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NEPHROLOGY FORUM

Acquired distal renal tubular acidosis

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Case presentation

A 67-year-old black man was admitted to the West Side Veterans Administration Hospital in Chicago because of weakness and clinical signs of volume contraction. He gave no history of vomiting, diarrhea, diuretic use, or any other obvious cause of volume depletion. Physical examination revealed an afebrile thin man with decreased skin turgor. His blood pressure, 100/80 mm Hg in the supine position, fell to 90/70 mm Hg on standing. Ophthalmic examination revealed early cataracts. The remainder of the physical examination was unremarkable. The patient had a history of chronic congestive heart failure, sickle-cell trait, mild renal insufficiency, chronic normochromic normocytic anemia, and recurrent urinary tract infections. A plain chest x-ray film showed cardiomegaly. An electrocardiogram was consistent with an old myocardial infarction but was otherwise unremarkable. An intravenous pyelogram performed several months previously showed distortion of the calyceal system in the right kidney without evidence of hydronephrosis or papillary necrosis. On admission, the BUN was 76 mg/dl; it decreased to 33 mg/dl after 2 days of fluid replacement with normal saline. In response to this treatment, his plasma sodium and total protein levels also fell from 150 to 135 mEq/liter and from 7.9 to 6.0 g/dl, respectively. Plasma potassium, measured at 7.0 mEq/liter, fell to 4.8 mEq/liter after hydration and administration of sodium polystyrene sulfonate.

After 2 weeks, the plasma potassium again rose to 7.0 mEq/liter, and a renal consultation was requested. At that time, the BUN was 56 mg/dl; plasma creatinine, 2.5 mg/dl; plasma sodium, 140 mEq/liter; chloride, 112 mEq/liter; and total CO_2, 17 mmol/liter; arterial blood pH was 7.32; $PaCO_2$, 33 mm Hg; and PaO_2, 82 mm Hg. Urine electrolytes were: sodium, 101 mEq/liter; potassium, 7 mEq/liter; and chloride, 66 mEq/liter. Urinalysis showed 5 to 10 red blood cells per high-power field. A 24-hour urine collection contained no protein; the endogenous creatinine clearance was 35 ml/min. After spontaneous voiding, the urine volume recovered by bladder catheterization was less than 20 ml. Following normal saline infusion for several days, plasma renin activity was 1.2 ng/ml/hr; plasma aldosterone, 0.9 ng/dl; and plasma potassium, 5.5 mEq/liter. After furosemide administration (40 mg orally at 6 P.M., 12 midnight, and 6 A.M.), the plasma renin activity was 7.2 ng/ml/hr, plasma aldosterone was 3.8 ng/dl, and plasma potassium was 5.1 mEq/liter.

In the presence of spontaneous metabolic acidosis (venous blood pH, 7.28; PCO_2, 43 mm Hg; and total CO_2, 19 mmol/liter), urine pH was 5.89. Ammonium excretion was 3.8 μmol/min; titratable acid excretion, 8.5 μmol/min; and net acid excretion, 12 μmol/min. Intravenous administration of sodium sulfate had no effect on urine pH (from 5.92 to 5.93) or potassium excretion (from 43 to 42 μmol/min), whereas sodium excretion increased from 25 to 110 μmol/min. Administration of acetazolamide also had little effect on potassium excretion as shown by a subnormal increase in fractional potassium excretion (from 10% to 14.5%). Renal sodium handling was examined while the patient ingested a low-salt diet for 14 days. During this time, the patient was given 0.1 mg of fludrocortisone daily. On the 10th day of a diet containing 40 mEq of sodium and 60 mEq of potassium, sodium and potassium excretion exceeded and fell below intake by 52 and 19 mEq per 24 hours, respectively. After 4 additional days of a diet containing 10 mEq of sodium, the 24-hour sodium excretion fell to 23 mEq, a value still greater than the dietary intake. Plasma potassium ranged from 6.1 to 6.6 mEq/liter throughout the 14 days of observation. Dietary sodium restriction was terminated on the 14th day because the patient had lost 1.6 kg in weight and had developed a postural change in blood pressure and pulse.

Discussion

DR. NEIL A. KURTZMAN (*Professor of Medicine and Physiology, and Chief, Section of Nephrology, University of Illinois College of Medicine, Chicago, Illinois*): Although described earlier [1, 2], distal renal tubular acidosis was first put in perspective by Albright, Burnett, and Parson in 1946 [3]. They described a syndrome consisting of hypokalemia, hyperchloremic metabolic acidosis, inability to lower the urine pH below 5.5, nephrocalcinosis, and nephrolithiasis; additional features included osteomalacia or rickets. Because the establishment of a large pH gradient between urine and blood is a function of the distal nephron, the syndrome was named distal renal tubular acidosis (DRTA).

Until recently, DRTA was considered to have a single pathogenesis. The prevailing view was that the disorder resulted from an inability to generate or maintain a steep hydrogen ion gradient across the distal nephron rather than from failure to secrete protons. This hypothesis was based on the observation that maximal reabsorptive capacity for bicarbonate during

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bicarbonate loading is either normal or increased in patients with this syndrome [4]. Because hydrogen ion secretion is thought to be the mechanism responsible for bicarbonate reabsorption, Seldin and Wilson reasoned that hydrogen ion secretion in the distal nephron was intact [4]. The observation by Reynolds [5] that titratable acid excretion in patients with DRTA increased during sodium phosphate administration also suggested intact distal proton secretory capacity.

For these and other reasons, Seldin and Wilson proposed that the failure of patients with DRTA to lower urine pH during acidemia did not result from a failure in distal proton secretion, but rather was the consequence of an inability to generate or maintain a steep pH gradient across the distal nephron. Accordingly, DRTA often was referred to as "gradient" RTA. More recently, the expansion of our knowledge concerning the control of distal urinary acidification and the development of a number of experimental models of DRTA have enlarged and modified our understanding of the pathogenesis of this syndrome. I plan to discuss the mechanisms and evaluation of urine acidification in some detail, emphasizing this newer information before turning to a discussion of the clinical features of DRTA.

Acidification of urine

Acidification occurs in two general segments of the nephron. The proximal tubule is responsible for the reabsorption of the great bulk of filtered bicarbonate. More than 90% of the absorbed bicarbonate is transported in this segment. Under ordinary conditions, the distal tubule and collecting duct reclaim the remaining 10% of the filtered bicarbonate, lower the urine pH to its final value, and titrate most of the nonbicarbonate urinary buffers. Although the proximal tubule and distal nephron overlap with respect to their acidification functions, as an approximation the proximal tubule can be considered as the site of bicarbonate reclamation, and the distal nephron the site of acid excretion. In the distal nephron (mainly the collecting duct), hydrogen ion secretion titrates the two main urinary buffers, phosphate and ammonia, and results in the excretion of acid in the form of titratable acid and ammonium. Acidification in the cortical collecting tubule is indirectly coupled to sodium transport and is influenced by transepithelial voltage [6]. Active sodium reabsorption in this nephron segment generates a negative electrical potential within the lumen that favors the active secretion of protons. Acidification in the medullary collecting tubule is not influenced by sodium transport and occurs against an electrical gradient [6, 7]. The potential difference in this nephron segment is oriented lumen positive, most likely the result of active proton secretion. The magnitude of proton secretion is greater in the medullary than in the cortical segment of the collecting tubule.

