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Parathyroid Hormone, Calcitonin, Vitamin D, and Other Compounds Related to Mineral Metabolism

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DRUG LIST

GENERIC NAME	PAGE	GENERIC NAME	PAGE
Alendronate	760	Pamidronate	760
Calcitonin	756	Parathyroid hormone	760
Calcitriol	760	Plicamycin	759
Cholecalciferol	757	Risedronate	760
Dihydroxycholesterol	757	Tiludronate	760
Ergocalciferol	757	Zoledronic acid	760
Etidronate	760		

The principal hormones involved in calcium metabolism and bone remodeling are *parathyroid hormone* (PTH), *calcitonin*, and *vitamin D* (D_3). Other hormones, such as the thyroid hormones, growth hormone, androgens, estrogens, and the glucocorticoids also influence mineral homeostasis and bone metabolism. The three primary target tissues for these hormones are bone, kidney, and intestine. These three hormones and their target tissues maintain serum calcium levels, extracellular calcium levels, and bone integrity.

CALCIUM HOMEOSTASIS

Calcium is the principal extracellular electrolyte regulated by PTH, calcitonin, and D_3 . *Extracellular calcium* is a critical component of signal transduction across the plasma membrane, which regulates a wide spectrum of physiological events including muscle contraction, secretion of neurotransmitters and hormones, and the ac-

tion of growth factors, cytokines, and protein hormones. *Intracellular calcium* is an important cofactor in many enzymatic reactions. Plasma calcium exists in three forms: *ionized* (50%), *protein bound* (46%), and *complexed* to organic ions (4%). Total plasma calcium concentration is normally tightly maintained within the range of 4.5 to 5.7 mEq/L, primarily by the actions of PTH and D_3 , which regulate bone resorption and calcium absorption from the intestine and kidney. The calcium-lowering actions of calcitonin may regulate postprandial plasma calcium deposition into bone and prevent hypercalcemia.

The regulation of serum calcium concentration is a complex process that requires the coordinated responses of these three hormones and their target tissues. The model shown in Figure 66.1 consists of three wings depicting overlapping feedback loops that represent the interrelationship between *bone* (wing 1), *intestine* (wing 2), and *kidney* (wing 3) in modulating calcium homeostasis. The left side of the model (A loops) de-

scribes events that increase blood calcium in response to *hypocalcemia*, whereas the right side (B loops) describes events that decrease blood calcium in response to *hypercalcemia*.

Hypocalcemia directly increases PTH synthesis and release and inhibits calcitonin release. PTH in turn restores plasma calcium by initially stimulating transport of free or labile calcium from bone into the blood. PTH also increases renal 1,25-dihydroxycholecalciferol ($1,25\text{-(OH)}_2\text{D}_3$) production, which is the most active form of D_3 . $1,25\text{-(OH)}_2\text{D}_3$ induces enterocyte differentiation in the intestine, which in turn results in increased absorption of calcium. Finally, during long periods of hypocalcemia, PTH can mobilize more stable calcium deep in the hydroxyapatite of bone by activating deep osteoclasts.

Hypercalcemia, in contrast, results in calcitonin synthesis and release, while PTH release and formation of $1,25\text{-(OH)}_2\text{D}_3$ are inhibited. Calcitonin inhibits bone resorption directly by reducing osteocyte activity. Calcitonin also induces an initial phosphate diuresis, followed by increased renal calcium, sodium, and phosphate excretion.

PARATHYROID HORMONE

PTH is secreted from the parathyroid glands in response to a low plasma concentration of ionized (free) calcium. PTH immediately causes the transfer of labile calcium stores from bone into the bloodstream. PTH increases rates of dietary calcium absorption by the intestine indirectly via the vitamin D_3 system activation of enterocyte activity. Within the kidney, PTH directly stimulates calcium reabsorption and a phosphate diuresis.

Chemistry

PTH is a single-chain polypeptide composed of 84 amino acid residues that is devoid of disulfide bonds and has a molecular weight of 9500. Biological activity of the human hormone resides primarily in the amino terminal end of the protein (i.e., amino acids 1–34). This portion of PTH has full biological activity both in vivo and in vitro. Synthetic fragments of the 1–34 portion of the PTH molecule have been synthesized. A paraneoplastic hormone, *PTH related peptide (PTHrP)* has been identified, isolated, and synthesized. PTHrP is

structurally homologous to the amino terminal portion of PTH and interacts with the PTH receptor in bone and kidney. This hormone is responsible for hypercalcemia in certain forms of malignancy. It has been used as a therapeutic agent in osteoporosis in some clinical trials.

