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CHAPTER
EIGHTEEN

METABOLIC ALKALOSIS

The introduction to acid-base disorders presented in Chap. 17 should be read before proceeding with this discussion. Primary metabolic alkalosis is characterized by an elevation in the arterial pH (or a reduction in the H^+ concentration), an increase in the plasma HCO_3^- concentration, and compensatory hypoventilation, resulting in a rise in the P_{CO_2}. A high HCO_3^- concentration, however, is not diagnostic of metabolic alkalosis, since it can also represent the renal compensation to chronic respiratory acidosis. These disorders can be differentiated by measurement of the extracellular pH, which is reduced in chronic respiratory acidosis. In addition, a plasma HCO_3^- concentration of 40 meq/L or more indicates at least some degree of metabolic alkalosis, since this level is greater than that generally achieved by the renal compensation to severe chronic hypercapnia.

PATHOPHYSIOLOGY

The pathophysiology of metabolic alkalosis is most easily understood by asking two separate questions:

- How do patients become alkalotic?
- Why do they remain alkalotic, since renal excretion of the excess HCO_3^- should rapidly restore normal acid-base balance?

Generation of Metabolic Alkalosis

A primary elevation in the plasma HCO_3^- concentration is usually induced by H^+ loss from the gastrointestinal tract (as with vomiting or nasogastric suction) or in the urine (as with the diuretic therapy) (Table 18-1). These H^+ ions are derived from the intracellular dissociation of H_2CO_3:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Thus, there will be an *equimolar generation of HCO_3^- for each milliequivalent of H^+ that is lost*.

Metabolic alkalosis can also be produced by the administration of HCO_3^-, by H^+ movement into the cells, and by certain forms of volume contraction. A transcellular H^+ shift typically occurs with hypokalemia. As the plasma K^+ concentration falls, K^+ moves out of the cells down a favorable concentration gradient to partially replete the extracellular stores. Electroneutrality is maintained in this setting by a reciprocal shift of H^+ (and Na^+) into the cells.[1,2] The net effect is an *extracellular alkalosis with a paradoxical intracellular acidosis*.[3,4] K^+ repletion can reverse the H^+ shift and lower the extracellular pH toward normal.[1,2]

Table 18-1 Causes of metabolic alkalosis

Loss of hydrogen
- A. Gastrointestinal loss
  1. Removal of gastric secretions—vomiting or nasogastric suction[a]
  2. Antacid therapy, particularly with cation-exchange resin
  3. Chloride-losing diarrhea
- B. Renal loss
  1. Loop or thiazide-type diuretics[a]
  2. Mineralocorticoid excess[a]
  3. Postchronic hypercapnia
  4. Low chloride intake
  5. High-dose carbenicillin or other penicillin derivative
  6. Hypercalcemia, including the milk-alkali syndrome
- C. H^+ movement into cells
  1. Hypokalemia[a]
  2. Refeeding (?)

Retention of bicarbonate
- A. Massive blood transfusion
- B. Administration of $NaHCO_3$
- C. Milk-alkali syndrome

Contraction alkalosis
- A. Loop or thiazide-type diuretics
- B. Gastric losses in patients with achlorhydria
- C. Sweat losses in cystic fibrosis

[a] Most common causes.

A *contraction alkalosis* occurs when the fluid that is lost contains Cl^- but little or no HCO_3^-. In this setting, which is most commonly due to diuretics, the extracellular volume contracts around a relatively constant quantity of extracellular HCO_3^-. As a result, the plasma HCO_3^- concentration rises (Fig. 18-1).[5] The severity of this process is generally limited by buffering of the excess extracellular HCO_3^- by cell and bone buffers.[6]

Patients with metabolic alkalosis are almost always *hypochloremic*, usually because of chloride loss with H^+ with gastrointestinal or renal losses. As described in the next section, hypochloremia is thought to play a major role in the maintenance of metabolic alkalosis by limiting HCO_3^- excretion.

Maintenance of Metabolic Alkalosis

The kidney possesses the ability to correct a metabolic alkalosis by excreting the excess HCO_3^- in the urine. For example, normal subjects given 1000 meq of $NaHCO_3$ per day for 2 weeks excrete virtually all of the excess HCO_3^- and develop only a minor increase in the plasma HCO_3^- concentration.[7] Since the disorders that cause metabolic alkalosis are associated with a much smaller HCO_3^- load, the *perpetuation of metabolic alkalosis requires an impairment in renal HCO_3^- excretion*

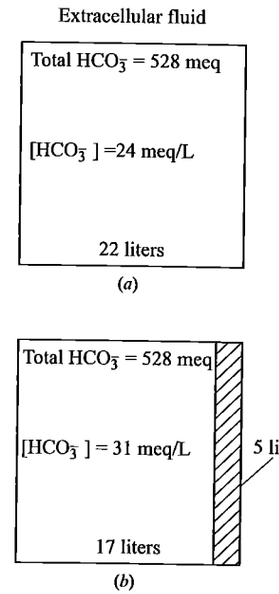

Figure 18-1 Mechanism of contraction alkalosis. (*a*) The volume and HCO_3^- concentration of the extracellular fluid in an as yet untreated 70-kg man whose extracellular volume has increased from 17 to 22 liters because of congestive heart failure. (*b*) If the excess NaCl is lost isotonically after the administration of diuretic, there will be a reduction in the extracellular volume. Since the quantity of extracellular HCO_3^- is initially unchanged, the HCO_3^- concentration in the extracellular fluid will increase from 24 to 31 meq/L.

(Table 18-2).* Both a reduction in glomerular filtration rate (and therefore in the filtered HCO_3^- load) and an elevation in tubular reabsorption contribute to this process.[8-11] It is likely that the latter is more important, since a low filtration rate alone, as in chronic renal insufficiency, does not appear to predispose to metabolic alkalosis.

As was reviewed in Chap. 11, HCO_3^- reabsorption occurs by H^+ secretion from the tubular cell into the lumen. The proximal tubule plays the major role in this process, reabsorbing approximately 90 percent of the filtered HCO_3^-, mostly via Na^+-H^+ exchange. The remaining HCO_3^- is primarily reabsorbed in the loop of Henle via Na^+-H^+ exchange and in the collecting tubules via an active H^+-ATPase pump in the luminal membrane.

A variety of factors may contribute to the increase in HCO_3^- reabsorption that is seen in metabolic alkalosis, including volume and chloride depletion, hyperaldosteronism, and hypokalemia.

Effective circulating volume depletion The increase in net HCO_3^- reabsorption in effective volume depletion (which includes edematous states such as heart failure and cirrhosis; see page 259) can be viewed as an appropriate response from the viewpoint of volume regulation. If the excess HCO_3^- were excreted in the urine, it would obligate concurrent Na^+ loss to maintain electroneutrality, further diminishing tissue perfusion.

The effect of volume status on HCO_3^- reabsorption is dependent upon the degree of volume depletion. As an example, a 4-meq/L increase in HCO_3^- reabsorptive capacity (from 25 to 29 meq/L of glomerular filtration rate) can be seen with the ingestion of a very low Na^+ diet (10 meq/day), even though the patient is clinically euvolemic.[12] On the other hand, HCO_3^- reabsorptive capacity can exceed 35 meq/L with marked reductions in tissue perfusion, thereby allowing a relatively severe metabolic alkalosis to persist.[9,10]

Table 18-2 Causes of impaired HCO_3^- excretion that allow metabolic alkalosis to persist

Decreased glomerular filtration rate
A. Effective circulating volume depletion
B. Renal failure (usually associated with metabolic acidosis)
Increased tubular reabsorption
A. Effective circulating volume depletion
B. Chloride depletion (also decreases bicarbonate secretion)
C. Hypokalemia
D. Hyperaldosteronism

* In this regard, metabolic alkalosis is similar to other "excess" disorders, such as hyponatremia (too much water), hyperkalemia (too much K^+), and edema (too much Na^+). In each of these conditions, renal excretory capacity for the retained solute or water is normally so high that a defect in renal excretion must be present for the disorder to persist.

Despite the clear relationship between hypovolemia and increased HCO_3^- reabsorption, the mechanism by which this occurs is incompletely understood. Micropuncture studies in experimental animals suggest that increased proximal reabsorption, if it occurs, cannot quantitatively explain the reduction in HCO_3^- excretion.[13-15] It is probable that this relative lack of change reflects the interaction of several counterbalancing factors.[16] Both angiotensin II, released in response to hypovolemia, and the elevated tubular fluid HCO_3^- concentration increase proximal HCO_3^- reabsorption—the former by enhancing the activity of the Na^+-H^+-exchanger,[17] and the latter by allowing more H^+ ions to be secreted before approaching the minimum pH that the proximal tubule can achieve.[15,16] On the other hand, metabolic alkalosis itself decreases the activity of the Na^+-H^+ antiporter, an effect that is probably mediated in part by a parallel rise in renal tubular cell pH.[18]

The net effect is that the decrease in HCO_3^- excretion in metabolic alkalosis associated with volume depletion is primarily due to enhanced net HCO_3^- reabsorption in the distal nephron.[14,15] Secondary hyperaldosteronism may contribute to this response. Aldosterone directly stimulates the H^+-ATPase pump in the cortical and medullary collecting tubules.[19,20] In addition, aldosterone can indirectly increase net H^+ secretion (and therefore HCO_3^- reabsorption) by promoting Na^+ transport in the cortical collecting tubule.[21,22] The reabsorption of cationic Na^+ creates a lumen-negative potential difference; this electrical gradient then promotes H^+ accumulation in the lumen by minimizing the rate of passive back-diffusion.

Concurrent Cl^- depletion (induced by vomiting or diuretics) and hypokalemia also appear to play an important role in the increase in distal HCO_3^- reabsorption. To the degree that *Na^+ is reabsorbed but Cl^- cannot follow to dissipate the electrical gradient*, there will be a greater increase in luminal negativity and therefore a greater stimulus to H^+ secretion.[23] The net effect of the almost complete reabsorption of filtered HCO_3^- is the paradoxical finding of *an acid urine despite the presence of extracellular alkalemia*.[23]

These changes are reversed with correction of the fluid and chloride deficits. In this setting, reversal of the metabolic alkalosis requires increased HCO_3^- excretion, a change that is primarily mediated by decreased net HCO_3^- reabsorption in the distal nephron.[24]

Chloride depletion The above discussion has suggested a central role for volume depletion in the maintenance of metabolic alkalosis. It has been suggested, however, that it is *Cl^- depletion*, rather than decreased tissue perfusion, that is actually of primary importance.[13,14,25] Consistent with this hypothesis is the observation that repair of the volume deficit by the administration of albumin does not reverse the increase in distal HCO_3^- reabsorption and does not correct the alkalosis.[14] On the other hand, the administration of non-Na^+-containing Cl^- salts (such as potassium or choline chloride) does not restore normovolemia but does result in decreased net acid excretion and a reduction in the plasma HCO_3^- to normal.[13,14,25]

There are three mechanisms by which Cl^- depletion could perpetuate a metabolic alkalosis, independent of Na^+ balance[13]:

- The activity of the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane of the macula densa cell is primarily determined by the availability of Cl^- (see Fig. 4-3). Thus, hypochloremia will decrease Cl^- delivery to the macula densa, resulting in less NaCl reabsorption. The latter change will promote the release of renin, leading to secondary hyperaldosteronism[26] and increased distal H^+ secretion.
- The luminal H^+-ATPase pump in the intercalated cells in the collecting tubules is probably associated with passive cosecretion of Cl^- to maintain electroneutrality.[27] A decline in the tubular fluid Cl^- concentration will facilitate this process by maximizing the transtubular gradient for Cl^- secretion.
- It has been assumed that the appropriate HCO_3^- loss in metabolic alkalosis results from diminished reabsorption of filtered HCO_3^-. It now appears, however, that at least some of the urinary HCO_3^- is derived from *HCO_3^- secretion* by a subpopulation of intercalated cells in the cortical collecting tubule in which the H^+-ATPase pump is located on the basolateral rather than the luminal membrane (see page 338) (Fig. 18-2).[28,29] The final step in this process seems to involve Cl^-/HCO_3^- exchange across the luminal membrane. The energy for this transport is supplied by the highly favorable inward gradient for Cl^-, since the cell Cl^- concentration is very low. Lowering the tubular fluid Cl^- concentration in metabolic alkalosis will diminish this gradient, thereby minimizing the ability to secrete HCO_3^-.

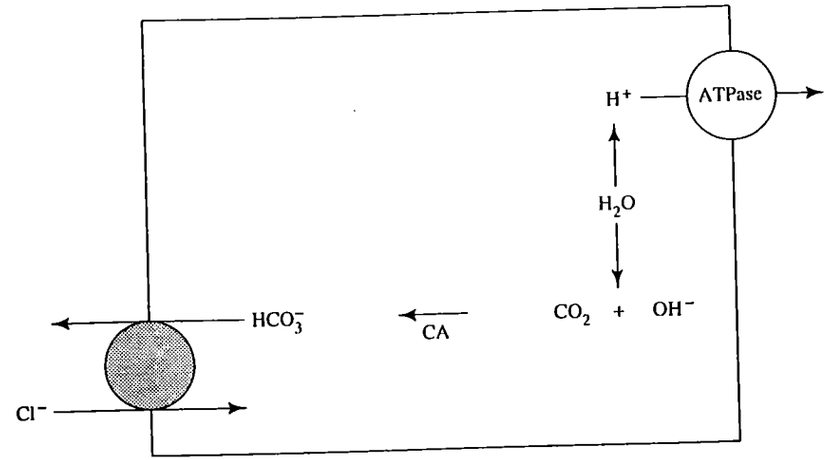

Figure 18-2 Transport mechanisms involved in the secretion of bicarbonate into the tubular lumen in the type B intercalated cells in the cortical collecting tubule. Water within the cell dissociates into hydrogen and hydroxyl anions. The former are secreted into the peritubular capillary by H-ATPase pumps in the basolateral membrane. The hydroxyl anions combine with carbon dioxide to form bicarbonate in a reaction catalyzed by carbonic anhydrase (CA). Bicarbonate is then secreted into the tubular lumen via chloride-bicarbonate exchangers in the luminal membrane. The favorable inward concentration gradient for chloride (lumen concentration greater than that in the cell) provides the energy for bicarbonate secretion.

In summary, the relative roles of volume and Cl^- depletion are unresolved. This issue is not of great clinical importance, however, since the administration of NaCl will simultaneously correct both problems and allow the excess HCO_3^- to be excreted in the urine (see "Treatment," below).[9,29,30] This HCO_3^- diuresis is primarily due to diminished distal HCO_3^- reabsorption and/or enhanced distal HCO_3^- secretion.[13,24,28,29]

It is important to emphasize that hypovolemia has *two separate and independent effects* in metabolic alkalosis. To the degree that renal HCO_3^- reabsorption is enhanced, volume and chloride depletion from any cause will tend to perpetuate an alkalosis. However, hypovolemia will *produce* an alkalosis only when the fluid lost contains an excess of H^+ ions or an excess of Cl^- in relation to HCO_3^-, thereby raising the plasma HCO_3^- concentration by contraction (Fig. 18-1). Thus, the vomiting or diuretic therapy often induce a metabolic alkalosis, but bleeding, which is associated with the loss of Cl^- and HCO_3^- in concentrations similar to those in the plasma, does not.

Hypokalemia Hypokalemia is a potent stimulus to H^+ secretion and HCO_3^- reabsorption (see Fig. 11-16).[31,32] At least three factors may contribute to this relationship:

- The concurrent intracellular acidosis, induced by transcellular K^+/H^+ exchange,[1,2] will tend to increase H^+ secretion.
- There is a second proton pump in the distal nephron, a H^+-K^+-ATPase that actively reabsorbs K^+ as well as secreting H^+.[33-35] Electroneutrality is maintained by H^+ and K^+ movement in opposite directions across the luminal membrane. Active K^+ reabsorption by this pump appears to be appropriately stimulated by hypokalemia, an effect that could also enhance H^+ secretion.[33,35-37] Thus, hypokalemia and aldosterone, which stimulate the H^+-K^+-ATPase and H^+-ATPase pumps, respectively, appear to have a potentiating effect on distal hydrogen secretion and therefore on the development and maintenance of metabolic alkalosis.[38] It is of interest in this regard that many of the causes of metabolic alkalosis (such as diuretic therapy, vomiting, and primary hyperaldosteronism) are associated with both a reduction in the plasma K^+ concentration and increased aldosterone release.
- Severe hypokalemia may cause, by an unknown mechanism, a reduction in chloride reabsorption in the distal nephron.[39,40] As a result, Na^+ reabsorption at this site is associated with a greater luminal electronegativity and therefore a greater tendency for H^+ secretion.[40]

The effect of hypokalemia is relatively small when HCO_3^- reabsorption is already stimulated by volume depletion (Fig. 18-3).[41] It appears to be of primary importance, however, in states of primary mineralocorticoid excess, as with an aldosterone-producing adrenal adenoma.[40-42] In this setting, aldosterone-induced Na^+ retention is transient, with marked volume expansion and edema being prevented by the phenomenon of aldosterone escape (see page 185). As a result, Na^+ intake and excretion are roughly equal, and it is hypokalemia, not volume depletion, that is now responsible for perpetuation of the alkalosis. Correction of the K^+ deficit returns the plasma HCO_3^- concentration toward normal in this setting, both by decreasing net acid excretion in the urine[9,40-42] and, as most of the exogenous K^+ enters the cells to replete cellular stores, by movement of H^+ ions back into the extracellular fluids.[1,2]

Respiratory Compensation

The development of alkalemia is sensed by the respiratory chemoreceptors, resulting in a decline in ventilation and an *appropriate* elevation in the P_{CO_2}. On average, the P_{CO_2} rises 0.7 mmHg for every 1.0-meq/L increment in the plasma HCO_3^- concentration.[43,49] Thus, if the plasma HCO_3^- concentration is 34 meq/L (or 10 meq/L greater than normal), there should be a 7 mmHg increase in the P_{CO_2} to approximately 47 mmHg.

Values significantly different from this predicted value represent superimposed respiratory acidosis or alkalosis.

The respiratory compensation may be partially or completely impaired in the presence of underlying respiratory alkalosis or hypoxemia. As an example, patients with heart failure or cirrhosis frequently develop metabolic alkalosis as a result of diuretic therapy. However, both of these disorders are often associated with a primary respiratory alkalosis (see Chap. 21), which can prevent the appropriate compensatory hypoventilation.

Hypoxemia, on the other hand, is generally less likely to affect the ventilatory response. Hypoventilation will lower the P_{O_2} at the same time as it raises the P_{CO_2}.[45] However, the hypoxemic stimulation to respiration in alkalemic patients does not become prominent until the P_{O_2} is below 50 mmHg (see page 649). Thus,

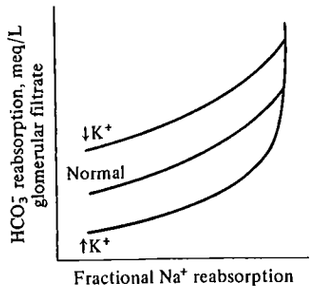

Figure 18-3 HCO_3^- reabsorption as a function of the fraction of the filtered Na^+ that is reabsorbed and the state of K^+ balance. HCO_3^- reabsorption is enhanced by both volume depletion (high fractional Na^+ reabsorption) and hypokalemia, conditions that therefore can perpetuate metabolic alkalosis. (*Redrawn form Kurtzman NA, White MG, Rogers PW,* Arch Intern Med *131:702, 1973. By permission of the American Medical Association, copyright 1973.*)

in the absence of underlying lung disease, the fall in P_{O_2} in metabolic alkalosis will not usually be sufficient to impair the compensatory response. As a result, the P_{CO_2} in a previously normal subject can exceed 60 mmHg in severe metabolic alkalosis.[36]

What is less clear is the degree to which the change in respiration actually protects the extracellular pH. Studies in experimental animals indicate that the rise in P_{CO_2} in metabolic alkalosis increases net H^+ excretion and therefore *further elevates the plasma HCO_3^- concentration.*[47] These changes probably result from a reduction in renal tubular cell pH induced by the increment in P_{CO_2}; the relative intracellular acidosis will stimulate H^+ secretion, thereby raising the plasma HCO_3^- concentration. The net effect is that, after several days, the *arterial pH is the same as it would have been if no respiratory compensation had occurred,* because of equivalent elevations in the extracellular P_{CO_2} and HCO_3^- concentration (see page 580).[47]

ETIOLOGY

Metabolic alkalosis can be produced by a variety of disorders, most of which are characterized by enhanced HCO_3^- reabsorption due to volume, Cl^-, and/or K^+ depletion (Table 18-1).[11]

Gastrointestinal Hydrogen Loss

Removal of gastric secretions Gastric juice contains high concentrations of HCl and lesser concentrations of KCl. Each milliequivalent of H^+ secreted generates 1 meq of HCO_3^-. Under normal conditions, the increase in the plasma HCO_3^- concentration is only transient, since the entry of the acid into the duodenum stimulates an equal amount of pancreatic HCO_3^- secretion.[48] However, there is no stimulus to HCO_3^- secretion if the gastric juice is removed, either by vomiting or by nasogastric suction. The net result is an increase in the plasma HCO_3^- concentration and metabolic alkalosis.[23,49,50] The tendency toward alkalosis is enhanced by the concomitant volume and K^+ depletion.

Metabolic alkalosis also can occur after removal of gastric acid secretions in patients with achlorhydria (little or no gastric acid secretion). In this setting, contraction (due to the loss of a high Cl^- low HCO_3^- fluid) rather than H^+ loss is responsible for the elevation in the plasma HCO_3^- concentration.

A somewhat similar sequence can be induced by chronic therapy with an antacid, such as magnesium hydroxide. The hydroxide component buffers gastric H^+, while the magnesium combines with pancreatic HCO_3^- to form insoluble magnesium carbonate. If only these reactions occurred, there would be equivalent H^+ and HCO_3^- loss and no change in acid-base balance. However, some of the magnesium combines with other constituents in the intestinal lumen, such as fats and phosphates. As a result, some of the secreted HCO_3^- remains soluble and is

absorbed, leading to a mild alkaline load that produces no problems as long as renal function is normal.[51]

The outcome may be different in patients with advanced renal failure who are also treated with a cation-exchange resin (Kayexalate) for hyperkalemia.[49,52] In this setting, some of the magnesium binds to the resin, leaving more HCO_3^- in a soluble form in the intestinal lumen and able to be absorbed. The renal failure is important in perpetuating the alkalosis, since it prevents excretion of the excess HCO_3^-.

Congenital chloridorrhea Since the enteric fluids below the stomach are alkaline, diarrhea usually leads to metabolic acidosis. However, a rare condition, *congenital chloridorrhea*, is associated with a specific intestinal defect in Cl^- reabsorption and HCO_3^- secretion, resulting in a high fecal Cl^- concentration that can reach 140 meq/L and a low fecal pH.[49,53] Loss of this fluid tends to produce metabolic alkalosis; a similar problem can occur in some patients with a villous adenoma.[49]

Congenital chloridorrhea is induced by mutations in the down-regulated adenoma gene, which is presumably an intestinal anion transporter or a regulator of such a transporter.[54] Treatment generally consists of a high chloride intake to prevent volume depletion. However, such an approach also increases the severity of the diarrhea because of the chloride malabsorption. Decreasing gastric chloride secretion with a proton pump inhibitor such as omeprazole may produce 15 to 20 percent reductions in stool volume and Cl^- excretion.[55]

Factitious diarrhea Factitious diarrhea due to laxative abuse is often associated with metabolic acidosis resulting from loss of HCO_3^--containing fluid.[49,56] However, many patients develop metabolic alkalosis.[49,56,57] How this occurs is not well understood, but hypokalemia may play an important role.

Renal Hydrogen Loss

Mineralocorticoid excess and hypokalemia The conditions associated with primary mineralocorticoid excess, such as primary hyperaldosteronism, are discussed in Chap. 27, since hypokalemia is typically the most prominent abnormality in these patients. As described above, aldosterone can promote H^+ secretion and the development of metabolic alkalosis by directly stimulating the distal H^+-ATPase pump and by making the lumen more electronegative via enhanced Na^+ reabsorption.[19-22] These transport processes involve different cells in the cortical and medullary collecting tubule, with Na^+ reabsorption occurring in the principal cells and H^+ secretion occurring in the intercalated cells (see Chap. 5).

Hypokalemia due to concomitant urinary K^+ loss plays an essential role in the maintenance of the metabolic alkalosis in this setting.[9,40-42] If K^+ depletion is prevented, there is a lesser increment in net H^+ excretion and only a minor elevation in the plasma HCO_3^- concentration.[42]

For these effects on H^+ and K^+ secretion to occur, there must be *adequate delivery of Na^+ and water to the distal secretory site* (see page 184). This is not a

problem in primary hyperaldosteronism, in which the patient tends to be mildly volume-expanded due to the stimulus to distal Na^+ retention. However, distal delivery is reduced in patients with effective circulating volume depletion. As a result, the associated secondary hyperaldosteronism does not lead to excessive H^+ and K^+ loss.[22,58] Thus, uncomplicated patients with heart failure or cirrhosis typically have a normal K^+ concentration and are not alkalemic. However, hypokalemia and metabolic alkalosis may rapidly ensue if distal delivery is enhanced by the administration of diuretics.

Diuretics The loop and thiazide-type diuretics are commonly associated with metabolic alkalosis, the severity of which varies directly with the degree of diuresis. Both volume contraction and, more importantly, increased urinary H^+ loss contribute to this problem.[5,6,59] The latter is primarily due to enhanced distal H^+ secretion, which results from the interplay of three factors: hypersecretion of aldosterone due to the associated hypovolemia; increased distal flow, since these agents inhibit NaCl and water reabsorption proximal to the H^+ secretory sites in the collecting tubules; and the concomitant development of hypokalemia.

