinine 1.8 mg %, FBS 98 mg %, Na 137 mEq/L, K 3.5 mEq/L, Cl 108 mEq/L, CO_2 16 mEq/L, TSP 8.8 gm %, A/G 5.4/3.3 (electrophoresis shows A/G-1.9/1 and gamma-globulins equal to 16%), Ca 9.9 mg %. Audiogram revealed non-functioning right ear. X-rays revealed the absence of nephrocalcinosis or stone shadows.

SPECIAL STUDIES:

1. Na_2SO_4 Infusion (with 9-α fluorohydrocortisone)

	μEq/min					Serum mEq/L		
	pH	NH_4^+	T. A.	HCO_3^-	Net Acid	Na^+	K^+	HCO_3^-
Control	6.6	63	24	5	82	131	4.3	13
After	6.5	78	15	1	92	135	3.7	13

2. NH_4Cl 5-7 gm daily

	Urine mEq/day					Serum mEq/L			
	pH	NH_4^+	T. A.	HCO_3^-	Net Acid	Na^+	K^+	Cl^-	HCO_3^-
Control	6.8	32	8	10	30	140	4.0	116	20
Day 6	6.7	49	18	8	59	137	4.0	121	14

3. Tm HCO_3^- 2.8 mEq/100 ml. A leak of HCO_3^- into the urine was present, however, at serum HCO_3^- levels of as low as 12 mEq/L.

4. The patient was treated with Metahydrin and Potassium Chloride; this regimen resulted in correction of the acidosis and hypokalemia.

Case 2. [redacted]

The history of this 17 year-old [redacted] girl dates back to age 5 months when she was hospitalized for "failure to thrive". She stated that she was small relative to her playmates since, but that she did well until age 12 years when she noted the onset of pain in her knees and hips. In addition, she reported muscular weakness on exercise requiring periods of rest before physical activity could be resumed. The patient also stated that she had polyuria, frequency, nocturia and polydypsia all her life. She was seen by a number of physicians and told to have proteinuria and glycosuria.

On [redacted], 1965, she sustained a spontaneous fracture of her right femur and was admitted to [redacted] where an intramedullary nail was inserted. Bone specimen taken at the time of surgery revealed osteomalacia. Extensive studies at that time revealed the following: renal glycosuria, aminoaciduria, hypouricemia, hypophosphatemia, elevated alkaline phosphatase, hypokalemia and mildly depressed CO_2 combining power. Urine pH varied between 5 and 7.5. Skeletal films revealed loss of the lamina dura, diffuse demineralization and subperiosteal resorption of the phalanges. Multiple rib fractures were also reported. The diagnosis of the Fanconi syndrome was made and the patient transferred to [redacted] for further evaluation.

PHYSICAL EXAMINATION:

Ht. 4'7" (142 cm), Wt. 57 lbs. (26 kg), B. P. 110/80, P. 76, R. 17.

The patient was an underdeveloped and undernourished girl. Otherwise the physical examination was unremarkable.

LABORATORY FINDINGS:

Hb. 11.7 gm %, WBC 10,700/cu mm (normal differential), Platelets 408,000. Urinalysis: pH 5.5, Sp. Gr. 1.024, Protein 100 mg %, Sugar 2+, Acetone: small, 0-1 RBC/HPF, 0-5 WBC/HPF, Hyaline and Granular Casts. BUN 14 mg %, Creatinine 1.0 mg %, FBS 100 mg %, Na 138 mEq/L, K 3.4 mEq/L, Cl 108 mEq/L, CO_2 19 mEq/L, TSP 7.8 gm %, A/G = 5.2/2.6, Ca 9.6 mg %, P. 2.5 mg %, Alkaline Phosphatase 30 B.U. X-ray: resorption of distal ends of clavicles, subperiosteal resorption of symphysis pubis and of the digits.