Synthesis and Secretion

Plasma calcium concentration is the principal factor regulating PTH synthesis and release. The increase in PTH synthesis and secretion induced by hypocalcemia is believed to be mediated through activation of parathyroid gland adenylyl cyclase and a subsequent increase in intracellular cyclic adenosine monophosphate (cAMP).

Formation of PTH begins with the synthesis of several precursor molecules. *PreproPTH* is the initial peptide that is synthesized within the parathyroid gland, and it serves as a precursor to both proPTH and PTH. PreproPTH is formed within the rough endoplasmic reticulum, transported into the cisternal space, and then cleaved to form proPTH. The proPTH polypeptide is transported into the cisternal space, where another proteolytic cleavage occurs, forming PTH.

PTH in Target Tissues

PTH has two levels of action in bone. First, in response to acute decreases in serum calcium, PTH stimulates surface osteocytes to increase the outward flux of calcium ion from bone to rapidly restore serum calcium. Thus, during brief periods of hypocalcemia, PTH release results in mobilization of calcium from labile areas of bone that lie adjacent to osteoclasts. This effect is not associated with any significant increase in plasma phosphate or bone resorption. Second, PTH induces transformation of osteoprogenitor cells into osteoclasts, which increase bone formation. Thus, PTH has anabolic action on bone formation at physiological levels, and it is this action that allows it to be used pharmacologically to treat osteoporosis. However, in conditions that result in chronic calcium deficiency or prolonged hypocalcemia (e.g., renal osteodystrophy, vitamin D deficiency, or malabsorption syndromes), PTH mobilizes deep osteocytes in periacicular bone and can result in significant bone resorption and eventual osteopenia as it attempts to maintain normal concentrations of ionic or free plasma calcium.

In the kidney, PTH stimulates the conversion of 25-(OH)D₃ into 1,25-(OH)₂D₃. Intrarenal 1,25-(OH)₂D₃ causes an amplification of the PTH-induced calcium reabsorption and phosphate diuresis. 1,25-(OH)₂D₃ enhances PTH action in bone also. Once again, *PTH does not directly affect intestinal calcium absorption*, but it does so indirectly through induction of 1,25-(OH)₂D₃ synthesis and enhanced enterocyte absorption.

CALCITONIN

Calcitonin release is normally stimulated by rising serum calcium levels and suppressed by hypocalcemia. The major physiological effects of calcitonin are inhibition of bone resorption and deposition of postabsorptive calcium into bone following a meal, which prevents postprandial hypercalcemia.

Chemistry

Calcitonin is a single-chain polypeptide composed of 32 amino acid residues having a molecular weight of approximately 3600. A cysteine disulfide bridge at the 1-7 position of the amino terminal end of the peptide is essential for biological activity; however, the entire amino acid sequence is required for optimal activity.

Synthesis and Secretion

The regulation of calcitonin synthesis and release from the parafollicular C cells of the thyroid gland is calcium dependent. *Rising serum calcium is the principal stimulus responsible for calcitonin synthesis and release.* Other hormones, such as glucagon, gastrin, and serotonin, also stimulate calcitonin release. Calcitonin has been isolated in tissues other than the parafollicular C cells (parathyroid, pancreas, thymus, adrenal), but it is not known whether this material is biologically active.

Secretagogues, such as gastrin and pancreozymin, may contribute significantly to the regulation of endogenous calcitonin. In fact, it has been postulated that gastrin-induced calcitonin release following meals may help regulate the postprandial calcium deposition in bone.

A calcitonin precursor has been identified within the thyroid parafollicular C cells. It is thought to function in a manner analogous to that of proPTH to facilitate intracellular transport and secretion of the hormone. The metabolic degradation of calcitonin appears to occur in both the liver and kidney.

Although blood calcitonin levels are normally low, excessive levels have been found in association with medullary carcinoma of the thyroid and more rarely carcinoid tumors of the bronchus and stomach. Serum calcitonin levels are used to screen and monitor patients who have or are suspected of having medullary carcinoma of the thyroid.

Mechanism of Action

Calcitonin interacts with specific plasma membrane receptors within target organs to initiate biological effects. This interaction has been directly linked to the generation of cAMP via adenylyl cyclase activation.

