RENAL TUBULAR ACIDOSIS OF RENAL INSUFFICIENCY: THE IMPORTANCE OF AMMONIA AVAILABILITY

by

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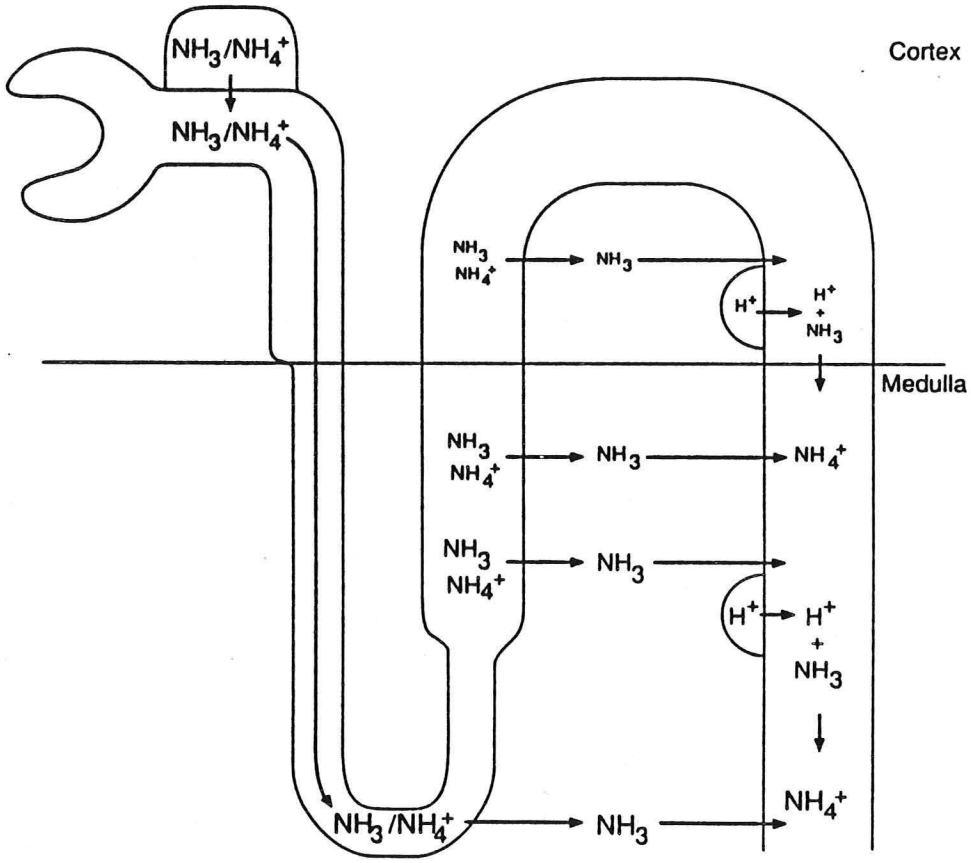

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HYPERCHLOREMIC (NON-ANION GAP) METABOLIC ACIDOSIS

Hyperchloremic (non-anion gap) metabolic acidosis can result from separate pathogenetic mechanisms: 1) a loss of bicarbonate ions as such from the body through the gastrointestinal tract or kidney; 2) an increase in the load of acid chloride presented to body buffers from exogenous sources; and 3) a decrease in the kidney's ability to excrete acid. Table 1 displays the differential diagnosis of hyperchloremic (non-anion gap) metabolic acidosis.

Table I
Differential Diagnosis of Hyperchloremic (Non-Anion Gap) Metabolic Acidosis

Dilution acidosis
Acid chloride loads
Gastrointestinal bicarbonate loss
Renal tubular acidosis

When isotonic saline is infused rapidly, particularly in patients with acute or chronic renal failure, the plasma bicarbonate declines reciprocally in relation to chloride (Garella et al, 1975). However, in most cases, an acute volume expansion to a degree capable of causing marked hemodynamic alterations results in only a minimal depression of serum bicarbonate.

The rapid infusion of HCl or compounds capable of being metabolized to HCl (NH_4Cl, and basic amino acid HCl salts) have an obvious potential for producing hyperchloremic metabolic acidosis (Emmett and Seldin, 1985). This situation may occur when hyperalimentation solutions containing disproportionately greater quantities of basic amino acid chloride salts in relation to acidic amino acid salts, are given to children or patients with impaired renal function (Fraley et al, 1978; Heird et al, 1972). When these basic amino acids are catabolized, hydrochloric acid is released.

The most common cause of hyperchloremic metabolic acidosis is gastrointestinal bicarbonate loss. The prototypic form of hyperchloremic metabolic acidosis due to gastrointestinal bicarbonate loss is that seen with diarrhea. With severe diarrhea, stool bicarbonate is high and chloride low relative to plasma and with continued fecal loss, a hyperchloremic metabolic acidosis develops (Teree et al, 1965). In addition to stool bicarbonate loss, external loss of pancreatic or biliary secretions can also cause a hyperchloremic acidosis. Cholestryramine, calcium chloride and magnesium sulfate ingestion can result in hyperchloremic metabolic acidosis, particularly in patients with renal insufficiency (Kleinman, 1974; Oster et al, 1975). These compounds promote a loss of bicarbonate in the stool. In addition, hyperchloremic metabolic acidosis

may develop in patients with ureteral diversion procedures. The ileum and colon both contain $Cl:HCO_3$ exchangers, and when urine high in chloride maintains a prolonged contact time with the gut wall, bicarbonate will be secreted into stool (D'Agostino et al, 1953). This is especially true with ureterosigmoidostomies, but may also occur with ureteroileal diversions utilizing long loop segments or when stomal stenosis develops (Eiseman and Bricker, 1952; Madsen, 1964; Stamey, 1956).

RENAL TUBULAR ACIDOSIS

Metabolic acidosis is a characteristic feature of a wide variety of renal diseases. In these diseases, the acid-base disturbance reflects a failure of tubular function to keep pace with the normal demands for bicarbonate reabsorption, net acid excretion, or both. Thus, all forms of renal acidosis, whether due to generalized parenchymal diseases or to specific transport defects, are properly considered renal tubular in origin (Relman, 1968). The term renal tubular acidosis (RTA) has been used to characterize a group of disorders of diverse cause in which defective renal acid excretion, bicarbonate reabsorption, or both, occur. Displayed in Table 2 are the types of renal tubular acidosis.

Table II
Types of Renal Tubular Acidosis (RTA)

Associated with hypokalemia
- Proximal RTA (Type II)
- Hypokalemia distal RTA (Type I)

Associated with hyperkalemia
- Hyperkalemic distal RTA (Type IV)

Associated with renal insufficiency
- RTA of renal insufficiency

Renal tubular acidosis associated with hypokalemia, either proximal (Type II) or hypokalemic distal (Type I) are relatively uncommon in adults. They have been recently reviewed (Carvana and Buckalew, 1988; DuBose and Alpern, 1989; Rocher and Tannen, 1986) and will not be covered in this discussion. This discussion will center on the renal tubular acidosis syndromes commonly occurring with renal insufficiency, hyperkalemic distal RTA (Type IV) and what has been called the RTA of renal insufficiency (Cogan and Rector, 1986; DuBose and Alpern, 1989). These two syndromes are by far the most common renal tubular acidoses that we see.

Net Acid Excretion

The kidney excretes 50 to 100 mEq of hydrogen ion each day to balance the net acid load induced by the endogenous acid production of metabolism and loss of potential base through the gastrointestinal tract. The term net acid excretion is used to describe the quantitative contributions of the kidney to the maintenance of acid-base balance, and is calculated by the formula:

$$\text{Net Acid Excretion} = [NH_4^+]_u V + [TA]_u V - [HCO_3^-]_u V$$

where $[NH_4^+]_u V$ is the rate of ammonium excretion; $[TA]_u V$ is the rate of titratable acid excretion; and $[HCO_3^-]_u V$ is the rate of bicarbonate excretion. Thus, the kidney has two major roles in acidification. First, the kidney must reabsorb or reclaim the 4500 mEq of bicarbonate filtered day and; secondly, the kidney must excrete sufficient quantities of ammonium and titratable acid to regenerate the bicarbonate consumed by extrarenal buffering processes. Both of these processes are accomplished by the same general mechanism, which is acidification of the tubular fluid. Normally, the kidney reabsorbs almost all of the filtered bicarbonate. The kidney is able to lower the urine pH to 4.5 by establishing steep hydrogen ion concentration gradients in the distal nephron. However, without the presence of non-bicarbonate buffers in the urine only 0.1 mEq/liter of hydrogen ion would be excreted (Gennari et al., 1982). The major urinary buffers are filtered phosphate and secreted ammonia. Because these buffers are normally sufficiently plentiful, we can excrete the required amount of acid without reducing the urine pH below approximately 6.0. Phosphate, creatinine, and to a minor extent, other filtered buffers able to be titrated in the pH range achievable in the distal nephron (4.5-5.5), are called titratable acids. Titratable acid is the term used to describe the technique for measuring this component of net acid excretion i.e., the back titration of the urine to the pH of the blood. The pK' for the second dissociation of phosphoric acid is 6.8 ($H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H^+$) and is approximately 90% titrated at a pH of 5.8. Creatinine, acetate and other buffers have a pK' value of 5.0 or less and thus contribute little to hydrogen ion buffering over the physiologic range of urine pH. Therefore, phosphate excretion accounts for almost all of the titratable acid excretion, but only about 40% of overall net acid excretion. Many ingested acids have very low pKa's (such as sulfuric and hydrochloric acid) and their conjugate anion cannot be re-acidified even at a urine pH of 4.5. The kidney compensates for these untitratable anions by forming and excreting ammonia/ammonium in the urine. Thus, the requirements for effective distal nephron acid secretion are: 1) intact hydrogen ion secretion; and 2) adequate delivery of non-bicarbonate buffer to the distal nephron.

ROLE OF AMMONIA IN RENAL ACID EXCRETION

Ammonium excretion normally contributes a little over half the net acid excretion per day. Net acid excretion can vary over a broad range to excrete a systemic acid or alkali load and thus preserve systemic acid-base balance

(Lemann et al, 1965; Pitts et al, 1948; Relman et al, 1961; Sartorius et al, 1949; Schiess et al 1948). Alterations in ammonium excretion account for both normal day-to-day variations in acid excretion and for most changes in acid excretion called forth by metabolic and respiratory acid-base disturbances (DeSousa et al,1974; Gennari et al, 1972; Schwartz et al, 1965). This is best exemplified in the balance studies of Relman et al (1961) shown in Figure 1.

In these studies where a chronic acid load was induced by adding ammonium chloride to the diet, net acid excretion increased to match the increase in acid intake. Approximately 90% of the increase in net acid excretion was due to increased ammonium excretion. In fact, in humans under conditions of chronic metabolic acidosis, ammoniagenesis may increase as much as threefold (Tizianello et al, 1982).

To understand how the kidney regulates acid-base balance in the body, it is necessary to understand how the kidney controls the production and transport of ammonium.

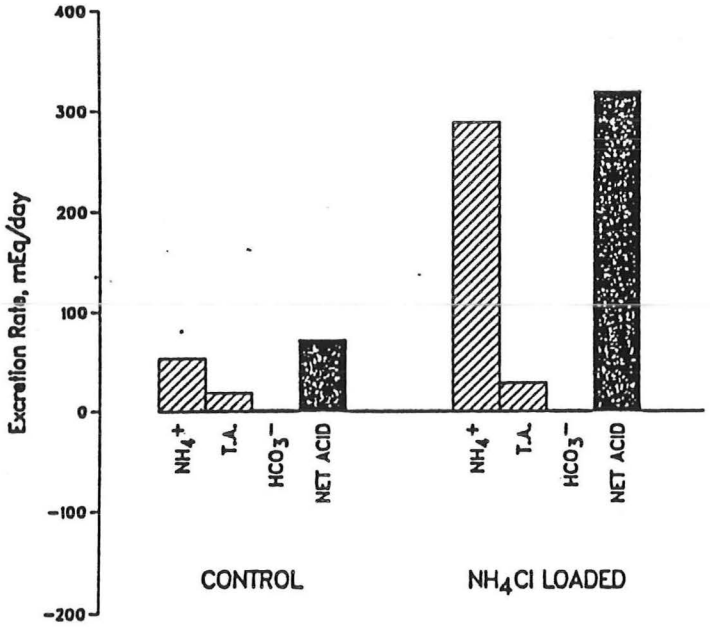


Figure 1. Components of Net Acid Excretion in Normal Humans [Modified from Relman et al (1961)]

Ammonia Production in the Proximal Tubule

Almost all of the ammonium excreted in the urine is produced by the kidney (Van Slyke et al, 1943) in the proximal tubule (Good and Burg, 1984). Most ammonia is derived from glutamine, which is taken up by both the luminal and basolateral membranes of the proximal tubule cell (Pitts, 1973). Glutamine is

transported into mitochondria where it is deaminated to ∝-ketoglutarate (Pitts, 1973). ∝-ketoglutarate enters the tricarboxylic acid cycle and is broken down to malate which is then transported out of the mitochondria. In the cytosol, malate is metabolized to CO_2 and H_2O (Halperin and Jungas, 1983). As one ammonium is excreted into the luminal fluid, one bicarbonate (from ∝-ketoglutarate) exits across the basolateral membrane to enter the extracellular fluid. This process serves to regenerate that bicarbonate "lost" due to titration of endogenous acids produced through metabolism.

In chronic metabolic acidosis, as was discussed earlier, ammonia production is markedly increased. The adaptation responsible for increased glutamine metabolism and ammoniagenesis appears to be due to an increased capacity of the specific mitochondrial glutamine carrier (Simpson, 1988). The reader is further referred to several excellent reviews on ammoniagenesis (Halperin et al, 1986; Pitts, 1973; Simpson, 1988; Tannen, 1978).

