Renal

UTHSCD MEDICAL GRAND ROUNDS

RENAL TUBULAR ACIDOSIS

I. Physiology
II. Pathophysiology
III. Clinical

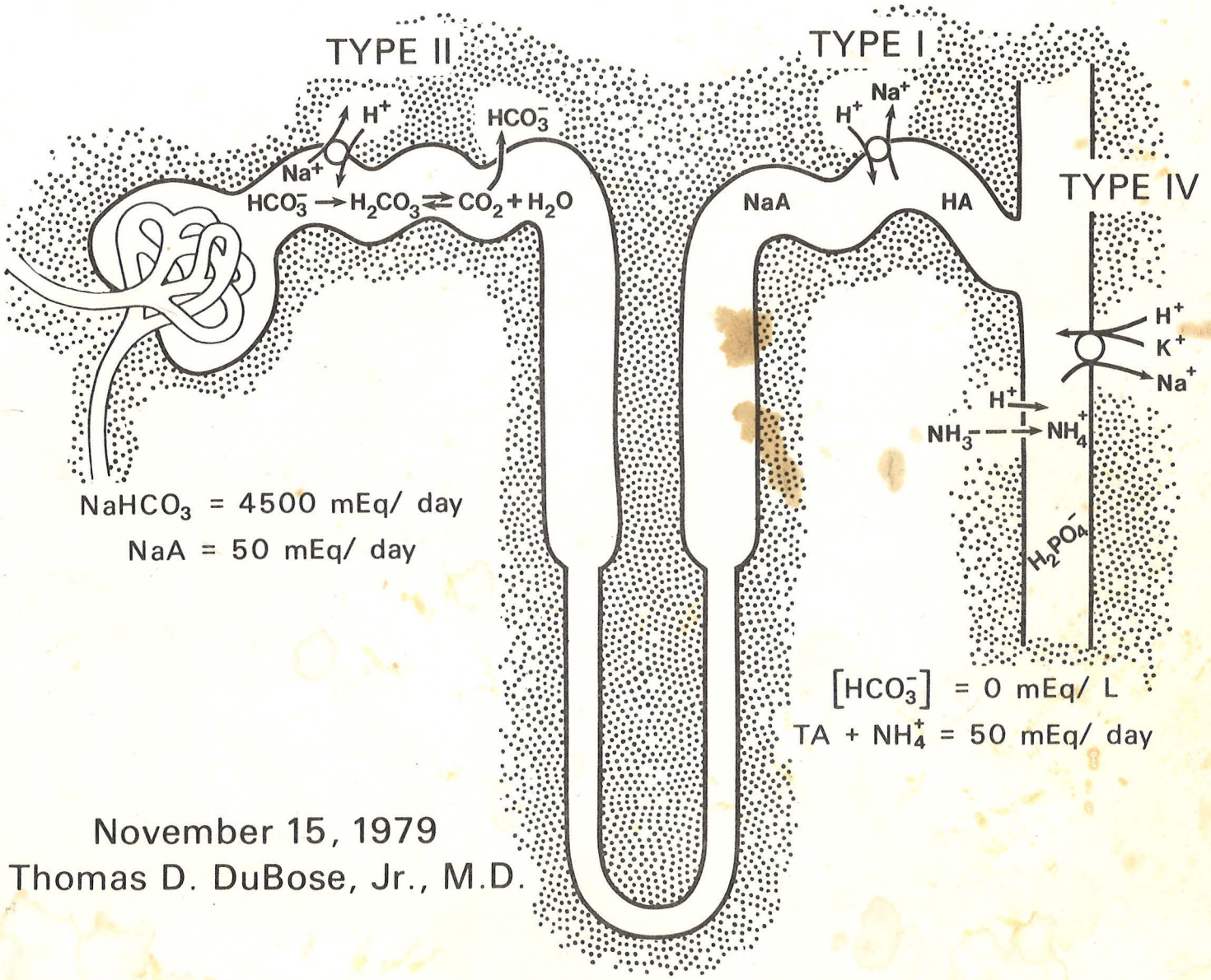

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TABLE OF CONTENTS

I. THE ROLE OF THE KIDNEY IN ACID-BASE HOMEOSTASIS

Acid-base homeostasis in man is characterized by the maintainence of systemic arterial pH within a very narrow range despite acid and alkaline loads originating from the daily intake and degradation of foods. As illustrated by the familiar Henderson-Hasselbach equation (Fig. 1), the arterial pH represents an interplay between both metabolic and respiratory components.

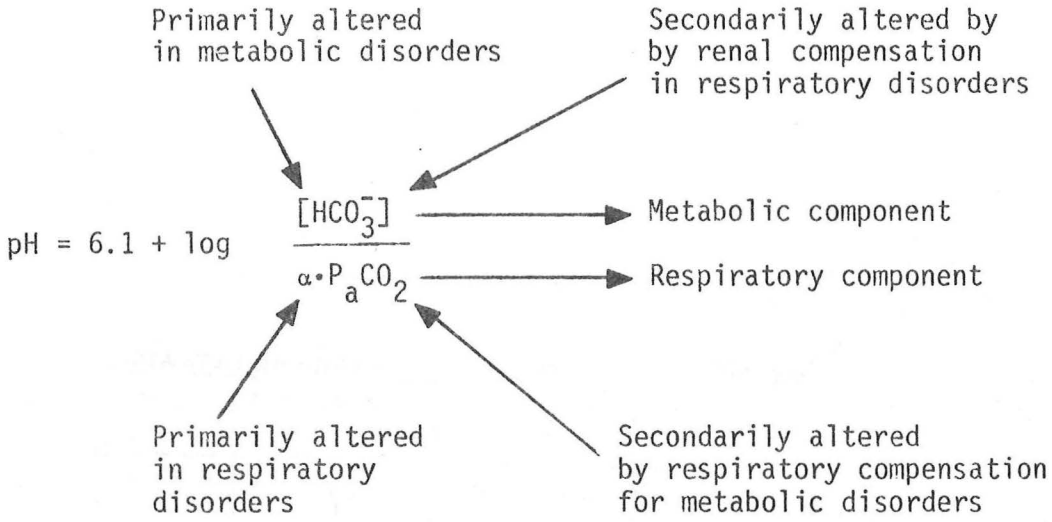

Figure 1. Henderson-Hasselbalch equation.

The first lines of defense against alteration in body pH are the extracellular and intracellular buffers. The major extracellular buffer is bicarbonate and the buffering capacity of the HCO_3^- - CO_2 system is greatly extended by the regulation of CO_2 gas tension by the respiratory system. In acid-base disorders, the numerator, or the bicarbonate concentration is primarily altered in metabolic acidosis or alkalosis but can be secondarily altered during renal compensation for respiratory disturbances. Conversely, the denominator is primarily altered by respiratory acidosis or alkalosis and secondarily by respiratory compensation for metabolic disturbances.

Urinary Acidification: The kidney's role in acid-base homeostasis is to stabilize the serum bicarbonate concentration. This is accomplished by two processes:

1) Reabsorption of virtually all of the filtered bicarbonate.

2) Regeneration of the sodium bicarbonate lost by the buffering of metabolic acids (products of breakdown of food stuffs, sulfuric and phosphoric acids).

These two distinct processes are outlined in Fig. 2.

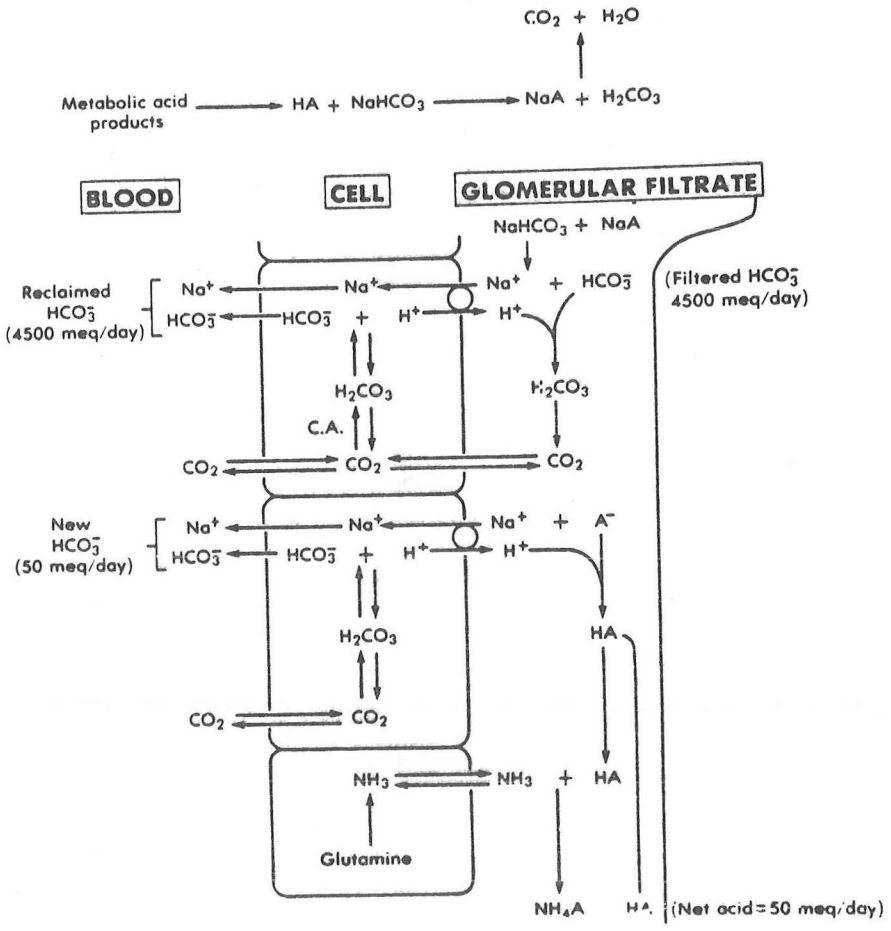

Figure 2: Normal mechanism of urine acidification; bicarbonate reclaimation and regeneration. From (1)

It is generally accepted that both of these processes occur by H^+ secretion (1-7) although reabsorption of HCO_3^- per se has also been proposed (8,9).