VITAMIN D₃ (CHOLECALCIFEROL)

Vitamin D₃, through its active metabolite, 1,25-(OH)₂D₃, also plays an important role in maintaining calcium homeostasis by enhancing intestinal calcium absorption, PTH-induced mobilization of calcium from bone, and calcium reabsorption in the kidney.

Synthesis and Activation

The primary supply of vitamin D₃ in humans is not obtained from the diet but rather is derived from the ultraviolet photoconversion of 7-dehydrocholesterol to vitamin D₃ in skin. Thus, vitamin D₃ synthesis varies with the seasons. D₃ is a prohormone and requires further metabolic conversion to exert biological activity in its target organs (Fig. 66.2). The liver and the kidney are the major sites of metabolic activation of this endogenous sterol hormone. The initial transformation of D₃ occurs in the liver and is catalyzed by the enzyme 25-OH-D₃-hydroxylase

to form 25-(OH)D₃; this is the primary circulating form of D₃. Circulating 25-(OH)D₃ is then converted by the kidney to the most active form of D₃, 1,25-(OH)₂D₃, by the 1-(OH)-D₃-hydroxylase enzyme. Blood concentrations of 1,25-(OH)₂D₃ are approximately one five-hundredth of those of 25-(OH)D₃. 1, 25-(OH)₂D₃ is converted to the metabolite 24R,25-(OH)₂D₃, which is capable of suppressing parathyroid secretion.

In addition to the endogenous metabolites, some exogenous sterols possess biological activity similar to that of D₃. *Ergocalciferol* (vitamin D₂) is derived from the plant sterol ergosterol and may act as a substrate for both the 25-hydroxylase and the 1-hydroxylase enzyme systems of the liver and kidney to form 25-(OH)D₂ and 1,25-(OH)₂D₂, respectively. *Ergocalciferol* (vitamin D₂) is the form used in commercial vitamins and supplemented dairy products. *Dihydrotachysterol*, another sterol that is used as a therapeutic agent, also functions as a substrate for the hydroxylase enzymes in the liver and kidney.

Mechanism of Action

1, 25-(OH)₂D₃ exerts its influence within target tissues through high-affinity sterol-specific intracellular receptor proteins. The D₃ receptor, similar to steroid receptor systems, translocates the hormone from the cell cytoplasm to the nucleus, where biological response is initiated via transcription and translation (Fig. 66.3).

BISPHOSPHONATES

The bisphosphonates are synthetic organic compounds that are incorporated directly into the hydroxyapatite of bone and then inhibit osteoclastic bone resorption. This antiresorptive action makes them useful in the pharmacological treatment of hypercalcemia, osteoporosis, and Paget's disease.

Chemistry

The bisphosphonates have a common structure, P-C-P, which is similar to the structure of the native pyrophosphate P-O-P found in bone hydroxyapatite. The different compounds in clinical use vary by the attachments to the R component of the native molecule.

Mechanism of Action

The bisphosphonates inhibit osteoclastic resorption of bone by binding to the hydroxyapatite crystals of bone. When osteoclasts first attach to bone in the active resorptive sites, the bisphosphonates are released from that bone. The release of these compounds locally prevents further osteoclastic attachment to those resorptive surfaces. The bisphosphonates also may inhibit resorption by inducing apoptosis of osteoclasts and by inhibiting release of interleukins and other compounds involved in bone resorption. The net result of actions of these compounds is inhibition of bone osteoclastic resorption. This action allows new bone formation to catch up in the remodeling process and can result in a net gain in bone density.

CLINICAL USES OF PARATHYROID HORMONE, CALCITONIN, VITAMIN D, AND BISPHOSPHONATES

These hormones and drugs are used most commonly for disorders of calcium and bone metabolism rather than to correct specific hormone deficiencies. For example, the use of PTH replacement in hypoparathyroidism in the past was not practical because of the difficulty in ob-

taining purified hormone and the fact that it is injected subcutaneously. With the recent ability to produce large quantities of recombinant PTH (rPTH), its use will be more common, especially for severe osteoporosis.

Hypercalcemia of Malignancy

Hypercalcemia is a common clinical condition that can accompany a variety of other medical conditions, such as sarcoidosis, vitamin D toxicity, hyperparathyroidism, and malignancy. When calcium levels are exceptionally high, adjunctive measures for the control of plasma calcium levels are necessary, as this is a medical emergency. Various modalities in combination are used to treat this condition; intravenous hydration with normal saline and the use of loop diuretics (e.g., furosemide) to induce calcium diuresis are the most important supportive measures.

