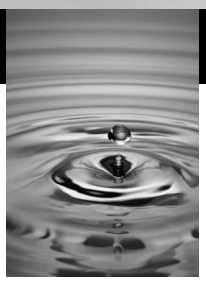
interaction in human plasma by means of in vivo ultrafiltration and equilibrium dialysis, *Acta Med Scand* 422(suppl):1, 1964.
70. van Sluijs FJ, de Vries HW, de Bruijne JJ, et al: Capillary and venous blood compared with arterial blood in the measurement of acid-base and blood gas status of dogs, *Am J Vet Res* 44:459, 1983.
71. van Slyke DD, Hastings AB, Hiller A, et al: Studies of gas and electrolyte equilibria in blood. XIV. The amounts of alkali bound by serum albumin and globulin, *J Biol Chem* 79:769, 1920.
72. Walser M: Roles of urea production, ammonium excretion, and amino acid oxidation in acid-base balance, *Am J Physiol* 250:F181, 1986.
73. Whitehair KJ, Haskins SC, Whitehair JG, et al: Clinical applications of quantitative acid-base chemistry, *J Vet Intern Med* 9:1, 1995.
74. Zweens J, Frankena H, van Kampen EJ, et al: Ionic composition of arterial and mixed venous plasma in the unanesthetized dog, *Am J Physiol* 233:F412, 1977.



CHAPTER • 10

METABOLIC ACID-BASE DISORDERS

Stephen P. DiBartola

Metabolic disturbances of acid-base balance are associated with many disease states, and identification of the acid-base disturbance may facilitate diagnosis of the underlying disease process. For example, observation of hypochloremic metabolic alkalosis on a serum biochemical profile of a vomiting dog may lead to recognition of gastrointestinal obstruction as the cause. The regulation of normal acid-base balance is considered in detail in Chapter 9.

METABOLIC ACIDOSIS

Metabolic acidosis is characterized by a primary decrease in plasma HCO_3^- concentration, increased $[H^+]$, decreased pH, and a secondary, or adaptive, decrease in P_{CO_2}. In one study, metabolic acidosis was the most common acid-base disturbance in dogs and cats.[53]

Metabolic acidosis can be caused by loss of HCO_3^--rich fluid from the body, addition of fixed acid to the body or its production by metabolism within the body, or failure of renal excretion of fixed acid. Loss of HCO_3^--rich fluid usually occurs via the gastrointestinal tract (e.g., small bowel diarrhea) but also may occur via the kidneys (e.g., carbonic anhydrase inhibitors, proximal renal tubular acidosis). The HCO_3^- concentration of diarrheal fluid exceeds that of plasma, whereas its Cl^- concentration is lower. The loss of such fluid results in a hyperchloremic metabolic acidosis. Examples of the addition of fixed acid to the body include toxins (e.g., ethylene glycol, salicylate) and compounds used therapeutically (e.g., ammonium chloride, cationic amino acids). Examples of metabolic production of fixed acid within the body include lactic acidosis and diabetic ketoacidosis. Renal failure, hypoadrenocorticism, and distal renal tubular acidosis are examples of impaired urinary excretion of fixed acid. Small bowel diarrhea, renal failure, hypoadrenocorticism, diabetic ketoacidosis, and lactic acidosis during cardiovascular collapse are the most common causes of metabolic acidosis in small animal practice.

Body Buffer Response to an Acute Acid Load

When HCl was infused acutely into nephrectomized dogs, approximately 40% of the acid was buffered by extracellular HCO_3^-, 10% by red cell buffers (primarily hemoglobin), and 50% by intracellular buffers of soft tissues and bone (primarily proteins and phosphates).[207] In nonnephrectomized unanesthetized dogs infused intermittently with HCl, intracellular buffers contributed approximately 50% of the buffer response, regardless of the magnitude of the H^+ load.[195] Within a few minutes of an acute fixed acid load, administered H^+ is buffered by HCO_3^- in plasma water. Plasma proteins and phosphates play a minor role in this acute response. Some of the administered acid enters red cells and is buffered by hemoglobin. The CO_2 produced by the combination of the H^+ with HCO_3^- ions is rapidly removed from the body by alveolar ventilation. Within 30 minutes, the acid load has been distributed to the interstitial fluid, where HCO_3^- again plays the dominant role in the acute buffer response. After several hours, H^+ enters intracellular water in exchange for sodium and potassium ions. These hydrogen ions are buffered within cells by proteins and phosphates. In early studies,[195,207] serum potassium concentration increased, but serum sodium concentration decreased after infusion of HCl. The relative roles of these buffers are depicted in Fig. 10-1.

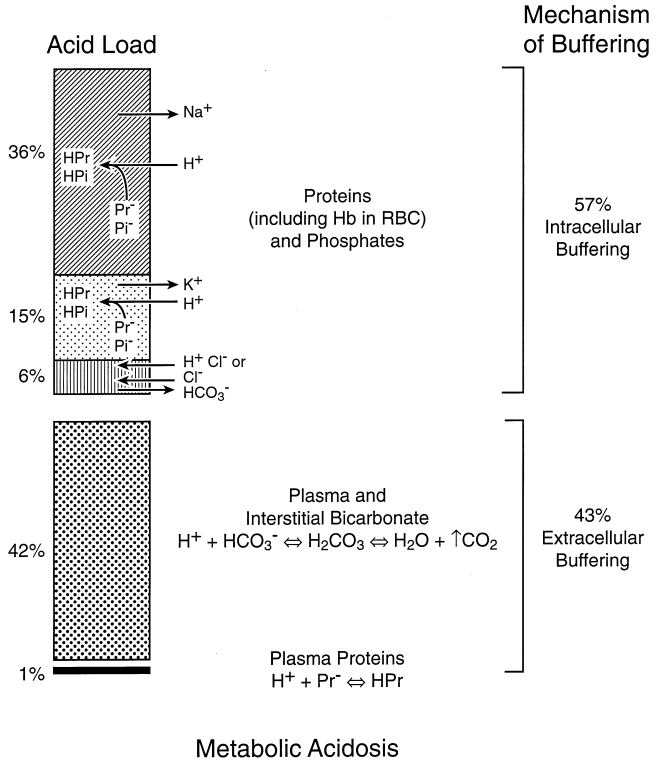


Fig. 10-1 Distribution of buffer response to a fixed acid load. (Drawing by Tim Vojt. Adapted from Pitts RF: *Physiology of the kidney and body fluids*, ed 2, Chicago, 1968, Year Book Medical Publishers, p. 171.)

Respiratory Response to an Acute Acid Load

A fixed acid load increases $[H^+]$ and thereby stimulates peripheral and central chemoreceptors to increase alveolar ventilation. This effect begins within hours and is complete within 12 to 24 hours. In humans, there is an approximately 1.2-mm Hg reduction in P_{CO_2} for each 1-mEq/L decrement in plasma HCO_3^- concentration to a minimum P_{CO_2} of approximately 10 mm Hg.[88,180] In dogs with uncomplicated metabolic acidosis induced by chronic feeding of HCl, the observed compensatory respiratory response is an approximately 0.7-mm Hg decrement in P_{CO_2} per 1-mEq/L decrement in plasma HCO_3^- concentration.* In these studies, the smallest observed respiratory response was an approximately 0.5-mm Hg decrement in P_{CO_2} per mEq/L decrement in plasma HCO_3^- concentration,[2] and the largest response was a 1.1-mm Hg decrement in P_{CO_2} per mEq/L decrement in plasma HCO_3^- concentration.[58] Data are limited on the respiratory response of cats to metabolic acidosis, but there is some evidence that the cat fails to develop respiratory compensation to the same extent as observed in the dog in spontaneous[219] and NH_4Cl-induced metabolic acidosis.[38,75,123,196,197]

The classical explanation of the respiratory response to metabolic acidosis is that the increase in $[H^+]$ (decrease in pH) stimulates ventilation, and the resultant decrease in P_{CO_2} returns the HCO_3^-/P_{CO_2} ratio and pH toward normal. This is true in acute metabolic acidosis, but the resultant secondary hypocapnia has been observed to decrease plasma HCO_3^- concentration further in chronic metabolic acidosis, presumably by reducing renal HCO_3^- reabsorption. This secondary hypocapnia contributes to 40% of the observed decrease in plasma HCO_3^- concentration during chronic HCl acidosis.[133] Thus chronic metabolic acidosis decreases plasma HCO_3^- concentration by two mechanisms: the effect of the administered HCl on body buffers and a reduction in renal HCO_3^- reabsorption that accompanies secondary hyperventilation. In this study, serum potassium concentration decreased during development of chronic HCl acidosis (contrary to what is typically described for acute metabolic acidosis caused by mineral acids), whereas serum sodium concentration was unchanged.[133]

Renal Response to an Acute Acid Load

The role of the kidney is to excrete the fixed acid load imposed by the underlying disease process responsible for metabolic acidosis. The kidney accomplishes this task primarily by augmenting its excretion of NH_4^+. Titratable acidity changes little unless there is a change in the filtered load of phosphate. Chloride ions accompany

**References 2,43,48,58,127,133-135.*

the NH_4^+ into urine while HCO_3^- is regenerated and reabsorbed into extracellular fluid (ECF) to restore HCO_3^- that was titrated during the acute fixed acid load. Within 48 hours of a fixed acid load, approximately 25% of the added acid has been excreted in the urine, and the remainder is excreted during the next 4 days.[215] The kidney can increase its NH_4^+ excretion as much as five- to ten-fold during chronic metabolic acidosis.[203,218,221] There is some evidence that cats do not adapt to metabolic acidosis by enhanced renal ammoniagenesis.[123] The role of the kidney in regulation of acid-base balance is discussed further in Chapter 9.

Clinical Features of Metabolic Acidosis

The clinical signs in small animals with metabolic acidosis are more likely to be caused by the underlying disease responsible for metabolic acidosis than by the acidosis itself. In humans, respiratory compensation for metabolic acidosis leads to characteristic hyperventilation, recognized by a deep, rhythmic breathing pattern (i.e., Kussmaul's respirations). Such a characteristic respiratory pattern has not been described in small animal patients, and metabolic acidosis is usually suspected by observation of a low total CO_2 content on a biochemical profile and confirmed by blood gas analysis.

Severe acidosis has serious detrimental effects on cardiovascular function, including decreased cardiac output, decreased arterial blood pressure, and decreased hepatic and renal blood flow.[3] Myocardial contractility is decreased when blood pH falls below 7.20.[147,166] Impaired contractility may result from a decrease in myocardial intracellular pH (pH_i) and displacement of calcium ions from critical binding sites on contractile proteins. Acidosis may predispose the heart to ventricular arrhythmias or ventricular fibrillation. Acidosis has a direct arterial vasodilating effect that is offset by increased release of endogenous catecholamines. However, the inotropic response to catecholamines is impaired, and this may be associated with a reduction in the number of β-adrenergic receptors.[137] Acidosis has a direct vasoconstrictive effect on the venous side of the circulation, which tends to centralize blood volume and predisposes to pulmonary congestion. Acidosis shifts the oxygen-hemoglobin dissociation curve to the right, thus enhancing O_2 release from hemoglobin, but this effect is offset by a decrease in red cell 2,3-diphosphoglycerate, which develops after 6 to 8 hours of acidosis and shifts the curve back to the left.[147]

Acidemia produces insulin resistance that impairs peripheral uptake of glucose and inhibits anaerobic glycolysis by inhibiting phosphofructokinase.[6] During severe acidosis, the liver may be converted from a consumer to a producer of lactate.[130] Severe acidosis also impairs the ability of the brain to regulate its volume, leading to obtundation and coma. Acute mineral acidosis causes hyperkalemia by a transcellular shifting of potassium from intracellular fluid to ECF in exchange for hydrogen ions. This effect causes a very variable change in serum potassium concentration and is not observed with organic acidosis.[5] Acute reduction in blood pH causes displacement of calcium ions from negatively charged binding sites (e.g., $-COO^-$ groups) on proteins (primarily albumin) as these sites become protonated, and an increase in ionized serum calcium concentration results. Chronic metabolic acidosis leads to release of buffer (mainly calcium carbonate) from bone, and osteodystrophy and hypercalciuria result.

Diagnosis of Metabolic Acidosis

Metabolic acidosis is associated with several different diseases and should be considered in any severely ill patient. Often, the diagnosis is first suspected by review of the electrolyte and total CO_2 results on the patient's biochemical profile. It is confirmed by blood gas analysis. The causes of metabolic acidosis may be divided into those associated with a normal anion gap (hyperchloremic metabolic acidosis) and those associated with an increased anion gap (normochloremic metabolic acidosis) (Box 10-1).

Box 10-1 Causes of Metabolic Acidosis

Increased Anion Gap (Normochloremic)
Ethylene glycol intoxication
Salicylate intoxication
Other rare intoxications (e.g., paraldehyde, methanol)
Diabetic ketoacidosis*
Uremic acidosis†
Lactic acidosis

Normal Anion Gap (Hyperchloremic)
Diarrhea
Renal tubular acidosis
Carbonic anhydrase inhibitors (e.g., acetazolamide)
Ammonium chloride
Cationic amino acids (e.g., lysine, arginine, histidine)
Posthypocapnic metabolic acidosis
Dilutional acidosis (e.g., rapid administration of 0.9% saline)
Hypoadrenocorticism‡

*Patients with diabetic ketoacidosis may have some component of hyperchloremic metabolic acidosis in conjunction with increased anion gap acidosis.[6,8]
†The metabolic acidosis early in renal failure may be hyperchloremic and later convert to typical increased anion gap acidosis.[222]
‡Patients with hypoadrenocorticism typically present with hypochloremia caused by impaired water excretion, absence of aldosterone, impaired renal function, and lactic acidosis. These factors prevent manifestation of hyperchloremia.

The anion gap represents the difference between the commonly measured plasma cations and the commonly measured anions. This concept is discussed in detail in Chapters 9 and 12. The normal electrolyte composition of canine plasma is compared with that in normal (hyperchloremic) and increased (normochloremic) anion gap metabolic acidosis in Fig. 10-2. The anion gap concept is useful in the diagnostic approach to the patient with metabolic acidosis, but it must not be taken literally. In reality, electroneutrality is maintained, and there is no actual anion gap. Normally, the anion gap is made up of the net negative charge on sulfates, phosphates, plasma proteins, and organic anions (e.g., lactate, citrate). Recent studies have shown that in normal dogs and cats, a substantial portion of the anion gap arises from the negative charge on plasma proteins. The net protein charge of plasma at pH 7.40 was calculated to be 16.0 mEq/L in dogs,[52] and this value was determined to be 13.7 mEq/L in cats.[141] Factors other than metabolic acidosis may also affect the value of the anion gap, and these are discussed in Chapter 12.

When the anion gap is calculated as $[(Na^+ + K^+) - (Cl^- + HCO_3^-)]$, normal values in dogs are in the range of 12 to 25 mEq/L.[3,52,176,201] Values for anion gap may be somewhat higher in cats (17 to 31 mEq/L) than in dogs (13 to 25 mEq/L) because of some unaccounted protein and phosphate charge.[52,141] In other studies, the mean anion gap for normal cats (calculated as described above) was approximately 20 mEq/L.[37,40,41] If the observed metabolic acidosis is characterized by a high anion gap, it is assumed to have arisen from an acid that does not contain chloride as its anion. Examples include some inorganic acids (e.g., phosphates, sulfates) or organic acids (e.g., lactate, ketoacids, salicylate, metabolites of ethylene glycol). In this setting, titration of body buffers by the acid results in accumulation of an anion other than chloride. If the observed metabolic acidosis is characterized by a normal anion gap, there is a reciprocal increase in the plasma chloride concentration to balance the decrease in plasma HCO_3^- concentration. In the following discussion, the causes of metabolic acidosis have been divided into those associated with a normal anion gap and those associated with an increased anion gap.

Disorders Associated with a Normal Anion Gap

Diarrhea

The concentration of HCO_3^- in intestinal fluid usually is higher than that of plasma, whereas its Cl^- concentration is lower. This results from the addition of alkaline

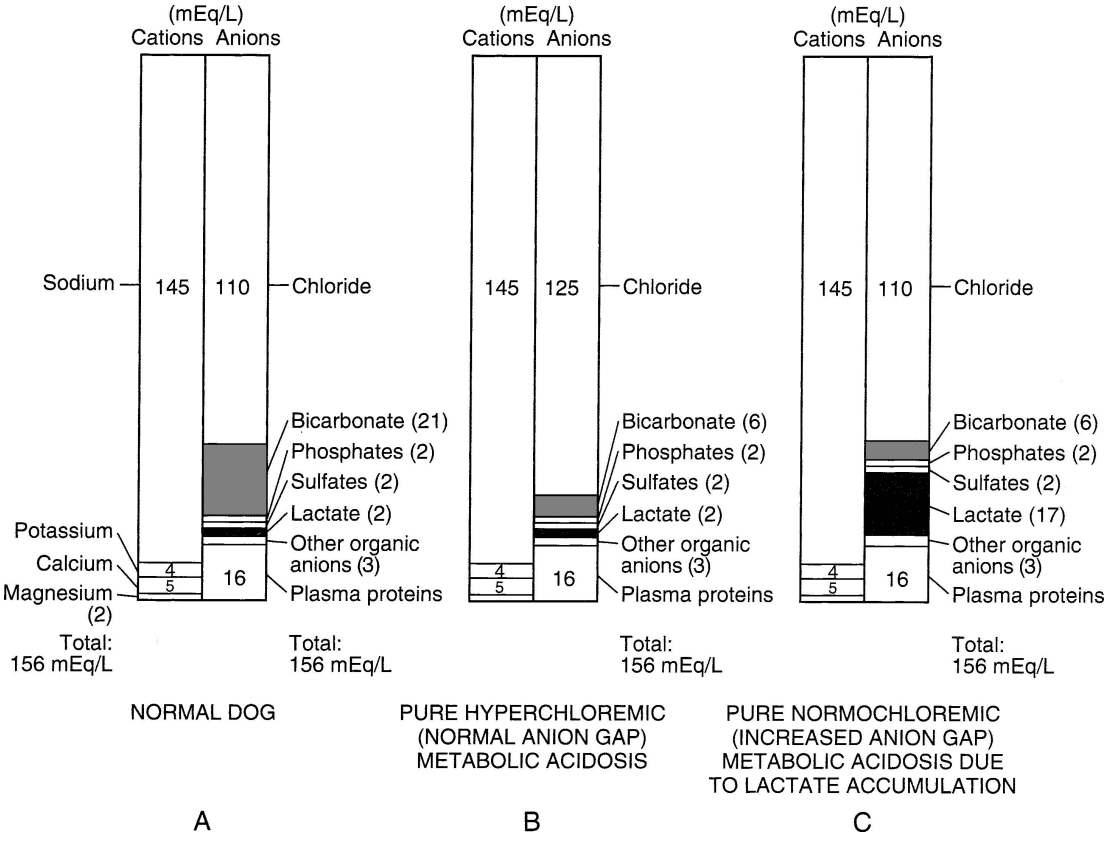


Fig. 10-2 Theoretical examples of electrolyte distribution in **(A)** normal canine plasma, **(B)** a dog with pure hyperchloremic (normal anion gap) metabolic acidosis, and **(C)** a dog with normochloremic (increased anion gap) metabolic acidosis caused by lactate accumulation (i.e., lactic acidosis). (Adapted from Toto RD: Metabolic acid-base disorders. In Kokko JP, Tannen RL, editors: *Fluids and electrolytes*, ed 2, Philadelphia, 1990, WB Saunders, p. 324.)

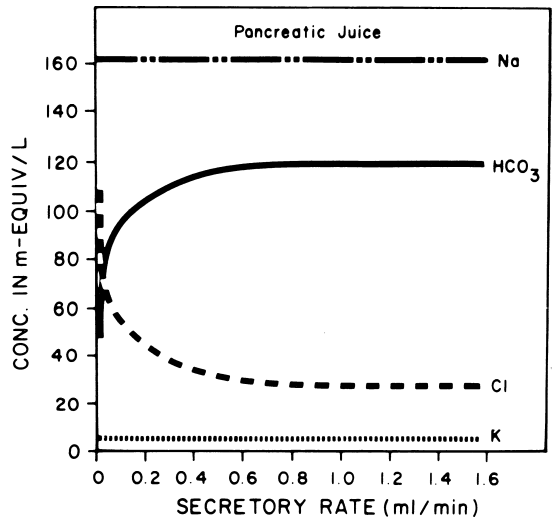


Fig. 10-3 Influence of secretory rate on electrolyte composition of canine pancreatic juice. Note the inverse relationship between Cl^- and HCO_3^- concentrations and the relatively constant concentrations of Na^+ and K^+. (From Cohen JJ, Kassirer JP: *Acid-base*. Boston, 1982, Little, Brown, & Co., p. 135.)

pancreatic and biliary secretions to luminal contents and from secretion of HCO_3^- in exchange for Cl^- in the ileum (Fig. 10-3 and Table 10-1). In some diseases of the small intestine, increased delivery of ileal contents to the colon may overwhelm the considerable capacity of the colon for reabsorption of fluid and electrolytes. As a result, severe acute small bowel diarrhea may cause loss of HCO_3^- in excess of Cl^- with resultant hyperchloremic metabolic acidosis. The acidosis is not purely hyperchloremic but rather is mixed if volume depletion and impaired tissue perfusion lead to lactic acid accumulation.

In one study of 134 dogs with gastroenteritis caused by parvoviral infection, only 13% had low total CO_2 concentrations.[108] In another study of 17 dogs with parvoviral gastroenteritis, 59% had normal pH at presentation.[97] In the animals with abnormal blood gas results, alkalemia (6 of 17) was more common than acidemia (1 of 17). The majority (64%) of the dogs in this study were presented for both vomiting and diarrhea. Hypochloremia is more common than hyperchloremia in parvoviral gastroenteritis.[97,108] In another study consisting of 25 puppies with parvoviral enteritis, plasma concentrations of sodium, potassium, chloride, and bicarbonate were lower than those of control dogs; however, increases in serum L-lactate concentration were uncommon, and increases in serum D-lactate concentration were not observed.[155] Most dogs in this study had mild compensated metabolic acidosis.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is characterized by hyperchloremic metabolic acidosis caused by either decreased HCO_3^- reabsorption (proximal RTA) or defective acid excretion (distal RTA) in the presence of a normal glomerular filtration rate (GFR). RTA is uncommonly recognized in small animal practice.