SPECIAL STUDIES:

1. Na_2SO_4 Infusion (with 9-α fluorohydrocortisone)

	Urine μEq/min					Serum mEq/L		
	pH	NH_4^+	T. A.	HCO_3^-	Net Acid	Na^+	K^+	HCO_3^-
Control	6.7	27	5	12	20	132	3.8	21
After	4.4	22	17	0	39	140	3.1	21

This was repeated 1 week later:

Control	6.5	32	12	8	36	134	4.0	21
After	4.6	29	24	0	53	139	3.5	18

2. NH_4Cl 3-5 gm/day

	Urine mEq/day					Serum mEq/L			
	pH	NH_4^+	T. A.	HCO_3^-	Net Acid	Na^+	K^+	Cl^-	HCO_3^-
Control	6.7	24	8	6	26	135	4.3	112	19
Day 9	5.6	76	37	0	113	141	3.8	115	12

3. Renal concentrating capacity (16 hours of water restriction followed by 0.25 cc Pitressin in oil): Sp. Gr. 1.025, Osmolality 743.

4. Kyle Test:

	Period No.	C_p	C_{Cr}	Serum Calcium
		ml/min		mg %
Day 1	1	17	38	9.9
	2	19	44	
	3	25	39	
Day 2	1	17	38	11.3
	2	18	40	
	3	20	40	

5. GFR corrected to 1.73 sq. meter = 85 cc/min.

Tm HCO_3^- = 2.0 mEq/100 ml (normal = 2.8).

6. The patient was treated with Naqua, Aldactone A, Dyrinium and Potassium Chloride with resulting correction of the acidosis and correction of the hypokalemia. The effect of this regimen on aminoacid excretion is shown below:

	Before		After			Normal
Amino Acid mg/24 hr	1/11/66	6/5/66	6/14/66	6/25/66	3/20/67	
Lysine	962	895	460	336	311	7-100
Histidine	650	677	409	328	337	113-246
Glycine	756	686	789	484	300	68-200
Alanine	786	803	1,069	616	193	30- 70
Serine	766	894	656	420	416	27- 73
Threonine	961	1,207	758	462	419	9- 77
Glutamine	2,489	2,704	2,754	2,174	1,232	?
Phenylalanine	430	836	872	483		?
Tyrosine	-	-	-	-	-	-

I. PHYSIOLOGIC CONSIDERATIONS:

The observation that diet and endogenous metabolism influence urinary acid dates back to Claude Bernard.

A. Sources of Acid:

1. Organic Acids Derived From Neutral Compounds: Such acids as pyruvic, lactic and citric derived from carbohydrates, and acetoacetic from neutral fat, are intermediary products and ultimately broken down to CO_2 and H_2O and contribute little, therefore, to acid production except in special circumstances.

Uric acid, derived from nucleoproteins, is an exception to this rule.

2. Oxidation of Sulfur-containing Compounds: This source of inorganic sulfate accounts for about 50% of total acid production. Examples of such compounds are methionine, cystine and cysteine.

3. Hydrolysis of Ortho- and Pyro-phosphate Esters: These are derived from phosphoproteins and nucleoproteins. The contribution of phospholipids has recently been emphasized: A normal diet is estimated to contain phosphalipid equivalent to two egg yolks, corresponding to 12 mEq H^+ or about 20% of the physiological acid production.

The net hydrogen derived from phosphoesters depends on the nature of the ester and the pH at which it exists. Phosphoprotein from meat, for example, yields little net hydrogen.

B. Rate of Acid Production:

Estimated to be equal to 1 mEq/kg/day or 70 mEq/day/1.73 m^2.

C. Fate of Metabolic Acid:

Acid generated in the body rapidly reacts with body buffers (bicarbonate, dibasic phosphate, protein) yielding a neutral salt and a weak acid with a low dissociation constant. The major extracellular buffer is bicarbonate:

$$H^+A + B^+HCO_3^- \longrightarrow B^+A^- + H_2CO_3 \longrightarrow CO_2\uparrow + H_2O,$$

D. Conservation of Body Buffer:

In addition to about 70 millimoles of buffer decomposed daily by metabolic acid, there is an even larger potential source of buffer loss consisting of about 4000 milliequivalents of HCO_3^- filtered through the glomerulus every day. The conservation of buffer is achieved by two processes:

1. Reabsorption of Filtered Bicarbonate: At a plasma level below 28 mEq/L all of the filtered bicarbonate is reabsorbed. This is accomplished by a process of hydrogen secretion occurring in the proximal tubule predominently (75-90% of filtered HCO_3^-). This process of hydrogen secretion depends, at least in part, on carbonic anhydrase; it is directly proportional to blood pCO_2; it is enhanced by a deficit of potassium and suppressed by a surfiet of this ion; and is enhanced by maneuvers that lead to a shrinkage of effective blood volume (interpreted as Cl^- deficit).