A. Proximal Tubule (upper panel, Fig. 2)

1. Normal Physiology

Quantitatively the vast majority of the filtered load of bicarbonate is reabsorbed by the proximal tubule. Micropuncture studies, have demonstrated that 80-90% of the filtered load is reabsorbed by this nephron segment (4,5,10). In this process H^+ is secreted into bicarbonate-containing tubular fluid forming carbonic acid which dehydrates in the lumen and enters the cells as CO_2. Under the influence of carbonic anhydrase, bicarbonate is formed, and passively diffuses down a favorable concentration gradient into peritubular fluid. By the same process, H^+ also is supplied for secretion. This differs from the reabsorption of the bicarbonate ion per se. The distinction between these two mechanisms have been based on the demonstration of an acid or negative disequilibrium pH in the proximal tubule during inhibition of carbonic anhydrase (4,10,11). Studies in which this technique has been employed have uniformly supported H^+ secretion as the mechanism by which this process occurs. Recent evidence in our laboratory indicates that H^+ secretion is the predominate if not the single mechanism by which bicarbonate is reabsorbed in the proximal tubule (7).

This high bicarbonate reabsorptive rate, in the proximal tubule, an epithelia generally considered to exibit "pump-leak" characteristics, is accomplished, despite this inherent limitation, as a result of the availability of the enzyme carbonic anhydrase. This enzyme accelerates the dehydration of carbonic acid (H_2CO_3) the product of the reaction between secreted H^+ and filtered HCO_3^-. Recent histochemical and membrane vesicle studies have demonstrated that carbonic anhydrase is present in the brush border of the proximal tubular epithelial cells

(12). Furthermore, numerous previous studies (4,11) as well as recent evidence from our own laboratory (7,13) have demonstrated that proximal tubular fluid is in functional contact with this enzyme. The end result of this relationship is to permit a lower lumen-to-peritubular capillary H^+ concentration gradient, thus reducing the gradient against which H^+ is secreted.

As traditionally conceived, H^+ secretion, in the proximal tubule occurs in exchange for sodium (3). With the use of brush border membrane vesicles, Murer, Hopfer and Kinne (14) have suggested an electrically neutral sodium-proton exchange pump. Support for such a tightly coupled Na^+-H^+ system has been evident in the studies of McKinney and Burg (15) in the isolated rabbit proximal tubule. However, several other laboratories in which this system was examined in the rat proximal tubule have determined that Na^+-H^+ transport may be uncoupled and that the coupling ratio may vary from 1:1 to 1:6, depending on the availability and type of buffer in the perfusate. Whether these discrepant results represent a true species difference between rat and rabbit, or if the differences represent variations in technique remains to be seen. The studies of Malnic (16) for example, have suggested that since partial substitution of sodium will decrease net sodium, but not net bicarbonate reabsorption, the coupling ratio between Na^+ and H^+ may vary depending on the physiologic conditions in vivo. This indicates that a minimal peritubular sodium concentration may be necessary to sustain acidification. Bicarbonate reabsorption is accomplished then by H^+ secretion, predominately in the proximal tubule by an active process. Malnic and associates have demonstrated that there is no evidence of saturation of HCO_3^- transport in single nephrons in vivo up to a luminal HCO_3^- concentration of 100 mM. (17).

2. Factors Which Can Modify Proximal Tubular Capacity for Bicarbonate Reabsorption

Under normal conditions it appears that the kidney is set to protect a serum bicarbonate of 26mEq/L since values greater than this are

associated with bicarbonate excretion. In man, especially in disease states, several additional factors are capable of modifying the capacity of the proximal tubule to reabsorb bicarbonate (Table I).

Table I Factors Which Can Modify the Capacity of the Proximal Tubule to Reabsorb Bicarbonate

Extracellular fluid volume
p_aCO_2
Potassium
Calcium
Phosphorous
PTH

The kidney appears to respond primarily to the volume needs of the host and will do so at the expense of acid-base status. For example, effective volume expansion decreases HCO_3^- reabsorption while effective volume contraction results in the opposite. The studies of Kurtzman (18), Slatopolsky (19), and Purkerson (20), have emphasized the importance of ECF volume status on bicarbonate reabsorption. Bicarbonate reabsorption is directly proportional to the pCO_2 of blood (21). An increase in pCO_2 lowers intracellular pH and provides more H^+ for secretion. Serum potassium levels and renal bicarbonate reabsorption are inversely related. Hypokalemia increases and hyperkalemia decreases proximal bicarbonate reabsorption. PTH infusion can result in bicarbonaturia apparently by reducing net proximal reabsorption of bicarbonate perhaps as a result of increased backleak of reabsorbed bicarbonate. Both hyperphosphatemia and hypercalcemia increase HCO_3^- reabsorption and hypophosphatemia and hypocalcemia decrease HCO_3^- reabsorption. All of these factors must be considered and ruled out as potential contributors before an acidification defect can be diagnosed.

B. Distal Tubule and Collecting Duct

1. Normal Physiology

The capacity for bicarbonate reabsorption in the distal tubule is much less than in the proximal nephron (5). It should be emphasized that since the capacity for HCO_3^- reabsorption in the distal nephron is low, any process (primary or secondary) which would increase delivery of HCO_3^- out of the proximal tubule, should overwhelm the distal tubule and result in significant HCO_3^- wasting. This is precisely the defect in proximal renal tubular acidosis (RTA), a disease that affects only the proximal segment but results in marked bicarbonate wasting because of the inability of the functionally normal distal tubule to reabsorb the additional bicarbonate load.

The distal tubule is primarily responsible for excreting fixed acid. The excretion of titratable acid (TA) in association with H^+ secretion generates one new HCO_3^- for each H^+ secreted. Similarily one new bicarbonate ion is formed when ammonium (NH_4^+) salts are excreted. This process is depicted in the lower panel in Fig. I. Net acid excretion (NAE) is defined as follows:

$$NAE = TA + NH_4^+ - HCO_3^-$$

Net acid excretion is equal to the sum of titratable acid excretion and ammonium excretion minus any bicarbonate appearing in the urine. This important process allows regeneration of the bicarbonate lost by extracellular buffering. The importance of such a process can be illustrated by the following consideration: The average individual consumes an acid-ash diet which results in net production of noncarbonic acids (such as sulfuric acid, phosphoric acid, and organic acids) at a rate of 1.0mEq/kg/day. Since these acids titrate or consume bicarbonate in the extracellular fluid forming their sodium salts plus

carbonic acid, the loss of these salts (NaA) by the kidney would soon result in a serious metabolic acidosis. The distal tubule is capable of excreting H^+ as titratable acid (TA) (primarily phosphate) or as ammonium (NH_4^+). This process results in the excretion of about 75mEq per day of hydrogen ion buffered by phosphate and ammonia. For each H^+ secreted in this process a HCO_3^- ion is produced and returned to the ECF via the renal vein as "regenerated" bicarbonate (Fig. 2).

Net acid excretion, therefore, represents a measure of the distal tubule's ability to regenerate bicarbonate. In a normal subject, in balance, net acid excretion equals net acid production (NAP) and acid-base homeostasis is maintained.

$$NAE = NAP$$

The contribution of net acid excretion, as accomplished by the distal tubule, can be illustrated further. Normally, the amount of bicarbonate escaping reabsorption in the proximal tubule, and thus the amount delivered to the distal nephron is quite small. In the distal tubule hydrogen is secreted at a rate adequate to reclaim the small fraction of bicarbonate escaping proximal reabsorption and at a rate sufficient to titrate $HPO_4^=$ and NH_3 to provide for the excretion of 60-70 mEq of H^+ per day. Distal hydrogen secretion depends upon the ability of this nephron segment to increase and maintain the H^+ gradient between the lumen and peritubular capillary. By reduction of the bicarbonate in tubular fluid to negligible concentrations, a pH in tubular fluid of less than 6.4 is achieved. This represents a ten fold hydrogen ion concentration gradient between lumen and blood. The $HPO_4^=/H_2PO_4^-$ buffer system is limited by two factors: 1) the relatively small amount of available buffer (even maximal rates of TA excretion can be no greater than 30-40 mM/day), and 2) the pK of the $HPO_4^=/H_2PO_4^-$ system (6.8) which means that at a pH of 5.8 more than 90% of the available $HPO_4^=$ is already titrated. Therefore even maximal rates of TA excretion is not adequate to provide an NAE equivalent to net acid production.

The remainder of secreted H^+ is excreted as NH_4^+. Ammonia (NH_3) is produced within the renal tubule and diffuses freely between the lumen of the tubule and peritubular capillary. In the acid environment of distal tubular fluid, NH_3 is trapped as NH_4^+ and is excreted in the urine. Any process which limits the availability of phosphate (phosphate depletion) or the ability of the kidney to produce ammonia (reduced renal mass, hyperkalemia) can reduce net acid excretion and eventually result in metabolic acidosis.

With chronic acid loading net acid excretion increases, albeit delayed for 3-4 days, primarily as a result of a marked increase in ammoniagenesis. The mechanism by which this adaptive process is accomplished is a point of considerable controversy. It is clear, however, that renal extraction and utilization of glutamine within the mitochondria is increased in acidosis.

2. Factors Which Can Modify the Ability of the Distal Tubule to Secrete H^+.

The capacity of the distal tubule to secrete H^+ is modulated by the delivery of nonbicarbonate sodium salts to this segment (NaA) (Fig. 2) and by its reabsorptive capacity for sodium. This latter process is determined by the level of aldosterone.

It is the collecting tubule which is capable of generating high pH gradients between the tubular lumen and blood. It is also this segment in which aldosterone exerts its major effect (22). H^+ and K^+ appear to compete for a common secretory site coupled in some fashion (but not 1:1) with Na^+ reabsorption. Although clinical states associated with mineralocorticoid excess are associated with metabolic alkalosis, and mineralocorticoid deficiency is associated with metabolic acidosis, a direct effect of aldosterone on H^+ secretion in the mammalian kidney has not yet been demonstrated. A direct effect has been difficult to demonstrate since aldosterone increases sodium reabsorption which would be expected to produce conditions favorable for H^+ secretion.