Evaluation of distal acidification

Minimal urine pH during metabolic acidosis

Measurement of the urine pH is the first step in assessing the integrity of distal urinary acidification. When systemic pH is below 7.35, the urine pH is usually less than 5.5 in normal individuals. Finding the urine pH below 5.5 suggests, but does not prove, that acidification mechanisms are intact. For example, a urine pH below 5.5 can be found in patients with distal RTA due to selective aldosterone deficiency. Moreover, a urine pH below 5.5 can be found in patients with proximal RTA in whom the plasma bicarbonate concentration has fallen to values below the decreased "threshold" for bicarbonate reclamation in the proximal tubule [8–10].

The urine pH should be measured on freshly voided urine obtained in the morning and collected under mineral oil to prevent the loss of carbon dioxide. If the patient is acidemic, there is no need to perform an ammonium chloride loading test because mild acidemia should be sufficient to provoke a maximal decline in urine pH. Urine pH can be influenced by the patient's position and by the rate of urine flow. Since the recumbent position can increase pH [11], the patient should void, if possible, in the upright position. If systemic acidemia is not present, ammonium chloride should be given orally in a dose of 0.1 g/kg daily for 3 to 5 days [11]. Alternatively, a single dose may be given and the urine collected hourly over the next 2 to 8 hours. We prefer the 3-day test because it seems to give more reliable results and allows time for a maximal increase in ammonium excretion [12, 13]. The urine pH in normal subjects falls below 5.5 (usually below 5.0) by the first day and remains below 5.5 for the duration of the test. Ammonium excretion normally increases at least threefold by the third day of ammonium chloride administration [13].

The finding of a urinary pH above 5.5 in the presence of systemic acidemia and in the absence of urinary tract infection strongly suggests the diagnosis of DRTA. Patients with salt-retaining diseases may respond abnormally to acidemia owing to inadequate distal delivery of sodium even though distal acidification is intact. An adequate history and the measurement of sodium concentration in the collected urine can eliminate this possibility. There are a few patients, however, in whom urine pH can fall below 5.5 even though there is a defect in distal acidification [13, 14]. Evidence of such a defect can be disclosed by measuring the urine PCO_2 during bicarbonate loading, as I will discuss later.

Excreted acid appears in the urine either as titratable acidity or ammonium. Because acid excretion when corrected for GFR does not fall in renal insufficiency—indeed it may rise—and because many patients with impaired distal acidification have renal insufficiency, it is important to compare net acid excretion (titratable acid + ammonium − bicarbonate) during an ammonium chloride loading test or during spontaneous acidemia with values obtained from controls having similar GFRs.

Calcium chloride is an alternative acidifying agent that can be used in patients who cannot tolerate ammonium chloride or in whom its use is contraindicated (for example, patients with liver insufficiency) [14]. This compound is given in a dose of 2 mEq/kg orally. It results in an acidification response almost identical to that observed following the administration of ammonium chloride.

Urine PCO_2 as an index of distal acidification

Urine PCO_2 during sodium bicarbonate infusion. After alkalinization of the urine produced by systemic sodium bicarbonate infusion, the urine PCO_2 reaches a value considerably above that of blood [12, 13, 15–17]. Normally the urine PCO_2 rises above 70 mm Hg after maximal alkalinization of the urine (pH 7.8 or greater) provided that the urine bicarbonate concentration exceeds 80 mEq/liter. Although the factors controlling the generation of urinary PCO_2 are still not completely elucidated hydrogen ion secretion is considered responsible for a major component of the increase [13, 15].

Because the urine PCO_2 exceeds that of blood under conditions of bicarbonate loading, and because the PCO_2 of intrarenal blood was assumed to be equal to that of systemic blood, the term U-B PCO_2 gradient came into vogue. This value is obtained by subtracting the value for the PCO_2 of systemic blood from that of urine. The observation that U-B PCO_2 was lower in subjects with DRTA than in normal individuals strengthened the view that this index was a useful measure of distal urinary acidification [15].

There are several caveats that must be observed in the use of the U-B PCO_2 gradient to assess urine acidification. First, as I mentioned, the urine must be maximally alkaline and contain bicarbonate in high concentration. Second, we now know that the PCO_2 of intrarenal blood varies considerably from that of systemic blood [18–21]. Furthermore, because carbon dioxide is diffusible and because the PCO_2 of intrarenal blood approximates that of intratubular urine at the same level in both proximal and distal nephron, there is little reason to believe that carbon dioxide gradients exist across the tubule [18, 21]. Thus a more proper and more direct measure of urinary acidification is likely the urine PCO_2 itself rather than the U-B PCO_2 gradient [22]. Under conditions in which the blood PCO_2 remains unchanged, an examination of the U-B PCO_2 gradient is essentially the same as examining the urine PCO_2. When blood PCO_2 changes, however, use of the gradient may produce erroneous conclusions owing to the presence of two variables. For example, using the U-B PCO_2 gradient as an index of distal acidification recently led to the conclusion that acute hypercapnia inhibits distal urinary acidification [23]. The oppposite conclusion would have been reached had urine PCO_2 been used as the index of distal acidification.

The rationale for using the urine PCO_2 as an index of acidification is that secretion of a proton into urine containing bicarbonate results in the generation of carbonic acid which, in turn, produces carbon dioxide. The more the hydrogen ion secretion, the higher the urine PCO_2. The test is performed by infusing a 1 M solution of sodium bicarbonate at a rate of 3 ml/min into a peripheral vein. Timed urine collections over approximately 15 to 30 minutes are obtained by spontaneous voiding in the upright position. Urine should be collected under mineral oil for measurement of urine pH and urine PCO_2. Bicarbonate concentration is calculated using the Henderson-Hasselbalch equation correcting the pK′ for ionic strength. Venous blood samples are obtained at the midpoint of every other urine collection for determination of pH and PCO_2. The test is terminated after the pH of at least three consecutive urine collections is above 7.8. An infusion lasting approximately 180 to 260 minutes is usually required. A convenient way of visualizing the results is to plot urine PCO_2 against urine bicarbonate concentration.

Urine PCO_2 during neutral sodium phosphate infusion. A critical dependency of urine PCO_2 on urinary phosphate concentration exists when the pH of urine is close to the pK′ of a phosphate buffer system (that is, 6.8) [24–27]. In a highly alkaline urine (pH greater than 7.8), phosphate concentration plays no role in the generation of urine PCO_2, because almost all the phosphate is in its alkaline form and incapable of donating a proton that could titrate bicarbonate to carbon dioxide [24–26]. At a urine pH of about 6.8, however, the urine bicarbonate concentration is sufficient to generate carbonic acid and carbon dioxide provided acidification is stimulated, but the urine bicarbonate concentration per se plays no role in the kidney's ability to generate a high urine PCO_2 as it does during bicarbonate loading. At this pH, half the phosphate is in its acid form and thus is capable of titrating bicarbonate to carbon dioxide.

The test is performed by infusing neutral phosphate (1 mmol/liter total body water dissolved in 180 ml of normal saline) at a rate of 1 ml/min for 3 hours. This procedure usually results in a two- to threefold increase in plasma phosphate concentration [12, 13, 25, 26]. Urine phosphate concentration must increase to at least 20 mmol/liter in 2 to 3 successive collections after the beginning of the phosphate infusion. Under these conditions, urine PCO_2 is consistently 25 mm Hg above that of blood, both in normal individuals and in patients with renal insufficiency [12, 13, 25, 26].