Distal Renal Tubular Acidosis. In **distal** (**classic** or **type 1**) **RTA,** the urine cannot be maximally acidified because of impaired hydrogen ion secretion in the collecting ducts, and urine pH typically is above 6.0, despite moderately to markedly decreased plasma HCO_3^- concentration. Increased urine pH (>6.0) in the presence of acidosis is the hallmark of distal RTA. Urinary tract infection by a urease-positive organism (e.g., *Proteus* sp., *Staphylococcus aureus*) must be ruled out before considering distal RTA. Urinary net acid excretion is decreased, but bicarbonaturia usually is mild because urinary HCO_3^- concentration is only 1 to 3 mEq/L in the pH range of 6.0 to 6.5. Nephrolithiasis (usually calcium phosphate stones), nephrocalcinosis (resulting from alkaline urine pH and decreased urinary citrate concentration), bone demineralization (resulting from loss of bone buffer stores during chronic acidosis), and urinary potassium wasting with hypokalemia are features of distal RTA in human patients. Mutations in cytosolic carbonic anhydrase, the basolateral Cl^-/HCO_3^- anion exchanger, and luminal H^+-ATPase that affect function of the α-intercalated cells have been associated with inherited forms of distal renal tubular acidosis in humans.[159] Urinary fractional excretion of HCO_3^- is normal (<5%) in distal RTA

TABLE 10-1 Electrolyte Composition of Luminal Fluid at the End of Individual Segments of the Gastrointestinal Tract

Segment End	Na^+ (mEq/L)	K^+ (mEq/L)	HCO_3^- (mEq/L)	Cl^- (mEq/L)
Duodenum	60	15	15	60
Jejunum	140	6	30	100
Ileum	140	8	70	60
Colon	40	90	30	15*

From Sleisinger MH, Fordtran JS, editors: Gastrointestinal diseases, ed 3, Philadelphia, 1983, WB Saunders, p. 258.

**The large anion gap in luminal fluid at the end of the colon is caused by the presence of organic anions resulting from bacterial metabolism. These organic anions represent functional base loss in the stool because they could have been metabolized in the body to yield HCO_3^-.*

when plasma HCO_3^- concentration is increased to normal by alkali administration.

A diagnosis of distal RTA may be confirmed by an ammonium chloride tolerance test during which urine pH is monitored (using a pH meter) before and at hourly intervals for 5 hours after oral administration of 0.2 g/kg NH_4Cl. Under such conditions, the urine pH of normal dogs decreased to a minimum value of 5.16 at 4 hours after administration of ammonium chloride.[199] Dogs in this study also developed systemic acidosis (pH approximately 7.22 and HCO_3^- approximately 14 mEq/L at 2 hours after ammonium chloride administration). The amount of alkali required to correct the acidosis in human patients with distal RTA is variable but typically less than that required in proximal RTA. The required dosage of alkali in distal RTA may be as little as 1 mEq/kg/day (i.e., that required to offset daily endogenous acid production) or more than 2 to 4 mEq/kg/day. A combination of potassium and sodium citrate (depending on potassium balance) may be the preferred source of alkali.[181]

Proximal Renal Tubular Acidosis. In **proximal (type 2) RTA,** renal reabsorption of HCO_3^- is markedly reduced and urinary fractional excretion of HCO_3^- is increased (>15%) when plasma HCO_3^- concentration is increased to normal. Bicarbonaturia is absent and urine pH is appropriately low when metabolic acidosis is present and plasma HCO_3^- concentration is decreased because distal acidifying ability is intact. When plasma HCO_3^- concentration is decreased, the filtered load of HCO_3^- is reduced, and almost all of the filtered HCO_3^- is reabsorbed in the distal tubules, despite the presence of the proximal tubular defect. Thus proximal RTA can be viewed as a "self-limiting" disorder in which plasma HCO_3^- stabilizes at a lower than normal concentration after the filtered load falls sufficiently that distal HCO_3^- reabsorption can maintain plasma HCO_3^- at a new but lower steady-state concentration. Mutations in renal tubular transport proteins such as the electrogenic basolateral $Na^+/3HCO_3^-$ cotransporter[65] and one of the five forms of the luminal Na^+/H^+ antiporter have been implicated in the pathogenesis of inherited forms of proximal renal tubular acidosis in humans.[105]

Other abnormalities of proximal tubular function typically accompany impaired HCO_3^- reabsorption in proximal RTA, and these include defects in glucose, phosphate, sodium, potassium, uric acid, and amino acid reabsorption. This combination of proximal tubular defects is known as Fanconi's syndrome. Serum potassium concentration usually is normal in affected human patients at the time of diagnosis, but alkali therapy may precipitate hypokalemia and aggravate urinary potassium wasting, presumably by increasing distal delivery of sodium and HCO_3^-.

The diagnosis of proximal RTA is made by finding an acid urine pH (<5.5 to 6.0) in the presence of hyperchloremic metabolic acidosis and normal GFR but an increased urine pH (>6.0) and increased urinary fractional excretion of HCO_3^- (>15%) after plasma HCO_3^- concentration has been increased to normal by alkali administration. If present, the detection of other defects in proximal tubular function (e.g., glucosuria with normal blood glucose concentration) establishes the diagnosis. Correction of metabolic acidosis by alkali therapy is more difficult in proximal RTA than in distal RTA because of the marked bicarbonaturia that occurs when plasma HCO_3^- concentration is increased to normal. Alkali dosages in excess of 10 mEq/kg/day may be required to correct the plasma HCO_3^- concentration, and such therapy may result in frank hypokalemia. Thus potassium citrate may be the preferred source of alkali.

Multiple renal tubular reabsorptive defects resembling Fanconi's syndrome have been reported in young basenji dogs.[23-25,70] Clinical findings included polyuria, polydipsia, weight loss, dehydration, and weakness. Affected dogs had abnormal fractional reabsorption of glucose, bicarbonate, phosphate, sodium, potassium, and urate, and they had isolated cystinuria or generalized aminoaciduria. The renal tubular disorder in affected basenji dogs is thought to be the result of a metabolic or membrane defect affecting sodium movement or increased back leak or cell-to-lumen flux of amino acids. In one study, brush border membranes isolated from basenji dogs with Fanconi's syndrome had decreased sodium-dependent glucose transport but no abnormality of cystine uptake despite the observed reabsorptive defect for cystine.[143] Defective urinary concentrating ability leads to isosthenuria or hyposthenuria, and GFR may be normal initially but decreased later in the course of the disease. Hypokalemia has also been observed late in the course of the disease.[70] Death usually results from acute renal failure and papillary necrosis or acute pyelonephritis. A distinctive renal lesion is hyperchromatic karyomegaly of renal tubular cells.

Fanconi's syndrome has been observed sporadically in other breeds[71,129,142,168,198] and has been reported in association with administration of some drugs.[14,25,146] In one case, Fanconi's syndrome developed in association with primary hypoparathyroidism and resolved after treatment with calcium and calcitriol.[77] Rickets in growing children and osteomalacia in adults are features of Fanconi's syndrome in human patients that usually are not observed in affected dogs. However, congenital Fanconi's syndrome and renal dysplasia were associated with histologic features of rickets in two Border terriers.[56] The skeletal abnormalities in one of the affected dogs resolved after treatment with calcitriol and potassium phosphate. Transient Fanconi's syndrome and proximal renal tubular acidosis also have been reported

in a dog with high liver enzyme activities, and toxin exposure was considered as a possible explanation.[103]

In one report, an 8-year-old female German shepherd had hyperchloremic metabolic acidosis, polyuria, polydipsia, isosthenuria, glucosuria with normal blood glucose concentration, and alkaline urine pH (7.46) after oral administration of NH_4Cl.[62] The metabolic acidosis was unresponsive to $NaHCO_3$ administration at dosages up to 4 mEq/kg/day. This dog appeared to have distal (type 1) RTA and renal glucosuria. In another case of apparent distal RTA, a 5-year-old mixed breed dog was presented for evaluation of anorexia and was determined to have alkaline urine pH with hyperchloremic metabolic acidosis.[176] In another report, an 8-year-old female German shepherd was presented for polyuria, polydipsia, weight loss, and lethargy.[21] It had a normal GFR, metabolic acidosis, hyposthenuria, and intermittent glucosuria. Fractional reabsorption of sodium, glucose, and HCO_3^- was decreased, but reabsorption of chloride, phosphate, potassium, urate, and amino acids was normal. The dog gained weight, and its clinical signs were reversed after treatment with $NaHCO_3$ at approximately 10 mEq/kg/day. This dog appeared to have proximal (type 2) RTA.

Distal RTA has been reported in two cats with pyelonephritis caused by *Escherichia coli*.[68,219] Clinical signs included polyuria, polydipsia, anorexia, lethargy, enlarged kidneys, and isosthenuria. In one cat, urine pH was 5.0 at the time pyelonephritis was first diagnosed, but distal RTA was documented at a later time by the presence of hyperchloremic metabolic acidosis, alkaline urine pH, and failure to lower urine pH after oral administration of NH_4Cl.[68] Findings were similar for the other cat, but hyperphosphaturia and persistent hypokalemia also were detected.[219] Distal RTA and hepatic lipidosis were reported in another cat without urinary tract infection.[26] The clinical features of proximal (type 2) and distal (type 1) RTA are summarized in Table 10-2.

Hyporeninemic hypoaldosteronism, characterized by hyperkalemia with decreased plasma renin and aldosterone concentrations, occurs in some human patients, notably those with diabetes mellitus who also have mild to moderate renal insufficiency.[57] The hyperchloremic metabolic acidosis observed in these patients has been called **type 4 RTA.** This syndrome has not been characterized in veterinary medicine but should be considered in dogs and cats with hyperkalemia and mild to moderate hyperchloremic metabolic acidosis after hypoadrenocorticism has been ruled out by an adrenocorticotropic hormone (ACTH) response test. The diagnosis may be established by finding an inappropriately decreased plasma aldosterone concentration in the presence of hyperkalemia.

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors, such as acetazolamide, decrease proximal tubular reabsorption of HCO_3^- in the kidney by noncompetitive inhibition of luminal and cellular carbonic anhydrase. Hypokalemia is caused by increased sodium delivery to the distal nephron and its reabsorption there in exchange for potassium. As hyperchloremic metabolic acidosis develops, the filtered load of HCO_3^- decreases and the effect of carbonic anhydrase inhibitors on HCO_3^- reabsorption is limited. Acetazolamide given at 7 to 10 mg/kg three times daily causes self-limiting hyperchloremic metabolic acidosis, mild to moderate hypokalemia, and mild hypocalcemia in dogs.[96,186] The effects of acetazolamide were greatest after 3 days of administration, and blood chemistry results stabilized after 5 days of administration.[186] Acetazolamide is used most commonly in small animal practice for the treatment of glaucoma.

TABLE 10-2 Clinical Features of Proximal and Distal Renal Tubular Acidosis

Clinical Feature	Proximal RTA	Distal RTA
Hypercalciuria	Yes	Yes
Hyperphosphaturia	Yes	Yes
Urinary citrate	Normal	Decreased
Bone disease	Less severe	More severe
Nephrocalcinosis	No	Yes
Nephrolithiasis	No	Yes (calcium phosphate)
Hypokalemia	Mild	Mild to severe
Potassium wasting	Worsened by $NaHCO_3$	Improved by $NaHCO_3$
Alkali required for treatment	>10 mEq/kg/day	<3 mEq/kg/day
Other defects of proximal tubular function*	Yes	No
Reduction in plasma HCO_3^-	Moderate	Variable (can be severe)
$FE_{HCO_3^-}$ at normal plasma HCO_3^- concentration	>15%	<5%
Urine pH during acidemia	<5.5	>6.0
Urine pH after NH_4Cl	<5.5	>6.0

**Decreased fractional reabsorption of sodium, potassium, phosphate, urate, glucose, and amino acids.*
FE, *Fractional excretion.*

Ammonium Chloride

Administration of NH_4Cl is equivalent to administration of HCl because the NH_4^+ is converted in the liver to urea and H^+. Ammonium chloride has been used commonly as a urinary acidifier in dogs and cats. A study of cats receiving 800 mg of NH_4Cl per day as powder or tablet showed that venous blood pH and HCO_3^- concentrations were decreased to values at the lower end of the normal range.[196] A combination product supplying 580 mg each of NH_4Cl and D,L-methionine had a more marked effect on venous blood pH and HCO_3^- concentrations than that observed with 800 mg of NH_4Cl alone, but results were still within the reported normal range.[197] In another study of cats, NH_4Cl at 300 mg/kg/day did not significantly alter venous blood pH, P_{CO_2}, or HCO_3^- concentration, but 400 mg/kg/day significantly decreased blood HCO_3^- concentration during the course of the study.[75] Ammonium chloride at a dosage of 535 mg/kg/day administered to dogs over 6 days caused hyperchloremic metabolic acidosis and was associated with hypokalemia, presumably related to increased aldosterone secretion.[136] In another study of dogs, NH_4Cl at 200 mg/kg/day reduced urine pH to approximately 5.0 and produced mild metabolic acidosis without change in serum potassium concentration.[193]

In young, growing and adult dogs, addition of NH_4Cl to the diet leads to demineralization of bone.[29,112] Chronic acid feeding has also been reported to affect bone metabolism in cats. Diets containing 3% NH_4Cl slowed growth of young cats, decreased blood pH and HCO_3^- concentrations, and lowered urine pH. Urinary calcium excretion increased in these cats, and bone demineralization was observed on histologic examination of caudal vertebrae.[28] Adult cats fed 1.5% NH_4Cl for 6 months developed hyperchloremic metabolic acidosis and negative balance for calcium and potassium,[38] but no significant changes in trabecular bone remodeling or bone mineral density were found.[39] In one study, administration of NH_4Cl to cats fed a potassium-restricted diet resulted in hypokalemia, possibly by reducing gastrointestinal absorption of potassium.[67] Results of these studies indicate that NH_4Cl should be used with caution and blood gases should be monitored during therapy.

Infusion of Cationic Amino Acids

Metabolism of cationic amino acids (e.g., lysine, arginine, histidine) results in production of H^+ as the NH_4^+ from these amino acids is converted to urea in the liver. For this reason, amino acid–containing fluids used in total parenteral nutrition can contribute to hyperchloremic metabolic acidosis. Other contributing factors are the presence of sulfur-containing amino acids (e.g., methionine, cysteine) in the fluid and development of hypophosphatemia during refeeding, which may reduce renal excretion of titratable acid.

Posthypocapnic Metabolic Acidosis

During compensation for chronic respiratory alkalosis, renal net acid excretion decreases with consequent reduction in plasma HCO_3^- and increase in plasma Cl^- concentrations. When the stimulus for hyperventilation is removed and P_{CO_2} increases, pH decreases because it requires 1 to 3 days for the kidneys to increase net acid excretion and to increase plasma HCO_3^- concentration. Until this occurs, a state of "posthypocapnic" metabolic acidosis exists. Recovery is spontaneous as long as sodium and phosphate are available in the diet to allow the appropriate increase in renal net acid excretion.[79]

Dilutional Acidosis

Dilutional acidosis refers to a decrease in plasma HCO_3^- concentration that occurs when extracellular volume is expanded using an alkali-free chloride-containing solution such as 0.9% NaCl. The high chloride concentration of 0.9% NaCl and the highly resorbable nature of the chloride ion in the renal tubules contribute to the decrease in plasma HCO_3^- concentration and the increase in Cl^- concentration. Dilutional acidosis can be corrected by substitution of a solution with a lower chloride concentration (e.g., lactated Ringer's solution, 0.45% NaCl).

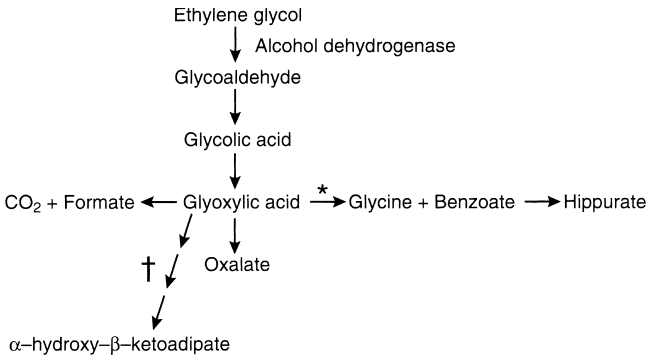
Hypoadrenocorticism

Aldosterone increases renal tubular lumen negativity by enhancing sodium reabsorption in the collecting duct and secondarily increases hydrogen ion secretion. It also directly stimulates H^+ secretion by increasing the activity of the luminal H^+-ATPase pump in the medullary collecting duct. These effects allow urinary excretion of H^+ and K^+ when distal delivery of sodium is decreased. Deficiency of aldosterone in hypoadrenocorticism results in metabolic acidosis and hyperkalemia. Metabolic acidosis of variable severity is common in dogs with hypoadrenocorticism.[145,175] In one study, low total CO_2 concentration suggesting the presence of metabolic acidosis was found in 81 of 200 (41%) dogs with hypoadrenocorticism.[175] In a study of 10 cats with hypoadrenocorticism, 3 were reported to have decreased serum total CO_2 concentrations.[174] Treatment of hypoadrenocorticism includes volume expansion with 0.9% NaCl and replacement of deficient mineralocorticoids and glucocorticoids.

Disorders Associated with an Increased Anion Gap

Ethylene Glycol Ingestion

Ethylene glycol (EG) is an organic solvent (molecular mass, 62 daltons) used in commercial antifreeze solutions. Ingestion of antifreeze by dogs and cats is a common cause of oliguric acute renal failure in small animal practice, and mortality exceeds 80% in affected animals.[51,84,211] EG itself is not toxic, but it is converted in the liver to



* Pyridoxine is a cofactor for this reaction.
† Thiamine is a cofactor for this reaction.

Fig. 10-4 Metabolism of ethylene glycol.

several metabolites that cause severe metabolic acidosis and acute renal failure (Fig. 10-4). It is rapidly absorbed from the gastrointestinal tract and is undetectable in plasma of dogs 48 hours after administration.[161,190]

Pathophysiology. EG is first metabolized in the liver to glycoaldehyde by alcohol dehydrogenase. Glycoaldehyde uncouples oxidative phosphorylation and may contribute to neurologic signs observed early in the course of intoxication. Subsequent steps in metabolism produce glycolic and glyoxylic acids. Glycolic acid is primarily responsible for the severe metabolic acidosis that occurs in animals poisoned by EG.[44] Renal tubular injury results from glycoaldehyde, glycolic acid, and glyoxylic acids, and calcium oxalate crystals are deposited within renal tubules. The observation of these birefringent crystals in the presence of acute tubular nephrosis confirms the diagnosis of EG intoxication.

Vomiting, polydipsia, and polyuria may occur soon after ingestion of EG, but the owners of poisoned animals often do not detect these signs. Within 12 hours of ingestion, neurologic signs (e.g., lethargy, ataxia, stupor, seizures, coma) may develop. Cardiac and pulmonary manifestations (e.g., tachypnea, tachycardia) occur 12 to 24 hours after ingestion but rarely are detected in clinical cases. Oxalate crystals may be detected in the urine as early as 3 to 6 hours after ingestion of EG.[60,61] Renal failure occurs in dogs as early as 24 to 48 hours after ingestion and is manifested by anorexia, lethargy, vomiting, and oliguria or anuria.[86] In cats, azotemia may develop within 12 to 24 hours after ingestion of EG.[60] Unfortunately, most dogs and cats with EG poisoning are presented for veterinary attention after renal failure has already developed.

A severe normochloremic (i.e., high anion gap) metabolic acidosis occurs within 3 hours of EG ingestion and persists for at least 24 hours.[60,61,86,211] Serum hyperosmolality and osmolal gap peak 1 to 6 hours after ingestion and persist for 12 to 24 hours,[60,61,86] but the osmolal gap may be normal in animals presented later in the course of the disease.[211] Calcium oxalate dihydrate crystals ("Maltese cross" or "envelope" forms) may be observed in the urine, but calcium oxalate monohydrate crystals ("picket fence" or "dumbbell" forms) are observed more commonly. Calcium oxalate dihydrate crystals occasionally are found in the urine of normal dogs and cats, whereas calcium oxalate monohydrate crystals rarely are seen except in animals that have ingested EG (Fig. 10-5).[60,211] Crystals previously referred to as hippurates actually are calcium oxalate monohydrate crystals.[120,210] Other laboratory findings include azotemia, isosthenuria, hypocalcemia, hyperphosphatemia, and hyperglycemia.[211] Hyperphosphatemia observed very early in the course of EG intoxication (3 to 12 hours after ingestion) probably is the result of the high phosphorus content of rust-retardant antifreeze preparations.[51,61] Hyperechogenicity of the renal cortex is observed on renal ultrasonography as early as 5 hours after ingestion of EG.[1]

Treatment. The response to treatment depends on the amount of EG ingested and the amount of time that elapses before treatment. In early studies, dogs that ingested less than 10 mL/kg EG were saved if treated within 2 to 4 hours of ingestion,[15,161,190] and cats survived up to 6 mL/kg EG if treated within 4 hours.[172] Treatment consists of inducing vomiting with apomorphine or performing gastric lavage with activated charcoal if ingestion has been recent (<8 hours before presentation). Severe hypocalcemia is corrected with calcium gluconate, and $NaHCO_3$ is administered to combat metabolic acidosis. A $NaHCO_3$ dosage of 1 to 2 mEq/kg may be used empirically. Calcium gluconate and $NaHCO_3$ must not be given simultaneously because calcium carbonate crystals form, and the solution becomes turbid. Attempts to stimulate urine production with furosemide (2 to 4 mg/kg) or mannitol (1 g/kg) usually are futile.