2. Regeneration of Bicarbonate: Decomposed buffer is regenerated by the excretion of an equivalent amount of acid by the kidney. Since at the minimum urine pH of 4.0 only 0.03 - 0.1 mEq/L of H^+ can be present in the free form, excreted acid is all buffered by NH_3 and by inorganic phosphate (and to a lesser extent creatinine and other organic acids). Acid excreted buffered by nonammonia buffers is estimated from the titration of the urine up to plasma pH and referred to as titratable acid.

   a. Ammonium: Accounts for about 2/3 of excreted acid and derived principally from the amide and amino nitrogen of glutamine. Ammonia is highly diffusible; it enters the lumen and reacts with $H^+ \longrightarrow NH_4^+$. Rate of excretion is dependent on tubular fluid pH at levels of 6.2 or below. Above this level of tubular fluid pH its excretion increases with increasing urine flow. The rate of excretion at any urinary pH is enhanced by chronic acidosis, adrenal steroids and by potassium depletion.

   b. Titratable Acid: Normally small; depends on the rate of excretion of buffer, the pK of the buffer and urinary pH. There is no intrinsic limitation to H^+ secretion when buffer is increased.

1. Relman, A. S. Renal acidosis and renal excretion of acid in health and disease. Advances in Internal Medicine 12:295, 1964.

2. Elkinton, J. R. Hydrogen ion turnover in health and in renal disease. Ann Int. Med. 57:660, 1962.

3. Hunt, J. N. Influence of dietary sulphur on the urinary output of acid in man. Clin. Sci. 15:119, 1956.

4. Lemann, J., Jr., and A. S. Relman. Relation of sulfur metabolism to acid-base balance and electrolyte excretion: Effects of DL-methionine in normal man. J. clin. Invest. 38:2215, 1959.

5. Relman, A. S., E. J. Lennon, and J. Lemann, Jr. Endogenous production of fixed acid and the measurement of the net balance of acid in normal subjects. J. clin. Invest. 40:1621, 1961.

6. Lennon, E. J., J. Lemann, Jr., and A. S. Relman. Effect of phosphoproteins on acid balance in normal subjects. J. clin. Invest. 41:637, 1962.

7. Richet, G., R. Ardaillou, and C. Amiel. Phospholipids, an alimentary source of H^+ ions. III Inter. Congress of Nephrology, Wash., D. C., September 1966.

8. Pitts, R. F. Physiology of the kidney and body fluids. Year Book Med. Pub., Inc. Chicago, 1963.

9. Rector, F. C , Jr. Role of the kidney in the homeostatic control of hydrogen ion concentration in body fluids. Proc. 23rd. Int. Congress of Physiological Sci. Tokyo. September 1965.

II. ACIDOSIS:

A condition due to accumulation of acid or loss of base that tends to produce a downward deviation of blood pH but not dependent on it. In metabolic acidosis the acid is other than carbonic and the base lost is bicarbonate of the ECF.

An acid is a substance that gives up a proton (or hydrogen ion) and a base is any substance that accepts a proton. Acids and bases are not anions and cations respectively.

10. Winters, R. W. Terminology of acid-base disorders. Ann. Int. Med. 63:873, 1965.

11. Relman, A. S. Editorial. What are "Acids" and "Bases"? Amer. J. Med. 17:435, 1954.

12. Schwartz, W. B., and A. S. Relman. A critique of the parameters used in the evaluation of acid-base disorders. "Whose-Blood Buffer Base" and "Standard Bicarbonate" compared with blood pH and plasma bicarbonate concentration. New England J. Med. 268:1382, 1963.

13. Austin, W. H. Acid-base balance. A review of current approaches and techniques. Am. Heart J. 69:691, 1965.

14. Cohen, J. J. A new acid-base nomogram featuring hydrogen ion concentration. Henderson revisited. Ann. Int. Med. 66:159, 1967.

15. Davis, R. P. Logland: A Gibbsian view of acid-base balance. Editorial, Am. J. Med. 42:150, 1967.

16. Lennon, E. J., and J. Lemann, Jr. Defense of hydrogen ion concentration in chronic metabolic acidosis. A new evaluation of an old approach. Ann. Int. Med. 65:265, 1966.