Ammonia Transport From the Proximal Tubule to the Collecting Tubule

The pathway of ammonium transfer from its major site of production in the proximal tubule to the final urine is summarized in Figure 3. It should be emphasized that this figure is not intended to show mechanisms of transport. NH_4^+/NH_3 in the figure can therefore represent either NH_4^+ direct transfer or a combination of H^+ and NH_3 movement.

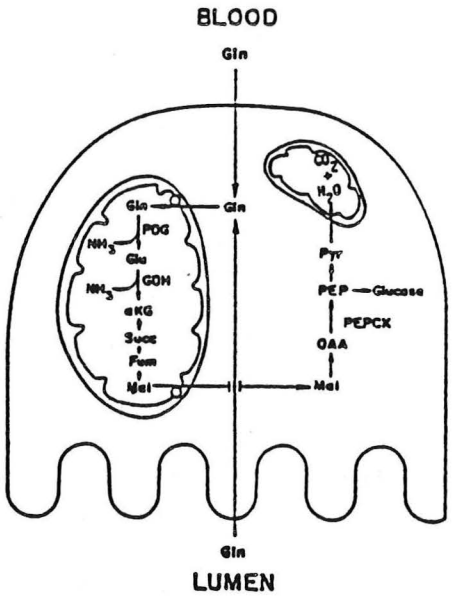


Figure 2. Ammonia Production in the Proximal Tubule [From Alpern, Warnock, and Rector, The Kidney, 1986]

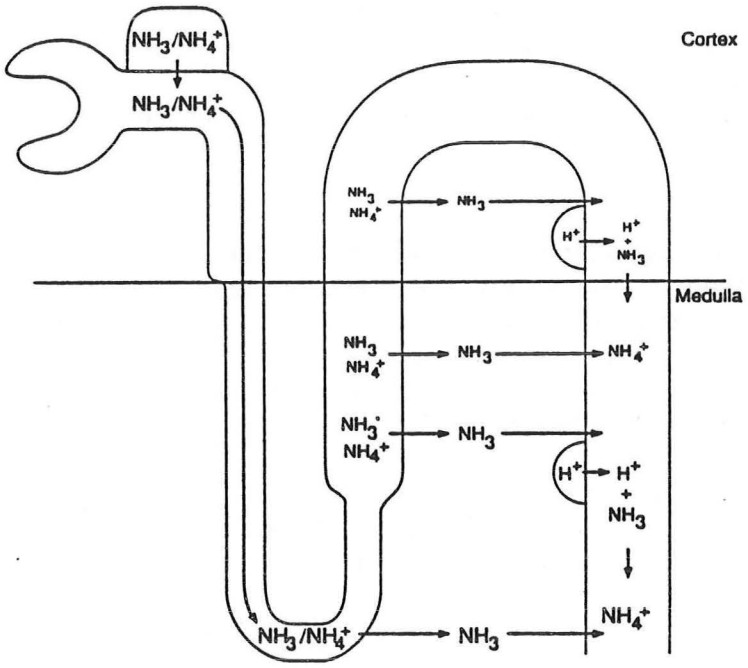


Figure 3. Ammonia Transport From the Proximal Tubule to the Collecting Tubule

Briefly, ammonium produced in the proximal tubule is secreted into the lumen and carried into the renal medulla (Buerkert el al, 1983; Hayes et al, 1964; Sajo et al, 1981). The thin descending limb of Henle adds further ammonium to the luminal fluid such that greater than 100% of the excreted ammonium is found at the bend of Henle's loop (Buerkert et al, 1983). Ammonium is reabsorbed actively along the ascending limb, primarily in the thick ascending limb, such that only 1/3 of that secreted in the proximal tubule reaches the distal tubule (Good et al, 1984). Ammonium accumulates in the medullary interstitium to concentrations greater than cortex or systemic blood (Buerkert et al, 1982; Good et al, 1987; Robinson and Owen, 1965; Stern et al, 1985). The fact that ammonium is actively absorbed in the thick ascending limb against a concentration gradient, and evidence exists for a recycling pathway between ascending and descending limbs of Henle (Garvin and Knepper, 1987; Good et al, 1984), suggests that ammonium accumulation in the medullary interstitium occurs by counter-current multiplication as initially proposed by (Robinson and Owen, 1965; Sullivan, 1965). Ammonium in the medullary interstitium is then secreted across the collecting duct epithelium by a combination of active H^+ secretion and passive NH_3 movement down a concentration gradient, to become trapped in the acidic luminal fluid of the distal nephron. Thus, most of the ammonium absorbed

in the ascending limb of Henle is ultimately shunted into the collecting ducts and excreted. For an excellent extensive review of ammonium transport in the kidney, see Knepper et al (1989).

EFFECT OF LUMINAL pH ON THE RATE OF H^+ SECRETION

The effect of luminal pH on the rate of H^+ secretion in the distal nephron has been best examined in the turtle urinary bladder, the functional analogue of the mammalian collecting tubule. Studies by Steinmetz and Lawson (1971) and later confirmed by Al-Awqati (1978) have shown that active transcellular proton secretion decreases as luminal pH decreases. A linear relationship exists over the pH range 7.4-4.4 (see Figure 4).

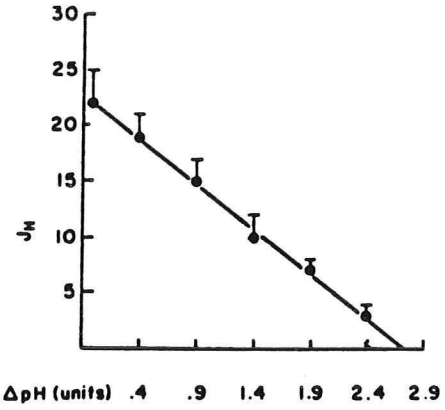
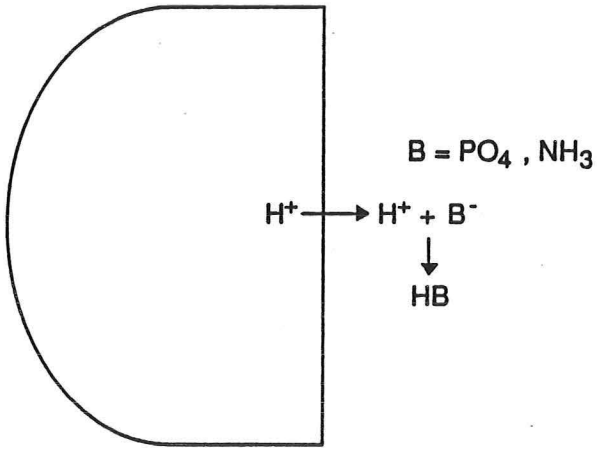


Figure 4. Effect of luminal pH on the rate of hydrogen ion secretion in the turtle urinary bladder (Adapted from Al-Awqati, 1978)

ROLE OF BUFFERS IN DISTAL NEPHRON ACIDIFICATION

As mentioned earlier, the distal nephron must secrete that amount of protons generated, in order for one to maintain normal acid-base balance. Although this 50-100 mEq of protons is small (compared to the 4500 mEq of protons required for bicarbonate reclamation), failure of the distal nephron to perform this act will result in the cumulative development of metabolic acidosis. Only 10 mEq per liter of protons would lower urine pH to 2.0 and subject the luminal tissues to extremes of acidity. Moreover, as mentioned earlier only 0.1 mEq per liter of protons would be required to lower the urine pH to 4.5; the maximal

lower limit of urinary pH. To rid the body of the 50-100 mEq of acid generated from metabolism, the kidney utilizes non-bicarbonate buffers such as ammonium, phosphate and creatinine to increase the rate of acid excretion without exposing the luminal tissues to the extremes of low pH values. However, as shown in Figure 5, a paradox develops when decreases in buffer delivery to the distal nephron occurs. That is, net acid excretion and hydrogen ion secretion decrease, but urine pH also decreases as the limited hydrogen ion secreted is unbuffered.



Paradox: Decreases in buffer delivery lead to
↓ H^+ secretion and
↓ Urine pH

Figure 5. Role of Buffers in Distal Nephron Acidification.

HYPERKALEMIC DISTAL RENAL TUBULAR ACIDOSIS

With this background, we will now discuss the most common of the renal tubular acidosis syndromes, hyperkalemic distal renal tubular acidosis. To understand hyperkalemic distal renal tubular acidosis, one must review the anatomy and physiology of the collecting tubule.

Mechanism and Regulation of Distal Acidification

ANATOMIC AND PHYSIOLOGICAL COMPONENTS OF THE DISTAL NEPHRON

The distal nephron is divided into several segments which as a group are called the collecting tubule (Madsen and Tischer, 1986). For the purpose of this discussion, we will consider the two most potent acidifying segments of the

collecting tubule: the cortical collecting tubule and the medullary collecting tubule.

Cell Types in the Cortical Collecting Tubule

The cortical collecting tubule contains three major cell types as shown in Figure 6: the principal cell, the Type A intercalated or proton secreting cell, and the Type B intercalated or bicarbonate secreting cell (Madsen and Tischer, 1986). The major function of the principal cell is to reabsorb sodium and secrete potassium. The Type A intercalated cell secretes protons and thus reabsorbs bicarbonate. The Type B intercalated cell secretes bicarbonate.

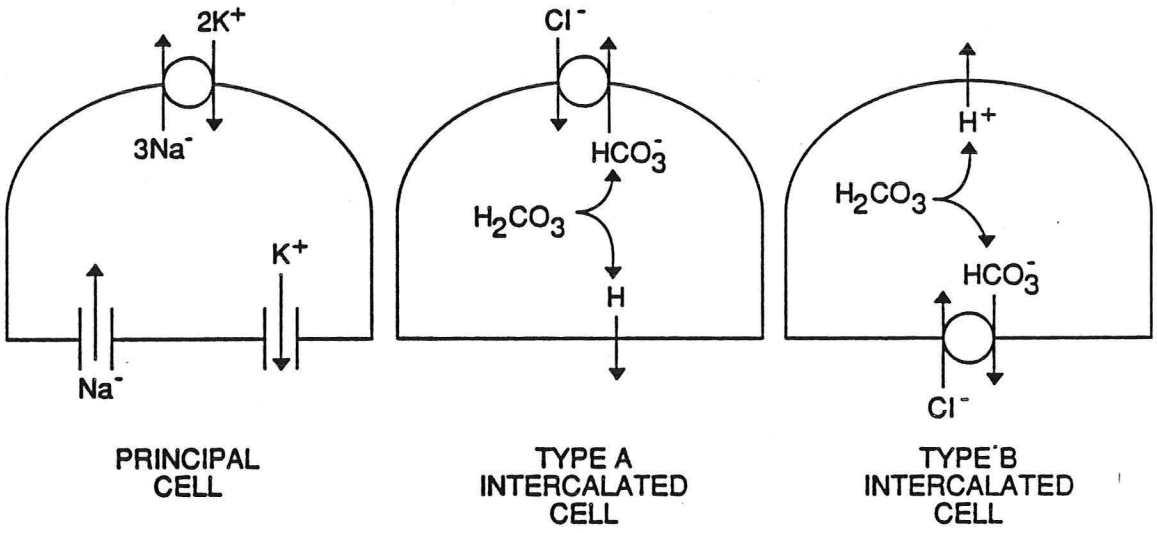


Figure 6. Cell Types in the Cortical Collecting Tubule.

Na^+ Reabsorption/K^+ Secretion

The principal cell contains an apical membrane amiloride-sensitive sodium channel. Sodium moves from the lumen across the apical membrane through these sodium channels into the cell down its electrochemical potential gradient (Stokes, 1982). Sodium is extruded from the cell by an energy-consuming process through the Na-K-ATPase pump. The process of sodium absorption generates a lumen-negative transepithelial potential difference (MacKnight et al, 1980). Potassium moves in an opposite direction. Potassium enters the cell through the Na-K-ATPase and exits across a barium-sensitive apical membrane potassium channel down its electrochemical potential gradient. In the cortical collecting tubule potassium secretory rates and sodium absorption rates are linearly related (Stokes, 1981); sodium absorption is required for potassium secretion; and, the ratio of sodium absorption to potassium secretion closely approximates the

stoichiometry of the Na-K-ATPase pump as determined in the red cell (Garrahan and Glynn, 1967), frog skin (Nielsen, 1979), and turtle colon (Kirk et al, 1980).

H^+ Secretion/HCO_3^- Absorption

The type A intercalated cell reabsorbs bicarbonate by active electrogenic proton secretion (Koeppen and Helman 1982, Stoner et al, 1974). This is felt to be mediated by an apical membrane proton translocating ATPase (Stone and Xie, 1988). Bicarbonate which accumulates in the cell as a result of proton secretion exits the basolateral membrane in exchange for chloride via a chloride:bicarbonate exchanger similar to the red blood cell band 3 glycoprotein (Schuster et al, 1986). Accumulated intracellular chloride exits across the basolateral membrane which is highly chloride permeable (Koeppen 1985). Because the overall process of H^+ secretion is electrogenic, a parallel anion conductance is required (Fischer et al, 1983). Chloride is the parallel anion and it moves in a paracellular manner as the apical membrane is highly impermeable to chloride (Koeppen, 1987; Stone et al, 1983).

The cortical collecting tubule can both reabsorb and secrete bicarbonate and the direction and magnitude of transport depends on the acid-base status of the animal. Bicarbonate secretion is induced by systemic alkalosis whereas bicarbonate absorption is found under conditions of acidosis (McKinney and Burg, 1977). Since this discussion concerns metabolic acidosis, the bicarbonate secreting Type B intercalated cell will not be discussed. The reader is referred to an excellent discussion by (Koeppen et al, 1985).