Alcohol dehydrogenase has greater affinity for ethanol than EG. For this reason, 20% ethanol has been administered intravenously to affected dogs at a dosage of 5.5 mL/kg every 4 hours for five treatments and then every 6 hours for four additional treatments.[85] Cats are treated with 20% ethanol at a dosage of 5 mL/kg every 6 hours for five treatments and then every 8 hours for four additional treatments. This treatment is unlikely to be of benefit if more than 12 to 24 hours have elapsed since ingestion of EG. 4-Methylpyrazole (Antizol, Orphan Medical, Minnetonka, MN) is a pharmacologic inhibitor of alcohol dehydrogenase that has become available to treat dogs with EG toxicosis.[59,61] In dogs, it is superior to ethanol because it does not cause central nervous system (CNS) depression, but it must be administered within 8 hours of EG ingestion. The dosage of 4-methylpyrazole used in dogs with EG intoxication is 20 mg/kg

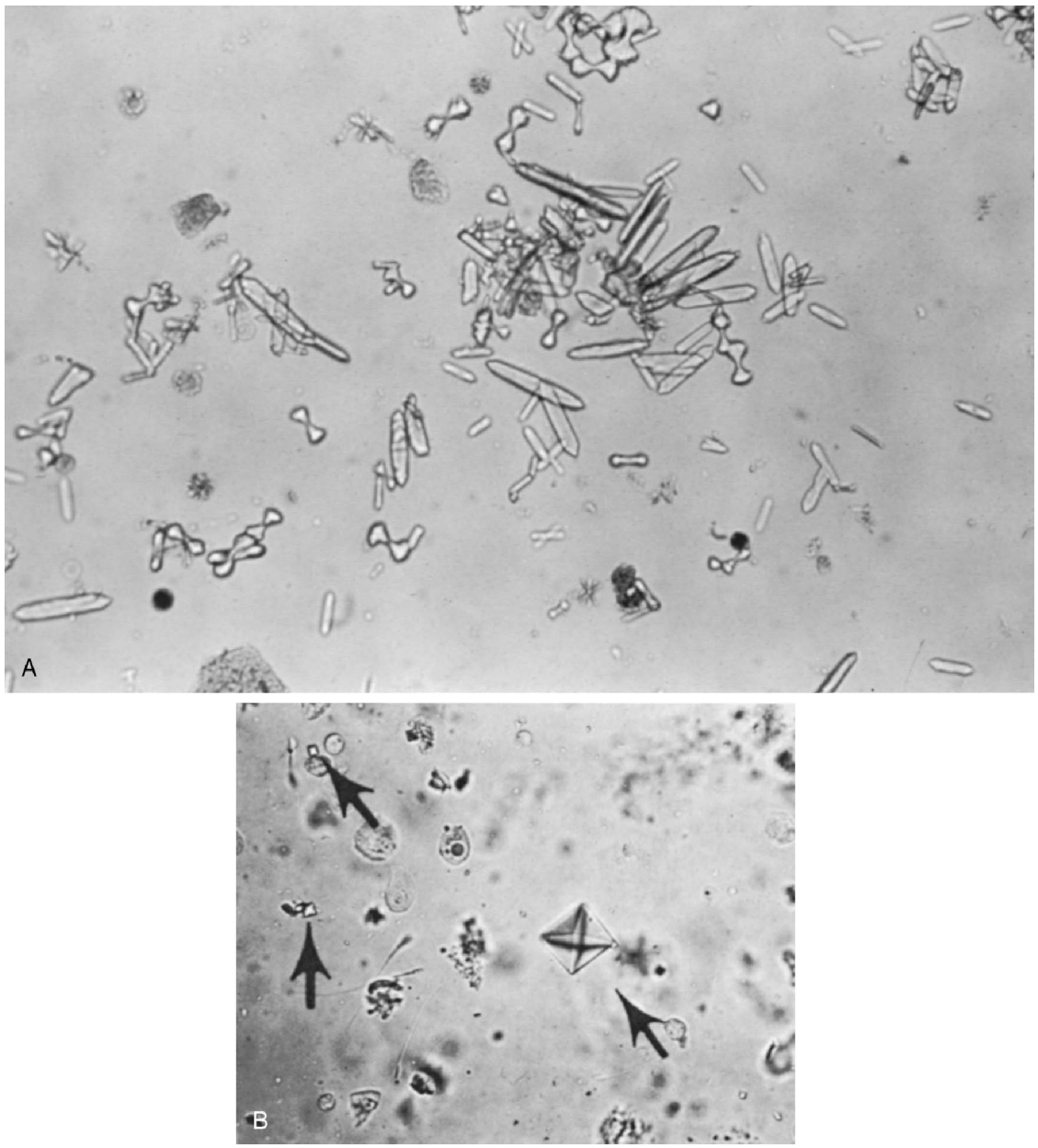


Fig. 10-5 Photomicrographs of **(A)** calcium oxalate monohydrate and **(B)** dihydrate crystals in urine sediment. (From Chew DJ, DiBartola SP: Diagnosis and pathophysiology of renal disease. In Ettinger SJ, editor: *Textbook of veterinary internal medicine,* Philadelphia, 1989, WB Saunders, p. 1907.)

intravenously, followed by 15 mg/kg intravenously at 12 and 24 hours and 5 mg/kg intravenously at 36 hours.[51,59,61] Unfortunately, 4-methylpyrazole is not efficacious in EG-intoxicated cats unless administered at the same time as the EG is consumed. The observed lack of effectiveness of 4-methylpyrazole in EG-intoxicated cats may be related to a shorter half-life of EG in cats (2 to 5 hours) compared with dogs (8 to 10 hours) and more rapid development of acute renal failure in cats or to decreased efficacy of 4-methylpyrazole as an inhibitor of alcohol dehydrogenase in cats.[60] Thiamine promotes conversion of glyoxylate to glycine, and pyridoxine promotes conversion of glyoxylate to α-hydroxy-β-ketoadipate (see Fig. 10-4). These vitamins may be administered to promote alternative pathways of glyoxylate metabolism, but efficacy has not been demonstrated for such treatment. In one study, all nonazotemic dogs treated with 4-methylpyrazole within 2 to 8.5 hours after EG ingestion survived, whereas only 1 of 21 azotemic dogs treated 8.5 to 38 hours after ingestion survived.[51]

Peritoneal dialysis or hemodialysis is necessary if the animal has anuric or oliguric renal failure at the time of presentation. Early dialysis may also be helpful to remove toxic intermediate metabolites. Despite dialysis, affected

dogs may progress to end-stage renal disease and become dependent on dialysis. The prognosis for survival in adult dogs and cats with anuric or oliguric acute renal failure caused by EG intoxication is unfortunately very poor.[51,211]

Salicylate Intoxication

Aspirin (acetylsalicylic acid) is hydrolyzed to salicylic acid ($pK_a' = 3.0$) in the liver. Salicylate intoxication is uncommon in small animal practice and is an example of a mixed acid-base disturbance characterized by metabolic acidosis and respiratory alkalosis. Salicylate intoxication in anesthetized, spontaneously breathing dogs resulted in a mixed respiratory alkalosis and metabolic acidosis.[202] The stimulation of ventilation is caused by a direct effect of salicylate on the medullary respiratory center. Salicylate also uncouples oxidative phosphorylation in mitochondria, and the associated disturbances in carbohydrate metabolism lead to metabolic acidosis characterized by an increased anion gap associated with accumulation of lactic acid, ketoacids, and other organic acids. Salicylate usually makes a minor contribution to the observed increase in unmeasured anions.

Gastric lavage with activated charcoal should be performed if ingestion occurred less than 6 to 12 hours before admission. Administration of $NaHCO_3$ promotes removal of salicylate from tissues and enhances its urinary excretion by the mechanism of **diffusion trapping.** Alkalinization of ECF and urine increases the proportion of drug present in the ionized form and thus favors diffusion of more nonionized salicylic acid from cells into ECF and urine, where it can be trapped as the poorly diffusible ionized form. An attempt should be made to maintain urine pH above 7.5 during alkaline diuresis with $NaHCO_3$, especially if metabolic acidosis is the predominant acid-base disturbance. Alkalinization should be carried out with caution, if at all, when respiratory alkalosis is the predominant acid-base disturbance. Glucose infusion is recommended to prevent reduction in CNS glucose concentration. Hypokalemia may develop during treatment as a result of $NaHCO_3$ administration and diuresis, and parenteral fluids should be supplemented with potassium as needed.

Diabetic Ketoacidosis

Pathophysiology. Overproduction of acetoacetic acid ($pK_a' = 3.58$) and β-hydroxybutyrate ($pK_a' = 4.70$) by the liver occurs in diabetes mellitus because of a deficiency of insulin and relative excess of glucagon. An increase in glucagon and decrease in insulin shift the liver from its normal role in esterification of fatty acids into triglycerides to β-oxidation of fatty acids into ketoacids. At the normal pH of ECF (7.40), these organic acids are completely dissociated, and the hydrogen ions that are released titrate HCO_3^- and other body buffers. Acetone is formed by the nonenzymatic decarboxylation of acetoacetate and does not contribute additional fixed acid. The pathophysiology and treatment of diabetic ketoacidosis are discussed in detail in Chapter 20.

Metabolic acidosis is common in dogs and cats with diabetic ketoacidosis. In one series, mean plasma HCO_3^- concentration in 72 dogs with diabetic ketoacidosis was approximately 11 mEq/L at the time of diagnosis with a range of 4 to 20 mEq/L, whereas the mean HCO_3^- concentration in 20 affected cats was 13 mEq/L with a range of 8 to 22 mEq/L.[73] In an early study of dogs with diabetes mellitus, mean plasma HCO_3^- concentration was 13.7 mEq/L in eight survivors (range, 9.3 to 21.0 mEq/L) and 18.1 mEq/L in five nonsurvivors (range, 13.4 to 30.2 mEq/L).[124] In another study of dogs with diabetic ketoacidosis, mean arterial pH and HCO_3^- concentration were 7.201 (range, 6.986 to 7.395) and 11.1 mEq/L (range, 4.1 to 19.7 mEq/L) before treatment and 7.407 ± 0.053 and 18.2 ± 0.7 mEq/L 24 hours after treatment.[128] Only three dogs (those with pH < 7.1) received sodium bicarbonate treatment. Metabolic acidosis with median pH of 7.14 (range, 7.04 to 7.24) and HCO_3^- concentration of 10 mEq/L (range, 6 to 15 mEq/L) was found in 25 of 33 cats evaluated by venous blood gas analysis in a survey of cats with diabetic ketoacidosis.[27] Cats with HCO_3^- concentrations below 14 mEq/L received bicarbonate supplementation of their fluids. In another series of diabetic cats, median total CO_2 was 13 mEq/L in ketoacidotic cats and 15 mEq/L in nonketoacidotic cats.[55] In a study of 116 dogs with diabetes mellitus, 43 (37%) had diabetic ketoacidosis with median venous blood pH of 7.228 (range, 6.979 to 7.374) and median bicarbonate concentration of 10.1 mEq/L (range, 4.0 to 19.3 mEq/L).[69]

The nitroprusside reagent (e.g., Acetest, Bayer, Tarrytown, NY) detects only ketone (–C=O) groups (e.g., acetoacetate, acetone). The concentration of β-hydroxybutyrate typically exceeds that of acetoacetate in uncontrolled diabetic ketoacidosis, and the dipstick reaction underestimates the degree of ketonuria. This problem can be overcome by adding a few drops of hydrogen peroxide to urine, which nonenzymatically converts β-hydroxybutyrate to acetoacetate.[157] When insulin is administered and metabolism of ketones proceeds, there is a shift toward acetoacetate, and the dipstick reaction transiently becomes more strongly positive. This possibility should be recognized by the clinician and should not cause concern. In a study of 116 diabetic dogs (of which 88 had not previously received insulin), all ketotic and ketoacidotic dogs and 21 of 32 (66%) "non-ketotic" dogs (i.e., negative urine dipstick test for ketones) had abnormally high serum β-hydroxybutyrate concentrations (>0.15 mmol/L) at presentation.[69] The increase in unmeasured anions (as reflected in the anion gap) gives a rough estimate of the concentration of ketoanions in serum. However, this estimate is inaccurate if lactic acidosis develops because lactate also is an unmeasured anion.

To some extent, the anions of these ketoacids are excreted in the urine along with sodium and potassium for electroneutrality. These organic anions are lost from the body and cannot be metabolized to HCO_3^- after correction of diabetic ketoacidosis with insulin therapy. Their loss thus contributes to depletion of body buffer and cation stores. Osmotic diuresis is induced by hyperglycemia and also contributes to the whole-body cation deficit. The extent of impairment in renal function may determine whether patients with diabetic ketoacidosis have an increased anion gap metabolic acidosis or hyperchloremic metabolic acidosis at the time of presentation. Patients with severe volume depletion have an increased anion gap because of retention of ketoanions, whereas those without volume depletion have hyperchloremia as a result of increased urinary excretion of the sodium and potassium salts of ketoanions and retention of chloride.[4,8]

Treatment. The best treatment for the acidosis of uncontrolled diabetes mellitus is fluid therapy and insulin. Insulin administration allows glucose utilization by skeletal muscle and adipose tissue, decreases hepatic glucose production, prevents lipolysis and ketogenesis, and permits peripheral metabolism of ketoacids. Several regimens for administration of insulin to ketoacidotic dogs and cats have been described.[74] The particular protocol of insulin administration is probably less crucial to the ultimate outcome than the individualized care provided by the veterinarian during management of the diabetic animal.

Several factors may contribute to a delay in the repair of the HCO_3^- deficit in patients with diabetic ketoacidosis.[89] Ketoacid anions that have been excreted in the urine are lost to the body and cannot be metabolized to HCO_3^-. After treatment with fluids and insulin, recovery may be faster in patients with a high anion gap because the retained ketoanions are metabolized, yielding HCO_3^-.[6,8] Thus withholding alkali may be more rational for diabetic patients with high anion gap metabolic acidosis than for those with hyperchloremic metabolic acidosis. Dilutional acidosis may occur if ECF volume (ECFV) is expanded with alkali-free solutions such as 0.9% saline. If hyperventilation persists, it may impair renal reabsorption of HCO_3^-, and renal acid excretion may require several days to become fully augmented.

The use of $NaHCO_3$ to treat diabetic ketoacidosis is highly controversial, and clear benefits of its use have not been demonstrated in human patients. For example, there was no difference in recovery (based on rate of decrease of blood glucose and ketone concentrations and rate of increase of blood or cerebrospinal fluid [CSF] pH or HCO_3^- concentration) when $NaHCO_3$ was or was not administered to human patients with diabetic ketoacidosis who presented with blood pH values in the range of 6.90 to 7.14.[152] In another study, treatment with $NaHCO_3$ delayed resolution of ketosis in diabetic ketoacidosis.[164]

There are several theoretical arguments against the use of $NaHCO_3$ in diabetic ketoacidosis. Acidosis in the CNS may develop after $NaHCO_3$ administration. The blood-brain barrier is permeable to CO_2 but less permeable to the charged HCO_3^- ion. If $NaHCO_3$ is administered, pH increases in ECF as the HCO_3^-/P_{CO_2} ratio increases, and compensatory hyperventilation decreases somewhat. As a result, P_{CO_2} increases and CO_2 diffuses into the CNS. However, bicarbonate diffusion into CNS lags behind that of CO_2. During this time, the HCO_3^-/P_{CO_2} ratio and pH in the CNS may decrease. This has been referred to as **paradoxical CNS acidosis.**[177] The frequency of occurrence of this complication and its clinical significance are uncertain.[121]

The pathophysiology of diabetic ketoacidosis also affects oxygen delivery to tissues. Chronic acidosis shifts the oxygen-hemoglobin dissociation curve to the right, thus enhancing delivery of oxygen to the tissues. Conversely, phosphorus deficiency in diabetes decreases red cell 2,3-diphosphoglycerate concentration and causes a shift of the oxygen-hemoglobin dissociation curve back to the left. Correction of acidosis with $NaHCO_3$ shifts the curve farther to the left and potentially decreases oxygen delivery to tissues. However, administration of insulin and fluid therapy also lead to correction of the acidosis and should have a similar effect on the oxygen-hemoglobin dissociation curve.

Overzealous therapy with $NaHCO_3$ may contribute to late development of metabolic alkalosis because insulin promotes metabolism of retained ketoacid anions to HCO_3^-. This excess HCO_3^- should be readily excreted in the urine if renal function is adequate. Other potentially detrimental effects of $NaHCO_3$ therapy include aggravation of hyperosmolality as a consequence of the obligatory sodium load, tetany resulting from a sudden decrease in ionized serum calcium concentration, and precipitation of severe hypokalemia as extracellular potassium ions move into cells during administration of insulin and correction of acidosis. For all these reasons, $NaHCO_3$ is not used unless severe acidosis (pH < 7.1 to 7.2) is present and then only in small amounts (see section on Treatment of Metabolic Acidosis).

Uremic Acidosis

Pathophysiology. The metabolic acidosis of chronic renal failure is usually mild to moderate in severity (plasma HCO_3^- concentration, 12 to 15 mEq/L) and may be hyperchloremic early in the course of the disease process.[222] Later in the course of the disease, the anion gap increases because of retention of phosphates, sulfates, and organic anions. Acid-base status is usually well preserved in chronic renal failure until GFR decreases to 10% to 20% of normal. In retrospective studies of small animal patients with chronic renal failure, plasma HCO_3^-

concentrations were less than 16 mEq/L in 40% of dogs with chronic renal failure caused by amyloidosis[64] and less than 15 mEq/L in 63% of cats with chronic renal failure of various causes.[63] A high anion gap was observed in 43% of affected dogs (>25 mEq/L) and in 19% of affected cats (>35 mEq/L) in these studies. In acute renal failure, there has been insufficient time for the kidneys to adapt to the disease state, and the metabolic acidosis of acute renal failure is usually more severe than that observed in chronic renal failure. Complications such as sepsis and marked tissue catabolism may contribute to the severity of metabolic acidosis in acute renal failure.

Delivery of HCO_3^- from the proximal tubules to the distal nephron is increased in chronic renal failure.[218] In dogs with experimentally induced unilateral renal disease, renal HCO_3^- reabsorption was not different in the diseased and control kidneys, but bicarbonaturia developed when the normal kidney was removed, and the contralateral diseased kidney was forced to function in a uremic environment.[151] The osmotic diuresis characteristic of uremia may thus contribute to the increased delivery of HCO_3^- to the distal tubules. Increased parathyroid hormone concentration as a result of renal secondary hyperparathyroidism does not seem to have important adverse effects on HCO_3^- reabsorption in experimentally induced renal disease in dogs.[10,191,192] The ability to lower urine pH maximally is preserved in chronic renal failure.

The main method by which the diseased kidney responds to chronic retention of fixed acid is by enhanced renal ammoniagenesis. Total ammonium excretion decreases during progressive chronic renal disease, but ammonium excretion is observed to be markedly increased when expressed per 100 mL GFR or per remnant nephron.[66,187] On a per-nephron basis, the diseased kidney can increase its ammonium excretion three- to five-fold.[203,218,221] This adaptive mechanism seems to be fully expended when the GFR decreases to less than 20% of normal. At this point, the diseased kidneys can no longer effectively cope with the daily fixed acid load, and a new steady state is established at a lower than normal plasma HCO_3^- concentration. The relatively mild decrease in plasma HCO_3^- concentration that is observed in chronic renal failure has been attributed to the contribution of the large reservoir of buffer (e.g., calcium carbonate) in bone. However, the capacity of the skeleton to buffer the amount of acid that accumulates in long-standing chronic renal failure has been questioned.[163] The decrease in total ammonium excretion that occurs in chronic renal failure may be counterbalanced by decreased urinary excretion of organic anions (e.g., citrate, lactate, pyruvate, ketoanions).[50] Metabolism of these retained organic anions would result in a net gain of HCO_3^- that would offset the decreased excretion of H^+ in the form of NH_4^+.

The amount of phosphate buffer available in urine in chronic renal failure is relatively fixed and likely to be at its maximum because of hyperphosphatemia and the effects of increased plasma parathyroid hormone concentration.[187,203] Furthermore, phosphorus binders and dietary phosphorus restriction are commonly used to treat chronic renal failure and may limit the amount of phosphate that can contribute to titratable acidity. When expressed on a per-nephron basis, however, titratable acidity is increased in chronic renal failure.[150]

Treatment. Whether to treat well-compensated mild to moderate metabolic acidosis in adult patients with chronic renal failure is controversial. The potential benefits of such treatment include minimizing potential depletion of bone buffers, preventing the catabolic effects of uremic acidosis on muscle protein, preventing tubulointerstitial damage resulting from complement activation by ammonia, and improving the patient's ability to combat a superimposed acidotic crisis (e.g., acute diarrhea).[182] Thus treatment with oral $NaHCO_3$ at a dosage of 0.5 to 1.0 mEq/kg/day or an amount sufficient to maintain plasma HCO_3^- concentration at 15 mEq/L or above is reasonable if the patient can tolerate the associated sodium load. One teaspoon of baking soda contains 5 g $NaHCO_3$ (1.3 g of which is sodium). An advantage of using calcium carbonate (e.g., Tums [GlaxoSmithKline, Brentford, UK], Os-Cal [GlaxoSmithKline]) as a phosphorus binder in chronic renal failure is that this compound can serve as both a source of alkali and a source of calcium, if small amounts of calcitriol (2 to 3 ng/kg/day) are also provided. The patient should be monitored for development of hypercalcemia when calcium carbonate and calcitriol are administered concurrently. Potassium and sodium citrate should not be used for alkali therapy in chronic renal failure patients that also are being treated with aluminum-containing phosphorus binders (e.g., aluminum hydroxide, aluminum carbonate) because citrate can increase aluminum absorption from the gastrointestinal tract in this clinical setting.[148]

Lactic Acidosis

Lactic acidosis is characterized by an accumulation of lactate in body fluids and a plasma lactate concentration greater than 5 mEq/L.[130] The pK_a' of lactic acid is 3.86, and it is completely dissociated at the normal pH of ECF (7.40). Lactic acidosis has been divided into two categories (Box 10-2).[49,100,122] In type A (hypoxic) lactic acidosis, mitochondrial function is normal but O_2 delivery to tissues is inadequate. In type B (nonhypoxic) lactic acidosis, there is adequate O_2 delivery to tissues but defective mitochondrial oxidative function and abnormal carbohydrate metabolism. Inborn errors of metabolism affecting gluconeogenesis and mitochondrial oxidative function are documented to cause type B lactic acidosis in humans.

Box 10-2 Causes of L-Lactic Acidosis*

Type A: hypoxic
Increased oxygen demand
  Severe exercise
  Convulsions
Decreased oxygen availability
  Reduced tissue perfusion
    Cardiac arrest, cardiopulmonary resuscitation
    Shock
    Hypovolemia
    Left ventricular failure
    Low cardiac output
    Acute pulmonary edema
  Reduced arterial oxygen content
    Hypoxemia ($Po_2 \leq 30$ mm Hg)
    Extremely severe anemia (packed cell volume < 10%)

Type B: nonhypoxic
Drugs and toxins
  Phenformin
  Salicylates
  Ethylene glycol
  Many others[130]
Diabetes mellitus
Liver failure
Neoplasia (e.g., lymphosarcoma)
Sepsis
Renal failure
Hypoglycemia
Hereditary defects
  Mitochondrial myopathies
  Defects in gluconeogenesis

*D-Lactic acidosis occurs with short bowel syndrome in humans and has been observed in cats fed propylene glycol.[40,41]

Defects in mitochondrial oxidative function are called mitochondrial myopathies and are caused by hereditary defects in specific mitochondrial enzyme systems. A number of case reports suggest that similar defects occur in dogs.[104,165,167,216] Pyruvate dehydrogenase deficiency is suspected to occur in Clumber spaniels.[98,113] This discussion focuses on type A (hypoxic) lactic acidosis.

