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NEPHROLOGY FORUM

Acid-base balance in dialysis patients

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Case presentation

A 52-year-old man with end-stage renal disease has been receiving hemodialysis treatments 3 times weekly for 8 years. He currently works 35 hours per week as a maintenance electrician, does not smoke, and drinks an occasional beer. The cause of his renal failure is presumed to be glomerulonephritis, although the diagnosis has not been established. He was first noted to have proteinuria while in the armed services in 1956. A renal biopsy was attempted but was unsuccessful. The patient states that everything "cleared up," but no further medical followup occurred until January 1975, when he sought medical attention because of shortness of breath. At that time he was found to have pulmonary edema and a blood pressure of 230/130 mm Hg. Serum creatinine concentration was 4.4 mg/dl and he had nephrotic-range proteinuria. His blood pressure was controlled with methyldopa, hydralazine, and furosemide, but nonetheless he developed progressive renal failure. In mid-1975 the serum creatinine was 4.1 mg/dl; sodium, 140 mEq/liter; potassium, 4.7 mEq/liter; total CO_2, 20 mmol/liter; and chloride, 101 mEq/liter. By November 1976, serum creatinine had risen to 14.1 mg/dl; BUN, 140 mg/dl; sodium, 142 mEq/liter; potassium, 4.4 mEq/liter; total CO_2, 8 mmol/liter; and chloride, 114 mEq/liter. Dialysis was begun with a standard hollow-fiber kidney, using an acetate-containing bath solution. Soon thereafter, because of persistently high blood urea nitrogen levels before dialysis, a high-clearance dialysis cartridge was substituted. He currently is dialyzed using a cuprophane hollow-fiber kidney with a urea clearance of 168 ml/min (Erika B-10) for 4.5 hours 3 times weekly. His dialysis bath solution contains acetate, 37 mEq/liter; sodium, 135 mEq/liter; potassium, 2 mEq/liter; chloride, 105 mEq/liter; calcium, 3.5 mEq/liter; magnesium, 1.5 mEq/liter; and dextrose, 11 mM. He is a large, muscular man who weighs 110 kg, and who finds it difficult to restrict his protein intake.

Since beginning dialysis, predialysis total CO_2 content has ranged from 14 to 20 mmol/liter, but on most occasions has been 15 to 17 mmol/liter. A representative predialysis blood sample in 1977 showed the following electrolyte concentrations: sodium, 140 mEq/liter, potassium, 6.0 mEq/liter; total CO_2, 15 mmol/liter; chloride, 103 mEq/liter. In 1981, a predialysis blood sample drawn from his fistula for acid-base analysis showed the following values: pH, 7.33; $PaCO_2$, 33 mm Hg; and calculated bicarbonate concentration, 16.9 mEq/liter. In 1982, representative predialysis values showed a serum creatinine of 16.8 mg/dl; BUN, 91 mg/dl; sodium, 143 mEq/liter; potassium, 5.7 mEq/liter; total CO_2, 16 mmol/liter, and chloride, 109 mEq/liter. In January 1985, his serum creatinine was 19.2 mg/dl; BUN, 104 mg/dl; sodium, 142 mEq/liter; potassium, 4.8 mEq/liter; total CO_2, 14 mmol/liter; and chloride, 105 mEq/liter.

Except for early access problems, the patient's course has been relatively uncomplicated. During his first 3 years of hemodialysis, he was hospitalized 7 times for fistula revisions. Over the last 5 years, he has been hospitalized only twice, once for revision of a fistula, and once for a foot infection secondary to a work-related injury. He remains overweight and has developed adult-onset diabetes, as well as hypertriglyceridemia, both controlled with diet alone. His predialysis blood pressure ranges from 140–150/80–90 mm Hg. At the end of dialysis, his blood pressure is typically 130/80 mm Hg. He has taken methyldopa intermittently for blood pressure control, but currently is not taking any antihypertensive medication. In 1981, SGOT and SGPT increased significantly for a period of several months; it was presumed that he had contracted non-A, non-B hepatitis. This problem resolved without hospitalization or specific treatment.

Serum phosphate level has remained persistently elevated. The patient currently takes a combination of calcium carbonate (Tums) and aluminum hydroxide (Amphogel) for this problem. The most recent values for calcium and phosphorus were 9.7 and 6.2 mg/dl, respectively. A parathyroid hormone level was 2.5 ng/ml in 1980; at that time the serum ionized calcium was 2.3 mEq/liter. The alkaline phosphatase was in the normal range until this year, when it increased to 141 IU. Bone films in 1980 showed some demineralization but no evidence of parathyroid bone disease.

The patient generally feels well. He tolerates the removal of 1 to 3 liters of fluid at each dialysis treatment, although he occasionally feels "washed out." He has not required transfusions, and he maintains a hematocrit from 29% to 32%. He has decided not to pursue the possibility of a kidney transplant.

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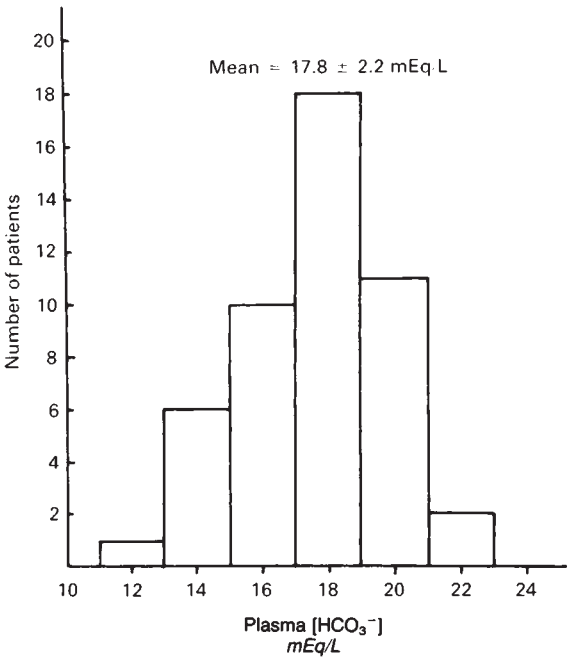

Fig. 1. *Distribution of predialysis plasma bicarbonate concentration in 48 patients receiving chronic hemodialysis therapy.* All patients were dialyzed against a single-pass bath containing acetate, 37 mEq/liter, and no bicarbonate. The mean value ± SD is shown above the graph.