III. RENAL AZOTEMIC ACIDOSIS:

Characterized by advanced azotemia, a fall in plasma HCO_3^- and a rise in sulfate, phosphate and other organic anions. The plasma chloride is usually unchanged but may be increased in some instances where the acidosis is disproportionate to the degree of azotemia. The latter cases are particularly prone to hyperkalemia. Hyperchloremia, however, may occur in the course of renal insufficiency from any cause.

It has been stated that renal acidosis of any type is due to a tubular defect. Evidence will be presented here to suggest this may not be so.

A. Urinary Acidification:

The ability to generate high H^+ gradient and lower urinary pH is unimpaired in these patients when serum HCO_3^- is artificially or spontaneously reduced. The delay in achieving a maximally acid urine is most likely due to the massive osmotic diuresis in the diseased nephron sweeping HCO_3^- to the distal site where hydrogen secretory capacity is expended in the absorption of HCO_3^- instead of the generation of H^+ gradient. This is corroborated by studies with Na_2SO_4 infusion at a time when serum HCO_3^- is normal and when it is low. In the former circumstance the urine becomes alkaline, in the latter it becomes more acid. The alkalinization of the urine is presumably the result of the osmotic effect of the sulfate.

B. Titratable Acid Excretion:

The excretion of titratable acid in renal disease has been reported to be somewhat reduced. Since urinary pH may be reduced to maximally acid levels, any reduction in titratable acid excretion must have represented a diminished excretion of buffer. With the reduction in renal mass the remaining functioning nephrons must have an abundance of buffer and any reduction in buffer must represent diminished dietary intake. Actually, when azotemic patients were fed a diet comparable to the control subjects the excretion of titratable acid was normal.

C. Bicarbonate Reabsorption:

The maximum hydrogen secretory capacity as measured by Tm of HCO_3^- is normal both in clinical and experimental renal disease. This method of measurement, however, may not detect small reductions in Tm or a small splay. When plasma HCO_3^- was allowed to fall spontaneously it was noted that some azotemic patients wasted HCO_3^- in the urine at levels of plasma HCO_3^- where ordinarily the urine would be free of HCO_3^-. The delivery of alkaline fluid to the distal hydrogen secretory site limits the excretion of titratable acid and NH_3 and contributes to the generation of acidosis. A similar phenomenon is seen in experimental unilateral renal disease; this is associated with increased fractional excretion of sodium and most likely represents a state of osmotic diuresis.

D. Ammonium Excretion:

The most consistent finding in azotemic acidosis is a reduction in NH_4^+ excretion. It increases little with the administration of acidifying salts and whereas normally it is 1 1/2 to 2 times the titratable acid, it accounts for only about 1/3 of total acid excretion in azotemic acidosis. The reduced excretion, however, is the outcome of diminished renal mass and when corrected to the filtration rate and the urine pH it is normal.

17. Seligson, D., L. W. Bluemle, Jr., G. D. Webster, Jr., and D. Senesky. Organic acids in body fluids of the uremic patient. J. clin. Invest. 38:1042, 1959.

18. Galloway, R. E., and J. M. Morgan. Serum pyruvate and lactate in uremia. Metabolism 13:818, 1964.

19. Lathem, W. Hyperchloremic acidosis in chronic pyelonephritis. New Eng. J. Med. 258:1031, 1958.

20. Schwartz, W. B., and A. S. Relman. Acidosis in renal disease. New Eng. J. Med. 256:1184, 1957.

21. Seldin, D. W., N. W. Carter, and F. C. Rector, Jr. Consequences of renal failure and their management. p. 173 In: Diseases of the Kidney, M.B. Straus and L.G. Welt, Eds.; Little, Brown, and Company, Boston, 1963.

22. Seldin, D. W., A. J. Coleman, N. W. Carter, and F. C. Rector, Jr. The effect of Na_2SO_4 on urinary acidification in chronic renal disease. J. Lab. Clin. Med. (In Press) 1967.

23. Bricker, N. S., S. Klahr, H. Lubowitz, and R. E. Rieselbach. Renal function in chronic renal disease. Med. 44:263, 1965.