We have used the response of urinary PCO_2 to phosphate infusion to determine the mechanisms responsible for impaired distal acidification in DRTA [28]. We reasoned that if DRTA is the result of impaired distal proton secretion, the urine PCO_2 should not increase normally in response to either bicarbonate or neutral phosphate loading. If, on the other hand, the cause of DRTA were a back-leak of acid, then the response of urine PCO_2 to phosphate administration might be normal, whereas the response to bicarbonate infusion would be decreased. We reasoned as follows: If proton secretion were intact but the ability to maintain a gradient were reduced, then phosphate administration would stimulate proton secretion and cause the secreted hydrogen ion to form acid phosphate, a moiety that is much less diffusible than the carbonic acid formed during titration of bicarbonate. The reaction of acid phosphate with bicarbonate to form carbonic acid and carbon dioxide would be delayed and would occur at a location in the nephron or urinary tract where back diffusion could not take place. Thus, theoretically at least, a back-leak defect might respond normally to neutral phosphate administration. It should be mentioned that there are distal acidification defects in which the urine PCO_2 does not rise normally during bicarbonate infusion but does respond appropriately to phosphate administration; I will talk about these later [12, 13, 24]. Thus, phosphate infusion is a stronger stimulus to the generation of carbon dioxide than is bicarbonate.

Sodium sulfate infusion

Normal subjects lower the urine pH below 5.5 provided distal sodium delivery is adequate and sodium reabsorption is avid. The latter requirement can be accomplished by administering 9-fludrohydrocortisone, 1 mg orally, 12 hours before the sodium sulfate test is performed. The first requirement is achieved by the acute administration of the salt of a poorly reabsorbable ion such as sodium sulfate. Sodium sulfate stimulates acidification by increasing negative voltage in the cortical collecting tubule [25, 26, 29–31]. A properly performed sodium sulfate test yields a fall in urine pH below 5.5 (usually 5.0) whether or not systemic acidosis is present. Urine collections should be continued for 2 to 3 hours after the end of the sodium sulfate infusion, because some subjects have a delayed response. Typically 500 ml of a 4% solution of sodium sulfate is infused over a 45- to 60-minute period. In addition to a fall in urine pH below 5.5, sodium sulfate infusion induces a marked increase in potassium and ammonium excretion. The sodium sulfate test provides the

same information as that obtained by infusion of sodium neutral phosphate. We have yet to observe a subject who responded differently to the two procedures.

Bicarbonate reabsorption

Because patients with DRTA have intact proximal acidification, and because the measurement of maximal bicarbonate reabsorptive capacity during bicarbonate loading is mainly a function of proximal acidification, the "Tm" for bicarbonate reabsorption in these patients is not reduced [4]. In fact, it tends to be somewhat increased. This increase probably results from some degree of volume contraction commonly found in these subjects along with their chronic acidemia. Acidemia can stimulate proximal acidification by increasing intracellular pH. Because patients with DRTA cannot lower urine pH below 5.5, and usually not below 6.0, small amounts of bicarbonate are always present in the urine. Thus, a characteristic small leak of bicarbonate is seen during the performance of a bicarbonate titration curve in these patients when the plasma bicarbonate is less than normal. This response contrasts with the bicarbonate-free urine normally elaborated under such circumstances. It is rarely necessary to perform a full titration experiment. A proximal defect in acidification can effectively be excluded by demonstrating a fractional excretion of bicarbonate below 5% when the plasma bicarbonate is above 20 mEq/liter [10, 32].

Experimental defects in urinary acidification

Experimentally, three main defects in distal acidification have been identified. The defects are due to an inability to generate a negative potential difference in the collecting duct (a voltage-dependent defect), to a back-leak of acid, or to aldosterone deficiency.

Voltage-dependent defects

Urinary tract obstruction. We studied urinary acidification in dogs with unilateral ureteral obstruction [32]. One ureter was ligated for 24 hours. The ligature was then removed and the ureters from the postobstructed kidney and the normal kidney were cannulated. Bicarbonate was infused and the U-B PCO_2 gradient measured. These studies showed that the ability to raise the urine PCO_2 (at any given urine bicarbonate concentration) was lost by the postobstructed kidney. The normal kidney, by contrast, exhibited the typical increase in U-B PCO_2 gradient just described for bicarbonate loading. The postobstructed kidney also demonstrated reduced potassium excretion during bicarbonate loading.

To further characterize this disorder, we studied the ability to raise urine PCO_2 during phosphate administration. When phosphate was administered to animals with unilateral ureteral obstruction, urine PCO_2 rose normally in the nonobstructed kidney but failed to change appreciably in the urine obtained from the postobstructed kidney.

We also studied the effect of sodium sulfate infusion in these animals. Sodium sulfate, unlike phosphate, is not a buffer; it exerts its acidifying response through a voltage-dependent mechanism. Because the sulfate ion is nonreabsorbable, the reabsorption of sodium in the cortical collecting tubule unaccompanied by sulfate generates a highly negative electrical potential within the lumen, favoring secretion of protons and potassium. Thus, in addition to acidifying the urine, sodium sulfate infusion results in kaliuresis. Again, the postobstructed kidney responded in a markedly abnormal fashion [33]. Urine pH fell only to about 6.5, and the increment in ammonium excretion was markedly attenuated. Furthermore, compared to the normal kidney, significantly less potassium was excreted. The final study performed in these animals was desoxycorticosterone acetate administration. This mineralocorticoid decreases urinary sodium excretion by acting at the cortical collecting tubule [34]. The postobstructed kidney was markedly resistant to the sodium-retaining effects of this agent. Thus, this study demonstrated defects in urinary acidification, sodium reabsorption, and potassium excretion in the postobstructed kidney. Because all these are functions of the collecting tubule, we postulated that defective collecting tubule transport was a major feature of urinary tract obstruction of short duration. For reasons I will discuss, we concluded that a failure to generate a negative potential difference in the collecting tubule was the mechanism responsible for the defect.

Table 1. Effects of urinary obstruction and amiloride on urinary function

	Urinary obstruction	Amiloride
Ability to lower urine pH	Decreased	Decreased
U-B PCO_2 in alkaline urine	Decreased	Decreased
U-B PCO_2 with phosphate infusion	Decreased	Decreased
Urinary acidification following sulfate infusion	Decreased	Decreased
Sodium excretion	Increased	Increased
Potassium excretion	Decreased	Decreased

Amiloride. We next turned our attention to the effects on urinary acidification of the potassium-sparing diuretic amiloride [35]. As shown in Table 1, amiloride administration in dogs had the same effect on urine pH, urine PCO_2, and electrolyte excretion as did unilateral ureteral obstruction. This finding suggested that the defect in transport induced by urinary tract obstruction might be the same as that resulting from amiloride administration. Using amiloride as a probe, we further studied the effect of amiloride on urinary acidification using the turtle bladder [35], an experimental analogue of the mammalian collecting tubule. By exposing this membrane to amiloride, we hoped to obtain indirect evidence of the nature of the acidification defect induced by urinary tract obstruction.

