Disorders of Phosphate Balance

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The physiologic concentration of serum phosphorus (phosphate) in normal adults ranges from 2.5 to 4.5 mg/dL (0.80–1.44 mmol/L). A diurnal variation occurs in serum phosphorus of 0.6 to 1.0 mg/dL, the lowest concentration occurring between 8 AM and 11 AM. A seasonal variation also occurs; the highest serum phosphorus concentration is in the summer and the lowest in the winter. Serum phosphorus concentration is markedly higher in growing children and adolescents than in adults, and it is also increased during pregnancy [1,2].

Of the phosphorus in the body, 80% to 85% is found in the skeleton. The rest is widely distributed throughout the body in the form of organic phosphate compounds. In the extracellular fluid, including in serum, phosphorous is present mostly in the inorganic form. In serum, more than 85% of phosphorus is present as the free ion and less than 15% is protein-bound.

Phosphorus plays an important role in several aspects of cellular metabolism, including adenosine triphosphate synthesis, which is the source of energy for many cellular reactions, and 2,3-diphosphoglycerate concentration, which regulates the dissociation of oxygen from hemoglobin. Phosphorus also is an important component of phospholipids in cell membranes. Changes in phosphorus content, concentration, or both, modulate the activity of a number of metabolic pathways.

Major determinants of serum phosphorus concentration are dietary intake and gastrointestinal absorption of phosphorus, urinary excretion of phosphorus, and shifts between the intracellular and extracellular spaces. Abnormalities in any of these steps can result either in hypophosphatemia or hyperphosphatemia [3–7].

The kidney plays a major role in the regulation of phosphorus homeostasis. Most of the inorganic phosphorus in serum is ultrafilterable at the level of the glomerulus. At physiologic levels of serum phosphorus and during a normal dietary phosphorus intake, approximately 6 to 7 g/d of phosphorous is filtered by the kidney. Of that

CHAPTER 7

amount, 80% to 90% is reabsorbed by the renal tubules and the rest is excreted in the urine. Most of the filtered phosphorus is reabsorbed in the proximal tubule by way of a sodium gradient-dependent process (Na-P_i cotransport) located on the apical brush border membrane [8–10]. Recently two distinct Na-P_i cotransport proteins have been cloned from the kidney (type I and type II Na-P_i cotransport proteins). Most of the hormonal and metabolic factors that regulate renal tubular phosphate reabsorption, including alterations in dietary phosphate content and parathyroid hormone, have been shown to modulate the proximal tubular apical membrane expression of the type II Na-P_i cotransport protein [11–16].

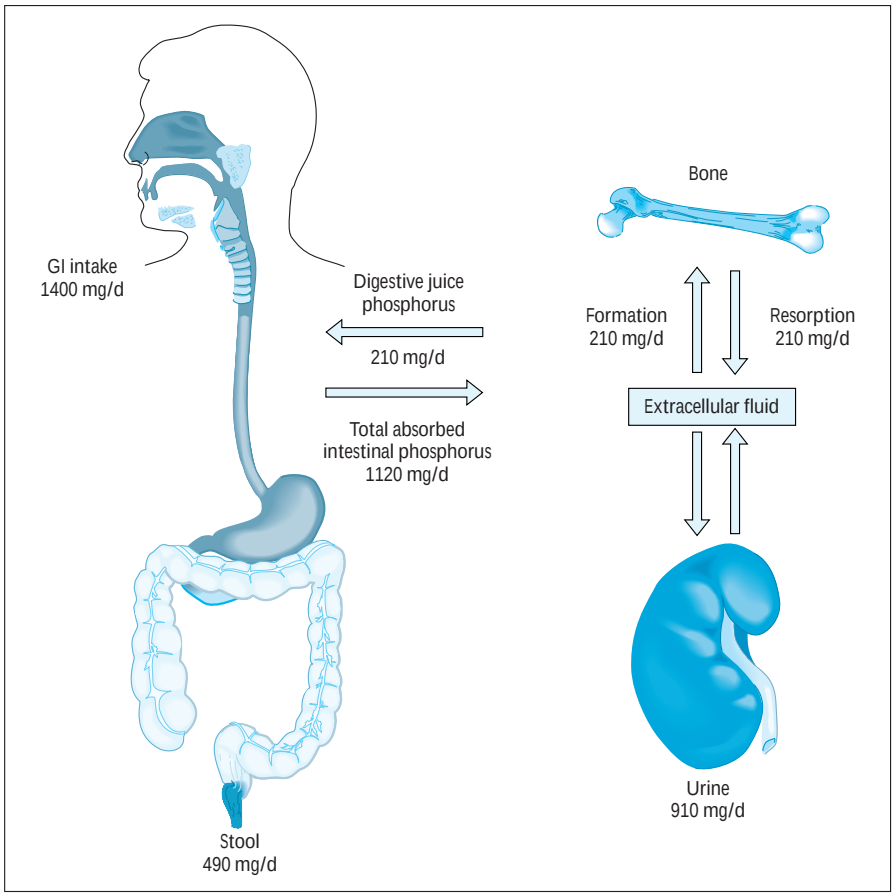

FIGURE 7-1
Summary of phosphate metabolism for a normal adult in neutral phosphate balance. Approximately 1400 mg of phosphate is ingested daily, of which 490 mg is excreted in the stool and 910 mg in the urine. The kidney, gastrointestinal (GI) tract, and bone are the major organs involved in phosphorus homeostasis.

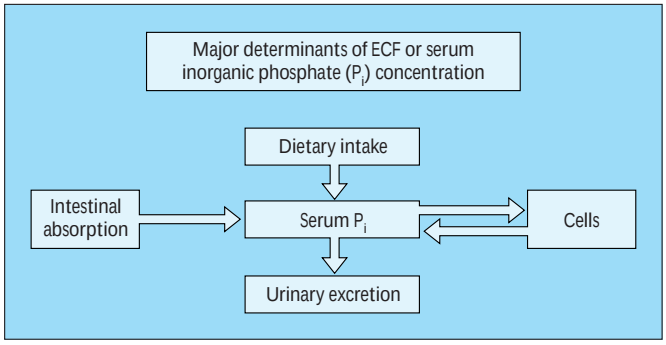

FIGURE 7-2
Major determinants of extracellular fluid or serum inorganic phosphate (P_i) concentration include dietary P_i intake, intestinal P_i absorption, urinary Pi excretion and shift into the cells.

