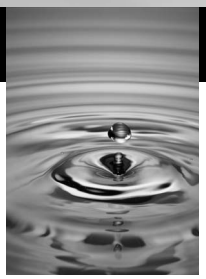

CHAPTER • 7

DISORDERS OF PHOSPHORUS: HYPOPHOSPHATEMIA AND HYPERPHOSPHATEMIA

Stephen P. DiBartola and Michael D. Willard

Phosphorus plays an essential role in cellular structure and function.[86] A constituent of structural phospholipids in cell membranes and of hydroxyapatite in bone, phosphorus also is an integral component of nucleic acids and of phosphoproteins involved in mitochondrial oxidative phosphorylation. Energy for essential metabolic processes (e.g., muscle contraction, neuronal impulse conduction, epithelial transport) is stored in high-energy phosphate bonds of adenosine triphosphate (ATP). The compound 2,3-diphosphoglycerate (2,3-DPG) decreases the affinity of hemoglobin for oxygen and facilitates the delivery of oxygen to tissues. Cyclic adenosine monophosphate (cAMP) is an intracellular second messenger for many polypeptide hormones. Phosphate is also an important urinary buffer, and urinary phosphate constitutes the majority of titratable acidity (see Chapter 9).

Phosphorus is important in the intermediary metabolism of protein, fat, and carbohydrate and as a component of glycogen. It stimulates glycolytic enzymes (e.g., hexokinase, phosphofructokinase) and participates in the phosphorylation of many glycolytic intermediates. Nicotinamide adenine dinucleotide phosphate ($NADP^+$) is a coenzyme for important biochemical reactions. Phosphate regulates the activity of enzymes such as the glutaminase essential for ammoniagenesis (stimulated by increased phosphate concentrations) and the 1α-hydroxylase required for vitamin D activation (stimulated by decreased phosphate concentrations).

PHYSICAL CHEMISTRY

Phosphorus exists in organic (phospholipids and phosphate esters) and inorganic (orthophosphoric and pyrophosphoric acids) forms in the body. Almost all serum phosphorus is in the form of orthophosphate. Orthophosphoric acid is governed by the following set of equilibria:

$$\underset{\text{pKa 2.0}}{H_3PO_4} \rightleftharpoons \underset{\text{pKa 6.8}}{H_2PO_4^{1-}} + H^+ \rightleftharpoons \underset{\text{pKa 12.4}}{HPO_4^{2-}} + H^+ \rightleftharpoons PO_4^{3-} + H^+$$

The pKa for the reaction between $H_2PO_4^{1-}$ and HPO_4^{2-} is 6.8 at the ionic strength and temperature of extracellular fluid (ECF), and these are the two prevailing ionic species at the normal ECF pH of 7.4. At this pH, H_3PO_4 and PO_4^{3-} are present in negligible amounts, and plasma inorganic phosphorus principally consists of $H_2PO_4^{1-}$ and HPO_4^{2-}. At a pH of 7.4, the HPO_4^{2-}:$H_2PO_4^{1-}$ ratio is 4.0, and the average valence of phosphate in serum reflects this ratio. There is four times as much HPO_4^{2-} as $H_2PO_4^{1-}$ at a pH of 7.4, and therefore the average valence of phosphate at this pH is $(4/5)(-2) + (1/5)(-1) = -1.8$. Because the valence and number of milliequivalents (mEq) of phosphate in ECF are influenced by pH, it is easier to measure phosphate in millimoles (mmol) or milligrams (mg) of elemental phosphorus. Serum phosphorus concentrations typically are reported as elemental phosphorus and expressed as milligrams of elemental phosphorus per deciliter of serum. One millimole of phosphate contains 31 mg of elemental phosphorus. To convert mg/dL to mmol/L, divide mg/dL by 3.1. At a pH of 7.4, 1 mmol of phosphate equals 1.8 mEq, and conversion from mmol/L to mEq/L requires multiplication by 1.8.

Even though phosphorus circulates in organic and inorganic forms, clinical laboratories typically measure inorganic phosphate. Approximately 10% to 20% of the inorganic phosphate in serum is protein bound, and the remainder circulates as free anion or is complexed to sodium, magnesium, or calcium. The free and complexed fractions are available for ultrafiltration by the renal glomeruli.

BODY STORES AND DISTRIBUTION

Phosphate is the body's major intracellular anion, and translocation in and out of the intracellular compartment can rapidly change serum phosphorus concentration. Gradual changes in total body phosphate can be

accommodated without noticeable changes in serum phosphorus concentration, resembling the situation with potassium (the major intracellular cation). Approximately 80% to 85% of total body phosphate is inorganic hydroxyapatite in bone, whereas 15% is in soft tissues such as muscle.[55,83] Most soft tissue phosphorus is organic and can be readily converted to the inorganic form as needed. The ECF compartment contains less than 1% of total body phosphorus stores.

NORMAL SERUM CONCENTRATIONS

Normal serum phosphorus concentrations in adult dogs range from 2.5 to 6.0 mg/dL, but they are higher in dogs younger than 1 year.[15,72,119,154] Serum phosphorus concentrations are highest in puppies less than 8 weeks of age (up to 10.8 mg/dL may be considered normal) and gradually decrease into the adult range after 1 year of age.[68] Sex-related changes are not reported.[121] The effect of age is less pronounced in cats, but immature cats have a tendency for higher serum concentrations.[30] Bone growth and an increase in renal tubular reabsorption of phosphorus mediated by growth hormone presumably contribute to this age effect. Feeding also affects serum phosphorus concentration. A carbohydrate meal or infusion (e.g., 5% dextrose) decreases serum phosphorus concentration because phosphate shifts into intracellular fluid as a result of stimulation of glycolysis and formation of phosphorylated glycolytic intermediates in muscle, liver, and adipose cells. In contrast, protein intake increases serum phosphorus concentration because of the relatively high phosphorus content of protein-rich diets.

Time of sampling affects the observed serum phosphorus concentration. People have substantial variation in serum phosphorus concentrations throughout the day.[92] Acid-base balance also influences serum phosphorus concentration. Respiratory alkalosis stimulates glycolysis (by activating phosphofructokinase) and decreases serum phosphorus concentration. Thus the measured serum phosphorus concentration is affected by several variables and does not accurately indicate total body phosphorus stores. Measuring serum phosphorus concentration after a 12-hour fast minimizes confounding factors, but the clinician must understand that the magnitude of hypophosphatemia or hyperphosphatemia may be incorrectly assessed if only one serum or plasma sample is analyzed.

Hemolysis may affect laboratory results because phosphate is present in erythrocytes. Human erythrocytes contain 8 μmol/dL red cells, whereas canine erythrocytes contain 35 μmol/dL and feline erythrocytes contain 26 μmol/dL.[28] Hyperlipidemia and hyperproteinemia sometimes cause overestimation of serum phosphorus concentration, depending on the methodology used.[63,90] Thrombocytosis and monoclonal gammopathy also may cause spurious increases in serum phosphorus concentration.[87,95,100] Mannitol and other drugs may interfere with some assay systems, leading to erroneous measured values.[57,157] Icterus and hemolysis were reported to result in artifactual hypophosphatemia in dogs with immune-mediated hemolytic anemia.[67] Artifactual hypophosphatemia can occur in some automated systems but not in others. Thus occurrence of hypophosphatemia in patients without known predisposing factors should prompt consideration of laboratory error.

DIETARY INTAKE

The average phosphorus content of commercial pet foods is approximately 1% on a dry matter basis. Dogs and cats ingest 0.5 to 3.0 g of phosphorus per day, depending on their body size and energy requirements. The source of dietary phosphorus markedly affects absorption and excretion of phosphorus in cats.[53] The amount of phosphorus absorbed by the gastrointestinal tract, the amount excreted in the urine, and the extent of postprandial hyperphosphatemia were increased when monobasic and dibasic salts of phosphorus were fed but decreased when phosphorus originated from poultry, meat, and fish meal.

INTESTINAL ABSORPTION

Ingested organic phosphate is hydrolyzed in the gastrointestinal tract, liberating inorganic phosphate for absorption. Net intestinal phosphate absorption (i.e., the difference between dietary and fecal phosphate) is approximately 60% to 70% of the ingested load, and absorption is a linear function of phosphorus intake. In an animal in zero phosphorus balance, urinary phosphate excretion equals net intestinal phosphate absorption.

Intestinal phosphate absorption occurs via two mechanisms. Passive diffusion is the principal route and occurs primarily through the paracellular pathway. Active mucosal phosphate transport is a sodium-dependent, saturable carrier-mediated process. Calcitriol (1,25-dihydroxycholecalciferol) increases active intestinal mucosal phosphate transport, but this mechanism is probably important only during dietary phosphate deficiency. Both transport mechanisms function in the duodenum, whereas diffusion is the primary mechanism in the jejunum and ileum. Intestinal alkaline phosphatases may facilitate absorption by freeing inorganic phosphate for transport. Optimal phosphate transport occurs in an alkaline environment, and HPO_4^{-2} is the main ionic species transported. Decreased intestinal phosphate absorption may occur with vitamin D deficiency and in malabsorptive states.

There is no evidence of a direct effect of parathyroid hormone (PTH) on intestinal phosphate absorption, and

observed effects are probably mediated by the role of PTH in conversion of 25-hydroxycholecalciferol to calcitriol. High dietary ratios of calcium to phosphorus (>3 to 4) may suppress intestinal phosphate absorption, presumably through binding of phosphate by calcium and formation of poorly absorbed calcium phosphate complexes. During phosphate deprivation, the kidney dramatically reduces phosphate excretion to negligible amounts in fewer than 3 days. Obligatory gastrointestinal loss continues for at least 3 weeks, but there is a diminution in the amount lost.[92] This gastrointestinal loss may cause a cumulative negative phosphorus balance during phosphate deprivation.