24. Slatopolsky, E., L. Gradowska, C. Kashemsant, R. Keltner, C. Manley, and N. S. Bricker. The control of phosphate excretion in uremia. J. clin. Invest. 45:672, 1966.

25. Wrong, O., and H E. F. Davies. The excretion of acid in renal disease. Quart. J. Med. N. S. 28:259, 1959.

26. Findley, T., and A P. Briggs. Uremic acidosis: Some alternative views. Am. Heart J. 66:142, 1963.

27. Briggs, A. P., W. H. Waugh, W. S. Harms, and T. Findley. Pathogenesis of uremic acidosis as indicated by urinary acidification on a controlled diet. Metabolism 10:749, 1961.

28. Roberts, K. E., H. T. Randall, P. Vanamee, and J. W. Poppell. Renal mechanism involved in bicarbonate absorption. Metabolism 5:404, 1956.

29. Morrin, P.A.F., N.S. Bricker, S.W. Kime, Jr., and C. Klein. Observations on the acidifying capacity of the experimentally diseased kidney in the dog. J. clin. Invest. 41:1297, 1962.

30. Morrin, P.A.F., W. B. Gedney, L. N. Newmark, and N.S. Bricker. Bicarbonate reabsorption in the dog with experimental renal disease. J. clin. Invest. 41:1303, 1962.

31. Steinmetz, P. R., R. P. Eisinger, and J. Lowenstein. The excretion of acid in unilateral renal disease in man. J. clin. Invest. 44:582, 1965.

32. Schwartz, W. B., P. W. Hall, III, R. M. Hays, and A. S. Relman. On the mechanism of acidosis in chronic renal disease. J. clin. Invest. 38:39, 1959.

33. Dorhout-Mees, E. J., M. Machado, E. Slatopolsky, S. Klahr, and N. S. Bricker. The functional adaptation of the diseased kidney. III Ammonium Excretion. J. clin. Invest. 45:289, 1966.

34. Preuss, H. G., B. B. Davis, J. F. Maher, B. B. Wise, and G. E. Schreiner. Ammonia metabolism in renal failure. Ann. Int. Med. 65:54, 1966.

E. THE STEADY STATE:

If the acidotic state were allowed to proceed uncorrected the serum bicarbonate eventually reaches a new low level at which it stabilizes. This has been attributed to the lowering of plasma HCO_3^-, reduced filtered HCO_3^-, and diminished access of HCO_3^- to the distal nephron thereby allowing the kidney to put out titratable acid and acid output becomes equal to production.

Balance studies, however, revealed that, in the steady state, these acidotic patients were in positive hydrogen balance. The retained acid amounted to about 1/3 of the total hydrogen ion production and ranged between 20 and 50 mEq per day. A similar response was seen in normal subjects fed NH_4Cl. Balance studies revealed that after significant titration of extra- and intra-cellular buffers bone provided buffer reserve with a resulting negative calcium balance. In patients with azotemic renal disease the daily losses of calcium averaged -5.3 ± 3.8 mEq. Over a period of 10 years this rate of loss would expend 1/3 of total skeletal calcium in the adult. Correction of the acidosis prevented this loss.

Analysis of bone from uremic patients revealed a significant reduction in calcium and carbonate concentrations. The loss of calcium and carbonate appeared related to the degree of azotemia and acidosis. It was also directly related to the duration of azotemia.

35. Goodman, A. D., J. Lemann, Jr., E. J. Lennon, and A. S. Relman. Production, excretion, and net balance of fixed acid in patients with renal acidosis. J. clin. Invest. 44:495, 1965.

36. Lennon, E. J., J. Lemann, Jr., and J. R. Litzow. The effects of diet and stool composition on the net external acid balance of normal subjects. J. clin. Invest. 45:1601, 1966.

37. Lemann, J., Jr., E. J. Lennon, A. D. Goodman, J. R. Litzow, and A. S. Relman. The net balance of acid in subjects given large loads of acid or alkali. J. clin. Invest. 44:507, 1965.

38. Lemann, J., Jr., J. R. Litzow, and E. J. Lennon. The effects of chronic acid loads in normal man: Further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. J. clin. Invest. 45:1608, 1966.

39. Litzow, J. R., J. Lemann, Jr., and E. J. Lennon. The effect of treatment of acidosis on calcium balance in patients with chronic azotemic renal disease. J. clin. Invest. 46:280, 1967.