The turtle bladder is believed to contain a proton pump at its mucosal surface [36, 37]. This pump, which operates in the absence of sodium transport, secretes hydrogen ion into the lumen of the bladder. The secretion of a proton results in the formation of a bicarbonate ion, which passively diffuses across the serosal membrane of the bladder. The serosal membrane contains sodium-potassium ATPase, which transports sodium out of the cell into the serosal medium. This sodium transport generates a transepithelial gradient such that the mucosal surface is negative and the serosal surface positive. This positive potential difference at the serosal surface provides part of the energy for the passive movement of the bicarbonate out of the cell. Because a negative electrical potential within the lumen would favor the secretion of protons, most physiologists study acidification by the turtle bladder in the "short-circuited"

state, eliminating the negative potential difference either by the passage of current or by paralyzing the sodium pump with ouabain [38]. Acidification continues, albeit at a reduced level, under these circumstances; its persistence constitutes a major piece of evidence for an independent, active proton pump.

When amiloride was added to the mucosal solution in the turtle bladder under short-circuited conditions in a concentration of 10^{-5} M, we noted no effect on hydrogen ion secretion even though there was a marked fall in potential difference, measured under open-circuited conditions [35]. Thus, amiloride has no direct effect on hydrogen ion secretion in this membrane. This result is not surprising because amiloride blocks sodium entry into the cell at the mucosal surface. We then repeated the studies under open-circuited conditions. As has been demonstrated by others [39], opening the circuit in the turtle bladder results in an increase in acidification. This phenomenon is easily explained by the generation of an electrically favorable gradient for proton secretion. When we added amiloride to the mucosal solution, hydrogen ion secretion fell to the level observed during the short-circuited condition. Potential difference also fell to zero. This result suggested that the effect of amiloride on acidification was an indirect one attributable to its effect on transepithelial voltage; this possibility was confirmed by other studies in which we added amiloride to the turtle bladder under open-circuited conditions. As in the previous experiments acidification fell, as did potential difference. At this point, the potential difference was returned to the control level by the passage of current. Amiloride remained in the mucosal solution. Despite the presence of amiloride, return of the potential difference to its control value completely restored acidification to the level prevailing prior to the addition of amiloride. These experiments confirmed that amiloride inhibits acidification in the turtle bladder and, we infer, in the collecting tubule, through an indirect effect on sodium transport and transepithelial voltage.

Lithium. The administration of toxic amounts of lithium results in another form of experimental DRTA in which acid excretion is impaired because the generation of a negative electrical potential within the lumen is inhibited [40, 41]. Animals treated with lithium uniformly develop hyperchloremic metabolic acidosis if their lithium blood levels exceed 3 mEq/liter. These animals are not hyperkalemic, however. Furthermore, although they cannot lower the urine pH appropriately and cannot increase urine PCO_2 with bicarbonate loading as much as normal animals, they do respond normally to the infusion of either sodium phosphate or sodium sulfate [24, 30]. A probable explanation for these observations is as follows. Hyperkalemia does not develop because lithium probably inhibits transport along the entire nephron, so that its tendency to reduce potassium secretion in the distal nephron is counterbalanced by a reduction in potassium reabsorption more proximally. Lithium interferes with the generation of a negative voltage within the lumen, as demonstrated in the turtle bladder [42], by competing with sodium for transport. The normal acidification response of the whole kidney to the infusion of either sodium phosphate or sodium sulfate likely results from increased distal delivery of sodium; this increase reestablishes normal sodium transport in the distal nephron.

These observations suggested that DRTA might develop in humans through a similar mechanism [43]. That is to say, the proton pump might be intact, but overall acidification might be reduced as a consequence of impaired sodium transport somewhere in the distal nephron, presumably the cortical collecting tubule. Impaired sodium transport at this site would result in a reduced transepithelial potential difference, which secondarily would reduce acidification. The features of such a defect are summarized in Table 2. A patient with voltage-dependent RTA with a tendency to waste sodium would have a normal or increased plasma aldosterone level and would have hyperkalemia in addition to metabolic acidosis. The urine pH would be inappropriately high for the degree of acidemia, and the response to acidifying stimuli abnormal.

Table 2. Features of voltage-dependent distal renal tubular acidosis

1. Sodium wastage
2. Normal or increased plasma aldosterone
3. Hyperkalemia
4. Hyperchloremic metabolic acidosis
5. Abnormally high urine pH during acidemia
6. Decreased U-B PCO_2 in alkaline urine
7. Abnormal response to sulfate or phosphate infusion

Back-leak of acid

The only form of impaired distal acidification that can be attributed with reasonable certainty to the back-leak of acid is that seen following the administration of the antifungal antibiotic amphotericin B [43, 44]. This defect has proved difficult to study in intact animals because animals tend to develop renal failure before they manifest complete DRTA. Accordingly, our understanding of this defect is largely based on studies in the turtle bladder [45, 46]. In this membrane, amphotericin induces a single defect, that is, an inability to maintain a steep pH gradient between the serosal and mucosal sides of the membrane. Assuming that proton secretion is intact and acid back-diffusion increased, amphotericin-treated subjects with impaired distal acidification should have low urine PCO_2 during bicarbonate loading. The ability to lower the urine pH during systemic acidosis should likewise be impaired. The response to either sodium phosphate or sodium sulfate administration should be normal owing to the integrity of the proton pump and the trapping of acid in the lumen as acid phosphate or secondary to an increase in potential difference.

There is an additional way that a gradient defect could lead to impaired urinary acidification. Rather than back-diffusion of acid from tubular urine to blood, it is at least theoretically possible for bicarbonate to "back-diffuse" from blood to the tubular urine [28]. Acidification would be decreased by this phenomenon although the urine PCO_2 during bicarbonate loading would not be suppressed. Bicarbonate back-leak would be associated with either a normal or increased urine PCO_2 during such a procedure, owing to the direct addition of bicarbonate to an aqueous medium.

Aldosterone deficiency

Aldosterone deficiency in animals, induced by adrenalectomy with selective replacement of pure glucocorticoid hormone, results in hyperkalemic metabolic acidosis. The ability of these aldosterone-deficient animals to lower the urine pH in response to acidemia is intact [47, 48]. This finding agrees with the studies in the turtle bladder that show that aldosterone affects the conductance of the membrane for protons but does not

affect the proton driving force; that is, the ability to generate pH gradients is maintained [49, 50]. Furthermore, the ability to raise the urine PCO_2 in response to either bicarbonate or phosphate loading is normal in aldosterone-deficient animals [26, 47]. Similarly, the ability to lower the urine pH in response to sulfate infusion is intact [47]. Ammonium and potassium excretion in response to sulfate infusion, however, is reduced as compared to normals [47]. Thus the acidosis in this disorder seems best explained as the consequence of impaired ammonium excretion which, in turn, is likely the result of both aldosterone deficiency and its accompanying hyperkalemia.

Clinical distal renal tubular acidosis

Clinical DRTA can be classified under five major categories according to the underlying abnormality in distal acidification. In my discussion, I will weave together the clinical features and the relevant experimental underpinning of these disorders.

Voltage-dependent DRTA

Urinary tract obstruction. Since the prototypic animal model of a voltage-dependent acidification defect is obstructive uropathy, as I discussed earlier, it seemed logical to see whether this disorder was present in patients with urinary tract obstruction. We found a sizable number of patients with hyperkalemic metabolic acidosis in association with a variety of types of obstructive uropathy [31]. Fractional excretion of potassium at any given level of GFR was considerably lower than that observed in patients with similar degrees of renal insufficiency who were not hyperkalemic. Thus, the hyperkalemia was at least partly of renal origin.