Posthypercapnic alkalosis Chronic respiratory acidosis is associated with a compensatory increase in H^+ secretion and therefore in renal HCO_3^- reabsorption (see Chap. 20).[60] This represents an appropriate response, since the rise in the plasma HCO_3^- concentration returns the extracellular pH toward normal. The net effect is that acidemia is not a major problem in uncomplicated patients.

Treatment with mechanical ventilation in this disorder can lead to a rapid reduction in the P_{CO_2}. The plasma HCO_3^- concentration, however, will remain elevated, resulting in the development of metabolic alkalosis and, because of the fall in P_{CO_2}, an acute rise in cerebral pH that can produce serious neurologic abnormalities and death.[61] As a result, the P_{CO_2} should be lowered slowly and carefully in patients with chronic hypercapnia; there is no need for rapid lowering, since the extracellular pH is generally well protected.[60]

Several factors may contribute to maintenance of the alkalosis in this setting. Initially, there may be a "memory" effect, as the hypercapnia-induced stimulation of HCO_3^- reabsorption persists even though the P_{CO_2} has been returned toward normal.[62] How this occurs is not clear; however, the original increment in H^+ secretion takes 3 to 5 days to reach its maximum level,[60] and reversal of this process may be equally slow. Chronic respiratory acidosis is also associated with both hypoxemia (which can lead to renal vasoconstriction)[63] and Cl^- loss in the urine, resulting in hypochloremia and volume depletion.[64] Increased cosecretion of Cl^- with the distal H^+-ATPase pump may be in part responsible for the chloruresis.[27] As a result, a posthypercapnic alkalosis will tend to persist until Cl^- balance is restored.[64]

Low chloride intake Metabolic alkalosis may be induced in infants by the inadvertent administration of formula containing Na^+ but almost no Cl^-.[65] The ensuing Cl^- depletion diminishes the amount of Cl^- in the tubular lumen, which can

promote the development of metabolic alkalosis by two mechanisms: Tubular Na^+ reabsorption must occur in exchange for H^+ (or K^+), since less Cl^- is available,[22,23] and there is a more favorable gradient for Cl^- to be cosecreted into the lumen with H^+ by the H^+-ATPase pump.[27] Once the alkalosis has developed, the decrease in Cl^- delivery will, as noted above, contribute to perpetuation of the high plasma HCO_3^- concentration by impairing HCO_3^- secretion.[28,29]

High-dose carbenicillin or penicillin A similar problem can occur with the intravenous administration of high doses of Na^+ carbenicillin or some other penicillin derivatives.[66,67] Intravenous carbenicillin, for example, contains 4.7 meq/g of Na^+, or 141 meq if 30 g is given. As the Na^+ carbenicillin is filtered, carbenicillin acts as a nonreabsorbable anion. Consequently, some distal Na^+ reabsorption must occur in exchange for K^+ and H^+, resulting in hypokalemia and metabolic alkalosis.[68] The relatively low tubular fluid Cl^- concentration in this setting also may play a contributory role.

Hypercalcemia Renal H^+ secretion and HCO_3^- reabsorption are increased by hypercalcemia,[69,70] possibly leading to a mild metabolic alkalosis.[71] Both the mechanism by which this might occur and the role of concurrent changes in parathyroid hormone (PTH) secretion are unclear. Patients with primary hyperparathyroidism tend to have a mild metabolic acidosis, a change that has been thought to result from a decrease in proximal HCO_3^- reabsorption.[72] However, some other factor may be important in this setting, since the chronic continuous administration of PTH to normal humans *increases* net acid excretion and produces a small elevation, not a reduction, in the plasma HCO_3^- concentration.[73]

Regardless of the mechanism, similar factors probably contribute in the *milk-alkali syndrome*, in which the chronic ingestion of milk and/or calcium carbonate–containing antacids leads to hypercalcemia and metabolic alkalosis.[74-76] The carbonate load raises the plasma HCO_3^- concentration, while the combination of hypercalcemia and renal insufficiency (which is mostly due to the hypercalcemia) prevents the urinary excretion of the excess HCO_3^-.[75] The most common cause at present is the administration of calcium carbonate as a phosphate binder to patients with chronic renal failure.[76]

Intracellular Shift of Hydrogen

Hypokalemia Hypokalemia is a frequent finding in patients with metabolic alkalosis. This association is due to several factors: (1) The common causes of metabolic alkalosis (vomiting, diuretics, mineralocorticoid excess) directly induce both H^+ and K^+ loss, (2) hypokalemia causes a transcellular shift in which K^+ leaves and H^+ enters the cells, thereby raising the extracellular pH,[1,2] and (3) hypokalemia increases net acid excretion and HCO_3^- reabsorption,[31,32,40-42] an effect that is probably due in part to the associated intracellular acidosis.

Refeeding Patients who are refed carbohydrate after a prolonged fast can acutely develop metabolic alkalosis.[77] Since there is neither volume contraction nor a demonstrable increase in urinary acid excretion, it has been proposed that an intracellular shift of H^+ may be responsible. The mechanism by which this might occur is unknown.

Refeeding is also associated with Na^+ retention, which may be responsible for perpetuation of the alkalosis.[77] Increased secretion of insulin, resulting from the carbohydrate ingestion, may contribute to this response.

Retention of Bicarbonate

Because of the ability of the kidney to excrete HCO_3^-, it is difficult to produce more than a small increment in the plasma HCO_3^- concentration by the chronic administration of as much as 1000 meq of HCO_3^- per day.[7] However, a significant alkalemia can be produced by the acute infusion of base or by the chronic administration of alkali in a patient in whom renal HCO_3^- excretion is impaired (as in the milk-alkali syndrome).

Administration of organic anions Organic anions, such as lactate, are rapidly metabolized in the body to HCO_3^-.[78] For example,

$$CH_3CHOHCOO^-(\text{lactate}) + 3O_2 \rightarrow 2CO_2 + 2H_2O + HCO_3^-$$

The same is true for acetate, citrate, and, in the presence of insulin, the anions of the ketoacids.[79]

As a result, the administration of organic anions can lead to the development of metabolic alkalosis. Most bank blood, for example, is anticoagulated with acid-citrate-dextran. Each unit (500 mL) of blood contains 16.8 meq of citrate, which generates HCO_3^- as it is metabolized. Although citric acid also is present, it has only a transient effect on the systemic pH, since it is rapidly converted into CO_2 and H_2O. In general, more than eight units of blood must be given acutely to produce a significant elevation in the plasma HCO_3^- concentration.[80]

Citrate-induced alkalosis also may occur when citrate is used in place of heparin as an anticoagulant in hemodialysis patients who are at high risk for bleeding.[81] In this setting, the rise in the plasma HCO_3^- concentration may persist for several days because of the absence of renal function.

A similar problem may occur after the administration of some human plasma protein fractions (Protenate, Plasmatein), which are used as volume expanders.[82] The solutions contain acetate (as a source of HCO_3^-) and citrate (as a preservative) in a total concentration of 40 to 50 meq/L. The metabolism of these anions can lead to a significant elevation in the plasma HCO_3^- concentration.

Administration of sodium bicarbonate The most common indication for $NaHCO_3$ therapy is in the treatment of metabolic acidosis. However, HCO_3^- therapy can result in metabolic alkalosis if given in excessive amounts. This is particularly true in lactic acidosis[83] and ketoacidosis,[79] in which endogenous HCO_3^- is replaced

during the initial buffering reaction by lactate or β-hydroxybutyrate. As a result, there is *no loss of potential* HCO_3^- (excluding those anions excreted in the urine), since the organic anion can be metabolized back to HCO_3^- once the underlying abnormality is corrected.

The net effect is that the administration of HCO_3^- in these disorders* creates an excess of potential HCO_3^-, leading to a post-correction metabolic alkalosis. In extreme cases, the systemic pH has reached 7.90, with the plasma HCO_3^- concentration exceeding 60 to 70 meq/L, after the indiscriminate use of $NaHCO_3$ during cardiopulmonary resuscitation.[83] A similar problem can occur with massive $NaHCO_3$ ingestion as long as there is an underlying defect in HCO_3^- excretion, such as renal insufficiency.[84]

Contraction Alkalosis

The mechanism of a contraction alkalosis, in which NaCl and water are lost without HCO_3^-, is illustrated in Fig. 18-1. This problem is most commonly seen with loop or thiazide-type diuretics;[5] it can, however also occur with vomiting (even in patients with achlorhydria, in whom NaCl replaces HCl in the gastric secretions) or with cystic fibrosis (where the sweat Cl^- concentration can exceed 70 to 100 meq/L, while the HCO_3^- concentration is well below that of the plasma).[85]

In the absence of massive fluid losses, the direct effect of contraction is largely minimized by the release of H^+ from cell buffers, thereby lowering the plasma HCO_3^- concentration toward normal:[6]

$$HCO_3^- + HBuf \rightarrow Buf^- + H_2CO_3 \rightarrow CO_2 + H_2O$$

Thus, with diuretic therapy or vomiting, it is the urinary or gastrointestinal losses of H^+ that are primarily responsible for the metabolic alkalosis.[6] The major contribution of volume contraction is in maintenance of the alkalosis by preventing excretion of the excess HCO_3^- in the urine.

SYMPTOMS

Patients with metabolic alkalosis may be asymptomatic or complain of symptoms related either to volume depletion (weakness, muscle cramps, postural dizziness) or to hypokalemia (polyuria, polydipsia, muscle weakness). Complaints directly related to alkalemia, however, are uncommon. Paresthesias, carpopedal spasm, and light-headedness occur in acute respiratory alkalosis but are seen much less frequently in metabolic alkalosis. This difference is probably related to the degree of alkalosis in the central nervous system: HCO_3^-, a polar compound, crosses the blood-brain barrier much more slowly than the lipid-soluble CO_2, producing a

* The indications for the use of HCO_3^- in lactic acidosis and ketoacidosis are discussed in Chaps. 19 and 25.

lesser increase in the cerebrospinal fluid pH.[86] Thus, the potentially severe neurologic abnormalities that may be seen in posthypercapnic alkalosis[61] are probably due to the sudden fall in P_{CO_2}, not the persistent elevation in the plasma HCO_3^- concentration.

The physical examination is not usually helpful, revealing only signs of volume depletion, such as reduced skin turgor, low estimated jugular venous pressure, and postural hypotension, in selected cases. There may, however, be relatively specific findings in patients with self-induced vomiting. These include ulcers, calluses, and scarring on the dorsum of the hand; dental erosions due to chronic exposure to the acid gastric secretions; and puffy cheeks resulting from hypertrophy of the salivary glands.[50]

DIAGNOSIS

The etiology of metabolic alkalosis almost always is obtainable from the history. If there is no pertinent history, then the most likely diagnoses are *surreptitious vomiting or diuretic ingestion or one of the causes of mineralocorticoid excess.* The urine Cl^- concentration can be helpful in differentiating between these conditions (Table 18-3).

Urine Chloride Concentration

The combination of hypovolemia and hypochloremia in patients with vomiting or cystic fibrosis or those taking diuretics should induce maximum renal Cl^- conservation, usually lowering the urine Cl^- concentration to less than 25 meq/L. (This excludes the period during which the diuretic is acting, when Cl^- excretion is elevated.) These patients may also show the physical findings of volume depletion or of self-induced vomiting described above. In contrast, the signs of hypovolemia are absent and the urine Cl^- concentration exceeds 40 meq/L in patients with mineralocorticoid excess or alkali loading, who are generally volume-expanded and in whom Cl^- excretion is equal to intake.

Metabolic alkalosis is the major clinical setting in which the *urine* Cl^- *concentration may be a more accurate estimate of volume status than is the urine* Na^+

Table 18-3 Urine Cl^- concentration in patients with metabolic alkalosis

Less than 25 meq/L	Greater than 40 meq/L
Vomiting or nasogastric suction	Primary mineralocorticoid excess
Diuretics (late)	Diuretics (early)
Factitious diarrhea	Alkali load (bicarbonate or other organic anion)
Posthypercapnia	Bartter's or Gitelman's syndrome
Cystic fibrosis	Severe hypokalemia (plasma $[K^+] < 2.0$ meq/L
Low chloride intake	

concentration.[87] Although hypovolemia leads to Na^+ retention, this may be counteracted by the necessity for Na^+ to be excreted with the excess HCO_3^-. As depicted in Fig. 18-3, the maximum reabsorptive capacity for HCO_3^- may be markedly increased by volume depletion and the associated Na^+ retention. This response, however, takes 3 to 4 days to reach completion, leading to variability in the urinary findings (Table 18-4).[23,49]

In the first few days of vomiting, there is a high filtered HCO_3^- concentration and hyperaldosteronism but an inability to maximally conserve HCO_3^-. As a result, some of the excess HCO_3^- is delivered out of the proximal tubule as $NaHCO_3$, and some of this Na^+ is then exchanged for K^+ in the cortical collecting tubule under the influence of aldosterone. The net effect is relatively high rates of Na^+, K^+, and HCO_3^- excretion, the latter leading to an alkaline urine pH. The urinary loss of potentially large amounts of K^+ during this early period is primarily responsible for the K^+ depletion that commonly occurs with persistent or massive vomiting; gastric losses play a lesser role, since K^+ concentration in gastric secretions is only 5 to 10 meq/L. The urine Cl^- concentration is appropriately reduced at this time, the only urinary sign pointing toward hypovolemia.

The urinary chemistries change dramatically once HCO_3^- reabsorptive capacity increases sufficiently to reabsorb all of the filtered HCO_3^-.[23] At this time, excretion of Na^+, K^+, HCO_3^-, and Cl^- are all reduced, and there is a paradoxically acid urine pH (Table 18-4). This late phase is dependent upon volume and Cl^- depletion being severe enough to allow all of the filtered HCO_3^- to be reabsorbed. Some patients ingest enough NaCl so that the filtered HCO_3^- concentration remains above reabsorptive capacity, leading to persistent urinary changes similar to those in the early phase. Again, it is the low urine Cl^- concentration that will point toward the correct diagnosis.

The urine Cl^- concentration may not be useful in patients who are unable to maximally conserve Cl^- because of a defect in tubular reabsorption. This abnormality may occur with renal insufficiency or with severe hypokalemia (plasma K^+ concentration below 2.0 meq/L), in which distal Cl^- reabsorption appears to be impaired.[39,40,88] In these settings, the urine Cl^- concentration may be elevated despite the presence of volume depletion.

Metabolic Alkalosis versus Respiratory Acidosis

An elevated plasma HCO_3^- concentration, hypercapnia, and hypoxemia all may be found in chronic respiratory acidosis as well as in metabolic alkalosis (see Chap.

Table 18-4 Variation in urine electrolytes with vomiting

Time	$[Na^+]$	$[K^+]$	$[Cl^-]$	$[HCO_3^-]$	pH
Days 1–3	↑	↑	↓	↑	> 6.5
Late	↓	↓	↓	↓	< 5.5

20). If uncomplicated, these disorders can be easily differentiated by measuring the arterial pH. However, this distinction becomes more difficult when the patient with underlying chronic lung disease develops a superimposed metabolic alkalosis. As an example, consider the following case history:

Case History 18-1 A 45-year-old man with a long smoking history reports 1 week of recurrent vomiting and has the following arterial blood values on room air:

$$pH = 7.49$$
$$P_{CO_2} = 55 \text{ mmHg}$$
$$[HCO_3^-] = 40 \text{ meq/L}$$
$$P_{CO_2} = 68 \text{ mmHg}$$

Comment The high P_{CO_2} is compatible with either an appropriate respiratory compensation to metabolic alkalosis or underlying lung disease in this chronic smoker. The simplest way to establish the correct diagnosis is to treat the metabolic alkalosis and follow the P_{CO_2}, which should return to normal if there is no impairment in pulmonary function.

It also may be helpful in selected cases to calculate the alveolar-arterial (A-a) oxygen gradient (see page 663):[89]

$$\text{(A-a) } O_2 \text{ gradient} = P_{I_{O_2}} - 1.25P_{CO_2} - Pa_{O_2}$$
$$= 150 - (1.25 \times 55) - 68$$
$$= 13 \text{ mmHg}$$

where $P_{I_{O_2}}$ refers to the partial pressure of oxygen in the inspired air (150 mmHg at sea level) and Pa_{O_2} is the partial pressure of oxygen in arterial blood. A normal (A-a) O_2 gradient suggests that pulmonary function is normal and that this patient has a pure metabolic alkalosis. However, the converse is not necessarily true. An increased gradient is not diagnostic of chronic respiratory acidosis, since it can be seen in many acute and chronic pulmonary diseases not associated with CO_2 retention.

TREATMENT

Metabolic alkalosis can be corrected most easily be the urinary excretion of the excess HCO_3^-. This does not occur spontaneously because, in the patient with relatively normal renal function, volume, Cl^-, and/or K^+ depletion leads to enhanced net HCO_3^- reabsorption.[9-11] Therefore, the aim of therapy is to repair these deficits, which will have two beneficial effects: a decrease in HCO_3^- reabsorption, thereby allowing the excess HCO_3^- to be excreted, and, with K^+ repletion, a

direct reduction in the plasma HCO_3^- concentration because of the reciprocal shift of K^+ into and H^+ out of the cells.[1,2] As will be seen, this requires the *administration of Cl^-, as NaCl, KCl, or HCl.*[30,90,91]

Treatment should also be directed at the underlying disease and at diminishing further H^+ loss. In patients with continued vomiting or nasogastric suction, for example, the administration of an H_2-blocker or proton pump inhibitor can markedly reduce the rate of gastric H^+ secretion.[92]

Saline-Responsive Alkalosis

The most common causes of metabolic alkalosis are vomiting, nasogastric suction, and diuretic therapy. In these disorders (and with posthypercapnia and a low chloride intake), the increase in HCO_3^- reabsorption that maintains the alkalosis can be reversed by the oral or intravenous administration of NaCl and water, e.g., as half-isotonic or isotonic saline (Table 18-5).[30,90,91] This regimen can lower the plasma HCO_3^- concentration in three ways:

- By reversal of the contraction component.
- By removing the stimulus to renal Na^+ retention, thereby permitting $NaHCO_3$ excretion in the urine.
- By increasing distal Cl^- delivery, which will promote HCO_3^- secretion in the cortical collecting tubule. Studies in experimental animals suggest that increased HCO_3^- secretion is the primary factor responsible for the corrective bicarbonaturia following NaCl administration.[29]

The therapeutic effectiveness of this regimen can be followed at the bedside by measuring the *urine pH*. The urine pH is often below 5.5 prior to therapy as a result of enhanced H^+ secretion. However, when volume and Cl^- replacement are sufficient to allow the excess HCO_3^- to be excreted, the urine pH will exceed 7.0 and occasionally 8.0. The urine Cl^- concentration will remain below 25 meq/L until the Cl^- is corrected.

The efficacy of fluid repletion is dependent upon the administration of Na^+ with the only *reabsorbable* anion, Cl^-.[90,93] As this Na^+ enters the glomerular filtrate, it is reabsorbed with Cl^-, resulting in volume expansion. The outcome

Table 18-5 Causes of metabolic alkalosis according to saline responsiveness

Saline-responsive	Saline-resistant
Vomiting or nasogastric suction	Edematous states
Diuretics	Mineralocorticoid excess
Posthypercapnia	Severe hypokalemia
Low chloride intake	Renal failure

is different if Na^+ is given with an impermeant anion, such as SO_4^{2-}. Reabsorption of this Na^+ in the distal nephron must now be accompanied by H^+ (or K^+) secretion to maintain electroneutrality.[93] The resulting increase in H^+ secretion will generate more HCO_3^- in the plasma, leading to exacerbation of the alkalosis.

Although adequate NaCl repletion will usually normalize the plasma HCO_3^- concentration, it will not reverse any K^+ depletion that might be present. As with Na^+, the administration of K^+ with any anion other than Cl^- results in an increase in H^+ secretion, preventing correction of the alkalosis.[90,94] This is important clinically, since many of the commercial K^+ supplements contain HCO_3^-, acetate, or citrate. Only KCl will be effective.

The requirement for Cl^- replacement also applies to those patients who are treated with an acid infusion (see below). HCl will be effective, because the initial buffering of the excess acid will generate NaCl:

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3 \rightarrow CO_2 + H_2O \qquad (18\text{-}1)$$

In comparison, the administration of nitric acid will generate $NaNO_3$:

$$HNO_3 + NaHCO_3 \rightarrow NaNO_3 + H_2CO_3 \rightarrow CO_2 + H_2O$$

The delivery of this Na^+ to the distal nephron with impermeant NO_3^- will again increase distal H^+ secretion.[95] The net effect is excretion of the administered acid and persistence of the alkalosis.

With the exception of patients with hypotension, shock, or severe associated electrolyte disturbances, *gradual* saline or half-isotonic saline repletion is preferable, since it will restore normovolemia while minimizing the risk of volume overload and pulmonary edema. The optimal rate of fluid replacement is somewhat arbitrary. A regimen that has been successful is the infusion of the appropriate replacement fluid at the rate of 50 to 100 mL/h *in excess of the sum* of the urine output, estimated insensible losses (approximately 30 to 50 mL/h), and any other losses that may be present (such as diarrhea or tube drainage).

Saline-Resistant Alkalosis

The administration of saline is occasionally ineffective in correcting the alkalosis. This typically occurs in edematous states and in those disorders in which K^+ depletion, not hypovolemia, is responsible for perpetuation of the alkalosis (Table 18-5).

Edematous states Patients with heart failure, cirrhosis, or the nephrotic syndrome often develop metabolic alkalosis following diuretic therapy. Both a reduction in the effective circulating volume, leading to Na^+-avidity, and renal insufficiency can contribute to the inability to excrete the excess HCO_3^- in these disorders. However, the administration of saline is not indicated, since it will increase the degree of edema, perhaps precipitating pulmonary edema in the presence of heart failure. Corrective therapy consists of withholding diuretics if possible, acetazolamide, HCl, or dialysis.

Acetazolamide (250 to 375 mg, once or twice a day, given orally or intravenously) is a carbonic anhydrase inhibitor that increases the renal excretion of $NaHCO_3$ (see Chap. 15).[96,97] This serves the dual purpose of treating both the edema and the alkalosis. As with the use of saline in saline-responsive states, the efficacy of acetazolamide can be assessed by monitoring the urine pH, which should exceed 7.0 if HCO_3^- excretion is substantially enhanced. K^+ balance must be carefully followed, since acetazolamide increases urinary K^+ excretion.[96,97]

Acetazolamide can also be used in edematous patients with cor pulmonale and chronic hypercapnia.[98,99] Correction of the alkalemia may be particularly important in this setting, since the rise in pH can further depress ventilation.[98] There are, however, some potential problems, as acetazolamide can induce both a transient, further elevation in the P_{CO_2} (usually 3 to 7 mmHg) and marked acidemia if there is an excessive reduction in the plasma HCO_3^- concentration.[100,101] The exacerbation of the hypercapnia, which is generally not clinically important, is due to partial inhibition of carbonic anhydrase in red cells. This enzyme catalyzes the hydration of CO_2 to H_2CO_3, a reaction that is essential for CO_2 transport by the red cells and therefore for the elimination of CO_2 by the lungs.

If acetazolamide is ineffective and the alkalemia is moderately severe, HCl can be used to lower the plasma HCO_3^- concentration.[102,103] The amount of HCl required to normalize the plasma HCO_3^- concentration is equal to the HCO_3^- excess, which can be estimated from

$$HCO_3^- \text{ excess} = HCO_3^- \text{ space} \times HCO_3^- \text{ excess per liter}$$

In metabolic alkalosis, the HCO_3^- space is approximately 50 percent of the lean body weight.[104] If the normal plasma HCO_3^- concentration is 24 meq/L, then

$$HCO_3^- \text{ excess} = 0.5 \times \text{lean body weight (kg)} \times (\text{plasma } [HCO_3^-] - 24)$$

Thus, in a 60-kg patient with a plasma HCO_3^- concentration of 40 meq/L,

$$HCO_3^- \text{ excess} = 0.5 \times 60 \times (40 - 24)$$
$$= 480 \text{ meq}$$

It should be noted that this formula *underestimates* the acid requirement of a patient in a nonsteady state. As an example, continued losses from nasogastric suction must be added on to the initial estimate of the HCO_3^- excess.

HCl is usually given as an isotonic solution (150 meq each of H^+ and Cl^- in 1 liter of distilled water) over 8 to 24 h.[11,102] Since HCl is very corrosive, it should be infused into a major vein, such as the subclavian or femoral vein. However, a peripheral vein can be safely used if the HCl is buffered in an amino acid solution and infused with a fat emulsion.[103]

Ammonium chloride and arginine hydrochloride, which result in the formation of HCl, should not be given, since they may lead to appreciable toxicity. Ammonium chloride is converted into HCl and ammonia in the liver; the ensuing accumulation of ammonia makes this drug contraindicated in patients with advanced liver disease. Furthermore, an ammonia-related metabolic encephalopathy, characterized by lethargy and coma, may occur even in patients with normal hepatic and renal function.[105] Arginine hydrochloride, on the other hand, can induce potentially life-threatening hyperkalemia.[106,107] This effect is thought to result from the movement of cellular potassium into the extracellular fluid as the cationic arginine enters the cells.