Normal Physiology. Lactate is a metabolic end product. Its production allows regeneration of cytosolic nicotinamide adenine dinucleotide (NAD^+) during anaerobic metabolism, and its ultimate fate is reoxidation back to pyruvate:

$$\underset{\text{(pyruvate)}}{CH_3COCOO^- + NADH + H^+} \underset{\text{lactate dehydrogenase}}{\rightleftharpoons} \underset{\text{(lactate)}}{CH_3CHOHCOO^- + NAD^+}$$

The equilibrium of this reaction is far to the right, and the normal ratio of lactate to pyruvate is 10:1. The main determinants of cytosolic lactate concentration are the concentration of pyruvate and the $NADH/NAD^+$ ratio, both of which are affected by mitochondrial oxidative function.

Pyruvate is produced in the cytosol by anaerobic glycolysis (Embden-Meyerhof pathway). Under aerobic conditions, NADH is oxidized to NAD^+ in the mitochondria and pyruvate enters the mitochondria for conversion to acetylcoenzyme A (CoA) and utilization in the tricarboxylic acid (Krebs) cycle, or it is converted to oxaloacetate and used for gluconeogenesis in the liver and renal cortex. Under anaerobic conditions (e.g., tissue hypoxia), oxidative pathways in the mitochondria are disrupted, and NAD^+ must be replenished by reduction of pyruvate to lactate in the cytosol. Thus lactate accumulation is the price to be paid for maintaining energy production under anaerobic conditions.

At rest, skin, red cells, brain, skeletal muscle, and gut all produce lactate. During tissue hypoxia, skeletal muscle and gut become the major producers of lactate. The liver and kidney are the main consumers of lactate, using it for gluconeogenesis (primarily in the liver) or oxidizing it to CO_2 and water. Protons are consumed when lactate is metabolized:

Gluconeogenesis

$$2CH_3CHOHCOO^- + 2H^+ \rightarrow C_6H_{12}O_6$$

Oxidative metabolism

$$CH_3CHOHCOO^- + H^+ + 3O_2 \rightarrow 3CO_2 + 3H_2O$$

Both of these reactions require normal mitochondrial oxidative function. The protons are consumed when adenosine triphosphate (ATP) is synthesized from adenosine diphosphate (ADP) and when NADH is oxidized to NAD^+ in the mitochondria.[122,130] Protons are released by hydrolysis of ATP to ADP and by reduction of NAD^+ to NADH, reactions that occur mainly in the cytosol. The protons do not arise from dissociation of lactic acid because the anion lactate is the predominant metabolite at normal hepatocyte pH_i (pH_i = 7.00 to 7.20). Thus lactic acidosis reflects imbalance between ATP hydrolysis and synthesis and between reduction and oxidation of NAD^+. The protons produced during anaerobic glycolysis are buffered by bicarbonate and nonbicarbonate buffers. Protons are consumed and the buffers replenished when lactate is metabolized to glucose or oxidized to CO_2 and water.

Pathophysiology. Lactic acidosis occurs when production of lactate by muscle and gut exceeds its utilization by liver and kidney. Both pathways of lactate utilization depend on intact mitochondrial oxidative

function, and clinical settings characterized by tissue hypoxia are the most common causes of lactic acidosis (see Box 10-2). Hepatic uptake of lactate is decreased when arterial P_{O_2} decreases to approximately 30 mm Hg.[209] Severe acidosis further impairs hepatic uptake of lactate, and the liver eventually becomes a producer rather than a consumer of lactate.[126]

In an experimental model of hypoxic lactic acidosis (type A) induced by ventilating dogs with 8% O_2, lactate concentration was more than 5 mEq/L, pH was less than 7.2, HCO_3^- concentration was less than 12 mEq/L, P_{O_2} was less than 30 mm Hg, and hepatocyte pH_i was less than 7.00.[9] When a similar degree of acidosis was created by infusing lactic acid into dogs with normal P_{O_2}, hepatocyte pH_i remained greater than 7.00, and hepatic extraction of lactate (as a percentage of the delivered load) was approximately three times higher than that observed in the hypoxic animals. Hypoxemia reduces hepatic O_2 uptake, and hepatocyte pH_i decreases, presumably as a result of CO_2 accumulation within cells. This study demonstrated that impaired hepatic extraction of lactate is related to decreased hepatic O_2 uptake and pH_i but not to arterial pH. During severe hypoxia, increased lactate production by gut and muscle and decreased hepatic extraction of lactate lead to progressive lactic acidosis. Impaired hepatic extraction of lactate and increased splanchnic production also contribute to the lactic acidosis of sepsis in dogs.[42]

Clinical Features. Lactic acidosis may occur in several clinical settings, especially those associated with poor perfusion and tissue hypoxia (e.g., cardiac arrest and cardiopulmonary resuscitation, shock, left ventricular failure). The clinician should strongly consider the possibility of lactic acidosis in such settings (see Box 10-2). Usually, lactic acidosis results from accumulation of the L isomer of lactate. D-Lactic acidosis, characterized by the accumulation of the D isomer, is rare but has been reported in human patients with "short-bowel syndrome" in whom gut bacteria metabolize glucose to D-lactate. D-Lactic acidosis also has been observed in cats fed propylene glycol[40,41] and has been documented in a cat with pancreatic insufficiency presumably as a consequence of intestinal bacterial overgrowth.[169]

Lactic acidosis should be suspected whenever there is an unexplained increase in unmeasured anions (i.e., an unexplained increase in the anion gap). Confirmation requires measurement of plasma lactate concentration, but this has not been performed commonly in small animal practice. Care should be taken to avoid vascular stasis when collecting venous blood for lactate determinations, and blood samples should be centrifuged immediately after collection to avoid a spurious increase in lactate concentration related to anaerobic glycolysis by red cells. Lactate concentrations in dogs have been reported in many experimental studies.* From results of these studies, normal plasma lactate concentrations in dogs are expected to be less than 2 mEq/L. Control plasma lactate concentrations in cats were 1.46 mEq/L in one study.[11]

Racing caused venous lactate concentrations in greyhounds to increase from 0.57 to 28.93 mEq/L, but lactate concentrations returned to 0.53 mEq/L 3 hours after exercise.[106] Arterial pH decreased from 7.365 to 6.997 and returned to 7.372 3 hours after exercise, and HCO_3^- concentration decreased from 21.1 to 3.1 mEq/L and returned to 20.5 mEq/L 3 hours after exercise. Plasma potassium concentration does not increase in response to organic acidosis as it does in acute mineral acidosis.[5] In the racing greyhounds, there was no change in plasma potassium concentration despite severe lactic acidosis.

Cardiac Arrest and Cardiopulmonary Resuscitation. Oxygen delivery to and CO_2 removal from tissues are dependent on adequate tissue perfusion. Cardiac arrest is an extreme example of impaired tissue perfusion. During cardiopulmonary resuscitation (CPR), reduced tissue perfusion and reduced O_2 delivery cause anaerobic metabolism and lactic acidosis. In dogs, lactate concentrations increased linearly during the time between cardiac arrest and the onset of CPR.[33] Lactate concentrations increased progressively during closed-chest CPR in dogs[34] and remained stable but did not decrease during 30 minutes of open-chest CPR.[33] In this model, closed-chest CPR did not provide adequate tissue perfusion and O_2 delivery to halt anaerobic metabolism.

During CPR, arterial blood gases reflect alveolar-arterial gas exchange, whereas mixed venous blood gases reflect tissue acid-base status and oxygenation.[140] Respiratory alkalosis develops in arterial blood as a result of mechanical ventilation, whereas respiratory acidosis develops in venous blood because of poor tissue perfusion and impaired transport of accumulated CO_2 to the lungs. In one study of human patients undergoing CPR, average arterial pH was 7.41, whereas average mixed venous pH was 7.15.[220] Arterial P_{CO_2} averaged 32 mm Hg and mixed venous P_{CO_2} was 74 mm Hg, whereas arterial and venous HCO_3^- concentrations were similar.

Closed-chest CPR, initiated after 6 minutes of cardiac arrest, was studied in dogs.[189] Sodium bicarbonate (2 mEq/kg) was administered after 20 minutes of cardiac arrest. Administration of $NaHCO_3$ increased both arterial and venous pH. Before $NaHCO_3$, arterial P_{CO_2} was approximately 40 mm Hg, and with CPR it decreased to 20 mm Hg as a result of mechanical ventilation. After $NaHCO_3$, arterial P_{CO_2} increased to 30 mm

**References 32,47,72,76,78,83,99,101,102,106,108,114, 119,131,139,140,154,179,213,214.*

Hg. Venous P_{CO_2} was nearly 50 mm Hg, and it slowly increased during 30 minutes of cardiac arrest to 60 mm Hg in untreated dogs. Bicarbonate treatment caused venous P_{CO_2} to increase transiently to 100 mm Hg, and it decreased to 70 mm Hg 10 minutes after $NaHCO_3$ administration. The pH of CSF was not changed by $NaHCO_3$ administration.

The normal arteriovenous pH gradient in dogs is 0.01 to 0.04.[7,18,138] Reduced cardiac output increases arteriovenous pH and P_{CO_2} gradients as a result of arterial hypocapnia and venous hypercapnia.[7,18,140,220] The ventilation-to-perfusion ratio is increased because of decreased pulmonary blood flow, accounting for the observed arterial hypocapnia. Venous hypercapnia results from anaerobic metabolism and a greater than normal addition of CO_2 to venous blood from hypoperfused tissues and diminished CO_2 excretion in the lungs because of pulmonary hypoperfusion. These increases in arteriovenous pH and P_{CO_2} gradients occur only if pulmonary ventilation continues. Respiratory arrest abolishes arteriovenous pH and P_{CO_2} gradients.[7] In summary, arterial P_{CO_2} is not an accurate reflection of CO_2 removal from tissues during CPR, and analysis of mixed venous P_{CO_2} is recommended.[7,18,138,140,220]

During CPR and ventilation with 100% O_2, arterial P_{O_2} may be normal, but tissue perfusion is low (20% to 25% of normal).[100] After $NaHCO_3$ administration, additional CO_2 is produced, and venous hypercapnia persists if ventilation is inadequate. Improving tissue perfusion is much more important during CPR than is $NaHCO_3$ administration. Effective cardiac compression and adequate perfusion allow delivery of O_2 to and removal of CO_2 from tissues. Conversely, tissue acidosis is aggravated and pH_i is decreased by $NaHCO_3$ administration if the CO_2 generated cannot be removed from the tissues by the lungs. The increase in tissue CO_2 decreases pH_i because CO_2 diffuses more rapidly into cells than does the charged HCO_3^-, thereby lowering the intracellular HCO_3^-/P_{CO_2} ratio. Intracellular acidosis of the myocardium leads to impaired cardiac contractility, decreased cardiac output, and aggravation of lactic acidosis. Thus the main goals of CPR are to provide adequate tissue perfusion by effective cardiac compression and to ventilate the patient with 100% O_2. In one study of short (5 minutes) and prolonged (15 minutes) cardiac arrest in dogs, $NaHCO_3$ administration improved acidosis without a significant increase in P_{CO_2}.[217] The authors concluded that $NaHCO_3$ might be useful to reverse the acidosis of cardiac arrest if ventilation is adequate and $NaHCO_3$ is administered in a reasonable therapeutic window.

Lymphosarcoma in Dogs. Dogs with lymphosarcoma had higher lactate concentrations than control animals, and their lactate concentrations increased significantly 30 minutes after administration of 500 mg/kg dextrose.[214] Blood lactate concentrations were higher before and 1 hour after infusion of lactated Ringer's solution in dogs with lymphosarcoma as compared with control animals.[213] Blood lactate concentration returned to baseline during the second hour of the 6-hour infusion. The authors concluded that dogs with stage III or IV lymphosarcoma might have abnormal carbohydrate metabolism and a transient inability to handle lactate loads. Tumors may produce increased amounts of lactate as a result of excessive anaerobic metabolism and possibly as a result of less than normal hepatic extraction of lactate. Induction of remission with doxorubicin chemotherapy did not improve hyperlactatemia in dogs with lymphosarcoma.[162]

Treatment. The outcome of lactic acidosis depends on the severity and reversibility of the underlying disease process responsible for the acid-base disturbance. If treatment of lactic acidosis is to be successful, prompt diagnosis and correction of the underlying disease state are crucial. Tissue perfusion and oxygen delivery should be improved by aggressive fluid therapy to expand ECFV. Ventilation with O_2 should be considered if the patient's spontaneous ventilation is inadequate. Infections should be treated with appropriate antimicrobial agents, and cardiac output should be improved, if necessary, by administration of inotropic agents. If the underlying disease cannot be corrected, the prognosis for patients with lactic acidosis is very poor. If the underlying disease can be corrected, the accumulated lactate is metabolized, yielding an equivalent amount of HCO_3^-, and the acidosis is reversed.

When the pH of the patient's blood decreases to below 7.1 to 7.2, administration of alkali is justified to prevent the detrimental effects of severe acidosis on the cardiovascular system (e.g., impaired myocardial contractility, impaired cardiovascular responsiveness to catecholamines, increased susceptibility to ventricular arrhythmias). Small doses of $NaHCO_3$ should be administered to increase the patient's pH to 7.2.[3,100,130]

Approximately 10% to 15% of administered $NaHCO_3$ is converted immediately to CO_2.[100] It is essential that ventilation increase to allow removal of accumulated CO_2 from the body. It is probably safe to administer $NaHCO_3$ if the patient can reasonably be expected to increase ventilation spontaneously. If not, administration of $NaHCO_3$ may be detrimental. In any case, $NaHCO_3$ should be administered slowly to minimize the increase in mixed venous P_{CO_2}.

The volume of distribution (V_d) of administered HCO_3^- is variable, depending on the severity of the acidosis.[2] Thus there is no simple way to calculate the dosage of $NaHCO_3$ required to increase the pH to 7.2. Volumes of distribution of 0.21 and 0.5 have been recommended for calculation of the bicarbonate space.[3,100] Sodium bicarbonate should be used cautiously and only in amounts necessary to increase the pH to 7.2. It

should be administered slowly over several minutes to a few hours, and at least 30 minutes should be allowed to elapse after the infusion before judging its effect.[3]

The use of $NaHCO_3$ in lactic acidosis is controversial.[156,204] Using the canine model of hypoxic lactic acidosis described above,[9] affected dogs were left untreated, treated with 2.5 mEq/kg $NaHCO_3$, or treated with 2.5 mEq/kg 1 M NaCl.[81,82] Animals treated with bicarbonate showed a greater decrease in pH and HCO_3^- concentration and higher lactate concentration than the other groups. Gut lactate production was greater in dogs that received $NaHCO_3$ than in dogs that received NaCl, and portal vein P_{CO_2} was higher in the group that received $NaHCO_3$. Arterial blood pressure and cardiac output declined in the untreated group and the group that received $NaHCO_3$ but were higher in the group that received NaCl. Increased portal vein P_{CO_2} and hepatic accumulation of lactate presumably caused hepatocyte pH_i to decrease. The ability of the liver to extract lactate depends on adequate hepatic blood flow and normal hepatocyte pH_i, both of which are decreased in this model. During hypoxia (P_{O_2} < 30 mm Hg), the liver is unable to increase its lactate extraction, despite an increased load delivered from the ischemic gut. The investigators concluded that use of $NaHCO_3$ during lactic acidosis might not be effective and might even be detrimental.

Dichloroacetate (DCA) stimulates the enzyme pyruvate dehydrogenase, which converts pyruvate to acetyl CoA.[54] In the canine model of hypoxic lactic acidosis described before,[9] DCA was compared with NaCl.[80] DCA increased pH and HCO_3^- concentration and maintained a constant lactate concentration, whereas NaCl treatment was associated with a decrease in pH and HCO_3^- concentration and an increase in lactate concentration. Hepatic lactate extraction increased with DCA, whereas liver and muscle accumulation of lactate decreased. Muscle pH_i increased with DCA, but neither treatment changed arterial blood pressure or cardiac output. DCA was also studied in a cardiac arrest model in dogs.[200] This study compared DCA, DCA and $NaHCO_3$, $NaHCO_3$, and no treatment. Bicarbonate treatment increased arterial pH, but DCA did not. DCA did not decrease lactate concentration or increase pH in either the peripheral circulation or CNS. In a canine model of hemorrhagic shock, DCA administration decreased arterial lactate concentrations but was associated with decreased cardiac stroke volume, decreased myocardial efficiency, and reduced myocardial lactate consumption.[13] Thus there are conflicting results regarding the usefulness of DCA in canine models of lactic acidosis.

Carbicarb is an equimolar mixture of Na_2CO_3 and $NaHCO_3$ that limits the generation of CO_2 during the buffering process:

$$Na_2CO_3 + H_2O + CO_2 \rightarrow 2HCO_3^- + 2Na^+$$

However, some of the HCO_3^- generated from this reaction can buffer H^+ released from nonbicarbonate buffers and generate CO_2 in the presence of carbonic anhydrase:

$$2HCO_3^- + 2H^+ \rightarrow 2H_2CO_3 \rightarrow 2H_2O + 2CO_2$$

In the canine model of hypoxic lactic acidosis described earlier,[9] 2.5 mEq/kg Carbicarb was compared with 2.5 mEq/kg $NaHCO_3$.[19] Arterial pH increased after administration of Carbicarb but decreased after $NaHCO_3$. Mixed venous P_{CO_2} was unchanged after Carbicarb administration but increased after $NaHCO_3$. Arterial lactate concentration increased after administration of $NaHCO_3$ but stabilized after Carbicarb, whereas lactate utilization by gut, muscle, and liver improved with Carbicarb but decreased after $NaHCO_3$. Hepatocyte pH_i increased after Carbicarb and decreased after $NaHCO_3$. Arterial blood pressure decreased to a lesser extent and cardiac output stabilized with Carbicarb, whereas cardiac output decreased with $NaHCO_3$. It was concluded that Carbicarb had a beneficial effect on myocardial contractility. Myocardial contractility may decrease after $NaHCO_3$ administration as a result of increased venous P_{CO_2} and decreased myocardial pH_i. Decreased cardiac output follows and leads to decreased blood flow and decreased O_2 delivery to gut, muscle, and liver, resulting in decreased lactate utilization and increased production. Carbicarb improved arterial pH without impairing myocardial contractility, presumably because it did not increase venous P_{CO_2}. This study suggests that Carbicarb is superior to $NaHCO_3$ in the treatment of lactic acidosis in dogs.

In another study, Carbicarb was compared with sodium bicarbonate and hypertonic saline in a canine model of hemorrhagic shock.[17] All dogs received identical sodium loads. Groups that received Carbicarb and sodium bicarbonate experienced similar increases in serum bicarbonate, but arterial P_{CO_2} increased more in bicarbonate-treated dogs than in those treated with Carbicarb. Hemodynamics, oxygen delivery, and oxygen consumption improved in all three groups, and these effects were attributed to the sodium load. Carbicarb, $NaHCO_3$, and NaCl were compared in a model of hypoxic lactic acidosis in anesthetized, mechanically ventilated dogs.[178] Carbicarb increased arterial pH, base excess, and cardiac index without an increase in lactate. Bicarbonate increased P_{CO_2}, but no adverse effects of $NaHCO_3$ on hemodynamics or pH_i were detected.

A sodium-free 0.3 N solution of tromethamine (THAM) is another CO_2-consuming alkalinizing agent that is capable of buffering both nonvolatile (H^+) and volatile (H_2CO_3 derived from CO_2) acid. THAM and sodium bicarbonate had similar buffering ability when evaluated in dogs with experimentally induced metabolic acidosis.[149] Dogs treated with THAM did not experience the transient hypernatremia and hypercapnia that were observed in bicarbonate-treated dogs.

Treatment of Metabolic Acidosis

The main goal in treatment of metabolic acidosis is prompt diagnosis and specific treatment of the underlying cause of the acid-base disorder. Correction of the underlying disease that is responsible for the patient's metabolic acidosis may be all that is necessary (e.g., fluids and insulin in diabetic ketoacidosis). In some instances, however, the underlying disease cannot be corrected (e.g., chronic renal failure), and alkali therapy must be considered.

In general, administration of $NaHCO_3$ should be reserved for clinical settings in which the patient's blood pH is less than 7.1 to 7.2, and $NaHCO_3$ should be administered only in amounts necessary to increase the pH to 7.2. Therapy with sodium bicarbonate is less likely to be harmful in animals with simple hyperchloremic metabolic acidosis (normal anion gap) because of the absence of unmeasured organic anions. In patients with normochloremic metabolic acidosis (increased anion gap), unmeasured organic anions (e.g., ketoacids, lactate) are present and can be metabolized to HCO_3^- during recovery. Administration of $NaHCO_3$ in such a setting may result in late development of metabolic alkalosis. This complication should not be serious if renal function is normal because the kidneys can excrete the excess HCO_3^-.

Severe acidosis may lead to life-threatening cardiovascular complications (e.g., impaired cardiac contractility, impaired pressor response to catecholamines, sensitization to ventricular arrhythmias).[147] Thus if blood pH is less than 7.1 to 7.2, judicious treatment with $NaHCO_3$ is justified. The aim of therapy should be to increase the patient's pH to 7.2 ($[H^+]$ = 63 nEq/L), at which point the risk of life-threatening hemodynamic complications is reduced.

For example, consider a 10-kg dog with a pH of 7.000, $[H^+]$ = 100 nEq/L, $[HCO_3^-]$ = 6 mEq/L, and P_{CO_2} = 25 mm Hg. We assume that normal values are a pH of 7.387, $[H^+]$ = 41 nEq/L, $[HCO_3^-]$ = 21 mEq/L, and P_{CO_2} = 36 mm Hg and that the normal compensatory respiratory response to metabolic acidosis is a 0.7-mm Hg decrement in P_{CO_2} per 1.0 mEq/L decrement in $[HCO_3^-]$. How much $NaHCO_3$ must be administered to increase the dog's pH to 7.200 ($[H^+]$ = 63 nEq/L)? This may be determined using the Henderson equation:

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

Thus the desired $[HCO_3^-]$ would be 24(25)/63 or 9.5 mEq/L if we assume that the P_{CO_2} will not change. However, alveolar hyperventilation is likely to subside somewhat as the acidemia is partially corrected. If we assume that the P_{CO_2} will increase to 28 mm Hg, the required $[HCO_3^-]$ is 24(28)/63 or 10.7 mEq/L. Thus we want to increase the dog's $[HCO_3^-]$ to 9.5 to 10.7 mEq/L.