Hormonal Control of Collecting Tubule Transport

It is important to point out at this time that aldosterone markedly effects sodium reabsorption, potassium secretion, and proton secretion. Aldosterone stimulates sodium reabsorption making the lumen-negative transepithelial voltage more negative (O'Neil and Helman, 1981). Potassium secretion is also increased, most likely secondary to the increased lumen-negative transepithelial voltage (O'Neil and Helman, 1981) but aldosterone may also increase potassium conductance directly (Helman and O'Neil, 1977; Sansom et al., 1989). Aldosterone stimulates bicarbonate reabsorption (proton secretion) secondarily, by creating a more favorable electrical gradient due to increased sodium reabsorption [(voltage-dependent), O'Neil and Helman, 1977; Schwartz and Burg, 1978]. In addition, mineralocorticoids have been demonstrated to stimulate proton secretion directly even in the complete absence of sodium (Koeppen and Helman, 1982). The effects of aldosterone will be discussed in more detail later.

In summary, the cortical collecting tubule reabsorbs sodium, secretes potassium and can either reabsorb or secrete bicarbonate depending on the prevailing acid-base status. All of these processes can be altered under conditions of aldosterone deficiency or generalized cortical collecting tubule dysfunction, which may result in the development of the clinical syndrome of

hyperkalemic distal renal tubular acidosis.

Cell Types in the Medullary Collecting Tubule

The cortical collecting tubule empties into the medullary collecting tubule. Unlike the cortical collecting tubule, the medullary collecting tubule is composed predominantly by only one cell type, the Type A intercalated cell [(Ridderstrale et al., 1988), see Figure 7].

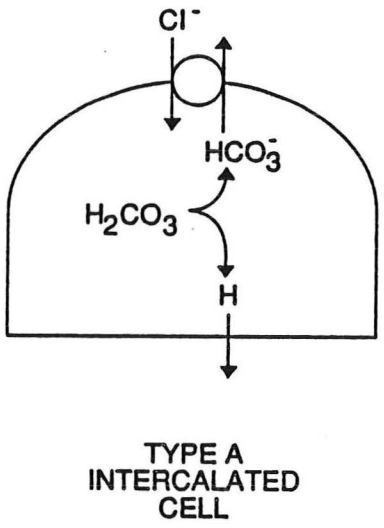


Figure 7. Cell types in the medullary collecting tubule.

Bicarbonate reabsorption is felt to operate by mechanisms identical to those in the Type A intercalated cell of the cortical collecting tubule. However, there is no active net sodium absorption or potassium secretion in the medullary collecting tubule (Stokes, 1982). The medullary collecting tubule also differs from the cortical collecting tubule in that it secretes protons at a higher rate (Lombard et al, 1983; Laski et al 1983); there is no evidence for bicarbonate secretion (Lombard et al, 1983; Jacobson, 1984); there is independence of proton transport from sodium (Stone et al, 1983) and there is a spontaneous lumen-positive transepithelial voltage due to the sole operation of the electrogenic proton translocating ATPase (Lombard et al, 1983). Similar to the cortical collecting tubule, mineralocorticoids stimulate bicarbonate reabsorption in the medullary collecting tubule (Stone et al, 1983). A generalized dysfunction solely of the medullary collecting tubule would result in a deficient proton secretion rate alone and could give a clinical picture of hypokalemic distal renal tubular acidosis (Type 1).

Effects of Aldosterone on Proton Secretion

As mentioned previously, aldosterone stimulates proton secretion directly. This is best exemplified in the studies of Al-Awqati et al (1976) utilizing the turtle urinary bladder (see Figure 8).

Al-Awqati and co-workers found that aldosterone stimulated proton secretion within two hours, at a time before sodium transport was stimulated. This direct

effect on proton secretion was also present when sodium transport was inhibited by ouabain and when sodium transport-induced changes in transepithelial voltage were prevented (short-circuit state). As one can see, mineralocorticoids do not affect the limiting luminal pH gradient but rather increase the rate of H^+ secretion at high luminal pH values. This sodium-independent effect of mineralocorticoids on hydrogen ion secretion has also been found in the cortical collecting tubule (Koeppen and Helman, 1982) and medullary collecting tubule (Stone et al, 1983).

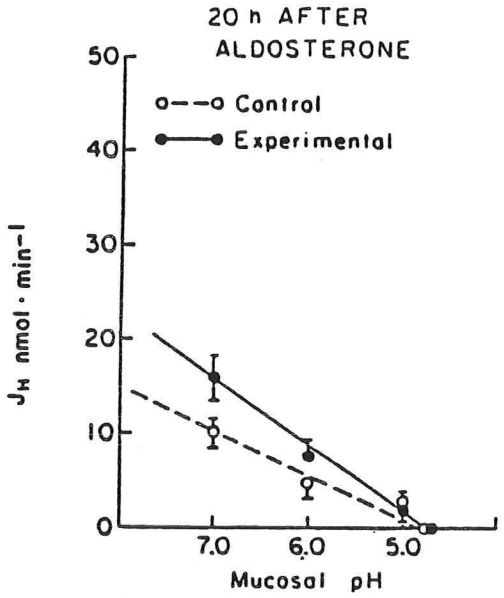


Figure 8. Aldosterone Directly stimulates H^+ secretion in the turtle urinary bladder (Adapted from Al-Awqati et al, 1976)

Direct Effects of Aldosterone Deficiency On H^+ Secretion

The direct effects of aldosterone deficiency on H^+ secretion in the cortical and medullary collecting tubule are shown in Figure 9.

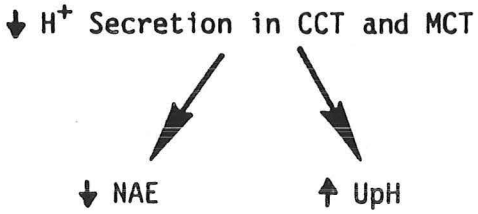


Figure 9. Direct Effects of Aldosterone Deficiency On H^+ Secretion.

Decreased H^+ secretion by the collecting tubule will result in a decrease in net acid excretion and also an increase in urine pH.

Indirect Effects of Aldosterone Deficiency On H^+ Secretion: Role of Hyperkalemia

Hyperkalemia in patients with aldosterone deficiency is an expected consequence of a diminished mineralocorticoid effect on potassium secretion in the cortical collecting tubule (Sebastian et al, 1980). Hyperkalemia has two important effects on ammonia handling in the kidney, which are shown in Figure 10.

Ammonia Production: Effects of Hyperkalemia

Hyperkalemia decreases ammonia production and secretion in the proximal tubule. The precise site of metabolic inhibition of ammonia production by hyperkalemia in the proximal tubule is controversial. Hyperkalemia may inhibit the glutamate dehydrogenase enzyme or inhibit the mitochondrial glutamine transporter and/or phosphate-dependent glutaminase (Sastrasinh and Tannen, 1983; Slepper et al, 1982). Changes in proximal tubule ammonium secretion during hyperkalemia appear to be modulated by the effects of peritubular potassium concentration on ammonium production rather than by an effect of luminal potassium (Knepper et al, 1989).

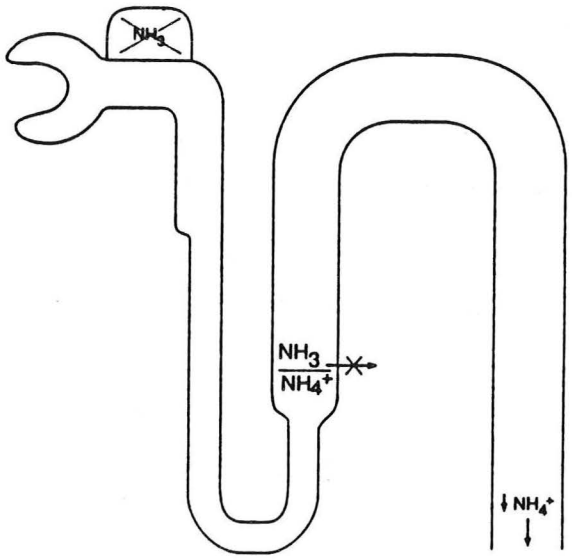


Figure 10. Hyperkalemia Decreases Ammonia Availability To the Collecting Tubule

Ammonia Delivery to the Distal Nephron: Effects of Hyperkalemia

Hyperkalemia also alters ammonia transport in the thick ascending limb of Henle. Active reabsorption of ammonium accounts for 2/3 of the net NH_4^+/NH_3 transport out of the lumen into the medullary interstitium, with passive NH_4^+/NH_3 absorption accounting for the rest (Garvin et al, 1988; Good, 1988; Good, 1987).

As depicted in Figure 11, active transport of ammonium is dependent on the ability of NH_4^+ to substitute for K^+ on the apical Na^+-K^+-$2Cl^-$ cotransporter and is almost completely inhibited by furosemide (Garvin et al, 1988). The furosemide-insensitive NH_4^+ absorption (passive) is completely inhibited by ouabain suggesting that this passive flux would involve apical entry of NH_4^+ via apical membrane K^+ channels (Garvin et al, 1988). These results were recently confirmed by Kikeri et al (1989) who in addition, found the apical membrane of the thick ascending limb of Henle to be highly impermeable to NH_3. This apical membrane impermeability to NH_3 would prevent dissipation of ammonia gradients created by the active and passive NH_4^+ transport processes.

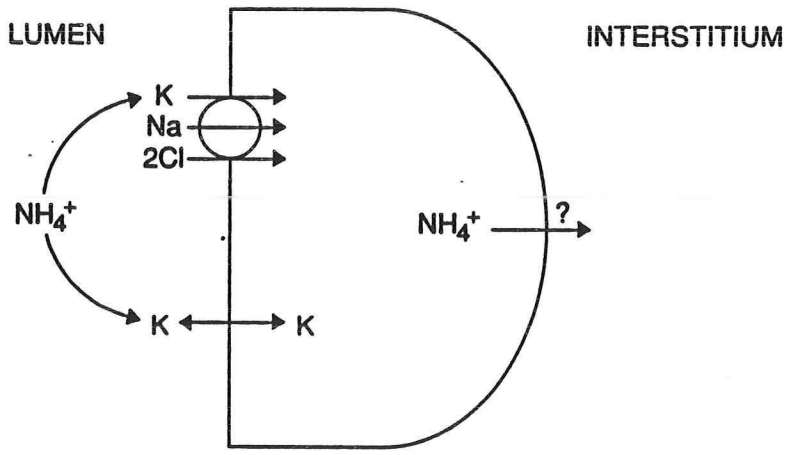


Figure 11. NH_4^+ Absorption in the Thick Ascending Limb of Henle.

During states of hyperkalemia, the associated large increase in medullary potassium concentrations (Battilana et al, 1978; Diezi et al, 1973) would be expected to inhibit NH_4^+ absorption in the medullary thick ascending limb of Henle by effectively competing with NH_4^+ for both active and passive transport processes. Clinically, this appears to be the case in selective aldosterone deficiency. DuBose and Caflisch (1988) found that the maintenance of the metabolic acidosis during mineralocorticoid deficiency is associated with a

failure of the renal medulla to increase ammonium accumulation. Although no measurements of medullary interstitial K^+ concentrations were made, the animals were significantly hyperkalemic (5.8 ± 0.3 mEq/L). This potassium load would markedly increase the luminal K^+ concentration above the level of potassium required to inhibit ammonium transport in vitro [(24 mM), Good, 1987; Good, 1988].

To summarize, the indirect effects of aldosterone deficiency on H^+ secretion mediated through hyperkalemia are shown in Figure 12.

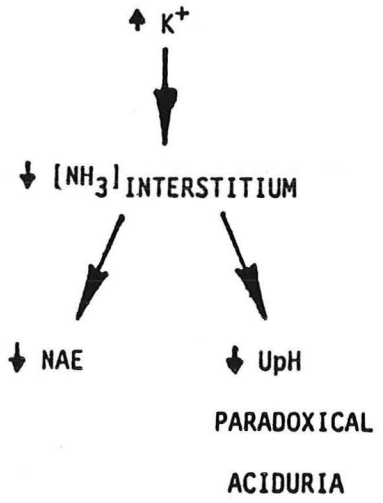


Figure 12. Indirect Effects of Aldosterone Deficiency On H^+ Secretion: Role of Hyperkalemia

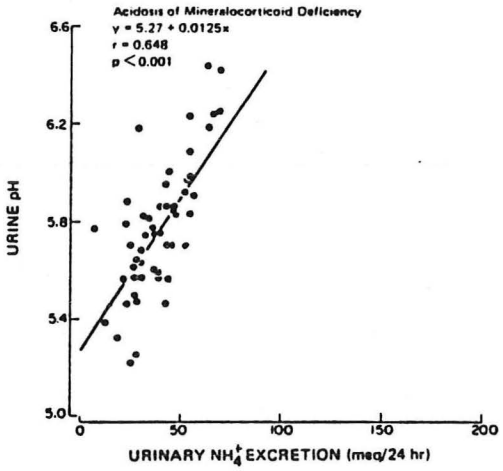


Figure 13. Relation between urine pH and urine ammonium excretion in patients with aldosterone deficiency (Adapted from Hulter et al, 1977)

Hyperkalemia results in a decreased ammonia accumulation in the medullary interstitium by inhibiting proximal tubule ammonia production and effectively competing for ammonium transport and diffusion out of the lumen of the thick ascending limb of Henle. This leads to decreased ammonium accumulation in the urine and thus a decrease in net acid excretion. However, despite the decrease in net acid excretion the urine pH falls paradoxically, as less buffer is available to titrate secreted H^+ ions.

Clinically, this paradox can be seen under the conditions of metabolic acidosis induced by mineralocorticoid deficiency, as seen in Figure 13.

