

# Endocrine Regulation of Calcium, Phosphate, and Bone Metabolism

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## CHAPTER OUTLINE

- AN OVERVIEW OF CALCIUM AND PHOSPHORUS IN THE BODY
- MECHANISMS OF CALCIUM AND PHOSPHATE HOMEOSTASIS
- REGULATION OF PLASMA CALCIUM AND PHOSPHATE CONCENTRATIONS
- ABNORMALITIES OF BONE MINERAL METABOLISM

## KEY CONCEPTS

1. When plasma calcium levels fall below normal, spontaneous action potentials can be generated in nerves, leading to tetany of muscles, which, if severe, can result in death.
2. About half of the circulating calcium is in the free or ionized form, about 10% is bound to small anions, and about 40% is bound to plasma proteins. Most of the phosphorus circulates free as orthophosphate.
3. The majority of ingested calcium is not absorbed by the GI tract and leaves the body via the feces; by contrast, phosphate is almost completely absorbed by the GI tract and leaves the body mostly via the urine.
4. Secretion of parathyroid hormone (PTH), a polypeptide hormone produced by the parathyroid glands, is stimulated by a decrease in plasma-ionized calcium. PTH plays a

- vital role in calcium and phosphate homeostasis, and acts on bones, kidneys, and intestine to raise the plasma calcium concentration and lower the plasma phosphate concentration.
5. Vitamin D is converted to the active hormone 1,25-dihydroxycholecalciferol by sequential hydroxylation reactions in the liver and kidneys. This hormone stimulates intestinal calcium absorption and, thereby, raises the plasma calcium concentration.
6. Calcitonin, a polypeptide hormone produced by the thyroid glands, tends to lower the plasma calcium concentration, but its physiological importance in humans has been questioned.
7. Osteoporosis, osteomalacia and rickets, and Paget's disease are the most common forms of metabolic bone disease.

The plasma calcium concentration is among the most closely regulated of all physiological parameters in the body. Typically, it varies by only 1 to 2% daily or even weekly. Such stringent regulation in a biological system usually implies that the parameter plays an important role in one or more critical processes.

Phosphate also plays a variety of important roles in the body, although its concentration is not as tightly regulated as that of calcium. Many of the factors involved in regulating calcium also affect phosphate.

### AN OVERVIEW OF CALCIUM AND PHOSPHORUS IN THE BODY

Calcium plays a key role in many physiologically important processes. A significant decrease in plasma calcium can rapidly lead to death. A chronic increase in plasma calcium can

lead to soft tissue calcification and formation of stones. Phosphorus also plays important roles in the body.

### Calcium Plays Key Roles in Nerve and Muscle Excitation, Muscle Contraction, Enzyme Function, and Bone Mineral Balance

Calcium affects nerve and muscle excitability, neurotransmitter release from axon terminals, and excitation-contraction coupling in muscle cells. It serves as a second or third messenger in several intracellular signal transduction pathways. Some enzymes use calcium as a cofactor, including some in the blood-clotting cascade. Finally, calcium is a major constituent of bone.

Of all these roles, the one that demands the most careful regulation of plasma calcium is the effect of calcium on nerve excitability. Calcium affects the sodium permeability of nerve membranes, which influences the ease with which

action potentials are triggered. Low plasma calcium can lead to the generation of spontaneous action potentials in nerves. When motor neurons are affected, tetany of the muscles of the motor unit may occur; this condition is called **hypocalcemic tetany**. Latent tetany may be revealed in certain diagnostically important signs. **Trousseau's sign** is a characteristic spasm of the muscles of the forearm that causes flexion of the wrist and thumb and extension of the fingers. It may occur spontaneously or be elicited by inflation of a blood pressure cuff placed on the upper arm. **Chvostek's sign** is a unilateral spasm of the facial muscles that can be elicited by tapping the facial nerve at the point where it crosses the angle of the jaw.