40. Pellegrino, E. D., and R. M. Blitz. The composition of human bone in uremia. Observations on the reservoir functions of bone and demonstration of a labile fraction of bone carbonate. Medicine 44:397, 1965.

41. Reidenberg, M. M., B. L. Haag, B. J Channick, C. R. Shuman, and T.G.G. Wilson. The response of bone to metabolic acidosis in man. Metabolism 15:236, 1966.

VI. RENAL TUBULAR ACIDOSIS:

A syndrome characterized by a low serum HCO_3^- and an equivalent elevation of Cl^-. Other associated findings are hypokalemia often resulting in paralysis; hypercalciuria and hyperphosphaturia leading to osteomalacia, nephrocalcinosis and renal stones; and finally polyuria and impaired concentrating capacity.

A. Pathophysiology:

1. Bicarbonate Reabsorption: The hydrogen secretory capacity as revealed from the study of Tm for HCO_3^- is normal. There is, however, a small "leak" of HCO_3^- into the urine even at very low plasma levels. This is thought, however, not to be a net loss of HCO_3^- since it is accompanied by NH_4^+.

2. Titratable Acid Excretion: Excretion of acid is greatly reduced. This is not due to a reduced hydrogen secretory capacity; the infusion of neutral phosphate solutions markedly increases the excretion of titratable acid.

3. Ammonium Excretion: The excretion of acid bound to NH_3 is also reduced. When appropriate corrections for filtration rate and urine pH are made, however, the excretion of NH_4^+ is found to be normal or relatively increased.

4. Urinary Acidification: Even in the face of acid loads the urine pH does not fall below 6.0. This is not due to a leak of HCO_3^- but rather an inability to establish high H^+ gradients between tubular fluid and plasma. The HCO_3^- leak is obligated by the high fixed urine pH. The high urine pH also explains the impairment of titratable acid and ammonium excretion.

5. Renal Enzymes: Relative to the degree of acidosis and the mild to moderate impairment of filtration rate, the response to acetazolamide in this syndrome is considered normal. Furthermore, gastric acidity is normal. There is no evidence for a deficiency of carbonic anhydrase, therefore, and this is confirmed by an assay of a biopsy specimen. Glutaminase and other enzymes were also normal.

B. PATHOGENESIS:

1. Hyperchloremic Acidosis: The impaired excretion of H^+ results in the loss of sodium and of potassium in the urine. Sodium loss shrinks plasma volume and stimulates the retention of NaCl. The loss of HCO_3^- due to defective regeneration and the retention of salt both lead to hyperchloremic acidosis.

2. Hypokalemia: The impaired H^+ excretion results in increased Na^+-for-K^+ exchange. Furthermore, the shrinkage of plasma volume, by stimulating aldosterone, enhances this exchange. The result is an excessive loss of potassium in the urine.

3. Osteomalacia, Nephrocalcinosis and Nephrolithiasis: Metabolic acidosis results in a positive balance of acid. The retained acid titrates bone resulting in osteomalacia and hypercalciuria. Intracellular buffer is also titrated and intracellular acidosis supervenes. This in turn leads to a marked reduction in citrate excretion in the urine. The excretion of excessive amounts of calcium with a dearth of citrate results in nephrocalcinosis and nephrolithiasis.

4. Impaired Urine Concentration: This results from nephrocalcinosis, hypokalemia and pyelonephritis.

C. FANCONI SYNDROME:

Hyperchloremic acidosis has been reported in this syndrome This syndrome is characterized by the presence of osteomalacia (rickets and dwarfism in children), albuminuria, aminoaciduria, ketonuria, renal glycosuria, hypophosphatemia with hyperphosphaturia, hypouricemia and, in children, cystinosis. It differs from renal tubular acidosis in the absence of nephrocalcinosis and nephrolithiasis. Since citrate excretion is equally low it has been proposed that calcium is complexed with the organic acids excreted in the urine.

D. "PROXIMAL" RENAL TUBULAR ACIDOSIS:

From the foregoing it can be concluded with reasonable assurance that renal tubular acidosis is the result of a distal tubular defect.