The majority of these patients, however, clearly had low levels of circulating aldosterone. It was thus possible that the hyperkalemic metabolic acidosis was the result of aldosterone deficiency and that the obstructive uropathy was just coincidental. To investigate this possibility, urinary acidification was measured during either spontaneous or induced acidemia. Numerous studies in animals and humans have demonstrated that, although overall urinary acidification is reduced in mineralocorticoid deficiency, the ability to lower the urine pH is retained [26, 31, 47, 48, 51, 52]. Therefore, the finding of hyperkalemic metabolic acidosis, aldosterone deficiency, and an inappropriately high urine pH would indicate the presence of at least two disorders. Our patients with obstructive uropathy segregated into three distinct groups. The patients who did not have aldosterone deficiency all were unable to lower their urine pH below 5.5 during acidemia. Some of the patients wth aldosterone deficiency also failed to lower the urine pH appropriately and thus exposed the presence of two distinct disorders, aldosterone deficiency and hyperkalemic DRTA. The remaining patients with aldosterone deficiency lowered the urine pH below 5.5 and were considered to have pure aldosterone deficiency. As a further test for the presence of true DRTA (defined as the inability to lower urine pH below 5.5), sodium sulfate was infused in all patients who were unable to lower the urine pH during acidemia. Despite the potent acidifying stimulus of this maneuver, these patients still were unable to lower the urine pH below 5.5. Thus, it is clear that obstructive uropathy is associated with acquired DRTA. In sharp contradistinction to the original form of DRTA described by Albright and coworkers [3], this disorder is accompanied by hyperkalemia rather than hypokalemia.

Hemoglobin S. Other disorders associated with this type of DRTA are those syndromes that share the presence of hemoglobin S [53]. The functional pattern of disturbance noted in these patients is similar to that just described for patients with obstructive uropathy. Some of these patients have pure aldosterone deficiency, whereas others have aldosterone deficiency superimposed on hyperkalemic RTA. Fractional potassium excretion is abnormal for the prevailing GFR. All these patients studied by us, save one with volume contraction, had chronic renal insufficiency [53]. Earlier studies had demonstrated an impairment in potassium excretory capacity in patients with hemoglobin S [54]. These patients, however, did not have hyperkalemia or metabolic acidosis; they also did not have renal insufficiency. Thus, tubular defects are relatively common in patients with hemoglobin S, but they are expressed fully only when renal insufficiency develops.

Lithium. As yet there are no reports of metabolic acidosis in patients treated with lithium for affective disorders. We studied a large number of patients taking lithium for varying periods of time [12]. None of these patients had either an abnormal serum potassium level or metabolic acidosis. All were able to lower pH appropriately following the administration of ammonium chloride. Urinary concentrating capacity, reduced in patients who had taken lithium for protracted periods, was relatively normal in those who had received the drug for shorter periods. All patients, however, failed to raise the urine PCO_2 during bicarbonate loading. Nonetheless, they did respond normally to sodium phosphate infusion. We infer from these data that these patients had a mild acidification defect that was uncovered only by this experimental manipulation. We suggested that the definition of incomplete DRTA should be expanded to include those patients in whom the urine PCO_2 does not rise appropriately following sodium bicarbonate administration. This expanded definition does not require that such patients be unable to lower the urine pH normally. Using such a definition, all patients receiving lithium appear to have incomplete DRTA. The clinical importance of this finding awaits further elaboration. Whether overt metabolic acidosis will develop in these patients with longer exposure to lithium is not known. It is reasonable to expect that, should another stress be added to the acid excretory system, metabolic acidosis indeed can occur on the background of lithium therapy.

Aldosterone deficiency

Over the past few years the syndrome of isolated hypoaldosteronism first described by Hudson et al [55], has been recognized frequently [51, 52, 56–59]. A common feature of this disorder is hyperchloremic metabolic acidosis. The defect in urinary acidification in these patients does not result from impaired proximal bicarbonate reabsorption. Because aldosterone exerts its renal effect in the collecting tubule, the hyperchloremic acidosis in this disorder has been attributed to a defect in distal nephron function. This type of defect (hyperkalemic hyperchloremic DRTA) is often called type-IV RTA [51]. In our view, this term lacks precision because patients with aldosterone resistance and voltage-dependent DRTA have similar features [56]. For this reason, we favor the terms aldosterone deficiency, aldosterone resistance, and hyperkalemic DRTA. These terms identify the primary defect involved; further, this precise definition has important therapeutic implications and suggests the appropriate therapy.

Patients with aldosterone deficiency lower urine pH in a fashion similar to normal subjects. The urine is appropriately acidic both during systemic acidosis [26, 31, 51, 52] and during sodium sulfate loading [26]. The urine PCO_2 also increases appropriately both during bicarbonate [47] and phosphate loading [26]. Why aldosterone deficiency does not impair distal acidification but does result in systemic acidosis is not clear. Although inhibitory effects of aldosterone deficiency and hyperkalemia on urinary ammonia formation have been proposed [48, 51, 56], experimental animals with aldosterone deficiency can increase urinary ammonium excretion normally, at least on an acute basis [47]. A decrease in GFR might be a major factor [51, 52, 56–59]. A combination of reduced GFR and aldosterone deficiency might be required to produce the acidosis; the adaptive increase in ammonium excretion per remaining nephron mass (that is, an increase in ammonium excretion corrected for GFR) characteristic of renal insufficiency [60] is lacking in such patients [53]. Hyperkalemia also exerts a direct depressive effect on urinary ammonium excretion [58, 61]. Finally, the effects of hyperkalemia and aldosterone deficiency on ammonia production might be additive [53].

Aldosterone resistance

The features of renal tubular acidosis due to aldosterone resistance are similar to those of aldosterone deficiency, except that blood aldosterone concentration is normal or elevated in the former. Aldosterone resistance can be differentiated from hyperkalemic DRTA; patients with hyperkalemic DRTA cannot lower urine pH during acidosis, whereas patients with aldosterone resistance can decrease urine pH during acidemia.

The clinical picture that best illustrates aldosterone resistance is the form described in children [62, 63]. One of the major manifestations of this disorder is sodium wastage that is well in excess of that occurring with aldosterone deficiency [64, 65].

Another form of hyperkalemic hyperchloremic acidosis unassociated with salt wastage has been described [66–69]. In one patient, mineralocorticoid administration failed to increase potassium excretion even when coupled with intravenous infusion of sodium chloride [69]. Infusion of sodium sulfate resulted in a normal increase in urinary potassium excretion, however. It has been proposed that the basic cause of the defect might be the patient's inability to generate a negative potential difference in the lumen of the distal nephron as a result of increased permeability of the distal nephron to chloride, that is, a "chloride shunt" [69]. This defect is associated with a normal acidification response to systemic acidosis or sulfate administration [69]. It is likely that these patients would raise urinary PCO_2 normally if they were infused with either bicarbonate or phosphate, but none has been tested.

In this regard, the syndrome resembles a form of voltage-dependent DRTA that responds normally to phosphate and sulfate administration [26]. It differs from that syndrome in that patients with a "chloride shunt" can lower urine pH normally during acidosis [69]. Furthermore, as a result of enhanced sodium chloride reabsorption, low-renin hypertension is a main feature of a "chloride shunt" [69]. This mechanism might explain the association between hypertension and hyperkalemic acidosis [66–69].

Patients whose aldosterone levels are normal or elevated in the presence of DRTA, hyperkalemia, and a urine pH below 5.5 still can have aldosterone deficiency. It could be argued that these patients' aldosterone levels are relatively low when their hyperkalemia is taken into account. Studies on the effects of chronic mineralocorticoid administration are needed to determine which of these patients have aldosterone deficiency and which are resistant to aldosterone.