Studies in the amphibian urinary bladder, however, clearly support a direct effect of aldosterone on H^+ transport. Al-Awqati and associates have observed that aldosterone can increase H^+ transport in the amphibian urinary bladder independent of sodium transport and even in the presence of ouabain (23). This suggests a direct effect of mineralocorticoid on H^+ conductance. Furthermore, Mueller and Steinmetz (24) have demonstrated that spironolactone, a competitive inhibitor of aldosterone can result in decreased sodium transport while having no effect on H^+ transport. In addition, these investigators have observed that spironolactone can actually increase H^+ transport in steroid-depleted bladders. These recent observations suggest that aldosterone exerts an effect on H^+ secretion and sodium reabsorption via different receptors.

Selective hypoaldosteronism in dogs and other experimental animals can result in metabolic acidosis with associated hyperkalemia. Although low aldosterone levels per se cannot produce a metabolic acidosis in man, the hyperkalemia which accompanies selective hypoaldosteronism can directly suppress renal ammoniagenesis and reduce net acid excretion and can, in this way, be associated with metabolic acidosis.

3. The Urine-to-Blood PCO_2 Gradient as an Index of Distal Nephron Hydrogen Secretion.

Pitts and Lotspeich were the first to observe that during the excretion of a highly alkaline urine, urinary pCO_2 exceeded systemic arterial blood pCO_2 (3). Furthermore, they noted that the so called U-B pCO_2 difference could be obliterated by carbonic anhydrase infusion. These investigators suggested that elevations in urinary pCO_2 in an alkaline urine occur as a result of distal H^+ secretion. The H_2CO_3 thus formed would dissociate at the uncatalyzed rate since distal tubular fluid is not in functional contact with carbonic anhydrase. By this model, the majority of the CO_2 would be formed beyond the terminal nephron, where, because of surface volume relationships, conditions for CO_2 diffusion would be unfavorable.

The physio-chemical basis for the formation of high urine pCO_2 has been the subject of recent studies by Arruda and Kurtzman (25), Halperin and Steinbaugh (26) and has been reviewed in detail by Maren (27). Suffice it to say that the original hypothesis of Pitts and Lotspeich has withstood the test of time. The clinical application of U-B pCO_2 gradient has been elucidated by Halperin and associates (26). These investigators have suggested that the U-B pCO_2 gradient when expressed as a function of urine $[HCO_3^-]$ concentration is abnormally low in conditions associated with defective H^+ secretion in the distal tubule. These authors have suggested that this relationship could serve as a diagnostic aid in distal or classical RTA. There are three variables which must be considered when evaluating U pCO_2 as an index of distal H^+ secretion.

At a high urine pH (>8.0) the urine pCO_2 depends solely on the concentration of HCO_3^- in the urine. At a urine pH below 8.0 nearer the pK of phosphate (6.8), sodium acid phosphate can contribute H^+ ions and serve to elevate the urine pCO_2. The second problem, concentrating ability, is not a concern when the U-B pCO_2 gradient is plotted as a function of urine HCO_3^- and compared with normal controls. When these factors are considered, the urine pCO_2 may serve as an index of distal H^+ secretion. Either a decrease in H^+ secretory rate, or a back diffusion of H^+ or H_2CO_3 in an abnormally permeable tubule could serve to lower the urine pCO_2. Examples of defects of this type will be considered in the section on distal RTA.

II. THE PATHOPHYSIOLOGICAL BASIS FOR METABOLIC ACIDOSIS OF RENAL ORIGIN

There are four distinct types of "renal acidoses" and these are listed in Table 2. From (28)

Table 2 The Types of Renal Acidosis

Proximal RTA (Type II)
"Classical" or Distal RTA (Type I)
Hyperkalemic, Hyperchloremic Acidosis with
Renal Insufficiency (Type IV RTA)
"Uremic" Acidosis

The first three disorders in Table 2 represent abnormalities of renal tubular function and are the subject of this review. Uremic acidosis is characterized by a decreased rate of renal production of ammonia due to a reduction in renal mass, and an abnormally reduced rate of bicarbonate reabsorption per nephron due to a marked diminution in the number of nephrons. The ability to distinguish between these four disorders requires a consideration of the pathophysiological features.

The pathophysiological basis of acidosis in renal tubular disease is a subnormal rate of renal H^+ ion secretion at a normal plasma HCO_3^- level. Metabolic acidosis occurs because either the renal input of new bicarbonate is insufficient to regenerate the bicarbonate lost in buffering endogenous acid as in distal RTA, or the filtered bicarbonate is lost by renal bicarbonate wasting as occurs in proximal RTA. In either condition, because of loss of either $NaHCO_3$ (proximal RTA) or NaA (distal RTA), effective extracellular volume is reduced and as a result the avidity for proximal chloride reabsorption (derived from the diet) is increased and results in a hyperchloremic metabolic acidosis.

The pathophysiologic basis of the metabolic acidosis of renal origin may occur, then, as a result of several types of abnormalities in tubular H^+ transport.

A. Proximal (Type II) - Bicarbonate Wasting Renal Tubular Acidosis

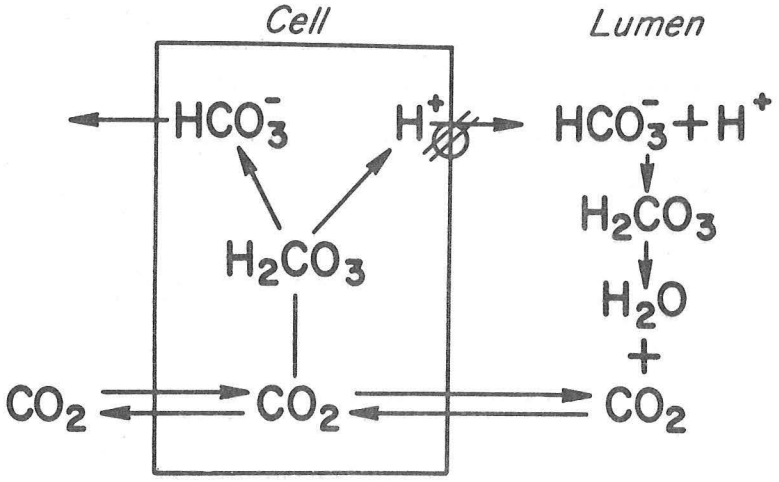

Figure 3: Pathophysiological Basis for Proximal (Type II) RTA

The primary abnormality in this disorder appears to be an abnormality in the ability of the proximal tubule to reabsorb bicarbonate presumably as a result of a decrease in H^+ secretion (Fig. 3). This defect is manifest by a self-limited bicarbonaturia. This defect allows a portion of the filtered bicarbonate to escape reabsorption in the proximal tubule and to be delivered into the normal distal nephron which has a low capacity for bicarbonate reabosrption and thus bicarbonate appears in the urine (bicarbonate wasting). As a result the serum bicarbonate concentration and thus the filtered load of bicarbonate is reduced. Furthermore, as a result of loss of $NaHCO_3$, a mild degree of sodium depletion results. The combined effect of Na loss as $NaHCO_3$ and a reduced filtered load of HCO_3^- eventually reaches a point at which the reduced reabsorptive capacity in the proximal tubule is matched and bicarbonate wasting ceases. At this point the urine is again acid (<6.0) and excretion of TA and NH_4^+ in the distal tubule (because of the low bicarbonate delivery) returns to normal. This is illustrated in Fig. 4.

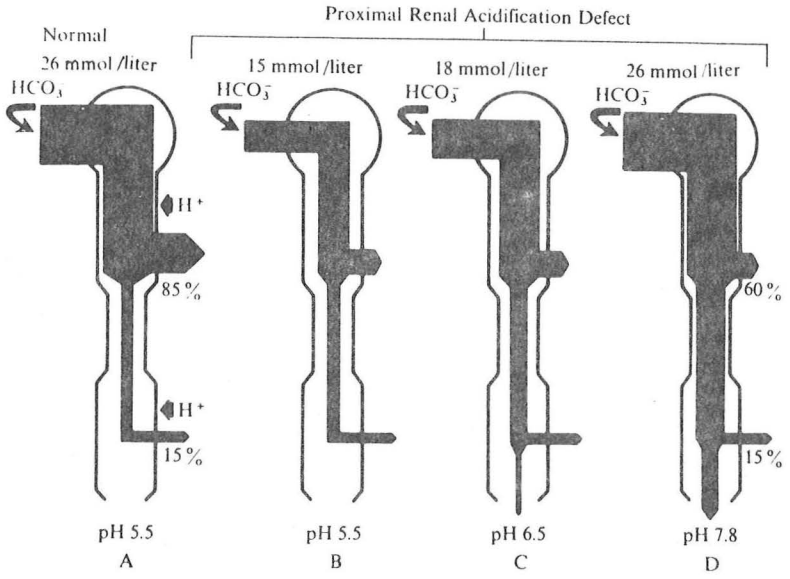

Figure 4: Proximal Renal Acidification Defect
From: Sebastian and Morris (28)

The degree of bicarbonate wasting in patients with Type II RTA at a normal or near normal plasma bicarbonate concentration exceeds 15% of the filtered load ($FE_{HCO_3^-} > 15\%$). This denotes a defect in the proximal tubule since normally much less than this amount of bicarbonate is reabsorbed distally.

B. Distal (Type I) - or Classical Renal Tubular Acidosis

In contrast to proximal (Type II) RTA, patients with distal (Type I) RTA do not acidify their urine despite severe metabolic acidosis. This disorder is due to a reduction in net H^+ secretion in the distal nephron. The pathophysiological basis for this defect could be a result of either: 1) impaired H^+ secretion (secretory defect) or 2) an abnormally permeable distal tubule resulting in increased back-diffusion of normally secreted H^+; or backleak of the H_2CO_3 formed from

the reaction between H^+ and filtered HCO_3^-. These two possibilities are illustrated in Fig. 5.

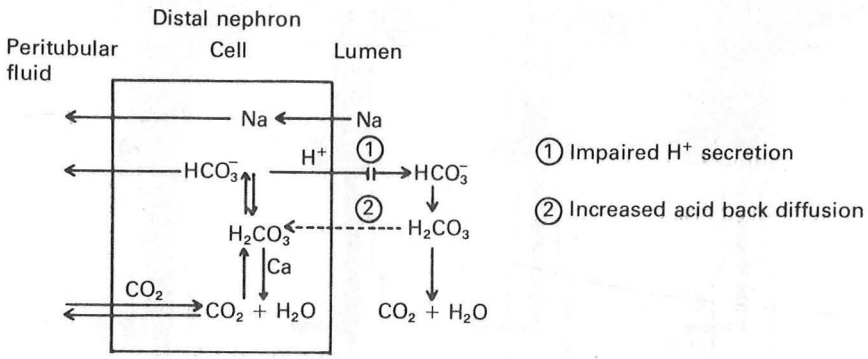

Figure 5: Pathophysiological Basis for Distal (Type I) RTA
from: Arruda and Kurtzman (29).