Recently, studies on childhood Fanconi, hereditary fructose intolerance and renal medullary cystic disease revealed a depression of the Tm for HCO_3^- to values of 1.6 to 2.3 mEq/100 ml GFR. These patients, in the presence of acidosis, were capable of dropping urine pH to values below 5.5. These findings point to a proximal defect and a normally functioning distal tubule.

42. Seldin, D. W., and J. D. Wilson. Renal tubular acidosis, Chapter 54 in the metabolic basis of inherited disease. Stanbury, Wyngaarden, and Fredrickson,Eds. p. 1230; McGraw Hill, Inc., 1965.

43. Latner, A. L., and E. D. Burnard. Idiopathic hyperchloremic renal acidosis of infants. (Nephrocalcinosis Infantum). Observations on the site and nature of the lesion. Quart. J. Med. N.S. 19:285, 1950.

44. Smith, L. H., Jr., and G. E Schreiner: Studies on renal hyperchloremic acidosis. J. Lab. Clin. Med. 42:347, 1954.

45. Reynolds, T. B. Observations on the pathogenesis of renal tubular acidosis. Amer. J. Med. 25:503, 1958.

46. Frick, P. G., M. E Rubini, and W. H. Meroney. Recurrent nephrolithiasis associated with an unusual tubular defect and hyperchloremic acidosis. Am. J. Med. 25:590, 1958.

47. Elkinton, J. R., E. J. Huth, G. D. Webster, Jr., and R. A. McCance. The renal excretion of hydrogen ion in renal tubular acidosis. I. Quantitative assessment of the response to ammonium chloride as an acid load. Amer. J. Med. 29:554, 1960.

48. Webster, G. D., Jr., E. J. Huth, J. R. Elkinton, and R. A. McCance. The renal excretion of hydrogen ion in renal tubular acidosis. II. Quantitative response to the carbonic anhydrase inhibitor, acetazolamide. Amer. J Med. 29:576, 1960.

49. Morris, R. C., C. F. Piel, and E. Audion: Renal tubular acidosis. Effects of sodium phosphate and sulfate on renal acidification in two patients with renal tubular acidosis. Pediatrics 36:899, 1965.

50. Yaffe, S. J., J. M. Craig, and F. X. Fellers: Studies on renal enzymes in a patient with renal tubular acidosis. Amer. J. Med. 29:168, 1960.

51. Elkinton, J. R. Renal acidosis. Editorial. Amer. J. Med. 28:165, 1960.

52. Dedmon, R. E., and O. Wrong . The excretion of organic anion in renal tubular acidosis with particular reference to citrate. Clin. Sci. 22:19, 1962.

53. Morissey, J. F., M. Ochoa, Jr., W. D. Lotspeich, and C. Waterhouse. Citrate excretion in renal tubular acidosis. Ann. Int. Med. 58:159, 1963.

54. Simpson, D. P. Influence of plasma bicarbonate concentration and pH on citrate excretion. Amer. J. Physiol. 206:875, 1964.

55. Simpson, D. P. Effect of acetazolamide on citrate excretion in the dog. Amer. J. Physiol. 206:883, 1964.

56. Wallis, L A., and R L. Engle, Jr. The adult Fanconi Syndrome. II. Review of eighteen cases. Amer. J. Med. 22:13, 1957.

57. Milne, M. D., S. W. Stanbury, and A. E. Thomson. Observations on the Fanconi syndrome and renal hyperchloremic acidosis in the adult. Quart. J. Med. N. S. 21:61, 1952.

58. Morris, R. C. Fructose-Induced disruption of renal acidification in patients with hereditary fructose intolerance. J. clin. Invest. 44:1076, 1965.

59. Morris, R. C. Evidence for an acidification defect of the proximal renal tubule in experimental and clinical renal disease. J. clin. Invest. 45:1048, 1966.