Renal Tubular Phosphate Reabsorption

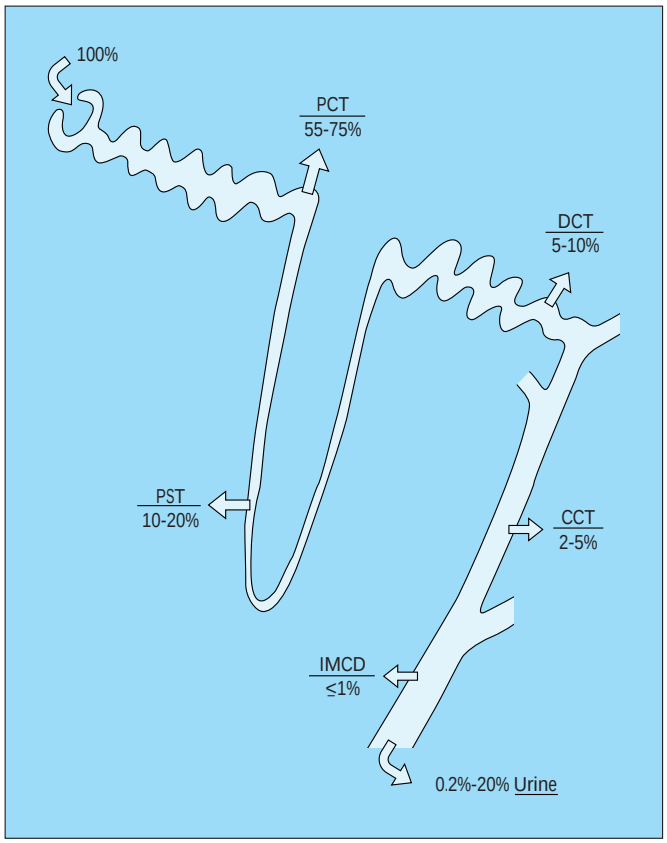

FIGURE 7-3

Renal tubular reabsorption of phosphorus. Most of the inorganic phosphorus in serum is ultrafilterable at the level of the glomerulus. At physiologic levels of serum phosphorus and during a normal dietary phosphorus intake, most of the filtered phosphorous is reabsorbed in the proximal convoluted tubule (PCT) and proximal straight tubule (PST). A significant amount of filtered phosphorus is also reabsorbed in distal segments of the nephron [7,9,10]. CCT—cortical collecting tubule; IMCD—inner medullary collecting duct or tubule; PST—proximal straight tubule.

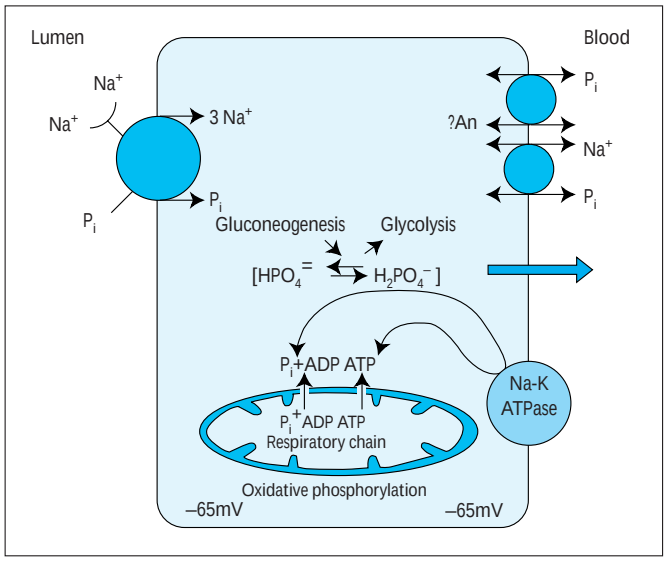

FIGURE 7-4

Cellular model for renal tubular reabsorption of phosphorus in the proximal tubule. Phosphate reabsorption from the tubular fluid is sodium gradient–dependent and is mediated by the sodium gradient–dependent phosphate transport (Na-P_i cotransport) protein located on the apical brush border membrane. The sodium gradient for phosphate reabsorption is generated by then sodium-potassium adenosine triphosphatase (Na-K ATPase) pump located on the basolateral membrane. Recent studies indicate that the Na-P_i cotransport system is electrogenic [8,11]. ADP—adenosine diphosphate; An—anion.

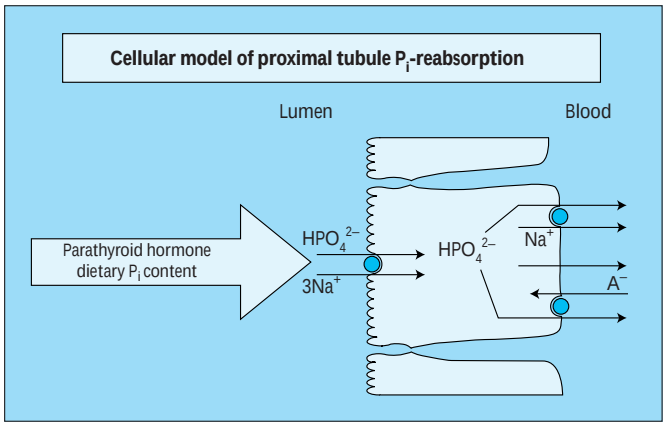

FIGURE 7-5

Celluar model of proximal tubular phosphate reabsorption. Major physiologic determinants of renal tubular phosphate reabsorption are alterations in parathyroid hormone activity and alterations in dietary phosphate content. The regulation of renal tubular phosphate reabsorption occurs by way of alterations in apical membrane sodium-phosphate (Na-P_i) cotransport $3Na^+$-HPO^{2-}_4 activity [11–14].

FACTORS REGULATING RENAL PROXIMAL TUBULAR PHOSPHATE REABSORPTION

Decreased transport	Increased transport
High phosphate diet	Low phosphate diet
Parathyroid hormone and parathyroid-hormone–related protein	Growth hormone
Glucocorticoids	Insulin
Chronic metabolic acidosis	Thyroid hormone
Acute respiratory acidosis	1,25-dihydroxy-vitamin D_3
Aging	Chronic metabolic alkalosis
Calcitonin	High calcium diet
Atrial natriuretic peptide	High potassium diet
Fasting	Stanniocalcin
Hypokalemia	
Hypercalcemia	
Diuretics	
Phosphatonin	

FIGURE 7-6

Factors regulating renal proximal tubular phosphate reabsorption.