Until recently, Type I RTA was felt to be due to an inability to produce or maintain the normal steep hydrogen ion concentration gradient present in the distal portion of the nephron (collecting tubule). This hypothesis was based on three observations: 1) the urine pH could not be reduced below 6.0 even with severe systemic acidosis, 2) total bicarbonate reabsorptive capacity was not reduced, and 3) titratable acidity could be increased during phosphate infusion. This was assumed to result from either the inability to secrete H^+ against steep gradients or increased permeability to H^+ ions (gradient defect). Halperin and associates (26) suggested another explanation. These investigators argued that secretion could be demonstrated in gradient-limited models if the urine were made sufficiently alkaline (pH > 7.5) so as to produce a favorable gradient for H^+ secretion from cell to lumen. They subsequently demonstrated that the U-B pCO_2 gradient (see Section I) could be utilized as an index of distal H^+ secretion. With this technique Halperin and associates could not demonstrate H^+ secretion in their distal RTA patients despite urine pH

values as high as 7.7 to 8.1. Based on these observations they suggested that distal RTA was due to impaired H^+ secretion (secretory defect) rather than a gradient defect. The findings of Halperin et al. are summarized in Fig. 6.

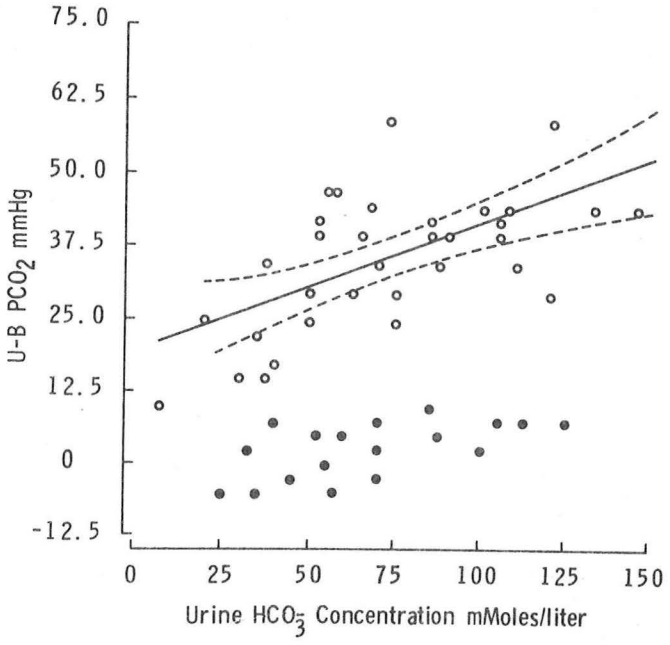

Figure 6: U-B pCO_2 in Controls (open circles) and Patients with Distal RTA (closed circles). From (26)

An alternative explanation for these observations has been advanced by Sebastian, McSherry, and Morris (30). These investigators have noted that if the distal tubule were abnormally permeable to H_2CO_3, back-diffusion of the undissociated acid could dissipate the disequilibrium pH normally produced by H_2CO_3 accumulation (4). Therefore, the U-B pCO_2 would be reduced but could not be utilized to distinguish between the two types of defects. As indirect support for this hypothesis, they also noted that the defect in acidification produced by amphotericin-B nephrotoxicity is a result of an abnormally increased permeability of the normally "tight" collecting tubule epithelium. In vitro studies of the turtle urinary bladder indicate that amphotericin-B impairs acidification by increasing the permeability of the

luminal membrane to H^+ (31). Recent studies from Taher and associates have also demonstrated that toluene "sniffing" can result in a similar permeability defect (59,31).

Recently, Arruda and Kurtzman have suggested that infusion of sulfate and phosphate could be used to differentiate between distal acidification defects due to back-diffusion or secretion of H^+ (29). Such an approach is outlined in Table 3.

Table 3 Distinction between a gradient RTA and Secretory RTA.

	Secretory defect	Gradient defect
Minimal urine pH during acidosis or with NH_4Cl	>5.5	>5.5
Urine-blood pCO_2 gradient in maximally alkaline urine (urine pH >7.8)	<10 mm Hg	<10 mm Hg
Urine pH following Na_2SO_4 infusion	>5.5	<5.5
Urine-blood pCO_2 gradient during neutral phosphate infusion (urine pH 6.8–7.4)	<10 mm Hg	30 mm Hg

From: Arruda and Kurtzman (29).

These investigators observed that the defect due to lithium administration, by these criteria, was an example of a "gradient defect", while the defect observed after unilateral ureteral obstruction was due to a "secretory defect". The validity of the use of these maneuvers to classify acidification defects in naturally occurring disease is not known.

In summary, the physiologic observations in patients with distal RTA can be explained by either of these two types of defects. Whether this disease is a homogenous entity due to one of the proposed mechanisms,

or a heterogenous disorder with differing types of pathophysiologic dysfunction is not known. It appears however, that aside from certain permeability defects induced by agents such as amphotericin-B and toluene, most chronic forms of distal RTA are associated with reduced rates of active H^+ secretion in the cortical and medullary collecting tubules.

C. Pathophysiological Bases of Renal Hyperchloremic Acidosis with Hyperkalemia (Type VI RTA)

Type IV RTA is characterized by an abnormally low net secretion of both H^+ and K^+ in the distal nephron. An important accompanying feature of this disorder is an abnormally low rate of ammonium excretion due, in part, to hyperkalemia. The hyperkalemia observed in these patients is in sharp contrast to the hypokalemia which occurs in both Type I and II RTA. Although Type IV RTA involves a defect in H^+ and K^+ transport, indicating an abnormality involving the distal nephron, unlike classical distal RTA (Type I), patients with Type IV RTA *can* lower urine pH during systemic acidosis or after challenge with an NH_4Cl load. This defect appears to be determined by either decreased ammonia production, H^+ secretion or both. The role of aldosterone in collecting tubule H^+ and K^+ secretion in exchange for sodium has already been discussed (Section I). It is of interest then that this form of RTA is often caused by a hyporeninemic form of hypoaldosteronism. The ability of patients with this disorder to lower urine pH is consistent with *in vitro* studies which indicate that aldosterone has no effect on the force of the H^+ pump, i.e. to maintain H^+ gradients, but increases the rate of H^+ secretion by increasing conductance through the active transport pathway or even by an equivalent mechanism such as the synthesis of new pump sites (23). Aldosterone also increases H^+ secretion indirectly by virtue of the increase in lumen negative potential difference resulting from increased sodium reabsorption.

The effects of aldosterone on potassium excretion may also influence the effect of the hormone or renal acidification. Potassium depletion

enhances, and potassium excess decreases the ability of the proximal tubule to reabsorb bicarbonate. Chronic potassium loading also suppresses renal ammonia production. Any impairment in renal acidification associated with aldosterone deficiency may be due in part to a reduction in renal potassium secretion and the consequent hyperkalemia.

The effects of aldosterone deficiency on urinary acidification has been extensively evaluated by Hulter, Sebastian and associates (32) in adrenalectomized dogs maintained on glucocorticoid and mineralocorticoid hormonal replacement. When the administration of mineralocorticoid hormones is selectively discontinued, net acid excretion decreases, and hyperkalemia and hyperchloremic acidosis occurs. The reduction in net acid excretion is due largely to a reduction in excretion of ammonium, which in turn appears to be due to diminished renal production of ammonia, since it occurs in the absence of an increase in urine pH or a decrease in urine flow. Urine pH remains constant or decreases (to values as low as 5.2). The reduction in ammonia production appears to be due in part to hyperkalemia, since the excretion rate of ammonium correlates inversely with the plasma potassium concentration. Urinary ammonium excretion does not decrease on discontinuation of mineralocorticoid if the occurence of hyperkalemia is prevented by concomitantly restricting potassium intake. Since net acid excretion still decreases, this suggests that the impairment of acidification is not entirely a consequence of impaired ammonia production. Further studies from these investigators suggest that aldosterone deficiency impairs the ability of the distal nephron to secrete H^+ at normal rates but does not impair its ability to generate the usual H^+ concentration gradient from blood to urine.

An impairment in renal acidification like that in dogs with selective mineralocorticoid deficiency has been identified in patients with hypoaldosteronism secondary to impaired renin secretion (33). These patients have persisting hyperchloremic acidosis and hyperkalemia, moderate decreases in glomerular filtration rate, but no glucocorticoid deficiency. During acidosis the urine is bicarbonate free and quite

acid, but ammonium and net acid excretion is subnormal when compared to normal subjects ingesting similar diets. Ammonium excretion varies inversely with plasma potassium concentration. In a study of four such patients prolonged administration of the synthetic mineralocorticoid Florinef increased urinary potassium and net acid excretion, corrected hyperkalemia, and improved the degree of acidosis. Except in the patient with the lowest glomerular filtration rate (13 ml/min), the increased acid excretion was due entirely to increased ammonium excretion. Urine pH decreased initially in each patient, but in the three patients with the highest filtration rates (25 ml/min), it increased as ammonium excretion increased, indicating that renal ammonia production increased. Urinary ammonium excretion correlated inversely with serum potassium concentration (Fig. 7) and did not decrease on discontinuation of therapy if hyperkalemia was prevented by potassium restriction. Acidosis recurred even though ammonium excretion did not decrease, due to an increase in urine pH and reduction in titratable acid excretion. These findings indicate that administration of mineralocorticoid hormone in patients with hyporeninemic hypoaldosteronism can augment both renal H^+ secretion and by correction of hyperkalemia, renal ammonia production, and thereby ameliorate metabolic acidosis. The finding of a substantial ameliorative effect with "physiological replacement" amounts of mineralocorticoid suggests that the deficiency of aldosterone is a major factor in the pathogenesis of Type 4 RTA in these patients.