Mineralocorticoid excess States of primary mineralocorticoid excess are characterized by mild volume expansion and a rate of urinary Na^+ excretion that is equal to intake (due to aldosterone escape; see page 185). The alkalosis in this setting is resistant to saline, since neither renal Na^+ avidity nor Cl^- depletion is the limiting factor in HCO_3^- excretion.[41] In contrast, it is the combination of hypokalemia and hypersecretion of aldosterone that is responsible for perpetuation of the alkalosis.[9,10,41,42] Correction of the hypokalemia tends to lower the plasma HCO_3^- concentration in two ways:[41] by allowing increased HCO_3^- excretion and by causing H^+ ions to move out of the cells into the extracellular fluid.[1,2]

Successful treatment requires the restoration of normal mineralocorticoid activity (see Chap. 27). This can be achieved by surgical removal of an adrenal adenoma or by the use of a K^+-sparing diuretic, such as amiloride or the aldosterone antagonist spironolactone.[108]

Severe hypokalemia Patients with metabolic alkalosis and hypovolemia may be resistant to saline therapy in the presence of severe K^+ depletion.[88] In this setting, the total K^+ deficit usually is greater than 800 to 1000 meq, the plasma K^+ concentration generally is less than 2.0 meq/L, and the urine Cl^- concentration exceeds 15 meq/L despite the presence of volume depletion. This defect in Cl^- conservation, which appears to be due to diminished distal Cl^- reabsorption,[39,40] may explain the negative response to saline. If Cl^- reabsorption is impaired and the availability of K^+ for exchange with Na^+ is limited, then Na^+ reabsorption must be accompanied by increased H^+ secretion and HCO_3^- reabsorption,[40] thereby preventing a HCO_3^- diuresis. Diminished Cl^- reabsorption could also impair corrective HCO_3^- secretion in the cortical collecting tubule, a process that appears to be mediated by Cl^-/HCO_3^- exchange.

These effects of severe hypokalemia are readily reversible. The replacement of only one-half of the K^+ deficit will normalize Cl^- reabsorption and restore saline responsiveness, as the administration of saline will now correct the alkalosis.[88]

Renal failure Rarely, a patient with renal failure develops metabolic alkalosis, usually as a result of marked gastric losses by nasogastric suction. In this setting, either HCl or dialysis can be used if the alkalemia is severe.[109] However, a special, low-buffer dialysis solution must be used, since normal solutions contain 35 to 40 meq/L of bicarbonate or an organic anion (such as acetate), which generates HCO_3^- when metabolized.[109]

PROBLEMS

18-1 A patient with cirrhosis and ascites is admitted to the hospital with acute gastrointestinal bleeding due to ruptured esophageal varices. He is taken to surgery, where a portacaval shunt is performed. He is given a total of 19 units of blood before and during the surgery. Although the ascites was removed during the surgery, it begins to reaccumulate postoperatively. His laboratory tests were normal preoperatively, but the following values are obtained 12 h after surgery:

$$\text{arterial pH} = 7.53$$
$$P_{CO_2} = 50 \text{ mmHg}$$
$$[HCO_3^-] = 40 \text{ meq/L}$$

(a) What is responsible for the development of the metabolic alkalosis?
(b) What would you expect the urine pH and Na^+ concentration to be?
(c) How would you correct the alkalosis?

18-2 A 45-year-old woman with peptic ulcer disease reports 6 days of persistent vomiting. On physical examination, the blood pressure is found to be 100/60 without postural change, the skin turgor is decreased, and the jugular neck veins are flat. The initial laboratory data are

Plasma $[Na^+]$	=	140 meq/L	BUN	=	80 mg/dL
$[K^+]$	=	2.2 meq/L	[Creatinine]	=	1.9 mg/dL
$[Cl^-]$	=	86 meq/L	Urine pH	=	5.0
$[HCO_3^-]$	=	42 meq/L	$[Na^+]$	=	2 meq/L
Arterial pH	=	7.53	$[K^+]$	=	21 meq/L
P_{CO_2}	=	53 mmHg	$[Cl^-]$	=	3 meq/L

(a) How would you treat this patient?

Twenty-four hours after appropriate therapy has been started, the plasma HCO_3^- concentration is 30 meq/L. The following urinary values are obtained:

$$\text{Urine } [Na^+] = 100 \text{ meq/L}$$
$$[K^+] = 20 \text{ meq/L}$$
$$[Cl^-] = 3 \text{ meq/L}$$

(b) How do you account for the discrepancy between the high urine Na^+ concentration and the low urine Cl^- concentration?

18-3 A 22-year-old woman complains of easy fatigability and weakness for 1 year. She has no other symptoms. The physical examination is unremarkable, including a normal blood pressure. The following laboratory tests have been repeatedly present during this time:

$$\text{Plasma } [Na^+] = 141 \text{ meq/L}$$
$$[K^+] = 2.1 \text{ meq/L}$$
$$[Cl^-] = 85 \text{ meq/L}$$
$$[HCO_3^-] = 45 \text{ meq/L}$$
$$\text{Urine } [Na^+] = 80 \text{ meq/day}$$
$$[K^+] = 170 \text{ meq/day}$$

(a) What is the differential diagnosis?
(b) What test would you order next?

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CHAPTER

NINETEEN

METABOLIC ACIDOSIS

The introduction to acid-base disorders in Chap. 17 should be read before proceeding with this discussion. Metabolic acidosis is a clinical disturbance characterized by a low arterial pH (or an increased H^+ concentration), a reduced plasma HCO_3^- concentration, and compensatory hyperventilation, resulting in a decrease in the P_{CO_2}. A low plasma HCO_3^- concentration, however, is not diagnostic of metabolic acidosis, since it also results from the renal compensation to chronic respiratory alkalosis. These disorders can be easily differentiated by measurement of the arterial pH. In addition, a plasma HCO_3^- concentration of 10 meq/L or less is indicative of metabolic acidosis, as the renal compensation to chronic hypocapnia does not produce this degree of hypobicarbonatremia (see Chap. 21).

PATHOPHYSIOLOGY

From the reaction of H^+ with the primary extracellular buffer, HCO_3^-.

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O \qquad (19\text{-}1)$$

it can be appreciated that metabolic acidosis can be produced in two ways: by the addition of H^+ ions or by the loss of HCO_3^- ions. The latter increases the extracellular H^+ concentration by driving the buffering reaction to the left.

Response to an Acid Load

The response of the body to an increase in the arterial H^+ concentration involves four processes (see Chaps. 10 and 11): extracellular buffering, intracellular and bone buffering, respiratory compensation, and the renal excretion of the H^+ load. The first three act to minimize the increase in H^+ concentration until the kidneys restore acid-base balance by eliminating the excess H^+ in the urine. Since each of these processes has important clinical implications, they will be considered separately.

Extracellular buffering Because of its high concentration, HCO_3^- is the most important buffer in the extracellular fluid. The ability of HCO_3^- to prevent large changes in the arterial pH (or H^+ concentration) can be appreciated if we use the law of mass action to express the relationship between H^+, HCO_3^-, and P_{CO_2} (see page 308):

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (19\text{-}2)$$

If the normal P_{CO_2} is 40 mmHg and the plasma HCO_3^- concentration is 24 meq/L (equal to 24 mmol/L), then

$$[H^+] = 24 \times \frac{40}{24}$$
$$= 40 \text{ nanoeq/L} \qquad (pH = 7.40)$$

Let us assume that 12 meq of H^+ is added to each liter of the extracellular fluid. As this H^+ is buffered by HCO_3^-, the plasma HCO_3^- concentration will fall from 24 to 12 meq/L. If the P_{CO_2} remains constant,

$$[H^+] = 24 \times \frac{40}{12}$$
$$= 80 \text{ nanoeq/L} \qquad (pH = 7.10)$$

Even though 12 meq (or 12 million nanoeq) of H^+ has been added to each liter, the free H^+ concentration has increased by only 40 nanoeq/L or 40×10^{-6} meq/L. Thus, more than 99.99 percent of the extra H^+ ions has been taken up by HCO_3^-, thereby preventing the H^+ concentration from exceeding 160 nanoeq/L (pH equals 6.80), the highest level that is generally compatible with life.

Intracellular buffering and the plasma potassium concentration H^+ ions also are able to enter the cells and be taken up by the cell and bone buffers, including proteins, phosphates, and bone carbonate:

$$H^+ + Pr^- \leftrightarrow HPr$$

On the average, 55 to 60 percent of an acid load will eventually be buffered by the cells and bone, although higher values may occur with severe acidemia when extracellular HCO_3^- stores are markedly reduced.[1-3] As a result, the addition of 12 meq of H^+ to each liter of extracellular fluid will lower the plasma HCO_3^- concentration by 5 meq/L or less, not by 12 meq/L. If the new plasma HCO_3^- concentration is 19 meq/L and the P_{CO_2} remains at 40 mmHg, then

$$[H^+] = 24 \times \frac{40}{19}$$

$$= 51 \text{ nanoeq/L} \qquad (pH = 7.29)$$

Thus, the contribution of cellular and bone buffers results in better maintenance of the extracellular H^+ concentration than was seen above when only extracellular HCO_3^- buffering was available (pH = 7.10).

The intracellular entry of H^+ ions in metabolic acidosis is associated in part with the movement of K^+ out of the cells to maintain electroneutrality.[4-6] This response leads to a variable rise in the plasma K^+ concentration that is most prominent in those forms of metabolic acidosis that are due to an excess of nonorganic acid, as occurs with renal failure or diarrhea.[5] In the latter setting, the plasma K^+ concentration may be below normal as a result of concurrent intestinal losses, but it is still higher than it would have been in the absence of acidemia.[6]

For reasons that are incompletely understood, the fall in pH in the organic acidosis (such as ketoacidosis, lactic acidosis, or that following certain ingestions) seems to have little effect on K^+ distribution (see page 379).[5,7,8] Hyperkalemia is often present in these disorders, but is primarily due to other factors. In diabetic ketoacidosis and nonketotic hyperglycemia, for example, the combination of insulin deficiency (which retards K^+ entry into cells) and hyperglycemia (which pulls water and, by solvent drag, K^+ out of the cells) frequently leads to hyperkalemia, despite usually marked K^+ depletion due to urinary and gastrointestinal losses.[7,9] Correction of these problems with insulin therapy results in a rapid fall in the plasma K^+ concentration, thereby unmasking the true state of K^+ balance. Hyperkalemia can also occur in lactic acidosis, but it is due to hypoperfusion-induced tissue breakdown and renal failure, not to acidemia.

Respiratory compensation Metabolic acidosis stimulates both the central and peripheral chemoreceptors controlling respiration, resulting in an increase in alveolar ventilation. The ensuing fall in P_{CO_2} will then raise the extracellular pH toward normal. This increase in ventilation begins within 1 to 2 h and reaches its maximum level at 12 to 24 h.[10] It is characterized more by an increase in tidal volume than by an increase in respiratory rate, and may, if the acidemia is severe, reach a maximum of as much as 30 L/min (normal equals 5 to 6 L/min).[11] This degree of hyperventilation (called Kussmaul's respiration) is usually apparent on physical examination and should alert the physician to a possible underlying metabolic acidosis.

Studies in otherwise normal patients with metabolic acidosis have revealed that, on the average, the *P_{CO_2} will fall 1.2 mmHg for every 1.0-meq/L reduction in the plasma HCO_3^- concentration* down to a minimum P_{CO_2} of 10 to 15 mmHg.[12] Suppose, for example, that an acid load lowers the plasma HCO_3^- concentration to 9 meq/L. This decrease of 15 meq/L should be associated with an 18 mmHg (15 × 1.2) fall in the P_{CO_2} to approximately 22 mmHg (pH equals 7.23). Thus, in pure metabolic acidosis with a plasma HCO_3^- concentration of 9 meq/L, the *normal P_{CO_2} is roughly 22 mmHg, not 40 mmHg.*

Values substantially different from the predicted P_{CO_2} represent mixed acid-base disorders (Table 19-1). Thus, a "normal" P_{CO_2} of 40 mmHg (pH equals 6.98) in this setting is indicative of a combined metabolic and respiratory acidosis, as might occur in a patient with chronic lung disease. On the other hand, a lower than expected P_{CO_2} of 15 mmHg (pH equals 7.40) suggests a combined metabolic acidosis and respiratory alkalosis, as might be seen with salicylate intoxication (see below).

Although compensatory hyperventilation minimizes the degree of acidemia, this *protective effect appears to last for only a few days.* This limitation occurs because the fall in P_{CO_2} directly lowers renal HCO_3^- reabsorption, resulting in HCO_3^- loss in the urine and a further reduction in the plasma HCO_3^- concentration.[13] It is thought that these changes reflect a hypocapnia-induced rise in renal tubular cell pH, which diminishes H^+ secretion and HCO_3^- reabsorption (see page 360).

The net effect is that the *arterial pH in chronic metabolic acidosis is the same whether or not the respiratory compensation has occurred.*[13] As shown in the example in Table 19-2, for example, the arterial pH is 7.29 in uncompensated metabolic acidosis. The compensatory 6 mmHg decrease in the P_{CO_2} then lowers the plasma HCO_3^- concentration from 19 to 16 meq/L, returning the arterial pH to 7.29. Fortunately, severe metabolic acidosis is usually acute (lactic acidosis, ketoacidosis, ingestions), and the hypocapnia is protective in this setting.

Renal hydrogen excretion The metabolism of a normal adult diet results in the generation of 50 to 100 meq of H^+ per day, which must then be excreted in the urine if acid-base balance is to be maintained.[14] This process involves two basic steps: reabsorption of the filtered HCO_3^- and secretion of the dietary acid load.

Table 19-1 Arterial measurements in hypothetical acid-base disorders

Acid-base status	Plasma [HCO_3^-], meq/L	P_{CO_2}, mmHg	Arterial pH
Normal	24	40	7.40
Pure metabolic acidosis	9	22	7.23
Combined metabolic and respiratory acidosis	9	40	6.98
Combined metabolic acidosis and respiratory alkalosis	9	15	7.40

Table 19-2 Arterial pH in chronic metabolic acidosis with and without respiratory compensation

	Arterial		
Clinical state	pH	$[HCO_3^-]$, meq/L	P_{CO_2}, mmHg
Baseline	7.40	24	40
Metabolic acidosis			
No compensation	7.29	19	40
Compensation			
Acute	7.37	19	34
Chronic	7.29	16	34

The filtered HCO_3^- must be reabsorbed, since urinary HCO_3^- loss will increase the net acid load and lower the plasma HCO_3^- concentration. Ninety percent of HCO_3^- reabsorption occurs in the proximal tubule and the remainder in the thick ascending limb and the distal nephron (see Chap. 11).

The dietary acid load is excreted by the secretion of H^+ ions from the tubular cell into the lumen. These H^+ ions then combine either with the urinary buffers (particularly HPO_4^{2-} in a process called titratable acidity) or with NH^3:[15]

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^- \quad (19\text{-}3)$$

$$H^+ + NH_3 \rightarrow NH_4^+ \quad (19\text{-}4)$$

In general, 10 to 40 meq of H^+ is excreted each day as titratable acidity and 30 to 60 meq as NH_4^+. These processes are essential for the maintenance of acid-base balance, because the rate of excretion of *free* H^+ ions is extremely low. At the minimum urine pH of 4.50, for example, the free H^+ concentration is less than 0.05 meq/L.

In the absence of therapy with $NaHCO_3$, the correction of metabolic acidosis usually requires the urinary excretion of the excess H^+. The kidney responds to this increased H^+ load by augmenting cellular NH_4^+ production and subsequent excretion,[15,16] changes that may be mediated by the extracellular acidemia producing a parallel reduction in the renal tubular cell pH (see page 347).[17,18] The net effect is that NH_4^+ excretion can exceed 250 meq/day with severe acidemia.[19,20]

In contrast, there generally is only a limited ability to enhance titratable acidity, since phosphate excretion remains relatively constant.[15] One exception occurs in diabetic ketoacidosis, where excreted ketone anions (particularly β-hydroxybutyrate) can act as urinary buffers, increasing titratable acid excretion by up to 50 meq/day.[19] The net effect is that total acid excretion can reach a maximum rate of 500 meq/day (more than five times normal) in patients with severe metabolic acidosis.[19,20]

Generation of Metabolic Acidosis

From this discussion, it can be seen that metabolic acidosis can be induced by two basic mechanisms: an inability of the kidney to excrete the dietary H^+ load or an increase in the generation of H^+ as a result of either the addition of H^+ or the loss of HCO_3^- (Table 19-3). Decreased H^+ excretion produces a *slowly developing acidemia*, since only that fraction of the 50- to 100-meq daily H^+ load that is not excreted will be retained. In comparison, an acute increase in the H^+ load (as with lactic acidosis) can overwhelm renal excretory capacity, leading to the *rapid onset* of severe metabolic acidosis.

Anion Gap

Calculation of the anion gap is often helpful in the differential diagnosis of metabolic acidosis (Table 19-4).[21-23] The anion gap is equal to the difference between the plasma concentrations of the major cation (Na^+) and the major measured anions ($Cl^- + HCO_3$):

Table 19-3 Causes of metabolic acidosis

Inability to excrete the dietary H^+ load
- A. Diminished NH_4^+ production
  - 1. Renal failure[a]
  - 2. Hypoaldosteronism (type 4 renal tubular acidosis)[a]
- B. Diminished H^+ secretion
  - 1. Type 1 (distal) renal tubular acidosis

Increased H^+ load or HCO_3^- loss
- A. Lactic acidosis[a]
- B. Ketoacidosis[a]
- C. Ingestions
  - 1. Salicylates
  - 2. Methanol or formaldehyde
  - 3. Ethylene glycol
  - 4. Paraldehyde
  - 5. Sulfur
  - 6. Toluene
  - 7. Ammonium chloride
  - 8. Hyperalimentation fluids
- D. Massive rhabdomyolysis
- E. Gastrointestinal HCO_3^- loss
  - 1. Diarrhea[a]
  - 2. Pancreatic, biliary, or intestinal fistulas
  - 3. Ureterosigmoidostomy
  - 4. Cholestyramine
- F. Renal HCO_3^- loss
  - 1. Type 2 (proximal) renal tubular acidosis

[a] Most common causes.

Table 19-4 Anion gap in major causes of metabolic acidosis

High anion gap[a]
- A. Lactic acidosis: lactate, D-lactate
- B. Ketoacidosis: β-hydroxybutyrate
- C. Renal failure: sulfate, phosphate, urate, hippurate
- D. Ingestions
  1. Salicylate: ketones, lactate, salicylate
  2. Methanol or formaldehyde: formate
  3. Ethylene glycol: glycolate, oxalate
  4. Paraldehyde: organic anions
  5. Toluene: hippurate (usually presents with normal anion gap)
  6. Sulfur: SO_4^{2-}
- E. Massive rhabdomyolysis

Normal anion gap (hyperchloremic acidosis)
- A. Gastrointestinal loss of HCO_3^-
  1. Diarrhea
- B. Renal HCO_3^- loss
  1. Type 2 (proximal) renal tubular acidosis
- C. Renal dysfunction
  1. Some cases of renal failure
  2. Hypoaldosteronism (type 4 renal tubular acidosis)
  3.. Type 1 (distal) renal tubular acidosis
- D. Ingestions
  1. Ammonium chloride
  2. Hyperalimentation fluids
- E. Some cases of ketoacidosis, particularly during treatment with insulin

[a] The substances after the colon represent the major retained anions in the high anion gap acidoses.

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-]) \qquad (19\text{-}5)$$

The approximate normal values for these ions are 140, 108, and 24 meq/L, respectively, leading to an anion gap of 5 to 11 meq/L. (This is lower than previously measured values, since a higher plasma Cl^- concentration is measured with the newer autoanalyzers.[24] As a result, knowing the normal range in a particular laboratory is often essential if the anion gap is to be interpreted properly.

The negative charges on the plasma proteins account for most of the missing anions, as the charges on the other cations (K^+, Ca^{2+}, and Mg^{2+}) and anions (phosphate, sulfate, and organic anions) tend to balance out. Thus, the normal value for the anion gap must be adjusted downward in patients with hypoalbuminemia; the approximate correction is a reduction in the anion gap of 2.5 meq/L for every 1 g/dL decline in the plasma albumin concentration.[22]

The factors that can affect the anion gap can be more easily appreciated if Eq. (19-5) is rewritten in the following way. In addition to being equal to the difference between measured cations and anions, the anion gap is also equal to the difference between *unmeasured* anions and cations:

$$\text{Anion gap} = \text{unmeasured anions} - \text{unmeasured cations} \qquad (19\text{-}6)$$

Thus, an increase in anion gap can be produced by a fall in unmeasured cations (hypocalcemia, hypokalemia, or hypomagnesemia, where the change is only 1 to 3 meq/L) or, more importantly, by an elevation in the amount of unmeasured anions. This can be induced by a high plasma albumin concentration (as with hypovolemia-induced hemoconcentration) or by the accumulation of a variety of different anions.

These relationships can be applied to the different causes of metabolic acidosis, in which there is rapid extracellular buffering of the excess acid by HCO_3. If the acid is HCl, then

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3 \rightarrow CO_2 + H_2O \qquad (19\text{-}7)$$

In this setting, there is a milliequivalent-for-milliequivalent replacement of extracellular HCO_3^- by Cl^-; thus, there is no change in the anion gap, since the sum of ($[Cl^-] + [HCO_3^-]$) remains constant. This disorder is called a *hyperchloremic acidosis*, because of the associated increase in the plasma Cl^- concentration.

Gastrointestinal or renal loss of $NaHCO_3$ indirectly produces the same result. The kidney retains NaCl in this setting in an effort to preserve the extracellular volume, leading to a net exchange of HCO_3^- for Cl^-.

Conversely, if H^+ accumulates with any anion other than Cl^-, extracellular HCO_3^- will be replaced by an unmeasured anion (A^-):

$$HA + NaHCO_3 \rightarrow NaA + H_2CO_3 \rightarrow CO_2 + H_2O \qquad (19\text{-}8)$$

The ensuing accumulation of A^- leads to an elevation in the anion gap. In this setting, identification of the specific disease process usually can be obtained by measuring the plasma concentrations of creatinine, glucose, and lactate and by checking the plasma for the presence of ketones and intoxicants (particularly salicylates, methanol, and ethylene glycol) (Table 19-4).

A simple example of how this approach can be used is illustrated by the following case history:

Case History 19-1 A 27-year-old man with insulin-dependent diabetes mellitus has not been taking his insulin and is admitted to the hospital in a semicomatose condition. The following laboratory data are obtained:

Plasma $[Na^+]$	=	140 meq/L	Arterial pH	=	7.10
$[K^+]$	=	7.0 meq/L	P_{CO_2}	=	20 mmHg
$[Cl^-]$	=	105 meq/L	[Glucose]	=	800 mg/dL
$[HCO_3^-]$	=	6 meq/L	Plasma ketones	=	4+
Anion gap	=	29 meq/L			

Comment The high anion gap, hyperglycemia, and ketonemia all point to the diagnosis of diabetic ketoacidosis. Note that the increase in the anion gap of approximately 18 meq/L (from 11 to 29) is the same as the fall in the plasma HCO_3^- concentration (from 24 to 6 meq/L).

Although a high anion gap is helpful in the differential diagnosis of metabolic acidosis, it is not always possible to identify the extra unmeasured anions.[22-25] This is particularly true when there is only a minor elevation in the anion gap (to less than 20 meq/L); in this setting, the correct diagnosis may not be evident, since ketones, lactate, renal failure, and ingestions all may be missing. In comparison, one of these disorders is generally present when the anion gap exceeds 25 meq/L.

Another potential problem is that the distinction between a high and a normal anion gap acidosis is not always absolute. Patients with diarrhea, for example, tend to develop a normal anion gap acidosis because of HCO_3^- loss in the stool. If the fluid losses are severe, however, hemoconcentration (leading to hyperalbuminemia), lactic acidosis (due to hypoperfusion), and hyperphosphatemia (resulting from acidemia-induced release of phosphate from the cells) all may combine to raise the anion gap.[26] This combination of normal and high anion gap acidosis can be detected by comparing the change (Δ) in anion gap to the change (Δ) in plasma HCO_3^- concentration.

Δ Anion gap/Δ plasma HCO_3^- concentration In addition to the level of the anion gap, the relationship between the increase in the anion gap and the fall in the plasma HCO_3^- concentration may be helpful diagnostically. Use of this parameter is dependent upon an accurate assumption of the change in anion gap, which requires an estimate of the normal anion gap if no prior measurements are available. As described above, the normal value of approximately 8 meq/L[24] must be adjusted downward in patients with hypoalbuminemia, with the approximate correction being a 2.5-meq/L fall in the anion gap for every 1-g/dL reduction in the plasma albumin concentration.[22]

Failure to make this correction will underestimate the change in anion gap. Suppose, for example, the anion gap is 15 meq/L in a patient with a plasma albumin concentration of 2 g/dL. The Δ anion gap is 7 meq/L using 8 meq/L as the baseline value; however, accounting for the hypoalbuminemia leads to a baseline anion gap of roughly 3 meq/L $[8 - (2.5 \times 2)]$, resulting in a higher Δ anion gap of 12 meq/L.

Although Eq. (19-8) seems to imply that there should be a 1 : 1 relationship between the elevation in anion gap and the fall in plasma HCO_3^- concentration, this is usually not the case. As described above, more than 50 percent of the excess H^+ is buffered by the cells, *not by HCO_3^-*. In contrast, *most of the excess anions remain in the extracellular fluid*, since their distribution is pH-dependent. The extracellular fluid has a slightly higher pH (and lower H^+ concentration) than the cells; as a result, the following reaction is driven to the left:

$$H^+ + BHB^- \leftrightarrow HBHB$$

where BHB^- refers to the β-hydroxybutyrate$^-$ anion and HBHB refers to the undissociated β-hydroxybutryric acid. The net effect is that the extracellular fluid has, in relation to the cells, a relatively high concentration of β-hydroxybutyrate$^-$, which is less able to enter the cells because anions cannot easily cross the lipid bilayer of the cell membrane.

As a result, the *elevation in the anion gap usually exceeds the fall in the plasma HCO_3^- concentration*; in lactic acidosis, for example, the Δ/Δ ratio averages about 1.6 : 1.[27] It should be appreciated, however, that hydrogen buffering in cells and bone takes several hours to reach completion. Thus, the ratio may be close to 1 : 1 with very acute lactic acidosis (as with seizures or exercise to exhaustion), since there has not been time for nonextracellular buffering to occur.