Acquired normokalemic DRTA

If acquired DRTA develops because of an abnormality linked directly to acidification, such as failure of the proton pump or loss of the tubular membranes' capacity to maintain large pH gradients between tubular urine and blood, hyperkalemia should not develop [28]. Hypokalemia might develop eventually, depending on the interrelationship among distal sodium delivery, circulating aldosterone levels, and the prevailing GFR. Patients with this type of disorder are not hyperkalemic and cannot lower urine pH below 5.5 during acidemia [26]. Furthermore, they do not raise the urine PCO_2 appropriately when challenged with sodium phosphate. It is tempting to speculate that these patients have pure failure of the proton pump in the collecting tubule. We hypothesized that if the acidification defect were due to passive back-diffusion of acid rather than to proton pump failure, such patients would respond normally to phosphate or sulfate administration, because the proton pump would be intact [41]. The presence of sulfate or phosphate in the tubule would retard the backflux of acid, permitting a normal response.

The only example of such a back-diffusion or gradient type of disorder definitively known to exist is that secondary to the administration of amphotericin B [43–45]. Thus far, patients with DRTA secondary to this agent have not been systematically studied, either with phosphate or sulfate administration. Until such studies become available, the distinction between these two disorders must remain hypothetical.

Another form of acquired normokalemic DRTA is associated with chronic transplant rejection [25]. Whereas aldosterone deficiency can be superimposed on this disorder and in turn cause hyperkalemia, in its pure form the defect is characterized by normokalemia, an inability to lower urine pH despite the presence of hyperchloremic metabolic acidosis, and an abnormal response to phosphate administration. These findings suggest failure of the proton pump. This type of DRTA can be the first manifestation of chronic rejection.

Rate-dependent DRTA

We recently described 4 patients, only one of whom had metabolic acidosis at the time of study, in whom the only abnormality of urinary acidification was an inability to raise urine PCO_2 during bicarbonate infusion [13]. According to the expanded definition I just offered, 3 of these patients have incomplete DRTA, whereas the fourth has complete DRTA. Because the only abnormality in these patients is an inability to raise urine PCO_2, and because urine PCO_2 during bicarbonate loading is thought to reflect the rate rather than the force of the proton pump in the distal nephron, we postulated that these patients had a rate-dependent defect. In other words, proton secretion was slowed but not eliminated. In the presence of an acidifying stimulus such as systemic acidemia or phosphate administration, acid excretion could be provoked to a "normal" level. Our formulation is that these patients have an early form of one of the other defects in distal acidification just described. Prolonged observation of these patients is needed to settle this issue. Furthermore, both possibilities might be cor-

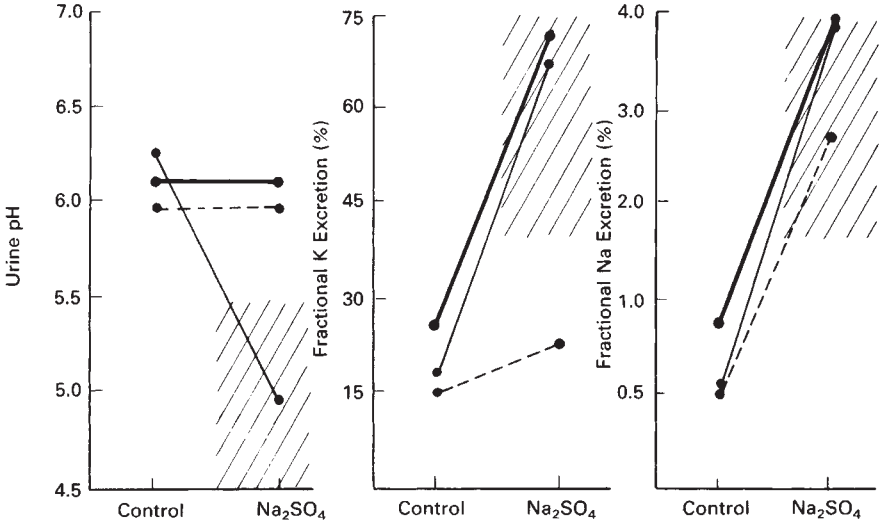

Fig. 1. *The use of sodium sulfate to distinguish "classic" DRTA from voltage-dependent DRTA.* The thin lines represent a normal subject; the dotted lines, a patient with hyperkalemic DRTA; and the bold line, a patient with classic DRTA. Reprinted by permission of Grune & Stratton (ref. 56).

rect. Some patients with this type of abnormality might have a rate-dependent defect, whereas others might initially present with this pattern and later manifest the typical pattern of one of the forms of DRTA I have described.

Evaluation of the patient with DRTA

The general principles behind our approach to patients with DRTA are shown in Figure 1 [56]. Patients with most forms of DRTA do not lower the urine pH appropriately when challenged with sodium sulfate. But potassium excretion rises normally in patients with "classic" DRTA, whereas patients with voltage-dependent DRTA fail to exhibit a normal increase in urine potassium.

Table 3 summarizes the clinical approach to the classification of RTA [70]. Patients should first be divided into two groups according to the level of serum potassium, the first group consisting of those with normal or low serum potassium, and the second comprising patients with hyperkalemia. The first group can be subdivided into two additional groups, those who retain the ability to lower urine pH below 5.5 during acidemia and those who lack such ability. Proximal RTA must be excluded in both groups. Isolated proximal RTA is extraordinarily rare. When proximal RTA develops, it almost invariably occurs as part of the Fanconi syndrome [32]. Thus, the presence of aminoaciduria, renal glucosuria, phosphaturia, and uricosuria suggests its presence. The diagnosis can be clarified by the studying of bicarbonate reabsorption. This can be done by measuring fractional bicarbonate excretion when the serum bicarbonate concentration exceeds 20 mEq/liter. Under such conditions, fractional bicarbonate excretion is less than 5% in patients with DRTA, and it usually exceeds 15% in patients with proximal RTA [32]. When the diagnosis of proximal RTA has been excluded, DRTA can be diagnosed in the patients whose urine pH is greater than 5.5. Patients who maintain the ability to acidify the urine during acidemia should be challenged with intravenous sodium bicarbonate. If these patients have a rate-dependent defect, then the ability to raise urine PCO_2 during this procedure will be lost, and the diagnosis of DRTA is established.

The second group of patients, those with acidosis associated with hyperkalemia, should likewise be divided into two subtypes, those with urine pH below 5.5 and those with urine pH above this value. In the former group, plasma aldosterone concentration should be measured. If plasma aldosterone is low and plasma cortisol is normal, the diagnosis of selective aldosterone deficiency is established. The finding of a low plasma cortisol in association with a low aldosterone value establishes the diagnosis of adrenal insufficiency. The finding of a normal or high aldosterone concentration suggests aldosterone resist-

Table 3. Clinical approach to the classification of renal tubular acidosis[a]

1. Hyperchloremic acidosis with normal or low plasma potassium

Urine pH during acidosis	
<5.5	>5.5
Exclude proximal renal tubular acidosis Measure ammonium and titratable acidity Measure urine PCO_2 during $NaHCO_3$ infusion (i.e., look for a "rate-dependent" defect)	Diagnosis of distal renal tubular acidosis if bicarbonate excretion is not high

2. Hyperchloremic acidosis with hyperkalemia

Urine pH during acidosis		
<5.5		>5.5
Plasma aldosterone		Hyperkalemic distal renal tubular acidosis
Low plasma cortisol	Normal or high aldosterone resistance	Look for specific cause (i.e., obstructive uropathy)
Normal Selective aldosterone deficiency	Low Adrenal insufficiency	

[a] Adapted with permission of Grune & Stratton (ref. 70).

ance. In the group of patients with a urine pH greater than 5.5, the diagnosis of hyperkalemic DRTA is established without further evaluation. In these patients, one should look for a specific cause, such as obstructive uropathy.