RENAL HANDLING

The kidney adjusts tubular reabsorption of filtered phosphate to maintain zero balance. Normally, 80% to 90% of the filtered phosphate load is reabsorbed by the renal tubules, and renal dysfunction is the most common cause of hyperphosphatemia.[29,141]

Phosphate crosses the luminal membranes of the proximal renal tubular cells by brush border sodium-phosphate cotransporters. The main transport protein in the proximal tubules (type IIa sodium-phosphate cotransporter) translocates three sodium ions and one divalent phosphate ion across the luminal membrane and thus promotes luminal electronegativity.[148] Luminal entry is the rate-limiting step and the target for physiologic and pathophysiologic mechanisms that alter phosphate reabsorption.[106] High dietary intake of phosphorus decreases proximal tubular reabsorption, whereas low dietary intake can result in nearly 100% proximal tubular reabsorption of phosphate. These dietary effects occur independently of changes in the plasma concentrations of phosphaturic hormones. PTH is the most important regulator of renal phosphate transport, and it decreases the tubular transport maximum for phosphate reabsorption (T_{maxPi}) in the proximal tubule where most phosphate reabsorption occurs. Apparently, no reabsorption occurs in the thin ascending limb or thick ascending limb of Henle's loop, and the presence of a reabsorptive mechanism in the distal convoluted tubule is uncertain. Phosphate reabsorption is inhibited in the early proximal tubule by volume expansion with saline, but there may be a more distal reabsorptive site (at some point beyond the last portion of the proximal tubule accessible by micropuncture) that is sensitive to PTH and unaffected by saline volume expansion.

The effects of calcitriol on renal phosphate transport are difficult to separate from the effects of calcitriol on PTH secretion and on phosphate transport in other organs (e.g., intestine, bone). Growth hormone increases proximal renal tubular phosphate reabsorption, which partially accounts for the increased serum phosphorus concentrations found in immature animals. Insulin and thyroxine also increase proximal tubular reabsorption of phosphate, whereas calcitonin and atrial natriuretic peptide inhibit proximal tubular phosphate reabsorption. High doses of adrenocorticotropic hormone (ACTH) or glucocorticoids increase renal phosphate excretion and may decrease serum phosphorus concentration.

The effects of acid-base balance on proximal tubular transport of phosphate are complex.[106] Acute metabolic acidosis does not affect renal tubular reabsorption of phosphate, but chronic metabolic acidosis results in decreased proximal tubular transport, an effect possibly mediated by glucocorticoids. Respiratory acidosis decreases and respiratory alkalosis increases proximal tubular reabsorption of phosphate. Volume expansion increases urinary phosphate excretion and causes natriuresis because phosphate is cotransported with sodium in the proximal tubule.

HYPOPHOSPHATEMIA

CLINICAL EFFECTS OF HYPOPHOSPHATEMIA

Hypophosphatemia can have many detrimental effects. The most severe cellular damage seems to occur when there is concurrent phosphate depletion.[92] Hypophosphatemia decreases erythrocyte concentrations of ATP, which increases erythrocyte fragility, leading to hemolysis. Hemolysis usually is not observed until serum phosphorus concentration decreases to 1.0 mg/dL or less. Hypophosphatemia also reduces erythrocyte 2,3-DPG concentrations, which impairs oxygen delivery to tissues. Leukocytes in hypophosphatemic patients have impaired chemotaxis, phagocytosis, and bacterial killing.[35] This altered function may promote sepsis in hypophosphatemic patients receiving total parenteral nutrition. Platelet-associated abnormalities include shortened survival time, impaired clot retraction, megakaryocytosis in the bone marrow, and thrombocytopenia. In starved dogs made hypophosphatemic by infusion of amino acids, hemolytic anemia, thrombocytopenia, and impaired clot retraction resulted, ostensibly because of depletion of cellular ATP stores.[156] Clinically, hemolysis has been reported in hypophosphatemic dogs and cats with diabetic ketoacidosis, hepatic lipidosis, and other disorders.[2,75,152] Hemolysis was reported in four other hypophosphatemic diabetic cats, but cause and effect were obscured by the possibility of Heinz body anemia.[21]

Neuromuscular effects of hypophosphatemia include weakness and pain associated with rhabdomyolysis, as well as anorexia, vomiting, and nausea secondary to intestinal ileus.[83,84] Decreased phosphate may impair central nervous system glucose utilization and ATP production, leading to metabolic encephalopathy, which has a wide range of manifestations in people (e.g., coma, seizure, confusion, irritability).[92,155] Reversible impairment of cardiac contractility occurs in dogs with experimentally

induced hypophosphatemia and in people with naturally occurring hypophosphatemia.[59,60,158] Hypophosphatemia also causes proximal tubular bicarbonate wasting, reduction in titratable acidity, and impaired renal ammoniagenesis. However, serious acid-base disturbances do not arise in phosphate-deprived dogs.[134] Phosphate deficiency produces bone demineralization via effects of PTH and calcitriol, and release of carbonate from bone may prevent serious metabolic acidosis. Hypomagnesemia frequently is found in hypophosphatemic people, but the reasons for this association are not clear.[30]

Causes of Hypophosphatemia

Hypophosphatemia may be caused by translocation of phosphate from extracellular to intracellular fluid (maldistribution), increased loss (decreased renal reabsorption of phosphate), or decreased intake (decreased intestinal absorption of phosphate).[92,122] Clinical conditions associated with hypophosphatemia are presented in Box 7-1.

Translocation related to administration of a carbohydrate load (e.g., 5% dextrose infusion) is a common cause of hypophosphatemia in hospitalized people.[13,74] Insulin facilitates entry of glucose and phosphate into cells, where glucose is phosphorylated to glycolytic intermediates. Interestingly, infusion of a higher concentration (e.g., 10% dextrose) for a shorter time seems to be less detrimental than infusing 4% glucose continuously.[92] Malnourished patients receiving total parenteral nutrition are particularly susceptible to hypophosphatemia because of the accelerated rate of tissue repair as phosphate is incorporated into new cells and phosphate utilization during glycolysis.[83,122] Respiratory alkalosis likewise causes translocation because it stimulates glycolysis by activating phosphofructokinase.[83] This effect has been demonstrated in experimental dogs but was marked only when hyperventilation was combined with glucose administration.[17] Increased intracellular pH may be more important than increased extracellular pH for causing hypophosphatemia in respiratory alkalosis, which could explain why severe hypophosphatemia may occur in people with severe respiratory failure who are mechanically ventilated.[92]

Diabetic patients are especially at risk for hypophosphatemia. They often have total body phosphate deficits because of loss of muscle mass, urinary phosphate losses, and impaired tissue use of phosphate related to insulin deficiency. Most diabetic cats in one study had mild hypophosphatemia at presentation, whereas 20 of 48 ketotic cats in another study were hypophosphatemic.[21,130] Another study found only 7 of 104 diabetic cats to be hypophosphatemic. However, stratification of the cats into ketoacidotic and nonketoacidotic groups revealed that 5 of 38 ketoacidotic cats were hypophosphatemic and only 2 of 66 nonketotic cats were hypophosphatemic.[36] Interestingly, serum phosphorus concentrations are often normal to increased at presentation in diabetic people, perhaps because of metabolic acidosis by organic acids (e.g., β-hydroxybutyrate), insulin deficiency, osmotic effects of hyperglycemia, or renal insufficiency.[81,108]

Administration of large doses of insulin makes hypophosphatemia even more likely in diabetic ketoacidotic patients. Severe hypophosphatemia has been reported in dogs and cats treated for diabetic ketoacidosis.[2,21,152] Hypophosphatemia developed or worsened after insulin administration, and clinical signs (e.g., hemolysis, seizures) thought related to hypophosphatemia developed in 11 animals. Interestingly, four of these cats developed hemolytic anemia despite intravenous supplementation of potassium phosphate, and it is not clear whether the anemia was caused by inadequate phosphate supplementation or Heinz body formation.[21]

Although it is not documented in dogs and cats, hypophosphatemia may occur in people with certain rapidly growing tumors. Ostensibly, the rapidly dividing cells use phosphorus, removing it from the blood.[92]

Increased urinary loss of phosphorus often produces moderate hypophosphatemia in primary hyperparathyroidism, but clinical signs are caused by hypercalcemia.*

Box 7-1 Causes of Hypophosphatemia

Maldistribution (Translocation)
- Treatment of diabetic ketoacidosis
- Carbohydrate load or insulin administration
- Respiratory alkalosis or hyperventilation
- Total parenteral nutrition or nutritional recovery
- Hypothermia

Increased Loss (Reduced Renal Reabsorption)
- Primary hyperparathyroidism
- Renal tubular disorders (e.g., Fanconi's syndrome)
- Proximally acting diuretics (e.g., carbonic anhydrase inhibitors) (?)*
- Eclampsia
- Hyperadrenocorticism (?)

Decreased Intake (Reduced Intestinal Absorption)
- Dietary deficiency (?)
- Vomiting (?)
- Malabsorption (?)
- Phosphate binders
- Vitamin D deficiency

Laboratory Error

*(?) Importance in veterinary medicine uncertain.

References 11,27,82,91,151,153.

If 2.5 mg/dL is considered the lower limit of normal, serum phosphorus concentration was decreased in approximately one third of reported cases associated with parathyroid adenoma, but in six of six cases associated with parathyroid hyperplasia.[40] Hypophosphatemia is seen inconsistently in cats with primary hyperparathyroidism.[39,77] The fractional excretion of phosphorus (FE_{Pi}) was increased in a few affected dogs.[151] The normal FE_{Pi} was found to be 7.5% ± 4.6% in 10 normal dogs but 10% to 23% in a dog with primary hyperparathyroidism.[27]

Fanconi's syndrome in basenjis is associated with decreased renal fractional reabsorption of phosphate, but serum phosphorus concentrations are normal.[16] The renal tubular transport abnormality may be caused by metabolic or membrane defects affecting sodium transport, and the observed phosphaturia may be secondary to natriuresis.[101] Loop diuretics (e.g., furosemide) and distally acting diuretics (e.g., thiazides) have little effect on renal phosphate excretion, but proximally acting diuretics (e.g., carbonic anhydrase inhibitors) may increase renal excretion of phosphate secondary to their effects on proximal tubular sodium reabsorption. In one study, acetazolamide (10 mg/kg intravenously three times daily) did not cause hypophosphatemia when administered to dogs over a 7-day period.[123] Eclampsia in the bitch may be associated with hypophosphatemia and hypocalcemia.[7,9] Presumably, increased PTH secretion in response to hypocalcemia leads to decreased renal reabsorption of phosphate.