As can be seen, a reduced availability of ammonia for diffusion into tubular fluid (as a consequence of hyperkalemia) reduces intraluminal buffering of secreted hydrogen ion and intraluminal (urine) pH decreases. This low urine

pH occurs despite a decreased rate of hydrogen ion transport which is also a result of aldosterone deficiency. The decreased H^+ secretory rate is manifest when ammonia delivery is not limiting. During mineralocorticoid deficiency-induced acidosis, the pH of the urine varies directly with the excretion rate of ammonium, which in turn varies inversely with plasma potassium concentration (Hulter et al, 1977; Sebastian et al, 1985). In normal humans under conditions of stable chronic metabolic acidosis, a similar linear relationship exists between urine pH and ammonium excretion (Madison and Seldin, 1958). That is, urine pH rises under conditions of increased delivery of ammonia to the distal nephron and buffers H^+ secretion.

If one prevents the development of hyperkalemia in mineralocorticoid-deficient dogs, the direct effect of mineralocorticoid deficiency on hydrogen ion secretion is unmasked. As seen in Figure 14, mineralocorticoid-deficient dogs allowed to become hyperkalemic (Group I) have both a reduced rate of renal ammonium excretion and net acid excretion but still have a low urine pH. If similar studies are performed in dogs maintained normokalemic by dietary potassium restriction (Group II), the ammonium excretion rate is not reduced. However, net acid excretion continues to fall and urine pH rises as the H^+ ion secretory defect induced by mineralocorticoid deficiency is unmasked. Thus, prevention of hyperkalemia in mineralocorticoid deficiency-induced acidosis makes this disorder appear similar to a classic hypokalemic distal renal tubular acidosis (inability to lower urine pH despite metabolic acidosis).

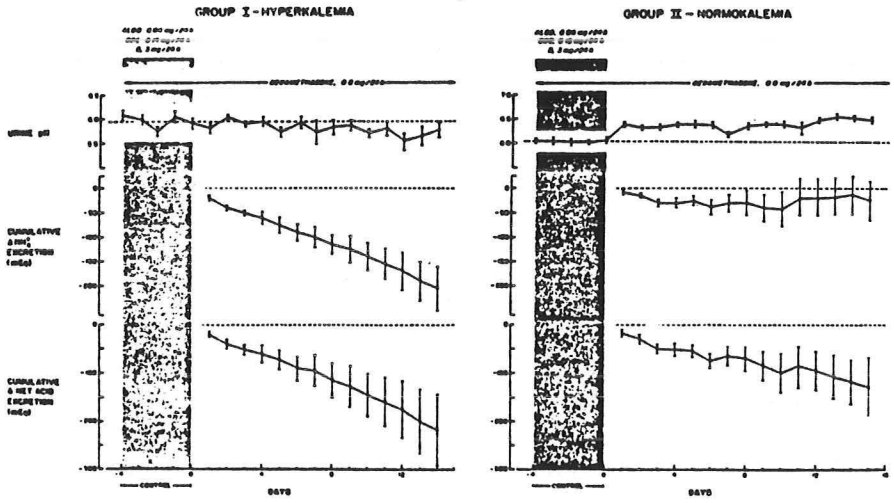


Figure 14. Urine pH, NH_4^+ Excretion, and Net Acid Excretion Under Conditions of Aldosterone Deficiency With and Without Hyperkalemia (Adapted from Hulter et al, 1977)

Table III summarizes the abnormalities which may give rise to collecting tubule acidification defects. The three major etiologies which may give rise to acidification defects in the collecting tubule are: 1) H^+ pump defects which may affect both the cortical and medullary portions of the collecting tubule; 2) reduced electrical augmentation of H^+ secretion (voltage-dependent) which only affects the cortical portion of the collecting tubule; and, 3) lack of H^+ acceptors which affects both the cortical and medullary portions of the collecting tubule.

Table III
Acidification Defects in the Collecting Tubule

1. H^+ pump defects (cortical or medullary)
   - a. Lack of stimulator (Aldosterone deficiency)
   - b. Structural damage to the collecting tubule cells containing the H^+ pump
2. Reduced electrical augmentation of H^+ secretion (cortical)
   - a. Low rate of sodium reabsorption in the cortical collecting tubule
     - 1) Low sodium delivery
     - 2) Low sodium pumping
   - b. Excessive chloride permeability
3. Lack of H^+ acceptors (cortical or medullary)
   - a. Defective synthesis or delivery of NH_3/NH_4^+

Pathogenesis of Hyperkalemic Distal RTA

The etiologies of hyperkalemic distal renal tubular acidosis can be grouped into two major categories: disorders associated with aldosterone deficiency and disorders associated with an abnormal cortical collecting tubule.

Table IV
Etiologies of Hyperkalemic Distal Renal Tubular Acidosis

1. Decreased Aldosterone
   a. Primary mineralocorticoid deficiency
   b. Hyporeninemic hypoaldosteronism
2. Abnormal Cortical Collecting Tubule (Aldosterone Resistance)
   a. Pseudohypoaldosteronism Types I & II
   b. Chronic tubulointerstitial disease
   c. Drugs

ETIOLOGIES OF PRIMARY MINERALOCORTICOID DEFICIENCY

The hyperkalemic distal RTA disorders which occur as a result of aldosterone deficiency can be subgrouped into two categories: primary mineralocorticoid deficiency, and hyporeninemic hypoaldosteronism. I will first discuss those disorders of primary mineralocorticoid deficiency which result in the development of hyperkalemic distal renal tubular acidosis.

Table V.
Etiologies of Primary Mineralocorticoid Deficiency

Combined gluco- and mineralocorticoid deficiency
- Addison's Disease
- Bilateral adrenalectomy
- Bilateral adrenal destruction
- Congenital adrenal enzyme defects
  - 21-Hydroxylase deficiency
  - 3-ß-Hydroxydehydrogenase deficiency
  - Desmolase deficiency

Isolated mineralocorticoid deficiency
- Familial and acquired corticosterone methyloxidase I and II deficiency
- Chronic heparin administration
- Chronic idiopathic hypoaldosteronism
- Transient mineralocorticoid deficiency of infancy
- Inhibition of formation of angiotensin II:
  - Administration of converting enzyme inhibitors
- Acquired adrenal insensitivity to angiotensin II
  - ? Cyclosporine

In all instances of primary mineralocorticoid deficiency one can develop salt wasting with hyponatremia, hyperkalemia, and metabolic acidosis. In some instances there may be signs of glucocorticoid deficiency as well. The degree of hyperkalemia, hyponatremia and development of metabolic acidosis will depend on the absolute deficiency of aldosterone which exists.

Combined Gluco- and Mineralocorticoid Deficiency

Destruction of the adrenal cortex by hemorrhage, infection, invasion by tumors, or autoimmune processes results in Addison's disease. The resultant glucocorticoid and mineralocorticoid deficiency is recognized clinically by hypoglycemia, anorexia, weakness, and a failure to respond to stress. Addison's disease is usually associated with renal salt wasting, hyperkalemia, and metabolic acidosis (DeFronzo, 1980; Szylman et al, 1975; Schambelan et al, 1980) although patients who ingest liberal quantities of sodium chloride, limit their potassium intake, and ingest glucocorticoids may only manifest mild metabolic acidosis and hyperkalemia (Miller et al, 1975; Sebastian et al, 1980). These findings suggest that the effect of aldosterone deficiency to reduce K^+ and H^+ secretion can be partially offset by increasing the delivery of Na^+ to the distal nephron through provision of abundant dietary Na^+. However, unrestricted dietary intake of potassium in these patients is clearly associated with an exaggerated increase in plasma potassium concentration, revealing the underlying impairment of renal potassium handling (Miller et al, 1975; Sebastian et al, 1986). Diagnosis of generalized adrenal insufficiency is confirmed by the finding of subnormal plasma cortisol and 17-hydroxycorticoid following ACTH administration, subnormal plasma and urine aldosterone levels, and by increased baseline plasma ACTH and plasma renin activity levels (Sebastian et al, 1986).

The most common congenital adrenal defect in steroid biosynthesis is 21-hydroxylase deficiency, which is associated with salt wasting, hyperkalemia, and metabolic acidosis in a small fraction of the patients (Oetliker and Zurbrugg, 1970). The defect may be isolated to the glucocorticoid pathway, sparing mineralocorticoid synthesis (Oetliker and Zurbrugg, 1970). With the combined defect, mineralocorticoid deficiency typically results in salt wasting, hyperkalemia, and metabolic acidosis (Iversen, 1955; New et al, 1983). Because the adrenogenital syndrome occurs as a result of a shift of glucocorticoid precursors to androgen synthesis, increased levels of 17-hydroxyprogesterone and progesterone are found. These compounds may contribute in part to the clinical manifestations of aldosterone deficiency as these steroids can act as mineralocorticoid receptor antagonists and inhibit the renal action of aldosterone (Sebastian et al, 1986).

Isolated Mineralocorticoid Deficiency

Hyponatremia, hyperkalemia, and metabolic acidosis can occur as a result of isolated mineralocorticoid deficiency from a variety of familial and acquired disorders.

A deficiency of the mixed function oxidase enzyme, corticosterone methyloxidase, required for the hydroxylation of corticosterone to 18-hydroxycorticosterone (Type I) and for dehydrogenation of 18-hydroxycorticosterone to aldosterone (Type II) may be genetic or acquired (David et al, 1968; Rosler et al, 1977; Ulick, 1976; Veldhius et al, 1980; Veldhius and James, 1981). The requirements for mineralocorticoid supplementation and/or a high salt intake decrease with age in the familial forms. However, these patients are susceptible to volume depletion hyponatremia, hyperkalemia, and metabolic acidosis under conditions of a low salt intake. The presence of the Type II defect can be established by the demonstration of an increase in the serum values of 18-hydroxycorticosterone (Kater et al, 1985).

One potential form of acquired corticosterone methyloxidase deficiency deserves mention. Chronic heparin therapy has been shown to reduce aldosterone levels in man (Conn et al, 1966; O'Kelly et al, 1983).

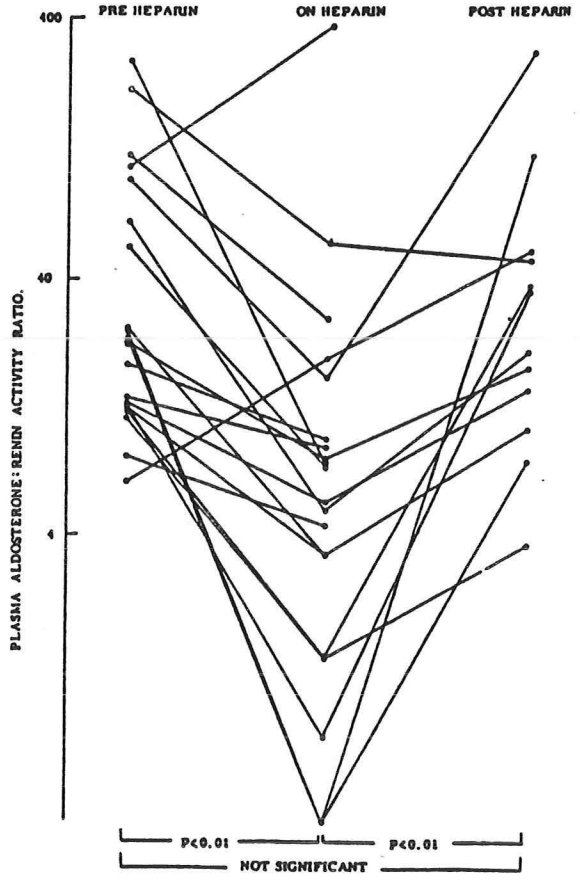


Figure 15. The effect of heparin administration on plasma aldosterone to renin activity ratios. (Adapted from O'Kelly et al, 1983)

As shown in Figure 15, chronic heparin of at least 4 days in duration (dosage, 5000 IU subcutaneously bid to 10,000 IU intravenously q 6°) substantially decreased the aldosterone to renin activity ratio, which was reversible following at least 2 days of heparin discontinuation. The aldosterone to renin activity ratio is an index of aldosterone responsiveness to angiotensin II. In addition, the inhibitory effect of heparin on aldosterone secretion appears to increase with time, at least during the first 12 days of therapy, (see Figure 16). Hyperkalemic distal renal tubular acidosis can develop in patients on chronic heparin therapy as shown in Figure 17 (Leehey et al, 1981; Phelps et al, 1980; Wilson and Goetz, 1964; Kutyrina et al, 1987).