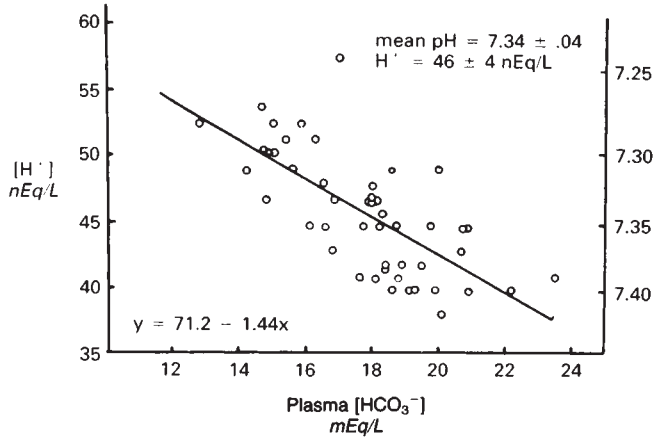

Fig. 2. *Relationship between plasma bicarbonate concentration and plasma hydrogen ion concentration* (left-hand ordinate) *or pH* (right-hand ordinate) *in 48 patients receiving chronic hemodialysis therapy.* Mean pH and hydrogen ion concentration (± SD) are shown above the graph. The line drawn through the points was calculated using linear regression analysis.

Discussion

DR. F. JOHN GENNARI (*Director, Nephrology Division, University of Vermont College of Medicine, Burlington, Vermont*): As this patient illustrates, metabolic acidosis is present in most patients undergoing hemodialysis treatment for end-stage renal disease. In this review, I will characterize the nature of this acid-base disturbance, address the question of its cause, and consider the potential short-term and long-term adverse effects of this disorder. If these issues can be clarified, a rational basis

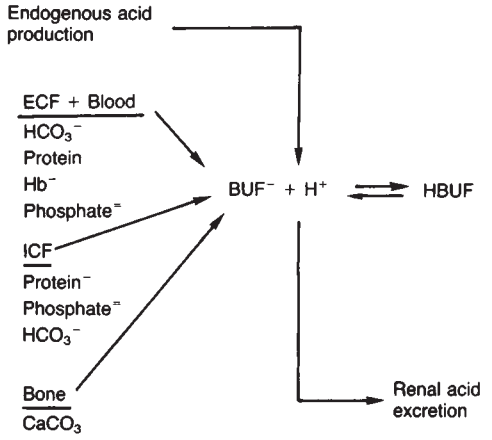

Fig. 3. *Schematic representation of acid balance in normal individuals.* The acid produced is excreted quantitatively to maintain balance. Because renal acid excretion is not immediate, the hydrogen ions produced are buffered until they can be excreted. Intracellular, extracellular, and bone buffer substances contribute to this normal buffer response. When the acid is excreted, new bicarbonate ions are added to the body, increasing pH. As a result, body buffers are back-titrated to their original condition and body buffer stores are maintained. (Modified from Ref. 20.)

can be developed for deciding whether specific treatment for this disorder is necessary.

First, I would like to put the problem into quantitative perspective. Several years ago, I assessed the acid-base status of the patients in our dialysis unit. Blood was obtained for pH and PCO_2 measurements from the A-V fistulas of 48 stable outpatients just before dialysis. Mean calculated plasma bicarbonate concentration was 17.8 ± 2.2 (SD) mEq/liter, with 45 of 48 patients having values between 14 and 20 mEq/liter (Fig. 1). This mean value is comparable to reports in the literature from other centers; predialysis bicarbonate concentration has been found to range from 16 to 22 mEq/liter [1–7]. This range reflects, in large part, differences in dialysis techniques. Predialysis bicarbonate concentration is determined not only by patient-specific factors, but also by the type of dialysis treatment the patient receives. The low bicarbonate concentration is clearly associated with acidemia. As Figure 2 shows, hydrogen ion concentration increases as bicarbonate concentration falls. The mean value is 46 nEq/liter or a pH of 7.34. As might be expected, PCO_2 decreases in direct relation to the fall in bicarbonate, by approximately 1 mm Hg per mEq/liter. This change is consistent with the respiratory response typically seen in uncomplicated metabolic acidosis.

Having now characterized this acid-base disturbance in a traditional fashion, I would like to take a slightly untraditional turn. I want to ask next whether the metabolic acidosis in hemodialysis patients is one in which continued positive acid balance occurs, or whether net hydrogen ion balance over the long term is essentially zero. These two alternatives have far different implications.

Hydrogen ion balance

For background to this issue, I will review briefly acid balance in normal individuals (Fig. 3). As a result of metabolism of the foods we ingest and an associated gastrointestinal alkali loss, approximately 50 to 100 mEq of hydrogen ions are added

to the body each day; these must be excreted by the kidney to maintain acid balance. The addition of these acids is termed endogenous acid production. Careful balance studies in humans have demonstrated, in fact, that an equivalent amount of acid is excreted by the kidney each day [8, 9]. Because renal acid excretion is not immediate, the hydrogen ions produced by metabolism must be buffered transiently by proton acceptors in the body. As Figure 3 illustrates, a variety of extracellular, intracellular, and bone-buffer substances contribute to this process. At a normal bicarbonate concentration, extracellular bicarbonate stores account for slightly less than one-half the buffer response [10–12]. When bicarbonate is the buffer, this anion is consumed because the carbonic acid formed is volatile and excreted as carbon dioxide via the lungs. Other buffers can be renewed by back-titration with alkali. As the kidney excretes the acid load, equivalent amounts of new bicarbonate are generated that titrate non-bicarbonate buffers to their original state and replenish body bicarbonate stores. In patients with renal failure, administered bicarbonate serves precisely the same purpose as does renal generation of bicarbonate by acid excretion.

Metabolic acidosis in renal failure

When renal mechanisms for acid excretion fail, acid necessarily is retained because daily production continues. Despite continued acid retention, the plasma bicarbonate level eventually stabilizes, and bone carbonate becomes an increasingly important buffer substance [13–15]. In patients with untreated uremic acidosis, bone carbonate stores are significantly decreased [14, 15]. Another example of metabolic acidosis with continued acid retention is distal renal tubular acidosis (RTA); bone disease is a characteristic feature of long-standing distal RTA [16]. What is not often realized is that virtually all the experimental work in chronic metabolic acidosis has been carried out using NH_4Cl or HCl administration, a model in which continued acid retention also occurs [17, 18]. When HCl or its equivalent is administered daily, approximately 10% to 20% of the administered hydrogen ion is retained each day, even in the so-called steady state [17, 18]. In this model, Lemann, Litzow, and Lennon documented continued negative calcium balance in humans with chronic metabolic acidosis [17].

Chronic metabolic acidosis, however, also can occur without continued acid retention. Proximal RTA, or bicarbonate-wasting RTA, is an example [16, 19]. This relatively unusual disorder is characterized by defective bicarbonate reabsorption by the kidney; serum bicarbonate concentration falls to a level at which renal bicarbonate reabsorption can be accomplished and normal acid excretion can occur. In the steady state, individuals with proximal RTA are in acid balance, albeit at a low plasma bicarbonate concentration. In the absence of any associated tubular defects, this disorder produces a stable, long-term chronic metabolic acidosis with few adverse effects and no metabolic bone disease [19]. The only adverse effect seen is growth retardation. As I will demonstrate in this review, the metabolic acidosis occurring in patients receiving dialysis treatment is, by its very nature, quite similar to proximal RTA. A logical analysis of the events occurring during dialysis indicates that, over the long term, acid balance must be maintained. I introduced this concept previously [20], but will review it in greater detail here. My conclusion that acid balance is maintained in dialysis patients is supported by studies in which measured alkali addition during dialysis is compared with estimated acid production [1, 21]. Despite these measurements, there is continued concern that the acidosis in patients on dialysis, such as that in the patient presented here, will exacerbate bone mineral loss [1, 2, 5, 21, 22]. There is little evidence to support this notion.