E. THE SECONDARY SYNDROME:

In addition to the idiopathic variety of renal tubular acidosis and the Fanconi syndrome, a secondary form has been described in association with a number of diseases:

1. Paraldehyde Ingestion.
2. Hypercalcemia: from hyperparathyroidism or vitamin D excess.
3. Nephrotic Syndrome: rare in adults but frequent in children.
4. Mercaptopurine: given to a patient with nephrosis.
5. Renal Homotransplantation: patient receiving Imuran.
6. Outdated Tetracycline.
7. Thyroid Disease: reported with hyper- and with hypo-throidism.
8. Multiple Myeloma: usually associated with glycosuria and aminoaciduria. The only case reported with pure RTA probably did not have RTA but had hyperchloremic acidosis due to diarrhea (Ref. 71).
9. Hyperglobulinemic States.
10. Wilson's Disease.
11. Hereditary Fructose Intolerance.
12. Renal Medullary Cystic Disease.
13. Miscellaneous

60. Elkinton, J. R., E. J. Huth, J. K. Clark, E. S. Barker, and D. Seligson. Renal tubular acidosis with organic aciduria during paraldehyde ingestion. Six Year Study of An Unusual Case. Amer. J. Med. 23:977, 1957.

61. Fourman, P., B. McConkey, J. W. G. Smith: Defects of water reabsorption and of hydrogen-ion excretion by the renal tubules in hyperparathyroidism. Lancet 1: 619, 1960.

62. Doolan, P. D., M. D. Morris, and H. A. Harper: Aminoaciduria in an elderly man with the nephrotic syndrome and in a young man with a variant of the Fanconi syndrome. Ann. In. Med. 56:448, 1962.

63. Butler, H. E., Jr., J. M. Morgan, and C.M.C. Smythe. Mercaptopurine and acquired tubular dysfunction in adult nephrosis. Arch. Int. Med. 116:853, 1965.

64. Massry, Shaul G., H. G. Preuss, J. F. Maher, and G. E. Schreiner. Renal tubular acidosis after cadaver kidney homotransplantation. Studies on mechanism. Amer. J. Med. 42:284, 1967.

65. Gross, J. M. Fanconi syndrome (adult type) developing secondary to the ingestion of outdated tetracycline. Ann. Int. Med. 58:523, 1963.

66. Wegienka, L. C., and J M. Weller. Renal tubular acidosis caused by degraded tetracycline. Arch. Int. Med. 114:232, 1964.

67. Huth, E. J., R. L. Mayock, and R. M. Kerr. Hyperthyroidism associated with renal tubular acidosis. Discussion of possible relationship. Amer. J. Med. 26: 818, 1959.

68. Owen, E. E., and J. V. Verner, Jr. Renal tubular disease with muscle paralysis and hypokalemia. Amer. J Med. 28:8, 1960.

69. Harrison, J. F., and J. D. Blainey. Adult Fanconi syndrome with monoclonal abnormality of immunoglobulin light chain. J. clin. Path. 20:42, 1967.

70. Engle, R. L., Jr., and L. A. Wallis. Multiple myeloma and the adult Fanconi syndrome. I. Report of a case with crystal - like deposits in the tumor cells and in the epithelial cells of the kidney. Amer. J. Med. 22;5, 1957.

71. Sanchez, L. M., and C. A. Domz. Renal patterns in myeloma. Ann. Int. Med. 52:44, 1960.

72. Cohen, A., and B. J. Way. The association of renal tubular acidosis with hyperglobulinemic purpura. Australas. Ann. Med. 11:189, 1962.

73. Rector, F. C., Jr., C. B. Mullins, M.Ziff, J. D. Wilson, and R. C. Reynolds. Clinicopathologic conference. Texas State J. Med. 60:447, 1964.

74. Morris, R. C., Jr., and H. H. Fudenberg. Impaired renal acidification in patients with hypergammaglobulinemia. Medicine 46:57, 1967.

F. HEREDITY:

There are several reports now of persistent renal tubular acidosis occurring in families. The mode of inheritance appears to be an antosomal dominant with variable expressivity.

75. Huth, E. J., G. D. Webster, Jr., and J. R. Elkinton. The renal excretion of hydrogen ion in renal tubular acidosis. III. An attempt to detect latent cases in a family; comments on Nosology, Genetics and Etiology of the primary disease. Amer. J. Med. 29:586, 1960.

76. Schreiner, G. E., L. H. Smith, Jr., and L. H. Kyle. Renal hyperchloremic acidosis. Familial occurrence of nephrocalcinosis with hyperchloremia and low serum bicarbonate. Amer. J. Med. 15:122, 1953.

77. Randall, R. E., Jr., and W. H. Taggart. Familial renal tubular acidosis. Ann. Int. Med. 52:1108, 1961.