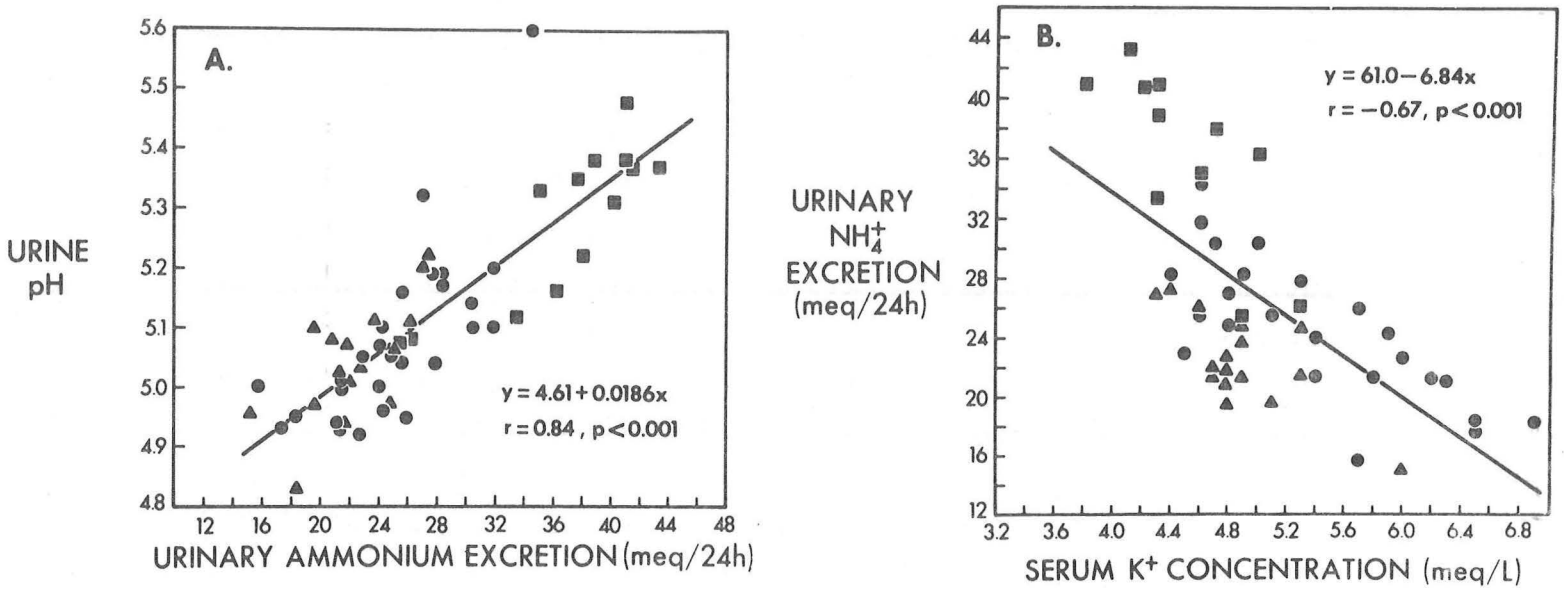

Figure 7: Relation between the rate of urinary ammonium excretion and serum K^+ concentration (a) and between urine pH and urinary ammonium excretion (b) during treatment with fludrocortisone in three patients with hyporeninemic hypoaldosteronism. (From Sebastian et al., 1977, New England Journal of Medicine, 297, 576) (33).

The specific mechanism for the hypoaldosteronism in this disorder has not been clearly delineated. Schambelan and associates have recently demonstrated that the vast majority (85%) of these patients have functionally significant hypoaldosteronism as a result of hyporeninemia (34). This could conceivably occur as a result of either 1) disease involving the juxtaglomerular (J-G) apparatus and thus reduced renin elaboration, or 2) functional hyporeninemia as a result of volume overexpansion. Support for both possibilities exist and are not necessarily mutually exclusive.

In diabetes mellitus, for example, at least three mechanisms for the hyporeninemia have been proposed: 1) decreased catecholamine stimulation of renin secretion secondary to autonomic neuropathy, 2) structural renal disease with disruption of the J-G apparatus, and 3) expanded extracellular fluid volume. Hyalinization of the afferent

arteriole might result in destruction of the juxtaglomerular cells and thereby reduce renin secretory capacity. This lesion, as well as the arteriolar sclerosis that results in an abnormal separation of the juxtaglomerular cells and macula densa cells, occurs commonly in diabetic patients with nephropathy. Oh and associates have demonstrated an increased extracellular volume in four patients with hyporeninemic hypoaldosteronism (35). Furthermore, when these patients were volume contracted by sodium restriction and furosemide administration there was an increase in plasma renin activity (PRA) and plasma aldosterone. However, Sebastian and Schambelan have recently reported 3 patients with Type IV RTA who responded to furosemide therapy, presumably as a result of an increase in K^+ excretion, correction of the hyperkalemia, and an increase in NAE which was due totally to an increase in NH_4^+ excretion. This finding again attests to the importance of hyperkalemia in the defect in urinary acidification in this disorder. The demonstration of an inactive form of renin (i.e., "big renin") in the plasma of diabetic patients suggests that the failure to convert a presumed renin "precursor" to the smaller active form of renin may underlie the hyporeninemia in some patients.

In patients with hyporeninemic hypoaldosteronism associated with diabetes mellitus, aldosterone secretion may be reduced in part because of an associated primary defect in adrenal hormonal synthesis. In one such patient the magnitude of the increase in aldosterone secretion for a given increase in plasma renin activity was markedly blunted in comparison with that observed in patients with hyporeninemic hypoaldosteronism as a group. The aldosterone secretory response to oral K^+ loading and to infusion of ACTH was also markedly blunted in this patient. In such patients a primary deficiency in both renin and aldosterone secretion may contribute to the pathogenesis of the mineralocorticoid deficiency.

In diabetic patients with hyporeninemic hypoaldosteronism, the severity of the hyperkalemia may be responsible, in part, for the associated defect in insulin secretion. In two insulin-dependent

diabetic patients with hyporeninemic hypoaldosteronism, paradoxic hyperkalemia occurred in response to glucose administration and during periods of spontaneous hyperglycemia (Selected reading 4).

Finally, in a very small number of patients with hyperkalemia, hypertension, and Type IV RTA, but without glomerular insufficiency, an alternative hypothesis has been proposed by Schambelan, Sebastian and Rector (36). These investigators have suggested that the primary disturbance in these few patients is an abnormally increased reabsorption of chloride in the distal tubule which shunts the sodium and mineralocorticoid dependent electrical driving force for potassium secretion resulting in hyperkalemia and secondarily augments distal Na^+ reabsorption resulting in volume expansion, hypertension, and hyporeninemic hypoaldosteronism.

In summary, Type IV RTA is a pathophysiologically heterogeneous disorder or group of disorders resulting from one or all of four possibilities:

1. Hyporeninemic hypoaldosteronism

    a. Disease or disruption of J-G apparatus

    b. Expansion of ECF volume

2. Decreased nephron mass - ammoniagenesis

3. Increased distal NaCl reabsorption - Distal chloride shunt.

4. Decreased response of collecting tubule to mineralocorticoid

III. CLINICAL MANIFESTATIONS, DIAGNOSIS, AND TREATMENT OF RENAL TUBULAR ACIDOSIS

A. Differential Diagnosis of Normal Anion Gap Hyperchloremic Metabolic Acidoses.

Abnormalities in renal tubular function leading to impairment of urinary acidification, if severe, will result in systemic metabolic acidosis of the normal anion gap, hyperchloremic variety. The mechanism of the hyperchloremia has already been discussed (Section I). It should be emphasized that of the disorders resulting in a hyperchloremic metabolic acidosis, renal tubular acidosis is the least common.

In evaluating patients with a normal anion gap and a hyperchloremic metabolic acidosis, the disorders in Table 4 should always be considered and the extrarenal disorders (A-F) must be ruled out prior to serious consideration of a diagnosis of renal tubular acidosis.

Table 4 - Causes of Hyperchloremic Metabolic Acidosis with Normal Anion Gap

A. Gastrointestinal disorders
   1. Diarrhea
   2. Pancreatic fistula

B. Ureterosigmoidostomy, Ureteroileostomy

C. Ingestion of Acids or Potential Acids
   Parenteral Hyperalimentation, NH_4Cl, $CaCl_2$, HCl

D. Posthypocapneic state

E. Rapid I.V. infusion (dilutional acidosis)

F. Carbonic Anhydrase Inhibitors

G. Renal disorders
   1. Renal tubular disorders
      a) Proximal RTA
      b) Distal RTA
      c) Type IV RTA
   2. Primary deficiency of urinary buffer (Phosphate depletion, impaired ammoniagenesis)
   3. Post renal transplantation

B. "Classical" or Distal RTA (Type I)

Distal RTA may be primary (hereditary or sporadic) or acquired (secondary) (37). Furthermore, either the primary or secondary variety may occur in either an incomplete or complete form.

1. "Complete" vs. "Incomplete" RTA

Patients with incomplete RTA are not persistently acidotic despite an inability to lower urine pH with an acid load. These patients are able to compensate for their acidification defect and remain in balance by increasing ammonia synthesis and NH_4^+ excretion (38). Hypercalciuria and hypocitraturia may occur despite normal acid-base parameters. Some of these patients eventually develop complete distal RTA with systemic acidosis, often after developing nephrocalcinosis. It appears, therefore, that "incomplete" RTA represents an early compensated state of RTA. In untreated patients with the complete form the urine pH is inappropriately high, net acid excretion is inappropriately low for the degree of systemic acidosis, and bicarbonate is present in the urine. Even when bicarbonate is administered and the plasma bicarbonate concentration is increased to normal, neither the urine pH nor the bicarbonate excretion increases greatly. In the adult patient the amount of bicarbonate excreted in the urine at a normal plasma bicarbonate concentration is a very small fraction (<5%) of the filtered load (28). All of these findings indicate a purely distal tubular defect. Furthermore, these patients are not able to increase urinary pCO_2 above arterial levels as occurs in normals during an alkaline diuresis. This confirms that the defect is confined to the distal tubule.

The wide variety of disorders in which distal RTA has been described are summarized in Table 5.