The *bisphosphonates are the most effective compounds available to treat hypercalcemia of malignancy*. Pamidronate (*Aredia*) and zoledronic acid (*Zometa*) can be infused intravenously and are the most effective compounds available for rapid reduction of serum calcium levels.

Calcitonin is also effective in reducing serum calcium levels in life-threatening hypercalcemia; however, it is not as rapid or as effective as the bisphosphonates. Subcutaneous administration of salmon (*Calcimar*) or human (*Cibacalcin*) calcitonin reduces serum calcium levels within 3 to 5 days in 75 to 90% of malignant hypercalcemias.

Plicamycin (*Mithracin*), an inhibitor of RNA synthesis in osteoclasts, reduces serum calcium levels when infused over 4 to 6 hours every 3 to 4 days. Plicamycin's effects are slower than those of the bisphosphonates; the drug is a bone marrow suppressant that can complicate clinical management if the patient is already receiving chemotherapy for the malignancy.

Osteoporosis

Postmenopausal osteoporosis is the most common form of osteoporosis. In perimenopausal women, the greatest amount of bone density is lost during the first 5 years after onset of menopause. Women going through menopause at a particularly early age are especially at risk for developing osteoporosis, and they should take some prophylactic regimen at the onset of menopause. Previously, estrogen replacement therapy (ERT), along with calcium supplementation and D_3 , were the standard of care. However, the benefits of ERT, including increased bone density, decreased risk of colon cancer, and decreased vaginal atrophy, must be weighed against the slightly increased risk of breast cancer, endometrial cancer, stroke, and deep vein thrombosis. While unopposed estrogen may slightly increase the incidence of

endometrial cancer, appropriate combinations with a progestin negate such risk. Other compounds are available for the prevention of osteoporosis. These include the selective estrogen receptor modulators (See Chapter 61), the bisphosphonates, and nasally administered calcitonin. For example, the bisphosphonates are now indicated for prophylaxis of osteoporosis when individuals are going to be treated with glucocorticoids or the gonadotropin antagonists.

Once bone loss is sufficient to result in a compression fracture, pharmacological therapy is much less effective. However, even after fractures have occurred, the use of the bisphosphonates and rPTH has been shown to increase bone densities and reduce the rate of subsequent fractures. Nasal calcitonin (200 units daily) is effective in promoting fracture healing and also exhibits an analgesic effect by reducing pain in persons with acute lumbar compression fractures. *Whatever compound is used for prophylaxis or treatment of osteoporosis, calcium and D_3 supplementation are required for maximum benefit.*

Drug-Induced Osteopenia

Chronic administration of many drugs, especially anticonvulsant medications, glucocorticoids, and GnRH agonists, are known to produce osteopenia and osteoporosis. The anticonvulsants inhibit formation of active D_3 ; chronic glucocorticoid therapy increases bone turnover by altering osteoblast differentiation and inhibiting collagen synthesis; and the GnRH agonists induce chemical hypogonadism.

Clinical trials have demonstrated that the use of the bisphosphonates, nasal calcitonin, or human rPTH combined with calcium and vitamin D supplementation is effective in preventing drug-induced osteoporosis. Thus, individuals receiving over the long term any medication that can induce osteomalacia should also take one of these compounds and have periodic bone density determinations.

Renal Osteodystrophy

Patients with chronic renal failure develop hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism, and severe metabolic bone disease. The secondary hyperparathyroidism is thought to be due to hyperphosphatemia and decreased 1, 25-(OH) $_2$ formation. Oral or intravenous 1,25-(OH) $_2$ D_3 (calcitriol) therapy along with oral phosphate-binding agents and calcium supplementation is effective in reducing the effects of renal osteodystrophy.

Paget's Disease

Paget's disease is an uncommon disorder of bone characterized by mixed lytic and sclerotic bone changes.

These individuals have areas of increased bone resorption and other areas of abnormal new bone formation. The abnormal bone formation can result in pain, deformity, and fracture of affected bones. The bisphosphonates and calcitonin are most commonly used in the treatment of this disease. Long-term continuous use of bisphosphonates can be associated with the induction of osteomalacia through a direct impairment of new bone formation. Therefore, the bisphosphonates are given in a cyclic pattern to treat Paget's disease.