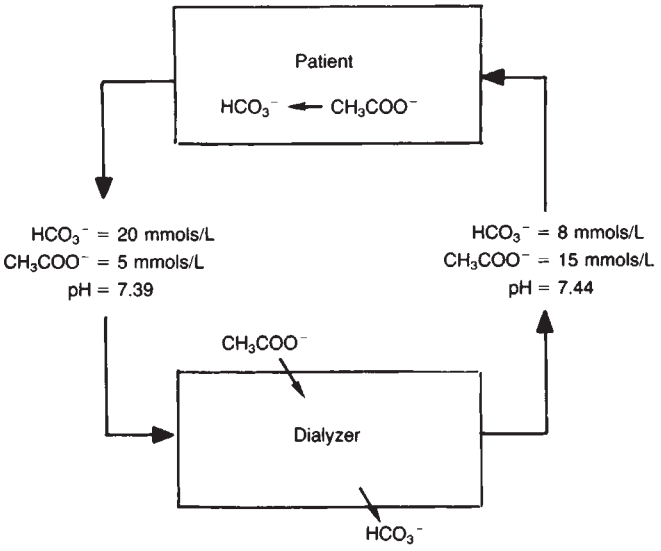

Fig. 4. *Schematic representation of the interaction between the patient and dialysis membrane during dialysis against an acetate-containing bath.* As the blood travels through the dialyzer, acetate diffuses in and bicarbonate diffuses out. In the body, acetate is metabolized forming new bicarbonate. See text for a full description of these events. (Modified from Ref. 20.)

Bicarbonate and acetate transfer during dialysis

To understand the state of acid balance in dialysis patients, we need to review the way that alkali is administered during hemodialysis treatments. Figure 4 illustrates the exchange and metabolic events that occur when a patient is dialyzed against a single-pass bath containing acetate but no bicarbonate. In the dialysis cartridge, bicarbonate diffuses out and acetate diffuses in, so that the blood leaving the dialysis cartridge has a low bicarbonate and a high acetate concentration [23, 24]. The pH does not fall because CO_2 also diffuses out; the PCO_2 in the blood that returns to the patient falls to less than 20 mm Hg [23]. In the body, acetate is metabolized rapidly, generating new bicarbonate, so that the bicarbonate concentration in the blood reentering the dialyzer is approximately 20 mEq/liter, and the acetate concentration is approximately 5 mEq/liter. Obviously the system is designed so that more acetate enters than bicarbonate leaves. The overall transfer either of acetate in or bicarbonate out can be calculated from its dialysance and the concentration gradient (ΔC) across the membrane (mass transfer = dialysance x ΔC). The dialysance of each of these anions is determined by the characteristics of the membrane, the rate of plasma ultrafiltration, and the flow rates of the blood and bath fluid through the cartridge. The dialysance of bicarbonate is approximately equal to the dialysance of urea; the dialysance of acetate is somewhat lower [1, 4, 23, 25]. We set the

concentration of acetate in the bath so that, for a given patient, acetate delivery is relatively constant for each dialysis. On the other hand, the bicarbonate concentration in the blood is not predetermined. It varies depending on the interplay between the rate of endogenous acid production and the rate of net alkali gain during dialysis.

Feedback regulation of bicarbonate concentration

Let's look a little more closely at that interplay. Acetate delivery is constant, but the rate of bicarbonate loss across the dialysis membrane varies inversely with the concentration of bicarbonate entering the cartridge. Net alkali gain is the difference between acetate entry and bicarbonate loss; therefore, more alkali is gained when plasma bicarbonate concentration is low, and vice versa. To illustrate the effect of this unique feedback system on predialysis bicarbonate concentration in a more quantitative fashion, I present a hypothetical example, shown in Table 1. In this example, I have estimated that 60 mmols of endogenous acid are generated by the patient each day, which translates into 420 mmols/week. Although this arbitrary value is in keeping with estimates obtained from the protein catabolic rate [21], no one has actually measured endogenous acid production in patients on dialysis. For the purposes of this analysis, however, the precise numbers are unimportant. As I will demonstrate, they only determine the particular bicarbonate level at which a steady state is achieved. The second important element in this analysis is a phenomenon unique to dialysis patients. In the anuric patient, the anions of the organic acids produced by metabolic processes are not lost from the body, except during dialysis. In the interdialytic period, they remain in the body and are available to accept protons if they undergo further metabolism. During dialysis, organic anion loss has been reported to range from 30 to 100 mmols per treatment [1, 21, 25]. Again the specific value used is unimportant for the purposes of this analysis. Assuming a high value of 100 mmols for each of three treatments per week and adding this lost "potential alkali" to the hydrogen ions generated endogenously, we obtain the alkali needed in this example to maintain balance, that is, 720 mmols/week. With 3 dialyses per week, 240 mmols are needed per dialysis.

Given this alkali requirement for balance, and the specifications of the dialysis treatment shown in the table, one can predict the steady-state predialysis bicarbonate concentration that will ensue. In this example, we assume bicarbonate dialysance to be 150 ml/min and acetate dialysance 120 ml/min; these values are comparable to those reported for standard dialysis cartridges [1]. Bath acetate concentration is 37 mM, and the system is assumed to have a single-pass bath. In such a dialysis, plasma acetate concentration rises rapidly to 2 mM in the first 30 minutes of dialysis, and then reaches a steady-state value close to 5 mM by the second or third hour [1, 4, 24]. Acetate entry in this example is calculated based on this profile of plasma acetate concentration. During the course of the usual dialysis, plasma bicarbonate concentration does not change notably [1, 3, 25]. The increase occurs after dialysis as the 3 to 5 mmols/liter of acetate remaining in the blood are metabolized [1]. Thus, bicarbonate loss is calculated on the basis of the bicarbonate concentrations shown in the table. Bath bicarbonate concentration is assumed to be zero.