Hypophosphatemia caused by dietary deficiency is unlikely in animals eating commercial diets with adequate protein content. A low-protein, low-phosphorus diet designed to dissolve struvite calculi (Prescription Diet S/D, Hill's Pet Nutrition, Inc., Topeka, KS) did not cause significant hypophosphatemia when fed to dogs over a 6-month period.[1] Urinary phosphorus excretion decreased and calcium excretion increased in this study. Although vomiting and malabsorptive diseases potentially can cause phosphate loss, these disorders rarely cause hypophosphatemia in dogs or cats.[29] Canine malabsorptive intestinal disorders often are characterized by hypocalcemia related to hypoalbuminemia, but serum phosphorus concentrations typically are normal.[18,52]

People have become hypophosphatemic after administration of magnesium and aluminum-containing antacids.[94] Whether phosphate depletion occurs depends on the patient's phosphorus intake, dosage of the phosphate binding agent, duration of administration, and the preexisting phosphate balance of the patient. Vitamin D deficiency may cause hypophosphatemia because hypocalcemia increases PTH secretion, which increases renal phosphate excretion. Decreased intestinal phosphate absorption presumably also plays a role in this setting.

It has been stated that 38% of hyperadrenocortical dogs have hypophosphatemia, but actual serum phosphorus concentrations were not reported.[113] In one study, an identifiable cause of hypophosphatemia could not be found in the majority of dogs with this serum biochemical abnormality.[29] Hypophosphatemia, hypercalcemia, hyperglycemia, azotemia, hypokalemia, and acidosis have been reported in a dog and cat with hypothermia caused by exposure to low environmental temperature.[124] The mechanisms responsible for these electrolyte and acid-base disturbances are uncertain, but translocation seems likely.

Disorders of renal tubular phosphate transport associated with hypophosphatemia in humans include X-linked hypophosphatemia, autosomal dominant hypophosphatemic rickets, oncogenic hypophosphatemic osteomalacia, and hereditary hypophosphatemic rickets with hypercalciuria.[148] Naturally occurring mutations in the npt2 gene encoding the type IIa sodium-phosphate cotransporter have not been identified in these disorders, but rather mutations have been found in other phosphate-regulating genes. X-linked hypophosphatemia is caused by a mutation in the PHEX gene (i.e., phosphate-regulating gene with homology to endopeptidases on the X chromosome), which is expressed in bone, whereas autosomal dominant hypophosphatemic rickets is caused by a mutation in the FGF-23 gene, a member of the fibroblast growth factor family. Oncogenic hypophosphatemic osteomalacia occurs as a result of secretion of a humoral phosphaturic factor secreted by neoplastic cells. Hereditary hypophosphatemic rickets with hypercalciuria is similar to X-linked hypophosphatemia and autosomal dominant hypophosphatemic rickets except that it is associated with appropriately increased serum concentrations of calcitriol, whereas the other hereditary disorders are not. Renal tubular disorders of phosphate transport have not been conclusively identified in dogs and cats, but hypophosphatemia, increased urinary FE_{Pi}, low serum 25-hydroxycholecalciferol concentration, osteopenia, and pathologic fractures were reported in a young cat thought to have abnormal renal tubular phosphate transport and defective hepatic 25-hydroxylation of vitamin D.[69]

TREATMENT OF HYPOPHOSPHATEMIA

Prevention, when possible, is preferred to therapy. The clinician should anticipate potential hypophosphatemia and either administer supplemental phosphorus (e.g., patients receiving total parenteral nutrition or insulin treatment for diabetic ketoacidosis) or carefully monitor the patient for hypophosphatemia (e.g., patients receiving phosphate binders).

If hypophosphatemia occurs, one should seek to correct the underlying condition responsible for it. Whether phosphorus is administered depends on the magnitude of the hypophosphatemia and whether clinical signs are present. Asymptomatic animals with low serum phosphorus concentrations but without phosphorus depletion and those with serum phosphorus concentrations

greater than 1.8 mg/dL and unlikely to decrease any lower (e.g., primary hyperparathyroidism) often do not require phosphate administration.

Phosphate supplementation is appropriate for asymptomatic patients deemed at risk for developing symptomatic hypophosphatemia (e.g., diabetic ketoacidotic cat with serum phosphorus concentration of 1.6 mg/dL) and for patients with clinical signs believed to result from hypophosphatemia. Interestingly, treatment of asymptomatic hypophosphatemia in diabetic people is controversial and is recommended only when severe (<2.0 mg/dL).[80] However, clinical experience in veterinary medicine suggests that anticipatory phosphorus supplementation is reasonable in some ketoacidotic cats.

Oral phosphate administration is safe but slow and unacceptable in vomiting patients and perhaps in patients with diarrhea. If the enteral route is chosen, feeding skim or low-fat milk or a buffered laxative (e.g., Phospho-Soda, Fleet Pharmaceuticals, Lynchburg, VA) usually is effective. Patients symptomatic because of hypophosphatemia generally need parenteral replacement therapy. Administering phosphate intravenously is potentially dangerous because it may cause hypocalcemia, tetany, soft tissue mineralization, renal failure, or hyperphosphatemia.[83] Therefore phosphorus administration typically has consisted of injecting small amounts slowly over hours to days and monitoring the patient repeatedly (e.g., 0.01 to 0.06 mmol/kg/hr in dogs and cats with measurement of serum phosphorus concentration every 6 to 8 hours).[75,152] Although such caution is wise, it is noteworthy that more aggressive phosphorus administration has been used in people (i.e., 0.16 to 0.64 mmol/kg over 4 to 12 hours in patients receiving total parenteral nutrition).[30] Other groups have used similarly large doses over even shorter times (e.g., 0.4 to 0.8 mmol/kg depending on the degree of hypophosphatemia over 30 minutes in patients with cardiac disease), also without problems.[158] Sodium phosphate and potassium phosphate are commonly used, but administration of glucose phosphate has been reported.[158] Selection of the particular form of phosphorus to administer is based on the patient's serum electrolyte concentrations.

Currently, it seems safest to administer phosphate by constant-rate infusion at rates that have been used successfully in dogs and cats and to monitor the serum phosphorus concentration every 6 to 8 hours. Theoretically, adding phosphorus to fluids containing calcium may cause precipitation of calcium phosphate, but this appears to depend on relative concentrations of calcium and phosphorus. Phosphorus usually is administered after diluting it in physiologic saline solution. The volume of distribution for administered phosphate varies tremendously among hypophosphatemic people, and redistribution of phosphate can occur rapidly. Therefore the dose necessary to replete a patient and the patient's response to therapy cannot be predicted. In two studies of hypophosphatemic cats, total amounts of phosphorus infused intravenously ranged from 0.138 to 1.26 mmol/kg, indicating a wide range of total body phosphate deficits.[2,75]

A conservative approach is to assume that intravenously administered phosphate remains in the ECF compartment (actually much of it enters the intracellular fluid). Development of hyperphosphatemia is unlikely with this approach. Prophylactic parenteral phosphate therapy (such as may be used for patients with diabetic ketoacidosis) may be reasonably estimated by giving one fourth to one half of the supplemented potassium as potassium phosphate and the rest as potassium chloride. However, decreased urinary phosphate excretion that develops during hypophosphatemia may persist during treatment and predispose to hyperphosphatemia. The products available for oral and parenteral use are summarized in Tables 7-1 through 7-3.

HYPERPHOSPHATEMIA

Clinical Effects of Hyperphosphatemia

Increased serum phosphorus concentration decreases serum calcium concentration so that the calcium phosphate solubility product ([Ca] × [Pi]) remains constant. Hypocalcemia (which may cause tetany) and soft tissue mineralization are the major clinical consequences of hyperphosphatemia.[149] After phosphate administration,

TABLE 7-1 Oral Preparations of Compounds Used as Phosphate Binders

Name of Product	Chemical Name	Company	Preparations
Basaljel*	Aluminum carbonate gel	Wyeth-Ayerst	Capsules, suspension, tablets
Aluminum hydroxide	Aluminum hydroxide gel	Various manufacturers	Tablets, capsules, suspension
Calcium carbonate	Calcium carbonate	Various manufacturers	Tablets, suspension
PhosLo	Calcium acetate	Braintree	Tablets, capsules
Calcium citrate	Calcium citrate	Various manufacturers	Tablets
Renagel	Sevelamer HCl	Genzyme	Tablets, capsules

**Product discontinued.*

TABLE 7-2 Preparations for Phosphate Supplementation (Preparations for Parenteral Use)

Compound	Composition (per mL)	pH	Osmolality (mOsm/kg)	Phosphate (mmol/mL)	Sodium (mEq/mL)	Potassium (mEq/mL)
Sodium phosphate	142 mg Na_2HPO_4, 276 mg $NaH_2PO_4 \cdot H_2O$	5.70	5580	3.000	4.0	0
Potassium phosphate	236 mg K_2HPO_4 224 mg KH_2PO_4	6.60	5840	3.003	0	4.36

TABLE 7-3 Preparations for Phosphate Supplementation (Preparations for Oral Use)

		Phosphorus		Phosphate		Potassium			
Product	Composition	mg	mEq	mg	mEq	mg	mEq	Company	Prep
K-Phos Neutral	Dibasic sodium phosphate, monobasic potassium phosphate, monobasic sodium phosphate	250	14.1	45	1.1	298	13	Beach	Tablets
Uro-KP Neutral	Dibasic sodium phosphate, monobasic potassium phosphate, monobasic sodium phosphate	250	14.1	49	1.3	250	11	Star	Tablets
Neutro-Phos	Dibasic sodium phosphate, monobasic potassium phosphate, monobasic sodium phosphate	250	14.1	278	7.1	164	7.1	Ortho-McNeill	Powder
Neutra-Phos-K	Dibasic potassium phosphate, monobasic potassium phosphate	250	14.1	556	14.2	0	0	Ortho-McNeill	Powder
K-Phos Original	Monobasic potassium phosphate	114	3.7	144	3.7	0	0	Beach	Tablet
K-Phos M.F.	Monobasic potassium phosphate, monobasic sodium phosphate	126	4.0	45	1.1	67	2.9	Beach	Tablet
K-Phos No. 2	Monobasic potassium phosphate, monobasic sodium phosphate	250	8.0	88	2.2	134	5.8	Beach	Tablet

Amounts given per tablet or per 75 mL of reconstituted liquid.
Prep, *Preparation*.

deposition of calcium and phosphate in bone and soft tissue may contribute to hypocalcemia. The magnitude of hypocalcemia is related to the rate at which serum phosphorus concentration increases, but the exact relationship is unpredictable. The risk of soft tissue mineralization increases when the [Ca] × [Pi] solubility product exceeds 60 to 70.