We still must determine how much $NaHCO_3$ to administer. This can be calculated using the formula:

$$\text{mEq } HCO_3^- = V_d \times \text{weight (kg)} \times HCO_3^- \text{ deficit/L}$$

where V_d is the volume of distribution for HCO_3^-. However, the volume of distribution of HCO_3^- varies inversely with the initial HCO_3^- concentration and changes for at least 90 minutes after HCO_3^- administration to dogs.[2] In this study, dogs with chronic metabolic acidosis and initial plasma HCO_3^- concentrations of 10 mEq/L were given 5 mEq/kg $NaHCO_3$ and had average V_d values of 60% at 30 minutes and 76% at 90 minutes. This increase in V_d represents distribution of administered HCO_3^- from extracellular to intracellular sites. Bicarbonate distributes to ECF within 15 minutes and to intracellular and bone buffers within 2 to 4 hours.[183] Thus it is impossible to assign a single value for the V_d of $NaHCO_3$ administered to dogs with metabolic acidosis. Any dosage recommendations must be considered only rough guidelines to treatment.

The dogs in this study[2] had ECFVs equal to approximately 24.5% of body weight as measured by radiosulfate space. If we arbitrarily choose 0.5, a value approximately twice ECFV:

$$HCO_3^- \text{ (mEq)} = 0.5 \times 10 \times (9.5 - 6) = 17.5 \text{ mEq}$$

or

$$HCO_3^- \text{ (mEq)} = 0.5 \times 10 \times (10.7 - 6) = 23.5 \text{ mEq}$$

Thus the desired amount of $NaHCO_3$ is between 17.5 and 23.5 mEq. The $NaHCO_3$ should be administered over the first few hours of therapy and blood gases reevaluated before making a decision about additional alkali administration. This amount of $NaHCO_3$ represents a dose of 1.7 to 2.3 mEq/kg, and an empirical dose of 2 mEq/kg could safely have been used.

In patients with severe acidosis, any additional small reduction in plasma HCO_3^- concentration represents a large percentage change and can markedly increase $[H^+]$ (and reduce pH).[184] For example, consider a normal dog with a pH of 7.387, $[H^+]$ = 41 nEq/L, P_{CO_2} = 36 mm Hg, and $[HCO_3^-]$ = 21 mEq/L that sustains a peracute reduction in $[HCO_3^-]$ of 2 mEq/L (new $[HCO_3^-]$ = 19 mEq/L) before respiratory compensation can develop. The new $[H^+]$ can be calculated from the Henderson equation as 24(36)/19 = 45 nEq/L (pH 7.347). This represents a 0.04-U change in pH and a 4-nEq/L change in $[H^+]$. Now consider a dog with a pH of 7.102, $[H^+]$ = 79 nEq/L, P_{CO_2} = 23 mm Hg, and $[HCO_3^-]$ = 7 mEq/L that sustains a peracute reduction in $[HCO_3^-]$ of 2 mEq/L (new $[HCO_3^-]$ = 5 mEq/L) before respiratory compensation can develop. The dog's

new $[H^+]$ is 24(23)/5 = 110 nEq/L (pH 6.959). This represents a 0.14-U change in pH and a 31-nEq/L change in $[H^+]$. This change in $[H^+]$ is almost eight times greater than that observed in the previous example. Thus a small change in $[HCO_3^-]$ has a much more dramatic effect on $[H^+]$ and pH when the initial $[HCO_3^-]$ concentration is very low. For this reason, patients with very low plasma HCO_3^- concentrations and pH values less than 7.1 to 7.2 should be treated promptly with small amounts of $NaHCO_3$ to increase their pH to the hemodynamically safe value of 7.2.

Potential complications of $NaHCO_3$ therapy include volume overload caused by administered sodium, tetany resulting from decreased serum ionized calcium concentration caused by increased binding of calcium to plasma proteins, decreased O_2 delivery to tissues because of increased affinity of hemoglobin for O_2, paradoxical CNS acidosis as hyperventilation abates and CO_2 diffuses into CSF, late development of alkalosis as metabolism of organic anions (e.g., ketoanions, lactate) replenishes body HCO_3^- stores, and hypokalemia as potassium ions enter and H^+ ions exit intracellular fluid in response to alkalinization of ECF.[94]

METABOLIC ALKALOSIS

Metabolic alkalosis is characterized by a primary increase in plasma HCO_3^- concentration, decreased $[H^+]$, increased pH, and a secondary or adaptive increase in P_{CO_2}. Metabolic alkalosis was the third most common acid-base disturbance in dogs and cats in one study.[53]

Metabolic alkalosis can be caused by loss of chloride-rich fluid from the body via either the gastrointestinal tract or kidneys or by chronic administration of alkali. In the normal animal, renal excretion of exogenously administered alkali is very efficient, and it is difficult to create metabolic alkalosis by administration of alkali unless there is some factor preventing renal HCO_3^- excretion. Most cases of metabolic alkalosis in small animal practice are caused either by vomiting of stomach contents or by administration of diuretics. In a review of 962 dogs evaluated by blood gas determinations, 20 (2%) were found to be alkalemic.[179] Of these 20 dogs, 13 had metabolic alkalosis and 7 had respiratory alkalosis. Of the 13 dogs with metabolic alkalosis, 10 had a history of gastrointestinal disease.

Classification of Metabolic Alkalosis

Patients with metabolic alkalosis may be divided into two groups.[90,109,110,185,212] One group has ECFV depletion and avid renal retention of sodium and chloride. These patients respond to chloride administration and are said to have **chloride-responsive metabolic alkalosis.** The other group has normal or increased ECFV, and all sodium chloride ingested on a daily basis is excreted in the urine. These patients do not respond to chloride administration and are said to have **chloride-resistant metabolic alkalosis.**

In most instances of chloride-responsive metabolic alkalosis, the chloride concentration of the fluid lost from the body is greater than that of the ECF, so there has been a disproportionate loss of chloride. For example, the chloride concentration of gastric fluid is approximately 150 mEq/L, whereas serum chloride concentration is approximately 110 mEq/L in the dog and 120 mEq/L in the cat. Chloride-responsive metabolic alkalosis is much more common in small animal practice than is chloride-resistant metabolic alkalosis.

Development of Chloride-Responsive Metabolic Alkalosis

The pathophysiology of chloride-responsive metabolic alkalosis can be understood by considering the events associated with selective removal of gastric HCl.[117,118,158] Loss of H^+ from the stomach is associated, milliequivalent for milliequivalent, with an increase in the concentration of HCO_3^- in ECF. Plasma HCO_3^- concentration and the filtered load of HCO_3^- in the kidneys increase. Natriuresis, kaliuresis, suppression of net acid excretion with bicarbonaturia, increased urine flow rate, and renal water loss follow, but bicarbonaturia is transient and insufficient to return plasma HCO_3^- concentration to normal.[158] These events occurred without any change in GFR in a study of dogs made alkalotic by hemofiltration and replacement of ECF with a solution containing HCO_3^- as the only anion.[20] It is thought that the abatement of bicarbonaturia was caused by renal sodium avidity, engendered by the volume deficit that developed as a result of the initial natriuresis and diuresis. Renal sodium avidity is thus established and contributes to perpetuation of the alkalosis and development of a potassium deficit as long as chloride intake remains deficient. These events constitute the **development phase** of chloride-responsive metabolic alkalosis.

Probably the most important factors in the **maintenance phase** of chloride-responsive metabolic alkalosis are ECFV depletion and the chloride deficit, two factors that are difficult to separate experimentally.[45,87,111,160,188] Other factors that contribute to perpetuation of metabolic alkalosis are the effects of aldosterone and the potassium deficit. Aldosterone concentration is increased by ECFV depletion and results in increased distal renal Na^+-H^+ and Na^+-K^+ exchange. This results in perpetuation of alkalosis and development of a potassium deficit. Potassium depletion leads to a transcellular shift of H^+ from ECF to intracellular fluid in exchange for potassium ions. When this shift occurs in renal tubular cells, it decreases pH_i and enhances H^+ secretion by the renal tubular cells, further aggravating the alkalosis. Hypokalemia also stimulates renal ammoniagenesis, presumably through stimulation of glutaminase via decreased pH_i. The increase in renal ammonium

excretion enhances renal acid excretion and contributes to increased plasma HCO_3^- concentration. Hypokalemia also may decrease GFR as a consequence of glomerular hemodynamic changes and may directly impair chloride reabsorption in the distal nephron, resulting in enhanced lumen electronegativity and facilitation of H^+ secretion into tubular fluid.

Response of the Body to Metabolic Alkalosis

The body's response to metabolic alkalosis is the reverse of its response to administration of a mineral acid such as HCl. The kidney is more effective in excreting an alkaline load than an acid load, provided that the subject is not sodium avid and sufficient chloride is provided.

Acute Buffer Response

In an early study of the buffer response to alkali, nephrectomized dogs were given 20 mEq/kg $NaHCO_3$ with a resultant increase in plasma HCO_3^- concentration to approximately 60 mEq/L.[206] Of the administered HCO_3^-, almost one third (32%) was titrated by intracellular buffers. Of this 32%, 4% was converted to carbonic acid by H^+ from lactic acid released into ECF from cells. Increased pH_i enhances cellular production of lactic acid by stimulation of phosphofructokinase. Approximately 2% entered red cells in exchange for chloride (so-called chloride shift), and 26% was titrated by H^+ released from intracellular proteins and phosphates while sodium and potassium ions entered cells to maintain electroneutrality. By comparison, intracellular buffers handle approximately 50% of a mineral acid load.[195,207]

Approximately two thirds (68%) of the HCO_3^- load was confined to ECF. In response to the increase in pH, plasma proteins buffered 1% of this HCO_3^-. That is, plasma proteins released hydrogen ions in numbers sufficient to convert 1% of the infused HCO_3^- to carbonic acid. The remaining 67% was retained in the ECF compartment and contributed to the observed increase in plasma HCO_3^- concentration. These buffer reactions are summarized in Fig. 10-6.

Respiratory Response to Metabolic Alkalosis

The decrease in $[H^+]$ that accompanies chronic metabolic alkalosis stimulates chemoreceptors and is responsible for the observed decrease in alveolar ventilation. Secondary or adaptive alveolar hypoventilation protects pH in the presence of increased plasma HCO_3^- concentration (Fig. 10-7). A review of studies of dogs with experimentally induced metabolic alkalosis suggests that for each 1.0-mEq/L increase in plasma HCO_3^- concentration, there is an adaptive 0.55- to 0.77-mm Hg increase in P_{CO_2}.[20,35,131,132,171] This adaptive hypoventilation is associated with some degree of hypoxemia. Arterial P_{O_2} decreased to 60 to 70 mm Hg in dogs made

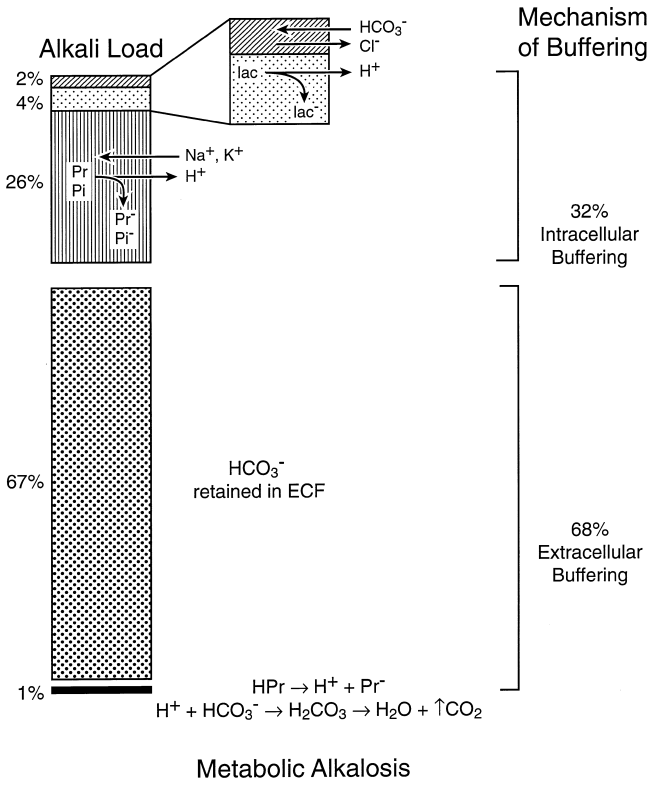


Fig. 10-6 Distribution of buffer response to a fixed alkaline load. (Drawing by Tim Vojt. Adapted from Pitts RF: *Physiology of the kidney and body fluids*, ed 2, Chicago, 1968, Year Book Medical Publishers, p. 173.)

alkalotic by feeding a diet with a chloride deficit and administering furosemide.[171]

The ventilatory response to metabolic alkalosis usually is considered to be less marked than the response to metabolic acidosis (i.e., a 0.6-mm Hg increase in P_{CO_2} for each 1-mEq/L increase in plasma HCO_3^- concentration in metabolic alkalosis as compared with a 1.2-mm Hg decrease in P_{CO_2} for each 1-mEq/L decrease in plasma HCO_3^- concentration in metabolic acidosis). This view has been challenged by a study of the ventilatory response of dogs to HCl acidosis and metabolic alkalosis induced by diuretics, removal of gastric acid, or mineralocorticoid administration.[132] The ventilatory responses to all of these experimental acid-base disturbances were not significantly different from one another, and it was concluded that an average change of 0.74 mm Hg P_{CO_2} can be expected for each 1.0-mEq/L change of plasma HCO_3^- concentration of metabolic origin. In one study, the respiratory compensation for metabolic alkalosis ranged from a 0.4- to 0.6-mm Hg increment in P_{CO_2} for each 1-mEq/L increment in HCO_3^- for arterial, mixed venous, and jugular venous samples in dogs made alkalotic by the administration of furosemide.[107] As a rule, a 1-mEq/L increase in plasma HCO_3^- concentration is expected to be associated with an adaptive 0.7-mm Hg increase in P_{CO_2} in dogs with metabolic alkalosis.

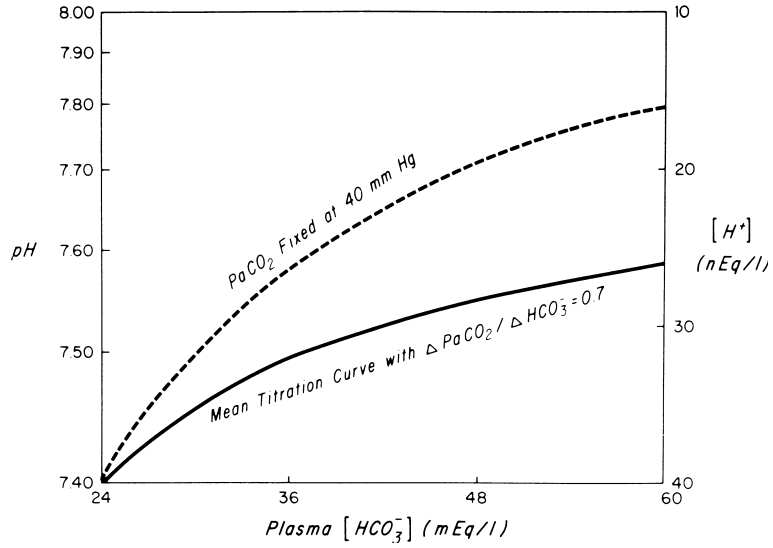


Fig. 10-7 Beneficial effect of respiratory adaptation on [H^+] and pH. (From Harrington JT, Kassirer JP: Metabolic alkalosis. In Cohen JJ, Kassirer JP, editors: *Acid-base*. Boston, 1982, Little, Brown & Co, p. 237.)

Renal Response to Metabolic Alkalosis

In the normal animal, the kidneys rapidly and effectively excrete administered alkali. Metabolic alkalosis persists only if renal excretion of HCO_3^- is impaired. This may occur if there is reduced GFR (decreased filtered load of HCO_3^-), a continued high rate of alkali administration, or some stimulus for the kidneys to retain sodium in the presence of a relative chloride deficit. In most dogs and cats with metabolic alkalosis, a combination of renal sodium avidity and diminished chloride availability is responsible for perpetuation of the alkalosis. A potassium deficit and hypokalemia develop as the kidneys increase Na^+-K^+ exchange in the distal nephron.

When sodium, chloride, and water are removed in proportion to their concentrations in ECF, sodium avidity develops but alkalosis does not.[91] When the sodium deficit in an alkalotic animal is repaired by infusing a fluid identical in composition to the alkalotic ECF, metabolic alkalosis is corrected by selective retention of chloride.[45] This occurs even when the filtered load of chloride is kept constant during the infusion of fluid.[46] Thus both sodium avidity and decreased chloride availability seem to be necessary for the perpetuation of metabolic alkalosis.

Potassium deficiency does not cause alkalosis but rather is a result of the alkalotic state. In fact, isolated potassium deficiency in dogs leads to mild metabolic acidosis.[30,31] When potassium retention is prevented but sodium chloride is supplied, alkalosis is corrected despite a persisting potassium deficit.[12,117,158] If potassium is supplied but chloride is not, alkalosis cannot be corrected.[116] Administration of potassium chloride leads to complete correction of both alkalosis and the potassium deficit.

The renal response to hypercapnia in metabolic alkalosis was studied in normal unanesthetized dogs made alkalotic by dietary chloride restriction and administration of ethacrynic acid.[131] Adaptive hypercapnia was allowed to develop and then prevented by exposure to hypoxia. During development of metabolic alkalosis, serum sodium concentration remained unchanged, but serum chloride, potassium, and phosphorus concentrations decreased, and lactate and unmeasured anion (i.e., anion gap) concentrations increased. With hypercapnia, plasma HCO_3^- concentration was maintained at 7.7 mEq/L above control values, whereas without hypercapnia it was maintained at 4.5 mEq/L above control values. Thus approximately 60% of the increase in plasma HCO_3^- concentration was caused by the renal response to chloride and volume depletion, whereas 40% of the increase could be attributed to adaptive hypercapnia. This response appeared to be a direct effect of P_{CO_2} on renal acid excretion and HCO_3^- reabsorption and was not related to any change in extracellular pH because the degree of alkalemia remained unchanged throughout the experiment. This portion of the increase in plasma HCO_3^- concentration (40%) may be considered maladaptive because it contributes to a higher extracellular pH. When metabolic alkalosis persists, this indiscriminate renal response to hypercapnia results in a further increase in plasma HCO_3^- concentration and abrogates the original beneficial effect of the increased plasma HCO_3^- concentration on extracellular pH.

Clinical Features of Metabolic Alkalosis

The clinical features of dogs and cats with metabolic alkalosis are usually those of the underlying disease process. Neurologic signs have been reported in human patients with severe metabolic alkalosis and include agitation, disorientation, stupor, and coma.[92] Muscle twitching and seizures may occur but have been observed rarely in dogs with severe metabolic alkalosis.

Clinical signs also may result from the accompanying potassium depletion. Signs of potassium depletion include muscle weakness of varying severity, cardiac arrhythmias, alterations in renal function (e.g., defective concentrating

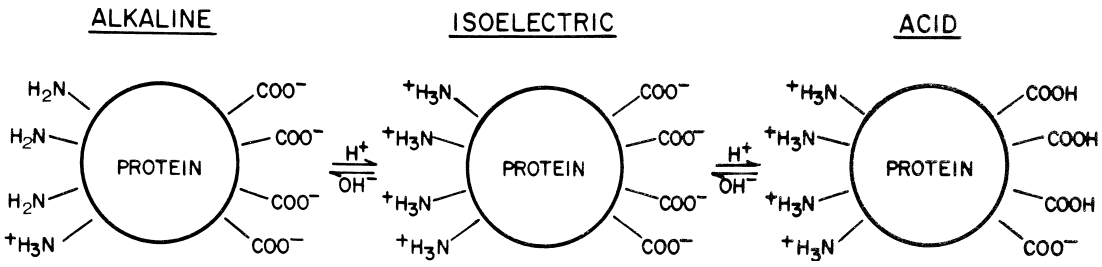


Fig. 10-8 Effect of alkalosis and acidosis on the charge of plasma proteins. (Modified from Pitts RF: *Physiology of the kidney and body fluids*, ed 2, Chicago, 1974, Year Book Medical Publishers, p. 186.)

ability), and gastrointestinal motility disturbances (e.g., ileus). These complications are discussed in Chapter 5.

Muscle twitching may occur as a result of decreased serum ionized calcium concentration because alkalosis increases the number of negative charges on proteins, allowing more calcium ions to be bound (Fig. 10-8). Serum ionized calcium concentration decreases and may account for neuromuscular irritability by rendering the threshold potential of cells more negative (i.e., bringing the resting potential closer to the threshold potential) (Fig. 10-9). Administration of a single dose (4 mEq/kg) of sodium bicarbonate to normal cats resulted in a 10% decrease in serum ionized calcium concentration and an 8% decrease in serum total calcium concentration. These changes persisted for 3 hours, but no clinical signs were observed.[36]

Metabolic alkalosis shifts the oxygen-hemoglobin dissociation curve to the left (Bohr effect) and impairs oxygen release from hemoglobin. This effect probably is not clinically significant because an increase in red cell 2,3-diphosphoglycerate concentration occurs after 6 to 8 hours of metabolic alkalosis and results in a shift of the curve back to the right.[16]

Fig. 10-9 Effect of hypocalcemia on the threshold potential (E_t) of cells. The height of the arrows is equal to the difference between the resting and threshold potentials and represents the excitability of the cell membrane. (From Rose BD: *Clinical physiology of acid-base and electrolyte disorders*, ed 3, New York, 1989, McGraw-Hill Co., p. 704.)

Diagnosis of Metabolic Alkalosis

Specific clinical manifestations of metabolic alkalosis have not been reported in dogs and cats. The clinician must have a high index of suspicion for this disorder when presented with an animal having compatible clinical signs, usually chronic vomiting of stomach contents. Thus an accurate history is the key to suspecting the diagnosis. Metabolic alkalosis also can be suspected from the results of routine serum biochemical tests. Blood gas analysis should be performed if decreased serum chloride and potassium concentrations are observed and total CO_2 content is increased. Blood gas analysis allows the clinician to determine whether primary metabolic alkalosis is present and whether the magnitude of respiratory compensation is as predicted (see earlier). The concentration of unmeasured anions (i.e., anion gap) in metabolic alkalosis may increase because of loss of hydrogen ions from nonbicarbonate buffers. The increased anion gap is primarily caused by increased numbers of negative charges on proteins and partially the result of the increase in plasma protein concentration that occurs as a consequence of ECFV depletion.[3]

Urine pH is low during the maintenance phase of metabolic alkalosis because of enhanced distal Na^+-H^+ exchange and reabsorption of all filtered HCO_3^-. However, urine pH is alkaline during development of and recovery from metabolic alkalosis. Thus urinary pH is of little diagnostic significance in metabolic alkalosis.