The patient presented illustrates a combined defect. He clearly has aldosterone deficiency, as documented by a plasma aldosterone concentration of 0.9 ng/dl when his plasma potassium was 5.5 mEq/liter. His ratio of plasma aldosterone to plasma potassium is 0.2. In our laboratory, this ratio normally exceeds 3. Lower values indicate aldosterone deficiency. After volume contraction with furosemide, plasma aldosterone was only 3.8 ng/dl, and serum potassium was 5.1 mEq/liter. The plasma renin activity increased normally; therefore this patient has normoreninemic hypoaldosteronism. That a second defect is present is adduced by the urinary pH. Under conditions of both systemic acidemia and sodium sulfate administration, urine pH was approximately 5.9. This failure to lower urine pH below 5.5 indicates the presence of true DRTA. Thus, the diagnosis of aldosterone deficiency and hyperkalemic DRTA is established. Because the patient failed to conserve sodium despite prolonged dietary deprivation in the presence of fludrocortisone administration, one should suspect that defective sodium reabsorption caused the DRTA.

Principles of treatment

In general, the normokalemic forms of DRTA require little more than small amounts of bicarbonate or equivalent alkali therapy. Because the distal nephron is charged with the excretion of an average of 100 mEq of acid per day, the maximal amount of bicarbonate required to treat such a patient is obviously 100 mEq. In practice, considerably less bicarbonate usually suffices, since most patients retain the capacity to excrete some acid.

Patients with hyperkalemic DRTA should first have their underlying disease treated if one is present and amenable to therapeutic intervention. The most important example of such a disease is obstructive uropathy. In general, distal sodium delivery should be encouraged and can be accomplished by administrating generous amounts of dietary sodium. Because these patients usually have renal insufficiency and commonly have cardiovascular disease, increasing dietary sodium can result in edema rather than in increased distal sodium delivery. In such cases, furosemide should be added to the regimen. This drug has two salutary effects: it encourages distal delivery and, by rendering the collecting tubule less permeable to chloride, favors the exchange of sodium for potassium or hydrogen to whatever extent such reserve remains. Mineralocorticoid therapy is sometimes useful in patients with aldosterone deficiency, although increasing distal delivery often suffices. Patients with aldosterone deficiency and a tendency to retain salt might require diuretic therapy (to encourage distal sodium delivery) with or without steroid treatment. Salt should not be restricted in these patients. Other forms of treatment, such as potassium-exchange resins and alkali administration also might be necessary [10, 56, 70].

Questions and answers

DR. NICOLAOS E. MADIAS: How specific is the acidification response to phosphate or sulfate infusion in identifying the acidification defect as "secretory," "voltage dependent," or "permeability dependent?" I would think for example that the severity of a secretory defect might well influence the response to these provocative maneuvers. Additionally, the anatomic locus of the defect might be an important consideration. Current evidence suggests that sodium transport augments acidification in the cortical collecting duct, but that hydrogen ion secretion is virtually sodium independent in the medullary collecting duct. Thus, a secretory defect involving the cortical collecting duct might be expected to respond to the above maneuvers; by contrast, no response would be expected if the defect involves the medullary portion of the collecting duct.

DR. KURTZMAN: You are correct in surmising that the severity or the "reversibility" of a defect might influence the response to sulfate or phosphate infusion. Examples of variable responses with presumably the same underlying defect are the amiloride [35, 39] and lithium [12, 40–42] models. In the former, the response is abnormal. In the latter, a normal response occurs. Both the amiloride and lithium models are thought to be examples of voltage-dependent defects. The variability in the response is likely the result of irreversible inhibition of sodium transport in the amiloride model, and a defect in sodium transport that can be overcome by increasing distal delivery of the cation in the lithium model. Also, a "weak" defect could be overcome by a powerful stimulus such as sulfate infusion and could produce a normal response.

A secretory defect involving either the cortical or medullary collecting tubule should yield a similar response. By secretory, I mean a defect limited to the hydrogen pump. Regardless of whether the cortical or medullary tubule is involved, the acidification response to sulfate and phosphate might be abnormal, whereas the handling of potassium with these maneuvers should be normal.

DR. MICHAEL P. MADAIO (*Division of Nephrology, NEMC*): What is your approach to the treatment of patients with voltage-dependent distal RTA? These individuals often remain hyperkalemic despite furosemide therapy.

DR. KURTZMAN: Patients with voltage-dependent defects should be treated by increasing distal sodium delivery as much as practicable. Furosemide therapy is helpful, although dietary salt intake should not be restricted in these individuals. As you mention, some patients respond poorly to diuretic treatment. In these individuals, potassium-exchange resins and sodium bicarbonate administration usually control acidosis and hyperkalemia. Of course, if obstructive uropathy is present it should be promptly corrected.

DR. JAMES STROM (*Acting Chief, Division of Nephrology, St. Elizabeth's Hospital, Boston*): Do you think that the defect in hereditary distal RTA is proton pump failure?

DR. KURTZMAN: We have no data concerning this entity. Other groups are using techniques similar to those I described today to investigate its pathogenesis. My guess is that it will turn out to be due to proton pump failure.

DR. STROM: How do you then explain the frequent presence of moderate to severe hypokalemia in these patients?

DR. KURTZMAN: The hypokalemia common in these patients presents no problem if one postulates failure of the proton pump. Sodium transport in the cortical collecting tubule should be intact. Thus, the development of a lumen-negative potential difference in the collecting tubule will be unaffected by the presence of this type of distal renal tubular acidosis. Accordingly,

because protons cannot be secreted effectively, potassium secretion will be favored.

DR. JOHN T. HARRINGTON: Would you comment on the alleged difference of some 40 mm Hg between urine and blood PCO_2 levels? Given the ready diffusability of carbon dioxide across biologic membranes, I find it difficult to conceive of such a difference.

DR. KURTZMAN: The best available current evidence suggests that whereas the urine and systemic blood PCO_2 are markedly different during bicarbonate loading, the tubular urine PCO_2 and vasa recta PCO_2 at the same level within the nephron are not different [18–21]. If such is the case, the urinary PCO_2 itself rather than the urinary minus blood PCO_2 value is the proper measure of urinary acidification [22].

DR. MADIAS: Would you comment on the recently described short furosemide test for the evaluation of distal acidification?

DR. KURTZMAN: This test was designed by Dr. Daniel Batlle and independently by Dr. Jose Arruda and associates [71, 72]. It is based on the fact that furosemide decreases chloride permeability. If such a decrease were to occur in the cortical collecting tubule, then chloride would be rendered an impermeant anion. Increased delivery of sodium chloride to the cortical collecting tubule under this circumstance would be equivalent to increased delivery of sodium sulfate. Therefore, normal individuals should lower urine pH and increase potassium excretion following the administration of furosemide. Thus far, the response of individuals with acidification defects to this test has been identical to that observed with sodium sulfate infusion [71]. A clear advantage of the furosemide test is that it can be carried out with only an orally administered test agent [71].