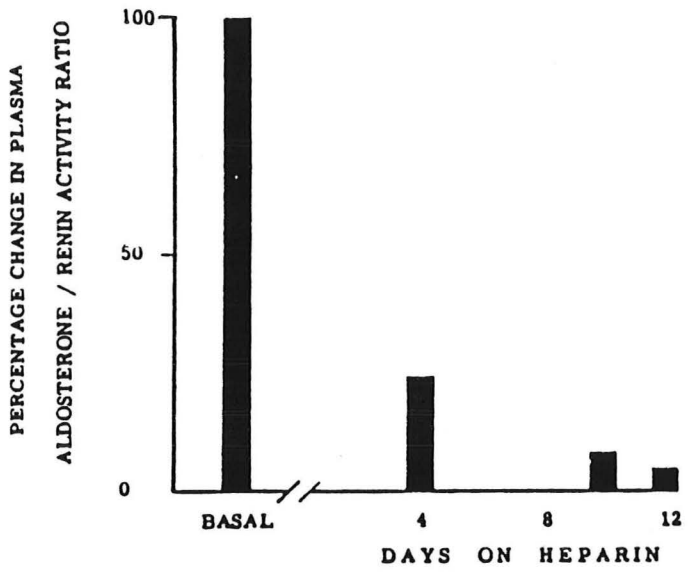


Figure 16. Effect of heparin on plasma aldosterone to renin activity ratios as a function of time

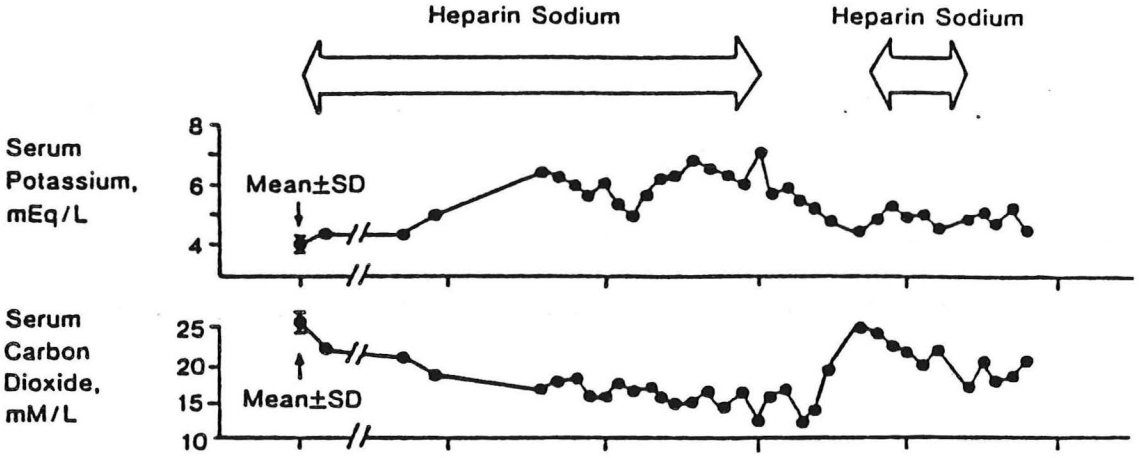


Figure 17. Hyperkalemic distal renal tubular acidosis as a result of chronic heparin therapy (Adapted from Leehey et al, 1981)

In this particular case, intravenous heparin at a dosage of 20,000 to 25,000 IU per day was administered for 41 days with the appearance of hyperkalemic metabolic acidosis. Plasma renin activity were levels increased and plasma aldosterone levels were low. Six days after discontinuation of

heparin therapy both the hyperkalemia and metabolic acidosis had resolved with return of aldosterone levels to normal. Readministration of heparin for six days again resulted in low aldosterone levels and a rise in plasma renin activity. Serum total CO_2 declined slightly and serum potassium rose slightly. Again values returned to normal following discontinuation of the heparin.

Heparin is believed to suppress biosynthesis of aldosterone by acting to suppress either the corticosterone methyloxidase I or II enzymes, or both (O'Kelly et al, 1983). Should we be looking for the development of hyperkalemic metabolic acidosis in all our patients on heparin? Probably not. In view of the predictable effect of heparin on aldosterone synthesis and widespread use of heparin, the rarity of heparin-induced hyperkalemia and metabolic acidosis probably requires some explanation. Most of our patients are only on heparin for short periods of time and the aldosterone deficiency produced, is typically partial rather than complete. Schultze et al (1971) have demonstrated that potassium homeostasis can be maintained when subnormal quantities of mineralocorticoid are provided. The effect of heparin is probably only of clinical significance when there is additional limitation of the renin-angiotensin-aldosterone axis. Thus, the possibility of heparin inducing hyperkalemic distal renal tubular acidosis should be kept in mind when heparin is administered to potentially susceptible patients such as patients with diabetes mellitus or tubulointerstitial renal disease, patients taking non-steroidal antiinflammatory agents, or patients with decreased delivery of sodium to the distal nephron (volume depletion).

In addition, another class of drugs, the converting enzyme inhibitors may decrease aldosterone levels as a result of subnormal circulating levels of angiotensin II (Atlas et al, 1979). Normally, frank hyperkalemia with or without metabolic acidosis does not develop unless there is additional limitation of the renin-angiotensin-aldosterone axis such as may occur in those conditions listed above (Ponce et al, 1985; Salkemi et al, 1988; Textor et al, 1982; Warren and O'Connor, 1980).

Cyclosporine, a potent immunosuppressive agent used in organ transplantation, can cause sustained hyperkalemia and hyperchloremic metabolic acidosis out of proportion to any reduction in glomerular filtration rate (Adu et al, 1983; Bantle et al, 1985; Petersen et al, 1984). In both spontaneously-hypertensive and normal rats, cyclosporine at 5 and 20 mg/kg per day induced a hyperreninemic hypoaldosterone state (Lustig et al, 1987; Stern et al, 1987). In addition, cyclosporine was found to decrease adrenal sensitivity to angiotensin II (Stern et al, 1987). Thus, in rats, cyclosporine appears to induce a state of hyperreninemic hypoaldosteronism. However, in cyclosporine-treated humans, plasma renin activity has been reported as normal (Bellett et al, 1985; Thompson et al, 1977) or low (Adu et al, 1983; Bantle et al, 1985; Textor et al, 1986), in association with low aldosterone levels. Thus, in humans it appears that cyclosporine may induce a state of hyporeninemic hypoaldosteronism.

ETIOLOGIES OF HYPORENINEMIC HYPOALDOSTERONISM

In contrast to patients with primary mineralocorticoid deficiency, patients in this group have low plasma renin activity values. In healthy subjects, angiotensin II derived from renin has a major tonic stimulatory effect on aldosterone secretion (Sebastian et al, 1986). Under conditions of low plasma renin activity, the resultant low angiotensin II levels leads to a state of clinically significant mineralocorticoid deficiency. Hyperkalemic distal renal tubular acidosis occurs in almost half of the patients with hyporeninemic hypoaldosteronism (DeFronzo, 1980). This disorder has been recognized with increasing frequency in adults as a cause of hyperkalemic hyperchloremic metabolic acidosis and is most typically seen in older patients with renal insufficiency secondary to diabetic nephropathy or chronic tubulointerstitial disease. It is important to recognize that both the hyperkalemia and metabolic acidosis are far out of proportion to the reduction in glomerular filtration rate.

Table VI
Etiologies of Hyporeninemic Hypoaldosteronism

Diabetic nephropathy
Chronic tubulointerstitial disease
Prostaglandin inhibitors
? Cyclosporine
? ß-blockers

Despite manifesting hyperkalemia and metabolic acidosis secondary to mineralocorticoid deficiency, sodium depletion and renal salt wasting are rarely present and may only become manifest under conditions of severe salt restriction (DeFronzo et al, 1980; Oh et al, 1974; Schambelan et al, 1980; Weidman et al, 1973). In fact, the degree of salt wasting found is usually no worse than that seen in patients with comparable levels of chronic renal insufficiency without hypoaldosteronism (Coleman et al, 1966). In contrast to the patients with primary mineralocorticoid deficiency where aldosterone secretion rates are almost zero, patients with hyporeninemic hypoaldosteronism may secrete low levels of aldosterone, driven by the hyperkalemia, which allow them to maintain salt balance (Cogan and Rector, 1986).

Schambelan et al (1980) investigated the prevalence of aldosterone deficiency in 31 patients with creatinine clearances less than 60 cc/min who were hyperkalemic. The urinary excretion of aldosterone to plasma potassium ratio $U_{aldo}V/K_s$ was markedly decreased in 75% of the patients, suggesting aldosterone deficiency. Thus, hypoaldosteronism occurs commonly in patients with chronic renal insufficiency who are hyperkalemia. Schambelan et al (1980) have also shown that the aldosterone deficiency contributes to the pathogenesis

of hyperkalemia in these patients. These authors found that the renal clearance of potassium was impaired in hyperkalemic patients with chronic renal insufficiency, and that the magnitude of this impairment was clearly related to the extent to which aldosterone secretion was subnormal. Although hyperkalemia is a result of aldosterone deficiency, normally the increased potassium concentration serves to directly stimulate adrenal aldosterone secretion even under conditions of hyporeninemia (Himathongkam et al, 1975). Chronic suppression of renin secretion may alter the ability of the adrenal gland to secrete aldosterone in response to hyperkalemia (Fredlund et al, 1977). Thus, hyporeninemic hypoaldosteronism not only results in the occurrence of hyperkalemia but in certain disorders it may also prevent the normal response to hyperkalemia (↑ aldosterone). In diabetic patients, subnormal plasma aldosterone responses to oral potassium loads have been noted prior to the development of hyporeninemic hypoaldosteronism (Perez and Oster, 1987) and suggests the additional presence of a primary adrenal defect which impairs aldosterone secretion in diabetic patients in response to hyperkalemia (? insulin deficiency).

Pathogenesis of Hyporeninemia in Hyporeninemic Hypoaldosteronism

The principal defect in hyporeninemic hypoaldosteronism is a reduced level of plasma renin activity which is unresponsive to the usual physiologic stimuli (Schambelan et al, 1972; Schambelan et al, 1980). This results in low levels of aldosterone secretion and the remaining aldosterone secretion is largely dependent on hyperkalemia (DeFronzo et al, 1980; Schambelan et al, 1980). Hyporeninemic hypoaldosteronism is a hormonal-abnormality syndrome which can occur in association with several different disease states. Thus, several different factors may contribute to the pathogenesis of hyporeninemia (see Table VII).

Table VII
Pathogenesis of Hyporeninemia in Hyperkalemic Distal Renal Tubular Acidosis

1. Chronic volume expansion
2. Arteriosclerosis of the juxtaglomerular apparatus
3. Autonomic neuropathy
4. Prostaglandin deficiency
5. Inadequate conversion of inactive (pro-) renin to active renin
   a. Prostacyclin deficiency
   b. Urinary kallikrein deficiency

Approximately 30% of patients with hyporeninemic hypoaldosteronism are hypertensive (Oh et al, 1974). A volume-dependent form of hypertension with physiologic suppression of renin elaboration is suggested by the presence of a low plasma renin activity. In fact, rather than wasting salt as might be

expected with hypoaldosteronism, there is a tendency to be in a mild chronic salt-retaining state (Oh et al, 1974). In general, patients with more advanced renal insufficiency due to glomerular disease, as opposed to tubulointerstitial disease, have a tendency to be volume expanded (Cogan and Rector, 1986). Thus, one theory for the development of hyporeninemia is chronic volume expansion. However, some patients may manifest mild salt wasting, so volume expansion cannot explain all cases of hyporeninemic hypoaldosteronism. In patients with diabetic nephropathy, primary destruction of the cells of the juxtaglomerular apparatus has been noted in some cases but not all (Phelps et al, 1980; Schinder and Sommers, 1966; Sparagna, 1974). Deficient release of renin also has been reported to occur with diabetic autonomic insufficiency and under conditions of prostaglandin deficiency (Norby et al, 1978; Tan et al, 1979). However, more recent studies have shown normal basal and stimulated renal production of prostaglandin E_2 in patients with hyporeninemic hypoaldosteronism (Farese et al, 1980; Hahn et al, 1981; Kaufman et al, 1986). Another possible mechanism is the inability to convert inactive (pro-) renin to active renin. Several studies have found increased levels of inactive renin and low levels of active renin in patients with hyporeninemic hypoaldosteronism (DeLeiva et al, 1976; Hahn et al, 1981; Kaufman et al, 1986; Nadler et al, 1986; Sowers et al, 1985; Tan et al, 1980). It has been postulated that prostacyclin deficiency (Nadler et al, 1986) or urine kallikrein deficiency (Kaufman et al, 1986) may result in this inability to convert inactive to active renin. Thus, to summarize, multiple factors may account for the low renin levels in hyporeninemic hypoaldosteronism and more than one may participate in certain patients.

Drug-Induced Hyporeninemic Hypoaldosteronism

Nonsteroidal antiinflammatory agents may produce a syndrome indistinguishable from spontaneous hyporeninemic hypoaldosteronism, except for the fact that the syndrome is fully reversible upon discontinuation of the drug (Tan et al, 1979; Grossman and Moss, 1983). Patients with volume depletion, older age, or moderate renal insufficiency are particularly susceptible to the development of hyperkalemia when taking nonsteroidal antiinflammatory agents (Zimran et al, 1985). In addition, patients with diabetic nephropathy (DeFronzo, 1980), patients taking potassium-sparing diuretics (Mor et al, 1983), angiotensin-converting enzyme inhibitors (Textor et al, 1982) or cyclosporine (Bantle et al, 1985) are particularly susceptible to the development of hyperkalemia and metabolic acidosis when taking nonsteroidal antiinflammatory agents. The mechanism whereby prostaglandin inhibitors induce a hyporeninemic state may be two-fold. Prostaglandin inhibitors may inhibit renin secretion directly (Berl et al, 1979; Henrich, 1981; Keeton and Campbell, 1981) or indirectly by producing a chronic volume-expanded state secondary to their sodium-retaining effects (Coles et al, 1983; Pinson and van Ypersele de Strihou, 1986).

Although in humans, renin release may be mediated by B_1 receptors (Torreti, 1982), the increase in serum potassium with ß-blockade is not mediated

by a decrease in plasma renin (Brown et al 1983; Traub et al, 1980). The rise in serum potassium is felt to be due to an inhibition of translocation from extracellular to the intracellular fluid compartments (Ponce et al, 1985) and is mediated by the inactivation of β_2 receptors on the skeletal muscle Na-K-ATPase (Brown et al, 1983).

DISORDERS ASSOCIATED WITH ABNORMAL CORTICAL COLLECTING TUBULE FUNCTION (ALDOSTERONE RESISTANCE)

Mineralocorticoid resistance also results in hyperkalemic hyperchloremic metabolic acidosis because of deficient effective mineralocorticoid activity (Emmett and Seldin, 1986). These disorders may result in salt wasting or salt retention but they are both characterized by an inability to respond to exogenous mineralocorticoids.