ADVERSE EFFECTS

With the exception of the possible development of a hypervitaminosis associated with high-dose administration of vitamin D₂ or D₃, the compounds discussed in this chapter are relatively safe. Allergic reactions to the injection of calcitonin and PTH have occurred and chronic use of some bisphosphonates has been associated with the development of osteomalacia. The principal side effects of intravenous bisphosphonates are mild and include low-grade fever and transient increases in serum creatinine and phosphate levels. Oral bisphosphonates are poorly absorbed and can cause esophageal and gastric ulceration. They should be taken on an empty stomach; the individual must remain upright for 30 minutes after ingestion.

Human Parathyroid Hormone

Human rPTH (1-34) has been produced by recombinant technologies, is now approved, and will soon be available for the treatment of osteoporosis. It is given subcutaneously, 25 µg/day cyclically for 12 to 18 months, to increase bone density in individuals with a history of fractures, severe osteopenia, or osteoporosis. PTHrP (1-36) has also been synthesized and is in early clinical trials.

Calcitonin

Calcitonin (*Miacalcin*, *Miacalcin Nasal Spray*) is a synthetic 32-amino acid polypeptide that is identical to salmon calcitonin. Salmon calcitonin is more potent than human calcitonin because of its higher affinity for the human calcitonin receptor and its slower metabolic clearance. Administration is by subcutaneous or intramuscular injection or by nasal spray. The absorption of the nasal form is slower than that of the parenteral routes.

Vitamin D Compounds

Vitamin D comes in many formulations, including multivitamin preparations, fish liver oils with or without vitamin A, combinations with calcium salts, and vitamin D preparations alone. Most forms of vitamin D contain either cholecalciferol (D₃) or ergocalciferol (D₂).

Cholecalciferol is pure vitamin D₃ derived from the ultraviolet conversion of 7-dehydrocholesterol to cholecalciferol. *Ergocalciferol* (vitamin D₂) is a sterol derived from yeast and fungal ergosterol. *Calcitriol* [*Rocaltrol*, 1,25-(OH)₂D₃] is the metabolically active vitamin D₃ compound. *Dihydroxycholesterol* is a synthetic compound that may act somewhat more quickly than either vitamin D₂ or D₃.

Bisphosphonates

Multiple bisphosphonates compounds are available for both oral and intravenous use. Some [alendronate (*Fosamax*) and etidronate (*Didronel*)] are used for osteoporosis, others [etidronate, tirludronate (*Skelid*), risedronate (*Actonel*)] for Paget's disease, and yet others [pamidronate (*Aredia*), zoledronic acid] for the hypercalcemia of malignancy.

Study QUESTIONS

- Why are elderly individuals more likely to be vitamin D deficient than young adults? All of the choices are true EXCEPT
 - They spend less time outdoors exposed to the sun, which is important in the synthesis of vitamin D.
 - Their appetite and intake of essential nutrients is diminished because of chronic medical conditions associated with aging.
 - The formation of the active form of vitamin D is diminished by chronic liver and renal conditions.
 - The vitamin D receptor has less affinity for D₃ with aging.
- A 48-year-old white man is noted to have osteopenia on a routine LS spine film while being evaluated for back pain. His bone density reveals osteoporosis of both his hip and LS spine. All of the choices are possible EXCEPT
 - He has been taking gabapentin (*Neurontin*) for the past 2 years for a seizure disorder.
 - He has Crohn's disease and has had to take prednisone off and on since age 16.

(C) He has had multiple calcium kidney stones over the past few years and has been on a low-calcium diet.

(D) He had glomerulonephritis at age 24 and developed chronic renal failure but received a kidney transplant 10 years ago.

(E) He drinks 2 to 3 glasses of wine each day at dinner.