Table 1 illustrates what happens over 4 hours of dialysis at

Table 1. Acid balance in hemodialysis patients: Theoretic considerations

A. Acid addition:	
1. From diet	420 mmols/week
2. Organic anion loss during dialysis	300 mmols/week
Total =	720 mmols/week
B. Alkali required = (assuming 3 dialyses/week)	240 mmols/dialysis
C. Dialysis specifications:	
1. 4 hrs duration	
2. Bath acetate = 37 mM	
3. $D_{acetate}$ = 120 ml/min; $D_{HCO_3^-}$ = 150 ml/min	

Predialysis Plasma HCO_3^-	Acetate in	HCO_3^- out	Net alkali	Alkali-240
mEq/L	*mmols*			
16	953	576	377	137
18	953	648	305	65
19	953	684	269	29
20	953	720	233	−7
22	953	792	161	−79

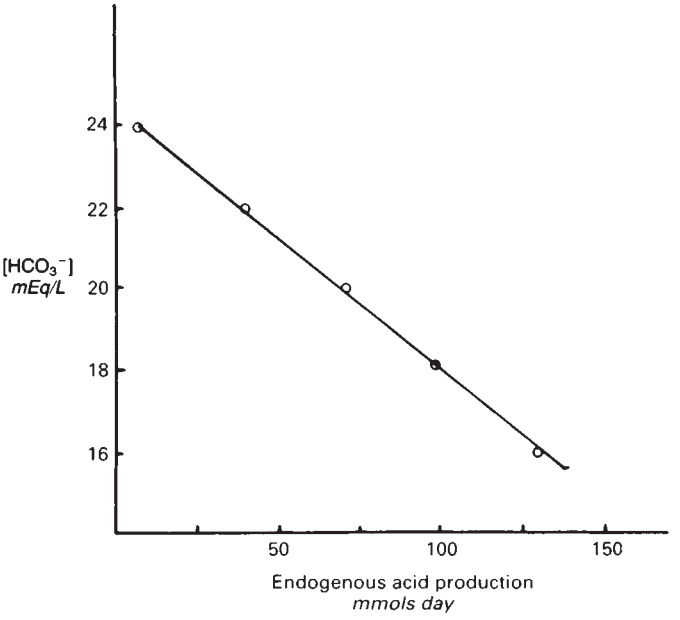

Fig. 5. *Theoretical relationship between endogenous acid production in mmols per day and predialysis plasma bicarbonate concentration in patients being dialyzed 3 times weekly against a single-pass, acetate-containing bath with constant dialysis characteristics.* In this system, long-term acid balance is zero, and predialysis bicarbonate concentration is determined by endogenous acid production.

varying predialysis plasma bicarbonate concentrations in this example. In each instance, the acetate entry is the same because we have set it. The amount of bicarbonate lost, however, is determined by the plasma bicarbonate concentration. At a predialysis bicarbonate concentration of 16 mEq/liter, 377 mEq of net alkali is gained during dialysis; this amount is approximately 137 mEq in excess of that required to maintain balance. Thus, if the patient has this predialysis plasma bicarbonate level, the bicarbonate concentration should be higher at the time of the next dialysis. At the other extreme shown in Table 1, if the predialysis plasma bicarbonate concentration is

Table 2. Cumulative H^+ balance over one week in 8 patients receiving acetate dialysis (three 4-hr treatments)[a]

		Acid in
1. Endogenous acid production[b]		375 ± 32 (SE)
2. Lactate loss		57 ± 4
3. 3-hydroxybutyrate loss		55 ± 15
	Total	487 mmols
		Alkali in
1. Acetate delivery		2341 ± 183
2. Bicarbonate loss		−1848 ± 150
	Total	493 mmols
	Hydrogen ion balance	−7 ± 28

[a] From Ref. 21.
[b] Calculated as 0.77 times protein catabolic rate.

22 mEq/liter, only 161 mEq of net alkali will be gained; this amount is less that that required to maintain balance. Thus, unneutralized, retained hydrogen ion will cause the next predialysis bicarbonate concentration to be lower. With time, predialysis bicarbonate concentration, given the assumptions in this example, will be maintained at somewhere between 19 and 20 mEq/liter. At this level, net alkali gain will equal acid production, and long-term acid balance will be zero. A more elegant model could be developed if one were to consider the distribution of acetate and bicarbonate across the red cell membrane, but such refinements would not alter the overall conclusion drawn from this analysis.

This analysis demonstrates that, with constant dialysis characteristics, predialysis serum bicarbonate concentration is inversely related to endogenous acid production (Fig. 5). Although positive acid balance occurs between each dialysis, by definition long-term acid balance has to be zero. This theoretical model holds unless there is some sustained buffer disequilibrium in the body, that is, unless the serum bicarbonate concentration does not reflect the status of other buffers in the body. This possibility is exceedingly unlikely. As I noted earlier, positive acid balance can continue in the face of a constant serum bicarbonate concentration in patients with metabolic acidosis due to renal insufficiency, distal RTA, or NH_4Cl administration [13, 17, 18]. In these instances, unrelenting acid accumulation is never counterbalanced by new alkali generation. By contrast, patients receiving hemodialysis treatments do not have a stable bicarbonate concentration. The bicarbonate level rises after dialysis and gradually declines over the interval between dialyses [4, 7]. In this setting, the fluctuating bicarbonate concentration reflects the depletion of alkali stores between dialyses and the replenishment of alkali stores during dialysis.

Estimates of acid balance in dialysis patients

My theoretical analysis is supported by measurements of alkali addition during acetate dialysis [1, 21]. Vreman and coworkers carried out measurements of net alkali gain and organic anion loss during dialysis in 20 patients receiving standard treatments against a single-pass acetate bath [1]. They found that, on average, 278 mmols of alkali were gained and 100 mmols of organic anion were lost per dialysis treatment. Thus, 178 mmols of alkali were available to offset acid production in the interdialytic interval. Net alkali addition, averaged over the course of one week in these patients, was 74 mmols/day, a value not significantly different from the estimated endogenous acid production. Mean predialysis bicarbonate concentration in these patients was 19.7 mEq/liter although, as in my survey, there was wide variability of values among patients, from 16 to 25 mEq/liter. This variability probably is related in large part to variations in the four types of dialysis cartridge used in the patients studied and in the length of dialysis.

More recently, Gotch and colleagues carried out a similar analysis in 8 patients [21]. The results, summarized in Table 2, also show acid balance over a one-week period. To estimate endogenous acid production in patients on dialysis, these workers developed an empiric formula based on observations in normal individuals. The authors reviewed the results of studies in which nitrogen balance and net acid excretion were measured under steady-state conditions, and they developed a coefficient relating acid excretion (equivalent to acid production in the steady state) to protein catabolic rate. Using this coefficient, and calculating protein catabolic rate from urea kinetic analysis in each of their dialysis patients, they derived a value for endogenous acid production. If this value is at all in error, it probably overestimates endogenous acid production; in individuals with normal renal function, approximately 30% to 50% of endogenous acid is due to organic acid production and excretion of the organic anion [8, 9]. As I noted earlier, organic anion loss in patients on dialysis only occurs during the dialysis treatment, and it is accounted for separately (Tables 1 and 2).

The requirement for alkali was much lower in the studies by Gotch and coworkers (Table 2) than it was in the studies by Vreman and colleagues [1] because of major differences in organic anion losses. The reason for this difference is unclear. In the former study, only 3-hydroxybutyrate and lactate losses were measured, whereas in the latter study, citrate, pyruvate, and acetoacetate losses also were measured. However, 3-hydroxybutyrate and lactate are the most important anions quantitatively. The presence or absence of glucose in the bath influences organic anion loss; acetoacetate and 3-hydroxybutyrate losses are much greater if the bath contains no glucose, presumably because of increased production of these two organic acids during dialysis [26]. In the study by Vreman and coworkers, the bath contained no glucose; Gotch and coworkers did not specify the bath glucose content. Both studies, of course, suffer from the problem of having no direct measurement of endogenous acid production. But I believe that their estimates are probably close to the mark because, as I indicated earlier, acid balance has to occur unless there is buffer disequilibrium in the body.