Causes of Metabolic Alkalosis

Metabolic alkalosis can be caused by continuous administration of alkali, disproportionate loss of chloride (chloride-responsive alkalosis), or excessive mineralocorticoid effect (chloride-resistant alkalosis). In some instances, the mechanism of metabolic alkalosis is unknown, and these examples are classified as miscellaneous. Most dogs with gastric dilatation-volvulus have metabolic acidosis or normal blood gas values at presentation,[153,223] but, uncommonly, metabolic alkalosis and hypokalemia have been reported.[115] The causes of metabolic alkalosis are listed in Box 10-3, and the pathophysiology of the major types of metabolic alkalosis is considered further here.

Box 10-3 Causes of Metabolic Alkalosis

Chloride Responsive
Vomiting of stomach contents
Diuretic therapy
Posthypercapnia

Chloride Resistant
Primary hyperaldosteronism
Hyperadrenocorticism

Alkali Administration
Oral administration of sodium bicarbonate or other organic anions (e.g., lactate, citrate, gluconate, acetate)
Oral administration of cation exchange resin with nonabsorbable alkali (e.g., phosphorus binder)

Miscellaneous
Refeeding after fasting
High-dose penicillin
Severe potassium or magnesium deficiency

Chloride-Responsive Metabolic Alkalosis

Chronic vomiting of stomach contents and administration of diuretics are the most common causes of chloride-responsive metabolic alkalosis in dogs and cats.

Administration of Alkali. Acute administration of 4 mEq/kg $NaHCO_3$ to normal unanesthetized cats resulted in mild increases in venous blood pH and HCO_3^- concentration lasting 180 minutes.[37] A slight decrease in serum chloride concentration persisted for 30 minutes, whereas a mild increase in P_{CO_2} persisted for 60 minutes. A solution of $NaHCO_3$ (6.6 mEq/L) infused over 30 minutes into anesthetized dogs caused transient increases in arterial P_{CO_2}, pH, base excess, and standard bicarbonate concentration.[95] Prompt renal excretion of administered $NaHCO_3$ presumably prevented any persistent change in acid-base values in these acute studies. Renal acid excretion decreases, urine pH increases, and administered $NaHCO_3$ is excreted within hours. There is an acute increase in carbonic acid and P_{CO_2} as body buffers release H^+ to combine with the administered HCO_3^-. The excess $NaHCO_3$ is excreted in the urine, increased ventilation occurs in response to increased P_{CO_2}, and acid-base balance is restored to normal.

When alkali is administered chronically, plasma HCO_3^- concentration becomes a function of the daily dosage administered but returns to normal within a few days after alkali administration is discontinued. If alkali is given to subjects rendered sodium avid by previous dietary salt restriction, smaller dosages of alkali result in greater increases in plasma HCO_3^- concentration than are observed when higher alkali dosages are used in subjects receiving normal amounts of dietary salt.

Sources of alkali other than $NaHCO_3$ may also contribute to metabolic alkalosis. Such organic anions include lactate that has accumulated during lactic acidosis, ketoacids in uncontrolled diabetes mellitus, and citrate in banked blood or that administered in an attempt to prevent recurrence of calcium oxalate urolithiasis. These organic anions yield HCO_3^- when metabolized:

$$Anion^- + O_2 \rightarrow HCO_3^- + CO_2 + H_2O$$

This reaction often serves to replace the HCO_3^- titrated during development of the acidosis (e.g., lactic acidosis, diabetic ketoacidosis). If $NaHCO_3$ has been administered during treatment, however, metabolism of the organic anion after correction of the acidosis can result in metabolic alkalosis. If renal function is normal and volume depletion is not present, the kidneys promptly excrete the excess HCO_3^- and restore normal acid-base balance.

Administration of nonabsorbable alkali (e.g., aluminum hydroxide used as a phosphorus binder in patients with renal failure) usually does not cause metabolic alkalosis. Neutralization of H^+ by $Al(OH)_3$ in the stomach results in the net addition of HCO_3^- to ECF. Combination of Al^{3+} with HCO_3^- secreted by the pancreas produces insoluble $Al_2(CO_3)_3$ in the duodenum, and there is no net increase in HCO_3^- ions in ECF. If, however, $Al(OH)_3$ is administered concurrently with a cationic exchange resin (e.g., polystyrene sulfonate), the resin can bind Al^{3+}, leaving HCO_3^- secreted by the pancreas to be reabsorbed in the small intestine, thus resulting in alkalinization of ECF. When renal failure is present, the kidneys have reduced capacity to excrete retained HCO_3^-, and metabolic alkalosis could result. This sequence of events is most likely to occur in an animal with oliguric renal failure that is treated concurrently with $Al(OH)_3$ for hyperphosphatemia and with polystyrene sulfonate for hyperkalemia.

Gastric Fluid Loss. The H^+ and Na^+ concentrations of gastric fluid are inversely related to one another, whereas the K^+ concentration is relatively stable (approximately 10 mEq/L). The Cl^- concentration is very high (approximately 150 mEq/L) and remains remarkably constant even when hypochloremia develops. Subtracting the sum of the Na^+ and K^+ concentrations of gastric fluid from the Cl^- concentration yields an approximation of the H^+ concentration. The composition of gastric fluid is compared with that of other body fluids in Fig. 10-10. When a dog or cat vomits stomach contents, water is lost along with large amounts of HCl and small amounts of potassium and sodium.

The H^+ produced during gastric acid secretion originates from the dissociation of carbonic acid; thus an equal number of HCO_3^- ions are generated in ECF. In the normal animal, gastric acid secretion does not

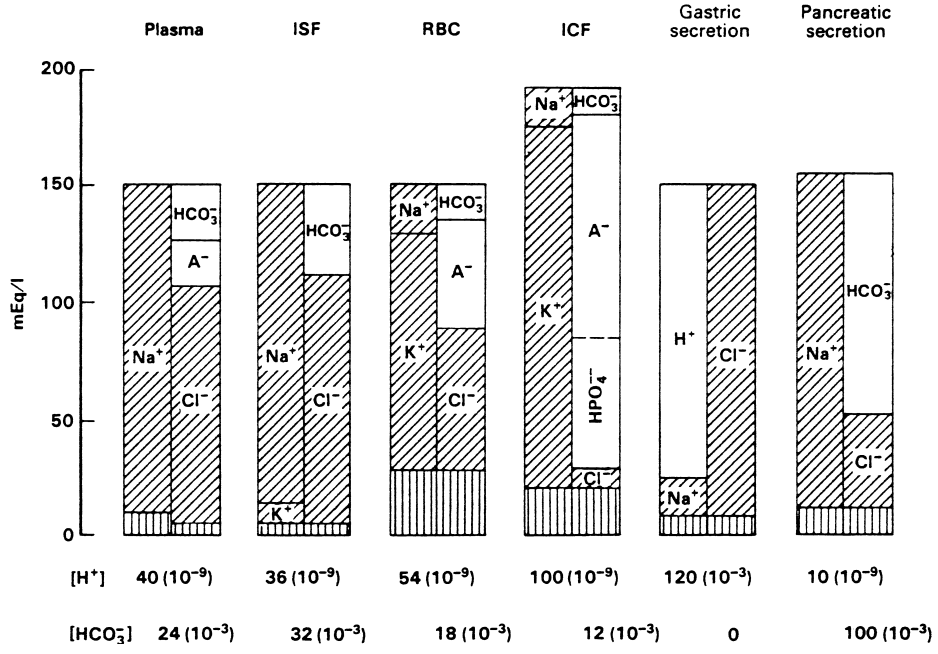


Fig. 10-10 Comparison of electrolyte composition of gastric juice to other body fluids using Gamblegrams. Strong ions are crosshatched. (From Jones NL: *Blood gases and acid-base physiology*, ed 2, New York, 1987, Thieme Medical Publishers, p. 133.)

disturb acid-base balance because the increase in ECF HCO_3^- concentration that accompanies parietal cell H^+ secretion is balanced by pancreatic HCO_3^- secretion in the duodenum, and Cl^- secreted into the stomach is recaptured lower in the gastrointestinal tract. When stomach contents are lost, H^+ and Cl^- are removed from this system, and HCO_3^- secreted into the duodenum by the pancreas is no longer titrated by gastric H^+ but is reabsorbed farther down in the gastrointestinal tract in place of Cl^-. The normal relationship between gastric and pancreatic secretions in the gastrointestinal tract is shown in Fig. 10-11. Continued loss of gastric fluid can result in marked increases in plasma HCO_3^- concentration, and chronic vomiting of stomach contents is the most common cause of metabolic alkalosis in small animal practice.

In studies of gastric alkalosis, experimental subjects are rendered sodium avid by feeding a low-salt diet. Gastric fluid is then continuously removed by nasogastric suction, and fluid and electrolyte losses other than HCl are quantitatively replaced.[117,118,158] The effects of repeated gastric drainage over 3 days on plasma HCO_3^- and chloride concentrations and on potassium, sodium, and chloride balance in experimental dogs are shown in Fig. 10-12. Note that the resulting metabolic alkalosis is corrected by provision of NaCl despite a progressively negative potassium balance. In the clinical setting, persistent vomiting of stomach contents leads to fluid and electrolyte losses (H^+ and Cl^- > Na^+ and K^+), and anorexia prevents adequate dietary intake of electrolytes. In patients with pyloric obstruction, gastrin secretion is

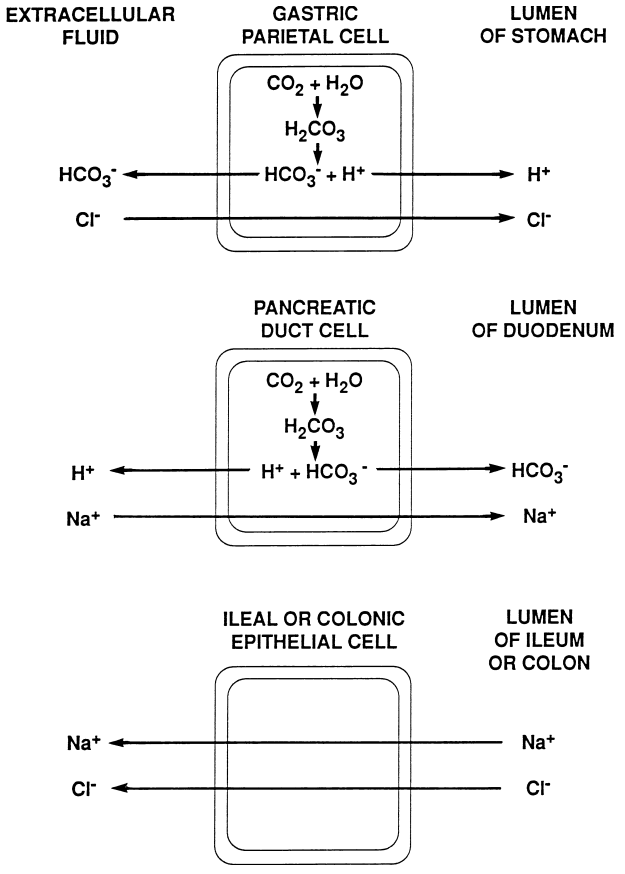


Fig. 10-11 Normal relationship between gastric and pancreatic secretions in the gastrointestinal tract. (Modified from Guyton AC: *Textbook of medical physiology*, ed 7, Philadelphia, 1986, WB Saunders, pp. 775-779.)

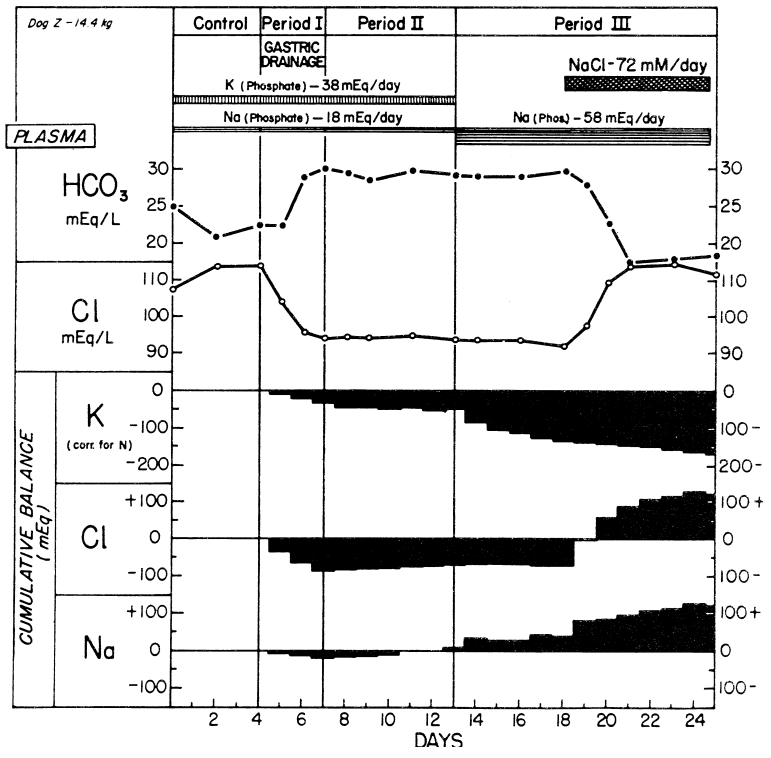


Fig. 10-12 Plasma composition and electrolyte balance in a representative study of selective HCl depletion. (From Needle MA, Kaloyanides GJ, Schwartz WB: The effects of selective depletion of hydrochloric acid on acid-base and electrolyte equilibrium. Reproduced from the *Journal of Clinical Investigation*, 43:1839, 1964, by copyright permission of the American Society for Clinical Investigation.)

enhanced, and gastric acid secretion is stimulated further. Overproduction of gastrin by a gastrin-secreting tumor may also stimulate gastric acid secretion. In one dog with gastrinoma, severe metabolic alkalosis and hypokalemia were associated with a history of chronic vomiting.[205]

Renal avidity for sodium and defense of the ECFV occur because of ongoing fluid and electrolyte losses in the vomiting animal or intake of a low-salt diet and nasogastric suction in the experimental setting. To maintain ECFV, the kidneys must reabsorb sodium by all available mechanisms. Because of ongoing loss of gastric HCl and insufficient dietary intake of salt, there is a chloride deficit; consequently, the kidneys must reabsorb less sodium with chloride and more sodium in exchange for hydrogen and potassium ions. The latter two mechanisms contribute to perpetuation of the metabolic alkalosis and development of potassium depletion as shown in Fig. 10-13. The low urine pH during the maintenance phase reflects increased distal Na^+-H^+ exchange in the sodium-avid state. This observation has led to the term "paradoxical aciduria" to describe the finding of low urine pH in patients with metabolic alkalosis. However, consideration of the relevant pathophysiology shows that this reduction in urine pH is the appropriate renal response under the circumstances. The extent of potassium depletion that develops is related to the severity and chronicity of the metabolic alkalosis.

Provision of chloride as the sodium or potassium salt allows correction of the alkalosis because the kidneys may now preferentially reabsorb sodium with chloride and rely less on Na^+-K^+ and Na^+-H^+ exchange.[12,116,117,158] This allows retained HCO_3^- to be excreted in the urine. Urine pH increases as HCO_3^- is excreted, indicating a favorable response to therapy. Chloride once again appears in the urine when the alkalosis is resolved. *The critical factor in resolution of this form of alkalosis is the provision of chloride as a resorbable anion.* Alkalosis can be corrected without provision of sodium or potassium as long as chloride is provided. Clinically, however, alkalosis is corrected by administering some combination of NaCl and KCl.

Diuretic Administration. Diuretics cause approximately equal losses of sodium and chloride in the urine, but the concentration of chloride in ECF is less than that of sodium by approximately 35 mEq/L. Thus these drugs may cause chloride-responsive metabolic alkalosis by a disproportionate loss of chloride in urine and creation of a relative chloride deficit in ECF. Increased renal sodium avidity is also an important factor in development of the metabolic alkalosis and potassium depletion that may occur during diuretic administration.

Loop diuretics inhibit NaCl reabsorption in the thick ascending limb of Henle's loop by competing with chloride for the Na^+-K^+-$2Cl^-$ luminal carrier. This causes increased delivery of sodium to the distal nephron, where accelerated Na^+-H^+ and Na^+-K^+ exchange occurs as the kidneys attempt to retain more sodium. Increased reliance of the kidneys on these mechanisms for sodium reabsorption contributes to metabolic alkalosis and potassium depletion. These complications are less likely

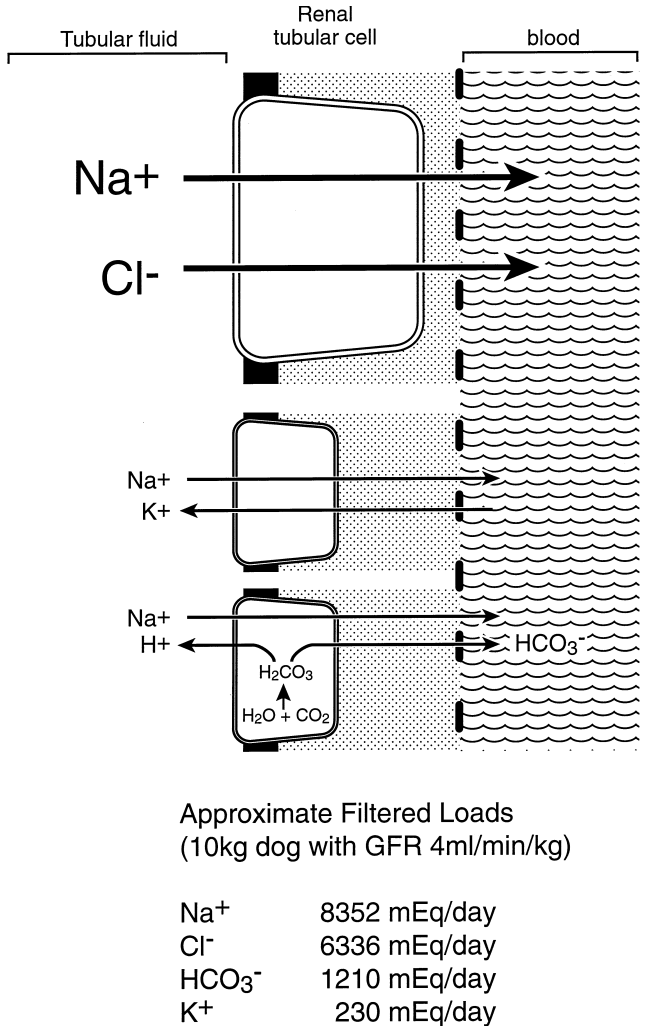


Fig. 10-13 Effects of chloride and potassium depletion on acid-base balance. See text for explanation. (Drawing by Tim Vojt.)

when thiazide diuretics are used. Thiazide diuretics inhibit NaCl transport in the distal tubule and connecting segment. They are less potent than the loop diuretics because their main effect occurs at sites in the nephron distal to those responsible for the majority of sodium reabsorption.

In response to hypokalemia, transcellular shifts of H^+ from ECF into renal tubular cells may occur in exchange for K^+. The resultant increase in intracellular H^+ concentration facilitates renal Na^+-H^+ exchange and aggravates metabolic alkalosis. Stimulation of the renin-angiotensin-aldosterone system by decreased effective circulating volume also favors increased Na^+-H^+ and Na^+-K^+ exchange in the distal nephron. These latter effects are probably important in most forms of chloride-responsive metabolic alkalosis.

Many animals treated with diuretics have congestive heart failure as their primary disease process. If the treatment plan for the animal includes a low-sodium diet, renal sodium avidity is guaranteed and increases the tendency toward metabolic alkalosis and potassium depletion. Complications from diuretic therapy are unlikely if the animal is drinking water and eating a diet with adequate amounts of chloride. However, complications can develop if the animal becomes anorexic.

Posthypercapnia. Blood pH increases rapidly when P_{CO_2} is suddenly reduced in patients with chronic hypercapnia. This has been called posthypercapnic metabolic alkalosis. In such patients, plasma HCO_3^- concentration has previously been increased by adaptive changes in renal HCO_3^- reabsorption. In response to the lowered P_{CO_2}, it takes several hours for the kidneys to decrease Na^+-H^+ exchange and begin to excrete the previously retained HCO_3^-. It may take several days for the kidneys to excrete all of the excess HCO_3^-, and sufficient chloride must be available during this time for reabsorption with sodium. Chloride deficiency during recovery from chronic hypercapnia plays a role in sustaining posthypercapnic metabolic alkalosis. Provision of chloride allows the alkalosis to be corrected.[194] Posthypercapnic metabolic alkalosis occurs most commonly in human patients with chronic pulmonary disease who are treated by mechanical ventilation. It is important that P_{CO_2} is decreased slowly and that adequate chloride intake is provided to prevent this complication.

Chloride-Resistant Metabolic Alkalosis

Several disorders in human medicine may cause chloride-resistant metabolic alkalosis. Of these, primary hyperaldosteronism and hyperadrenocorticism may occur in small animal practice. However, chloride-resistant metabolic alkalosis is rare in dogs and cats.

Primary Hyperaldosteronism. In primary hyperaldosteronism, increased secretion of aldosterone, usually by an adrenocortical tumor, results in sodium retention, volume expansion, hypernatremia, mild to moderate hypertension, potassium deficiency, hypokalemia, and metabolic alkalosis resistant to chloride administration. Plasma renin activity is low, but plasma aldosterone concentration is high. Affected human patients are in salt balance at an expanded ECFV and excrete ingested NaCl in the urine. Stimulation of distal nephron Na^+-H^+ and Na^+-K^+ exchange by excess mineralocorticoids is probably the most important pathophysiologic feature of primary hyperaldosteronism.

Several dogs and cats with primary hyperaldosteronism caused by aldosterone-producing adenomas or adenocarcinomas of the adrenal gland have been reported in the veterinary literature. Clinical features in affected animals included polyuria, polydipsia, weakness, hypertension, hypokalemia, hypernatremia, mild metabolic alkalosis, dilute urine, and extremely high serum aldosterone concentrations (for additional information and references see Chapter 5).