CAUSES OF HYPERPHOSPHATEMIA

Hyperphosphatemia in dogs and cats is primarily caused by decreased renal excretion, but increased intake and translocation also may be responsible (Box 7-2).[149] Translocation occurring during treatment of hemolymphatic malignancies may cause tumor lysis syndrome (i.e., hyperphosphatemia, hypocalcemia, hyperkalemia, hyperuricemia, and oliguric acute renal failure). Myeloblasts and lymphoblasts may contain up to four times as much phosphate as normal cells, and destruction of these cells causes release of phosphate. This syndrome is uncommon in small animal practice. In one study of dogs with multicentric lymphosarcoma, serum phosphorus concentrations were normal before therapy and did not change after treatment.[109] Urinary phosphorus excretion increased but probably because urine volume increased. There was no

Box 7-2 Causes of Hyperphosphatemia

Maldistribution (Translocation)
- Tumor cell lysis
- Tissue trauma or rhabdomyolysis
- Hemolysis
- Metabolic acidosis

Increased Intake
- Gastrointestinal
  - Phosphate enemas
  - Vitamin D intoxication (e.g., cholecalciferol-containing rodenticides, calcipotriene)
- Parenteral
  - Intravenous phosphate

Decreased Excretion
- Acute or chronic renal failure
- Uroabdomen or urethral obstruction
- Hypoparathyroidism
- Acromegaly (?)*
- Hyperthyroidism

Physiologic: Young Growing Animal

Laboratory Error (e.g., Lipemia, Hyperproteinemia) Depending on Methodology

*(?) Importance in veterinary medicine uncertain.

change in FE_{Pi} or renal function (as assessed by endogenous creatinine clearance). Chemotherapy in these dogs consisted of prednisone, vincristine, and L-asparaginase. However, acute tumor lysis syndrome has been reported in some animals with lymphosarcoma treated with chemotherapy with or without radiation therapy.[26,88,89] Severe hyperphosphatemia (23.6 and 13.7 mg/dL) occurred in a dog and a cat (respectively), and mild hyperphosphatemia (7.4 and 7.7 mg/dL) occurred in two other affected dogs.[26,88] Thus it may be prudent to promote diuresis by intravenous administration of fluids before beginning chemotherapy in patients with lymphosarcoma suspected of having large tumor burdens (e.g., hepatosplenomegaly).

Massive tissue injury with rhabdomyolysis may cause hyperphosphatemia. Subsequent development of acute renal failure related to myoglobinuria further contributes to hyperphosphatemia.[145] Hyperphosphatemia may occur after aortic thromboembolism in cats and was more common in nonsurvivors in one study.[144] Hemolysis can produce hyperphosphatemia because of the phosphorus content of erythrocytes. Lactic acidosis and diabetic ketoacidosis can be associated with hyperphosphatemia because acidosis caused by organic acids apparently results in breakdown of ATP to AMP and inorganic phosphate by an unknown mechanism.[108]

Increased intake of phosphorus may occur with intravenous administration of phosphate-containing fluids. Such therapy is uncommon in veterinary practice, except in treatment of diabetic ketoacidosis and total parenteral nutrition.[21,152] Increased absorption of phosphorus from the alimentary tract may occur with colonic infusion of hypertonic enema solutions or oral administration of sodium phosphate.[43] Such enemas have caused severe hyperphosphatemia in small dogs and cats.[8,73,131] Clinical signs in cats receiving phosphate enemas include lethargy, ataxia, vomiting, bloody diarrhea, mucous membrane pallor, and stupor. Laboratory abnormalities included marked hyperglycemia and hyperphosphatemia, mild hypernatremia, and lactic acidosis.[8] Severe hyperphosphatemia, azotemia, and metabolic acidosis were reported in a cat treated with a phosphate-containing urinary acidifier (pHos-pHaid) at twice the recommended dosage.[62]

Vitamin D increases intestinal absorption of calcium and phosphorus and may produce hyperphosphatemia in addition to hypercalcemia. In one study, administration of vitamin D_2 to dogs for 3 weeks caused hypercalcemia and azotemia, but serum phosphorus concentrations remained normal.[146] However, intoxication with cholecalciferol-containing rodenticides causes azotemia, hypercalcemia, and hyperphosphatemia in dogs and cats.[44,56,64,97,105] Topical medications containing calcipotriene, an analogue of calcitriol, also can cause hypercalcemia, hyperphosphatemia, metastatic soft tissue mineralization, and acute renal failure if ingested by dogs.[48,66,112]

Decreased urinary excretion is the main cause of hyperphosphatemia, and chronic renal failure is the most common cause of hyperphosphatemia in adult dogs and cats.[29] Chronic renal disease causes a progressive decrease in glomerular filtration rate (GFR), and the filtered load of phosphate (GFR × serum phosphorus concentration) decreases as GFR decreases. If phosphorus intake remains constant, phosphorus retention and transient hyperphosphatemia result. However, sustained hyperphosphatemia does not usually develop in early chronic renal failure because there is a compensatory increase in phosphate excretion by remnant nephrons. The effects of PTH on the kidney mediate this increase in the FE_{Pi}. When GFR decreases to 20% of normal or less (i.e., late chronic renal failure), this compensatory mechanism is exhausted, and hyperphosphatemia develops.

Renal secondary hyperparathyroidism is a consistent finding in progressive renal disease.[139,141] Hyperphosphatemia inhibits renal 1α-hydroxylase, which is present in the renal tubules (this inhibition impairs conversion of 25-hydroxycholecalciferol to calcitriol and thus reduces intestinal calcium absorption), and decreases serum ionized calcium concentration by the mass law effect ([Ca] × [Pi] = constant). The resultant hypocalcemia and the decreased serum calcitriol concentration stimulate PTH secretion. This increased PTH secretion increases renal excretion of phosphate and release of calcium and

phosphate from bone. It also stimulates production of calcitriol. These actions normalize serum phosphorus and ionized calcium concentrations. Thus calcium and phosphorus balance is maintained by a progressive increase in serum PTH concentration (in early chronic renal failure). However, as renal tubular destruction progresses, there are fewer proximal renal tubules and a decrease in the amount of 1α-hydroxylase enzyme present. This reduction in 1α-hydroxylase means that it is harder for increased concentrations of PTH to increase serum calcium concentration. It also means that calcitriol is not available to inhibit PTH secretion.[107] As serum phosphate concentrations persistently remain increased, other changes also occur. Persistent hyperphosphatemia in rats increases the number and size of parathyroid cells. This is important because some percentage of each cell's secretion is autonomous, and parathyroid hyperplasia means that there is a greater amount of nonsuppressible PTH secretion. Chronically increased PTH concentration leads to bone demineralization and other toxic effects of uremia (e.g., bone marrow suppression, uremic encephalopathy). In addition, uremia decreases the number of parathyroid gland calcitriol receptors, which subsequently decreases the responsiveness of parathyroid glands to the inhibitory effect of calcitriol on PTH release.[19,85,102,143] Thus both decreased calcitriol production and decreased numbers of parathyroid gland calcitriol receptors promote development of renal secondary hyperparathyroidism.

Renal secondary hyperparathyroidism can be prevented or reversed in dogs with experimentally induced chronic renal disease by reducing dietary phosphorus intake in proportion to the decrease in GFR.[78,138,140] Early in the course of chronic renal disease, decreased phosphorus intake stimulates renal 1α-hydroxylase activity, which increases calcitriol production. Increased calcitriol enhances intestinal calcium absorption, increases serum ionized calcium concentration, and decreases PTH secretion. Late in the course of chronic renal disease, the kidneys are unable to produce sufficient calcitriol to promote normal intestinal absorption of calcium. Phosphorus restriction in advanced renal disease still decreases PTH secretion by unknown mechanisms independent of serum ionized calcium or calcitriol concentrations.[143] These observations form the basis for restricting phosphorus in the medical management of chronic renal failure.