Use of high-mass-transfer dialysis membranes

Despite this theoretical and experimental evidence for zero acid balance, concern about metabolic acidosis in dialysis patients has led investigators to attempt to increase plasma bicarbonate concentration. One way of accomplishing this, in theory, is to increase the bath acetate concentration or to use a membrane with a higher acetate dialysance to deliver more of this bicarbonate precursor. The limitation to this approach is the rate at which the body can convert acetate to bicarbonate. This rate appears to vary considerably from patient to patient but, on average, ranges from 2.5 to 5 mmols/min [1, 4, 24]. Tolchin and coworkers demonstrated that this metabolic rate

can be overwhelmed by increasing bath acetate concentration and by using a high-mass-transfer dialysis cartridge [4]. In this setting, plasma acetate continues to rise during dialysis, rather than reaching a steady-state value. The rising plasma acetate limits acetate transfer from bath to patient by reducing the transmembrane concentration gradient for this anion. In addition, bicarbonate concentration falls, because of the high dialysance of bicarbonate inherent in these membranes. The fall in bicarbonate concentration occurs at the beginning of the treatment, and further bicarbonate loss is minimized. The end result of these effects on acetate and bicarbonate transfer is that net alkali gain is roughly equivalent to that achieved with a standard dialysis cartridge. At the end of dialysis, however, the patient is left with a low bicarbonate concentration and a high acetate concentration. From an acid-base standpoint, this is only transiently deleterious. The rise in bicarbonate concentration over the next few hours is directly proportional to the plasma acetate concentration at the end of dialysis [1]. From the point of view of the patient's symptoms during dialysis, however, this state of affairs is probably not desirable. The issue of patient symptoms is beyond the scope of the present review, but the limitations of trying to increase acetate delivery are obvious.

Before leaving the topic of acetate dialysis, I want to review acetate metabolism briefly. Acetate generates bicarbonate by picking up a hydrogen ion as it is metabolized to acetyl coenzyme A. Acetyl coenzyme A has many potential metabolic fates, but which road it takes is unimportant, from an acid-base perspective, so long as another organic acid is not the end product. Mudge and coworkers demonstrated in 1949 that acetate infusion was the equivalent of bicarbonate infusion in humans [27], and recent studies in dialysis patients indicate that 90% to 100% of infused acetate produces bicarbonate [4]. A major difference between bicarbonate and acetate is that acetate metabolism produces calories as well as alkali. Acetate metabolism accounts for up to 65% of the caloric needs during dialysis [28]. Moreover, acetate metabolism has been shown to stimulate organic acid production even when glucose is present in the bath [22, 26]. Replacement of acetate with bicarbonate in the bath blunts this stimulation but does not obliterate it [4, 22].

Bicarbonate supplementation/bicarbonate dialysis

Two other ways of raising plasma bicarbonate concentration in hemodialysis patients are bicarbonate (or bicarbonate precursor) administration and dialysis with bicarbonate in the bath. Both maneuvers have been used. Van Stone gave 12 patients the bicarbonate precursor sodium citrate, equivalent to 1 mEq/kg body weight per day [2]. On average, the patients took 75% of the dose, but even this amount should have been sufficient to closely approximate daily endogenous acid production. With this treatment, predialysis bicarbonate concentration increased from 17 to 21 mEq/liter. The cost of this therapy was increased weight gain between dialyses. Van Stone wondered why plasma bicarbonate concentration didn't completely return to normal in his patients. There are several explanations. The first I have already dealt with: the higher the predialysis bicarbonate concentration, the less alkali gained during the dialysis treatment. The second possibility is that daily bicarbonate administration actually stimulates organic acid production, increasing the acid load to be titrated. Bicarbonate administration has been shown to stimulate organic acid production in fasting states or when ketoacid production is increased [29–31]. The same effect of bicarbonate on lactic acid production is well recognized in lactic acidosis [32–34]. Van Stone did not measure organic anion loss during dialysis, so this possibility remains. Although unlikely, it is also possible that all the administered citrate was not absorbed from the gut. Van Stone postulates that bicarbonate concentration might remain low because the administered bicarbonate is replenishing some depleted non-bicarbonate buffer store, such as bone. Long-range studies are required to test this hypothesis, but I think it is exceedingly unlikely for the reasons discussed earlier.

The second option is the use of bicarbonate rather than acetate in the bath. In the '50s and early '60s, this was the standard approach to therapy. Because bicarbonate addition results in calcium carbonate precipitation in a highly alkaline medium, carbon dioxide had to be bubbled through the bath in the old systems to lower pH. After Mion and colleagues demonstrated in 1964 that acetate was a feasible alkali source during dialysis, acetate rapidly replaced bicarbonate because of its ease of delivery [35]. The use of bicarbonate as an alkali source in dialysis bath solutions has re-emerged in the past several years, and it now is used routinely for selected patients [5, 6, 21, 22]. The requirement for CO_2 has been bypassed by adding the bicarbonate just before the bath enters the dialysis cartridge. Obviously, one can raise the plasma bicarbonate concentration to whatever level one likes with this technique. In such a system, there is no limitation on bicarbonate delivery. Indeed, Graefe and coworkers raised plasma bicarbonate concentration to 33 mEq/liter over 4 hours of dialysis using a high-mass-transfer dialysis membrane, with a bath bicarbonate concentration of 35 mEq/liter [36]. This degree of acute alkalemia is probably not warranted, however. When used now, the goal is generally to increase postdialysis bicarbonate concentration to 25 to 29 mEq/liter. This level should result in a subsequent predialysis bicarbonate concentration in the range of 20 to 24 mEq/liter.