Table VIII
Disorders Associated with Abnormal Collecting Tubule Function (Cortical and Medullary)

Aldosterone Resistance
- a. Pseudohypoaldosteronism, Type I
- b. Pseudohypoaldosteronism, Type II
- c. Generalized distal nephron dysfunction
  - Chronic tubulointerstitial diseases
- d. Drugs
  - Spironolactone
  - Amiloride
  - Triamterene
  - Lithium

Pseudohypoaldosteronism Type I

Pseudohypoaldosteronism Type I, a familial disorder manifest during infancy, is characterized by renal salt wasting and a tendency toward hypotension (Cheek and Perry, 1948). Dehydration and hyponatremia secondary to salt wasting, and hyperkalemia due to renal potassium retention are associated with a hyperchloremic metabolic acidosis in this syndrome (Donnell et al, 1959). Plasma renin activity and aldosterone levels are elevated. The defect often improves as these children mature, but supplemental sodium chloride administration is usually required to prevent hyponatremia and hyperkalemic distal renal tubular acidosis. Sodium chloride also allows for improved growth (Donnell et al, 1959). Even as adults they remain sensitive to periods of salt restriction or to the effects of aldosterone blockade. This disorder has been attributed to an abnormality in the aldosterone receptor, which may be present in several target organs (Donnell et al, 1959; Oberfield et al, 1979), or to a deficiency of tubular Na-K-ATPase (Bierich and Schmidt, 1976).

Pseudohypoaldosteronism Type II

Pseudohypoaldosteronism Type II occurs in older children and adults and can be easily distinguished from Type I by the presence of hypertension, volume expansion and low plasma renin activity and aldosterone levels (Arnold and Healy, 1969; Brautbar et al, 1978; Gordon et al, 1970; Licht et al, 1985; Schambelan et al, 1981; Spitzer et al, 1973; Weinstein et al, 1974). Renin and aldosterone levels increase if volume expansion is corrected by thiazide diuretics or salt restriction (Gordon et al, 1970; Schambelan et al, 1981) but an impaired responsiveness to the kaliuretic effect of exogenous mineralocorticoid remains. This disorder represents a unique abnormality in the cortical collecting tubule in which there is an increased reabsorption of chloride relative to sodium (Schambelan et al, 1981). The enhanced reabsorption of chloride relative to sodium creates a lesser lumen-negative transepithelial voltage which impairs the sodium and mineralocorticoid-dependent voltage driving force for potassium and H^+ secretion. A model for this defect termed the distal chloride shunt is shown in Figure 18.

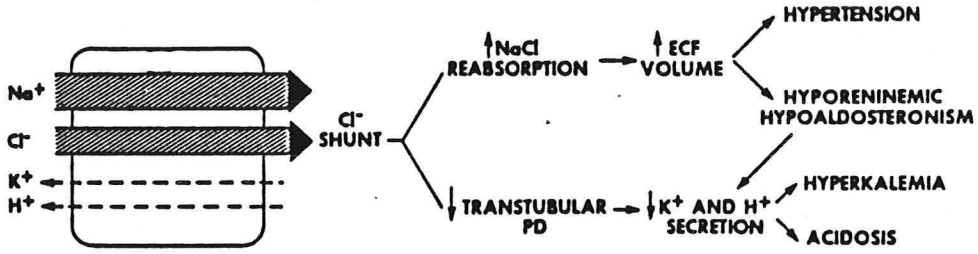


Figure 18. Pseudohypoaldosteronism Type II: The chloride shunt hypothesis. (Adapted from Schambelan et al, 1981)

An increase in the cortical collecting tubule permeability to chloride has been proposed as the defect. The combination of shunting of the transepithelial voltage and volume-mediated secondary hypoaldosteronism impairs the ability of the cortical collecting tubule to secrete potassium, resulting in hyperkalemia. The hyperkalemia in turn reduces ammoniagenesis and net acid excretion resulting in the development of metabolic acidosis. Exogenous mineralocorticoid does not produce a kaliuresis because of the shunted transepithelial voltage. Salt restriction and thiazide diuretics improve the electrolyte abnormalities presumably by decreasing cortical collecting tubule chloride reabsorption (Lee et al, 1980; Schambelan, 1981).

Chronic Tubulointerstitial Disease

A state of relative mineralocorticoid resistance may result from renal tubular damage (Luke et al, 1969). Hyperkalemic, hyperchloremic metabolic acidosis has been described in several chronic tubulointerstitial diseases which have normal or elevated aldosterone levels and are resistant to the effects of exogenous mineralocorticoids. Systemic lupus erythematosus (DeFronzo et al, 1977) obstructive uropathy (Battle et al, 1981; Carroll and Farber, 1964), sickle cell disease (Batlle et al, 1982; DeFronzo et al, 1979), allergic drug reactions (Cogan and Arieff, 1978) and renal transplantation (Batlle et al, 1981; DeFronzo et al, 1977) have all been reported to cause aldosterone resistance. In contrast to the chronic tubulointerstitial disorders which cause hyporeninemic hypoaldosteronism, in this instance urine pH can be greater than 5.5 even during acidosis. In fact, the lesion is very characteristic of the experimental animal model of hyperkalemic hyperchloremic metabolic acidosis induced by amiloride (Arruda et al, 1980; DuBose and Caflisch, 1985; Hulter et al, 1982; Husted and Steinmetz, 1979). A severe H^+ secretory defect in the medullary collecting tubule in addition to a potassium and H^+ secretory defect in the cortical collecting tubule could account for the urine and plasma findings in this group of disorders. It can be theorized that these chronic tubulointerstitial disorders may result in damage to both the cortical and medullary collecting tubules. Urine pH under conditions of acidosis will be dependent upon the extent of collecting tubule damage.

Drug-Induced Aldosterone Resistance

Several drugs which either impair the effect of aldosterone or block the ability of the collecting tubule to reabsorb sodium may result in the development of hyperkalemic hyperchloremic metabolic acidosis in experimental models. These drugs may result in hyperkalemia in patients with significant renal insufficiency but rarely result in the development of metabolic acidosis (Gabow et al, 1979; Hulter et al, 1981). Spironolactone, a competitive inhibitor of aldosterone, has both direct ($\downarrow$ H^+ secretion) and indirect (hyperkalemia) effects on collecting tubule acidification and has the potential to cause a hyperkalemic metabolic acidosis (Gabow et al, 1979; Hulter et al, 1981). Amiloride, triamterene, and lithium have direct (voltage-dependent) effects on cortical H^+ secretion and indirect (hyperkalemia) effects on both cortical and medullary collecting tubule H^+ secretion. The development of metabolic acidosis is thus based upon the degree of hyperkalemia with these agents, as they have no direct effect on medullary H^+ secretion. Lithium may only manifest an incomplete acidification defect without the spontaneous development of systemic acidosis in humans (Batlle et al, 1982).

RENAL TUBULAR ACIDOSIS OF RENAL INSUFFICIENCY

Metabolic acidosis is a consistent feature of chronic renal insufficiency. It occurs in the course of all generalized parenchymal diseases and reflects a

failure of the tubular acidification process to excrete the daily acid load (Relman, 1968). It is a widely held belief that the acidosis of chronic renal insufficiency is a feature of advanced renal dysfunction occurring when the glomerular filtration rate falls below 20 cc/min. This has been termed "uremic acidosis" and is an anion-gap metabolic acidosis. However, careful studies by Widmer et al., (1979) have shown that metabolic acidosis is a characteristic feature of even moderate renal insufficiency.

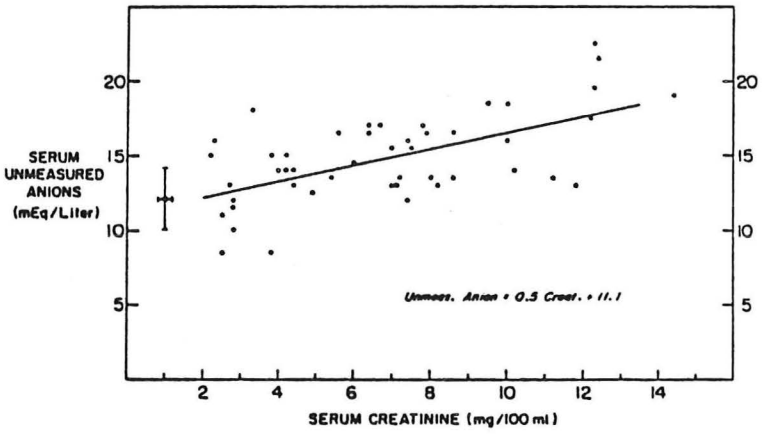


Figure 19. The Effect of Renal Insufficiency On Unmeasured Anions (From Widmer et al, 1979)

Comparing Figures 19 & 20, it is apparent that patients with stable, uncomplicated renal insufficiency of only moderate severity (serum creatinine level of 2-5 mg/dl) have a substantial decrease in serum total CO_2 content (20-22 mM/L). The level of unmeasured anions at this level of creatinine is not elevated. Not until the creatinine reaches the 7-8 mg/100 ml range (equivalent to a creatinine clearance of 10-12 cc/min) does the mean serum unmeasured anion concentration go above the normal 10-15 mEq/liter range.

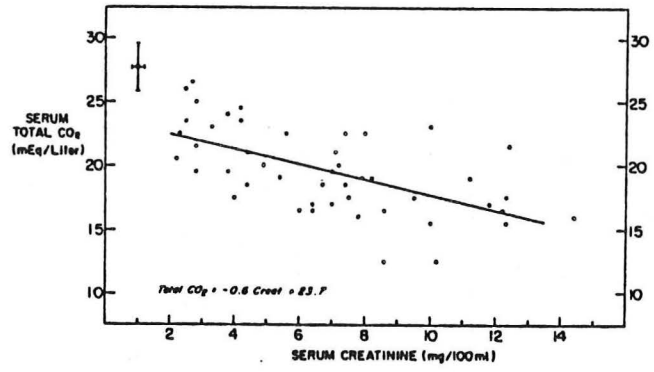


Figure 20. The effect of renal insufficiency on serum bicarbonate (From Widman et al, 1978)

Thus, patients with renal insufficiency begin to develop a hyperchloremic non-anion gap metabolic acidosis associated with normokalemia as the creatinine clearance falls below 40-50 cc/minute and do not develop an anion gap acidosis until the creatinine clearance is markedly reduced. The association between hypobicarbonatemia and an elevated anion gap in advanced renal insufficiency does not have the same pathogenetic significance as it does with other forms of anion gap acidoses. In the overproduction anion gap acidoses (lactic acidosis, diabetic ketoacidosis) or "toxic" anion gap acidoses (methanol, ethylene glycol) the anions of the acids remain in the circulation in place of bicarbonate. Thus, in these organic acidoses, the decline in serum bicarbonate usually bears a close quantitative relationship to the rise in unmeasured anions. In contrast, in uremic acidosis, the rise in unmeasured anions does not signify increased acid production or addition, but merely reflects the associated glomerular insufficiency and consequent retention of anions normally excreted by filtration. Thus, plasma bicarbonate in patients with renal insufficiency bears no predictable relationship to the rise in unmeasured anions (Harrington and Cohen, 1982).

Renal Tubular Acidosis of Renal Insufficiency: Mechanism of Development

Briggs et al (1961) studied patients with normal and impaired renal function placed on the same acid-ash protein diet.

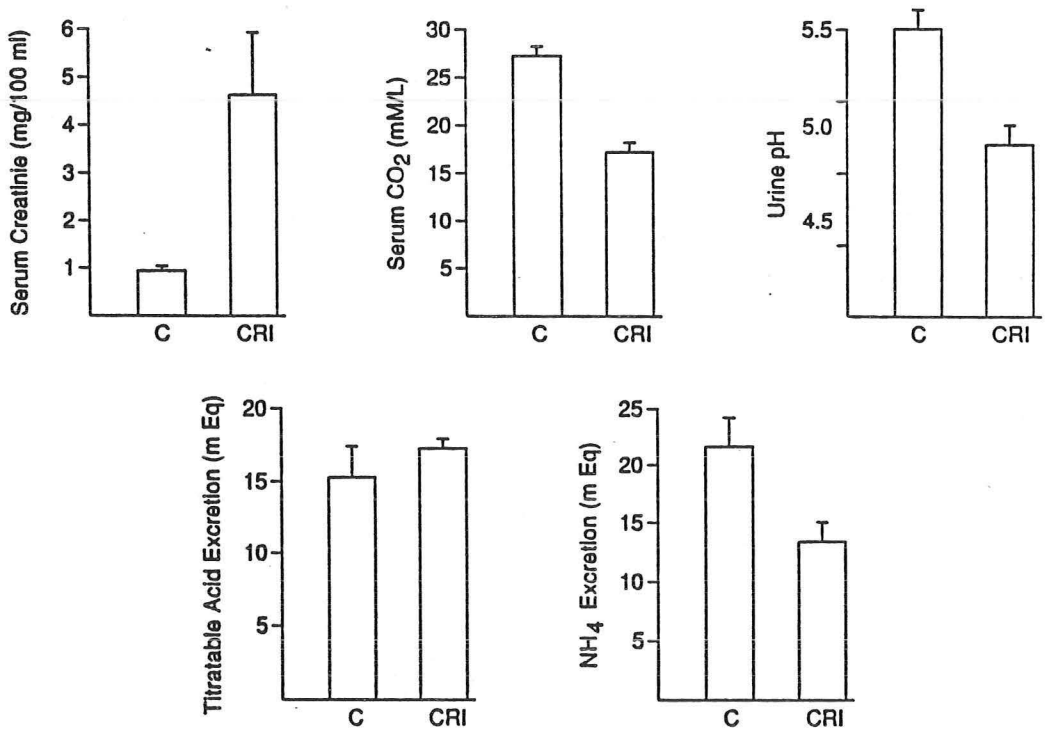


Figure 21. Plasma and urine parameters in patients with normal and moderate renal insufficiency (Adapted from Briggs et al, 1961)

Patients with a mean serum creatinine of 4.6 mg/100 ml were acidotic (mean serum total CO_2, 17.1 mM/L) but were able to lower their urine pH values appropriately (4.9). Net acid excretion (not shown) was reduced in the patients with renal insufficiency and was due to an impaired ability to excrete ammonia. Titratable acid excretion was actually slightly increased in the patients with renal insufficiency as compared to controls. Thus, in patients with acidosis due to renal insufficiency, the kidney is unable to excrete the quantity of acid produced endogenously (Gonick et al, 1969; Goodman et al, 1965; Litzow et al, 1967; Relman, 1968; Wrong and Davies, 1959). However, the ability of patients with primary renal disease to lower the urine pH during acidosis is maintained (Henderson and Palmer, 1915; Schwartz et al, 1959; Wrong and Davies, 1959), as the distal nephron H^+ secretory capacity remains normal (Briggs et al, 1961; Gonick et al, 1969; Goodman et al, 1965; Relman, 1964; Seldin et al, 1967; Simpson, 1971; Steinmetz et al, 1965; Van Slyke et al, 1926).