Phosphorus restriction also may prevent renal disease progression by minimizing renal interstitial mineralization.[3] In rats with experimentally induced chronic renal failure, detrimental histologic changes (e.g., interstitial mineralization, inflammation, fibrosis) could be prevented and residual renal function maintained by dietary phosphorus restriction.[71,79] In cats with experimentally induced renal disease, histologic changes were prevented by phosphorus restriction.[125] In a study in rats with 80% nephrectomy, diet was carefully controlled so that only phosphorus intake differed between groups, and a beneficial effect of phosphorus restriction was clearly demonstrated with regard to mortality, proteinuria, histologic changes, creatinine clearance, and serum lipid concentrations over a period of 14 weeks.[95] Similar beneficial effects were observed in dogs with 90% nephrectomy fed diets differing only in phosphorus content and followed for 12 months.[20] A similar experiment using 48 dogs with experimentally induced renal failure found that the amount of dietary phosphorus was more important in clinical management than the amount of dietary protein.[54] In studies of cats with naturally occurring chronic renal failure, renal secondary hyperparathyroidism was successfully managed using a combination of dietary restriction of phosphorus and administration of phosphate binders.[10,45]

In contrast to findings in early chronic renal failure, hyperphosphatemia is typical in acute renal failure because of insufficient time for compensatory mechanisms to develop. Hyperphosphatemia also occurs in uroabdomen or urethral obstruction because of urine reabsorption from the peritoneal cavity or decreased GFR caused by increased intratubular pressure resulting from urinary tract obstruction.[24,51]

Hypoparathyroidism in people causes mild hyperphosphatemia because renal reabsorption of phosphate is increased in the absence of PTH. Mild hyperphosphatemia also occurs in dogs with hypoparathyroidism but is overshadowed by the effects of hypocalcemia (e.g., muscle tremors, tetany, seizures, ataxia, behavioral aberrations).[22,23,103,136] Hyperphosphatemia has also been reported in cats with hypoparathyroidism.[118]

Acromegalic people may develop hyperphosphatemia because of growth hormone's effects on renal tubular phosphate reabsorption. Mild hyperphosphatemia has been reported in some acromegalic dogs and cats.[49,114,116] Thyroxine increases renal tubular phosphate reabsorption, which contributes to the increased serum phosphorus concentrations observed in hyperthyroid cats.[113,147,150] Hyperphosphatemia was reported in 21% of hyperthyroid cats in one study.[115]

TREATMENT OF HYPERPHOSPHATEMIA

Volume expansion with saline dilutes ECF phosphate and enhances renal phosphate excretion in dehydrated patients. Increasing GFR by volume expansion increases the filtered load of phosphate, and natriuresis impairs proximal tubular phosphate reabsorption. Administration of glucose (and insulin if necessary) may temporarily decrease serum phosphorus concentration by promoting phosphorus entry into cells, although such therapy is rarely, if ever, necessary. All sources of phosphorus intake should be curtailed. In the diet, phosphorus restriction is accomplished primarily by protein restriction. As a rule, low-protein diets are also low in phosphorus. Calcium

salts should not be administered to hyperphosphatemic patients because of the risk of metastatic soft tissue calcification. Iatrogenic calcinosis cutis recently has been reported in a dog and cat with hypoparathyroidism given calcium gluconate subcutaneously.[126,132]

In patients with severe, chronic renal failure, low-phosphorus diets are helpful but often insufficient. Dialysis is unpredictable because phosphate is a poorly diffusible ion. Therefore the most practical and effective way to treat hyperphosphatemia in patients with stable chronic renal failure is to decrease intestinal phosphate absorption by orally administered phosphate binders. Such administration helps prevent ingested and endogenously secreted phosphate from being absorbed. Phosphate binders work because the cation in the binder combines with dietary phosphate, producing insoluble, nonabsorbable phosphate compounds. Adsorption of phosphate ions on the surface of binder particles may also contribute to their effect. The rate at which a binder dissolves depends on its water solubility, the pH of the environment, and the dosage.[135]

The most widely used oral phosphate-binding agents contain aluminum or calcium and hydroxide, carbonate, or acetate (see Table 7-1).[33,70,141] The appropriate dosage must be determined empirically, but 90 to 100 mg/kg/day divided two or three times daily is a reasonable starting point. Lower dosages of calcium acetate (50 to 60 mg/kg/day) may be sufficient because it has a greater capacity to bind phosphate than does calcium carbonate.[98] Magnesium-containing compounds are not useful as phosphate binders because they cause diarrhea, and limited ability to excrete magnesium in renal failure patients increases the risk of hypermagnesemia.

Aluminum hydroxide and aluminum carbonate are commonly used phosphate binders. Aluminum hydroxide reduces intestinal phosphorus absorption in normal and uremic people.[32] Aluminum is a better binding agent for phosphate than calcium or magnesium in the acidic gastric environment.[135] This effect is less important at the higher intestinal pH. Aluminum-containing gels are better tolerated by many dogs and cats when given as tablets or capsules, but the desiccated form has a lower phosphate binding capacity than the liquid gel.[128] Aluminum oxide gel prepared to maximize phosphate binding has been studied in dogs.[128,129] Constipation is a common side effect of aluminum-containing phosphate binders.

In people undergoing hemodialysis, osteomalacia and dialysis encephalopathy have been correlated with the aluminum content of dialysis water.[110] In one study, encephalopathy occurred in dialysis patients receiving aluminum hydroxide despite a negligible aluminum content of dialysis water.[4] Aluminum can be absorbed from the intestinal tract in normal people[76] and uremic people,[12,32] and aluminum-induced bone disease can occur in nondialyzed patients after oral administration of aluminum hydroxide.[5]The toxicity of aluminum-containing phosphate binders in human patients with renal failure is now well established, and they have been replaced by calcium-containing phosphate binders.[46] It still is unclear whether aluminum-containing phosphate binders represent a hazard to dogs with chronic renal failure.

Calcium salts such as calcium carbonate and calcium acetate also have been used as phosphate binders. Calcium carbonate decreases intestinal phosphate absorption in normal and uremic people.* Calcium citrate also has been advocated as a phosphate binder but should not be given with aluminum-containing compounds because citrate enhances aluminum absorption.[37,59,104,111,137] Nausea, constipation, and hypercalcemia are potential side effects of calcium-containing phosphate binders. Simultaneous use of calcitriol and calcium-containing phosphate binders to manage renal secondary hyperparathyroidism increases the risk of hypercalcemia. Calcium acetate binds more phosphate than either calcium citrate or calcium carbonate, and less calcium is absorbed from the intestine during its use.[135] Calcium acetate binds phosphate better than aluminum carbonate at the neutral pH found in the small intestine, but aluminum carbonate is better at the lower gastric pH.[135] In vivo, both were about equally effective.

Phosphate binders are most effective when given with meals. In one study, calcium acetate reduced intestinal absorption of phosphate best when ingested just before or after a meal but was much less effective if given 2 hours after eating.[133] Approximately one third as much phosphate was removed from the body when calcium acetate was given during fasting versus as when it was given with a meal. The endogenous phosphate removed probably originated from basal intestinal secretions or passive diffusion into the intestine. Ingestion of a meal also decreased the absorption of calcium from the calcium acetate. Thus calcium-containing phosphate binders should be given with meals to reduce the risk of hypercalcemia.

The search for new phosphorus binders has continued because of the bone toxicity and encephalopathy associated with use of aluminum-containing compounds and the hypercalcemia and soft tissue (including cardiovascular) calcification associated with use of calcium-containing compounds.[46] Sevelamer hydrochloride is a cross-linked polymeric resin that binds phosphorus and releases chloride. It does not contain aluminum or calcium. Sevelamer reduces the risk of vascular and renal calcification that occurs in human patients with chronic renal failure treated with calcium-containing compounds.[34] It is very expensive, causes some adverse gastrointestinal effects, and has the potential to bind other substances (e.g., bile acids, cholesterol, vitamins) in addition to phosphorus. Initial reports suggested that sevelamer was similar in effective-

**References 6,31,57,93,99,142.*

ness to calcium acetate in binding phosphorus but with less risk of hypercalcemia.[14] However, a recent study found calcium acetate superior to sevelamer in control of hyperphosphatemia and calcium-phosphorus product.[120] Sevelamer decreased serum bicarbonate concentrations in this study, presumably as a result of the release and absorption of the hydrochloride moiety.

Lanthanum carbonate also contains no aluminum and no calcium, is not absorbed from the gastrointestinal tract, and acts as an efficient phosphorus binder.[46] Its effects are similar to those of calcium carbonate but without risk of bone toxicity or hypercalcemia.[41] Lanthanum is excreted primarily in bile and should not accumulate in patients with renal failure, but its long-term safety is unknown.

Phosphate binder effectiveness is monitored by measuring fasting serum phosphorus concentration. The goal is to maintain the serum phosphorus concentration in the normal range. In normophosphatemic patients with early renal insufficiency, one may monitor fasting FE_{Pi} to determine the efficacy of phosphate restriction. Dogs with spontaneous chronic renal failure (mean serum creatinine concentration, 2.3 mg/dL) had significantly higher FE_{Pi} values than control dogs (23% versus 5%), respectively, and FE_{Pi} decreased in both groups after feeding of Prescription Diet K/D.[65] In one dog with chronic renal failure, FE_{Pi} was below the mean value for the chronic renal failure group despite increased serum PTH concentration. It has been suggested that FE_{Pi} values less than 30% are indicative of adequate phosphate restriction.[50] This method is limited by the wide range of normal values for FE_{Pi}.[42,127] The response to phosphate binders may be relatively slow because the pool of accumulated phosphate is large and the persistent osteolytic effects of PTH provide a large endogenous phosphate load. Thus the clinician should not be discouraged if the patient responds slowly to phosphate binder therapy.