### Phosphate Participates in pH Buffering and Is a Major Constituent of Macromolecules and Bones

Phosphorus (usually as phosphate) also participates in many important metabolic processes. Phosphate serves as an important component of intracellular pH buffering and various metabolic intermediates. DNA, RNA, and phosphoproteins all contain phosphate as an integral part of their structure. Phosphate is also a major component of bones.

### The Distributions of Calcium and Phosphorus Differ

Table 36.1 shows the relative distributions of calcium and phosphate in a healthy adult. The average adult body contains approximately 1 to 2 kg of calcium, roughly 99% of it in bones. Despite its critical role in excitation-contraction coupling, only about 0.3% of total body calcium is located in muscle. About 0.1% of total calcium is in extracellular fluid.

Of the roughly 600 g of phosphorus in the body, most is in bones (86%). Compared with calcium, a much larger percentage of phosphorus is located in cells (14%). The amount of phosphorus in extracellular fluid is rather low (0.08% of body content).

Bones also contain a relatively high percentage of the total body content of several other inorganic substances (Table 36.2). About 80% of the total carbonate in the body is located in bones. This carbonate can be mobilized into the blood to combat acidosis; thus, bone participates in pH buffering in the body. Long-standing uncorrected acidosis can result in considerable loss of bone mineral. Significant percentages of the body's magnesium and sodium and nearly 10% of its total water content are in bones.

**TABLE 36.1** Body Content and Tissue Distribution of Calcium and Phosphorus in a Healthy Adult

	Calcium	Phosphorus
Total Body Content	1,300 g	600 g
Relative Tissue Distribution (% of total body content)		
Bones and teeth	99%	86%
Extracellular fluid	0.1%	0.08%
Intracellular fluid	1.0%	14%

**TABLE 36.2** Inorganic Constituents of Bone

Constituent	Percentage of Total Body Content Present in Bone
Calcium	99
Phosphate	86
Carbonate	80
Magnesium	50
Sodium	35
Water	9

### Calcium and Phosphorus Are Present in the Plasma in Several Forms

In humans, the normal plasma calcium concentration is 9.0 to 10.5 mg/dL. Plasma calcium exists in three forms: ionized or free calcium (50% of the total), protein-bound calcium (40%), and calcium bound to small diffusible anions, such as citrate, phosphate, and bicarbonate (10%). The association of calcium with plasma proteins is pH-dependent. At an alkaline pH, more calcium is bound; the opposite is true at an acidic pH.

Plasma phosphorus concentrations may fluctuate significantly during the course of a day, from 50 to 150% of the average value for any particular individual. In adults, the normal range of plasma concentrations is 3.0 to 4.5 mg/dL (expressed in terms of milligrams of phosphorus).

Phosphorus circulates in the plasma primarily as inorganic **orthophosphate** ( $\text{PO}_4$ ). At a normal blood pH of 7.4, 80% of the phosphate is in the  $\text{HPO}_4^{2-}$  form and 20% is in the  $\text{H}_2\text{PO}_4^-$  form. Nearly all plasma inorganic phosphate is ultrafilterable. In addition to free orthophosphate, phosphate is present in small amounts in the plasma in organic form, such as in hexose or lipid phosphates.