3. An 85-year-old black man is noted to have sclerosis of the sacroiliac joint on routine films for back pain. The radiologist suggests that this might indicate Paget's disease. Workup for this condition reveals minimal involvement of the pelvis and LS spine. How would you treat this patient?
 - (A) Reassure the patient and tell him that unless his symptoms become much worse, there will be no specific treatment.
 - (B) Begin calcitonin nasal spray to prevent further bone resorption and help with the pain.
 - (C) Use tiludronate in 18-month cycles to prevent progression of the disease to other parts of the body.
4. A 36-year-old white woman is noted to have a 1.5-cm nodule in the right lower lobe of her thyroid on routine examination. Her thyroid functions are normal and a ^{123}I uptake and scan of the thyroid produce normal findings. Her serum calcium levels were determined to be 14 mg/dL (normal levels 9 to 10.3 mg/dL). What is the most likely diagnosis?
 - (A) Hyperparathyroidism; serum calcium, PTH level, and ultrasound of the thyroid should be obtained.
 - (B) This may be a lymph node, not associated with any thyroid disease.
 - (C) She may have medullary carcinoma of the thyroid. Therefore, serum calcitonin, ret-Pro-Oncogene determination, and ultrasound of the thyroid should be obtained.
 - (D) This may be a thyroid carcinoma that is anterior in the thyroid and therefore not picked up by the ^{123}I scan. She should have thyroglobulin level measurement and ultrasound of the thyroid.

ANSWERS

1. **D.** There is no evidence that affinity for D_3 with its receptor is altered during aging. Aging is associated with vitamin D deficiency for several reasons. It is important for the elderly to receive vitamin D supplementation to prevent osteoporosis and the other problems associated with hypocalcemia. If they have chronic liver or renal conditions, use of one of the specific metabolites should be used, such as calcitriol.
2. **E.** There is no good evidence that moderate amounts of alcohol contribute to osteoporosis. All

of the other listed conditions can contribute to osteoporosis. Antiseizure medications interfere with activation of vitamin D; glucocorticoids stimulate bone resorption of calcium; renal loss of calcium can result in secondary hyperparathyroidism; and organ transplantation is associated with osteoporosis because of the glucocorticoids and other immunosuppressive medications used. Individuals chronically taking these medications should take a bisphosphonate for prophylaxis. In patients prone to form kidney stones, a low dose of a thiazide diuretic will often block the renal loss of calcium and prevent osteoporosis and further stone formation.

3. **A.** Paget's disease is often asymptomatic and picked up on plain bone films. Patients with Paget's disease should have their serum calcium level determined to make sure that they are not hypercalcemic from excessive bone resorption, their serum alkaline phosphatase measured as a marker of new bone formation, a bone scan to determine whether other bones are involved, and a 24-hour urinary hydroxyproline measurement to assess bone resorption. The patient who has minimal involvement and is biochemically normal does not need pharmacological therapy. No studies indicate that early treatment slows progression in individuals with the more severe form of this disorder.
4. **A.** Although all of the conditions can present as an asymptomatic nodule in the thyroid, the marked hypercalcemia in this patient makes hyperparathyroidism the probable diagnosis. Carcinomas of the thyroid are common, and outcomes are improved with early diagnosis. Medullary carcinoma and hyperparathyroidism caused by hyperplasia may be inherited and are associated with the multiple endocrine neoplasia syndromes.

SUPPLEMENTAL READING

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CASE Study Hypercalcemia

Alan Aldrich is a 67-year-old white man who goes to the emergency department with lethargy, increased thirst, and increased urination for 3 days. His family states that he has been somewhat confused for the past day and is not eating or drinking as much as he should. He has a history of chronic bronchitis, a 60-pack year history of smoking, and has lost 12 lb over the past month. Physical examination reveals an arousable thin elderly white man in no acute distress. Blood pressure is 110/60; pulse is 88; respiration rate is 22; temperature is 100.3°F (37.9°C). Chest radiography reveals chronic obstructive pulmonary disease with a questionable subpleural mass on the right. His initial blood chemistry revealed serum Ca^{++} , 13.8 mg/dL; alkaline phosphatase, 489; and elevated liver functions. What is the likely cause of his condition, and how would you treat it?

ANSWER: The cause of hypercalcemia most likely is malignancy. However, he may have longstanding hyperparathyroidism or milk alkali syndrome from the ingestion of large amounts of calcium carbonate to treat indigestion. He should be examined for each of these causes, but in the interim, this is a medical emergency and you have to treat empirically. The proper initial treatment is rehydration with 0.9% normal saline, use of a loop diuretic such as furosemide, and treatment with one of the intravenous preparations of a bisphosphonate, alendronate or zoledronic acid. Serum Ca^{++} is usually restored within 24 to 48 hours with this regimen. Retreatment with a bisphosphonate is often required if the patient has widespread bone metastasis. Once his serum Ca^{++} level is normalized, the diagnostic workup can be completed to determine the cause of the hypercalcemia.