REFERENCES

1. Abdullahi SU, Osborne CA, Leininger JR, et al: Evaluation of a calculolytic diet in female dogs with induced struvite urolithiasis, *Am J Vet Res* 45:1508-1519, 1984.
2. Adams LG, Hardy RM, Weiss DJ, et al: Hypophosphatemia and hemolytic anemia associated with diabetes mellitus and hepatic lipidosis in cats, *J Vet Intern Med* 7: 266-271, 1993.
3. Alfrey AC: Effect of dietary phosphate restriction on renal function and deterioration, *Am J Clin Nutr* 47:153-156, 1988.
4. Alfrey AC, LeGendre GR, Kaehny WD: The dialysis encephalopathy syndrome: possible aluminum intoxication, *N Engl J Med* 294:184-188, 1976.
5. Andreoli SP, Bergstein JM, Sherrard DJ: Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis, *N Engl J Med* 310:1079-1084, 1984.
6. Andreoli SP, Dunson J, Bergstein JM: Calcium carbonate is an effective phosphorus binder in children with chronic renal failure, *Am J Kidney Dis* 9:206-210, 1987.
7. Aroch I, Srebro H, Shpigel NY: Serum electrolyte concentrations in bitches with eclampsia, *Vet Rec* 145:318-320, 1999.
8. 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* 46:980-988, 1985.
9. Austad R, Bjerkas E: Eclampsia in the bitch, *J Small Anim Pract* 17:795-798, 1976.
10. Barber PJ, Rawlings JM, Markwell PJ, et al: Effect of dietary restriction on renal secondary hyperparathyroidism in the cat, *J Small Anim Pract* 40:62-70, 1999.
11. Berger B, Feldman EC: Primary hyperparathyroidism in dogs: 21 cases (1976-1986), *J Am Vet Med Assoc* 191:350-356, 1987.
12. Berlyne GM, Ben-Ari J, Pest D, et al: Hyperaluminaemia from aluminum resins in renal failure, *Lancet* 2:494-496, 1970.
13. Betro MG, Pain RW: Hypophosphatemia and hyperphosphatemia in a hospital population, *Lancet* 1:273-276, 1972.
14. Bleyer AJ, Burke SK, Dillon M, et al: A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients, *Am J Kidney Dis* 33:694-701, 1999.
15. Bloom F: *The blood chemistry of the dog and cat,* New York, 1960, Gamma Publications.
16. 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* 174:1094-1099, 1979.
17. Brautbar N, Leibovici H, Massry SG: On the mechanism of hypophosphatemia during acute hyperventilation: evidence for increased muscle glycolysis, *Miner Electrolyte Metab* 9:45-50, 1983.
18. Breitschwerdt EB, Halliwell WH, Foley CW, et al: A hereditary diarrhetic syndrome in the basenji characterized by malabsorption, protein losing enteropathy, and hypergammaglobulinemia, *J Am Anim Hosp Assoc* 16:551-560, 1980.
19. Brown AJ, Dusso A, Lopez-Hilker S, et al: 1,25-$(OH)_2$D receptors are decreased in parathyroid glands from chronically uremic dogs, *Kidney Int* 35:19-23, 1989.
20. Brown S, Finco D, Crowell WA, et al: Beneficial effect of moderate phosphate restriction in partially nephrectomized dogs on a low protein diet (abstract), *Kidney Int* 31:380, 1987.
21. Bruskiewicz KA, Nelson RW, Feldman EC, et al: Diabetic ketosis and ketoacidosis in cats: 42 cases (1980-1995), *J Am Vet Med Assoc* 211:188-192, 1997.
22. Bruyette DS, Feldman EC: Primary hypoparathyroidism in the dog, *J Vet Intern Med* 2:7-14, 1988.
23. Burk RL, Schaubhut CW: Spontaneous primary hypoparathyroidism in a dog, *J Am Anim Hosp Assoc* 11:784-785, 1975.
24. Burrows CF, Bovee KC: Metabolic changes due to experimentally-induced rupture of the canine urinary bladder, *Am J Vet Res* 35:1083-1088, 1974.
25. Busse JC, Gelbard MA, Byrnes JJ, et al: Pseudohyperphosphatemia and dysproteinemia, *Arch Intern Med* 147:2045-2046, 1987.
26. Calia CM, Hohenhaus AE, Fox PR, et al: Acute tumor lysis syndrome in a cat with lymphoma, *J Vet Intern Med* 10:409-411, 1996.

27. Carillo JM, Burk RL, Bode C: Primary hyperparathyroidism in a dog, *J Am Vet Med Assoc* 174:67-71, 1979.
28. Carlson GP: Fluid, electrolyte, and acid base balance. In Kaneko JJ, editor: *Clinical biochemistry of domestic animals,* ed 4, New York, 1989, Academic Press, pp. 543-575.
29. Chew DJ, Meuten DJ: Disorders of calcium and phosphorus metabolism, *Vet Clin North Am* 12:411-438, 1982.
30. Clark CL, Sacks GS, Dickerson RN, et al: Treatment of hypophosphatemia in patients receiving specialized nutrition support using a graduated dosing scheme. Results from a prospective clinical trial, *Crit Care Med* 23:1504-1511, 1995.
31. Clarkson EM, McDonald SJ, deWardener HE: The effect of a high intake of calcium carbonate in normal subjects and patients with chronic renal failure, *Clin Sci* 30:425-438, 1966.
32. Clarkson EM, Luck VA, Hynson WV, et al: The effect of aluminum hydroxide on calcium, phosphorus, and aluminum balances, the serum parathyroid hormone concentration and the aluminum content of bone in patients with chronic renal failure, *Clin Sci* 43:519-531, 1972.
33. Coburn JW, Salusky IB: Control of serum phosphorus in uremia, *N Engl J Med* 320:1140-1142, 1989.
34. Cozzolino M, Staniforth ME, Liapis H, et al: Sevelamer hydrochloride attenuates kidney and cardiovascular calcifications in long-term experimental uremia, *Kidney Int* 64:1653-1661, 2003.
35. Craddock PR, Yawata Y, VanSanten L, et al: Acquired phagocyte dysfunction, *N Engl J Med* 290:1403-1407, 1974.
36. Crenshaw KL, Peterson ME: Pretreatment of clinical and laboratory evaluation of cats with diabetes mellitus: 104 cases (1992-1994), *J Am Vet Med Assoc* 209:943-949, 1996.
37. Cushner HM, Copley JB, Lindberg JS, et al: Calcium citrate, a non–aluminum-containing phosphate-binding agent for treatment of CRF, *Kidney Int* 33:95-99, 1988.
38. Delmez JA, Kelber J, Norword KY, et al: Magnesium carbonate as a phosphorus binder: a prospective controlled crossover study, *Kidney Int* 49:163-167, 1996.
39. den Hertog E, Goossens MM, van der Linde-Sipman JS, et al: Primary hyperparathyroidism in two cats, *Vet Q* 19:81-84, 1997.
40. DeVries SE, Feldman EC, Nelson RW, et al: Primary parathyroid gland hyperplasia in dogs: six cases (1982-1991), *J Am Vet Med Assoc* 202:1132-1136, 1993.
41. D'Haese PC, Spasovski GB, Sikole A, et al: A multicenter study on the effects of lanthanum carbonate (Fosrenol™) and calcium carbonate on renal bone disease in dialysis patients, *Kidney Int* 63:S73-S78, 2003.
42. DiBartola SP, Chew DJ, Jacobs G: Quantitative urinalysis including 24-hour urinary protein excretion in the dog, *J Am Anim Hosp Assoc* 16:537-546, 1980.
43. DiPalma JA, Buckley SE, Warner BA, et al: Biochemical effects of oral sodium phosphate, *Dig Dis Sci* 41:749-753, 1996.
44. Dougherty SA, Center SA, Dzanis DA: Salmon calcitonin as adjunct treatment for vitamin D toxicosis in a dog, *J Am Vet Med Assoc* 196:1269-1272, 1990.
45. Elliott J, Rawlings JM, Markwell PJ, et al: Survival of cats with naturally-occurring chronic renal failure: effect of dietary management, *J Small Anim Pract* 41:235-242, 2000.
46. Emmett M: A comparison of clinically useful phosphorus binders for patients with chronic renal failure, *Kidney Int* 66:S25-S32, 2004.
47. Reference deleted in Pages.
48. Fan TM, Simpson KW, Trasti S, et al: Calcipotriol toxicity in a dog, *J Small Anim Pract* 39:581-586, 1998.
49. Feldman EC, Nelson RW: Disorders of growth hormone. In *Canine and feline endocrinology and reproduction,* ed 2, Philadelphia, 1996, WB Saunders, p. 60.
50. Finco DR: The role of phosphorus restriction in the management of chronic renal failure in the dog and cat, *Proc 7th Kal Kan Symposium,* 1983, pp. 131-134.
51. Finco DR, Cornelius LM: Characterization and treatment of water, electrolyte, and acid-base imbalances of induced urethral obstruction in the cat, *Am J Vet Res* 38:823-830, 1977.
52. Finco DR, Duncan JR, Schall WD, et al: Chronic enteric disease and hypoproteinemia in 9 dogs, *J Am Vet Med Assoc* 163:262-271, 1973.
53. Finco DR, Barsanti JA, Brown SA: Influence of dietary source of phosphorus on fecal and urinary excretion of phosphorus and other minerals by male cats, *Am J Vet Res* 50:263-266, 1989.
54. Finco DR, Brown SA, Crowell WA, et al: Effects of dietary phosphorus and protein in dogs with chronic renal failure, *Am J Vet Res* 53:2264-2271, 1992.
55. Fitzgerald F: Clinical hypophosphatemia, *Annu Rev Med* 29:177-189, 1978.
56. Fooshee SK, Forrester SD: Hypercalcemia secondary to cholecalciferol rodenticide toxicosis in two dogs, *J Am Vet Med Assoc* 196:1265-1268, 1990.
57. Fournier A, Moriniere P, Sebert JL, et al: Calcium carbonate, an aluminum-free agent for control of hyperphosphatemia, hypocalcemia, and hyperparathyroidism in uremia, *Kidney Int* 29:S114-S119, 1986.
58. Fraser D, Hones G, Kooh SW, et al: Calcium and phosphate metabolism. In Tietz NW, editor: *Fundamentals of clinical chemistry,* Philadelphia, 1987, WB Saunders, pp. 705-728.
59. Froment DH, Molitoris BA, Buddington B, et al: Site and mechanism of enhanced gastrointestinal absorption of aluminum by citrate, *Kidney Int* 36:978-984, 1989.
60. Fuller TJ, Carter NW, Barcenas C, et al: Reversible changes of the muscle cell in experimental phosphorus deficiency, *J Clin Invest* 57:1019-1024, 1976.
61. Fuller TJ, Nichols WW, Brenner BJ, et al: Reversible depression in myocardial performance in dogs with experimental phosphorus deficiency, *J Clin Invest* 62:1194-1200, 1978.
62. Fulton RB, Fruechte LK: Poisoning induced by administration of a phosphate-containing urinary acidifier in a cat, *J Am Vet Med Assoc* 198:883-885, 1991.
63. Glick MR, Ryder KW, Glick SJ: *Interferographs,* Indianapolis, 1991, Science Enterprises Inc.
64. Gunther R, Felice LJ, Nelson RK: Toxicity of a vitamin D_3 rodenticide to dogs, *J Am Vet Med Assoc* 193:211-214, 1988.
65. Hansen B, DiBartola SP, Chew DJ, et al: Clinical and metabolic findings in dogs with spontaneous chronic renal failure fed two different diets, *Am J Vet Res* 53:326-334, 1992.
66. Hare R, Dobbs C, Sayman K, et al: Calcipotriene poisoning in dogs, *Vet Med* 95:770-778, 2000.
67. Harkin KR, Braselton WE, Tvedten H: Pseudohypophosphatemia in two dogs with immune-mediated hemolytic anemia, *J Vet Intern Med* 12:178-181, 1998.
68. Harper EJ, Hackett RM, Wilkinson J, et al: Age-related variations in hematologic and plasma biochemical test results in Beagles and Labrador Retrievers, *J Am Vet Med Assoc* 223:1436-1442, 2003.