From the viewpoint of acid balance, however, it makes little difference whether the bath contains acetate or bicarbonate. Table 3 presents the balance considerations for bicarbonate dialysis. In this example, I again assume arbitrarily that 240 mEq of alkali must be gained per dialysis to maintain balance. Bicarbonate delivery during dialysis is determined, as noted earlier, by the dialysance of this anion and the transmembrane concentration gradient. This gradient diminishes as dialysis progresses because plasma bicarbonate concentration rises continually. To estimate the change in this gradient, we have assumed that the added bicarbonate is distributed in a volume of fluid equivalent to 50% body weight, on a minute-by-minute basis. This space of distribution assumes that over one-half the administered bicarbonate is consumed by titration of nonbicarbonate buffers. Whether this assumption is valid is unknown, but again, the general conclusion holds regardless of the specific kinetics or space of distribution. In this example, bath bicarbonate concentration is set at 32 mEq/liter. Given these conditions, excess alkali will be delivered if the predialysis plasma bicarbonate concentration is less than 20 mEq/liter, whereas alkali delivery will be insufficient if the predialysis plasma bicarbonate concentration is greater than 22 mEq/liter. In a system with these specifications, plasma bicarbonate concentration before dialysis will hover at approximately 21

Table 3. Acid balance with a bicarbonate-containing dialysis bath: Theoretic considerations

A. Alkali required = 240 mmols/dialysis
B. Dialysis specifications:
   1. Bath HCO_3^- = 32 mEq/L
   2. $D_{HCO_3^-}$ = 150 ml/min
   3. Duration = 4 hrs

Plasma HCO_3^- Initial	Final	Net alkali	Net alkali-240
mEq/L		*mmols*	
16	26.3	360	120
18	27.0	315	75
20	27.7	270	30
22	28.4	225	−15
24	29.5	180	−60

mEq/liter in a patient with this alkali requirement. At that level, acid balance will be maintained just as it is in the case of acetate dialysis.

Gotch and colleagues studied net alkali gain in 8 patients during the first week of dialysis with a bicarbonate-containing bath [21]. Endogenous acid production was estimated from protein catabolic rate as before, and lactate and 3-hydroxybutyrate losses were estimated from the serum concentrations and the dialysance of these anions. At the end of the week, hydrogen ion balance was minus 175 mEq, equivalent to a net gain of 175 mEq of bicarbonate (Table 4). Bicarbonate concentration rose (as would be expected with negative acid balance), but the increase in extracellular bicarbonate stores accounted for only 30% of the estimated net alkali gain. Thus, either 70% of the excess alkali was consumed by titration of nonbicarbonate buffers, or estimated acid production was incorrect. As I noted earlier, studies in normal individuals and experimental animals have shown that 50% to 60% of administered alkali is consumed in titrating nonbicarbonate buffers [10–12]; thus, these authors' estimate of acid production probably is close to the mark. It is also possible that the alkali delivery stimulated organic acid production. Their measurements of lactate and 3-hydroxybutyrate loss do not support this idea, nor do the observations by Ward and coworkers [22], but further work is needed to determine this point with certainty. Gotch, Sargent, and Keen raise the possibility that bone buffers might account for the "alkali deficit," but they have no evidence either for or against this hypothesis [21]. In my view, the alkali retention in these patients simply reflects the upward adjustment in predialysis serum bicarbonate concentration induced by the shift from acetate to bicarbonate dialysis. A similar study carried out after predialysis bicarbonate concentration stabilizes on bicarbonate dialysis could easily answer the question of whether some slowly equilibrating body buffer compartment is being retitrated. There is no evidence to date for such a compartment in patients on dialysis therapy. And if such a compartment does not participate in hydrogen ion economy in this setting, then acid balance will be maintained regardless of the dialysis technique. With bicarbonate dialysis, one trades off postdialysis alkalemia for the avoidance of predialysis acidosis. In the studies shown in Table 4, postdialysis pH was 7.49, and bicarbonate concentration was 29 mEq/liter.

I have talked thus far about machine-patient interactions.

Table 4. Cumulative H^+ balance in 8 patients during the first week of bicarbonate dialysis (three 4-hr treatments)[a]

	Acid in
1. Endogenous acid production[b]	352 ± 30 (SE)
2. Lactate loss	55 ± 6
3. 3-hydroxybutyrate loss	37 ± 12
Total	444 mmols
	Alkali in
1. Bicarbonate delivery	618 ± 77
Hydrogen ion balance	−175 ± 45

[a] From Ref. 21.
[b] Calculated as 0.77 times protein catabolic rate.

Obviously, endogenous acid production can vary in a given patient or among patients. It is likely that some of the variability in predialysis bicarbonate concentration among dialysis patients is due to fluctuations in endogenous acid production as well as to differences in dialysis membranes or duration of dialysis. Studies in normal individuals have demonstrated a correlation between variations in endogenous acid production, induced by variations in diet, and steady-state serum bicarbonate concentration [37].

Implications for dialysis therapy

The final question is whether the mild metabolic acidosis present in dialysis patients adds significantly to dialysis morbidity and mortality. Is the patient with a predialysis bicarbonate concentration of 15 mEq/liter and a pH of 7.30 worse off than a patient with a predialysis bicarbonate concentration of 22 mEq/liter and a pH of 7.40? As I've attempted to show in this Forum, the difference is probably unimportant with regard to bone demineralization. Bone disease related specifically to metabolic acidosis has not emerged as a problem in dialysis patients. On the other hand, there may be other adverse consequences. In children, acidemia retards growth [19]. Other effects are less clear, however. Cardiac contractility is diminished by acidosis, but the effect is only notable at pH values less than 7.20 [38]. Ventricular irritability might be increased as well [39]. The combination of a low pH and low bicarbonate is known to impede potassium entry into cells acutely [40], but whether the gradual fluctuations in pH and bicarbonate concentration occurring in patients on hemodialysis increase the likelihood of symptomatic hyperkalemia is unknown. Patients who have lower bicarbonate concentrations do not appear to have more generalized symptoms than do patients with higher bicarbonate concentrations. To my knowledge, no one has shown a correlation between plasma bicarbonate and survival or well-being on dialysis. Unless a specific morbidity can be identified, there appears to be little reason for attempting to increase bicarbonate concentration in adult hemodialysis patients.

I have limited my discussion today to hemodialysis, but of course the same principles hold for peritoneal dialysis [41]. The steady-state plasma bicarbonate concentration in such patients depends on the interplay between endogenous acid production and net alkali gain during dialysis. A major difference, from an acid-base perspective, between chronic ambulatory peritoneal dialysis (CAPD) and hemodialysis is that, with the former treatment, alkali is administered continually. Thus there is no

interdialytic period during which body buffers are titrated by endogenous acids. If buffer disequilibrium occurs, for example in bone, major differences should emerge when CAPD patients are compared with hemodialysis patients. Thus far, the only difference is that plasma bicarbonate concentration is slightly higher in CAPD than in hemodialysis patients in some, but not all, reports [41].

I have not included a discussion of carbon dioxide diffusion across the dialysis membrane in this review. In the most commonly used systems, a significant amount of CO_2 is lost during dialysis [23, 42], whereas when a closed-system, bath-regenerating cartridge is used, CO_2 is actually gained from the bath during dialysis [43]. These CO_2 fluxes have a significant impact on ventilation, but they do not influence acid balance.

Questions and answers

DR. JEROME P. KASSIRER: The measurements you have used are fairly imprecise. In particular, values for endogenous acid production are gross estimates, and one could easily miss 5 or even 10 mmol of acid accumulation per day, which over a period of years could amount to a substantial acid accumulation. Is there any corollary evidence of acid accumulation over time? For example, is bone carbonate disproportionately reduced in patients who have been on dialysis for 5 to 10 years?