TITRATABLE ACID EXCRETION IN RENAL INSUFFICIENCY

Titratable acid excretion, primarily a function of distal phosphate delivery, remains normal in patients with renal insufficiency. Two factors are responsible for the continued normal absolute phosphate delivery to the distal nephron in renal insufficiency. First, a reduction in fractional reabsorption of phosphate in the proximal tubule occurs due to secondary hyperparathyroidism (Slatopolsky et al, 1971). Secondly, serum phosphate rises as the glomerular filtration rate falls and the filtered load of phosphate declines less than the glomerular filtration rate. Thus, distal phosphate delivery and hence titratable acid formation are relatively well maintained in chronic renal disease but at the expense of serum hyperphosphatemia and secondary hyperparathyroidism (Cogan and Rector, 1986). As renal insufficiency with hyperchloremic metabolic acidosis progresses to glomerular filtration levels less than 10-15 cc/min, phosphate and other anions (sulfate and organic anions) accumulate converting the acidosis to the anion gap form (Widmer et al, 1979; Arruda, 1981; DuBose, 1982).

Titratable Acid Excretion in Renal Insufficiency

1. In renal insufficiency, phosphate excretion equals phosphate intake and thus is unchanged, however, at the expense of hyperphosphatemia.

2. Urine pH is low.

3. Therefore, titratable acid excretion remains normal.

4. Treatment with phosphate binders or dietary phosphate restriction may reduce serum phosphate to normal, decreasing phosphate delivery to the distal nephron.

5. Under these conditions, the rate of titratable acid excretion falls.

AMMONIUM EXCRETION IN CHRONIC RENAL INSUFFICIENCY

The principal defect in net acid excretion of patients with renal insufficiency is thus not the ability to secrete H^+ in the distal nephron but rather the inability to excrete ammonia as shown above [(Figure 21), (Briggs et al, 1961; Buerkert et al, 1983; Dorhout-Mees et al, 1966; Goodman et al, 1965; Morris et al, 1962; Schwartz et al, 1959; Steinmetz et al, 1965; Welbourne et al, 1972; Wrong and Davies, 1959).

As functional renal mass is reduced by disease, there is an adaptive increase in ammonia production by the remaining nephrons. A plateau in production of ammonia per nephron occurs at about 4 to 5 times the original level (Rector et al, 1955; Schoolwerth et al, 1975; Welbourne et al, 1972). A reduction in renal mass 4 to 5 fold can thus be compensated by a rise in ammonia production by the remaining nephrons, but further reductions in renal mass must then result in a decrease in ammonia production and excretion. However, ammonia production has not been found to be decreased in several experimental forms of renal insufficiency (Buerkert et al, 1983; Dorhout-Mees et al, 1966; Maclean and Hayslett, 1980; Schoolwerth et al, 1975). In fact, Buerkert et al (1983) in the rat remnant kidney model (two-thirds reduction in renal mass) found total ammonia delivery out of the proximal tubule to be no different from control rats; that is there was at least a three-fold increase in ammonia production by the remaining proximal tubules. Despite the normal proximal tubular production of ammonia in these rats with 2/3 reduction of renal mass, ammonium excretion fell 43%, even in the presence of a normal H^+ secretory capacity in the collecting tubule. Therefore, less ammonium was re-entrapped in the collecting tubule and excreted. It has been theorized that reductions in medullary solute concentrations during renal insufficiency lead to a failure to concentrate ammonia in the medullary interstitium, which results in less ammonia delivery to the collecting tubule (Buerkert and Martin, 1983, Buerkert et al, 1983; Finkelstein and Hayslett, 1974).

Renal Insufficiency

1. Even though net acid excretion and NH_4^+ excretion are decreased, urine pH is low during acidosis (<5.0).

2. Decreased NH_4^+ excretion is due to either:
   a. Decreased ammonia production secondary to decreased renal mass, or
   b. decreased ammonia delivery to the medullary interstitium secondary to disrupted medullary anatomy.

Thus, in summary, the hyperchloremic metabolic acidosis of renal insufficiency is due to a primary failure of the remaining nephrons to excrete ammonia. This may be due to decreased ammonia production or to disruption of the countercurrent system in the medulla resulting in reduced medullary

interstitial ammonia concentrations and less re-entrapment of ammonia by the distal nephron or a combination of both. The metabolic acidosis of renal insufficiency bears no predictable relationship to the rise in unmeasured anions and remains hyperchloremic and normokalemic until glomerular filtration rates fall to the point of causing organic anion and potassium retention (10-15 cc/min).

EXTRARENAL BUFFERING OF ACIDOSIS IN CHRONIC RENAL INSUFFICIENCY

The acidosis of chronic renal insufficiency generates approximately 10-20 mEq of positive acid balance per day (Goodman et al, 1965; Litzow et al, 1967) yet the plasma bicarbonate concentration does not fall progressively during prolonged periods of stable renal insufficiency. To a large extent the positive acid load is buffered by recruitment of the large buffer reserves (alkaline salts) in bone (Goodman et al, 1965; Lemann and Lennon, 1972; Lemann et al., 1966; Litzow et al, 1967; Pellegrino and Biltz, 1965). The finding of a negative calcium balance in patients with renal insufficiency supports the concept that bone buffering plays an important role in the renal tubular acidosis of renal insufficiency (Litzow et al, 1967). In fact, bone buffering has been estimated to account for approximately 20 mEq/day or almost forty percent of the daily acid production in these patients (Goodman et al, 1965). Although the majority of bone disease in these patients is attributable to secondary hyperparathyroidism, the fact that acidosis creates a negative calcium balance and may impair the hydroxylation of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol suggests that acidosis per se may participate in the bone disease associated with renal insufficiency (Lee et al, 1977). Despite the evidence indicating altered vitamin D metabolism in appropriately acidotic models, there is no clear indication that acidosis induces a primary disturbance of calcium regulating hormones in man (Cunningham and Avioli, 1982). Osteomalacia may complicate chronic acidotic states not associated with renal insufficiency. Treatment with alkali alone is effective in reversing the osteomalacia which occurs in these disorders (Cunningham et al., 1982). Thus, it has been suggested by some authors that the acidosis of renal insufficiency may benefit from treatment (Cunningham et al, 1982) although the issue remains controversial.

CLINICAL APPROACH TO HYPERCHLOREMIC (NON-ANION GAP) METABOLIC ACIDOSIS

When the serum electrolytes reveal a reduced serum bicarbonate and an elevation in chloride concentration, it is important to confirm the presence of acidosis by measuring an arterial pH. A very common finding in patients with these electrolyte abnormalities is chronic respiratory alkalosis as a result of hepatic or respiratory disease. A clue to the diagnosis of chronic respiratory alkalosis may be found in a slightly elevated anion gap.

Once metabolic acidosis is confirmed, a complete history usually can exclude dilutional acidosis, acidosis due to exogenous acid loads, and the

posthypocapneic state. The most common causes of hyperchloremic metabolic acidosis are gastrointestinal bicarbonate loss and renal tubular acidosis. At times, it may be difficult to distinguish between these two groups of disorders. For example, hypokalemia can occur with both gastrointestinal bicarbonate loss and hypokalemic proximal or distal renal tubular acidosis.

Extrarenal vs Renal: Use of the Urinary Anion Gap

The best method for distinguishing between extrarenal and renal causes of hyperchloremic metabolic acidosis is to measure the net acid excretion. Extrarenal causes of metabolic acidosis will have high levels of net acid excretion while renal causes will have low levels of net acid excretion. However, measuring net acid excretion requires special equipment and is time consuming. Urine pH cannot be used as an accurate index of net acid excretion, because it does not reflect ammonium excretion rates. In fact, urine pH, during severe diarrheal states associated with volume depletion, and metabolic acidosis may actually become >6.0 due to the high ammonium excretion rates. As discussed previously, high aldosterone levels under conditions of gastrointestinal bicarbonate loss with volume depletion may aggravate total body potassium loss by enhancing potassium secretion in the cortical collecting tubule. The combined state of metabolic acidosis and hypokalemia markedly stimulates renal ammonia synthesis and excretion. The increased distal delivery of ammonium will buffer H^+ secretion and actually raise urinary pH in these diarrheal states. Metabolic acidosis due to gastrointestinal bicarbonate loss with a high urine pH can be distinguished from renal tubular acidosis, since ammonium excretes rates are high in patients with gastrointestinal bicarbonate loss and low in patients with renal tubular acidosis (Goldstein et al, 1986; Halperin et al, 1985; Halperin et al, 1985). Halperin and associates have suggested that a reasonable estimate of urinary ammonium levels can be obtained by calculating the negative urine anion gap (Goldstein et al, 1986; Halperin et al, 1985). The urinary anion gap is calculated as follows:

Urinary Anion Gap

$$UAG = U_{Na} + U_K - U_{Cl}$$

(no nonreabsorbable anions present)

If UpH > 6.5 include $UHCO_3$

UAG > 0	Low urinary NH_4^+, RTA
UAG < 0	High urinary NH_4^+, extrarenal

Thus, by obtaining the urinary anion gap, a reasonable estimate of urinary ammonium excretion can be obtained, and allows one to separate extrarenal from renal causes of hyperchloremic metabolic acidosis (Batlle et al., 1988; Halperin et al., 1985; Goldstein et al, 1986).

Renal Tubular Acidosis: Characteristic Features

After determining renal tubular acidosis is present, a urine pH obtained under oil during a spontaneous state of acidosis, will be helpful to distinguish between the different types of renal tubular acidosis. Urine pH is influenced by the patient's position and urine flow. Ideally, it is preferable to ask the patient to void in an upright position, as recumbency may cause urine pH to rise (Batlle and Kurtzman, 1985).

Table IX
DIFFERENTIAL DIAGNOSIS OF RENAL TUBULAR ACIDOSIS

	[K]	U_{pH}	Inappropriate Glycosuria
Proximal	↓-Nl	Depends on blood pH	Yes
Hypokalemic distal	↓-Nl	$\geq$ 5.5	No
Hyperkalemic distal			
a. selective aldosterone deficiency	↑	< 5.5	No
b. aldosterone resistance	↑	< or > 5.5	No
Renal Insufficiency	Nl	< 5.5	No

In proximal RTA, copious bicarbonaturia (>15% of filtered bicarbonate) occurs when serum bicarbonate levels are normal and urine pH values are high. However, at lower serum bicarbonate levels a new equilibrium is reached where bicarbonate is totally reabsorbed from the urine and urine pH levels fall to below 5.5. Thus, in proximal RTA the urine pH is dependent upon the blood pH. These patients may be hypokalemic when bicarbonaturia is present but potassium levels may normalize when bicarbonaturia decreases. Proximal RTA is often associated with a generalized dysfunction of proximal tubular transport (Fanconi's syndrome) which is manifest by glycosuria, amino aciduria, phosphaturia, and uricosuria in addition to the bicarbonaturia (DuBose and Alpern, 1989).

The hallmark of hypokalemic distal RTA is the inability to lower urine pH below 5.5 during acidosis (Batlle et al., 1981; Kurtzman, 1983). In addition, these patients have a tendency to become hypokalemic. The hypokalemia is

multifactorial in origin (Sebastian et al, 1971). As these patients have a tendency to be chronically volume depleted, excessive potassium wasting may be secondary to hyperreninemia and hyperaldosteronism (Gill et al, 1967; Sebastian et al, 1971).

Hyperkalemic distal RTA is distinguished by the hyperkalemia which is out of proportion to the reduction in the glomerular filtration rate. In hyperkalemic distal RTA due to aldosterone deficiency, the urine pH will be <5.5. In patients with generalized collecting tubule dysfunction (aldosterone resistance), the urine pH is dependent upon the extent of the collecting tubule dysfunction. If both cortical and medullary collecting tubules are involved urine pH can be >5.5. However, if only cortical collecting tubule dysfunction is present urine pH may be <5.5.

In the RTA of renal insufficiency, patients will have a decreased glomerular filtration rate associated with normokalemia and a urine pH <5.5.

TREATMENT OF HYPERKALEMIC HYPERCHLOREMIC METABOLIC ACIDOSIS

Identification of the cause of hyperkalemic, hyperchloremic metabolic acidosis is necessary for proper management of this acid-base disorder (Batlle, 1981). Iatrogenic factors such as KCl supplements and drugs should be first ruled out. On occasion, drugs may unmask a subclinical state of hyporeninemic hypoaldosteronism. Volume contraction, if present, should be corrected to enhance distal delivery of sodium to promote both potassium and H^+ secretion.