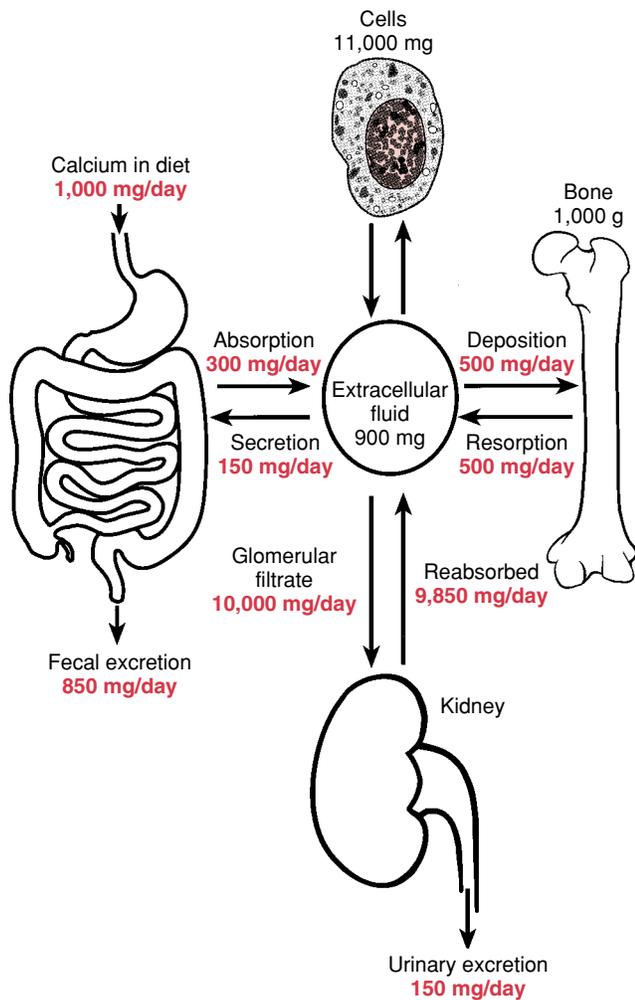
### The Homeostatic Pathways for Calcium and Phosphorus Differ Quantitatively

Both calcium and phosphate are obtained from the diet. The ultimate fate of each substance is determined primarily by the gastrointestinal (GI) tract, the kidneys, and the bones.

#### Calcium Handling by the GI Tract, Kidneys, and Bones.

The approximate tissue distribution and average daily flux of calcium among tissues in a healthy adult are shown in Figure 36.1. Dietary intakes may vary widely, but an "average" diet contains approximately 1,000 mg/day of calcium. Intakes up to twice that amount are usually well tolerated, but excessive calcium intake can result in soft tissue calcification or kidney stones. Only about one third of ingested calcium is actually absorbed from the GI tract; the remainder is excreted in the feces. The efficiency of calcium uptake from the GI tract varies with the individual's physiological status. The percentage uptake of calcium may be increased in young growing children and pregnant or nursing women; often it is reduced in older adults.

Figure 36.1 also indicates that approximately 150 mg/day of calcium actually enter the GI tract from the



**FIGURE 36.1** Typical daily exchanges of calcium between different tissue compartments in a healthy adult. Fluxes of calcium (mg/day) are shown in color. Total calcium content in each compartment is shown in black. Note that the majority of ingested calcium is eliminated from the body via the feces.

body. This component of the calcium flux partly results from sloughing of mucosal cells that line the GI tract and also from calcium that accompanies various secretions into the GI tract. This component of calcium metabolism is relatively constant, so the primary determinant of *net* calcium uptake from the GI tract is calcium absorption. Intestinal absorption is important in regulating calcium homeostasis.

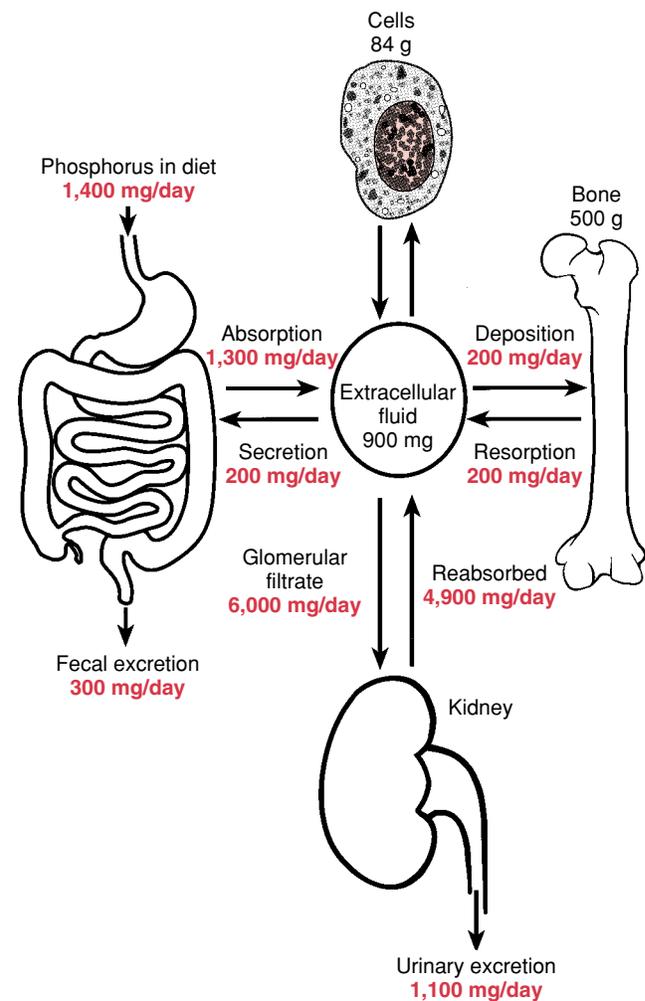
Bone in an average individual contains approximately 1,000 g of calcium. Bone mineral is constantly resorbed and deposited in the remodeling process. As much as 500 mg/day of calcium may flow in and out of the bones (see Fig. 36.1). Since bone calcium serves as a reservoir, both bone resorption and bone formation are important in regulating plasma calcium concentration.