DR. LOUIS BRENES (*Staff Physician, Internal Medicine, Clinica Americana, San Jose, Costa Rica*): When using the U-B PCO_2 difference as an index of distal urinary acidification, is there a lot of variation in the results of successive urine collections?

DR. KURTZMAN: If one waits until the urine pH exceeds 7.8 and then discards the first urine collected (to avoid artifact due to the mixing of acid and alkaline urine), the urine PCO_2 is remarkably constant in successive urine samples. The variation encountered in a given individual does not usually exceed 10 mm Hg.

DR. GEETHA NARAYAN (*Nephrology Fellow, NEMC*): Distal tubular sodium reabsorption is diminished in aldosterone deficiency. Why is the defect in hydrogen ion secretion not voltage dependent?

DR. KURTZMAN: That's a good question. I wish I knew the answer. The administration of amiloride to aldosterone-deficient animals results in the characteristic voltage-dependent effect seen when the drug is given to normal subjects. Thus, it would appear that the absence of aldosterone does not decrease nephron sodium transport sufficiently to prevent the generation of a voltage favorable for acidification [73].

DR. MADIAS: In the dog with isolated hypoaldosteronism, suppression of hyperkalemia results in an increment in urine ammonium excretion but also in an increase in urine pH and a fall in urine titratable acid excretion. Do patients with hypoaldosteronism respond similarly?

DR. KURTZMAN: Systematic studies of the effect of correcting hyperkalemia in patients with isolated hypoaldosteronism are not available. That the hyperkalemia plays an important role, however, has been demonstrated in studies showing the amelioration of metabolic acidosis in patients with isolated hypoaldosteronism following correction of hyperkalemia; these studies indicate that both urine pH and ammonium excretion increase when potassium falls [58, 74].

DR. JERRY MCCAULEY (*Division of Nephrology, NEMC*): How much does hyperkalemia per se contribute towards the defect in hydrogen ion secretion by inhibiting ammoniagenesis?

DR. KURTZMAN: In my view, a decrease in ammoniagenesis secondary to hyperkalemia is a major factor in the generation of the metabolic acidosis. It seems unlikely, however, that hyperkalemia has any direct effect on hydrogen ion secretion in the distal nephron.

DR. MADIAS: I am interested in that group of patients you alluded to that exhibits normal acid-base status, normal bicarbonate reabsorptive capacity, normal response to ammonium chloride loading and phosphate infusion, but a decreased ability to elevate the U-B PCO_2 during bicarbonate loading. In one sense, this is an "incompletely-incomplete" RTA. How do you identify these patients?

DR. KURTZMAN: You can find these patients only by having a high index of suspicion. If you study patients with moderate degrees of renal insufficiency—that is, those with a serum creatinine around 3 mg/dl—and significant interstitial renal disease, you are likely to find some patients with this "rate-dependent" defect.

DR. BRENES: Is it your contention that these patients are at risk of becoming acidemic later in time?

DR. KURTZMAN: Only further observation will answer your question. My guess is that some of these patients will progress and develop a more overt form of distal renal tubular acidosis. In others, a clinical expression of their disorder might occur only when extra stress is placed on the acidification system.

DR. MCCAULEY: What about "normal" individuals? Do minimal defects in acid excretion occur in the general population? Is there a genetic variant that has no clinical significance unless the individual is stressed?

DR. KURTZMAN: We have yet to see an individual totally free of renal disease whose urinary PCO_2 response was not normal. Patients with the rate-dependent defect all have other evidence of renal disease. Thus, I think the inability to raise the urine PCO_2 in response to bicarbonate infusion is not likely to be a variant without clinical significance.

DR. MADIAS: If you were to produce bicarbonaturia in these patients without associated alkalemia—for example, by administration of acetazolamide—what would their urinary response be as compared to normals?

DR. KURTZMAN: We haven't done the study you describe, so I can only speculate. The response of animals to the administration of acetazolamide seems to be indistinguishable from that observed following bicarbonate infusion; that is, the urine PCO_2 at any one urine bicarbonate concentration is the same with either maneuver [75]. Accordingly, I suspect that the response of these patients to acetazolamide would be the same as we have observed following bicarbonate administration.

DR. MADIAS: Why does nephrocalcinosis appear to be so much less common in acquired as opposed to hereditary distal RTA?

DR. KURTZMAN: Two reasons seem likely to explain the

difference. Patients with the acquired form almost invariably have renal insufficiency, and thus urinary calcium excretion is apt to be much lower than that in patients with the hereditary form. In addition, in acquired distal RTA the acidosis tends not to be as severe and not to be present for as long an interval. Thus a smaller liberation of bone calcium would be expected in the acquired form.

DR. MADAIO: Where do you think the abnormality is in patients with voltage-dependent RTA? Excluding the patients who take amiloride, what are the possibilities?

DR. KURTZMAN: I think the patients we have classified as having distal renal tubular acidosis on the basis of a voltage defect have decreased sodium transport in the cortical collecting tubule. The reduced rate of sodium transport decreases the lumen-negative voltage and results in the typical expression of this disorder. As to the nature of the transport defect, I can only speculate. An abnormality in sodium transport any place from the luminal membrane to the serosal membrane could cause this defect. In other words, multiple transport abnormalities might have the same clinical expression provided they all result in reduced sodium transport and lumen-negative voltage.

DR. DAVID CAHAN (*Chief, Nephrology Section, Faulkner Hospital, Boston*): What are your thoughts on the role of renin in the generation of hypoaldosteronism?

DR. KURTZMAN: Most patients with isolated hypoaldosteronism have low plasma renin activity. One can invoke several explanations to causally relate renin and aldosterone deficiency. Any disorder that impairs the ability to manufacture and release renin normally would result in decreased levels of angiotensin II and thus decreased synthesis and release of aldosterone. This aldosterone deficiency in turn would result in potassium retention and in hyperkalemia. Hyperkalemia should then directly stimulate the zona glomerulosa to make aldosterone, and a new steady state would eventuate. In view of the failure of patients with hypoaldosteronism to manufacture aldosterone despite hyperkalemia, there must be a defect in the adrenal response to hyperkalemia. This defect could result from an intrinsic abnormality in the adrenal gland itself, in which case one would postulate that the syndrome results from abnormalities in both the kidney and the adrenal. On the other hand, the response of the adrenal gland to hyperkalemia might be influenced by the level of circulating angiotensin II. Pratt demonstrated that captopril treatment in dogs prevented potassium from increasing plasma aldosterone concentration normally [76]. On the other hand, anephric patients can regulate aldosterone release in response to changes in plasma potassium concentration [77]. Finally, the association between aldosterone deficiency and hyporeninemia might be fortuitous. Aldosterone deficiency might develop as a consequence of adrenal disease but have no clinical expression as long as cardiovascular and renal function are normal. That is to say, as long as distal sodium delivery is high, hyperkalemia and metabolic acidosis probably will not develop even though aldosterone is present in subnormal amounts. With aging and the development of cardiovascular renal disease, decreased distal delivery of sodium could uncover dormant hypoaldosteronism. The same renal disease that allows clinical expression of the hormone deficiency also might result in renin deficiency. None of these possibilities is exclusive. It is quite likely that the syndrome of isolated hypoaldosteronism has more than one cause.

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