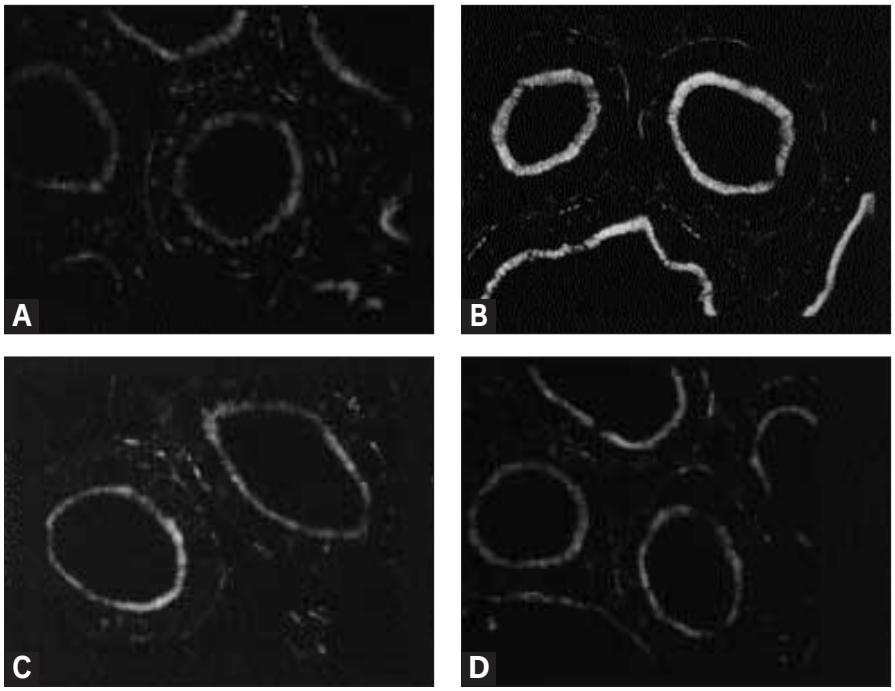

FIGURE 7-7 (see Color Plate)

Effects of a diet low in phosphate on renal tubular phosphate reabsorption in rats. **A,** Chronic high P_i diet. **B**, Acute low P_i diet. **C**, Colchicine and high P_i diet. **D**, Colchicine and low P_i diet. In response to a low phosphate diet, a rapid adaptive increase occurs in the sodium-phosphate (Na-P_i) cotransport activity of the proximal tubular apical membrane (**A**, **B**). The increase in Na-P_i cotransport activity is mediated by rapid upregulation of the type II Na-P_i cotransport protein, in the absence of changes in Na-P_i messenger RNA (mRNA) levels. This rapid upregulation is dependent on an intact microtubular network because pretreatment with colchicine prevents the upregulation of Na-P_i cotransport activity and Na-P_i protein expression (**C, D**). In this immunofluorescence micrograph, the Na-P_i protein is stained green (fluorescein) and the actin cytoskeleton is stained red (rhodamine). Colocalization of green and red at the level of the apical membrane results in yellow color [14].

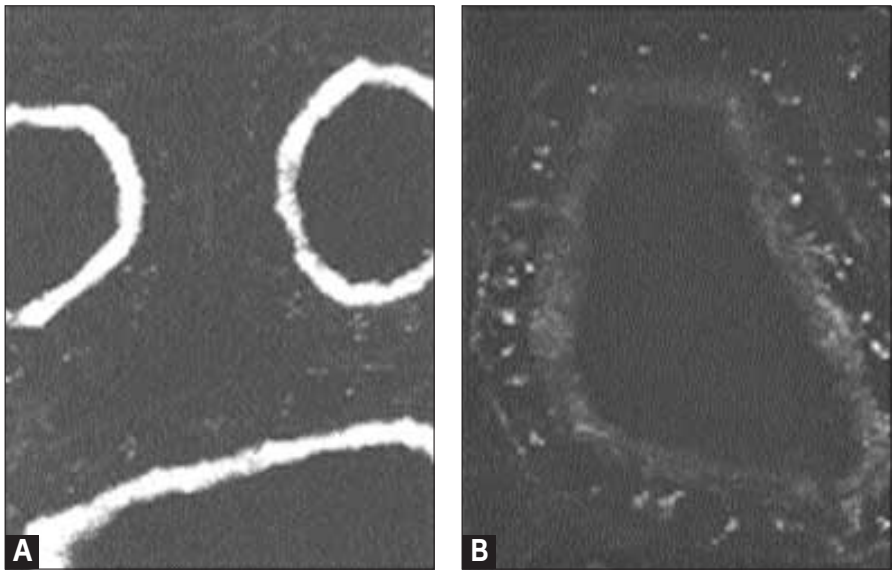

FIGURE 7-8 (see Color Plate)
Effects of parathyroid hormone (PTH) on renal tubular phosphate reabsorption in rats. In response to PTH administration to parathyroidectomized rats, a rapid decrease occurs in the sodium-phosphate ($Na\text{-}P_i$) cotransport activity of the proximal tubular apical membrane. The decrease in $Na\text{-}P_i$ cotransport activity is mediated by rapid downregulation of the type II $Na\text{-}P_i$ cotransport protein. In this immunofluorescence micrograph, the $Na\text{-}P_i$ protein is stained green (fluorescein) and the actin cytoskeleton is stained red (rhodamine). Colocalization of green and red at the level of the apical membrane results in yellow color [13]. **A**, parathyroidectomized (PTX) effects. **B**, effects of PTX and PTH.

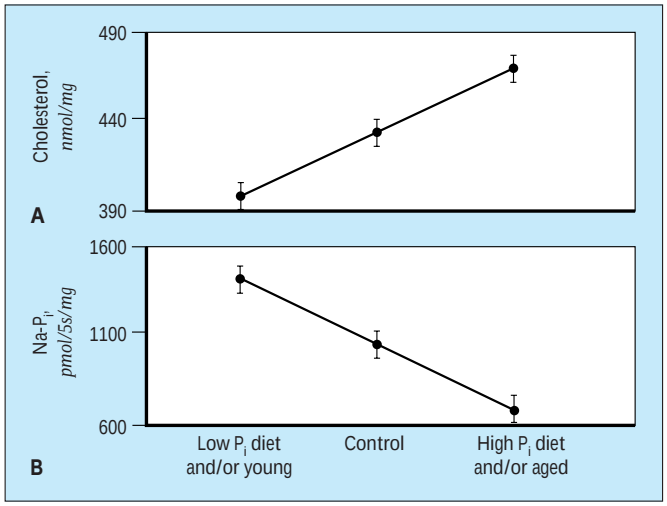

FIGURE 7-9
Renal cholesterol content modulates renal tubular phosphate reabsorption. In aged rats versus young rats and rats fed a diet high in phosphate versus a diet low in phosphate, an inverse correlation exists between the brush border membrane (BBM) cholesterol content (**A**) and $Na\text{-}P_i$ cotransport activity (**B**). Studies in isolated BBM vesicles and recent studies in opossum kidney cells grown in culture indicate that direct alterations in cholesterol content *per se* modulate $Na\text{-}P_i$ cotransport activity [15]. CON—controls.