Table 5 - Clinical Disorders Associated with Distal RTA (Type I)

A. Primary (no systemic disease)

1. Hereditary
2. Sporadic

B. Secondary

1. Disorders resulting in nephrocalcinosis

a. 1° Hyperparathyroidism
b. Vitamin D intoxication
c. Hyperthyroidism
d. Idiopathic hypercalcuria
e. Medullary sponge kidney
f. Wilson's disease
g. Fabry's disease

2. Autoimmune disorders

a. Hyperglobulinemic purpura
b. Cryoglobulinemia
c. Hyperglobulinemia (common)
d. Amyloidosis (rare)
e. Sjogren's syndrome
f. Thyroiditis
g. Fibrosing alveolitis
h. Primary biliary cirrhosis
i. Chronic active hepatitis
j. Systemic lupus erythematosis

3. Drugs or Toxins

a. Amphotericin B
b. Lithium carbonate
c. Toluene
d. Cyclamates
e. Analgesics (?)

4. Other Diseases

a. Renal transplantation (late)
b. Hereditary elliptocytosis
c. Sickle cell anemia
d. Marfan's syndrome
e. Carbonic anhydrase B deficiency

2. Autoimmune Disorders:

The frequency with which distal RTA complicates hyperglobulinemic states is especially striking in the "autoimmune disorders." Failure to maximally acidify the urine can be demonstrated in up to half of patients with biliary cirrhosis, Sjogren's syndrome, and hyperglobulinemic purpura. Round cell infiltration of the kidneys is frequently found in these disorders and, although yet unproven, the tubular dysfunction may have an immunologic basis. Except for Sjogren's syndrome and myeloma which can also be associated with proximal RTA, the vast majority of patients with hyperglobulinemia have a distal defect. Morris and Fudenberg evaluated 22 unselected patients with hyperglobulinema and found that 12 had either an overt or incomplete distal RTA (39). The autoimmune and hyperglobulineuric states associated with distal RTA includes: Hyperglobulineuric purpura, cryoglubulinemia, fibrosing alveolitis, Sjogren's syndrome, thyroiditis, primary biliary cirrhosis, lupoid hepatitis, and SLE. It should be pointed out that this association is more common in women in the fourth or fifth decade. It is not known how hyperglobulinemia results in RTA but it is clear that there is no correlation between the class or quantity of the circulating globulin and the renal defect. Hyperglobulinemia may serve as a marker and in this respect, when present should suggest this disorder. Amyloidosis is a rare cause of distal RTA but one case, reported by Luke, showed amyloid literally encasing the distal tubule (40). The patient did not have Bence Jones proteinuria or hyperglobulinemia.

3. Nephrocalcinosis

The distal acidification defect that complicates the major disorders of calcium metabolism is usually, but not always, associated with nephrocalcinosis. The latter may not yet be demonstrable by x-ray when RTA develops. Thus, hypercalciuria and nephrocalcinosis may cause or result from distal RTA (38). Primary hyperparathyroidism appears to result in distal RTA only when nephrocalcinosis has occurred. However, hyperparathyroidism may result in a hyperchloremic metabolic acidosis

not involving the distal nephron as a result of the decrease in net bicarbonate reabsorption in the proximal tubule associated with elevated levels of PTH. Earlier reports that PTH inhibits carbonic anhydrase have not been substantiated.

The increased incidence of complete and incomplete distal RTA in patients with medullary sponge kidney suggests that the cystic dilatation of collecting ducts that characterizes this disorder may disrupt acid secretion. The disease is generally benign unless complicated by RTA, stones, or infection.

4. Drugs or Toxins

Several drugs can result in a distal tubular acidification defect. These include amphotericin B, toluene, lithium carbonate, cyclamate, and certain analgesics. Amphotericin B nephrotoxicity occurs in as high as 90% of patients receiving a cumulative dose greater than 4-5 gms and is not reversible (41). Acidification defects which are reversible can be detected in a large number of patients receiving as little as 1.0 gm. Amphotericin B and toluene alter the permeability of the distal nephron thus allowing backleak of secreted hydrogen (42). A concentrating defect due to a direct antagonism by lithium of the effect of ADH on the collecting tubule cell is commonly observed. Lithium also impairs distal acidification in therapeutic doses in most patients although only incomplete RTA has been reported to date. The inability to elevate urine pCO_2 with HCO_3^- infusions suggests that lithium impairs distal H^+ secretion.

5. Edema-Forming States

There is evidence to suggest that avid Na^+ reabsorption by the proximal tubule may so severely limit distal Na^+ delivery that Na^+-H^+ exchange diminishes. Thus, the urine is inappropriately alkaline, net acid excretion is decreased, and a hyperchloremic acidosis may ensue. This has been most clearly defined in cirrhosis, where hyperglobulinemia may have an additive effect (43).

6. Renal Transplantation

The RTA associated with renal transplantation may be of either the proximal or distal variety. It appears that the distal variety is more common and occurs in association with chronic rejection (44).

Approximately 50 percent of patients receiving cadaver transplants will have evidence of incomplete RTA when challenged with an acid load months to years after renal transplantation. Kidneys from living related donors seem to have a lower incidence. The round cell infiltration of the transplanted kidney suggests that the functional disorder may be an expression of the overall immunologic defect. The development of overt acidosis is prevented by increased ammoniagenesis; therefore, any renal insult, including rejection, that impairs ammonia production will unmask the RTA by allowing the development of a hyperchloremic acidosis.

7. Childhood Variety of Distal RTA or "What happened to Type III?"

Until very recently it was assumed that the physiological character of distal RTA in children was not significantly different from the dysfunction described in affected adults. It is now clear, however, that renal bicarbonate wasting will occur predictably in most preadolescent children with distal RTA who are given alkali therapy in amounts sufficient to sustain correction of acidosis. Children with this syndrome will have a significantly greater fractional excretion of bicarbonate when compared to their adult counterparts. In fact, in children with hereditary distal RTA, true renal bicarbonate wasting will occur but will not be present in the affected parent. In adults therefore, modest amounts of alkali therapy should correct the metabolic acidosis while in children very high daily requirements are necessary. This is, in fact, what has been observed by McSherry and her collegues in treating children with a distal acidification defect but associated with significant bicarbonate wasting (Type III RTA) (45).

8. Complications of Distal RTA

In addition to systemic acidosis the characteristic disturbances associated with distal RTA include: renal sodium wasting (loss of NaA), ECF volume depletion, renal K^+ wasting and hypokalemia, muscle weakness or paralysis, hypercalciuria, nephrocalcinosis, nephrolithiasis and an impaired concentrating ability. Rickets and osteomalacia may be present (46).

During sustained correction of acidosis with alkali many (or all) of these complications will not occur, or will subside over a period of many years.

9. Diagnosis and Treatment (See III E-F)

C. Proximal Renal Tubular Acidosis (Type II)

1. Definition

Proximal RTA is characterized by significant renal bicarbonate wasting. This would be predictable based on our knowledge of the important role of the proximal tubule in bicarbonate reabsorption. However, since distal tubule acidification is not impaired, patients with this disorder, unlike Type I RTA can excrete an acid urine when the filtered load decreases to a level that does not surpass the reabsorptive capacity of the distal segment (i.e. plasma HCO_3^- of 15-17 mEq/L). In addition, this disorder is frequently associated with multiple defects in proximal tubular function so that bicarbonaturia, glycosuria, phosphaturia, and aminoaciduria may co-exist. The finding that more than 15% of the filtered bicarbonate is excreted in the urine at a normal, or near normal plasma bicarbonate concentration is an indication that the reabsorption of bicarbonate in the proximal tubule is impaired (28). Unlike the distal variety of RTA, proximal RTA is not recognized in an "incomplete" form.

2. Disorders Associated with Proximal RTA (Type II)

Type II RTA occurs in a variety of clinical disorders, and it usually occurs as part of a complex abnormality of the proximal tubule characterized by glucosuria, hyperaminoaciduria, and phosphaturia (Fanconi syndrome). These associated conditions are outlined in Table 6.

Table 6 - Clinical Disorders Associated with Proximal RTA (Type II)

A. Primary

1. Infants
   - Pure HCO_3^- wasting
   - Mixed proximal-distal defects

2. Adults

B. Secondary

1. Disorders of amino acid metabolism
   - Tyrosinemia
   - Cystinosis

2. Disorders of carbohydrate metabolism
   - Hereditary fructose intolerence
   - Galactosemia
   - Glycogen storage disease (Type I)

3. Disorders of protein metabolism
   - Multiple myeloma
   - Amyloidosis
   - Sjogren's syndrome

4. Heavy metal toxicity
   - Cadmium
   - Lead
   - Copper (Wilson's disease)
   - Mercury

5. Drugs
   - Sulfamyalon
   - Acetazolamide (Diamox)
   - Tetracycline (outdated)
   - 6-Mercaptopurine

6. Hyperparathyroidism (2°)
7. Renal transplantation (early)
8. Lowe's syndrome
9. York-Yendt syndrome

Pure HCO_3^- wasting occurs more commonly in infants but has been described in an occasional adult patient, the so-called York-Yendt syndrome (47). In many of these conditions the acidification defect occurs as part of a more complex dysfunction of the proximal tubule. The syndrome of renal glycosuria, increased renal clearance of phosphate, and hyperaminoaciduria has been designated the Fanconi syndrome. Adults and children with this syndrome commonly have bone pain, fractures and deformities secondary to rickets or osteomalacia secondary to phosphaturia. One particular disorder causing proximal RTA has been extensively studied by Morris and his associates, hereditary fructose intolerence (48). In this disorder of carbohydrate metabolism ingestion of fructose results in the abrupt onset of an acute Fanconi syndrome which is reversed on withdrawal of the hexose from the diet. These patients have a specific enzymatic defect, that is, the enzyme fructoaldolase is absent. This presumably results in accumulation of fructose - 1 - phosphate in proximal tubular cells which may directly impair H^+ secretion (49).

The disorders of protein metabolism include multiple myeloma and the hyperglobulinemic states especially Sjogren's syndrome. Light chains appear to have a direct toxic effect on proximal tubular cells as a result of reabsorption and catabolism. The majority of patients with Sjogren's syndrome will have an acidification defect, about 60% in some series. Most will have a distal defect while some exhibit a combination of a proximal defect and a distal defect. Interestingly, patients with Sjogren's syndrome will frequently exhibit a round cell infiltrate involving proximal and distal tubules. These infiltrates resemble the infiltrates present in the salivary glands characteristic of this disease (50). Certain heavy metals can cause proximal RTA but these tend to be mild.