Although the same principles apply to ketoacidosis, the ratio is often close to 1 : 1 in this disorder because the *loss of ketoacid anions in the urine* (which lowers the anion gap) tends to balance the effect of intracellular buffering of H^+.[27-30] The adequacy of renal function appears to be an important determinant of the rise in anion gap in ketoacidosis. Patients in whom the glomerular filtration rate is relatively normal have an elevation in filtered ketoacid load that exceeds tubular reabsorptive capacity.[31] As a result, they can excrete a large quantity of ketoacid anions in the urine,* thereby minimizing the rise in the anion gap and therefore in the Δ/Δ ratio.[28,30] In comparison, the anion gap will be higher when renal function is impaired, usually because of underlying renal disease or volume depletion induced by the glucose osmotic diuresis (see Chap. 25).[28,30] Anion loss in the urine is much less prominent in lactic acidosis, because the associated state of marked tissue hypoperfusion usually results in little or no urine output.

The loss of ketoacid anions in the urine also accounts for the observation that a *normal anion gap acidosis typically occurs during the treatment phase of ketoacidosis*.[28,30] In the above case history, there is a 20-meq/L elevation in the anion gap and a roughly equivalent decline in the plasma HCO_3^- concentration. After the administration of insulin, these ketoacid anions will be metabolized to HCO_3^- (see below). Thus, the anion gap will return to normal, but the plasma HCO_3^- concentration will increase by about 8 meq/L, not 20 meq/L, since *most of the generated HCO_3^- will effectively enter the cells to replenish the cell buffers*. At this time, the plasma HCO_3^- concentration will be 14 meq/L and the pH will still be acid, but here will be no excess unmeasured anions (i.e., the patient will have a normal anion gap acidosis). The acidemia in this setting is due to two factors: the previous production of ketoacids and the excretion of the ketoacid anions, which, if retained, could have been converted back into HCO_3^- after the administration of insulin; thus, loss of these anions is physiologically equivalent to the loss of HCO_3^-.

* Only those ketones that are excreted as the Na^+ or K^+ salt will lower the Δ/Δ ratio. Both β-hydroxybutyrate and acetoacetate also may be excreted as the intact acid or as the NH_4^+ salt. In these settings, H^+ is effectively lost with the anion, thereby correcting both the high anion gap and the fall in the plasma HCO_3^- concentration.

In addition to this sequence during treatment, some patients with ketoacidosis excrete ketones in the urine so efficiently that the anion gap is relatively normal *before* any therapy has been instituted.[29,30] A similar sequence, in which patients who overproduce organic acids can present with a normal anion gap, may occur in two other settings: D-lactic acidosis and toluene exposure (glue-sniffing). Filtered L-lactate, the normal isomer produced in humans, is reabsorbed in the proximal tubule via a Na^+-L-lactate cotransporter in the luminal membrane. This transporter is stereospecific and does not bind D-lactate, which may be overproduced in patients with a short bowel syndrome (see below). As a result, D-lactate is rapidly excreted in the urine, lowering the anion gap toward normal. However, the acidosis persists, since the H^+ ion is still retained.

Anion loss is even more rapid with toluene ingestion, which is associated with overproduction of hippuric acid.[32] Hippurate is both *filtered and secreted*; as a result, almost all of the hippurate delivered to the kidney enters the tubular lumen and is then excreted, since there is little hippurate reabsorption. The net effect is that many patients present with a normal anion gap and are mistakenly thought to have renal tubular acidosis.[32]

Summary In summary, the Δ/Δ ratio is normally between 1 and 2 in patients with an uncomplicated high anion gap metabolic acidosis. A value below 1 : 1 suggests a *combined high and normal anion gap acidosis*, as might occur when hemoconcentration and lactic acidosis are superimposed on severe diarrhea.[26] On the other hand, a value above 2 : 1 suggests that the fall in the plasma HCO_3^- concentration is less than expected because of a concurrent metabolic alkalosis. Consider the following case history:

Case History 19-2 A previously well 55-year-old woman is admitted with a complaint of severe vomiting for 5 days. Physical examination reveals postural hypotension, tachycardia, and diminished skin turgor. The laboratory findings include the following:

Plasma $[Na^+]$	=	140 meq/L	Arterial pH	=	7.23
$[K^+]$	=	3.4 meq/L	P_{CO_2}	=	22 mmHg
$[Cl^-]$	=	77 meq/L	Plasma ketones	=	trace
HCO_3^-	=	9 meq/L	[Creatinine]	=	2.1 mg/dL
Anion gap	=	54 meq/L			

Comment This patient has a high anion gap metabolic acidosis. Lactic acidosis is most likely in view of the physical findings and lack of significant ketonemia, renal failure, or history of an ingestion. However, the anion gap of 54 meq/L is markedly increased (45 meq/L above normal) while the reduction in the plasma HCO_3^- concentration is much smaller (15 meq/L, giving 9 meq/L), leading to a Δ/Δ ratio of 3 : 1. This disparity can be explained by a concomitant metabolic alkalosis due to vomiting, which raised the plasma HCO_3^- concentration without affecting the anion gap. Proof of this diagnosis came from evaluating the response to fluid repletion. As tissue perfusion was restored and metabolism of the excess lactate generated HCO_3^- (see below), the plasma HCO_3^- concentration rose from 9 to 37 meq/L and the pH became alkalemic. Thus, the 45-meq/L elevation in the anion gap was actually associated with a 28-meq/L fall in the plasma HCO_3^- concentration, a 1.7 : 1 ratio that is typical of lactic acidosis.[27]

Anion gap in renal failure To understand the changes in the anion gap that can occur in renal failure, it is first necessary to review the normal handling of acids. The dietary acid load is primarily due to the generation of H_2SO_4 from the metabolism of sulfur-containing amino acids.[14,33,34] This acid is rapidly buffered by HCO_3^- and other buffers, leading to the formation of Na_2SO_4:

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2CO_2 + 2H_2O$$

To maintain the steady state, both the $2H^+$ and the SO_4^{2-} must be excreted in the urine. As described above, the excretion of H^+, primarily as NH_4^+, is a tubular function. In comparison, the excretion of SO_4^{2-} is determined by the difference between filtration and some degree of tubular reabsorption. In general, progressive renal diseases lead to parallel impairments in glomerular filtration rate and tubular function; as a result, both the H^+ and SO_4^{2-} are retained, producing a high anion gap metabolic acidosis.[35,36] (Other retained anions in renal failure include phosphate, urate, and hippurate.[37]

These findings are different, however, if there is more prominent impairment in tubular function. In this setting, both H^+ secretion and SO_4^{2-} reabsorption will be diminished, with the latter maintaining the rate of SO_4^{2-} excretion (as Na_2SO_4) at near normal levels. Na^+ depletion is prevented by an equivalent increase in NaCl reabsorption. The net effect is H^+ and Cl^- retention, maintenance of SO_4^{2-} balance, and a normal anion gap metabolic acidosis.[35,36]

Anion gap in other conditions Small changes in the anion gap can occur in a variety of disorders other than metabolic acidosis.[21-23] A high anion gap, for example, can occur in nonketotic hyperglycemia with no or only mild metabolic acidosis as a result of the release of phosphate and perhaps other anions from the cells.[9]

An elevation in unmeasured plasma anions is also a common finding in metabolic alkalosis.[22,38] Three factors may contribute to this finding: (1) a rise in the plasma albumin concentration as a result of extracellular volume depletion; (2) an increase in the number of negative charges per albumin molecule, since the pH is further away from the isoelectric point for albumin of approximately 5.4; and (3) an appropriate alkalemia-induced increase in lactate production in an attempt to lower the pH toward normal. A high anion gap can also result from a reduction in unmeasured cations; this effect, however, is generally of minor importance, since hypokalemia, hypocalcemia, or hypomagnesemia will raise the anion gap by only a few milliequivalents per liter.

There are also settings in which a low anion gap (less than 5 meq/L) may be found. From Eq. (19-6), this phenomenon can be induced by a fall in unmeasured anions (primarily hypoalbuminemia) or by a rise in unmeasured cations.[39] The latter can occur with hyperkalemia, hypercalcemia, hypermagnesemia, severe lithium intoxication, or some cases of multiple myeloma in which a cationic IgG paraprotein is produced.[22,40,41]

In rare cases, the anion gap has a negative value.[42] This is most often due to a laboratory artifact in severe hypernatremia (at levels above 170 meq/L, the true concentration of sodium is underestimated), marked hyperlipidemia (where light scattering in the colorimetric assay can result in marked overestimation of the plasma chloride concentration, occasionally to above 200 meq/L), or bromide intoxication.[20,42,43] The last problem may be seen in patients taking pyridostigmine bromide for myasthenia gravis; it does not occur with Bromo-Seltzer, which no longer contains bromide.[42] In several of the commonly used laboratory assays for chloride, there is a greater affinity for bromide; as a result, each milliequivalent of bromide may be measured as 2 meq of chloride, leading to overestimation of the plasma chloride concentration and a low or even negative anion gap.

Urine anion gap Calculation of the urine anion gap may be helpful diagnostically in some cases with a normal anion gap metabolic acidosis.[44,45] The major measured cations and anions in the urine are Na^+, K^+, and Cl^-; thus, the urine anion gap is equal to

$$\text{Urine anion gap} = ([Na^+] + [K^+]) - [Cl^-] \quad (19\text{-}9)$$

$$\text{Urine anion gap} = \text{unmeasured anions} - \text{unmeasured cations} \quad (19\text{-}10)$$

In normal subjects excreting between 20 and 40 meq of NH_4^+ per liter (NH_4^+ being the major unmeasured urinary cation), the urine anion gap generally has a positive value or is near zero.[44,46] In metabolic acidosis, however, the excretion of NH_4^+ (and of Cl^- to maintain electroneutrality) should increase markedly if renal acidification is intact, resulting in a value that varies from -20 to more than -50 meq/L; the negative value in this setting occurs because the Cl^- concentration now exceeds that of Na^+ plus K^+. In comparison, the acidemia in renal failure and types 1 and 4 renal tubular acidosis is primarily due to impaired H^+ and NH_4^+ excretion, and the urine anion gap typically retains its normal positive value (Fig. 19-1).[44] Thus, use of the urine anion gap in conjunction with the urine pH and plasma K^+ concentration can help in arriving at the correct diagnosis (see "Renal Tubular Acidosis," below).

One simple example can illustrate the potential utility of the urine anion gap. Hypokalemia is a stimulus to renal NH_3 production, an effect that may be related to an intracellular acidosis induced by the transcellular shift of K^+ out of and H^+ into the cells (see page 356).[47] Diffusion of some of this excess NH_3 into the urine will drive Eq. (19-4) to the right, thereby lowering the H^+ concentration and raising the urine pH. Thus, a patient with diarrhea and hypokalemia may have metabolic acidosis and, because of the effect of NH_3, an increase in urine pH similar to that in type 1 renal tubular acidosis. The correct diagnosis in this setting

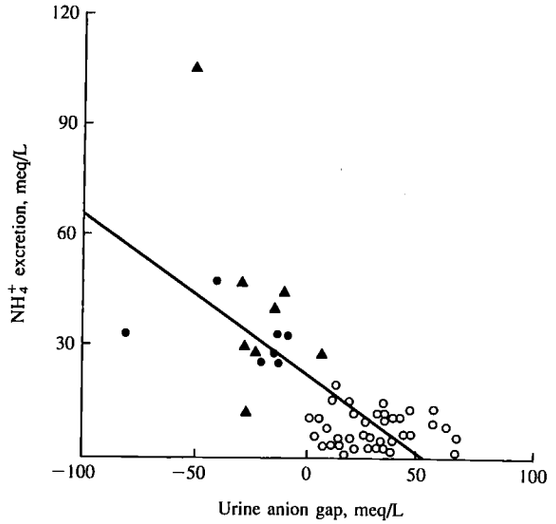

Figure 19-1 The relationship between the urine anion gap and the rate of NH_4^+ excretion in normal subjects receiving ammonium chloride (closed circles), in patients with metabolic acidosis due to diarrhea (closed triangles), and in patients with impaired urinary acidification due to type 1 or 4 renal tubular acidosis (open circles). The urine anion gap has a positive value in the last group, indicative of the defect in NH_4^+ excretion. (*From Batlle DC, Hizon M, Cohen E, et al.* N Engl J Med *318:594, 1988. By permission from the* New England Journal of Medicine.)

can be established by calculation of the urine anion gap, which will have a positive value in renal tubular acidosis but will be appropriately negative with diarrhea, since renal NH_4^+ excretion is not impaired in this disorder.[44]

There are, however, two conditions in which the urine anion gap cannot be used. The first is a high anion gap acidosis, such as ketoacidosis, where the excretion of unmeasured ketoacid anions in the urine will counteract the effect of NH_4^+.[44,45] As a result, the urine anion gap may be positive even though there is an appropriate increase in the rate of NH_4^+ excretion. The second is volume depletion with avid Na^+ retention (urine Na^+ concentration < 25 meq/L).[44] The associated decrease in distal Na^+ delivery impairs distal acidification, resulting in a reversible form of type 1 renal tubular acidosis, even though diarrhea may be the primary abnormality. Viewed in terms of the urine anion gap, the concurrent increase in Cl^- reabsorption prevents the excretion of NH_4Cl and the development of a negative anion gap.

The decreased acid excretion with volume depletion may play an important role in the genesis of the metabolic acidosis that may be seen with severe or persistent diarrhea.[45] Diarrheal fluid may contain as much as 50 meq/L of base. If renal function were normal, however, the fall in the plasma bicarbonate concentration would be limited by increased ammonium excretion, which can reach 150 to 200 meq/day. Concurrent volume depletion will limit this adaptive response, thereby increasing the severity of the acidosis.

Urine osmolal gap When the urine anion gap is positive and it is unclear whether increased excretion of unmeasured anions is responsible, the urine ammonium concentration can be estimated from calculation of the urine osmolal gap.[32,45] This calculation requires measurement of the urine osmolality and the urine

sodium, potassium, urea nitrogen, and, if the dipstick is positive, glucose concentrations. The calculated urine osmolality can then be estimated from

$$\text{Calculated urine osmolality} = 2 \times ([Na^+ + K]) + \frac{[\text{urea nitrogen}]}{2.8} + \frac{[\text{glucose}]}{18}$$

The multiple of 2 accounts for the anions accompanying sodium and potassium, while the divisors 2.8 and 18 reflect adjustments required to convert from the routinely used units of mg/dL to mmol/L or mosmol/kg.

The gap between the measured and calculated urine osmolality should largely represent ammonium salts. This calculation is not affected by unmeasured anions (such as β-hydroxybutyrate), since these anions will be accounted for by the cations sodium, potassium, and ammonium. Suppose, for example, that there is a 100-mosmol/kg difference between the measured and calculated urine osmolality; ammonium excretion in this setting should be approximately one-half this value (because of accompanying anions) or 50 meq/L, a level that is appropriate with metabolic acidosis.[48]

One circumstance in which the urine gap will be inaccurate is when large quantities of an intact (undissociated) acid are excreted, as most often occurs with β-hydroxybutyric acid in ketoacidosis. In this setting, the osmolal gap may be due primarily to β-hydroxybutyric acid rather than to ammonium salts. This error is likely to be small, however, since β-hydroxybutyric acid is excreted primarily as the ketoacid anion as a result of the relatively low pKa (4.7) of this acid. In one careful study of patients with diabetic ketoacidosis, the concentration of undissociated β-hydroxybutyric acid was less than 4 meq/L, while the concentration of ketoacid anions was more than six times higher.[19] Furthermore, the diagnosis of ketoacidosis is usually easily established from the history and routine laboratory data and does not require calculation of the urine anion or osmolal gaps.

ETIOLOGY AND DIAGNOSIS

This section will review the pathogenesis, etiology, and diagnosis of the different disorders that can cause metabolic acidosis. It will also include some specific aspects of therapy, although the general principles involved in the treatment of metabolic acidosis will be discussed separately later in the chapter.

Lactic Acidosis

Lactic acid is derived from the metabolism of pyruvic acid; this reaction is catalyzed by lactate dehydrogenase and involves the conversion of NADH into NAD^+ (reduced and oxidized nicotine adenine dinucleotide, respectively) (Fig. 19-2). Normal subjects produce 15 to 20 mmol/kg of lactic acid per day, most of which is generated from glucose via the glycolytic pathway or from the deamination of alanine.[49,50]

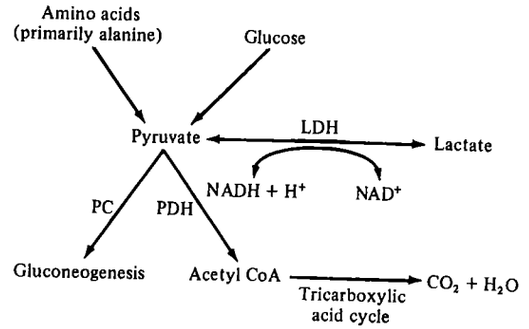

Figure 19-2 Major pathways of pyruvate and lactate metabolism. LDH is lactate dehydrogenase, PDH is pyruvate dehydrogenase, PC is pyruvate carboxylase, and NADH and NAD^+ are reduced and oxidized nicotine adenine dinucleotide, respectively.

Lactic acid is rapidly buffered, in part by extracellular HCO_3^-, resulting in the generation of lactate:

$$CH_3-CHOH-COOH + NaHCO_3 \rightarrow Na^+lactate^- + H_2CO_3 \rightarrow CO_2 + H_2O \quad (19\text{-}11)$$

In the liver and, to a lesser degree, the kidney, lactate is metabolized back to pyruvate, which is then converted into either CO_2 and H_2O (80 percent, catalyzed in part by pyruvate dehydrogenase) or glucose (20 percent, catalyzed in part by pyruvate carboxylase; Fig. 19-2). Either of these processes results in the *regeneration of the HCO_3^-* lost in the initial buffering of lactic acid:

$$\text{Lactate} + 3O_2 \rightarrow HCO_3^- + 2CO_2 + 2H_2O \quad (19\text{-}12)$$

$$2\,\text{Lactate} + 2H_2O + 2CO_2 \rightarrow 2HCO_3^- + \text{glucose} \quad (19\text{-}13)$$

These reactions require both the entry of pyruvate into the mitochondria and normal oxidative metabolism. In comparison, pyruvate will be preferentially converted into lactate in the cytosol in the presence of mitochondrial dysfunction or a marked reduction in tissue perfusion.

The normal plasma lactate concentration is 0.5 to 1.5 meq/L. Lactic acidosis is considered to be present if the plasma lactate level exceeds 4 to 5 meq/L in an acidemic patient.

Pathogenesis and etiology Excess lactate can accumulate when there is increased lactate production and/or diminished lactate utilization.[49-52] The former can occur by three mechanisms: enhanced pyruvate production, reduced pyruvate utilization, or, most commonly, an altered redox state within the cell in which pyruvate is preferentially converted into lactate (Table 19-5).[49,50] During glycolysis, NADH is generated and then reoxidized to NAD^+ in the mitochondria. If oxidation is impaired, however, NADH will accumulate, further promoting the conversion of pyruvate to lactate (Fig. 19-2). In this setting, the associated adenosine triphosphate (ATP) depletion may lead to vasodilatation and a further decline in systemic blood pressure. ATP normally closes ATP-dependent K^+ channels. Thus, ATP depletion in lactic acidosis leads to opening of these channels, resulting

Table 19-5 Etiology of lactic acidosis

Increased lactate production
- A. Increased pyruvate production
  1. Enzymatic defects in glycogenolysis of gluconeogenesis (as with type 1 glycogen storage disease)[53]
  2. Respiratory alkalosis, including salicylate intoxication[49,54]
  3. Pheochromocytoma[55,56]
- B. Impaired pyruvate utilization
  1. Decreased activity of pyruvate dehydrogenase or pyruvate carboxylase
     a. Congential[57]
     b. Possibly a role in diabetes mellitus, Reye's syndrome[58,59]
- C. Altered redox state favoring pyruvate conversion to lactate
  1. Enhanced metabolic rate
     a. Grand mal seizure[60]
     b. Severe exercise[61,62]
     c. Hypothermic shivering[63]
     d. Severe asthma[64]
  2. Decreased oxygen delivery
     a. Shock[45]
     b. Cardiac arrest
     c. Acute pulmonary edema[58]
     d. Carbon monoxide poisoning (↓ O_2 uptake by hemoglobin)[65]
     e. Severe hypoxemia (P_{O_2} < 25 to 30 mmHg)[66]
     f. Pheochromocytoma[55,56]
  3. Reduced oxygen utilization
     a. Cyanide intoxication (↓ oxidative metabolism), which may result from cyanide poisoning[67] or, during a fire, from smoke inhalation of vapors derived from the thermal decomposition of nitrogen-containing materials such as wool, silk, and polyurethane[68]
     b. Drug-induced mitochondrial dysfunction due to zidovudine or stavudine[69-72]
- D. D-Lactic acidosis[73-76]

Primary decrease in lactate utilization
- A. Hypoperfusion and marked acidemia[51,52,77]
- B. Alcoholism[78]
- C. Liver disease[49]

Mechanism uncertain
- A. Malignancy[79-82]
- B. Diabetes mellitus,[49] including metformin[83,84] in the absence of tissue hypoxia
- C. Acquired immune deficiency syndrome[85]
- D. Hypoglycemia[49]
- E. Idiopathic

sequentially in K^+ movement out of the cells, hyperpolarization of vascular smooth muscle cells, and decreased Ca^{2+} entry into these cells through voltage-dependent Ca^{2+} channels.[86] The fall in cell Ca^{2+} concentration produces smooth muscle relaxation and a reduction in systemic vascular resistance.

In certain disorders, the primary role of lactate overproduction is clear. As an example, plasma lactate levels may transiently be as high as 15 meq/L during a grand mal seizure[60] and 20 to 25 meq/L with maximal exercise, with the systemic pH falling to as low as 6.80.[61,87] Studies in these patients have demonstrated rapid recovery of acid-base balance, with a maximum rate of lactate utilization that can reach 320 meq/h.[49]

This high rate of lactate metabolism suggests that there must be some component of *decreased utilization* in those disorders in which lactate overproduction occurs more slowly. In shock, for example, the reduction in perfusion to the liver and an associated intracellular acidosis may combine to substantially diminish hepatic lactate metabolism.[51,52,88] The importance of these events has been demonstrated experimentally by the observation that infusing lactic acid to otherwise normal animals is associated with increased hepatic utilization and relative difficulty in lowering the extracellular pH.[51,52]

Most cases of lactic acidosis are due to marked tissue hypoperfusion in shock or during a cariodpulmonary arrest.[49,50,89] The prognosis is generally poor unless tissue perfusion can be rapidly restored.

The association of lactic acidosis with *diabetes mellitus* is less certain, since many cases in the past were associated with the use of phenformin and some of those today with metformin.[83,84] Nevertheless, a moderate degree of lactic acidosis may be seen in some patients with diabetic ketoacidosis.[49,90] How this occurs is not clear, although marked hypovolemia is likely to play an important role. Documentation of concurrent lactic acidosis may be clinically important, since the altered redox state in this setting also converts acetoacetate into β-hydroxybutyrate. Only the former is recognized by the nitroprusside tablet or dipstick used to detect the presence of ketones; as a result, a falsely negative result may be obtained and the diagnosis of ketoacidosis obscured when there is preferential production of β-hydroxybutyrate.[90]

The pathogenesis of the lactic acidosis found with *malignancies* is also unclear.[79-82] Anaerobic metabolism due to dense clusters of tumor cells and/or metastatic replacement of the hepatic parenchyma have been proposed, but lactic acidosis has occurred in patients with relatively small tumor burdens.[79,81] Direct lactate production by the neoplastic cells has also been suggested, but this would not explain the rarity of tumor-induced lactic acidosis. Regardless of the mechanism, removal of the tumor (or by chemotherapy, irradiation, or surgery) leads to correction of the acidosis.[79,81,82]

A mild degree of lactic acidosis also may be seen with *alcoholism*.[78] In this condition, lactate production is usually normal, but lactate utilization is diminished because of impaired hepatic gluconeogenesis. Although lactate levels generally do not exceed 3 meq/L in this setting, alcohol ingestion can potentiate the severity of other disorders that are associated with the overproduction of lactate.

There are rare patients with the acquired immune deficiency syndrome (AIDS) in whom lactic acidosis is associated with drug-induced mitochondrial dysfunction in the absence of sepsis or hypotension. Such an association has been described in patients with zidovudine-induced myopathy, characterized by elevated plasma creatine kinase concentrations and proximal muscle weakness,[91] and zidovudine- or stavudine-induced hepatic steatosis and hepatic failure.[69,70] The latter complication may, in some cases, be due to a concurrent deficiency of riboflavin, a precursor to a number of cofactors necessary for mitochondrial energy production. In several patients, nucleoside-induced lactic acidosis has been reversed by riboflavin therapy.[71,72] In addition, a seemingly idiopathic form of lactic acidosis can occur in the absence of zidovudine.[85]

D-lactic acidosis A unique form of lactic acidosis can occur in patients with jejunoileal bypass or, less commonly, small bowel resection or other cause of the short bowel syndrome. In these settings, glucose and starch are metabolized in the colon into D-lactic acid, which is then absorbed into the systemic circulation.[73-76] The ensuing acidemia tends to persist, since D-lactate is not recognized by L-lactate dehydrogenase, the enzyme that catalyzes the conversion of the physiologically occurring L-lactate into pyruvate.

Two factors tend to contribute to the overproduction of D-lactic acid in this disorder.[74] First, there is overgrowth of gram-positive anaerobes, such as lactobacilli, which are most able to produce D-lactate. Second, there is usually relatively little glucose and starch delivered to the colon because of extensive small-intestinal absorption. However, delivery of these substrates is markedly enhanced when the small bowel is bypassed, removed, or diseased.

Patients with this disorder present with episodic metabolic acidosis (usually occurring after high-carbohydrate meals) and characteristic neurologic abnormalities, including confusion, cerebellar ataxia, slurred speech, and loss of memory.[73-75] They may complain of feeling or appearing to be drunk in the absence of ethanol intake. It is not clear whether these symptoms are due to D-lactate itself or to some other toxin produced in the colon and then absorbed in parallel with D-lactate.