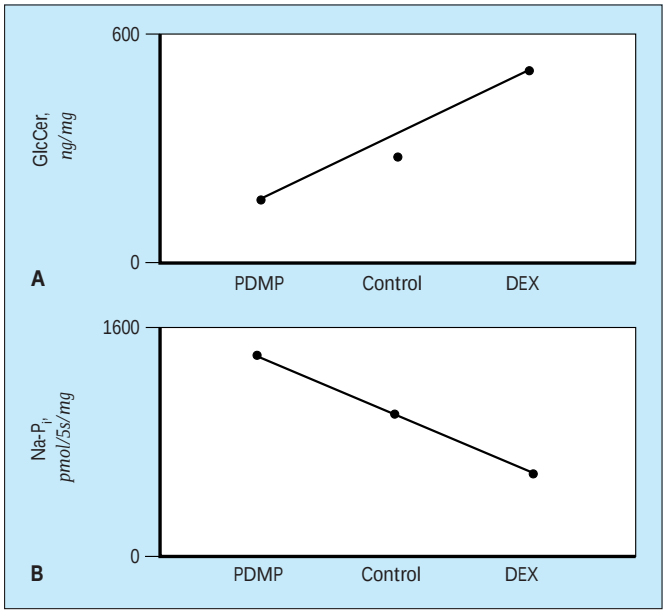

FIGURE 7-10
Renal glycosphingolipid content modulates renal tubular phosphate reabsorption. In rats treated with dexamethasone (DEX) and in rats fed a potassium-deficient diet, an inverse correlation exists between brush border membrane (BBM) glucosylceramide (GluCer)—and ganglioside GM_3, content and $Na\text{-}P_i$ cotransport activity. Treatment of rats with a glucosylceramide synthase inhibitor PDMP lowers BBM glucosylceramide content (**A**) and increases $Na\text{-}P_i$ cotransport activity (**B**) [16].

Hypophosphatemia/Hyperphosphatemia

MAJOR CAUSES OF HYPOPHOSPHATEMIA

Internal redistribution	Decreased intestinal absorption	Increased urinary excretion
Increased insulin, particularly during refeeding	Inadequate intake	Primary and secondary hyperparathyroidism
Acute respiratory alkalosis	Antacids containing aluminum or magnesium	Vitamin D deficiency or resistance
Hungry bone syndrome	Steatorrhea and chronic diarrhea	Fanconi's syndrome
		Miscellaneous: osmotic diuresis, proximally acting diuretics, acute volume expansion

FIGURE 7-11
Major causes of hypophosphatemia. (*From* Angus [1]; with permission.)

CAUSES OF MODERATE HYPOPHOSPHATEMIA

- Pseudohypophosphatemia
  - Mannitol
  - Bilirubin
  - Acute leukemia
- Decreased dietary intake
- Decreased intestinal absorption
  - Vitamin D deficiency
  - Malabsorption
  - Steatorrhea
  - Secretory diarrhea
  - Vomiting
  - PO^3_4-binding antacids
- Shift from serum into cells
  - Respiratory alkalosis
    - Sepsis
    - Heat stroke
    - Neuroleptic malignant syndrome
    - Hepatic coma
    - Salicylate poisoning
    - Gout
    - Panic attacks
    - Psychiatric depression
- Hormonal effects
  - Insulin
  - Glucagon
  - Epinephrine
  - Androgens
  - Cortisol
  - Anovulatory hormones
- Nutrient effects
  - Glucose
  - Fructose
  - Glycerol
  - Lactate
  - Amino acids
  - Xylitol
- Cellular uptake syndromes
  - Recovery from hypothermia
  - Burkitt's lymphoma
  - Histiocytic lymphoma
  - Acute myelomonocytic leukemia
  - Acute myelogenous leukemia
  - Chronic myelogenous leukemia in blast crisis
  - Treatment of pernicious anemia
  - Erythropoietin therapy
  - Erythrodermic psoriasis
  - Hungry bone syndrome
  - After parathyroidectomy
  - Acute leukemia
- Increased excretion into urine
  - Hyperparathyroidism
  - Renal tubule defects
    - Fanconi's syndrome
    - X-linked hypophosphatemic rickets
    - Hereditary hypophosphatemic rickets with hypercalciuria
    - Polyostotic fibrous dysphasia
    - Panostotic fibrous dysphasia
    - Neurofibromatosis
    - Kidney transplantation
    - Oncogenic osteomalacia
    - Recovery from hemolytic-uremic syndrome
  - Aldosteronism
  - Licorice ingestion
  - Volume expansion
  - Inappropriate secretion of antidiuretic hormone
  - Mineralocorticoid administration
  - Corticosteroid therapy
  - Diuretics
  - Aminophylline therapy

FIGURE 7-12
Causes of moderate hypophosphatemia. (*From* Popovtzer, *et al.* [6]; with permission.)

CAUSES OF SEVERE HYPOPHOSPHATEMIA

- Acute renal failure: excessive P binders
- Chronic alcoholism and alcohol withdrawal
- Dietary deficiency and PO^3_4-binding antacids
- Hyperalimentation
- Neuroleptic malignant syndrome
- Recovery from diabetic ketoacidosis
- Recovery from exhaustive exercise
- Kidney transplantation
- Respiratory alkalosis
- Severe thermal burns
- Therapeutic hypothermia
- Reye's syndrome
- After major surgery
- Periodic paralysis
- Acute malaria
- Drug therapy
  - Ifosfamide
  - Cisplatin
- Acetaminophen intoxication
- Cytokine infusions
  - Tumor necrosis factor
  - Interleukin-2

FIGURE 7-13
Causes of severe hypophosphatemia. (*From* Popovtzer, *et al.* [6]; with permission.)

CAUSES OF HYPOPHOSPHATEMIA IN PATIENTS WITH NONKETOTIC HYPERGLYCEMIA OR DIABETIC KETOACIDOSIS

Decreased net intestinal phosphate absorption	Increased urinary phosphate excretion	Acute movement of extracellular phosphate into the cells
Decreased phosphate intake	Glucosuria-induced osmotic diuresis	Insulin therapy
	Acidosis	

FIGURE 7-14
Causes of hypophosphatemia in patients with nonketotic hyperglycemia or diabetic ketoacidosis.