69. Henik RA, Forrest LJ, Friedman AL: Rickets caused by excessive renal phosphate loss and apparent abnormal vitamin D metabolism in a cat, *J Am Vet Med Assoc* 215:1644-1649, 1999.
70. Hercz G, Coburn JW: Prevention of phosphate retention and hyperphosphatemia in uremia, *Kidney Int* 32:S215-S220, 1987.
71. Ibels LS, Alfrey AC, Haut L, et al: Preservation of function in experimental renal disease by dietary restriction of phosphate, *N Engl J Med* 298:122, 1978.
72. Ikeuchi J, Yoshizaki T, Hirata M: Plasma biochemistry values of young Beagle dogs, *J Toxicol Sci* 16:49-59, 1991.
73. Jorgensen LS, Center SA, Randolph JF, et al: Electrolyte abnormalities induced by hypertonic phosphate enemas in two cats, *J Am Vet Med Assoc* 187:1367-1368, 1985.
74. Juan D, Elrazak MA: Hypophosphatemia in hospitalized patients, *JAMA* 242:163-164, 1979.
75. Justin RB, Hohenhaus AE: Hypophosphatemia associated with enteral alimentation in cats, *J Vet Intern Med* 9:228-233, 1995.
76. Kaehny WD, Hegg AP, Alfrey AC: Gastrointestinal absorption of aluminum from aluminum-containing antacids, *N Engl J Med* 296:1389-1390, 1977.
77. Kallet AJ, Richter KP, Feldman EC, et al: Primary hyperparathyroidism in cats: seven cases (1984-1989), *J Am Vet Med Assoc* 199:1767-1771, 1991.
78. Kaplan MA, Canterbury JM, Bourgoignie JJ, et al: Reversal of hyperparathyroidism in response to dietary phosphorus restriction in the uremic dog, *Kidney Int* 15:43, 1979.
79. Karlinsky ML, Haut L, Buddington B, et al: Preservation of renal function in experimental glomerulonephritis, *Kidney Int* 17:293, 1980.
80. Kassirer JP, Hricik DE, Cohen JJ: Phosphate. In *Repairing body fluids: principles and practice*, Philadelphia, 1989, WB Saunders, pp. 110-117.
81. Kebler R, McDonald FD, Cadnapaphornchai P: Dynamic changes in serum phosphorus level in diabetic ketoacidosis, *Am J Med* 79:571-576, 1985.
82. Klausner JS, O'Leary TP, Osborne CA: Calcium urolithiasis in two dogs with parathyroid adenomas, *J Am Vet Med Assoc* 191:1423-1426, 1987.
83. Knochel JP: The pathophysiology and clinical characteristics of severe hypophosphatemia, *Arch Intern Med* 137:203-220, 1977.
84. Knochel JP: Skeletal muscle in hypophosphatemia and phosphorus deficiency, *Adv Exp Med Biol* 103:357-366, 1978.
85. Korkor AB: Reduced binding of [^{3}H]1,25-dihydroxyvitamin D_3 in the parathyroid glands of patients with renal failure, *N Engl J Med* 316:1573, 1987.
86. Kreisberg RA: Phosphorus deficiency and hypophosphatemia, *Hosp Pract* 12:121-128, 1977.
87. Kristensen AT, Klausner JS, Weiss DJ, et al: Spurious hyperphosphatemia in a dog with chronic lymphocytic leukemia and an IgM monoclonal gammopathy, *Vet Clin Pathol* 20:45-48, 1991.
88. Laing EJ, Carter RF: Acute tumor lysis syndrome following treatment of canine lymphoma, *J Am Anim Hosp Assoc* 24:691-696, 1988.
89. Laing EJ, Fitzpatrick PJ, Norris AM, et al: Half-body radiotherapy in the treatment of canine lymphoma, *J Vet Intern Med* 3:102-108, 1989.
90. Leehey DJ, Daugirdas JT, Ing TS, et al: Spurious hyperphosphatemia due to hyperlipidemia, *Arch Intern Med* 145:743-744, 1985.
91. Legendre AM, Merkley DF, Carrig CB, et al: Primary hyperparathyroidism in a dog, *J Am Vet Med Assoc* 168:694-696, 1976.
92. Levine BS, Kleeman CR: Hypophosphatemia and hyperphosphatemia: clinical and pathophysiologic aspects. In Narins RG, editor: *Clinical disorders of fluid and electrolyte metabolism*, ed 5, New York, 1994, McGraw-Hill, pp. 1045-1090.
93. Lopez S, Galceran T, Slatopolsky E: Evaluation of calcium carbonate as an effective phosphorus-binding agent in the dog, *Clin Res* 32:452A, 1984.
94. Lotz M, Zisman E, Bartter FC: Evidence for a phosphorus depletion syndrome in man, *N Engl J Med* 278:409-415, 1968.
95. Lumlertgul D, Burke TJ, Gillum DM, et al: Phosphate depletion arrests progression of chronic renal failure independent of protein intake, *Kidney Int* 29:658, 1986.
96. Lutomski DM, Bower RH: The effect of thrombocytosis on serum potassium and phosphorus concentrations, *Am J Med Sci* 307:255-258, 1994.
97. MacKenzie CP, Burnie AG, Head KW: Poisoning in four dogs by a compound containing warfarin and calciferol, *J Small Anim Pract* 28:433-445, 1987.
98. Mai ML, Emmett ME, Sheikh MS, et al: Calcium acetate, an effective phosphorus binder in patients with renal failure, *Kidney Int* 36:690-695, 1989.
99. Malberti F, Surian M, Colussi G, et al: Calcium carbonate: a suitable alternative to aluminum hydroxide as phosphate binder, *Kidney Int* 33:S184-S185, 1988.
100. Mavrikakis M, Vaiopoulos G, Athanassiades P, et al: Pseudohyperphosphatemia in multiple myeloma, *Am J Hematol* 51:178-179, 1996.
101. 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* 38:8-15, 1989.
102. Merke J, Hugel U, Zlotkowski A, et al: Diminished parathyroid 1,25-dihydroxycholecalciferol receptors in experimental uremia, *Kidney Int* 32:350-353, 1987.
103. Meyer DJ, Terrell TG: Idiopathic hypoparathyroidism in a dog, *J Am Vet Med Assoc* 168:858-860, 1976.
104. 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.
105. Moore FM, Kudisch M, Richter K, et al: Hypercalcemia associated with rodenticide poisoning in three cats, *J Am Vet Med Assoc* 193:1099-1100, 1988.
106. Murer H, Hernando N, Forster I, et al: Proximal tubular phosphate reabsorption: molecular mechanisms, *Physiol Rev* 80:1373-1409, 2000.
107. Nagode LA, Chew DJ, Podell M: Benefits of calcitriol therapy and serum phosphorus control in dogs and cats with renal failure, *Vet Clin North Am* 26:1293-1330, 1996.
108. Oster JR, Perez GO, Vaamonde CA: Relationship between blood pH and potassium and phosphorus during acute metabolic acidosis, *Am J Physiol* 235:F345-F351, 1978.
109. Page RL, Leifer CE, Matus RE: Uric acid and phosphorus excretion in dogs with lymphosarcoma, *Am J Vet Res* 47:910-912, 1986.
110. Parkinson IS, Ward MK, Kerr DNS: Dialysis encephalopathy, bone disease, and anemia: the aluminum intoxication syndrome during regular hemodialysis, *J Clin Pathol* 34:1285-1294, 1981.
111. Partridge NA, Regnier FE, White JL, et al: Influence of dietary constituents on intestinal absorption of aluminum, *Kidney Int* 35:1413-1417, 1989.
112. Pesillo SA, Khan SA, Rozanski EA, et al: Calcipotriene toxicosis in a dog successfully treated with pamidronate disodium, *J Vet Emerg Crit Care* 12:177-181, 2002.