The classic neurologic findings plus the metabolic acidosis and the history of intestinal disease should strongly suggest the presence of D-lactic acidosis. Confirmation of the diagnosis requires a special enzymatic assay that uses D-lactate dehydrogenase and measures the generation of NADH as lactate is converted to pyruvate.[73-75] In contrast, the standard assay for lactate uses L-lactate dehydrogenase, which will not detect D-lactate.

An additional source of confusion may occur in D-lactic acidosis. Filtered D-lactate is *rapidly excreted* in the urine, being unable to bind to the Na^+-L-lactate cotransporter in the luminal membrane of the proximal tubule that normally promotes L-lactate reabsorption. As a result, patients with this disorder may have an anion gap that is normal or less than expected from the degree of reduction in the plasma HCO_3^- concentration.

Therapy in D-lactic acidosis consists of acute sodium bicarbonate administration to correct the acidemia and oral antimicrobial agents (such as metronidazole, neomycin, or vancomycin) to decrease the number of D-lactate producing organisms.[74-76] A low-carbohydrate diet (or the use of starch polymers rather than simple sugars) also is helpful, by diminishing carboyhydrate delivery to the colon.

Diagnosis Although the diagnosis of lactate acidosis can be made definitively only by the demonstration of an elevated plasma lactate concentration, there are often many suggestive clues in the history, physical examination, laboratory data, and response to therapy. These include a high anion gap; the presence of one of the disorders that can cause lactic acidosis; cool, clammy extremities and hypotension if shock is present; and continuing production of acid, as evidenced by an inability of exogenous HCO_3^- to raise the plasma HCO_3^- concentration.

The presence of an organic acidosis (primarily lactic acidosis or ketoacidosis) should also be suspected if effective treatment of the underlying problem (such as fluid repletion in hypovolemic shock) leads to a *spontaneous elevation in the plasma HCO_3^- concentration*. This occurs because metabolism of the organic anion, in this case lactate, results in the regeneration of HCO_3^- [Eqs. (19-12) and (19-13)].

Treatment Correction of the underlying disorder is the primary therapy in lactic acidosis. Reversal of circulatory failure, for example, will reduce further lactate production and allow metabolism of the excess lactate to HCO_3^-. (This spontaneous regeneration of HCO_3^- does not occur in D-lactic acidosis, since D-lactate cannot be metabolized.)

The role of $NaHCO_3$ administration in lactic acidosis has been a source of great controversy.[92] Proponents argue that raising the arterial pH may improve tissue perfusion, by reversing acidemia-induced vasodilatation and impaired cardiac contractility, and may diminish the risk of serious arrhythmias (see "Symptoms," below).[50,93] These potential benefits, however, must be weighed against the possible risks, which include volume overload, hypernatremia (a 5 percent $NaHCO_3$ solution contains almost 900 meq of Na^+ per liter), and overshoot metabolic alkalosis after normal hemodynamics has been restored.[94] In addition, metabolic acidosis may be in part protective during ischemia by minimizing hypoperfusion-induced tissue injury.[95]

In addition, both experimental[88,96,97] and human studies[80,97,98] have suggested that HCO_3^- therapy may be relatively ineffective, *producing only a transient elevation in the plasma HCO_3^- concentration* and possibly *worsening the intracellular acidosis*.[88,99,100] The seeming lack of efficacy of alkali therapy appears to be due in part to an associated *increase in net lactic acid production* (which also leads to a further rise in the anion gap).[88,96]

This unexpected change in lactate metabolism may be induced by the continued generation of CO_2, as a result of both cellular metabolic activity (including fibrillating myocardial cells during cardiac arrest)[99] and buffering of the excess H^+ ions by exogenous HCO_3^- [Eq. (19-1)].[88,101] This CO_2 then accumulates in the tissues, since pulmonary blood flow is reduced as part of the shock state.[102-104] The ensuing local hypercapnia can exacerbate the intracellular acidosis, leading to

decreased lactate utilization in hepatic cells and a decline in contractility in cardiac cells.[82,96,99,101] The latter effect can reduce the cardiac output, a change that will promote further lactic acid production.*

It must also be emphasized that this problem of CO_2 accumulation may *not be detectable in arterial blood.*[103,104] Blood entering the pulmonary circulation may be adequately cleared of CO_2, resulting in a relatively normal arterial P_{CO_2}. However, total CO_2 elimination is diminished because of the reduction in pulmonary blood flow with severe circulatory failure or cardiac arrest. As a result, the P_{CO_2} at the tissue level may be markedly elevated, a change that can be detected by measurement of *mixed venous blood.* In one study of patients undergoing cardiopulmonary resuscitation, the mean arterial pH and P_{CO_2} were 7.42 and 32 mmHg, respectively, whereas the mixed venous values were 7.14 and 74 mmHg.[103] This problem may be exacerbated by $NaHCO_3$ therapy, in part because buffering of H^+ ions in the blood by HCO_3^- increases the generation of CO_2.[103,104]

In summary, these findings make the optimal therapy of lactic acidosis uncertain at the present time. Some physicians have concluded that there is little indication for $NaHCO_3$ administration,[97] particularly during cardiac arrest.[100] However, most physicians give small amounts of $NaHCO_3$ to maintain the arterial pH above 7.10, since more severe acidemia can result in a deterioration in cardiovascular function. Careful monitoring, including measurement of mixed or central venous pH, is required to minimize side effects related to HCO_3^- administration.

There are three possible experimental alternatives to HCO_3^- therapy. One is the administration of Na_2CO_3 as a source of alkali: Buffering of excess H^+ ions by this compound will generate HCO_3^-, not CO_2, thereby minimizing the tendency to exacerbate the intracellular acidosis.[88,101] However, this agent has not been effective during cardiac arrest in experimental animals.[99,100] Although the extracellular pH may be increased, there is no improvement in the progressive decline in myocardial cell pH that results from continued CO_2 production by the fibrillating cells.

The second alternative is the administration of dichloroacetate (DCA). This compound stimulates pyruvate dehydrogenase activity, thereby minimizing lactate production by allowing pyruvate to be oxidized to CO_2 and H_2O (Fig. 19-2). Although there is evidence of benefit in experimental models of lactic acidosis, a controlled trial in humans showed that DCA produced a minor increase in the plasma bicarbonate concentration and arterial pH but no improvement in systemic hemodynamics or mortality.[106]

The third option is tromethamine (THAM). THAM is an inert amino alcohol that buffers acids and CO_2 by virtue of its amine ($-NH^2$) moiety via the following reactions:[107]

* Increased lactate accumulation following HCO_3^- administration may also diminish cardiac function by a second mechanism. Patients who undergo prolonged cardiopulmonary resuscitation often have up to a 50 percent reduction in the ionized Ca^{2+} concentration in the plasma, a change that can directly impair cardiac contractility.[105] The total plasma Ca^{2+} concentration, however, remains normal, indicating that increased binding of Ca^{2+} must be present. This effect is directly related to the severity of the acidemia and could represent Ca^{2+} binding to lactate.

$$THAM-NH_2 + H^+ = THAM-NH_3^+$$

$$THAM-NH_2 + H_2O + CO_2 = THAM-NH_3^+ + HCO_3^-$$

Protonated THAM is excreted in the urine at a slightly higher rate than creatinine clearance in conjunction with either chloride or bicarbonate. Thus, THAM supplements the buffering capacity of blood without generating carbon dioxide but is less effective in patients with renal failure. Reported toxicities include hyperkalemia, hypoglycemia, and respiratory depression; the last complication probably results from the ability of THAM to rapidly increase the pH and decrease the P_{CO_2} in the central nervous system.

Published clinical experience with THAM is limited, but the drug has been used to treat severe acidemia due to sepsis, hypercapnia, diabetic ketoacidosis, renal tubular acidosis, gastroenteritis, and drug intoxication.[107] Its clinical efficacy compared to that of sodium bicarbonate in the treatment of metabolic acidosis remains unproven, and THAM is of uncertain safety.

These findings are consistent with the primary importance of reversing the underlying disorder. Patients generally die from tissue ischemia rather than from acidemia itself.

Ketoacidosis

The biochemistry of ketoacidosis is discussed in detail in Chap. 25. Stated briefly, free fatty acids are converted in the liver into triglycerides, CO_2, and H_2O or into the ketoacids, acetoacetic acid and β-hydroxybutyric acid. Overproduction of ketoacids resulting in metabolic acidosis requires two factors: (1) an increase in free fatty acid delivery to the liver due to enhanced lipolysis, and (2) a resetting of hepatocyte function such that the free fatty acids are converted preferentially into ketoacids and not triglycerides.[108-110] *Both diminished activity of insulin and enhanced secretion of glucagon* (due in part to the insulin deficiency) contribute to these changes: the lack of insulin by increasing lipolysis, and the excess of glucagon by indirectly increasing fatty acyl CoA entry into the hepatic mitochondria, where it can be converted into ketones.[108-110]

Etiology Uncontrolled diabetes mellitus is the most common cause of ketoacidosis. Hyperglycemia is invariably present in this setting, with the plasma glucose concentration usually exceeding 400 mg/dL.

Fasting Fasting can also result in ketosis, as the appropriate hormonal milieu (low insulin, high glucagon) is established by the lack of carbohydrate intake. In comparison to the potentially severe ketoacidosis that can occur in uncontrolled diabetes, ketoacid levels do not exceed 10 meq/L with fasting. This limitation in the degree of ketone formation may reflect the ability of ketonemia to promote insulin secretion, eventually limiting the availability of free fatty acids.[111,112]

Alcoholic ketoacidosis The combination of alcohol ingestion and poor dietary intake is another cause of ketoacidosis.[113-115] The decrease in carbohydrate intake plus the inhibition of gluconeogenesis by alcohol[49] result in the necessary changes in insulin and glucagon secretion. In addition, ethanol directly enhances lipolysis, further increasing the supply of free fatty acids.[116]

The net effect may be a relatively severe acidosis that is often due to factors other than ketoacidosis alone.[115,117] Concurrent hypovolemia can lead to enhanced lactic acid production, and some of the ethanol will be metabolized into acetic acid.

These patients also frequently present with a mixed-base disturbance:[115]

- Metabolic alkalosis may result from vomiting, which is a common complicating problem. In some cases, the arterial pH may be relatively normal, and only the elevated anion gap points toward the presence of ketoacidosis.
- Patients with underlying chronic hepatic disease may have a chronic respiratory alkalosis (see Chap. 21).
- Urinary loss of the ketoacid anions can lead to a relatively normal anion gap in comparison to the fall in the plasma bicarbonate concentration (see "Anion Gap," above).

Other Increased ketoacid production can also occur in a variety of congenital organic acidemias (such as methylmalonic or isovaleric acidemia)[118,119] and may contribute to the acidemia associated with salicylate intoxication.[22] The mechanisms responsible for the increased ketone synthesis in these disorders are not completely understood.

Diagnosis The presence of alcoholic ketoacidosis should be suspected in a patient with a history of alcohol abuse who is found to have an otherwise unexplained high anion gap metabolic acidosis with a normal or only slightly elevated plasma glucose concentration. The osmolal gap—the difference between the measured and calculated plasma osmolality (see page 607)—also tends to be increased as a result of the accumulation of glycerol (derived from fat breakdown) and acetone and the possible presence of ethanol.[120] This finding, however, is of limited diagnostic utility, since the osmolal gap is also increased in other high anion gap acidoses, such as that due to methanol or ethylene glycol intoxication (see below).[121]

Confirmation of the presence of ketoacidosis requires the demonstration of ketonemia. This is generally done with nitroprusside (Acetest) tablets or reagent sticks. A 4+ reaction with serum diluted 1 : 1 is strongly suggestive of ketoacidosis. However, nitroprusside reacts with acetoacetate and acetone (produced by the decarboxylation of acetoacetic acid), but not with β-hydroxybutyrate.[90] The latter ketoacid is formed from the reduction of the β-aldehyde group of acetoacetate in a reaction utilizing NADH. β-Hydroxybutyrate makes up about 75 percent of the circulating ketones in diabetic ketoacidosis, but this value can reach 90 percent when NADH levels are elevated with concurrent lactic acidosis[90] or in alcoholic ketoacidosis (where NADH is generated from the oxidation of ethanol to acetic acid).[113]

In these settings, the nitroprusside test may underestimate the degree of ketonemia and ketonuria. Clinical awareness of the possibility of ketoacidosis is essential, since an assay for β-hydroxybutyrate is not available in most hospitals. An indirect method to circumvent this problem is to add a few drops of hydrogen peroxide to a urine specimen. This will nonenzymatically convert β-hydroxybutyrate into acetoacetate, which will then be detectable by nitroprusside.[122] An alternative, if available, is to directly measure β-hydroxybutyrate in the blood.

A different problem in diagnosis arises with sulfhydryl drugs, particularly captopril, which is widely used in the treatment of diabetic nephropathy and hypertension in diabetics. These drugs can interact with the nitroprusside reagent to produce a false-positive ketone test.[123] Thus, a positive nitroprusside test for ketonuria or ketonemia cannot be reliably interpreted in patients treated with captopril. In this setting, the diagnosis of diabetic ketoacidosis must be made on clinical grounds (otherwise unexplained high anion gap metabolic acidosis in a patient with uncontrolled diabetes) or by direct measurement of β-hydroxybutyrate.

Treatment Although insulin is the keystone to therapy in diabetic ketoacidosis, it may be dangerous in alcoholism or fasting, where the baseline plasma glucose concentration may be low. In these conditions, the administration of glucose and saline will augment endogenous insulin secretion, diminish that of glucagon, normalize fatty acid metabolism, and correct any fluid deficit that may be present.[114,115]

The role of HCO_3^- therapy is uncertain in ketoacidosis, as it is in lactic acidosis. Most patients with ketoacidosis will derive no benefit from exogenous alkali, since insulin-induced metabolism of the ketoacid anions will result in the rapid regeneration of HCO_3^- and at least partial correction of the acidemia.[30,124,125] There are, however, two settings in which HCO_3^- therapy may be beneficial: with marked acidemia (arterial pH < 7.00 to 7.10), and with a relatively normal anion gap, due to excretion of ketoacid anions in the urine.[30,93] In the latter condition, the quantity of HCO_3^- that can be generated from organic anion metabolism is minimized, and, in the absence of alkali therapy, restoration of acid-base balance will be a slow process, requiring renal excretion of the excess acid as NH_4^+.[30]

Hypophosphatemia is also a frequent complication of the treatment of ketoacidosis, since the rise in insulin levels promotes phosphate movement from the extracellular fluid into the cells. However, phosphate administration is generally not required unless marked hypophosphatemia occurs. When present, severe hypophosphatemia may be associated with marked and possibly life-threatening complications in these patients, including myocardial dysfunction.[126]

Renal Failure

Metabolic acidosis is a common complication of advanced renal disease and results from an inability of the diseased kidney to excrete the daily dietary acid

load.[35,36,127] The acidemia is generally not severe, although alkali therapy may still have a variety of beneficial effects.

Pathogenesis Renal insufficiency can affect all of the parameters involved in net acid excretion. With the initial reduction in glomerular filtration rate (GFR), hydrogen balance is maintained by increased ammonium excretion per functioning nephron.[127-130] However, total ammonium excretion begins to fall when the GFR is less than 40 to 50 mL/min (Fig. 19-3).[130,131] The net effect is the development of metabolic acidosis, resulting from an *inability to excrete all of the daily* H^+ *load*.[35,36,130]

Both decreased titratable acidity (primarily as phosphate) and reduced HCO_3^- reabsorption also may contribute to the decline in net acid excretion. Phosphate excretion is initially maintained in renal failure, in part by the associated secondary hyperparathyroidism (see page 202). However, net phosphorus absorption and therefore urinary excretion are diminished in patients with advanced disease, because of both dietary restriction and the use of oral phosphate binders, such as calcium carbonate, to prevent hyperphosphatemia.[130]

The role of impaired HCO_3^- reabsorption is uncertain;[127] the need to increase Na^+ excretion per functioning nephron to maintain Na^+ balance may lead to a modest increase in HCO_3^- excretion.[130,132,133] This defect, however, does not appear to play an important role in most cases.[133,134]

The fall in total ammonium excretion in renal failure usually does not represent tubular dysfunction per se. Ammonium excretion per total GFR (to account for the reduction in functioning renal mass) is three to four times normal, a level similar to the maximum achieved in normal subjects following an acid load.[127,129] This suggests that the reduction in total ammonium excretion reflects the *limited number of functioning nephrons*, since ammonium production is already proceeding at a maximal rate.[129]

As the patient approaches end-stage renal failure, the plasma HCO_3^- concentration usually, but not always, falls and then stabilizes at 12 to 20 meq/L.[35,36,130,135] Although H^+ ions continue to be retained, a further reduction in the plasma HCO_3^- concentration is prevented by buffering of the excess acid, primarily by bone buffers.[135,136] This process is manifested in part by the release of calcium from bone and its subsequent excretion in the urine. This negative calcium balance can be reversed with alkali therapy;[135] if it is untreated, however, the calcium loss can, over a prolonged period, lead to osteopenia.[136]

A plasma HCO_3^- concentration below 10 to 12 meq/L is usually due to a superimposed abnormality, such as hypoaldosteronism (in which hyperkalemia is a prominent finding; see Chap. 28), or another cause of metabolic acidosis, as with diarrhea. The latter problem can lead to a severe reduction in pH, since patients with renal failure cannot compensate for the increased H^+ load by increasing renal acid excretion.

Treatment Exogenous alkali therapy has not in the past been used to correct asymptomatic metabolic acidosis in adults with renal failure. The limited fall in the

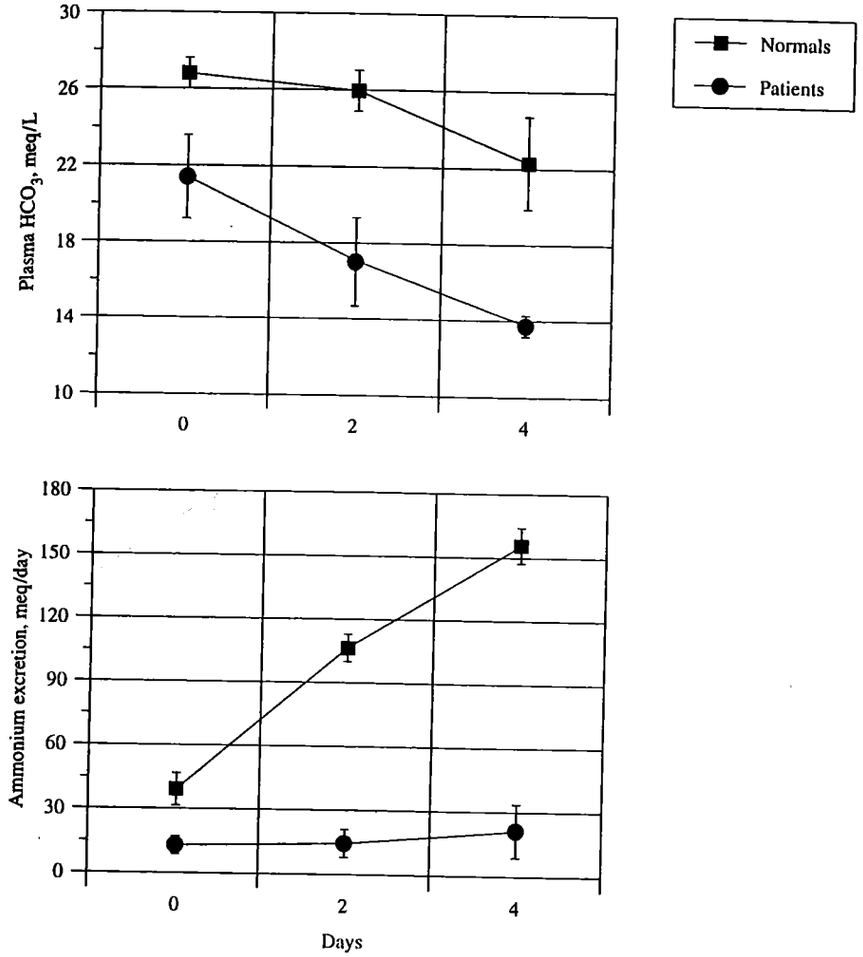

Figure 19-3 Effect of a dietary acid load on the plasma HCO_3^- concentration and urinary NH_4^+ excretion in normals (squares) and patients with chronic renal failure (circles). Normal subjects increase NH_4^+ excretion approximately fourfold with only a few meq/L reduction in the plasma HCO_3^- concentration. The patients with chronic renal disease had a low rate of NH_4^+ excretion at baseline (despite already having a mild metabolic acidosis) and showed no increment following the acid load. (*Data from Welbourne T, Weber M, Bank N,* J Clin Invest *51:1852, 1972, with permission.*)

plasma HCO_3^- concentration plus the respiratory compensation usually maintain the arterial pH near 7.30, a level that poses no danger to the patient. Furthermore, raising the pH in the presence of hypocalcemia can precipitate tetany, and the associated Na^+ load can increase the tendency toward volume expansion. As a result, the major indications for $NaHCO_3$ therapy have included a fall in the plasma HCO_3^- concentration below 12 meq/L; symptoms such as dyspnea, and

persistent hyperkalemia, since raising the pH will drive K^+ into the cells; and acidemia in children, which can impair growth.[137]

In adults, in whom growth is not an issue, there are least three potential reasons why even mild metabolic acidosis should be treated in the patient with renal failure:[138]

- Minimizing bone buffering of excess H^+ ions may minimize the loss of bone calcium and possibly prevent or delay the development of osteopenia.[135,136] Correction of the acidosis also can prevent progression of hyperparathyroid bone disease,[139] an effect that may be related to a diminished stimulus to secondary hyperparathyroidism.[138]
- Metabolic acidosis can lead to increased skeletal muscle breakdown and decreased albumin synthesis,[141-145] an effect that can be reversed by correction of the acidemia.[146,147] The catabolic state, which appears to be mediated in part by increased release of cortisol and diminished release of insulin-like growth factor-I (IGF-I), may contribute to loss of lean body mass and muscle weakness.[143,144] These problems may be exacerbated by the low-protein diet that may be prescribed in an attempt to slow the rate of progression of the renal failure (see page 48).[142]
- The adaptive increase in NH_3 production per nephron can lead to local complement activation and tubulointerstitial damage.[148] Preventing this response with alkali therapy may protect the kidney and slow the rate of progression of the underlying disease.[148]

Definitive studies on the treatment of metabolic acidosis in chronic renal failure in humans have not yet been performed. Nevertheless, some physicians have advocated the earlier use of alkali therapy in this setting, particularly in view of the observation that $NaHCO_3$ is better excreted (perhaps reflecting the impairment in HCO_3^- reabsorption) and therefore less likely to produce fluid overload than an equivalent quantity of NaCl.[149]

If alkali therapy is given, $NaHCO_3$ is the treatment of choice, while sodium citrate (citrate is rapidly metabolized to HCO_3^-) should be *avoided.* Citrate can markedly increase passive aluminum absorption, possibly predisposing to aluminum intoxication in patients with renal failure who are taking aluminum hydroxide to control hyperphosphatemia (see page 205).[150,151] Two factors are thought to contribute to this effect: (1) Citrate combines with aluminum to form a nondissociable but soluble and absorbable complex, and (2) citrate combines with Ca^{2+} in the intestinal lumen, leading to a reduction in the free Ca^{2+} concentration that increases the permeability of tight junctions.[150]

Ingestions

Salicylates Aspirin (acetylsalicylic acid) is rapidly converted into salicylic acid in the body. Although there is no absolute correlation between the plasma salicylate concentration and symptoms, most patients show signs of intoxication when the

plasma level exceeds 40 to 50 mg/dL (therapeutic range is 20 to 35 mg/dL).[156] Early symptoms include tinnitus, vertigo, nausea, vomiting, and diarrhea; more severe intoxication can cause altered mental status, coma, noncardiac pulmonary edema, and death. Fatal overdosage can occur after the ingestion of 10 to 30 g by adults and as little as 3 g by children. The diagnosis can be made with certainty only by measurement of the plasma salicylate concentration.

Increasing doses of aspirin cause a progressively greater risk of toxicity because of *saturation of protective mechanisms.*[157] At therapeutic levels, 90 percent of salicylate is protein bound and therefore limited to the vascular space; the drug is then partially glycinated in the liver to salicyluric acid, which is both less toxic and more rapidly excreted by the kidney than salicylate. With salicylate toxicity, however, the degree of protein binding falls to 50 percent and salicyluric acid formation becomes saturated. Thus, more drug is now able to reach the tissues, and, because of the decline in renal excretion, toxic levels persist for a longer period of time.

A variety of acid-base disturbances can occur with salicylate intoxication.[158] Salicylates stimulate the respiratory center directly,[159] resulting in a fall in the P_{CO_2} and respiratory alkalosis as the earliest abnormality.[156,158,160] Metabolic acidosis may then ensue, primarily because of the accumulation of organic acids, including lactate and ketoacids.[22,49,161] The respiratory alkalosis, which normally promotes lactic acid production in an attempt to minimize the rise in pH,[54] appears to play a contributory role in this process. In experimental animals, lactate accumulation is not seen if the initial fall in P_{CO_2} is prevented but gradually becomes more prominent if hypocapnia is allowed to occur.[161] Salicylic acid itself (mol wt 180) has only a minor effect, since a plasma level of 50 mg/dL represents a concentration that is less than 3 meq/L.