Hyperadrenocorticism. Metabolic alkalosis occurs in approximately one third of human patients with Cushing's syndrome.[93] It is more common in patients with adrenocortical carcinomas and in those with ectopic production of ACTH by nonadrenal malignancies than in those with pituitary-dependent hyperadrenocorticism. The frequency of metabolic alkalosis and serum electrolyte disturbances in dogs with hyperadrenocorticism is uncertain. Serum sodium and potassium concentrations often are normal in dogs with hyperadrenocorticism. This may reflect the fact that 80% to 85% of dogs with hyperadrenocorticism have pituitary-dependent disease. In a large group of dogs with hyperadrenocorticism, 21 of 52 (40%) dogs had increased serum sodium concentrations and 25 of 52 (48%) had decreased serum potassium concentrations.[125] The relative frequency of pituitary- and adrenal-dependent disease was not reported in this study. In another study, mild hypernatremia and hypokalemia were observed occasionally in dogs with hyperadrenocorticism, and total CO_2 content was increased in 33% of affected dogs.[173] In another report, hypokalemia was found in only 5% of dogs with pituitary-dependent hyperadrenocorticism but in 45% of those with adrenocortical neoplasia.[144] A high rate of secretion of cortisol and other corticosteroids such as desoxycorticosterone and corticosterone in patients with adrenocortical malignancies could be responsible for hypernatremia, hypokalemia, and metabolic alkalosis in adrenal-dependent hyperadrenocorticism.

Miscellaneous

Large doses of penicillin, ampicillin, or carbenicillin administered as a sodium salt can lead to hypokalemia and metabolic alkalosis in human patients. The drug may increase lumen electronegativity in the distal nephron by acting as a nonresorbable anion and enhancing Na^+-H^+ and Na^+-K^+ exchange. "Refeeding" alkalosis can occur in human patients when glucose is administered after prolonged fasting. The mechanism for this type of alkalosis is unknown. These types of metabolic alkalosis have not been reported in the veterinary literature.

TREATMENT OF METABOLIC ALKALOSIS

Acid-base disturbances are secondary phenomena. Diagnosis and definitive treatment of the responsible disease process are integral to the successful resolution of acid-base disorders. However, it must be remembered that alkalosis persists until chloride is replaced if vomiting of stomach contents or diuretic administration is responsible for the metabolic alkalosis. The goal of treatment in chloride-responsive metabolic alkalosis is to replace the chloride deficit while providing sufficient potassium and sodium to replace existing deficits. Definitive treatment of the underlying disease process (e.g., removal of a gastric foreign body) prevents recurrence of the metabolic alkalosis.

Patients with chronic pulmonary disease that have hypoxemia and hypercapnia are at greater risk from metabolic alkalosis than others because superimposition of metabolic alkalosis can further reduce ventilation and lead to worsening of hypoxemia. Thus metabolic alkalosis should be treated appropriately if present and avoided if not present. Giving oxygen to patients with metabolic alkalosis should also be avoided if possible because this may impair ventilation and further aggravate hypercapnia.

Potassium without chloride (e.g., potassium phosphate) corrects neither the alkalosis nor the potassium deficit because administered potassium is excreted in the urine. A chloride salt must be given for alkalosis to be resolved and potassium retention to occur. Provision of chloride as either the sodium or potassium salt corrects chloride-responsive metabolic alkalosis. This therapy allows the kidneys to reabsorb the sodium the body requires with chloride to maintain electroneutrality. Thus a NaCl solution (0.45% or 0.9%) with added KCl is the fluid of choice for dogs and cats with chloride-responsive metabolic alkalosis. It is best to use solutions containing NaCl and KCl because affected animals typically have been sick long enough to develop clinically significant potassium deficits. Administering 0.9% NaCl without KCl can cause diuresis and increased urinary excretion of potassium, thus worsening any potassium deficit. As shown in Fig. 10-12, provision of NaCl corrects metabolic alkalosis induced in dogs by gastric drainage, but the potassium deficit persists unless potassium is provided. A few days may be required to restore normal electrolyte and acid-base balance, but in nearly all instances, these measures are sufficient to resolve the alkalosis. In human patients with severe metabolic alkalosis or in those with severely impaired renal function, HCl or arginine HCl has been used for rapid correction of metabolic alkalosis, but there is no report of the use of these compounds in animals with metabolic alkalosis, and their use is not recommended.

H2-blocking drugs such as cimetidine, ranitidine, or famotidine may be considered as adjunctive therapy if gastric losses are ongoing because this approach reduces gastric acid secretion. For the patient with heart failure receiving loop diuretics, oral KCl administration is the best way to provide chloride without sodium and prevent further retention of fluid and aggravation of edema. Even in the presence of sodium avidity, provision of chloride lessens Na^+-H^+ and Na^+-K^+ exchange at distal nephron sites and prevents development of alkalosis when loop diuretics are used. Simultaneous use of distal blocking agents such as spironolactone, triamterene, or amiloride may also be considered. These drugs work in the principal cells of the cortical collecting tubule and impair Na^+-H^+ and Na^+-K^+ exchange by inhibiting aldosterone-sensitive sodium channels. In metabolic alkalosis caused by chronic administration of alkali, discontinuation of the source of alkali results in correction of the

alkalosis over a few days, provided that renal function is normal.

Chloride-resistant metabolic alkalosis is uncommon in comparison with chloride-responsive metabolic alkalosis. When present, its successful treatment requires that the underlying disease be diagnosed and treated before alkalosis can be resolved. Cases of chloride-resistant metabolic alkalosis are rare in veterinary medicine.

REFERENCES

1. Adams WH, Toal RL, Walker MA, et al: Early renal ultrasonographic findings in dogs with experimentally induced ethylene glycol nephrosis, *Am J Vet Res* 50:1370, 1989.
2. Adrogue HJ, Brensilver J, Cohen J, et al: Influence of steady-state alterations in acid-base equilibrium on the fate of administered bicarbonate in the dog, *J Clin Invest* 71:867, 1983.
3. Adrogue HJ, Brensilver J, Madias NE: Changes in the plasma anion gap during chronic metabolic acid-base disturbances, *Am J Physiol* 235:F291, 1978.
4. Adrogue HJ, Eknoyan G, Suki WK: Diabetic ketoacidosis: role of the kidney in the acid-base homeostasis re-evaluated, *Kidney Int* 25:591, 1984.
5. Adrogue HJ, Madias NE: Changes in plasma potassium concentration during acute acid base disturbances, *J Clin Invest* 71:456, 1981.
6. Adrogue HJ, Madias NE: Management of life-threatening acid-base disorders, *N Engl J Med* 338:26, 1998.
7. Adrogue HJ, Rashad MN, Gorin AB, et al: Arteriovenous acid-base disparity in circulatory failure: studies on mechanism, *Am J Physiol* 257:F1087, 1989.
8. Adrogue HJ, Wilson H, Boyd AE, et al: Plasma acid-base patterns in diabetic ketoacidosis, *N Engl J Med* 307:1603, 1982.
9. Arieff AI, Graf H: Pathophysiology of type A hypoxic lactic acidosis in dogs, *Am J Physiol* 253:E271, 1987.
10. Arruda JAL, Carrasquillo T, Cubria A, et al: Bicarbonate reabsorption in chronic renal failure, *Kidney Int* 9:481, 1976.
11. Atkins CE, Tyler R, Greenlee P: Clinical, biochemical, acid-base, and electrolyte abnormalities in cats after hypertonic sodium phosphate enema administration, *Am J Vet Res* 46:980, 1985.
12. Atkins EL, Schwartz WB: Factors governing correction of the alkalosis associated with potassium deficiency: the critical role of chloride in the recovery process, *J Clin Invest* 41:218, 1962.
13. Barbee RW, Kline JA, Watts JA: Depletion of lactate by dichloroacetate reduces cardiac efficiency after hemorrhagic shock, *Shock* 14:208-214, 2000.
14. Bark H, Perk R: Fanconi syndrome associated with amoxicillin therapy in the dog, *Canine Pract* 20:19, 1995.
15. Beckett SD, Shields RP: Treatment of acute ethylene glycol (antifreeze) poisoning in the dog, *J Am Vet Med Assoc* 158:472, 1971.
16. Bellingham AJ, Detter JC, Lenfant C: Regulatory mechanisms of hemoglobin oxygen affinity in acidosis and alkalosis, *J Clin Invest* 50:700, 1971.
17. Benjamin J, Oropello JM, Abalos AM, et al: Effects of acid-base correction on hemodynamics, oxygen dynamics, and resuscitability in severe canine hemorrhagic shock, *Crit Care Med* 22:1616, 1994.
18. Bergman KS, Harris BH: Arteriovenous pH difference—a new index of perfusion, *J Pediatr Surg* 23:1190, 1988.
19. Bersin RM, Arieff AL: Improved hemodynamic function during hypoxia with Carbicarb, a new agent for the management of acidosis, *Circulation* 77:227, 1988.
20. Borkan S, Northrup TE, Cohen JJ, et al: Renal response to metabolic alkalosis induced by isovolemic hemofiltration in the dog, *Kidney Int* 32:322, 1987.
21. Bovee KC: *Characterization and treatment of isolated renal tubular acidosis in a dog,* Washington, DC, 1984, American College of Veterinary Internal Medicine, p. 48.
22. Bovee KC, Joyce T, Reynolds R, et al: The Fanconi syndrome in basenji dogs: a new model for renal transport defects, *Science* 201:1129, 1978.
23. Bovee KC, Joyce T, Reynolds R, et al: Spontaneous Fanconi syndrome in the dog, *Metabolism* 27:45, 1978.
24. Bovee KC, Joyce T, Blazer-Yost B, et al: Characterization of renal defects in dogs with a syndrome similar to Fanconi syndrome in man, *J Am Vet Med Assoc* 174:1094, 1979.
25. Brown SA, Rackich PM, Barsanti JA, et al: Fanconi syndrome and acute renal failure associated with gentamicin therapy in a dog, *J Am Anim Hosp Assoc* 22:635, 1986.
26. Brown SA, Spyridakis LK, Crowell WA: Distal renal tubular acidosis and hepatic lipidosis in a cat *J Am Vet Med Assoc* 189:1350, 1986.
27. Bruskiewicz KA, Nelson RW, Feldman EC, et al: Diabetic ketosis and ketoacidosis in cats: 42 cases (1980–1995), *J Am Vet Med Assoc* 211:188, 1997.
28. Buffington CA, Cook NE, Rogers QR, et al: The role of diet in feline struvite urolithiasis syndrome. In Burger IH, Rivers JPW, editors: *Nutrition of the dog and cat,* London, 1989, Cambridge University Press, p. 357.
29. Burnell JM: Changes in bone sodium and carbonate in metabolic acidosis and alkalosis in the dog, *J Clin Invest* 50:327, 1971.
30. Burnell JM, Dawbron JK: Acid-base parameters in potassium depletion in the dog, *Am J Physiol* 218:1583, 1970.
31. Burnell JM, Teubner EJ, Simpson DP: Metabolic acidosis accompanying potassium deprivation, *Am J Physiol* 227:329, 1974.
32. Cain SM, Dunn JE: Transient arterial lactic acid changes in unanesthetized dogs at 21,000 feet, *Am J Physiol* 206: 1437, 1964.
33. Carden DL, Martin GB, Nowak RM, et al: Lactic acidosis as a predictor of downtime during cardiopulmonary arrest in dogs, *Am J Emerg Med* 3:120, 1985.
34. Carden DL, Martin GB, Nowak RM, et al: Lactic acidosis during closed-chest CPR in dogs, *Ann Emerg Med* 16:1317, 1987.
35. Chazan JA, Appleton FM, London AM, et al: Effects of chronic metabolic acid-base disturbances on the composition of cerebrospinal fluid in the dog, *Clin Sci* 36:345, 1969.
36. Chew DJ, Leonard M, Muir WW: Effect of sodium bicarbonate infusions on ionized calcium and total calcium concentrations in serum of clinically normal cats, *Am J Vet Res* 50:145, 1989.
37. Chew DJ, Leonard M, Muir WW: Effect of sodium bicarbonate infusion on serum osmolality, electrolyte concentrations, and blood gas tensions in cats, *Am J Vet Res* 52:12, 1991.
38. Ching SV, Fettman MJ, Hamar DW, et al: The effect of chronic dietary acidification using ammonium chloride on acid-base and mineral metabolism in the adult cat, *J Nutr* 119:902, 1989.

39. Ching SV, Norrdin RW, Fettman MJ, et al: Trabecular bone remodeling and bone mineral density in the adult cat during chronic dietary acidification with ammonium chloride, *J Bone Miner Res* 5:547, 1990.
40. Christopher MM, Eckfeldt JH, Eaton JW: Propylene glycol ingestion causes D-lactic acidosis, *Lab Invest* 62:114, 1990.
41. Christopher MM, Perman V, White JG, et al: Propylene glycol–induced Heinz body formation and D-lactic acidosis in cats, *Prog Clin Biol Res* 319:69, 1989.
42. Chrusch C, Bands C, Bose D, et al: Impaired hepatic extraction and increased splanchnic production contribute to lactic acidosis in canine sepsis, *Am J Respir Crit Care Med* 161:517-526, 2000.
43. Clark DD, Chang BS, Garella SG, et al: Secondary hypocapnia fails to protect "whole body" intracellular pH during chronic HCl-acidosis in the dog, *Kidney Int* 23:336, 1983.
44. Clay KL, Murphy RC: On the metabolic acidosis of ethylene glycol intoxication, *Toxicol Appl Pharmacol* 39:39, 1977.
45. Cohen JJ: Correction of metabolic alkalosis by the kidney after isometric expansion of extracellular fluid, *J Clin Invest* 47:1181, 1968.
46. Cohen JJ: Selective chloride retention in repair of metabolic alkalosis without increasing filtered load, *Am J Physiol* 218:165, 1970.
47. Cohen JJ, Brackett NC, Schwartz WB: The nature of the carbon dioxide titration curve in the normal dog, *J Clin Invest* 43:777, 1964.
48. Cohen JJ, Madias NE, Wolf CJ, et al: Regulation of acid-base equilibrium in chronic hypocapnia: evidence that the response of the kidney is not geared to the defense of extracellular $[H^+]$, *J Clin Invest* 57:1483, 1976.
49. Cohen RD, Woods RA: *Clinical and biochemical aspects of lactic acidosis,* London, 1976, Blackwell Scientific.
50. Cohen RM, Feldman GM, Fernandez PC: The balance of acid, base and charge in health and disease, *Kidney Int* 52:287, 1997.
51. Connally HE, Thrall MA, Forney SD, et al: Safety and efficacy of 4-methylpyrazole for treatment of suspected or confirmed ethylene glycol intoxication: 107 cases (1983–1995), *J Am Vet Med Assoc* 209:1880, 1996.
52. Constable PD, Stämpfli HR: Experimental determination of net protein charge and A_{tot} and K_a of nonvolatile buffers in canine plasma, *J Vet Intern Med* 19:507, 2005.
53. Cornelius LM, Rawlings CA: Arterial blood gas and acid base values in dogs with various diseases and signs of disease, *J Am Vet Med Assoc* 178:992, 1981.
54. Crabb DW, Young EA, Harris RA: The metabolic effects of dichloroacetate, *Metab Clin Exp* 30:1024, 1981.
55. Crenshaw KL, Peterson ME: Pretreatment clinical and laboratory evaluation of cats with diabetes mellitus: 104 cases (1992–1994), *J Am Vet Med Assoc* 209:943, 1996.
56. Darrigrand-Haag RA, Center SA, Randolph JF, et al: Congenital Fanconi syndrome associated with renal dysplasia in 2 Border terriers, *J Vet Intern Med* 10:412, 1996.
57. DeFronzo RA: Hyperkalemia and hyporeninemic hypoaldosteronism, *Kidney Int* 17:118, 1980.
58. DeSousa RC, Harrington JT, Ricanati ES, et al: Renal regulation of acid-base equilibrium during chronic administration of mineral acid, *J Clin Invest* 53:465, 1974.
59. Dial SM, Thrall M, Hamar DW: 4-Methylpyrazole as treatment for naturally acquired ethylene glycol intoxication in dogs, *J Am Vet Med Assoc* 195:73, 1989.
60. Dial SM, Thrall MAH, Hamar DW: Comparison of ethanol and 4-methylpyrazole as treatments for ethylene glycol intoxication in cats, *Am J Vet Res* 55:1771, 1994.
61. Dial SM, Thrall MAH, Hamar DW: Efficacy of 4-methylpyrazole for treatment of ethylene glycol intoxication in dogs, *Am J Vet Res* 55:1762, 1994.
62. DiBartola SP, Leonard PO: Renal tubular acidosis in a dog, *J Am Vet Med Assoc* 180:70, 1982.
63. DiBartola SP, Rutgers HC, Zack PM, et al: Clinicopathologic findings associated with chronic renal disease in cats: 74 cases (1973–1984), *J Am Vet Med Assoc* 190:1196, 1987.
64. DiBartola SP, Tarr MJ, Parker AT, et al: Clinicopathologic findings in dogs with renal amyloidosis: 59 cases (1976–1986), *J Am Vet Med Assoc* 195:358, 1989.
65. Dinour D, Chang MH, Satoh J, et al: A novel missense mutation in the sodium bicarbonate cotransporter (NBCe1/SLC4A4) causes proximal tubular acidosis and glaucoma through ion transport defects, *J Biol Chem* 279:52238-52246, 2004.
66. Dorhout-Mees EJ, Machado M, Slatopolsky E, et al: The functional adaptation of the diseased kidney. III. Ammonium excretion, *J Clin Invest* 45:289, 1966.
67. Dow SW, Fettman MJ, Smith KR, et al: Effects of dietary acidification and potassium depletion on acid-base balance, mineral metabolism and renal function in adult cats, *J Nutr* 120:569, 1990.
68. Drazner FH: Distal renal tubular acidosis associated with chronic pyelonephritis in a cat, *Calif Vet* 34:15, 1980.
69. Duarte R, Simoes DMN, Franchini ML, et al: Accuracy of serum β-hydroxybutyrate measurements for the diagnosis of diabetic ketoacidosis in 116 dogs, *J Vet Intern Med* 16:411-417, 2002.
70. Easley JR, Breitschwerdt EB: Glucosuria associated with renal tubular dysfunction in three basenji dogs, *J Am Vet Med Assoc* 168:938, 1976.
71. Escolar E, Perezalenza D, Diaz M, et al: Canine Fanconi syndrome, *J Small Anim Pract* 34:567, 1993.
72. Evans GO: Plasma lactate measurements in healthy beagles, *Am J Vet Res* 48:131, 1987.
73. Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* Philadelphia, 1996, WB Saunders p. 400.
74. Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* Philadelphia, 1996, WB Saunders, p. 411.
75. Finco DR, Barsanti JA, Brown SA: Ammonium chloride as a urinary acidifier in cats: efficacy, safety, and rationale for its use, *Mod Vet Pract* 67:537, 1986.
76. Fine A, Brosnan JT, Herzberg GR: Release of lactate by the liver in metabolic acidosis in vivo, *Metabolism* 33:393, 1984.
77. Freeman LM, Breitschwerdt EB, Keene BW, et al: Fanconi's syndrome in a dog with primary hypoparathyroidism, *J Vet Intern Med* 8:349, 1994.
78. Gennari FJ, Goldstein MB, Schwartz WB: The nature of the renal adaptation to chronic hypocapnia, *J Clin Invest* 51:1722, 1972.
79. Gougoux A, Kaehny WD, Cohen JJ: Renal adaptation to chronic hypocapnia: dietary constraints in achieving H^+ retention, *Am J Physiol* 229:1330, 1975.
80. Graf H, Leach W, Arieff AI: Effects of dichloroacetate in the treatment of hypoxic lactic acidosis in dogs, *J Clin Invest* 76:919, 1985.
81. Graf H, Leach W, Arieff AI: Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis, *Science* 227:754, 1985.