Of the drugs that produce proximal RTA, carbonic anhydrase inhibitors are the prototype. Daily treatment with acetazolamide, as in glaucoma, results in a mild but selflimiting hyperchloremic acidosis.

The serum bicarbonate usually stabilizes at 20-22 mEq/L. Sulfamylon, when applied to the skin of the burned patient can be absorbed and metabolized to a potent carbonic anhydrase inhibitor. Old tetracycline as a cause of RTA is observed less frequently because of improved methods of production and storage. Secondary hyperparathyroidism is occasionally associated with proximal RTA. Proximal RTA in the renal transplant recipient occurs in the immediate post-transplant period in a relatively large number of patients. While the proximal defect is usually transient, a chronic distal RTA can occur in association with chronic rejection.

3. Consequences of Proximal RTA

The findings associated with proximal RTA include volume depletion due to renal $NaHCO_3$ wasting and subsequent elevation in renin and aldosterone secretion with renal K^+ wasting. Since hypokalemia per se has a direct effect on the adrenal gland to blunt aldosterone secretion, the severity of potassium wasting is somewhat self-limiting. While $NaHCO_3$ given alone may aggravate the hypokalemia of proximal RTA, renal K^+ wasting in distal RTA is improved (51). Unlike distal RTA, the proximal variety is rarely, if ever, associated with nephrolithiasis or nephrocalcinosis despite hypercalciuria. The reason for the rarity of stone formation in proximal RTA is not entirely clear although several observers feel that the normal urine citrate excretion in this disorder exerts a protective effect (28).

4. Diagnosis and Therapy (See Section III E-F)

D. Hyperkalemic Hyperchloremic Metabolic Acidosis (Type IV RTA)

1. Definition

In contrast to the hypokalemia observed in Types I and II RTA, in some patients with a hyperchloremic metabolic acidosis, hyperkalemia is observed (52). Persisting hyperkalemia almost always reflects insufficient renal tubular secretion of potassium. In Type IV RTA the renal

clearance of potassium is reduced, while in Type I and II RTA renal potassium wasting is characteristic. As in proximal RTA, patients with Type IV RTA have the ability to acidify their urine during spontaneously occurring metabolic acidosis or after NH_4Cl administration. Bicarbonate wasting occurs but is of significantly less magnitude than in proximal RTA; usually less than 10% and often as low as 2-3% of the filtered load will be excreted at a normal plasma bicarbonate concentration. None of these patients have proximal tubular dysfunction such as aminoaciduria, glycosuria or phosphaturia. These findings constitute a separate pathophysiological dysfunction of the renal tubule. The features of Type IV RTA are consistent with a defect in the cation exchange segment in the distal tubule and collecting duct (see Section II) (28).

2. Disorders Associated with Hyperkalemia and Metabolic Acidosis

The wide spectrum of disorders associated with hyperkalemic metabolic acidosis are outlined in Table 7 (modified from Reference 28).

Table 7 - Clinical Disorders Associated with a Hyperkalemic Hyperchloremic Metabolic Acidosis

I. Aldosterone deficiency in patients without intrinsic renal disease

   A. Combined deficiency of aldosterone, deoxycorticosterone, and cortisone

      1. Addison's disease
      2. Bilateral adrenalectomy
      3. Congenital adrenal hyperplasia (21-hydroxylase deficiency)

   B. Isolated aldosterone deficiency

      1. Familial hypoaldosteronism
      2. Chronic idopathic hypoaldosteronism with high plasma renin

II. Isolated aldosterone deficiency in patients with chronic renal insufficiency

A. Hyporeninemia

1. Diabetic nephropathy
2. Pyelonephritis
3. Interstitial nephritis
4. Nephrosclerosis
5. Idiopathic
6. Renal transplantation with deficient renin secretion
7. Lupus nephritis with deficient renin secretion
8. Renal amyloidosis

III. Impaired renal tubule response to aldosterone + aldosterone deficiency

A. Selective tubule dysfunction with impaired renin secretion

B. Chronic tubulointerstitial disease with glomerular insufficiency

IV. Attenuated renal response to aldosterone (with secondary hyperreninemia and hyperaldosteronism)

A. Pseudo hypoaldosteronism
B. "Salt-wasting" nephritis

Isolated deficiency of aldosterone, once considered a rare condition has been reported with increasing frequency in the last five years (53). In adults with this disorder the production of glucocorticoids is intact and the hypoaldosteronism appears to be a direct consequence of impaired renal elaboration of renin (34). This syndrome has therefore been termed hyporeninemic hypoaldosteronism. The lengthy list of disorders associated with this condition (Table 7) is misleading since by far, the majority of these patients have some degree of renal insufficiency with clearances between 20 and 50 ml/min. Most patients have either diabetes mellitus or tubulo-interstitial renal disease. Hyporenemic hypoaldosteronism is commonly observed in this group of patients and could be due to either disease or involvement of the juxta-glomerular apparatus as a result of loss of renal mass or persistant volume overexpansion (see Section II). In addition, these patients have been noted to demonstrate a relative resistance to

mineralocorticoid (54). Decreased nephron mass may prevent an adequate production of ammonia. In part, this appears to be related to hyperkalemia since Kayexelate has been reported to correct the metabolic acidosis as well as the hyperkalemia in a few patients (55). In fact renal disease appears to be a necessary accompaniment for the overt clinical manifestation of this disorder. However, the degree of metabolic acidosis in these patients is out of proportion to the degree of renal insufficiency and is a result of decreased net acid excretion due to reduced ammonia excretion.

In our experience at Parkland Memorial Hospital and in the reported experience of other investigators, diabetes mellitus has been the most frequently associated disorder. Even before the recognition of the pathophysiologic role of impaired renin and aldosterone secretion, the frequent association of hyperkalemic hyperchloremic acidosis and "chronic pyelonephritis" was noted predominantly in patients with diabetes mellitus (56). The occurrence of hyporeninemic hypoaldosteronism has also been observed in association with a variety of tubulointerstitial diseases of the kidney, such as gout, lead nephropathy, and hypercalcemic nephropathy. In some cases the cause of the underlying renal disease is unknown.

E. Diagnosis of Renal Tubular Acidoses

A reasonable diagnostic approach to renal tubular acidosis is outlined in Table 8.

Table 8 - Diagnostic Approach to the Renal Tubular Acidoses (From Narins) (57).

I. Clinical suspicion
- A. Bone disease
- B. Muscle weakness
- C. Nephrocalcinosis
- D. Opaque kidney stones
- E. Normal anion gap acidosis
- F. Glycosuria
- G. Associated diseases known to cause RTA

II. Laboratory confirmation

A. Exclude other normal anion gap acidoses

B. Low buffer excretion; persistently low UpH, low PO_4, or ammonia excretion.

C. Proximal versus distal defect:

	Proximal	*Distal*
Associated wasting of: PO_4, glucose, amino or uric acids	Usual	Rare
Severe K depletion	Uncommon	Common
Nephrocalcinosis/ lithiasis	Rare	Common
Urine pH		
1st AM	< 6.0	> 6.0
Postacid load	< 5.3	> 5.3
Bicarbonate		
Fractional excretion	May be $> 15\%$	< 5–10%
$UpCO_2$	$UpCO_2 > B\ pCO_2$	$UpCO_2 = B\ pCO_2$
Ease of Replacement	Resistant (Need $>$ 3–5 mEq/kg/day)	Sensitive (Need $\leq$ 2–3 mEq/kg/day)

Obviously a high index of suspicion is required prior to confirmation of the diagnosis of RTA by laboratory means. Any of the conditions noted in Table 8 (I.) should be considered ample justification for screening procedures designed to evaluate the ability to acidify.

Practically speaking, the ability to acidify can be screened by simply measuring urine pH in a concentrated a.m. specimen collected under oil (measured immediately with a glass pH electrode). If the urine pH is greater than 6.0 units and RTA is suspected because of the presence of a persistant hyperchloremic acidosis, the 8-hour NH_4Cl loading test can be performed. In this test 0.1 gm/kg NH_4Cl tablets are crushed and placed in gelatin capsules. The patient takes the capsules p.o. over 45 min. (may continue diet). Urine is then collected hourly under oil for 8 hours and pH is determined immediately. Arterial blood gases are collected before and at 3 hours after NH_4Cl. A urine pH less than 5.5 units will rule out distal RTA while patients with proximal (Type II) or Type IV RTA will have

the ability to acidify. Do not use NH_4Cl in patients already acidotic or in patients with liver disease. In the presence of liver disease acidification can be assessed by administration of $CaCl_2$. The standard 72 hour NH_4Cl loading test is rarely necessary clinically and is used primarily in instances in which one wishes to measure titratable acid and NH_4^+ excretion. Na_2SO_4 may also be employed when an acid challenge is desired by intravenous means in patients unable to take NH_4Cl or $CaCl_2$ orally. This test is used primarily, however, to distinguish between a "secretory" and "gradient" type of distal RTA. The tests which assess urinary acidification by an acid challenge are summarized in Table 9.

Table 9 - Diagnostic Tests in RTA - Acid Challenge

I. NH_4Cl Loading - 8 hour test

Objective:	To define ability to acidify urine
Dose:	0.1 Gm/kg NH_4Cl tablets (crushed) and in capsules p.o. over 45 min. (may eat food)
Urine:	pH at baseline and $\bar{q}$ 2 hrs. under oil. Glass pH electrode immediately
Blood:	Arterial blood gases at beginning and at 3 hours
Interpretation:	UpH < 5.3. Be sure $[HCO_3^-]_p$ falls by at least 3-5 mEq/L. Normal response rules out Type I RTA. Type II and Type IV patients can acidify.
Caution:	Do not give with liver disease or existing acidosis

II. NH_4Cl Loading - 72 hr. test

Objective:	To quantitate NAE = TA + NH_4^+ (not required to diagnose RTA)
Dose:	0.1 Gm/kg/day in 3 divided doses
Urine:	24 hr urine on control day and on 3rd day for pH, TA, NH_4^+
Blood:	Lytes, blood gases at start of each urine collection
Interpretation:	

UpH	TA	NH_4^+
	mEq/d	
4.5-5.3	21-46	36-99

III. $CaCl_2$ Loading

Objective: Acid challenge in liver disease or in patients with GI irritation

$CaCl_2 + 2NaHCO_3 \rightarrow CaCO_3 + 2NaCl + CO_2 + H_2O$

Dose: 2.0 mEq/kg dissolved in water

Urine: As for NH_4Cl

Blood: As for NH_4Cl

Interpretation: As for NH_4Cl

IV. Na_2SO_4 Infusion

Objective: Not necessary for diagnosis of RTA. To distinguish between "secretory" and "gradient" types of distal RTA or Type I from Type II.