The net effect of these changes is that most adults have either a respiratory alkalosis or a mixed respiratory alkalosis–metabolic acidosis; pure metabolic acidosis is unusual.[158] In addition, approximately one-third of adults will also ingest one or more other medications, many of which are respiratory depressants and can lead to concurrent respiratory acidosis.[158]

Treatment The serious neurologic toxicity of salicylates, including death, is related to the cerebral tissue salicylate concentration; thus, a reduction in this level must be the first goal of therapy. This can in part be achieved by *alkalinization of the plasma* to an arterial pH between 7.45 and 7.50. To appreciate how this works, it is important to note that salicylic acid (HS) is a weak acid with a pK_a of 3.0. Thus, the Henderson-Hasselbalch equation for the reaction

$$H^+ + S^- \leftrightarrow HS \tag{19-14}$$

can be expressed as

$$pH = 3.0 + \log \frac{[S^-]}{[HS]} \tag{19-15}$$

where S^- represents the salicylate anion.

At the normal pH of 7.40, the ratio of HS to S^- is about 1 : 25,000; that is, only 0.004 percent of the total extracellular salicylate exists as HS. HS is nonpolar, lipid-soluble, and able to cross cell membranes; S^- is polar and crosses membranes poorly. As a result, the plasma and central nervous system (CNS) HS concentrations are in diffusion equilibrium, but not the S^- concentrations (Fig. 19-4).

If the systemic pH is increased, Eq. (19-14) will move to the left. As the plasma HS concentration falls, HS will leave the CNS (and other tissues) down a concentration gradient, where it will be trapped in the plasma as S^-. The fall in the CNS HS concentration then causes Eq. (19-14) to move to the right in the brain cell. This maintains the cellular HS concentration, thereby promoting further drug movement out of the CNS. For example, increasing the arterial pH from 7.20 to 7.50 will decrease the fractional concentration of HS from 0.006 to 0.003 percent. Although this change appears small, it will promote a significant reduction in tissue salicylate concentration. Note that alkalinization leads to an initial increment in the plasma salicylate concentration, but it is the tissue levels that are dangerous to the patient.

A second goal of treatment is rapid elimination of the drug from the body. Since salicylate is highly protein bound, it enters the urine primarily via secretion by the organic anion secretory pathway in the proximal tubule (see Chap. 3) rather than by glomerular filtration. The rate of salicylate excretion can be markedly enhanced by alkalinization of the urine, which, by the same process of nonionic diffusion, converts urinary HS to S^-, thereby minimizing the back-diffusion of secreted HS out of the tubular lumen.[162] As an example, raising the urine pH from 6.5 to 8.1 by the administration of $NaHCO_3$ can increase total salicylate excretion more than fivefold.[163]

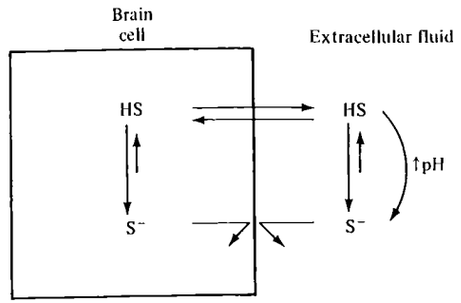

Figure 19-4 Schematic representation of the equilibrium distribution of salicylate (S^-) and salicylic acid (HS) between the extracellular fluid and the brain cell. HS is lipid-soluble and is in diffusion equilibrium; S^- is not in equilibrium, since it is charged and cannot readily cross the cell membrane. Alkalinization of the extracellular fluid causes the reaction, $H^+ + S^- \leftrightarrow HS$, to move to the left, reducing the extracellular HS concentration. This allows cellular HS to diffuse into the extracellular fluid down a concentration gradient. The decrease in the cellular HS concentration then causes some cellular S^- to be converted to HS, thereby promoting continued HS diffusion out of the brain. Similar considerations explain the increased movement of salicylate from the tubular cell into the lumen when the urine is alkalinized.

The efficiency of salicylate removal can also be enhanced by hemodialysis.[156,157,164] This procedure should be considered when the plasma salicylate concentration exceeds 80 mg/dL or the patient is comatose or has impaired renal function or fluid overload.

Another frequent problem of uncertain etiology is a low cerebrospinal fluid glucose concentration, which may contribute to the neurologic abnormalities.[156] Thus, the administration of glucose should be part of the initial therapy in all patients with salicylate intoxication.

In summary, the administration of alkali is an important component of therapy in the patient with salicylate intoxication and metabolic acidosis. If, however, respiratory alkalosis is the primary disturbance, further alkalinization is not necessary.

Methanol Methanol (wood alcohol, CH_3OH) is a component of shellac, varnish, deicing solutions, sterno, and other commercial preparations. It is metabolized to formaldehyde (in a reaction catalyzed by alcohol dehydrogenase) and then formic acid (Fig. 19-5). Symptoms and the high anion gap metabolic acidosis are usually delayed for 12 to 36 h after ingestion, since they are due to accumulation of these metabolites, particularly formic acid.[157,165,166] Early complaints include weakness, nausea, headache, and decreased vision, which can then progress to blindness, coma, and death. Funduscopic examination may reveal a retinal sheen due to retinal edema.

The minimum lethal dose is 50 to 100 mL, although smaller amounts can lead to permanent blindness. Similar clinical and acid-base disturbances may result from the ingestion of formaldehyde.[167]

Osmolal gap The diagnosis of methanol ingestion is made by a specific serum assay for methanol. In addition, the presence of methanol intoxication may be suspected indirectly by the demonstration of an *osmolal gap* between the measured and calculated plasma osmolality:[168,169]

$$\text{Calculated } P_{osm} = 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} + \frac{\text{BUN}}{2.8} \qquad (19\text{-}16)$$

Methanol is a small molecule (mol wt 32) that can achieve high osmolal concentration in the plasma. A level of 80 mg/dL, for example, is equivalent to 25 mosmol/kg. Thus, the measured plasma osmolality will exceed the calculated value in Eq. (19-16) by this amount. A similar but less prominent effect can be induced by ethylene glycol, which is a larger molecule (mol wt 62) that is present in lower molar concentrations than methanol. Salicylates, on the other hand, have only a minor effect, since their plasma level is almost always less than 5 mosmol/kg.[168]

Thus, a high osmolal gap in a patient with an *otherwise unexplained* high anion gap metabolic acidosis has been thought to be suggestive of the presence of either methanol or ethylene glycol intoxication. However, an elevated osmolal gap is a relatively nonspecific finding, since it is also seen in other high anion gap acidosis,

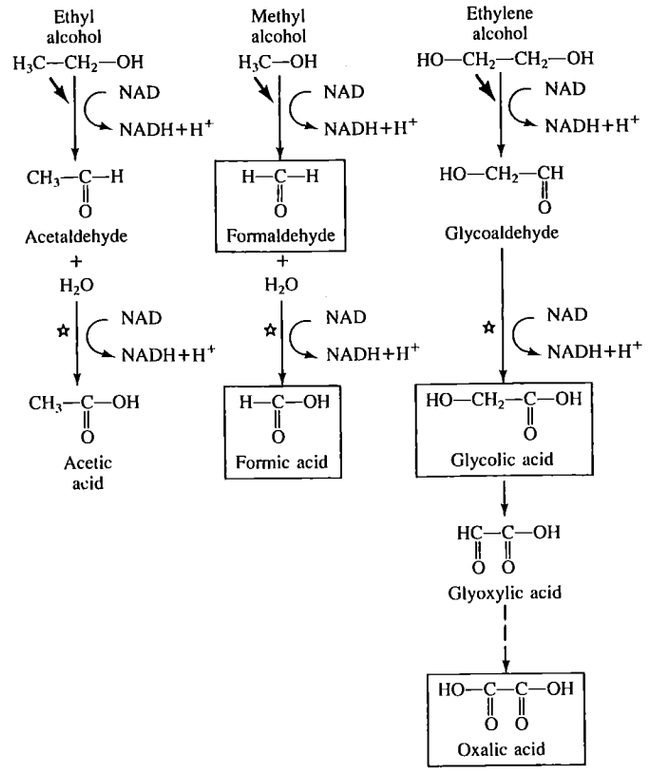

Figure 19-5 Pathways of metabolism of ethyl alcohol (ethanol), methyl alcohol (methanol), and ethylene glycol. Alcohol dehydrogenase (bold arrow) is a cytosolic enzyme that catalyzes the first oxidative step for each alcohol. Aldehyde dehydrogenase (star) is a mitochondrial enzyme that then catalyzes the second oxidative step. The products in boxes are those responsible for the major reactions associated with methanol or ethylene glycol intoxication. (*Adapted from Garella S,* Kidney Int *33:735, 1988. Reprinted by permission from* Kidney International.)

such as diabetic or alcoholic ketoacidosis, lactic acidosis, and in chronic, but not acute, renal failure (due to the retention of unidentified small solutes).[120,121,170,171] Furthermore, the osmolal gap must be correlated with concomitant measurement of the plasma ethanol concentration, since patients ingesting methanol or ethylene glycol often abuse alcohol as well.[121]*

The factors responsible for the osmolal gap in ketoacidosis and lactic acidosis have not been defined. In one study of alcoholic ketoacidosis and lactic acidosis, for example, the osmolal gap in these disorders averaged 27 and 17

* Detection of an osmolal group with an alcohol intoxication can be achieved only if the plasma osmolality is measured by freezing-point depression. In comparison, the osmotic contribution of volatile alcohols is not detected when a vapor pressure osmometer is used, since this technique assumes that only water is in the vapor phase.[172,173]

mosmol/kg, respectively.[121] Although ethanol contributed in many of these patients, the gap remained at 10 to 11 mosmol/kg after the effect of ethanol was subtracted. Several possibilities can explain at least part of the persistent osmolal gap in this setting:

- The release from the cells of smaller products of glycogen breakdown (other than lactate) into the circulation
- The accumulation of acetone in ketoacidosis

The net effect of these observations is that an elevated osmolal gap alone is not diagnostic of a particular disorder in the patient with a high anion gap metabolic acidosis. If, however, the history is not suggestive of either lactic acidosis or ketoacidosis, then a high osmolal gap (particularly if $\geq$ 25 mosmol/kg) strongly points toward methanol or ethylene glycol intoxication.[121] In this setting, prophylactic ethanol infusion can be initiated to prevent the formation of toxic metabolites, pending results of the assays for these toxins (see below).

An osmolal gap can also be found in a number of other conditions that are *not associated with metabolic acidosis*, including ethanol or isopropyl alcohol ingestions or after the administration of intravenous glycine (during transurethral resection of the bladder or prostate; see page 713) or mannitol.[170]

Treatment Prompt treatment is required to prevent death or permanent residue such as blindness after a methanol overdose. In addition to correcting the acidemia with $NaHCO_3$ and administering oral charcoal to minimize further drug absorption,[174] there are two basic aspects of therapy in the presence of severe poisoning: (1) administration of ethanol or fomepizole to prevent the formation of toxic metabolites and (2) hemodialysis to remove both the parent compound and metabolites.[175-177]

Intravenous or oral ethanol is an effective therapy because alcohol dehydrogenase, the enzyme that is necessary for the metabolism of methanol and ethylene glycol into their toxic metabolites (Fig. 19-5), has more than a 10-fold greater affinity for ethanol than for other alcohols.[157,176,178] This effect is most prominent when the plasma ethanol concentration is about 100 to 200 mg/dL, a level that can generally be achieved by the following regimen: a loading dose of 0.6 g/kg plus an hourly maintenance dose of 66 mg/kg in nondrinkers, 154 mg/kg in drinkers, and 240 mg/kg once hemodialysis is started.[176,179] If oral ethanol is given, the dose may have to be doubled if charcoal has been administered.[179] Regardless of the mode of administration, the plasma ethanol concentration should be monitored, since adjustments in dosage will be required in some patients.

The effect of ethanol has also been demonstrated in selected patients who become intoxicated with both methanol and ethanol.[180] In this setting, there may be very high plasma methanol levels, but no symptoms and no metabolic acidosis, since formaldehyde and formate production are minimized.

An alternative to ethanol is the administration of fomepizole (Antizol), which rapidly and competitively inhibits alcohol dehydrogenase more potently than

ethanol.[181-183] Small studies or case series have documented dramatic improvements in acidemia and prevention of renal injury when fomepizole is used to treat ethylene glycol intoxication.[184,185] Fomepizole also prolongs the half-life of ethanol; thus, the simultaneous use of both agents is *not* recommended. Fomepizole is usually well tolerated but occasionally produces headache, nausea, bradycardia, dizziness, eosinophilia, or mild, transient elevation in liver enzymes.

Hemodialysis is used to remove both the parent compound and metabolites.[157] Sorbent-based hemodialysis systems should be avoided, since drug clearance may be impaired because of rapid saturation of the cartridges.[186] Drug removal is also much slower with peritoneal dialysis,[177] which should not be used unless hemodialysis is not available.

In general, ethanol is begun at the time of diagnosis and continued until the plasma methanol concentration is below 20 mg/dL.[175] Hemodialysis should also be instituted if the plasma level is greater than 50 mg/dL, more than 30 mL have been ingested, acidemia is present, or visual acuity is decreased.[175]

Ethylene glycol Ethylene glycol is a component of antifreeze and solvents that is metabolized via alcohol dehydrogenase into a variety of toxic metabolites (Fig. 19-5). The most important appear to be glycolic acid and oxalic acid, which are responsible for both the clinical symptoms and the metabolic acidosis.[157,187,188] After ingestion, there are three clinical stages of varying severity.[189,190] During the first 12 h, neurologic symptoms predominate, ranging from drunkenness to coma. This is followed by the onset of cardiopulmonary abnormalities, such as tachypnea and pulmonary edema, and then flank pain and renal failure. The latter is primarily due to glycolate-induced damage to the tubules, although plugging of the tubular lumen by precipitated oxalate crystals may also contribute.[188,191] The lethal dose of ethylene glycol is approximately 100 mL.

The diagnosis, suspected from the history and the possible presence of envelope- and needle-shaped oxalate crystals in the urine,[191] can be confirmed by the demonstration of ethylene glycol in the serum. The standard assay using sodium periodate and Schiff's aldehyde reagent is generally accurate but can give a false-positive result if mannitol has been given to induce a diuresis.[192] The diagnosis may also be suspected indirectly by the presence of an osmolal gap in the plasma, although this is generally less prominent than with methanol, which is a smaller molecule (see "Methanol," above).

Treatment The specific treatment of ethylene glycol intoxication is identical to that for methanol: ethanol or fomepizole and hemodialysis.[157,178,179,182,184,185,189] Other modalities that may be helpful include a forced diuresis to minimize tubular blockade by oxalate crystals and the administration of pyridoxine and thiamine, which respectively promote the conversion of glyoxylate into glycine and α-hydroxy-β-ketoadipate, rather than the more toxic oxalate.[169]

Other toxins A variety of other toxins can rarely lead to metabolic acidosis. Sniffing of *toluene*, a component of paint thinners, model glues, and transmission fluid, can produce a metabolic acidosis, primarily via metabolism to hippuric acid.[32] However, the hippurate anion is both filtered and secreted and is therefore rapidly excreted in the urine. As a result, the patient may present with a minimally elevated or even normal anion gap, incorrectly suggesting the possible presence of renal tubular acidosis.[32] The ingestion of *elemental sulfur*, used as a folk remedy, is associated with the generation of sulfuric acid.[193] The anion gap remains normal in this disorder, since the excess sulfate is rapidly excreted in the urine. Inhalation of chlorine gas leads to the production of hydrochloric acid, producing a normal anion gap acidosis.[199]

Hyperalimentation fluids The administration of hyperalimentation fluids can produce a metabolic acidosis by two mechanisms. First, some of these solutions contain an excess of cationic amino acids, such as arginine and lysine. When these amino acids are utilized, H^+ ions are formed:[195]

$$R-NH_3^+ + O_2 \rightarrow \text{urea} + CO_2 + H_2O + H^+$$

This is in addition to the H^+ ions generated by the sulfur-containing amino acids in the solution. Second, starved patients may become hypophosphatemic when fed, resulting in a fall in phosphate and therefore titratable acid excretion. In this setting, the H^+ load associated with the metabolism of the administered protein is not as efficiently excreted, and metabolic acidosis is more likely to ensue.[196]

Gastrointestinal Loss of Bicarbonate

Diarrhea and fistulas The intestinal fluids below the stomach, including pancreatic and biliary secretions, are relatively alkaline. The net base in these fluids, which may have a total concentration of 50 to 70 meq/L,[197] consists of HCO_3^- as well as organic anions, which, if absorbed, would be metabolized to HCO_3^-.[198] As a result, diarrhea, a villous adenoma, or the removal of pancreatic, biliary, or intestinal secretions (by tube drainage, fistulas, or vomiting if there is intestinal obstruction) can lead to metabolic acidosis,[26,197] particularly if volume depletion or underlying renal disease limits the ability of the kidneys to adapt by increasing NH_4^+ excretion.[45]

The same sequence can occur in occult laxative abuse, which should be considered in any patient with a hyperchloremic metabolic acidosis and/or chronic diarrhea of unknown etiology.[199,200] As many as 15 percent of patients referred to tertiary care centers for evaluation of chronic diarrhea are found to have laxative abuse as the cause of their diarrhea.[201] However, for reasons that are not well understood, many patients with laxative abuse present with metabolic alkalosis rather than acidosis.[197,202]

The increase in stool output in diarrheal states can result from either increased intestinal secretion or decreased absorption of fluids that have been secreted.[203] Secretion, for example, may be increased with cholera, toxigenic *Escherichia coli*, or humoral substances released from tumors, such as vasoactive intestinal peptide.

Ureterosigmoidostomy and other forms of urinary division Implantation of the ureters into the sigmoid colon or, more recently, a short loop of ileum that opens at the abdominal wall (ureteroileostomy) has been used to treat patients with obstructive uropathy due to locally invasive tumor, surgical removal of the bladder for carcinoma, or less often neurologic bladder dysfunction. A hyperchloremic metabolic acidosis is a relatively common complication of ureterosigmoidostomy (occurring in up to 80 percent of cases) and is due to two factors:[197,204-207]

- The colon has an anion exchange pump, with luminal Cl^- being reabsorbed as HCO_3^- is secreted. Thus, when urinary Cl^- enters the colon, it will exchange for HCO_3^-, which will then be lost in the stool.[208]
- The colon can directly absorb NH_4^+, which is derived both from the urine and from urea-splitting bacteria in the colon.[197,204] In the liver, the NH_4^+ is metabolized into NH_3 and H^+. Hyperammonemic encephalopathy can occur in patients with underlying liver disease or a marked ammonia load due to a urinary tract infection with a urea-splitting organism.[209]

Metabolic acidosis is much less likely with a ureteroileostomy, since rapid drainage of urine into an ileostomy bag means that contact time between the urine and the intestine is normally too short for significant changes in urinary composition to occur. However, metabolic acidosis can be seen if contact time is increased because of malfunction of the loop (most often due to stomal stenosis).[204-207] Thus, a loopogram should be performed when an otherwise unexplained metabolic acidosis develops in a patient with a ureteroileostomy. Reabsorption of urinary ammonium appears to be more important to the fall in the plasma bicarbonate concentration in this setting than is secretion of bicarbonate in the ileum.[204,205]

Cholestyramine Cholestyramine chloride is an orally administered resin used in the treatment of hypercholesterolemia. It is nonreabsorbable and can act as an anion-exchange resin, exchanging its Cl^- for endogenous HCO_3^- and producing a metabolic acidosis.[210] This problem is most likely to occur if there is underlying renal disease, which can minimize renal excretion of the excess acid.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) refers to those conditions in which metabolic acidosis results from diminished net tubular H^+ secretion.[211,212] There are three major types of RTA, the characteristics of which are summarized in Table 19-6. Although these disorders are relatively unusual in adults (with the exception of type 4 RTA), they provide interesting examples of the different ways in which the renal regulation of acid-base balance can be impaired.

The acidosis associated with renal failure could also be included in this group. However, NH_4^+ excretion per total GFR in this disorder is equal to that achieved in acidemic patients with normal renal function.[129] Thus, as mentioned above, the major problem in renal failure is too few functioning nephrons, not diminished tubular function. In addition, the ability to maximally acidify the urine (urine pH $\leq$ 5.3) is usually maintained in renal failure, in contrast to type 1 and, in some circumstances, type 2 RTA.[127,130,131]

Table 19-6 Characteristics of different types of renal tubular acidosis[a]

	Type 1 (distal)	Type 2 (proximal)	Type 4
Basic defect	Decreased distal acidification	Diminished proximal HCO_3^- reabsorption	Aldosterone deficiency or resistance
Urine pH during acidemia	> 5.3	Variable: > 5.3 if above reabsorptive threshold; < 5.3 if below	Usually < 5.3
Plasma [HCO_3^-], untreated	May be below 10 meq/L	Usually 14 to 20 meq/L	Usually above 15 meq/L
Fractional excretion of HCO_3^- at normal plasma [HCO_3^-]	< 3% in adults, may reach 5%–10% in young children	> 15%–20%	< 3%
Diagnosis	Response to $NaHCO_3$ or NH_4Cl	Response to $NaHCO_3$	Measure plasma aldosterone concentration
Plasma [K^+]	Usually reduced or normal; elevated with voltage defect	Normal or reduced	Elevated
Dose of HCO_3^- to normalize plasma [HCO_3^-], meq/kg per day	1–2 in adults, 4–14 in children	10–15	1–3; may require no alkali if hyperkalemia corrected
Nonelectrolyte complications	Nephrocalcinosis and renal stones	Rickets or osteomalacia	None

[a] What had been called type 3 RTA is actually a variant of type 1 RTA (see below).

Type 1 (distal) RTA Type 1 RTA is characterized by a decrease in net H^+ secretion in the collecting tubules such that the urine pH, which can normally be lowered to a minimum of 4.5 to 5.0 in these segments, remains above 5.3. This defect in acidification diminishes NH_4^+ and titratable acid excretion, thereby preventing complete excretion of the dietary acid load. As a result, there is continued H^+ retention, leading to a progressive reduction in the plasma HCO_3^- concentration, which may fall below 10 meq/L.

Pathogenesis Acidification in the collecting tubules is primarily achieved via H^+ secretion by a luminal H^+-ATPase pump (see Fig. 5-3). This pump is located both

in the cortex (where it is present only in the *intercalated* cells) and in the medulla.[213,214] Although the H^+ secretory cells in the distal nephron do not transport Na^+,[213,215] net H^+ secretion in the cortical collecting tubule is indirectly influenced by Na^+ reabsorption in the adjacent *principal* cells (see Fig. 5-2). The removal of cationic Na^+ from the tubular fluid makes the lumen more electronegative, thereby promoting the accumulation of H^+ ions in the lumen by minimizing the degree of passive back-diffusion.[213,216,217] In comparison, H^+ secretion in the medulla largely occurs in the absence of Na^+ reabsorption by adjacent cells and therefore is essentially *Na^+-independent*.[213,218]

This brief review of distal acidification suggests that there are three mechanisms by which type 1 RTA can occur.[211,212,217]

- The most common problem is thought to be a defect in the H^+-ATPase pump, which may be present in the cortex and/or the medulla. It is likely that a number of different defects can directly or indirectly cause this problem: Three patients with Sjögren's syndrome have been described in whom immunocytochemical analysis of tissue obtained by renal biopsy showed complete absence of H^+-ATPase pumps in the intercalated cells.[219,220] How immunologic injury leads to this change is not known.

  There are also genetic forms of type 1 RTA. In patients with autosomal dominant disease, mutations in the gene for the chloride-bicarbonate exchanger (AE1 or band 3) have often been described.[221-223] This exchanger is responsible for returning bicarbonate generated within the cell during hydrogen secretion to the systemic circulation. Mutations have also been described in the gene encoding the B subunit of the H^+-ATPase pump; this disorder is associated with sensorineural deafness, suggesting that the pump is also required for normal function of the inner ear.[224]
- There can be a reduction in cortical Na^+ reabsorption, thereby diminishing the degree of luminal negativity and producing a *voltage-dependent defect*. This abnormality will lead to a concurrent impairment in K^+ secretion, which is also driven in part by the favorable electrical gradient (see Chap. 12).[225] Thus, hyperkalemia will accompany the metabolic acidosis; this problem has most often been described in patients with urinary tract obstruction and sickle cell disease.[217,226-228] In the former disorder, for example, a reduction in Na^+-K^+-ATPase activity may be responsible for the reduction in Na^+ reabsorption; there may also be a concomitant decrease in H^+-ATPase activity in the outer medulla, further decreasing the ability to secrete hydrogen ions.[229] Impaired distal hydrogen and potassium secretion may also occur with any cause of marked volume depletion, where the diminished distal delivery of Na^+ can induce a readily reversible form of type 1 RTA.[44,230]

  An alternative mechanism may explain the development of hyperkalemic type 1 RTA in some cases.[231] These patients may have two different defects: (1) an impairment in the H^+-ATPase pump, which is responsible for the RTA, and (2) hypoaldosteronism or aldosterone resistance induced by tubular injury, which is responsible for the hyperkalemia.
- There can be an increase in membrane permeability, which allows the back-diffusion of H^+ ions (or possibly H_2CO_3). A urine pH of 5.0, for example, is associated with a H^+ concentration that is *250 times greater* than that in the extracellular fluid. This gradient can be maintained only if the luminal membrane and tight junction are relatively impermeable to H^+. A *gradient defect* has been documented only in patients treated with amphotericin B, which is a potent tubular toxin.[211,232]

The possible site and mechanism of the acidification defect in type 1 RTA have been partially elucidated by the responses to furosemide and Na_2SO_4.[217] Both agents enhance luminal electronegativity by increasing Na^+ delivery to and reabsorption in the cortical collecting tubule; in addition, the presence of the impermeant anion SO_4^{2-} will tend to make the lumen more electronegative, since the gradient created by Na^+ transport cannot be dissipated by SO_4^{2-} reabsorption.

The changes that these agents induce in H^+ and K^+ excretion in normal subjects and those with type 1 RTA are shown in Table 19-7.[217,228]

- Normal subjects with metabolic acidosis will have an acid urine pH (< 5.3) that can be further lowered with furosemide or Na_2SO_4; the increase in electronegativity will also enhance K^+ excretion in this setting.
- Patients with diffuse impairment in the H^+-ATPase pump (due to decreased function or number) will have a persistently alkaline urine pH but a normal rise in K^+ excretion, since principal cell function is intact. A similar result will be seen if the pump dysfunction is limited to the cortical collecting tubule.