CAUSES OF HYPOPHOSPHATEMIA IN PATIENTS WITH ALCOHOLISM

Decreased net intestinal phosphate absorption	Increased urinary phosphate excretion	Acute movement of extracellular phosphate into the cells
Poor dietary intake of phosphate and vitamin D	Alcohol-induced reversible proximal tubular defect	Insulin release induced by intravenous solutions containing dextrose
Use of phosphate binders to treat recurring gastritis	Secondary hyperparathyroidism induced by vitamin D deficiency	Acute respiratory alkalosis caused by alcohol withdrawal, sepsis, or hepatic cirrhosis
Chronic diarrhea		Refeeding of the patient who is malnourished

FIGURE 7-15
Causes of hypophosphatemia in patients with alcoholism.

CAUSES OF HYPOPHOSPHATEMIA IN PATIENTS WITH RENAL TRANSPLANTATION

Increased urinary phosphate excretion
Persistent hyperparathyroidism (hyperplasia or adenoma)
Proximal tubular defect (possibly induced by glucocorticoids, cyclosporine, or both)

FIGURE 7-16
Causes of hypophosphatemia in patients with renal transplantation.

MAJOR CONSEQUENCES OF HYPOPHOSPHATEMIA

- Decreased erythrocyte 2,3-diphosphoglycerate levels, which result in increased affinity of hemoglobin for oxygen and reduced oxygen release at the tissue level
- Decreased intracellular adenosine triphosphate levels, which result in impairment of cell functions dependent on energy-rich phosphate compounds

FIGURE 7-17
Major consequences of hypophosphatemia.

SIGNS AND SYMPTOMS OF HYPOPHOSPHATEMIA

Central nervous system dysfunction	Cardiac dysfunction	Pulmonary dysfunction	Skeletal and smooth muscle dysfunction	Hematologic dysfunction	Bone disease	Renal effects	Metabolic effects
Metabolic encephalopathy owing to tissue ischemia	Impaired myocardial contractility	Weakness of the diaphragm	Proximal myopathy	Erythrocytes	Increased bone resorption	Decreased glomerular filtration rate	Low parathyroid hormone levels
Irritability	Congestive heart failure	Respiratory failure	Dysphagia and ileus	Increased erythrocyte rigidity	Rickets and osteomalacia caused by decreased bone mineralization	Decreased tubular transport maximum for bicarbonate	Increased 1,25-dihydroxy-vitamin D_3 levels
Paresthesias			Rhabdomyolysis	Hemolysis		Decreased renal gluconeogenesis	Increased creatinine phosphokinase levels
Confusion				Leukocytes		Decreased titratable acid excretion	Increased aldolase levels
Delirium				Impaired phagocytosis		Hypercalciuria	
Coma				Decreased granulocyte chemotaxis		Hypermagnesuria	
				Platelets			
				Defective clot retraction			
				Thrombocytopenia			

FIGURE 7-18
Signs and symptoms of hypophosphatemia. (*Adapted from* Hruska and Slatopolsky [2] *and* Hruska and Gupta [7].)

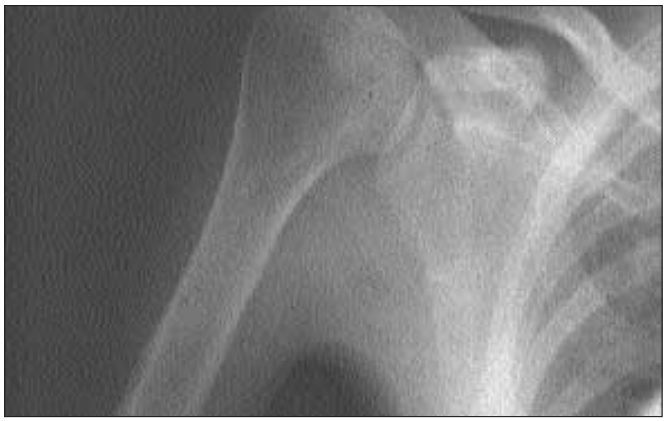

FIGURE 7-19
Pseudofractures (Looser's transformation zones) at the margins of the scapula in a patient with oncogenic osteomalacia. Similar to the genetic X-linked hypophosphatemic rickets, a circulating phosphaturic factor is believed to be released by the tumor, causing phosphate wasting and reduced calcitriol formation by the kidney. Note the radiolucent ribbonlike decalcification extending into bone at a right angle to its axillary margin. Pseudofractures are pathognomonic of osteomalacia with a low remodeling rate.

FIGURE 7-20 (see Color Plate)
Histologic appearance of trabecular bone from a patient with oncogenic osteomalacia. Undecalcified bone section with impaired mineralization and a wide osteoid (organic matrix) seam stained with von Kossa's stain is illustrated. Note the wide bands of osteoid around the mineralized bone. Absence of osteoblasts on the circumference of the trabecular bone portion indicates a low remodeling rate.

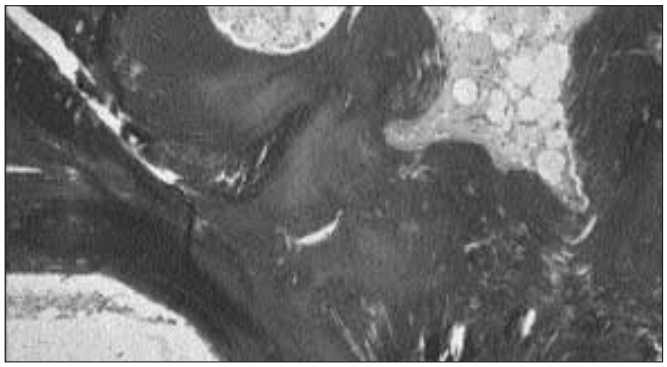

FIGURE 7-21(see Color Plate)
Microscopic appearance of bone section from a patient with vitamin D deficiency caused by malabsorption. The bone section was stained with Masson trichrome stain. Hypophosphatemia and hypocalcemia were present. Note the trabecular bone consisting of very wide osteoid areas (red) characteristic of osteomalacia.

USUAL DOSAGES FOR PHOSPHORUS REPLETION

Severe symptomatic hypophosphatemia (plasma phosphate concentration < 1 mg/dL)	Phosphate depletion	Hypophosphatemic rickets
10 mg/kg/d, intravenously, until the plasma phosphate concentration reaches 2 mg/dL	2–4 g/d (64 to 128 mmol/d), orally, in 3 to 4 divided doses	1–4 g/d (32 to 128 mmol/d), orally, in 3 to 4 divided doses

FIGURE 7-22
Usual dosages for phosphorus repletion.