Caution: Patient must be avidly reabsorbing Na^+ or Na_2SO_4 will produce osmotic diuresis. Avoid rapid acidosis by adding $NaHCO_3$.

Dose: Florinef 1.0 mg. p.o. 12 hrs. before study

4% Na_2SO_4 - 1 liter + 30 mEq $NaHCO_3$ i.v. over 40-60 min.

Urine: FE_{Na} must be $< 1.0\%$

Secretory defect UpH > 5.5

Gradient defect UpH < 5.5

Further evaluation is required to distinguish Type II and RTA. Although a bicarbonate loading test (to determine $T_m\ HCO_3^-$) has traditionally been recommended, I find this test far too difficult to be of practical significance. A simple and reliable alternative is simply to administer alkali p.o. ($NaHCO_3$ or Shohl's solution) over several days. As the plasma bicarbonate corrects toward normal (at least 20 mEq/L or higher) the fractional excretion of bicarbonate can be measured (28). In this test a spot urine total CO_2 content (autoanalyzer) is determined simultaneous with blood total CO_2 content as well as urine and plasma creatinine concentrations. The following calculation is then performed:

$$FE_{HCO_3^-}\ (\%) = (U/P_{HCO_3^-} \div U/P_{Cr}) \times 100$$

Interpretation:

$FE_{HCO_3^-}$ >15% = Proximal RTA

$FE_{HCO_3^-}$ =5-10% = Type IV RTA

$FE_{HCO_3^-}$ <5-10% = Distal RTA

For research purposes, or to define the $T_m\ HCO_3^-$, a standard bicarbonate loading test may be performed (Table 10). This may be useful in children with distal RTA with bicarbonate wasting and to distinguish Types I and II in difficult circumstances. Again, this is not necessary for the diagnosis of RTA.

Table 10 - Diagnostic Tests in RTA - $NaHCO_3$ Loading Test.
Type I vs Type II RTA

Note:	Must begin with acidotic subject. May require NH_4Cl day before.
Alternative:	$FE_{HCO_3^-}$
Dose:	Infuse 3.0% $NaHCO_3$ in order to produce stepwise increments in plasma bicarbonate. Avoid volume expansion.
Blood and Urine:	For each increase in plasma HCO_3^- of 4 mEq/L must have $[HCO_3^-]$ in blood and urine and GFR (do Glofil or creatinine clearance during $NaHCO_3$ infusion).
Interpretation:	Fig. 8

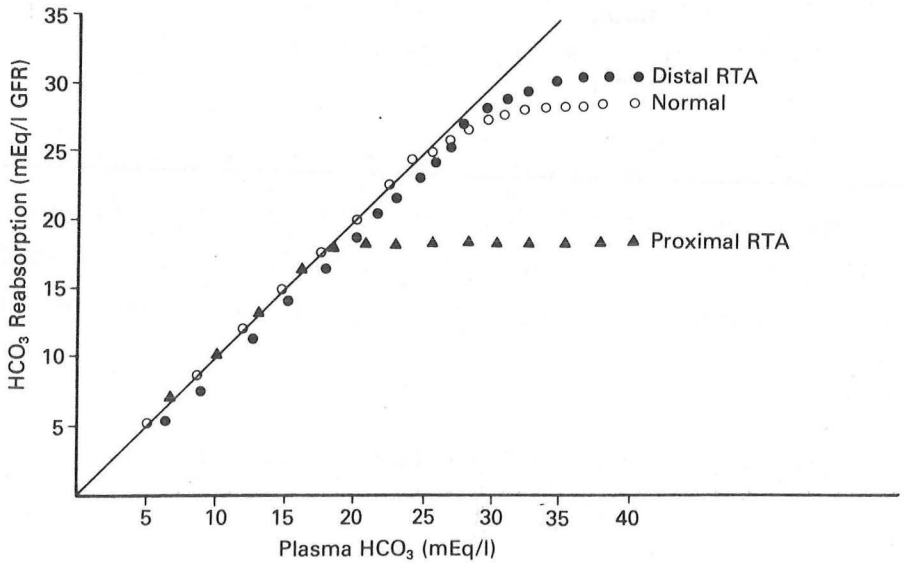

Figure 8. From Arruda and Kurtzman (29).

Finally the clinical findings aid tremendously in this differential. The contrasting features of these disorders are outlined in Table 11.

Table 11 - Contrasting Features of Types I, II, and IV RTA

Proximal RTA (II)	Distal RTA (I)	Type IV RTA
Resistant to Alkali	Adults always sensitive	Usually sensitive
High $FE_{HCO_3^-}$ >15%	$FE_{HCO_3^-}$ <5-8%	$FE_{HCO_3^-}$ = 5-15%
Urine pH <5.5 with NH_4Cl or spontaneous acidosis	Urine pH >5.5 even with acidosis	UpH <5.5 with acidosis
Low T_m HCO_3^-	Normal T_m HCO_3^-	Normal T_m HCO_3^-
U-$BpCO_2$ >20 mmHg	U-$BpCO_2$ <20 mmHg	?
NAE reduced but can be normal when plasma HCO_3^- reduced	NAE reduced for level of systemic acidosis	NAE reduced ($\downarrow NH_4^+$)
Hypokalemia	Hypokalemia	Hyperkalemia
Normal renal function initially	Normal renal function initially	C_{Cr} 20-50 ml/min
Stones or nephrocalcinosis rare if ever	Stones or nephrocalcinosis common	Rare - 1 case of idiopathic hypercalciuria
Phosphoglycosuria	No phosphoglycosuria	No phosphoglycosuria

The conditions known to be associated with these disorders are also helpful in the diagnosis (see Tables 5-7).

F. Therapy and Response

1. Distal RTA (Type I)

Shohl's solution (Na citrate 98 mg + citric acid 140 mg) is much better tolerated than $NaHCO_3$ tablets since CO_2 is not released in the GI tract. Shohl's contains 1 mEq Na^+/ml. About 50-100 ml is given daily in 3 divided doses. The alkali requirement is best determined by obtaining $FE_{HCO_3^-}$ (28). Commonly 1-2 mEq HCO_3^-/kg BW/d in adults and 5-10 mEq HCO_3^-/kg BW/d in children with bicarbonate wasting form (Type III) (28,45).

Response to therapy: Chronic alkali therapy is very beneficial in adults with distal RTA, and in addition to correcting the systemic acidosis, renal potassium and calcium wasting usually subsides (46). In addition, bone pain may be ameliorated and in time, healing can occur. Only if healing does not occur should Vit D + Ca^{++} be added (28) since this may increase the potential for nephrolithiasis. The major problem that frequently occurs is that any febrile illness, diarrhea or, seemingly simple disturbance can precipitate a serious crisis with metabolic acidosis and hypokalemia (57). During a crisis beware that a normal serum K^+ during metabolic acidosis signals severe total body K^+ depletion. In this case glucose containing solutions should be avoided and NaCl, $NaHCO_3$ and KCl should be infused simultaneously. In most children and infants with distal RTA sustained correction of systemic acidosis requires administration of much larger amounts of alkali, especially during periods of rapid growth. When the acidosis is vigorously treated in this manner, McSherry and her collegues have demonstrated that these children grow and develop normally and have no evidence of renal functional impairment for up to 10 years of followup (45). The prognosis in adult patients with Type I RTA is determined more by the severity of the associated disorder, i.e. Sjogren's syndrome, liver disease, autoimmune disease, etc. In most patients, however, the GFR will remain constant for years, even if reduced initially, as long as acid-base balance is maintained (57).

2. Proximal RTA (Type II)

1. $NaHCO_3$ or Shohl's solution (large amounts usually required-5-10 mEq/kg/d).
2. Thiazide diuretic to increase proximal reabsorption of HCO_3^-
3. KCl
4. Vit D + Ca^{++} to suppress PTH

In proximal RTA it is often impossible to totally correct the metabolic acidosis with alkali alone. To the extent that bone disease (osteomalacia) is associated with acidosis, an attempt to correct the acidosis should be made. Therefore, thiazide diuretics are frequently

employed to decrease ECF volume and increase proximal bicarbonate reabsorption (46). Since PTH plays a role in proximal bicarbonate reabsorption, and since proximal RTA is not associated with nephrolithiasis, Ca^{++} can be given orally to suppress PTH (57). It should be emphasized that although alkali therapy usually corrects the hypokalemia of distal RTA, worsening of the hypokalemia is usually observed in the proximal variety (51). Chronic KCl therapy is usually required, therefore.

3. Hyperkalemic Hyperchloremic Metabolic Acidosis (Type IV RTA)

    1. Alkali - usually modest amounts required (1.5-2.0 mEq/day) (28).

    2. Kayexalate - correction of hyperkalemia with Kayexalate may also correct acidosis by increasing NH_4^+ excretion (55). Restrict dietary K^+.

    3. Furosemide - helpful in volume expanded, hypertensive patients by reducing volume and increasing K^+ excretion resulting in increase in NH_4^+ excretion. Aldosterone secretion will increase in response to volume contraction in some patients.

    4. Florinef - (0.1 to 0.3 mg $\bar{q}d$) may be helpful in patients with impaired renal tubular responsiveness to mineralocorticoid. Avoid in patients with, or tendency toward, volume expansion or hypertension.

In Type IV RTA if the hyperkalemia is severe (rare in our experience) Kayexalate may be very beneficial and allow the correction of acidosis as well as hyperkalemia (55). Alkali is required when the acidosis is severe and then, only modest amounts are necessary. Although effective, Florinef is rarely necessary and should be reserved for those patients with selective aldosterone deficiency. A successful result may be achieved in the difficult patient by a combination of

Florinef and furosemide (58). In those patients with the most severe degree of hypoaldosteronism, the ameliorative effect of furosemide was noted to be greatly enhanced by pretreatment with small doses of Florinef (58).

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