DR. GENNARI: There are no data to answer this question, but of course it goes to the heart of the issue. Is there a sustained buffer dysequilibrium in chronic dialysis patients? I think not. To recapitulate the essence of my argument, the rise in bicarbonate with dialysis, and its gradual fall in the interdialytic period, support the notion that bicarbonate is reflecting other buffers in the body. In settings in which bicarbonate doesn't reflect acid balance, its concentration is low and stable, and acid retention is relentless. In addition, the lack of evidence of bone disease specifically related to acidosis even in long-term dialysis patients argues against continued carbonate consumption. Can I exclude acid retention based on my analysis? Of course not, but I think it is very unlikely. It would be interesting to compare bone carbonate in long-term dialysis patients with previous observations in patients with untreated uremic acidosis, but I think that if acidosis per se were a problem in dialysis patients, we all would have seen the problem by now. I refer you to the case presented here. Despite 8 years of metabolic acidosis, he is working full-time in an occupation that requires some physical exertion. He feels well and has no clinical bone disease.

DR. KASSIRER: So is it your belief that a patient with advanced renal failure is in positive hydrogen-ion balance before he or she is dialyzed and in acid balance after?

DR. GENNARI: Based on my analysis, I believe that further acid retention does not occur after dialysis is initiated. Whether the carbonate consumed in titrating retained acid before dialysis is started is regenerated is another question. Careful balance studies in stable patients before and after beginning dialysis are required to answer this question. In the absence of any data, my speculation is that only partial repair of lost carbonate occurs. I know of no signal other than alkalemia for the bone to replenish carbonate stores, and only transient alkalemia occurs postdialysis.

DR. JORDAN J. COHEN: You indicated that acetate levels in the blood rise rapidly at the onset of dialysis and reach a steady state determined by the acetate level in the bath. You also indicated that plasma bicarbonate concentration during dialysis is fairly stable. If acetate is being picked up continuously during the dialysis and not incrementing acetate concentration in the plasma, then it must be converted to bicarbonate, which is then lost in the bath. So the net result of all this is represented by the residual increment in plasma acetate at the end of dialysis. Can't we just look at that increment and judge directly how much net alkali has been gained without invoking assumptions about acetate and bicarbonate dialysance and the like?

In other words, wouldn't it be simpler to estimate the net increment in alkali gained by the dialysis procedure by just multiplying the residual increment in acetate concentration by the space of distribution for this anion?

DR. GENNARI: Your approach is of course a reasonable one, although it is simply observational and has no predictive power. Moreover, one still needs to estimate a space of distribution for administered acetate, and for bicarbonate if its concentration changes during the dialysis. The approach I outlined today has predictive power. If one knows the characteristics of the kidney used, one can estimate the expected rates of bicarbonate and acetate transfer. I did not mean to imply, however, that only one technique was available for assessing net alkali gain. I used existing data to make my point that net alkali addition is importantly influenced by the predialysis bicarbonate concentration.

DR. COHEN: According to your analysis, the predialysis bicarbonate concentration could be increased by reducing the dialysance of bicarbonate. Assuming it were desirable to increase bicarbonate concentration, does this strategy make any sense?

DR. GENNARI: No. One cannot reduce the dialysance of bicarbonate without reducing the dialysance of the other substances we are trying to remove. In the early days of acetate dialysis, membranes were less efficient, and plasma bicarbonate concentrations were higher. The cost was longer dialysis treatments, and no one wants to return to that situation.

DR. JOHN T. HARRINGTON: Patients in chronic renal failure are in positive acid balance by approximately 20 mmol/day during the last years of their progressive renal failure. If studies were carried out in the first 2 or 3 weeks of dialysis rather than in the chronic steady state of dialysis, you might be able to see a difference in net alkali or acid balance. This approach would be an indirect way of looking at bone carbonate stores. Have any such studies been performed?

DR. GENNARI: No. As I indicated earlier, such studies have not been carried out. I agree that the results would be of considerable interest.

DR. RONALD D. PERRONE (*Division of Nephrology, NEMCH*): John, in the beginning part of your talk you likened the chronic renal failure patient on dialysis to a patient with proximal renal tubular acidosis, in whom there is no net accumulation of acid. In one sense the situation of chronic dialysis is different in that there is a net accumulation of acid for 44 hours, followed by a 4-hour period of retitration, whereas in proximal RTA the daily acid load would be rapidly excreted. Could there be a deleterious effect of acid accumulation in this interval?

DR. GENNARI: I don't think there is anything specifically deleterious about acid accumulation in the interdialytic period,

as compared to any other setting in which acid is retained. The accumulating acid titrates body buffers. Bicarbonate is one of these buffers, and we can observe its concentration falling in the interdialytic period. As I stated earlier, the change in bicarbonate concentration reflects its participation in the buffer process. During dialysis, the alkali pool is replenished and is available for titration in the next interdialytic period.

DR. PERRONE: Is there any information about how long bone would take to reconstitute itself after titration of endogenous acid?

DR. GENNARI: The only information I am familiar with is the recent work of Bushinsky and coworkers [44]. These investigators studied calcium and proton fluxes in cultured mouse calvaria. They found that bone buffering in these cultures was rapid either when acid or alkali was added to the medium. Calcium left the bone cells in response to acid addition, and it reentered bone when alkali was added. These effects were apparent both at 3 hours and at 24 hours. Whether these bone cultures are an appropriate model of the response of long bone in the intact organism remains to be seen, although recent studies in intact rats indicate that a bone buffer response to acid administration is evident within 24 hours [45].

DR. ANDREW LEVEY (*Division of Nephrology, NEMCH*): Your analysis suggests that patients are in acid-base balance whether the dialysate contains acetate or bicarbonate, even though the plasma bicarbonate concentration is slightly higher if bicarbonate is the buffer. However there are differences in acid-base parameters during the dialysis treatment, and some have suggested that patients have fewer untoward symptoms during dialysis with bicarbonate-containing dialysate. Would you comment on these differences?

DR. GENNARI: I have deliberately avoided a discussion of patient symptoms. One can find evidence in support of whatever stance one wishes to take on this issue. Acetate administration to human subjects without renal failure produces no untoward symptoms [20, 27]. In patients on dialysis, some investigators are convinced that bicarbonate dialysis is associated with fewer symptoms [6, 36]. On the other hand, two recent double-blind studies failed to show any major differences, except in the occasional patient who has problems metabolizing acetate [46, 47].

DR. VINCENT CANZANELLO (*Fellow in Nephrology, NEMCH*): Regarding the results of blood gas specimens obtained from hemodialysis access sites, do you believe the type of vascular access (for example, primary side-to-side or end-to-side versus a synthetic arteriovenous fistula) is important?

DR. GENNARI: No. We measured PO_2 in all the samples obtained in our patients. The mean value obtained was 92 ± 14 (SD) mm Hg. Only 6 of the 48 PO_2 values were less than 80 mm Hg, and therefore we felt we had the equivalent of aterial blood.

DR. NICOLAOS E. MADIAS: Careful observations have documented the validity of employing blood from the arteriovenous fistula for determining the values for arterial blood gases [48].