PHOSPHATE PREPARATIONS FOR ORAL USE

Preparation	Phosphate, mg	Sodium, mEq	Potassium, mEq
K-Phos Neutral®, tablet (Beach Pharmaceuticals, Conestee, SC)	250	13	1.1
Neutra-Phos®, capsule or 75-mL solution (Baker Norton Pharmaceuticals, Miami, FL)	250	7.1	7.1
Neutra-Phos K®, capsule or 75-mL solution (Baker Norton Pharmaceuticals, Miami, FL)	250	0	14.2

FIGURE 7-23
Phosphate preparations for oral use.

PHOSPHATE PREPARATIONS FOR INTRAVENOUS USE

Phosphate preparation	Composition, mg/mL	Phosphate, mmol/mL	Sodium, mEq/mL	Potassium, mEq/mL
Potassium	236 mg K_2HPO_4 224 mg KH_2PO_4	3.0	0	4.4
Sodium	142 mg Na_2HPO_4 276 mg $NaH_2HPO_4.H_2O$	3.0	4.0	0
Neutral sodium	10.0 mg Na_2HPO 2.7 mg $NaH_2PO_4.H_2O$	0.09	0.2	0
Neutral sodium, potassium	11.5 mg Na_2HPO_4 2.6 mg KH_2PO_4	1.10	0.2	0.02

3 mmol/mL of phosphate corresponds to 93 mg of phosphorus.

FIGURE 7-24
Phosphate preparations for intravenous use. (*From* Popovtzer, *et al.* [6]; with permission.)

CAUSES OF HYPERPHOSPHATEMIA

Pseudohyperphosphatemia
Multiple myeloma
Extreme hypertriglyceridemia
In vitro hemolysis

Increased exogenous phosphorus load or absorption
Phosphorus-rich cow's milk in premature neonates
Vitamin D intoxication
PO^3_4-containing enemas
Intravenous phosphorus supplements
White phosphorus burns
Acute phosphorus poisoning

Increased endogenous loads
Tumor lysis syndrome
Rhabdomyolysis
Bowel infarction
Malignant hyperthermia
Heat stroke
Acid-base disorders
Organic acidosis
Lactic acidosis
Ketoacidosis
Respiratory acidosis
Chronic respiratory alkalosis

Reduced urinary excretion
Renal failure
Hypoparathyroidism
Hereditary
Acquired
Pseudohypoparathyroidism
Vitamin D intoxication
Growth hormone
Insulin-like growth factor-1
Glucocorticoid withdrawal
Mg^{2+} deficiency
Tumoral calcinosis
Diphosphonate therapy
Hypophosphatasia

Miscellaneous
Fluoride poisoning
β-Blocker therapy
Verapamil
Hemorrhagic shock
Sleep deprivation

FIGURE 7-25
Causes of hyperphosphatemia. (*From* Knochel and Agarwal [5]; with permission.)

CLINICAL MANIFESTATIONS OF HYPERPHOSPHATEMIA

Consequences of secondary changes in calcium, parathyroid hormone, vitamin D metabolism and hypocalcemia:	Consequences of ectopic calcification:
Neuromuscular irritability	Periarticular and soft tissue calcification
Tetany	Vascular calcification
Hypotension	Ocular calcification
Increased QT interval	Conduction abnormalities
	Pruritus

FIGURE 7-26
Clinical manifestations of hyperphosphatemia.

TREATMENT OF HYPERPHOSPHATEMIA

Acute hyperphosphatemia in patients with adequate renal function	Chronic hyperphosphatemia in patients with end-stage renal disease
Saline diuresis that causes phosphaturia	Dietary phosphate restriction
	Phosphate binders to decrease gastrointestinal phosphate reabsorption

FIGURE 7-27
Treatment of hyperphosphatemia.

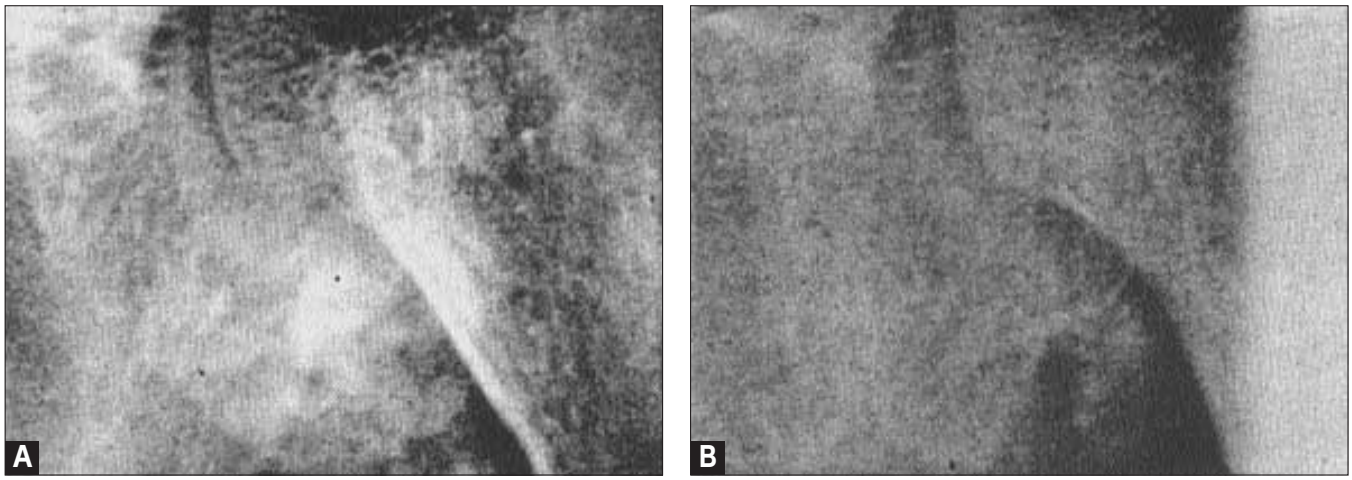

FIGURE 7-28

Periarticular calcium phosphate deposits in a patient with end-stage renal disease who has severe hyperphosphatemia and a high level of the product of calcium and phosphorus. Note the partial resolution of calcific masses after dietary phosphate restriction and oral phosphate binders. Left shoulder joint before (**A**) and after (**B**) treatment. (*From* Pinggera and Popovtzer [17]; with permission.)