Table 19-7 Response to furosemide in normals and different types of type 1 renal tubular acidosis[a]

Type of defect	Site	Urine		K^+ excretion	
		Acidosis	Furosemide	Baseline	Furosemide
Normal		< 5.3	Further decline	Normal	Increased
H^+-ATPase pump	Diffuse or CCT alone	> 5.5	> 5.5	Normal	Increased
H^+-ATPase pump	MCT	> 5.5	< 5.5	Normal	Increased
Voltage or Na^+ reabsorptive	CCT	> 5.5	> 5.5	Decreased	No response

[a] Similar responses will occur to Na_2SO_4. CCT equals cortical collecting tubule; MCT equals medullary collecting tubule.

- Patients with a pump defect that is *limited to the medulla* will have a relatively normal increase in both H^+ and K^+ excretion because cortical function is appropriately stimulated by the rise in luminal electronegativity.
- Patients with a primary impairment in cortical Na^+ reabsorption (a *voltage defect*) will have baseline hyperkalemia and no posttherapy increase in H^+ or K^+ excretion, since there is no enhancement in luminal electronegativity.[228,233] It is not possible to exclude the possibility that there is also a defect in pump function in this setting.

Although proximal HCO_3^- reabsorption is intact in this disorder, variable degrees of *fixed* bicarbonaturia are obligated by the high urine pH. If, for example, the urine P_{CO_2} is 46 mmHg (similar to that in venous blood), then, from the Henderson-Hasselbalch equation, the urinary HCO_3^- concentration will vary with the urine pH*:

$$\text{Urine pH} = pK_a' + \log \frac{[HCO_3^-]}{0.03P_{CO_2}} \qquad (19\text{-}17)$$

At a urine pH below 6.0, the urinary HCO_3^- concentration is negligible. In adults with type 1 RTA, the urine pH is usually less than 6.5, resulting in a relatively mild degree of urinary HCO_3^- loss with less than 3 percent of the filtered HCO_3^- being excreted (Fig. 19-6). The latter can be calculated from a formula similar to that for the fractional excretion of Na^+ (see page 407), using a random urine specimen collected under oil to minimize the evaporative loss of CO_2:

$$FE_{HCO_3^-}(\%) = \frac{\text{urine } [HCO_3^-] \times \text{plasma [creatinine]}}{\text{plasma } [HCO_3^-] \times \text{urine [creatinine]}} \times 100 \qquad (19\text{-}18)$$

In children, however, the minimum urine pH is generally higher and fixed HCO_3^- losses, which can be calculated from Eq. (19-17), are greater. When the urine pH exceeds 7.0, for example, the fractional excretion of HCO_3^- can reach 5 to 10 percent, thereby making an important contribution to the acidemia. This syndrome, which has been called *type 3 RTA*, occurs in infants, who within a few years have a lower urine pH and follow a course more typical of type 1 RTA.[235]

Plasma K^+ concentration The different types of acidification defects produce different changes in K^+ balance. Those patients who have an impairment in the H^+-ATPase pump or increased permeability to H^+ back-diffusion tend to have *urinary K^+ wasting and hypokalemia prior to therapy*.[236,237] Three factors may contribute to this problem:

- Single net distal H^+ secretion is diminished, more Na^+ reabsorption must now occur in exchange for K^+.

* The urine pK_a' varies with total electrolyte concentration and may be somewhat different from the plasma value of 6.10.[234]

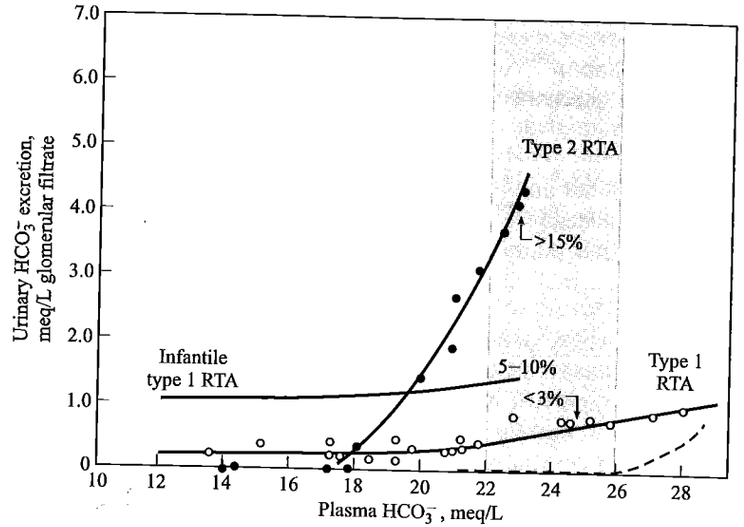

Figure 19-6 The relationship between urinary HCO_3^- excretion and the plasma HCO_3^- concentration in normal subjects (dashed line) and in patients with type 1 and type 2 RTA as $NaHCO_3$ is administered to raise the plasma HCO_3^- concentration toward normal. In the last condition, there is little urinary HCO_3^- and an acid urine pH when the plasma HCO_3^- concentration is below the maximal reabsorptive capacity. Above this level, however, there is a rapid increase in HCO_3^- excretion such that more than 10 to 15 percent of the filtered HCO_3^- is excreted at a normal plasma HCO_3^- concentration (shaded area). Patients with type 1 RTA, on the other hand, are similar to normal subjects except that there is a fixed degree of bicarbonaturia obligated by the high urine pH. In adults, this is generally less than 3 percent of the filtered load, but it can reach 5 to 10 percent in infantile type 1 RTA, in which there is a higher minimal urine pH. (*Adapted from Sebastian A, McSherry E, Morris RC Jr, in Brenner BM, Rector FC Jr (eds):* The Kidney. *Philadelphia, Saunders, 1976, chap 16, with permission.*)

- There may be a concurrent decrease in the activity of the second proton pump in the luminal membrane of the cortical and outer medullary collecting tubules, the H^+-K^+-ATPase pump that reabsorbs K^+ as well as secreting H^+ (see Chap. 11).[214,238] The main function of this pump may be to reabsorb K^+ in states of K^+ depletion, rather than to maintain acid-base balance. As a result, its inhibition may promote urinary K^+ wasting and hypokalemia as well as metabolic acidosis.[239]
- Metabolic acidosis leads to increased NaCl and water delivery out of the proximal tubule; the ensuing Na^+-wasting results in secondary hyperaldosteronism and increased K^+ losses. The latter defect in proximal function is a probable reflection of the low plasma HCO_3^- concentration and therefore the less quantity of HCO_3^- reabsorption by Na^+-H^+ exchange in the proximal tubule. The Na^+-H^+ exchanger plays an important role in proximal NaCl reabsorption, both by creating a gradient for passive Cl^- transport and by promoting active Cl^- transport by operating in parallel with a Cl^- formate$^-$ exchanger (see page 79).

Thus, any cause of metabolic acidosis will tend to diminish net proximal fluid reabsorption.[240] Acidemia can also directly impair Cl^- transport (via an unknown mechanism) in the cortical aspect of the thick ascending limb.[241]

These abnormalities and most of the urinary K^+ wasting can be reversed by correction of the acidemia.[236,237] Some defect may persist, however, in those patients with impaired pump activity, since there will still be a requirement to secrete more than normal amounts of K^+ in exchange for Na^+ in the cortical collecting tubule.[236,242]

In comparison, those patients with a voltage defect due to diminished distal Na^+ transport will have a lesser degree of luminal electronegativity and therefore will excrete less H^+ and K^+, resulting in *hyperkalemia* as well as metabolic acidosis.[211,217,226-228,243] These patients appear to have normal amounts of H^+-ATPase in the intercalated cells.[243] Although hyperkalemic acidosis is also found in type 4 RTA, this disorder is associated with low aldosterone levels and usually intact ability to reduce the urine pH below 5.3.[44,226]

Nephrocalcinosis Hypercalciuria, hyperphosphaturia, nephrolithiasis (with calcium phosphate or struvite stones), and nephrocalcinosis are frequently associated with untreated type 1 RTA.[244-248] In some families, hypercalciuria precedes the metabolic acidosis, suggesting that calcium-induced tubular damage is then responsible for the RTA.[244,245] In most cases, however, acidemia is directly responsible, both by increasing calcium phosphate release from bone during buffering of the excess H^+[135,249,250] and by directly reducing (via an uncertain mechanism) the tubular reabsorption of these ions.[251-253] The degree of hypercalciuria is generally proportional to the fall in the plasma HCO_3^- concentration.[254]

In addition to hypercalciuria and hyperphosphaturia, two other factors increase the tendency to stone formation in type 1 RTA: the persistently high urine pH, which promotes the precipitation of calcium phosphate, and low levels of citrate excretion. Citrate normally inhibits crystallization by forming a nondissociable but soluble complex with calcium, thereby decreasing the amount of free calcium available for stone formation[245-248,255] Both metabolic acidosis and hypokalemia may contribute to the hypocitraturia by lowering the tubular cell pH in the proximal tubule, the former directly and the latter by transcellular K^+/H^+ exchange (see page 356).[256,257] Intracellular acidosis promotes citrate utilization, leading sequentially to low citrate levels in the cell, a more favorable gradient for citrate reabsorption from the tubular lumen, and a decline in citrate excretion.[256] The acidemia-induced fall in luminal pH in the proximal tubule also may contribute to this response by converting filtered $citrate^{3-}$ into the more reabsorbable $citrate^{2-}$.[258]

Stone disease is less common in incomplete type 1 RTA.[248,260] In this setting, low urinary citrate levels may be of primary importance (see below).

All of the above changes in complete type 1 RTA typically respond to early and complete correction of the acidemia: less calcium phosphate release from bone, enhanced tubular reabsorption of these ions, an increase in urinary citrate excretion (although not necessarily to normal,[246,248,255] and prevention of nephrocalcinosis and nephrolithiasis,[246-248,261] even in the incomplete form.[248]

In general, *potassium citrate* (citrate is rapidly metabolized in HCO_3^-) is the preferred therapy.[248] It is better tolerated than HCO_3^- solutions, correction of hypokalemia will further increase citrate excretion, and the natriuresis associated with *sodium* citrate leads to an undesirable increase in calcium excretion, since Na^+ and calcium handling are indirectly linked in the proximal tubule and loop of Henle (see Chap. 3).[262,263]

In contrast, alkali therapy alone is less likely to prevent nephrocalcinosis in those patients with hereditary RTA in whom hypercalciuria is the primary defect.[244,245] In this setting, conventional therapy for calcium stones, such as a thiazide diuretic to diminish calcium excretion and neutral phosphate to increase the excretion of the crystallization inhibitor pyrophosphate, may be effective.[264-266]

Incomplete type 1 RTA Some patients with defective urinary acidification do not become acidemic, a syndrome that is referred to as *incomplete* type 1 RTA.[131,267,268] Patients with the incomplete form have a normal rate of ammonium excretion despite a high urine pH. Why this occurs is not clear, but the observation that they also have a low rate of citrate excretion (similar to the complete form) suggests that there may be a primarily abnormality in the proximal tubule, such as an intracellular acidosis.[268] This will promote proximal ammonium and H^+ secretion; by the mechanisms described above, both the intracellular and intraluminal acidosis can then enhance net citrate reabsorption.

The proposed increase in proximal ammonia production in combination with hypocitraturia can then explain the other findings in incomplete type 1 RTA:[268]

- The increase in ammonia production will drive the reaction, $NH_3 + H_4^+ \leftrightarrow NH_4^+$, to the right, thereby lowering the free hydrogen concentration and raising the urine pH, even though total ammonium excretion is normal.
- The combination of a high urine pH and low citrate excretion can promote the precipitation of calcium phosphate in the tubules and the interstitium, possibly leading to kidney stones or nephrocalcinosis.
- The direct toxic effect of NH_3 (which is freely diffusible and can accumulate in the medulla) and perhaps calcium phosphate precipitation may explain the occasional progression of incomplete to complete type 1 RTA with metabolic acidosis. According to this hypothesis, the impairment in collecting tubule function is a secondary process induced by the primary abnormality in the proximal tubule.

Etiology Many different conditions have been associated with type 1 RTA (Table 19-8).[212] The most common identifiable causes in adults are autoimmune disorders, such as Sjögren's syndrome and rheumatoid arthritis, hypercalciuria which is the primary defect in some families), toluene sniffing in

Table 19-8 Major causes of type 1 renal tubular acidosis

Primary
A. Idiopathic or sporadic
Hereditary
A. Familial, including hypercalciuria as the primary abnormality
B. Marfan's syndrome
C. Wilson's disease
D. Ehlers-Danlos syndrome
Disorders of calcium metabolism and nephrocalcinosis
A. Idiopathic or familial hypercalciuria
B. Primary hyperparathyroidism
C. Hypervitaminosis D
D. Medullary sponge kidney
Autoimmune diseases
A. Sjögren's syndrome
B. Rheumatoid arthritis
C. Systemic lupus erythematosus
D. Chronic active hepatitis
E. Primary biliary cirrhosis
F. Hypergammaglobulinemia in cirrhosis
G. Thyroiditis
Drugs and toxins
A. Amphotericin B
B. Ifosfamide
C. Lithium carbonate
D. Analgesic abuse
E. Light chains in multiple myeloma
F. Toluene
Associated with hyperkalemia
A. Urinary tract obstruction
B. Sickle cell anemia
C. Renal transplant rejection
D. Systemic lupus erythematosus
Marked volume depletion of any cause

recreational drug users (although, as noted above, overproduction of hippuric acid is the probable mechanism in this setting),[32] and marked volume depletion;[219,220,230,244,245,269,270] in comparison, hereditary RTA is most common in children.[261] In selected patients with Sjögren's syndrome, the correct diagnosis is delayed because the renal tubular acidosis can precede the characteristic extrarenal manifestations by 5 years or more.[269,271]

Clinical manifestations Patients with type 1 RTA are often asymptomatic, although they may have complaints related to stone disease, to severe acidemia itself (see "Symptoms," below), or to hypokalemia (weakness, fatigue, polyuria, polydipsia). The situation is potentially more serious in children, in whom failure to thrive (in infants) and decreased linear growth are common and reversible findings.[137,261]

Diagnosis The presence of type 1 RTA should be suspected in any patient with a normal anion gap metabolic acidosis and a urine pH greater than 5.3 in adults[44,131,132] or 5.6 in children.[242] In the absence of a high urine pH due to infection with a urea-splitting organism, the only other conditions that can produce this combination are type 2 RTA, volume depletion,[44,230] and hypokalemia (which increases urinary NH_3 production).[47] Measurement of the urine Na^+ concentration and the urine anion gap should be helpful in evaluating the contribution of the last two conditions: (1) a low urine Na^+ concentration (< 25 meq/L) can raise the urine pH by limiting distal Na^+ delivery and reabsorption,[44,230] and (2) the urine anion gap should be appropriately negative with hypokalemia alone, since there is no defect in NH_4^+ excretion in this setting.[44,272]

Types 1 and 2 RTA can be differentiated by the response to raising the plasma HCO_3^- concentration with $NaHCO_3$ (infused at a rate of 0.5 to 1.0 meq/kg/h). The urine pH and fractional excretion of HCO_3^- will remain constant in type 1 disease but will rise markedly in type 2 RTA, since the reabsorptive threshold for HCO_3^- is excreted in this setting (Fig. 19-6).

A different approach is required in patients with incomplete type 1 RTA, in whom the plasma HCO_3^- is normal. This disorder is usually suspected because the urine pH is persistently above 5.5 in a patient with a positive family history of RTA or calcium stone disease.[131,248,260,267] The diagnosis can be established by giving an acid load as NH_4Cl in a dose of 0.1 g/kg.[131,267] This should induce a 4- to 5-meq/L fall in the plasma HCO_3^- concentration within 4 to 6 h. The urine pH will remain above 5.3 in type 1 RTA but will be less than this value and usually below 5.0 in normal subjects, in whom acidemia stimulates maximal urinary acidification.

Treatment Correction of the acidosis is generally indicated in type 1 RTA to allow normal growth to occur in children;[137,273] to minimize stone formation, nephrocalcinosis, and possible osteopenia due to calcium loss from bone;[246-248,254] and to diminish inappropriate urinary K^+ losses.[236,237] The alkali requirement in this setting is variable, being equal to the fraction of the dietary H^+ load that is not excreted *plus* the fixed HCO_3^- losses obligated by the high urine pH (Fig. 19-6). In adults, the latter are relatively small, and only 1 to 2 meq/kg per day of alkali is usually necessary. In children, however, the urine pH and HCO_3^- losses are higher, and as much as 4 to 14 meq/kg per day in divided doses may be required.[137]

Many patients can be treated only with $NaHCO_3$ or sodium citrate* (Bicitra), since K^+ wasting is markedly diminished when the acidemia is corrected.[236,237]

* As described earlier, citrate should be avoided in patients who have developed renal failure, since it increases intestinal permeability and can lead to excessive aluminum absorption and tissue accumulation.[150] This is most likely to occur in patients with renal failure who are taking aluminum-containing antacids to control hyperphosphatemia (see page 206).

However, potassium citrate, alone or with sodium citrate (Polycitra), is indicated for hypokalemia or for calcium stone disease or nephrocalcinosis.[248,262,263]

Type 2 (proximal) RTA A different problem is present in type 2 RTA: decreased proximal HCO_3^- reabsorption (Table 19-6).[212,261] Normal subjects who are euvolemic reabsorb essentially all the filtered HCO_3^- until the HCO_3^- concentration in the plasma and, therefore, in the glomerular filtrate exceeds 26 to 28 meq/L (see Chap. 3). Above this level, the excess HCO_3^- is appropriately excreted in the urine. Approximately 90 percent of this HCO_3^- reabsorption occurs in the proximal tubule.

In type 2 RTA, proximal HCO_3^- reabsorption is reduced, as is total HCO_3^- reabsorptive capacity. If, for example, only 17 meq/L of glomerular filtrate can be reabsorbed, then HCO_3^- will be lost in the urine until the plasma HCO_3^- concentration reaches 17 meq/L. At this point, all the filtered HCO_3^- can again be reclaimed and a new steady state is achieved. Thus, type 2 RTA is a *self-limiting disorder* in which the plasma HCO_3^- concentration is usually between 14 and 20 meq/L.[261]

The absence of more severe acidemia in this condition is a probable reflection of the *intact reabsorptive capacity of the distal nephron*, particularly the outer medullary collecting tubule.[218] In experimental animals, for example, the administration of a carbonic anhydrase inhibitor can block up to 80 percent of proximal HCO_3^- reabsorption, but only 30 percent of the filtered HCO_3^- appears in the urine as a result of enhanced distal reabsorption.[274] A similar effect probably occurs in humans, as the *total absence* of proximal reabsorption lowers the plasma HCO_3^- concentration to only 11 to 12 meq/L.[275]

The clinical difference between types 1 and 2 RTA can be appreciated by examining the relationship between urinary HCO_3^- excretion and the plasma HCO_3^- concentration (Fig. 19-6). In normal subjects, HCO_3^- does not significantly appear in the urine until the plasma HCO_3^- concentration exceeds 26 meq/L. This relationship is shifted to a lower level in type 2 RTA. If maximal reabsorptive capacity is 17 meq/L, then administering alkali to raise the plasma HCO_3^- concentration above this level will lead to the excretion of increasing amounts of HCO_3^-. By the time the plasma HCO_3^- concentration reaches the normal range, more than 15 percent of the filtered HCO_3^- will appear in the urine, and the urine pH will exceed 7.5. In contrast, the urine can be made maximally acid (pH < 5.3) if the plasma HCO_3^- concentration is below 17 meq/L, since all the filtered HCO_3^- can now be absorbed and distal acidification is normal.

In comparison, the curve relating urinary HCO_3^- excretion and the plasma HCO_3^- concentration in type 1 RTA is similar to that in normal subjects except that the elevated urine pH obligates a fixed degree of bicarbonaturia. However, the distal defect prevents the excretion of all of the dietary acid load, and progressive and severe acidemia can occur.

The defect in HCO_3^- reabsorption in type 2 RTA may occur alone or as part of the Fanconi syndrome, in which a variety of other proximal functions are impaired, including the reabsorption of phosphate, glucose, amino acids, and urate.[265,266] In this setting, metabolic acidosis may be accompanied by hypophosphatemia, hypouricemia, aminoaciduria, and/or glucosuria at a normal plasma glucose concentration.

Pathogenesis The factors responsible for the defects in proximal transport in type 2 RTA are incompletely understood.[276] As described in Chap. 11, three factors are of primary importance in proximal HCO_3^- reabsorption: (1) the Na^+-H^+ exchanger in the luminal membrane, (2) the Na^+-K^+-ATPase pump in the basolateral membrane that provides the energy of Na^+-H^+ exchange by maintaining a low cell Na^+ concentration and therefore a favorable gradient for passive Na^+ entry into the cell, and (3) the enzyme carbonic anhydrase, which is located both in the cells, where it results in the generation of H^+ and HCO_3^-, and in the lumen, where it facilitates HCO_3^- reabsorption by catalyzing the dehydration of the H_2CO_3 that is formed by the combination of filtered HCO_3^- with secreted H^+.

It is likely that one or more of these factors must be impaired to account for the HCO_3^- reabsorptive defect in type 2 RTA.[276] As examples, defective carbonic anhydrase activity and, in cystinosis, ATP depletion have been described in selected patients.[277-279] In addition, the administration of a carbonic anhydrase inhibitor, such as acetazolamide in glaucoma or a topical sulfonamide antibiotic in extensive burns, often results in a mild metabolic acidosis.[280,281]

Proximal tubular dysfunction can also be seen in multiple myeloma, which may be the most common cause of type 2 RTA in adults.[282,283] It is likely that toxic light chains are reabsorbed by and then accumulate in the proximal tubular cells, leading via an uncertain mechanism to impaired tubular function.[284]

Another cause of type 2 RTA is the anticancer drug ifosfamide;[285,286] it is unclear whether the tubular toxicity is mediated by the parent drug or by the metabolite chloracetaldehyde.[287] In addition to HCO_3^- loss, other findings that may occur include phosphate wasting and hypophosphatemia (possibly leading to rickets in children), renal glucosuria, and aminoaciduria. Signs of distal damage also may be seen, including type 1 RTA and polyuria due to nephrogenic diabetes insipidus.[285]

K^+ balance Urinary K^+ wasting and hypokalemia are common in type 2 RTA, although the degree to which this occurs is variable.[236,288] Prior to treatment, the patient is in a steady state in which virtually all of the filtered HCO_3^- can be reabsorbed. In this setting, however, there is often persistent hyperaldosteronism and mild hypokalemia.[288] As described above, these changes are probably related to the decrease in proximal transport of HCO_3^-, which leads to diminished active and passive proximal NaCl reabsorption and a tendency to Na^+ wasting.[240] An additional problem is added with alkali therapy, as the elevation in the filtered HCO_3^- concentration above the reabsorptive threshold results in a marked increase in HCO_3^- and water delivery to the cortical collecting tubule (Fig. 19-6). This elevation in distal flow with the relatively nonreabsorbable anion HCO_3^- plus persistent hyperaldosteronism combine to further enhance urinary K^+ losses (Fig. 19-7).[288]

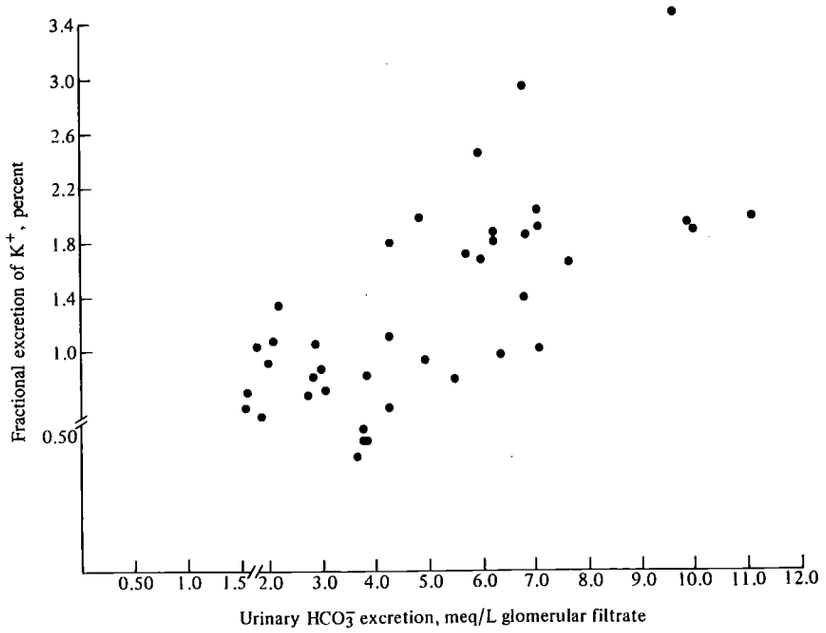

Figure 19-7 Relationship between the fractional excretion of filtered K^+ and urinary HCO_3^- excretion in patients with type 2 RTA in whom the plasma HCO_3^- concentration is maintained at normal levels (22 to 26 meq/L). (*Adapted from Sebastian A, McSherry E, Morris RC Jr,* J Clin Invest *50:231, 1971, by copyright permission of The American Society for Clinical Investigation.*)

Bone disease Rickets in children and osteomalacia or osteopenia in adults are relatively common in type 2 RTA, occurring in up to 20 percent of cases.[247] Although these skeletal abnormalities may also be present in other acidemic states, their frequency in type 2 RTA may be due in part to phosphate wasting and subsequent hypophosphatemia and to acquired vitamin D deficiency, since the proximal tubule is a major site of formation of calcitriol, the most active form of vitamin D (see Chap. 6). In addition, acidemia can directly impair growth in children.[261,273]

Nephrocalcinosis and nephrolithiasis do not occur in this disorder, in contrast to their frequency in type 1 RTA.[247] Two factors may combine to protect against this complication: the ability to lower the urine pH, which increases the solubility of calcium phosphate, and the presence of nonreabsorbed amino acids and organic anions (including citrate), which can form soluble complexes with calcium, thereby limiting the amount of free calcium available to precipitate with phosphate or oxalate.[247]

Etiology A variety of congenital and acquired disorders can cause type 2 RTA (Table 19-9). Idiopathic RTA and cystinosis are most common in children;

Table 19-9 Major causes of type 2 renal tubular acidosis

Primary
- A. Idiopathic or sporadic, may be transient in children

Hereditary
- A. Cystinosis
- B. Hereditary fructose intolerance (during fructose administration)
- C. Familial osteopetrosis (where there may be diminished carbonic anhydrase activity)
- D. Tyrosinemia
- E. Glycogen storage disease, type 1
- F. Wilson's disease
- G. Pyruvate carboxylase deficiency
- H. Lowe's syndrome
- I. Galactosemia

Acquired disorders
- A. Multiple myeloma, latent or fully expressed
- B. Hypocalcemia and vitamin D deficiency
- C. Drugs and toxins
  1. Ifosfamide
  2. Acetazolamide or other carbonic anhydrase inhibitor
  3. Streptozotocin
  4. Outdated tetracycline
  5. Lead
  6. Cadmium
  7. Mercury
- D. Amyloidosis
- E. Renal transplant rejection
- F. Sjögren's syndrome

carbonic anhydrase inhibitors and multiple myeloma (which may be latent) are most often responsible in adults.[238,282]

Diagnosis The presence of type 2 RTA should be suspected in any patient with an unexplained normal anion gap metabolic acidosis, even if the urine pH is below 5.3. Other findings suggestive of proximal tubule dysfunction may be very helpful in this setting, including hypophosphatemia, hypouricemia, and renal glucosuria.