DR. HARRINGTON: One argument that the acetate advocates have used is that there is a subgroup of "acetate-intolerant" patients. Acetate levels may rise to 15 mmol/liter in these patients, and it is argued that patients are more likely to be symptomatic during dialysis. Can you comment on this?

DR. GENNARI: Dr. Fitzgibbons and his coworkers have reported preliminary observations in a double-blind crossover comparison between bicarbonate and acetate dialysis [47]. They studied a subgroup of acetate-intolerant patients who were identified because of their symptoms; in these patients, the decrease in bicarbonate between the beginning and end of dialysis suggested a problem with acetate conversion to bicarbonate. As I mentioned earlier, these workers found that bicarbonate dialysis reduced symptoms only in this subgroup of patients. Unfortunately, they identified their acetate-intolerant patients by symptoms, so one cannot draw any conclusions concerning whether acetate intolerance is always associated with symptoms. Vinay and coworkers used the pattern of plasma bicarbonate during dialysis to estimate the incidence of acetate intolerance in hemodialysis patients [49]. In a preliminary report, they found that 18% of their patients were acetate intolerant by their criteria. The authors did not correlate acetate intolerance with untoward symptoms during dialysis, however.

DR. COHEN: John, I certainly agree with you that there is little evidence to suggest that the mild degree of acidosis characteristic of dialysis patients is harmful, particularly in the absence of persistently positive hydrogen-ion balance. The fact remains, however, that nature picked 24 mEq/liter as the bicarbonate concentration around which acid balance is normally maintained, at least at sea level. Not being able to detect or to document any deleterious effect of mild degrees of acidosis dosen't mean that some unwanted consequences might not accumulate, especially in view of the very long stretches of time during which dialysis patients are now exposed to a low bicarbonate level. My question is, if you wanted to design a strategy that would allow chronic dialysis patients to hover around a bicarbonate of 24 mEq/liter while enjoying the advantages of high-mass-transfer kidneys, what would you do?

DR. GENNARI: It is virtually impossible to achieve a bicarbonate concentration in the range of 24 mEq/liter using acetate dialysis with the dialysis membranes presently available. Thus, bicarbonate dialysis would be required if that were your goal. Even with bicarbonate dialysis, however, one would have to produce considerable postdialysis alkalemia to maintain a predialysis bicarbonate concentration in the 22 to 24 mEq/liter range. Alkalemia in itself might be associated with symptoms and, in theory, it could exacerbate tissue calcium phosphate deposition. If maintenance of a stable normal plasma bicarbonate concentration is your goal, then CAPD with appropriate dietary management is the only acceptable form of therapy. I would submit, however, that it makes little difference whether your plasma bicarbonate concentration is 20 or 24 mEq/liter, so long as acid balance is maintained.

DR. KASSIRER: Maybe we have been too worried about small alterations in fluid, electrolyte, and acid-base equilibrium. Although it is true that normal individuals live within an extremely narrow range of plasma electrolytes, plasma bicarbonate concentrations, and blood pHs, it may not matter much if they are off the mark by a few percent. A reduction of 4 or 5 mEq per liter in bicarbonate doesn't seem particularly harmful; neither does a fall in serum potassium of 1 mEq/liter or a potassium deficit of 100 to 200 mEq.

DR. COHEN: John, one price that patients do pay by having chronic metabolic acidosis is hyperventilation. I wouldn't argue that this is a very important issue but would merely point out that dialysis patients with a low bicarbonate have a persistent stimulus to ventilation which, under some circumstances, might

be burdensome.

DR. GENNARI: One would be hard pressed to make a case that the mild hyperventilation seen in dialysis patients is bad. The mean PCO_2 in our patients before dialysis was 34 mm Hg; the range was 28 to 41 mm Hg. These values represent the response to the trough bicarbonate level, and therefore PCO_2 is probably higher most of the time. To my knowledge, no ill effects of PCO_2 values in this range have been noted in humans.

DR. KASSIRER: I must admit your hypothesis has a sensible ring. If patients on dialysis for long periods do not develop hyperparathyroidism or osteomalacia, their bones remain intact. If there were positive acid balance of a sufficient amount over a period of time, you would expect these patients to develop a substantial osteopenia, which most do not.

DR. HARRINGTON: The problem with measuring bone carbonate has been that it has always been very complicated to measure. Are there better ways of doing it now to directly answer the question of how much acid is buffered by bone?

DR. GENNARI: To my knowledge there is no good way to assess the long-term effects of bone buffering, save for tissue analysis. Noninvasive techniques have been developed to evaluate bone density, but these techniques would not be useful for detecting whether bone carbonate stores (which are only a small fraction of bone mineral) are reduced.

DR. SUSAN HOU (*Division of Nephrology, Michael Reese Hospital*): If even the mild acidosis typically seen in patients undergoing hemodialysis is bad for growth, do children grow better when dialyzed with a bicarbonate bath?

DR. GENNARI: The question will probably never be answered. Because of the evidence in renal tubular acidosis that complete correction of acidemia can restore a normal growth pattern in children [50], pediatric nephrologists have routinely provided additional bicarbonate to children receiving hemodialysis. Obviously, growth impairment in children on dialysis is a multifactorial problem. The results of recent studies suggest that children grow better if they are receiving CAPD therapy than if they are hemodialyzed [51, 52]. There are clearly many differences between these two therapies, but one difference in these studies was that serum total CO_2 was higher in the patients receiving CAPD. In neither study, however, could the improvement in growth be correlated with the serum total CO_2 content.

DR. SERAFINO GARELLA (*Division of Nephrology, Michael Reese Hospital*): Do you think that examining external calcium balance would be another valid way of determining the presence of chronic positive acid balance and ongoing bone carbonate titration in the hemodialysis patients? In studies of chronic metabolic acidosis [17], external calcium balance was negative, the calcium losses occurring primarily through the urine. In anuric patients undergoing hemodialysis, calcium losses might take place through the dialyzer, where they might be quantitated. Alternatively, calcium released from bones might deposit in soft tissues. Could this phenomenon be responsible for the extensive calcium deposits seen in some patients on chronic hemodialysis? Are these the more acidemic patients?

DR. GENNARI: Calcium-balance studies, which would be difficult to carry out in dialysis patients, would not answer the question. We know already that the problem is primarily one of calcium distribution within the body rather than external balance. Calcium is not lost during dialysis. Bath calcium concentration is higher than serum ionized calcium by design; thus calcium addition is assured during dialysis. This addition is reflected by a transient elevation of serum calcium postdialysis. The problem is where the calcium ends up—in bone or in soft tissues. Many factors influence this distribution, including parathyroid hormone and phosphate concentration, in addition to pH. Unfortunately, we have no good way of measuring this pattern of distribution other than to look at bone mineral content. There is no evidence I know of to indicate that soft-tissue calcium deposition is higher in patients with lower bicarbonate levels. As I noted earlier, soft-tissue calcium deposition may be promoted by alkalemia.

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