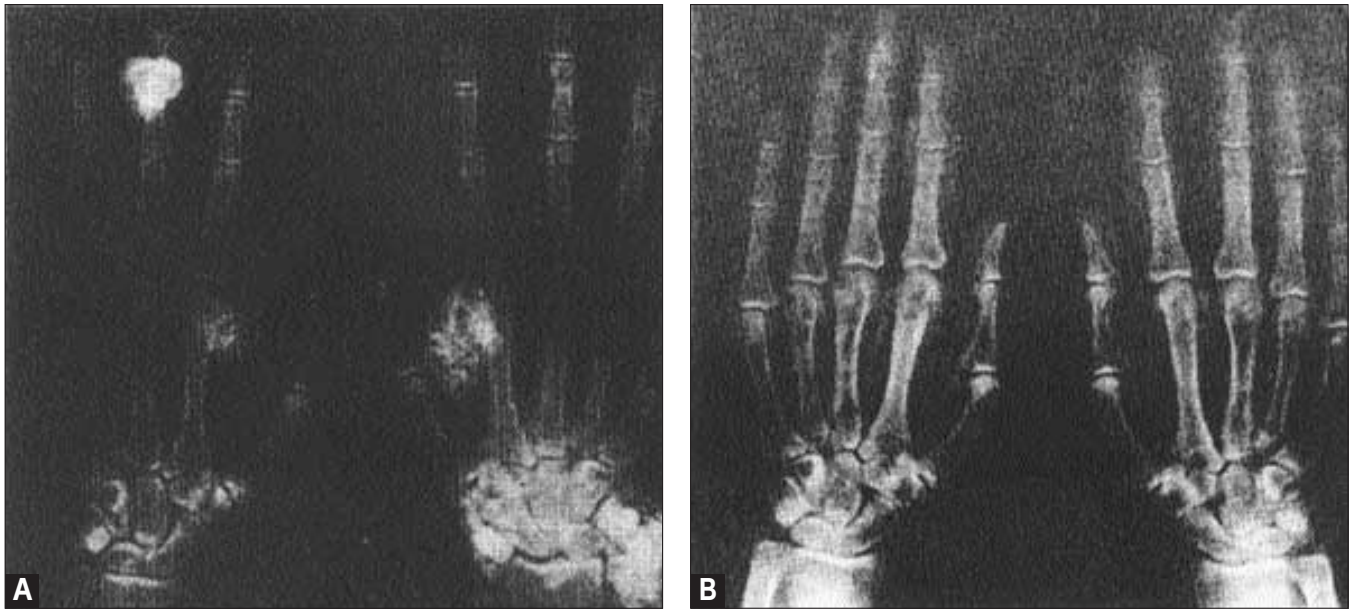

FIGURE 7-29

Resolution of soft tissue calcifications. The palms of the hands of the patient in Figure 7-28 with end-stage renal disease are shown before (**A**) and after (**B**) treatment of hyperphosphatemia. The patient has a high level of the product of calcium and phosphorus. (*From* Pinggera and Popovtzer [17]; with permission.)

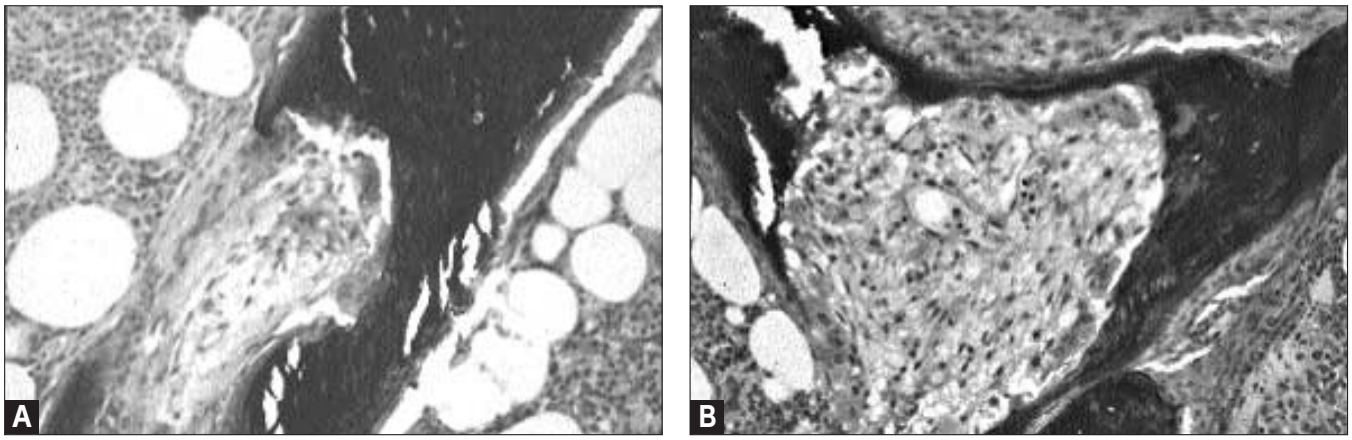

FIGURE 7-30

A, **B**, Bone sections from the same patient as in Figures 7-28 and 7-29, illustrating osteitis fibrosa cystica caused by renal secondary hyperparathyroidism with hyperphosphatemia.

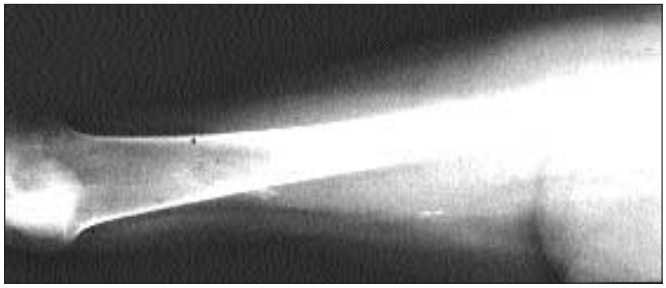

FIGURE 7-31

Roentgenographic appearance of femoral arterial vascular calcification in a patient on dialysis who has severe hyperphosphatemia. The patient has a high level of the product of calcium and phosphorus.