82. Graf H, Leach W, Arieff AI: Metabolic effects of sodium bicarbonate in hypoxic lactic acidosis in dogs, *Am J Physiol* 249:F630, 1985.
83. Graham TE, Barclay JK, Wilson BA: Skeletal muscle lactate release and glycolytic intermediates during hypercapnia, *J Appl Physiol* 60:568, 1986.
84. Grauer GF, Thrall MA: Ethylene glycol (antifreeze) poisoning in the dog and cat, *J Am Anim Hosp Assoc* 18:492, 1982.
85. Grauer GF, Thrall MA: Ethylene glycol (antifreeze) poisoning. In Kirk RW, editor: *Current veterinary therapy IX*. Philadelphia, 1986, WB Saunders, p. 206.
86. Grauer GF, Thrall MA, Henre BA, et al: Early clinicopathologic findings in dogs ingesting ethylene glycol, *J Am Vet Med Assoc* 45:2299, 1984.
87. Harrington JT: Metabolic alkalosis, *Kidney Int* 26:88, 1984.
88. Harrington JT, Cohen JJ: Metabolic acidosis. In Cohen JJ, Kassirer JP, editors: *Acid-base,* Boston, 1982, Little, Brown & Co., p. 128.
89. Harrington JT, Cohen JJ: Metabolic acidosis. In Cohen JJ, Kassirer JP, editors: *Acid-base,* Boston, 1982, Little, Brown & Co., p. 157.
90. Harrington JT, Kassirer JP: Metabolic alkalosis. In Cohen JJ, Kassirer JP, editors: *Acid-base,* Boston, 1982, Little, Brown & Co., p. 227.
91. Harrington JT, Kassirer JP: Metabolic alkalosis. In Cohen JJ, Kassirer JP, editors: *Acid-base.* Boston, 1982, Little, Brown & Co., p. 232.
92. Harrington JT, Kassirer JP: Metabolic alkalosis. In Cohen JJ, Kassirer JP, editors: *Acid-base.* Boston, 1982, Little, Brown & Co., p. 240.
93. Harrington JT, Kassirer JP: Metabolic alkalosis. In Cohen JJ, Kassirer JP, editors: *Acid-base.* Boston, 1982, Little, Brown & Co., p. 280.
94. Hartsfield SM: Sodium bicarbonate and bicarbonate precursors for treatment of metabolic acidosis, *J Am Vet Med Assoc* 179:914, 1981.
95. Hartsfield SM, Thurmon JC, Corbin JE, et al: Effects of sodium acetate, bicarbonate and lactate on acid-base status in anaesthetized dogs, *J Vet Pharmacol Ther* 4(1):51-61, 1981.
96. Haskins SC, Munger RJ, Helphrey MG, et al: Effect of acetazolamide on blood acid-base and electrolyte values in dogs, *J Am Vet Med Assoc* 179:914, 1981.
97. Heald RD, Jones BD, Schmidt DA: Blood gas and electrolyte concentrations in canine parvoviral enteritis, *J Am Anim Hosp Assoc* 22:745, 1986.
98. Herrtage ME, Houlton JE: Collapsing Clumber spaniels, *Vet Rec* 105:334, 1979.
99. Hetenyi G, Paradis H, Kucharczyk J: Glucose and lactate turnover and gluconeogenesis in chronic metabolic acidosis and alkalosis in normal and diabetic dogs, *Can J Physiol Pharmacol* 66:140, 1988.
100. Hindman BJ: Sodium bicarbonate in the treatment of subtypes of acute lactic acidosis: physiologic considerations, *Anesthesiology* 72:1064, 1990.
101. Honer WG, Jennings DB: P_{CO_2} modulation of ventilation and HCO_3^- buffer during chronic metabolic acidosis, *Respir Physiol* 54:241, 1983.
102. Hornbein TF, Pavlin EG: Distribution of H^+ and HCO_3^- between CSF and blood during respiratory alkalosis in dogs, *Am J Physiol* 228:1149, 1975.
103. Hostutler RA, DiBartola SP, Eaton KA: Transient proximal renal tubular acidosis and Fanconi syndrome in a dog, *J Am Vet Med Assoc* 224:1611-1614, 2004.
104. Houlton JE, Herrtage ME: Mitochondrial myopathy in the Sussex spaniel, *Vet Rec* 106:206, 1980.
105. Igarashi T, Sekine T, Inatomi J, et al: Unraveling the molecular pathogenesis of isolated proximal renal tubular acidosis, *J Am Soc Nephrol* 13: 2171-2177, 2002.
106. Ilkiw JE, Davis PE, Church DB: Hematologic, biochemical, blood gas, and acid base values in greyhounds before and after exercise, *Am J Vet Res* 50:583, 1989.
107. Ilkiw JE, Rose RJ, Martin ICA: A comparison of simultaneous collected arterial, mixed venous, jugular venous and cephalic venous blood samples in the assessment of blood gas and acid base status in dogs, *J Vet Intern Med* 5:294, 1991.
108. Jacobs RM, Weiser MG, Hall RL, et al: Clinicopathologic findings of canine parvoviral enteritis, *J Am Anim Hosp Assoc* 16:809, 1980.
109. Jacobson HR: Chloride-responsive metabolic alkalosis. In Seldin DW, Gebisch G, editors: *The regulation of acid-base balance,* New York, 1989, Raven Press, p. 431.
110. Jacobson HR: Chloride-resistant metabolic alkalosis. In Seldin DW, Gebisch G, editors: *The regulation of acid-base balance*, New York, 1989, Raven Press, p. 459.
111. Jacobson HR, Seldin DW: On the generation, maintenance, and correction of metabolic alkalosis, *Am J Physiol* 245:F425, 1983.
112. Jaffe HC, Bodansky A, Chandler JP: Ammonium chloride decalcification as modified by calcium intake: the relationship between generalized osteoporosis and osteitis fibrosa, *J Exp Med* 56:823, 1932.
113. Jarvinen A-K, Sankari S: Lactic acidosis in a Clumber spaniel, *Acta Vet Scand* 37:119, 1996.
114. Jennings DB, Davidson JSD: Acid-base and ventilatory adaptations in conscious dogs during chronic hypercapnia, *Respir Physiol* 58:377, 1984.
115. Kagan KG, Schaer M: Gastric dilatation and volvulus in a dog—a case justifying electrolyte and acid-base assessment, *J Am Vet Med Assoc* 182:703, 1983.
116. Kassirer JP, Berkman PM, Lawrenz DR, et al: The critical role of chloride in the correction of hypokalemic alkalosis in man, *Am J Med* 38:172, 1965.
117. Kassirer JP, Schwartz WB: Correction of metabolic alkalosis in man without repair of potassium deficiency: a reevaluation of the role of potassium, *Am J Med* 38:19, 1966.
118. Kassirer JP, Schwartz WB: The response of normal man to selective depletion of hydrochloric acid. Factors in the genesis of persistent gastric alkalosis, *Am J Med* 40:10, 1966.
119. Kazemi H, Valenca LM, Shannon DC: Brain and cerebrospinal fluid lactate concentration in respiratory acidosis and alkalosis, *Respir Physiol* 6:178, 1969.
120. Kramer JW, Bistline D, Sheridan P, et al: Identification of hippuric acid crystals in the urine of ethylene glycol–intoxicated dogs and cats, *J Am Vet Med Assoc* 184:584, 1984.
121. Kreisberg RA: Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment, *Arch Intern Med* 88:681, 1978.
122. Kreisberg RA: Pathogenesis and management of lactic acidosis, *Annu Rev Med* 35:181, 1984.
123. Lemieux G, Lemieux C, Duplessis S, et al: Metabolic characteristics of cat kidney: failure to adapt to metabolic acidosis, *Am J Physiol* 259:R277, 1990.
124. Ling GV, Lowenstine LJ, Pulley LT, et al: Diabetes mellitus in dogs: a review of initial evaluation, immediate and long-term management, and outcome, *J Am Vet Med Assoc* 170:521, 1977.

125. Ling GV, Stabenfeldt GH, Comer KM, et al: Canine hyperadrenocorticism: pretreatment clinical and laboratory evaluation of 117 cases, *J Am Vet Med Assoc* 174:1211, 1979.
126. Lloyd MH, Iles RA, Simpson BR, et al: The effect of simulated metabolic acidosis on intracellular pH and lactate metabolism in the isolated perfused rat liver, *Clin Sci* 45:543, 1973.
127. Lowance DC, Garfinkel HB, Mattern WD, et al: The effect of chronic hypotonic volume expansion on the renal regulation of acid-base equilibrium, *J Clin Invest* 51:2928, 1972.
128. Macintire DK: Treatment of diabetic ketoacidosis in dogs by continuous low-dose intravenous infusion of insulin, *J Am Vet Med Assoc* 202:1266, 1993.
129. MacKenzie CP, van den Broek A: The Fanconi syndrome in a whippet, *J Small Anim Pract* 23:469, 1982.
130. Madias NE: Lactic acidosis, *Kidney Int* 29:752, 1986.
131. Madias NE, Adrogue HJ, Cohen JJ: Maladaptive renal response to secondary hypercapnia in chronic metabolic alkalosis, *Am J Physiol* 238:F283, 1980.
132. Madias NE, Bossert WH, Adrogue HJ: Ventilatory response to chronic metabolic acidosis and alkalosis in the dog, *J Appl Physiol* 56:1640, 1984.
133. Madias NE, Schwartz WB, Cohen JJ: The maladaptive renal response to secondary hypocapnia during chronic HCl acidosis in the dog, *J Clin Invest* 60:1393, 1977.
134. Madias NE, Wolf CJ, Cohen JJ: Regulation of acid-base equilibrium in chronic hypercapnia, *Kidney Int* 27:538, 1985.
135. Madias NE, Zelman SJ: The renal response to chronic mineral acid feeding: a re-examination of the role of systemic pH, *Kidney Int* 29:667, 1986.
136. Magner PO, Robinson L, Halperin RM, et al: The plasma potassium concentration in metabolic acidosis: a re-evaluation, *Am J Kidney Dis* 11:220, 1988.
137. Marsh JD, Margolis TI, Kim D: Mechanism of diminished contractile response to catecholamines during acidosis, *Am J Physiol* 254:H20, 1988.
138. Martin GB, Carden DL, Nowak RM, et al: Comparison of central venous and arterial pH and P_{CO_2} during open chest CPR in the canine model, *Ann Emerg Med* 14:529, 1985.
139. Maskrey M, Jennings DB: Ventilation and acid-base balance in awake dogs exposed to heat and CO_2, *J Appl Physiol* 58:549, 1985.
140. Mathias DW, Clifford PS, Klopfenstein HS: Mixed venous blood gases are superior to arterial blood gases in assessing acid-base status and oxygenation during acute cardiac tamponade in dogs, *J Clin Invest* 82:833, 1988.
141. McCullough SM, Constable PD: Calculation of the total plasma concentration of nonvolatile weak acids and the effective dissociation constant of nonvolatile buffers in plasma for use in the strong ion approach to acid-base balance in cats, *Am J Vet Res* 64:1047-1051, 2003.
142. McEwan NA, Macartney L: Fanconi's syndrome in a Yorkshire terrier, *J Small Anim Pract* 28:737, 1987.
143. McNamara PD, Rea CT, Bovee KC, et al: Cystinuria in dogs: comparison of the cystinuric component of the Fanconi syndrome in basenji dogs to isolated cystinuria, *Metabolism* 38:8, 1989.
144. Meijer JC: Canine hyperadrenocorticism. In Kirk RW, editor: *Current veterinary therapy VII,* Philadelphia, 1980, WB Saunders, p. 975.
145. Melian C, Peterson ME: Diagnosis and treatment of naturally-occurring hypoadrenocorticism in 42 dogs, *J Small Anim Pract* 37:268, 1996.
146. Meyer DJ: Temporary remission of hypoglycemia in a dog with an insulinoma after treatment with streptozotocin, *Am J Vet Res* 38:1201, 1977.
147. Mitchell JH, Wildenthal K, Johnson RL: The effects of acid-base disturbances on cardiovascular and pulmonary function, *Kidney Int* 1:375, 1972.
148. Molitoris BA, Froment DH, MacKenzie TA, et al: Citrate: a major factor in the toxicity of orally administered aluminum compounds, *Kidney Int* 36:949-953,1989.
149. Moon PE, Gabor L, Gleed RD, et al: Acid-base, metabolic, and hemodynamic effects of sodium bicarbonate or tromethamine administration in anesthetized dogs with experimentally induced metabolic acidosis, *Am J Vet Res* 58:771, 1997.
150. Morrin PAF, Bricker NS, Kime SW, et al: Observations on the acidifying capacity of the experimentally diseased kidney of the dog, *J Clin Invest* 41:1297, 1962.
151. Morrin PAF, Gedney WB, Newmark LN, et al: Bicarbonate reabsorption in the dog with experimental renal disease, *J Clin Invest* 41:1303, 1962.
152. Morris LR, Murphy MB, Kitabchi AE: Bicarbonate therapy in severe diabetic ketoacidosis, *Ann Intern Med* 105:836, 1986.
153. Muir WW: Acid-base and electrolyte disturbances in dogs with gastric-dilatation volvulus, *J Am Vet Med Assoc* 181:229, 1982.
154. Musch TI, Friedman DB, Haidet GC, et al: Arterial blood gases and acid-base status of dogs during graded dynamic exercise, *J Appl Physiol* 61:1914, 1986.
155. Nappert G, Dunphy E, Ruben D, et al: Determination of serum organic acids in puppies with naturally-acquired parvoviral enteritis, *Can J Vet Res* 66:15-18, 2002.
156. Narins RG, Cohen JJ: Bicarbonate therapy for organic acidosis: the case for its continued use, *Ann Intern Med* 106:615, 1987.
157. Narins RG, Jones ER, Stom MC, et al: Diagnostic strategies in disorders of fluid, electrolyte and acid base homeostasis, *Am J Med* 72:496, 1982.
158. Needle MA, Kaloyandies GJ, Schwartz WB: The effects of selective depletion of hydrochloric acid on acid base and electrolyte equilibrium, *J Clin Invest* 43:1836, 1964.
159. Nicoletta JA, Schwartz GJ: Distal renal tubular acidosis, *Curr Opin Pediatr* 16:194-198, 2004.
160. Norris SH, Kurtzman NA: Does chloride play an independent role in the pathogenesis of metabolic alkalosis? *Semin Nephrol* 8:101, 1988.
161. Nunamaker DM, Medway W, Berg P: Treatment of ethylene glycol poisoning in the dog, *J Am Vet Med Assoc* 159:310, 1971.
162. Ogilvie GK, Vail DM, Wheeler SL, et al: Effects of chemotherapy and remission on carbohydrate metabolism in dogs with lymphoma, *Cancer* 69:233-238, 1992.
163. Oh MS: Irrelevance of bone buffering to acid-base homeostasis in chronic metabolic acidosis, *Nephron* 59:7, 1991.
164. Okuda Y, Adrogue HJ, Field JB, et al: Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis, *J Clin Endocrinol Metab* 81:314, 1996.
165. Olby NJ, Chan KK, Targett MP, et al: Suspected mitochondrial myopathy in a Jack Russell terrier, *J Small Anim Pract* 38:213, 1997.
166. Orchard CH, Kentish JC: Effects of changes of pH on the contractile function of cardiac muscle, *Am J Physiol* 258:C967, 1990.
167. Paciello O, Maiolino P, Fatone G, et al: Mitochondrial myopathy in a German shepherd dog, *Vet Pathol* 40:507-511, 2003.

168. Padrid P: Fanconi syndrome in a mixed breed dog, *Mod Vet Pract* 69:162, 1988.
169. Parker RA, Cohn LA, Wohlstadter DR, et al: D-lactic acidosis secondary to exocrine pancreatic insufficiency in a cat, *J Vet Intern Med* 19:106-110, 2005.
170. Pavlin EG, Hornbein TF: Distribution of H^+ and HCO_3^- between CSF and blood during respiratory acidosis, *Am J Physiol* 228:1145, 1975.
171. Penman RW, Luke RF, Jarboe TM: Respiratory effects of hypochloremic alkalosis and potassium depletion in the dog, *J Appl Physiol* 33:170, 1972.
172. Penumarthy L, Oehme FW: Treatment of ethylene glycol toxicosis in cats, *Am J Vet Res* 36:209, 1974.
173. Peterson M: Hyperadrenocorticism, *Vet Clin North Am* 14:731, 1984.
174. Peterson ME, Greco DS, Orth DN: Primary hypoadrenocorticism in ten cats, *J Vet Intern Med* 3:55, 1989.
175. Peterson ME, Kintzer PP, Kass PH: Pretreatment clinical and laboratory findings in dogs with hypoadrenocorticism—225 cases (1979–1993), *J Am Vet Med Assoc* 208:85, 1996.
176. Polzin DJ, Stevens JB, Osborne CA: Clinical evaluation of the anion gap in evaluation of acid-base disorders in dogs, *Compend Contin Educ Pract Vet* 4:102, 1982.
177. Posner J, Plum F: Spinal fluid pH and neurologic symptoms in systemic acidosis, *N Engl J Med* 277:605, 1967.
178. Rhee KH, Toro LO, McDonald GG, et al: Carbicarb, sodium bicarbonate, and sodium chloride in hypoxic lactic acidosis, *Chest* 104:913, 1993.
179. Robinson EP, Hardy RM: Clinical signs, diagnosis, and treatment of alkalemia in dogs: 20 cases (1982–1984), *J Am Vet Med Assoc* 192:943, 1988.
180. Rose BD: *Clinical physiology of acid-base and electrolyte disorders,* New York, 1994, McGraw-Hill Book Co., p. 542.
181. Rose BD: *Clinical physiology of acid-base and electrolyte disorders,* New York, 1994, McGraw-Hill Co., p. 588.
182. Rose BD: *Clinical physiology of acid-base and electrolyte disorders,* New York, 1994, McGraw-Hill Co., p. 564.
183. Rose BD: *Clinical physiology of acid-base and electrolyte disorders,* New York, 1994, McGraw-Hill Co., p. 591.
184. Rose BD: *Clinical physiology of acid-base and electrolyte disorders,* New York, 1994, McGraw-Hill Co., p. 589.
185. Rose BD: *Clinical physiology of acid-base and electrolyte disorders,* New York, 1994, McGraw-Hill Book Co., p. 515.
186. Rose RJ, Carter J: Some physiological and biochemical effects of acetazolamide in the dog, *J Vet Pharmacol Ther* 2:215, 1979.
187. Sabatini S: The acidosis of chronic renal failure, *Med Clin North Am* 67:845, 1983.
188. Sabatini S, Kurtzman NA: The maintenance of metabolic alkalosis: factors which decrease bicarbonate excretion, *Kidney Int* 25:357, 1984.
189. Sanders AB, Otto CW, Kern KB, et al: Acid-base balance in a canine model of cardiac arrest, *Ann Emerg Med* 17:667, 1988.
190. Sanyer JL, Oehme FW, McGavin MD: Systematic treatment of ethylene glycol toxicosis in dogs, *Am J Vet Res* 34:527, 1973.
191. Schmidt RW, Bricker NS, Gavellas G: Renal bicarbonate reabsorption in experimental uremia in the dog, *Kidney Int* 10:287, 1976.
192. Schmidt RW, Gavellas G: Bicarbonate reabsorption in dogs with experimental renal disease: effects of proportional reduction of sodium or phosphate intake, *Kidney Int* 12:393, 1977.
193. Schober KE: Investigation into intraerythrocytic and extraerythrocytic acid-base and electrolyte changes after long-term ammonium chloride administration in dogs, *Am J Vet Res* 57:743, 1996.
194. Schwartz WB, Hays RM, Pak A, et al: Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. II. Recovery, with special reference to the influence of chloride intake, *J Clin Invest* 40:1238, 1961.
195. Schwartz WB, Orning KJ, Porter R: The internal distribution of hydrogen ions with varying degrees of metabolic acidosis, *J Clin Invest* 36:373, 1957.
196. Senior DF, Sundstrom DA, Wolfson BB: Effectiveness of ammonium chloride as a urinary acidifier in cats fed a popular brand of canned cat food, *Feline Pract* 16:24, 1986.
197. Senior DF, Sundstrom DA, Wolfson BB: Testing the effects of ammonium chloride and DL-methionine on the urinary pH of cats, *Vet Med* 81:88, 1986.
198. Settles EL, Schmidt D: Fanconi syndrome in a Labrador retriever, *J Vet Intern Med* 8:390, 1994.
199. Shaw DH: Acute response of urine pH following ammonium chloride administration to dogs, *Am J Vet Res* 50:1829, 1989.
200. Sheikh A, Fleisher G, Delgado-Paredes C, et al: Effect of dichloroacetate in the treatment of anoxic lactic acidosis in dogs, *Crit Care Med* 14:970, 1986.
201. Shull RM: The value of anion gap and osmolal gap determinations in veterinary medicine, *Vet Clin Pathol* 7:12, 1978.
202. Silva PRM, Fonseca-Costa A, Zin WA, et al: Respiratory and acid-base parameters during salicylic intoxication in dogs, *Braz J Med Biol Res* 19:279, 1986.
203. Simpson DP: Control of hydrogen ion homeostasis and renal acidosis, *Medicine (Baltimore)* 50:503, 1971.
204. Stacpoole PW: Lactic acidosis: the case against bicarbonate therapy, *Ann Intern Med* 105:276, 1986.
205. Straus E, Johnson GF, Yalow RS: Canine Zollinger-Ellison syndrome, *Gastroenterology* 72:380, 1977.
206. Swan RC, Axelrod DR, Seip M, et al: Distribution of sodium bicarbonate infused into nephrectomized dogs, *J Clin Invest* 34:1795, 1955.
207. Swan RC, Pitts RF: Neutralization of infused acid by nephrectomized dogs, *J Clin Invest* 34:205, 1955.
208. Takano N: Blood lactate accumulation and its causative factors during passive hyperventilation in dogs, *Jpn J Physiol* 16:481, 1966.
209. Tashkin DP, Goldstein PJ, Simmons DH: Hepatic lactate uptake during decreased liver perfusion, *Am J Physiol* 223:968, 1972.
210. Thrall MA, Grauer GF, Mero KN: Clinicopathologic findings in dogs and cats with ethylene glycol intoxication, *J Am Vet Med Assoc* 184:37, 1984.
211. Thrall MA, Dial SM, Winder DR: Identification of calcium oxalate monohydrate crystals by X-ray diffraction in urine of ethylene glycol–intoxicated dogs, *Vet Pathol* 22:625, 1985.
212. Toto RD, Alpern RJ: Metabolic acid-base disorders. In Kokko JP, Tannen RL, editors: *Fluids and electrolytes,* Philadelphia, 1996, WB Saunders, p. 201.
213. Vail DM, Ogilvie GK, Fettman MJ, et al: Exacerbation of hyperlactatemia by infusion of lactated Ringer's solution in dogs with lymphoma, *J Vet Intern Med* 4:228, 1990.
214. Vail DM, Ogilvie GK, Wheeler SL, et al: Alterations in carbohydrate metabolism in canine lymphoma, *J Vet Intern Med* 4:8, 1990.
215. Valtin H, Gennari FJ: *Acid-base disorders: basic concepts and management,* Boston, 1987, Little, Brown & Co.

216. Vijayasarathy C, Giger U, Prociuk U, et al: Canine mitochondrial myopathy associated with reduced mitochondrial messenger RNA and altered cytochrome *c* oxidase activities in fibroblasts and skeletal muscle, *Comp Biochem Physiol* 109:887, 1994.
217. Vukmir RB, Bircher NG, Radovsky A, et al: Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest, *Crit Care Med* 23:515, 1995.
218. Warnock DG: Uremic acidosis, *Kidney Int* 34:278, 1988.
219. Watson ADJ, Culvenor JA, Middleton DJ, et al: Distal renal tubular acidosis in a cat with pyelonephritis, *Vet Rec* 119:65, 1986.
220. Weil MH, Rackow EC, Trevino R, et al: Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation, *N Engl J Med* 315:153, 1986.
221. Welbourne T, Weber M, Bank N: The effect of glutamine administration on urinary ammonium excretion in normal subjects and patients with renal disease, *J Clin Invest* 51:1852, 1972.
222. Widmer B, Gerhard RE, Harrington JT, et al: Serum electrolyte and acid-base composition: the influence of graded degrees of chronic renal failure, *Arch Intern Med* 139:1099, 1979.
223. Wingfield WE, Twedt DC, Moore RW, et al: Acid-base and electrolyte values in dogs with acute gastric dilatation-volvulus, *J Am Vet Med Assoc* 180:1070, 1982.

CHAPTER • 11

RESPIRATORY ACID-BASE DISORDERS

Rebecca A. Johnson and Helio Autran de Morais

"Life is a struggle, not against sin, not against the Money Power, not against malicious animal magnetism, but against hydrogen ions."

Henry Louis Mencken (1919)

Respiratory acid-base disorders are those abnormalities in acid-base equilibrium initiated by a change in arterial carbon dioxide tension (Pa_{CO_2}). Pa_{CO_2} is regulated by respiration; a primary increase in Pa_{CO_2} acidifies body fluids and initiates the acid-base disturbance called respiratory acidosis, whereas a decrease in Pa_{CO_2} alkalinizes body fluids and is known as respiratory alkalosis. The primary responsibility of the lungs is to exchange gases at the blood-gas interface. In the mammalian lung, oxygen and carbon dioxide move by diffusion from areas of high to low partial pressure. Diffusion of gases is directly proportional to the surface area of the interface and inversely proportional to the thickness of membrane (Fick's law). With a relatively large surface area and a very thin (<1 μm) blood-gas interface, the lungs are well suited for their role in gas exchange.

GAS TRANSPORT DURING RESPIRATION

OXYGEN

Contraction of the diaphragm moves gases down the continually branching airways until they reach the transitional and respiratory bronchioles, alveolar ducts, and alveoli. Within this respiratory zone, alveolar ventilation and gas exchange occur as oxygen moves down its concentration gradient and into the red blood cells. The