113. Peterson ME: Hyperadrenocorticism, *Vet Clin North Am* 14:731-749, 1984.
114. Peterson ME: Endocrine disorders in cats: four emerging diseases, *Comp Contin Educ Pract Vet* 10:1353-1362, 1988.
115. Peterson ME, Kintzer PP, Cavanagh PG, et al: Feline hyperthyroidism: pretreatment clinical and laboratory evaluation of 131 cases, *J Am Vet Med Assoc* 183:103-110, 1983.
116. Peterson ME, Taylor RS, Greco DS, et al: Spontaneous acromegaly in the cat. *Proc Am Coll Vet Intern Med,* Washington, DC, 1986, pp. 14-43.
117. Peterson ME, Taylor RS, Greco DS, et al: Acromegaly in 14 cats, *J Vet Intern Med* 4:192-201, 1990.
118. Peterson ME, James KM, Wallace M, et al: Idiopathic hypoparathyroidism in five cats, *J Vet Intern Med* 5:47-51, 1991.
119. Pickrell JA, Schluter SJ, Belasich JJ, et al: Relationship of age of normal dogs to blood serum constituents and reliability of measured single values, *Am J Vet Res* 35:897-903, 1974.
120. Qunibi WY, Hootkins RE, McDowell LL, et al: Treatment of hyperphosphatemia in hemodialysis patients: the Calcium Acetate Renagel Evaluation (CARE Study), *Kidney Int* 65:1914-1926, 2004.
121. Ralston Purina Company: *Normal blood values for cats and normal blood values for dogs,* St. Louis, 1975, Ralston Purina Company.
122. Ritz E: Acute hypophosphatemia, *Kidney Int* 22:84-94, 1982.
123. Rose RJ, Carter J: Some physiological and biochemical effects of acetazolamide in the dog, *J Vet Pharmacol Ther* 2:215-221, 1979.
124. Ross LA, Goldstein M: Biochemical abnormalities associated with accidental hypothermia in a dog and cat. Abstract. *Proc Am Coll Vet Intern Med,* St. Louis, 1981, p. 66.
125. Ross LA, Finco DR, Crowell WA, et al: Effect of dietary phosphorus restriction on the kidneys of cats with reduced renal mass, *Am J Vet Res* 43:1023, 1982.
126. Ruopp JL: Primary hypoparathyroidism in a cat complicated by suspect iatrogenic calcinosis cutis, *J Am Anim Hosp Assoc* 37:370-373, 2001.
127. Russo EA, Lees GE, Hightower D: Evaluation of renal function in cats, using quantitative urinalysis, *Am J Vet Res* 47:1308-1312, 1986.
128. Rutherford E, Mercado A, Hruska K, et al: An evaluation of a new and effective phosphorus binding agent, *Trans Am Soc Artif Intern Organs* 19:446-449, 1973.
129. Rutherford E, King S, Perry B, et al: Use of a new phosphate binder in chronic renal insufficiency, *Kidney Int* 17:528-534, 1980.
130. Schaer M: A clinical survey of 30 cats with diabetes mellitus, *J Am Anim Hosp Assoc* 13:23-27, 1977.
131. Schaer M, Cavanaugh P, Hause W, et al: Iatrogenic hyperphosphatemia, hypocalcemia and hypernatremia in a cat, *J Am Anim Hosp Assoc* 13:39-41, 1977.
132. Schaer M, Gin PE, Fox LE, et al: Severe calcinosis cutis associated with treatment of hypoparathyroidism in a dog, *J Am Anim Hosp Assoc* 37:364-369, 2001.
133. Schiller LR, Santa Ana CA, Sheikh MS, et al: Effect of the time of administration of calcium acetate on phosphorus binding, *N Engl J Med* 320:1110-1113, 1989.
134. Schmidt RW: Effects of phosphate depletion on acid-base status in dogs, *Metabolism* 27:943-952, 1978.
135. Sheikh MS, Maguire JA, Emmett M, et al: Reduction of dietary phosphorus absorption by phosphorus binders: a theoretical, in vitro, and in vivo study, *J Clin Invest* 83:66-73, 1989.
136. Sherding RF, Meuten DJ, Chew DJ, et al: Primary hypoparathyroidism in the dog, *J Am Vet Med Assoc* 176:439-444, 1980.
137. Slanina P, Falkeborn Y, Frech W, et al: Aluminum concentration in the brain and bone of rats fed citric acid, aluminum citrate or aluminum hydroxide, *Food Chem Toxicol* 27:391-397, 1984.
138. Slatopolsky E, Bricker NS: The role of phosphorus restriction in the prevention of secondary hyperparathyroidism in chronic renal disease, *Kidney Int* 4:141, 1973.
139. Slatopolsky E, Caglar S, Pennell JP, et al: On the pathogenesis of hyperparathyroidism in chronic renal insufficiency in the dog, *J Clin Invest* 50:492, 1971.
140. Slatopolsky E, Caglar S, Gradowska L, et al: On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorus intake, *Kidney Int* 2:147, 1972.
141. Slatopolsky E, Rutherford WE, Rosenbaum R, et al: Hyperphosphatemia, *Clin Nephrol* 7:138-146, 1977.
142. Slatopolsky E, Weerts C, Lopez-Hilker S, et al: Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis, *N Engl J Med* 315:157-161, 1986.
143. Slatopolsky E, Lopez-Hilker S, Delmez J, et al: The parathyroid-calcitriol axis in health and chronic renal failure, *Kidney Int* 38:S41-S47, 1990.
144. Smith SA, Tobias AH, Jacob KA, et al: Arterial thromboembolism in cats: acute crisis in 127 cases (1992-2001) and long-term management with low-dose aspirin in 24 cases, *J Vet Int Med* 17:73-83, 2003.
145. Spangler WL, Muggli FM: Seizure-induced rhabdomyolysis accompanied by renal failure in a dog, *J Am Vet Med Assoc* 172:1190-1194, 1978.
146. Spangler WL, Gribble DH, Lee TC: Vitamin D intoxication and the pathogenesis of vitamin D nephropathy in the dog, *Am J Vet Res* 40:73-83, 1979.
147. Taylor JA, Jacobs RM, Lumsden JH, et al: Perspectives on the diagnosis of feline hyperthyroidism, *Can Vet J* 30:477-481, 1989.
148. Tenenhouse HS, Murer H: Disorders of renal tubular phosphate transport, *J Am Soc Nephrol* 14:240-247, 2003.
149. Thatte L, Oster JR, Singer I, et al: Review of the literature: severe hyperphosphatemia, *Am J Med Sci* 310:167-174, 1995.
150. Turrel JM, Feldman EC, Nelson RW, et al: Thyroid carcinoma causing hyperthyroidism in cats: 14 cases (1981-1986), *J Am Vet Med Assoc* 193:359-364, 1988.
151. Weir EC, Morrdin RW, Barthold SW, et al: Primary hyperparathyroidism in a dog: biochemical, bone, histomorphometric, and pathologic findings, *J Am Vet Med Assoc* 189:1471-1474, 1986.
152. Willard MD, Zerbe CA, Schall WD, et al: Severe hypophosphatemia associated with diabetes mellitus in six dogs and one cat, *J Am Vet Med Assoc* 190:1007-1010, 1987.
153. Wilson JW, Harris SG, Moor WD, et al: Primary hyperparathyroidism in a dog, *J Am Vet Med Assoc* 164:942-946, 1974.
154. Wolford ST, Schroer RA, Gohs FX, et al: Effect of age on serum chemistry profile, electrophoresis and thyroid hormones in Beagle dogs two weeks to one year of age, *Vet Clin Pathol* 17:35-42, 1988.
155. Yawata Y, Craddock P, Hebbel R, et al: Hyperalimentation hypophosphatemia: hematologic and neurologic

dysfunction due to ATP depletion, *Clin Res* 31:729A, 1973.
156. Yawata Y, Hebbel RP, Silvis S, et al: Blood cell abnormalities complicating the hypophosphatemia of hyperalimentation: erythrocyte and platelet ATP deficiency associated with hemolytic anemia and bleeding in hyperalimented dogs, *J Lab Clin Med* 84:643-653, 1974.
157. Young DS: *Effects of drugs on clinical laboratory tests,* Washington, DC, 1995, AACC Press.
158. Zazzo JF, Troche G, Ruel P, et al: High incidence of hypophosphatemia in surgical intensive care patients. Efficacy of phosphorus therapy on myocardial function, *Intensive Care Med* 21:826-831, 1995.

APPENDIX TO CHAPTER 7

Calculation of Amount of PO_4^{3-} and H_3PO_4 Present in Extracellular Fluid at a pH of 7.4

The Henderson-Hasselbalch equation is derived from the formula for the dissociation constant of an acid. For the ionic species of phosphate of interest:

$$\begin{aligned} pH &= pKa + \log([PO_4^{3-}]/[HPO_4^{2-}]) \\ 7.4 &= 12.4 + \log(x) \\ \log(x) &= -5.0 \\ x &= 0.00001 \\ [PO_4^{3-}]/[HPO_4^{2-}] &= 0.00001 \\ [HPO_4^{2-}]/[PO_4^{3-}] &= 100{,}000 \end{aligned}$$

Thus at a pH of 7.4, there are 100,000 molecules of HPO_4^{2-} for every molecule of PO_4^{3-}.

$$\begin{aligned} pH &= pKa + \log([H_2PO_4^{1-}]/[H_3PO_4]) \\ 7.4 &= 2.0 + \log(x) \\ \log(x) &= 5.4 \\ x &= 251{,}189 \\ [H_2PO_4^{1-}]/[H_3PO_4] &= 251{,}189 \end{aligned}$$

Thus at a pH of 7.4, there are 251,189 molecules of $H_2PO_4^{1-}$ for every molecule of H_3PO_4.

$$\begin{aligned} pH &= pKa + \log([HPO_4^{2-}]/[H_2PO_4^{1-}]) \\ 7.4 &= 6.8 + \log(x) \\ \log(x) &= 0.6 \\ x &= 4.0 \\ [HPO_4^{2-}]/[H_2PO_4^{1-}] &= 4.0 \end{aligned}$$

From these calculations, it can be determined that, at a pH of 7.4, there will be 1,004,756 molecules of HPO_4^{2-}, 251,189 molecules of $H_2PO_4^{1-}$, and 10 molecules of PO_4^{3-} for every molecule of H_3PO_4. Therefore it can be seen that the amounts of H_3PO_4 and PO_4^{3-} present in ECF at a pH of 7.4 can be safely ignored.