The diagnosis of type 2 RTA can be established by raising the plasma HCO_3^- concentration toward normal with an infusion of $NaHCO_3$ (at a rate of 0.5 to 1.0 meq/kg/h). The urine pH, even if initially acid, will increase rapidly once the reabsorptive threshold for HCO_3^- is exceeded. As a result, the urine pH will be greater than 7.5 and the fractional excretion of HCO_3^- greater than 15 to 20 percent as the plasma HCO_3^- concentration approaches normal (Fig. 19-6).

Treatment Correction of the acidemia will allow normal growth to occur in children[261,273] and will promote healing of the bone disease (with phosphate and vitamin D supplementation if hypophosphatemia is also present).[247] The ade-

quately treated patient should be asymptomatic (unless there is a complicating systemic disease) and able to lead a normal life. Furthermore, idiopathic type 2 RTA in children may be transient, disappearing spontaneously after several years.[273]

Reversal of the acidemia is often difficult, however, because the exogenous alkali is rapidly excreted in the urine. As a result, 10 to 15 meq/kg/day of alkali is typically required to stay ahead of urinary excretion. In addition, an empirically determined fraction must be given as the K^+ salt, since the associated bicarbonaturia leads to increased urinary K^+ losses (Fig. 19-7).[288] Serial monitoring is also required in children, since growth can lead to substantial changes in alkali requirement.

Either HCO_3^- or citrate can be used as the source of alkali. In general, the latter is better tolerated and, when given in such high doses, may actually be slightly safer. The buffering of gastric H^+ ions by administered HCO_3^- can lead to the rapid formation of up to several hundred milliliters of CO_2 in the stomach. There are isolated case reports in which patients taking more than 20 meq of $NaHCO_3$ after eating a large meal developed gastric rupture due to the sudden increase in gastric volume.[289]

When large doses of alkali are ineffective or not well tolerated, the addition of a thiazide diuretic may be helpful.[290] The ensuing mild volume depletion will increase the proximal reabsorption of Na^+ and secondarily that of HCO_3^- (see Chap. 3).

Type 4 RTA Type 4 RTA refers to metabolic acidosis resulting from aldosterone deficiency or resistance. Aldosterone normally promotes distal K^+ and H^+ secretion as well as Na^+ reabsorption (see Chap. 6). The effect on H^+ secretion results both from direct stimulation of the H^+-ATPase pump[291] and from increased luminal electronegativity created by Na^+ reabsorption.[216] As a result, hypoaldosteronism impairs these processes, leading to hyperkalemia (which is generally more prominent) and metabolic acidosis (see Chap. 28).

In addition to the direct effect of aldosterone deficiency, hyperkalemia plays an important role in the metabolic acidosis by impairing NH_4^+ production and excretion.[292-294] This effect may result in part from an increase in the tubular fluid K^+ concentration competitively inhibiting the binding of NH_4^+ to the K^+ site on the Na^+-K^+-$2Cl^-$ carrier in the loop of Henle. As a result, there will be sequential reductions in NH_4^+ recycling within the medulla and in NH_3 secretion into the medullary collecting tubule (see page 341).[295] Reversing this process by correcting the hyperkalemia often leads to increased NH_4^+ excretion and correction of the metabolic acidosis.[294]

The metabolic acidosis seen with hypoaldosteronism is generally mild, with the plasma HCO_3^- concentration usually remaining above 15 meq/L. The urine pH in this disorder is generally but not always below 5.3,[44,296] distinguishing this disorder from the hyperkalemic form of type 1 RTA.[233] The low urine pH is also compatible with diminished NH_4^+ production as the primary abnormality, since total acid excretion is reduced because of the lack of available buffers, not impaired acidification.

The clinical characteristics of type 4 RTA are discussed in detail in Chap. 28 because of the general prominence of hyperkalemia in this disorder. Although mineralocorticoid replacement may be effective in treating the hyperkalemia and metabolic acidosis,[296,297] most patients have underlying renal insufficiency, and the associated Na^+ retention can exacerbate edema or hypertension. As a result, the combination of a low K^+ diet and a loop diuretic is often used.[298] The latter, by increasing distal Na^+ delivery, results in greater luminal electronegativity and an increase in K^+ and H^+ secretion.[228]

Massive Rhabdomyolysis

A rare cause of a high anion gap metabolic acidosis is massive rhabdomyolysis.[299] The presumed mechanism is the release of H^+ and organic anions from the damaged cells. This diagnosis should be suspected if there is a marked elevation in the plasma level of creatine kinase (as well as that of other muscle enzymes) and no other apparent cause for the acidemia.

SYMPTOMS

Metabolic acidosis can result in changes in pulmonary cardiovascular, neurologic, and musculoskeletal function. Since the respiratory compensation results in as much as a four- to eightfold increase in minute ventilation (see Fig. 11-16),[11,12] the patient may complain of dyspnea on exertion and, with severe acidemia, even at rest. Furthermore, the observation of hyperpnea (affecting the depth more than the rate of ventilation) on physical examination may be the only clue suggesting the presence of an underlying acidemic state.

A fall in the arterial pH to less than 7.00 to 7.10 can predispose toward potentially fatal ventricular arrhythmias and can reduce both cardiac contractility and the inotropic response to catecholamines.[93,300,301] The last effect may be mediated in part by decreased delivery of calcium to myofilaments and by decreased responsiveness of the myofilaments to calcium; how these changes might occur is not known.[301] This decrease in ventricular function may play an important role in the perpetuation of shock-induced lactic acidosis, and partial correction of the acidemia may be required before tissue perfusion can be restored.[93] As noted above, however, alkali therapy may actually worsen the intracellular acidosis in patients with circulatory failure.[99,100]

Neurologic symptoms ranging from lethargy to coma have been described in metabolic acidosis. These symptoms appear to be more closely related to the fall in pH in the cerebrospinal fluid (CSF) than to that in the plasma.[302] In general, neurologic abnormalities are much less prominent in metabolic acidosis than in respiratory acidosis. This may be due to the ability of lipid-soluble CO_2 to cross the blood-brain barrier much more rapidly than water-soluble HCO_3^-, thereby producing a greater fall in CSF pH.[303,304] When neurologic symptoms do occur in metabolic acidosis, a concurrent problem is more likely to be responsible, such

as the toxic effects of ingestions, diminished cerebral perfusion in shock, and hyperosmolality due to hyperglycemia in diabetic ketoacidosis.[305]

Chronic acidemia, as with renal failure or renal tubular acidosis, can lead to a variety of skeletal problems that are probably due in part to release of Ca^{2+} and phosphate during bone buffering of the excess H^+ ions.[135,249,250,264,306] Of particular importance is impaired growth in children.[137,271,307] Other abnormalities that may occur include osteitis fibrosa (from secondary hyperparathyroidism), rickets in children, and osteomalacia or osteopenia in adults.[247,308]

Correction of the acidemia may reverse these changes in patients without renal failure.[308] Therapy is generally less successful with advanced renal disease, since other factors also contribute to the bone abnormalities, such as hyperparathyroidism, vitamin D deficiency, and poor nutrition due to anorexia.[307,309,310] (The pathophysiology of renal osteodystrophy is reviewed in Chap. 6.)

In infants and young children, acidemia may also be associated with a variety of nonspecific symptoms, such as anorexia, nausea, weight loss, muscle weakness, and listlessness.[261] The last two symptoms may result in part from loss of lean body mass as a result of alterations in muscle protein metabolism.[141,145,146] These changes are reversible with the restoration of acid-base balance.

TREATMENT

The specific aspects of therapy for individual disorders have been discussed in the appropriate sections above. It is important, however, to review the general principles, particularly the type, quantity, and rate of alkali replacement.

General Principles

In most clinical situations, correction of the acidemia can be achieved by the administration of $NaHCO_3$. There are, however, some exceptions to this recommendation, since no alkali therapy may be required in lactic or ketoacidosis (where metabolism of the organic anions will regenerate HCO_3^-), and sodium and/or potassium citrate may be preferable for chronic treatment in renal tubular acidosis. THAM and sodium lactate have also been used but offer no particular advantage over $NaHCO_3$.[311,312]

The initial therapeutic goal in patients with severe acidemia is to raise the systemic pH to about 7.20, a level at which arrhythmias become less likely and cardiac contractility and responsiveness to catecholamines will be restored. Attainment of this pH usually requires only a small increment in the plasma HCO_3^- concentration. As an example, the following arterial blood values are obtained from a patient with chronic diarrhea:

$$\text{Arterial pH} = 7.10$$

$$P_{CO_2} = 20 \text{ mmHg}$$

$$[HCO_3^-] = 6 \text{ meq/L}$$

The level to which the plasma HCO_3^- concentration must be raised for the pH to reach 7.20 can be calculated from the Henderson-Hasselbalch equation:

$$\text{pH} = 6.10 + \frac{[HCO_3^-]}{0.03P_{CO_2}}$$

If we assume that the P_{CO_2} will remain constant, then

$$7.20 = 6.10 + \frac{[HCO_3^-]}{0.03 \times 20}$$

Since this equation is difficult to solve at the bedside, it is easier to express the relationship between these parameters in nonlogarithmic terms [Eq. (19-2)]:

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

Since the H^+ concentration is 63 nanoeq/L at a pH of 7.20 (see Table 19-1),

$$63 = 24 \times \frac{20}{[HCO_3^-]}$$

$$[HCO_3^-] = 8 \text{ meq/L}$$

This calculation slightly underestimates the initial HCO_3^- requirement, since the drive to compensatory hyperventilation will diminish as the acidemia is corrected, resulting in an elevation in the P_{CO_2}. If we assume that the P_{CO_2} will rise from 20 to 25 mmHg, then

$$63 = 24 \times \frac{25}{[HCO_3^-]}$$

$$[HCO_3^-] = 10 \text{ meq/L}$$

Thus, *only a small increase in the plasma HCO_3^- concentration is necessary to get the patient out of danger if there is a normal respiratory compensation.*

Rapid administration of HCO_3^- is important only in patients with severe metabolic acidosis. In this setting, even a minimal additional reduction in the plasma HCO_3^- concentration can result in a large percentage change and therefore can induce an immediately life-threatening degree of acidemia. For example, lowering the plasma HCO_3^- concentration from 24 to 22 meq/L in a patient with an initial pH of 7.40 and P_{CO_2} of 40 mmHg will have only a minor effect on the pH and H^+ concentration:

$$[H^+] = 24 \times \frac{40}{22}$$

$$= 44 \text{ nanoeq/L} \qquad (\text{pH} = 7.36)$$

However, a similar 2-meq/L reduction in a patient with an initial pH of 7.11, a plasma HCO_3^- concentration of 4 meq/L, and a P_{CO_2} of 13 mmHg will now decrease the pH to 6.81:

$$[H^+] = 24 \times \frac{13}{2}$$

$$= 156 \text{ nanoeq/L} \qquad (pH = 6.81)$$

Regardless of the initial severity, rapid correction of the pH to above 7.20 to 7.25 not only is unnecessary but can induce potentially important reductions in the CSF pH and in tissue oxygen delivery. The administration of $NaHCO_3$ will tend to lower minute ventilation and raise the P_{CO_2}. Since CO_2 crosses the blood-brain barrier much more rapidly than HCO_3^-, the brain will acutely sense only the elevation in the P_{CO_2}. Thus, the CSF pH will become more acid, with possible aggravation of the neurologic symptoms.[302] The increase in the arterial pH will also shift the hemoglobin dissociation curve to the left, increasing the affinity of hemoglobin for oxygen and possibly reducing tissue oxygen delivery.

Bicarbonate Deficit

The amount of HCO_3^- required to correct the acidemia can be estimated from the following formula:

$$HCO_3^- \text{ deficit} = HCO_3^- \text{ space} \times HCO_3^- \text{ deficit per liter} \qquad (19\text{-}19)$$

The apparent bicarbonate space is a reflection of total body buffering capacity. It is therefore determined both by the quantity of extracellular HCO_3^- and by the intracellular (proteins and phosphates) and bone (carbonate) buffers.[3] It has been measured empirically by administering HCO_3^- and then observing the ensuing elevation in the plasma HCO_3^- concentration.[2] If, for example, 100 meq raises the plasma HCO_3^- concentration by 5 meq/L, then the apparent bicarbonate space is 20 L.

At a normal plasma HCO_3^- concentration of 24 meq/L, excess H^+ ions are buffered proportionately through the total body water, and the apparent HCO_3^- space is about 50 percent of lean body weight (Fig. 19-8). However, the HCO_3^- space rises in metabolic acidosis, since the fall in the plasma HCO_3^- concentration means that there is an ever-increasing contribution from the nonbicarbonate buffers. Thus, the bicarbonate space is approximately 60 percent of lean body weight in mild to moderate metabolic acidosis, but can reach 70 percent or more as the plasma HCO_3^- concentration falls below 8 to 10 meq/L (Fig. 19-8).[2,3]

The bicarbonate space can be estimated from:[3]

$$\text{Bicarbonate space} = \left[0.4 + \left(2.6/P_{HCO_3^-}\right)\right] \times \text{lean body weight} \qquad (19\text{-}20)$$

It can exceed total body water or even lean body weight in severe metabolic acidosis, because almost all of the buffering is occurring within the cells and bone, where there is a virtually inexhaustible supply of buffer.

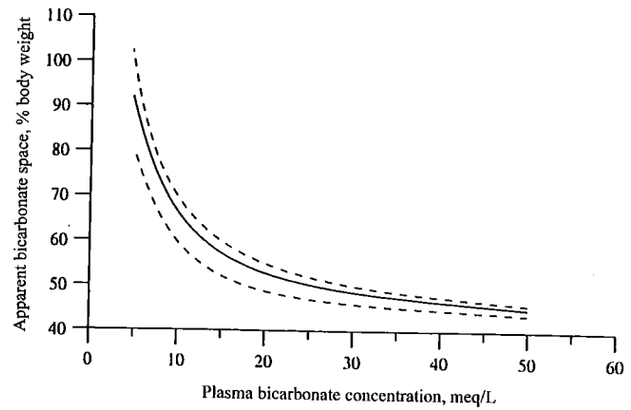

Figure 19-8 Variation in the apparent bicarbonate space according to the plasma bicarbonate concentration. At values below 10 meq/L, most of the buffering is performed by the intracellular and bone buffers, leading to a marked rise in the space of distribution that can exceed 70 percent of lean body weight in severe metabolic acidosis. (*From Fernandez PC, Cohen RM, Feldman GM,* Kidney Int *36:747, 1989. Reprinted by permission from* Kidney International.)

In the above patient with diarrhea, for example, the initial aim of therapy is to raise the plasma HCO_3^- concentration from 6 to 10 meq/L. If this patient weighed 70 kg, then

$$HCO_3^- \text{ deficit} = 0.7 \times 70 \times (10 - 6)$$

$$= 196 \text{ meq}$$

Thus, 196 meq of HCO_3^- can be given intravenously over the first several hours. If this is effective in raising the pH to a safe level, further HCO_3^- may be unnecessary, since increased renal H^+ excretion will slowly regenerate the lost HCO_3^-. Similarly, *exogenous alkali may not be required* if the initial arterial pH is greater than 7.20, the patient is asymptomatic, and the underlying process, such as diarrhea, can be controlled.

Needless to say, these are only rough guidelines and cannot replace serial measurements of the extracellular pH. In particular, the formula assumes a reasonably accurate estimate of lean body weight and assumes that the patient is in a steady state. If, for example, there is continuing acid production, as with severe diarrhea, then the HCO_3^- requirements will increase with time.

The degree to which exogenous HCO_3^- will raise the plasma HCO_3^- concentration and pH is also dependent upon when the measurements are made. As described above, excess H^+ ions are buffered first in the extracellular fluid and then in the cells. A similar sequence occurs when HCO_3^- is given to correct a metabolic acidosis. Acutely, the added HCO_3^- is limited to the vascular space, producing a large increase in the plasma HCO_3^- concentration. However, this change is attenuated as the exogenous HCO_3^- equilibrates through the total extra-

cellular fluid, which occurs within 15 min, and then equilibrates with the intracellular and bone buffers, which occurs in 2 to 4 h.

If, for example, we assume that the extracellular volume is 15 liters and the total HCO_3^- space is 49 liters in the above 70-kg patient with diarrhea, then the rapid infusion of 100 meq of HCO_3^- will produce a 7-meq/L increase in the plasma HCO_3^- concentration at 15 min, but only a 2-meq/L increase at 2 to 4 h. Thus, the extracellular pH will be greater if it is measured at 15 min, before equilibration with the intracellular buffers has occurred. As a result, it should be recognized that measurement of the pH shortly after HCO_3^- has been given may overestimate the final effect of therapy.

Plasma Potassium Concentration

K^+ depletion is common in patients with metabolic acidosis associated with gastrointestinal and/or renal losses of K^+. Despite this, the initial plasma K^+ concentration may be relatively normal, since metabolic acidemia (except for the organic acidoses) causes K^+ to move out of the cells into the extracellular fluid (see page 379).[5,8]

A similar effect frequently occurs in diabetic ketoacidosis, in which the combination of insulin deficiency and hyperglycemia (rather than acidemia) promotes K^+ movement into the extracellular fluid. Thus, patients with this disorder are commonly hyperkalemic at presentation, despite moderate to marked K^+ depletion (see Chap. 25).[9] The administration of insulin will reverse this sequence, redistributing K^+ into the cells and unmasking the true state of K^+ balance. As a result, careful monitoring of the plasma K^+ concentration is essential during the initial phases of therapy.

The potential risks of treatment are more immediate in the acidemic patient who is already hypokalemic at presentation. In this setting, there is a very large K^+ deficit, and the restoration of normal pH (or treatment with insulin in diabetic ketoacidosis) will further reduce the plasma K^+ concentration. Thus, initial therapy should consist of KCl alone (if the acidemia is not severe) or KCl with $NaHCO_3$ with careful monitoring of the pH, the plasma K^+ concentration, muscle strength, and the electrocardiogram. As much as 40 meq/h of KCl may be required to prevent life-threatening hypokalemia in some patients (see Chap. 27).

Metabolic Acidosis and Heart Failure

Sodium bicarbonate therapy is potentially dangerous in patients with left ventricular failure, since it can lead to increasing pulmonary congestion. Fortunately, alkali therapy is usually unnecessary when the underlying disorder is lactic acidosis due to acute pulmonary edema. In this setting, improvement in pulmonary function leads to spontaneous resolution of the acidemia as a result of HCO_3^- generation from the metabolism of lactate.[58]

However, specific therapy may be required in patients with severe acidemia (arterial pH < 7.10 to 7.15), particularly if the patient does not have a self-correcting organic acidosis, such as lactic or ketoacidosis. Acutely, small doses of $NaHCO_3$ (45 to 90 meq) can be cautiously administered. The risk of this regimen is relatively small, since more than one-half of the HCO_3^- will enter the cells to replenish the intracellular buffers.[1,2] Thus, there will be much less volume expansion than with an equivalent quantity of NaCl, which is restricted to the extracellular fluid.

Alternatively, peritoneal dialysis or hemodialysis can be used to correct both the fluid overload and the acidemia. The former is generally preferred in patients with severe heart disease, since it avoids the hemodynamic instability often associated with hemodialysis. The dialysate should preferably contain HCO_3^- as a source of alkali rather than lactate or acetate, which may not be normally metabolized in severe heart failure.[313]

PROBLEMS

19-1 The following laboratory tests are obtained from two patients. Would you administer $NaHCO_3$ to either one?

(*a*) Plasma $[Na^+] = 140$ meq/L
$[K^+] = 4.2$ meq/L
$[Cl^-] = 114$ meq/L
$[HCO_3^-] = 16$ meq/L

(*b*) Plasma $[Na^+] = 140$ meq/L
$[K^+] = 4.7$ meq/L
$[Cl^-] = 122$ meq/L
$[HCO_3^-] = 7$ meq/L
Arterial pH = 7.32
$P_{CO_2} = 14$ mmHg

19-2 A 31-year-old man with a history of epilepsy has a grand mal seizure. Laboratory tests taken immediately after the seizure has stopped reveal

Arterial pH = 7.14
$P_{CO_2} = 45$ mmHg
Plasma $[Na^+] = 140$ meq/L
$[K^+] = 4.0$ meq/L
$[Cl^-] = 98$ meq/L
$[HCO_3^-] = 17$ meq/L

(a) What is the acid-base disturbance?
(b) Does the patient need $NaHCO_3$?
(c) What will happen to his plasma K^+ concentration as the acidemia is corrected?

19-3 If HCO_3^- therapy sufficient to normalize the plasma HCO_3^- concentration is suddenly stopped, match the subsequent course with the type of RTA:

(a) Type 1 RTA in adults (minimum urine pH = 6.5)

(b) Type 1 RTA in infants (minimum urine pH = 7.2)
(c) Type 2 RTA

1. Rapid fall in plasma HCO_3^- concentration, which stabilizes at 16 meq/L
2. Rapid decrease in plasma HCO_3^- concentration, which falls below 10 meq/L
3. Slowly progressive decrease in plasma HCO_3^- concentration to less than 10 meq/L

If the plasma HCO_3^- concentration is raised to 22 meq/L with exogenous $NaHCO_3$, how would you distinguish among these three disorders?

19-4 Match the laboratory findings with the appropriate cause of a normal anion gap metabolic acidosis. The units in the table are meq/L.

	$[Na^+]$	$[K^+]$	$[Cl^-]$	$[HCO_3^-]$	Urine pH	Urine anion gap
1.	140	2.9	115	14	6.4	−45
2.	137	5.3	113	17	5.2	+18
3.	139	3.1	120	11	6.1	+23

(a) Hypoaldosteronism (type 4 RTA)
(b) Diarrhea due to laxative abuse
(c) Type 1 RTA

19-5 A 58-year-old man with a history of chronic bronchitis develops severe diarrhea caused by pseudomembranous colitis. It is noted that the volume of diarrheal fluid is approximately 1 L/h. Results of the initial laboratory tests are

$$\text{Plasma } [Na^+] = 138 \text{ meq/L}$$
$$[K^+] = 3.8 \text{ meq/L}$$
$$[Cl^-] = 115 \text{ meq/L}$$
$$[HCO_3^-] = 9 \text{ meq/L}$$
$$\text{Arterial pH} = 6.97$$
$$P_{CO_2} = 40 \text{ mmHg}$$

(a) What is the acid-base disorder?
(b) Assuming that the P_{CO_2} remains at 40 mmHg, to what level does the plasma HCO_3^- concentration have to be raised to increase the pH to 7.20?
(c) How much HCO_3^- would be required to raise the plasma HCO_3^- concentration to the desired level, assuming that the patient has a lean body weight of 80 kg?
(d) After the administration of this amount of HCO_3^- over 4 h, the plasma HCO_3^- concentration is still 9 meq/L. What is responsible for this inability to correct the acidemia?
(e) What would you estimate the total body K^+ stores in this patient to be?

19-6 A 50-year-old woman has severe chronic renal failure. The following laboratory data are obtained:

$$\text{Plasma } [Na^+] = 137 \text{ meq/L}$$
$$[K^+] = 5.4 \text{ meq/L}$$
$$[Cl^-] = 102 \text{ meq/L}$$
$$[HCO_3^-] = 10 \text{ meq/L}$$
$$\text{Arterial pH} = 7.22$$
$$P_{CO_2} = 25 \text{ mmHg}$$

(a) Why does metabolic acidosis develop in renal failure?
Thirty minutes after the administration of 88 meq of HCO_3^-, repeat blood tests reveal the following:

$$\text{Arterial pH} = 7.38$$
$$P_{CO_2} = 28 \text{ mmHg}$$
$$[HCO_3^-] = 16 \text{ meq/L}$$

In view of the improvement in the pH, no further HCO_3^- is given. However, on the next day, blood tests showed:

$$\text{Arterial pH} = 7.28$$
$$P_{CO_2} = 26 \text{ mmHg}$$
$$[HCO_3^-] = 12 \text{ meq/L}$$

(b) What factors might have been responsible for this reduction in the arterial pH?

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