Rapid correction of hyperkalemia induced by renal tubular disorders is usually not required unless electrocardiographic changes are present. When the serum potassium is greater than 5.5 mEq/L, restriction of dietary potassium intake to 40 mEq per day can usually maintain the potassium below 5.5 mEq/L.

Treatment - I

If serum potassium >5.5 mEq/L exists and cannot be corrected by dietary potassium restrictions:

Diuretics? vs Florinef?

1. In theory, one would give Florinef to patients with hypoaldosteronism and diuretics to patients with aldosterone resistance.

2. In practice, diuretics are given to patients with high blood pressure, and Florinef is used for patients with low blood pressure.

Diuretics vs Florinef

If dietary restriction of potassium is not sufficient to bring the serum potassium to <5.5 mEq/L, chronic therapy may need to be initiated with the specific pathophysiologic disturbance in mind. In theory, one would give mineralocorticoids to patients with hypoaldosteronism and diuretics to patients with aldosterone resistance or generalized distal nephron dysfunction. However, in practice diuretics are given to patients with high blood pressure and mineralocorticoids are used for patients with low blood pressure. The effectiveness of the diuretic furosemide in ameliorating metabolic acidosis and hyperkalemia in a patient with hyperkalemic distal renal tubular acidosis is shown in Figure 22.

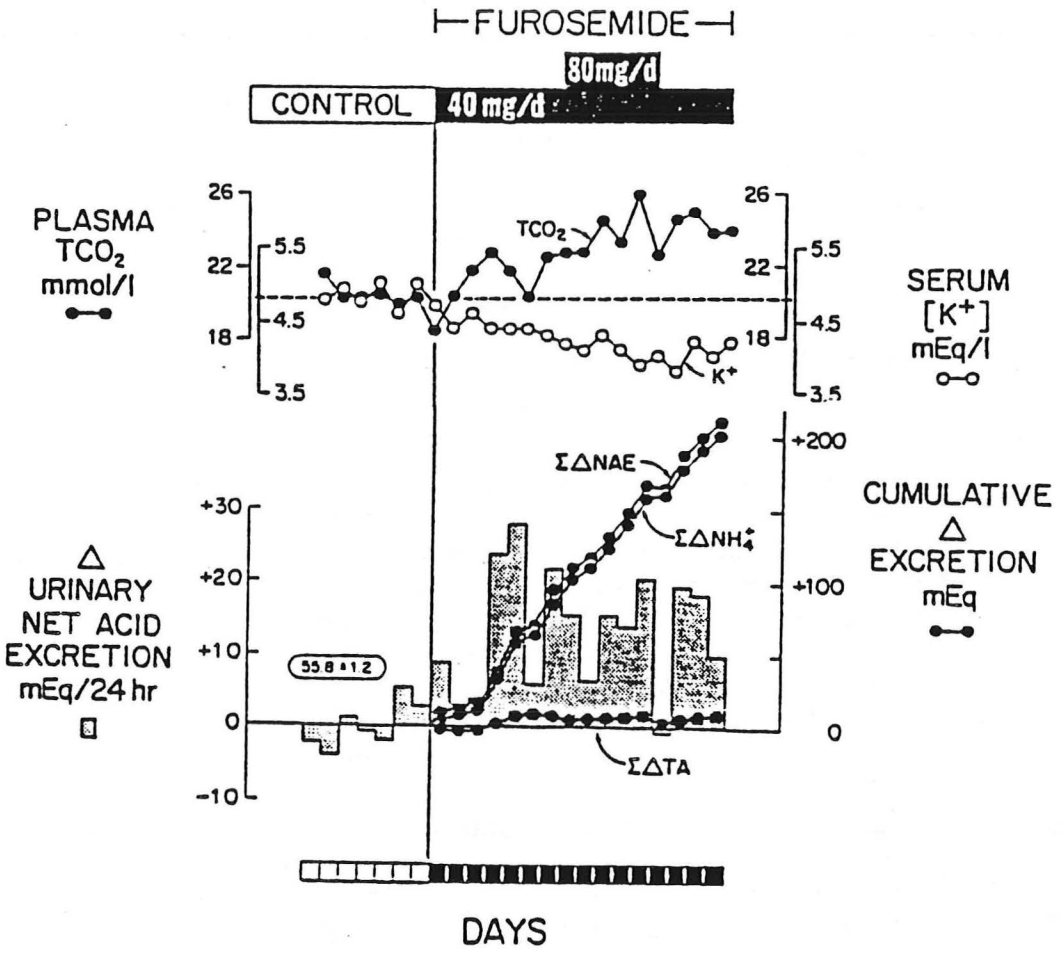


Figure 22. Diuretic treatment of hyperkalemic distal renal tubular acidosis. (Adapted from Sebastian et al, 1984)

Furosemide elicited a kaliuretic response in most patients with hyperkalemic distal renal tubular acidosis in this study of normotensive patients. Although blood pressure decreased significantly, hypotension was not induced and postural decreases in blood pressure were not changed. The kaliuretic effect of furosemide corrected the hyperkalemia. Net acid excretion was also increased by a marked increase in ammonium excretion secondary to the correction of the hyperkalemia (Sebastian et al, 1984). Only partial correction of the hyperkalemia was noted in two patients who also had the most severe aldosterone deficiency, but was corrected totally with 0.1-0.2 mg/day of Florinef and 120 mg/day of furosemide.

Although the major effect of furosemide is to enhance potassium secretion and thus secondarily increase ammonia production and excretion it may have other beneficial effects as well. Aldosterone deficiency secondary to chronic volume expansion, may be improved following furosemide therapy. In addition, furosemide increases the rate of H^+ secretion by enhancing distal delivery of sodium.

Florinef alone can correct the hyperkalemia and metabolic acidosis in those conditions associated with aldosterone deficiency, but "superphysiologic" doses (up to 0.4 mg/day) may be required (Sebastian et al, 1977). This raises the possibility that in addition to deficiency of aldosterone, some patients with hyporeninemic hypoaldosteronism may have some tubular hyporesponsiveness to aldosterone. This may not be a specific finding for hyporeninemic hypoaldosteronism since chronic renal insufficiency per se may limit the tubular response to aldosterone. Supernormal aldosterone levels are commonly found in patients with chronic renal insufficiency (Berl et al, 1978; Hene et al., 1982; Weidman et al, 1975). Failure to correct the metabolic acidosis in some patients with hyporeninemic hypoaldosteronism might reflect a failure to administer an appropriate amount of mineralocorticoid appropriate for the degree of renal insufficiency (Sebastian et al, 1985). In fact, Daughaday and Rendleman (1967) followed an adrenalectomized patient with chronic tubulointerstitial disease and found that increasing amounts of mineralocorticoid were required to correct the hyperkalemia and acidosis as the renal insufficiency progressed. Thus, Florinef can be effectively used to treat both the hyperkalemia and metabolic acidosis in patients with hyperkalemic distal RTA due to aldosterone deficiency but large doses may be required.

As shown in Figure 23, Florinef has a potent kaliuretic effect in patients with selective aldosterone deficiency. The reduction in serum potassium secondarily enhances ammonium excretion. In addition, a direct stimulatory effect on H^+ secretion is seen as an increase in titratable acid excretion. However, most patients with selective aldosterone deficiency are elderly with cardiovascular disease, hypertensive, or chronically volume expanded. Florinef in these cases may be more detrimental than beneficial. In younger patients without hypertension, or patients with primary gluco-mineralocorticoid deficiency, Florinef can probably be used safely. In cases of isolated

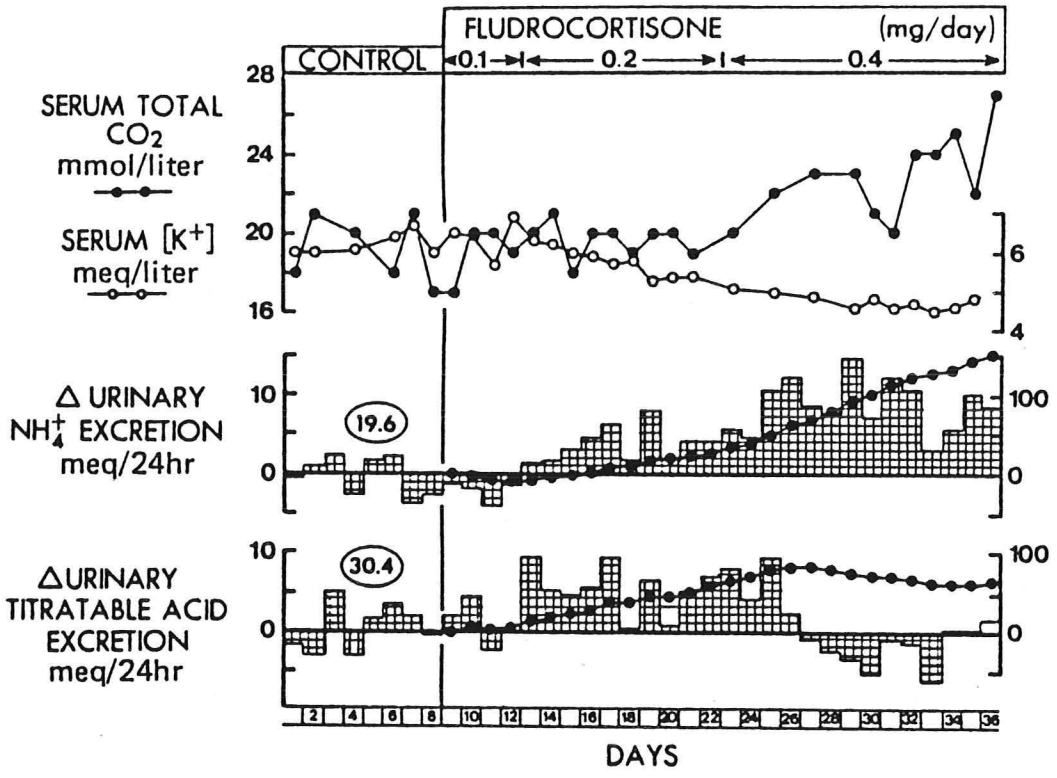


Figure 23. Mineralocorticoid (Florinef) treatment of hyperkalemic distal renal tubular acidosis. (Adapted from Sebastian et al, 1977)

mineralocorticoid deficiency, especially in older patients, other agents should be tried first and if necessary, Florinef should be given only in combination with furosemide.

Cation Exchange Resin (Kayexalate)

Occasionally, dietary potassium restriction, diuretics, and Florinef are either not effective or cannot be used, requiring other therapy. Sodium polystyrene sulfonate a cation exchange resin binds potassium to the resin in exchange for sodium and then is excreted in the stool. Usually sorbitol is taken as a cathartic agent along with Kayexalate. 1 mEq of potassium per 1 gram of resin is removed. Kayexalate may also increase gut absorption of potential

base via its affinity for calcium, providing an additional mechanism for correcting the acidosis (Van Ypersele, 1980). However, large doses of Kayexalate imposes a sodium load on the patient and should be used cautiously.

Treatment - II

If hyperkalemia cannot be corrected by diuretics, Florinef, or dietary potassium restriction:

1. Sodium polystyrene sulfonate (Kayexalate)

2. Sodium bicarbonate or sodium citrate

Alkali Therapy

In addition, hyperkalemia and acidosis can be treated with either sodium bicarbonate or alkali precursors (sodium citrate). Administration of either in doses equivalent to 1.5-2.0 mEq/kg/day can correct the acidosis and help prevent the dissolution of bone. Hyperkalemia may be partially corrected by 1) increased distal delivery of sodium with a non-reabsorbable anion (bicarbonate) enhancing distal potassium secretion, and 2) translocation of potassium into the cells in exchange for hydrogen as the extracellular fluid is alkalinized. Often the potassium can be kept below 5.0 mEq/L with just alkali therapy and dietary potassium restriction. Although this potentially imposes a sodium load in patients, under conditions of chronic renal insufficiency, patients will retain sodium bicarbonate only as long as the acidosis is present. Further sodium bicarbonate administration then exceeds the reabsorptive threshold and is excreted almost quantitatively without causing increases in weight or blood pressure (Husted et al, 1975). However, sodium bicarbonate administration should be balanced by a corresponding restriction in dietary sodium chloride (Husted and Nolph, 1977).

Correction of Acidosis

Usually the treatment of hyperkalemia will correct the acidosis. If the acidosis remains despite correction of the hyperkalemia, treatment of the acidosis with sodium bicarbonate or sodium citrate may be useful (see below).

TREATMENT OF THE ACIDOSIS OF RENAL INSUFFICIENCY

In patients with hyperchloremic metabolic acidosis secondary to renal insufficiency, treatment methodology is less clear. Decreased ammonium excretion due either to reduced renal mass or to altered medullary anatomy can not be corrected. The major question is whether the acidosis, which is usually mild, should be treated. On a theoretical basis, correction of the acidosis may

retard dissolution of bone in patients with renal insufficiency who already have mild renal osteodystrophy (Burnell, 1971; Goodman et al, 1965; Lemann et al, 1966; Lemann and Lennon, 1972; Litzow et al, 1967; Pellegrino and Biltz, 1965). Treatment with 0.5 to 1.5 mEq/kg/day of sodium bicarbonate will raise the serum bicarbonate level above 20 mEq/L. This will help retard the dissolution of bone and in addition, provide a margin of safety against the superimposition of independent acidifying processes (Madias and Perrone, 1988). Clinical studies separating out the effects of acidosis and secondary hyperparathyroidism in patients with renal insufficiency have not been performed.

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