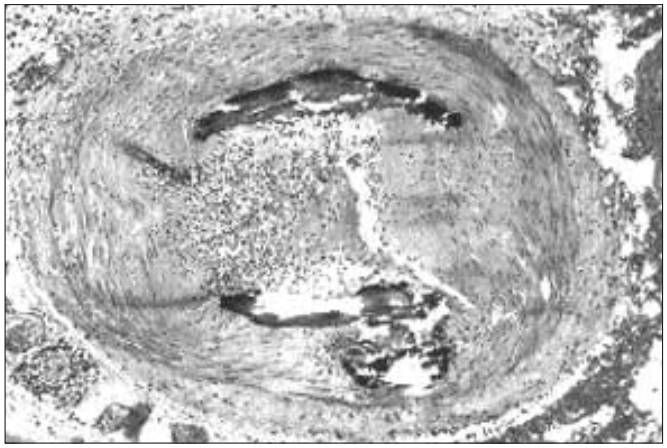

FIGURE 7-32 (see Color Plate)

Microscopic appearance of a cross section of a calcified artery in a patient with end-stage renal disease undergoing chronic dialysis. The patient has severe hyperphosphatemia and a high level of the product of calcium and phosphorus. Note the intimal calcium phosphate deposit with a secondary occlusion of the arterial lumen.

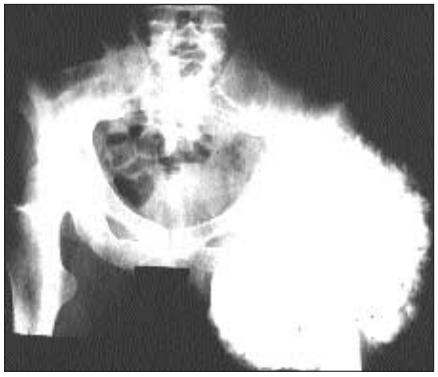

FIGURE 7-33

Massive periarticular calcium phosphate deposit (around the hip joint) in a patient with genetic tumoral calcinosis. The patient exhibits hyperphosphatemia and increased renal tubular phosphate reabsorption. Normal parathyroid hormone levels and elevated calcitriol levels are present. The same disease affects two of the patient's brothers.

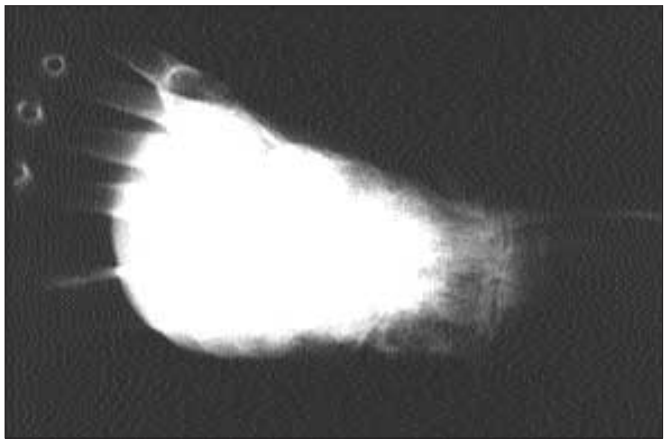

FIGURE 7-34
Massive periarticular calcium phosphate deposit in the plantar joints in the same patient in Figure 7-33 who has genetic tumoral calcinosis.

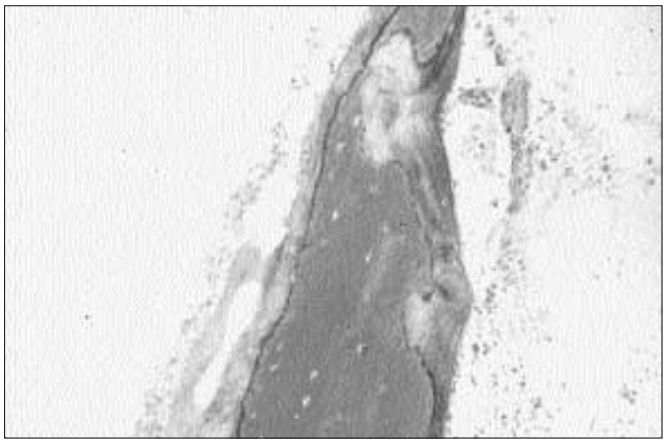

FIGURE 7-35 (see Color Plate)
Complications of the use of aluminum-based phosphate binders to control hyperphosphatemia. Appearance of bone section from a patient with end-stage renal disease who was treated with oral aluminum gels to control severe hyperphosphatemia. A bone biopsy was obtained 6 months after a parathyroidectomy was performed. Note the wide areas of osteoid filling previously resorbed bone.

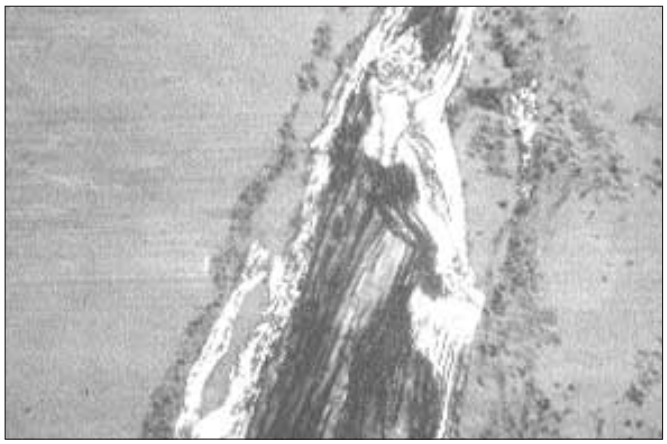

FIGURE 7-36 (see Color Plate)
The same bone section as in Figure 7-35 but under polarizing lenses, illustrating the partially woven appearance of osteoid typical of chronic renal failure.

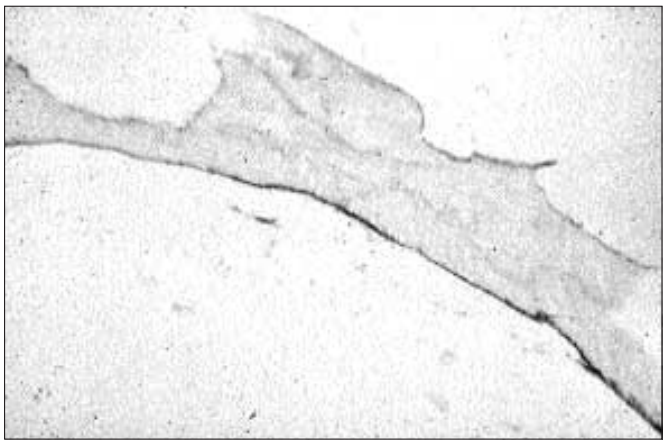

FIGURE 7-37 (see Color Plate)
The same bone section as in Figure 7-35 with positive aluminum stain of the trabecular surface. These findings are consistent with aluminum-related osteomalacia.

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