In overall calcium balance, the net uptake of calcium from the GI tract presents a daily load of calcium that will eventually require elimination. The primary route of elimination is via the urine, and therefore, the kidneys play an important role in regulating calcium homeostasis. The 150

mg/day of calcium excreted in the urine represent only about 1% of the calcium initially filtered by the kidneys; the remaining 99% is reabsorbed and returned to the blood. Therefore, small changes in the amount of calcium reabsorbed by the kidneys can have a dramatic impact on calcium homeostasis.

**Phosphate Handling by the GI Tract, Kidneys, and Bones.**

Figure 36.2 shows the overall daily flux of phosphate in the body. A typical adult ingests approximately 1,400 mg/day of phosphorus. In marked contrast to calcium, most (1,300 mg/day) of this phosphorus is absorbed from the GI tract, typically as inorganic phosphate. There is an obligatory contribution of phosphorus to the contents of the GI tract (about 200 mg/day), much like that for calcium, resulting in a net uptake of phosphorus of 1,100 mg/day and excretion of 300 mg/day via the feces. Thus, the majority of ingested phosphate is absorbed from the GI tract and little passes through to the feces.



**FIGURE 36.2** Typical daily exchanges of phosphorus between different tissue compartments in a healthy adult. Fluxes of phosphorus (mg/day) are shown in color. Total phosphorus content in each compartment is shown in black. Note that the majority of ingested phosphorus is absorbed and eventually eliminated from the body via the urine.

Because most ingested phosphate is absorbed, phosphate homeostasis is greatly influenced by renal excretory mechanisms. Since the majority of circulating phosphate is readily filtered in the kidneys, tubular phosphate reabsorption is a major process regulating phosphate homeostasis.

## MECHANISMS IN CALCIUM AND PHOSPHATE HOMEOSTASIS

As indicated above, the GI tract, kidneys, and bone each play a role in the regulation of calcium and phosphate homeostasis.

### Calcium and Phosphate Are Absorbed Primarily by the Small Intestine

Calcium absorption in the small intestine occurs by both active transport and diffusion. The relative contribution of each process varies with the region and with total calcium intake. Uptake of calcium by active transport predominates in the duodenum and jejunum; in the ileum, simple diffusion predominates. The relative importance of active transport in the duodenum and jejunum versus passive diffusion in the ileum depends on several factors. At very high levels of calcium intake, active transport processes are saturated and most of the uptake occurs in the ileum, partly because of its greater length, compared with other intestinal segments. With moderate or low calcium intake, however, active transport predominates because the gradient for diffusion is low.

Active transport is the regulated variable in controlling calcium uptake from the small intestine. Metabolites of vitamin D provide a regulatory signal to increase intestinal calcium absorption. Under the influence of 1,25-dihydroxycholecalciferol, calcium-binding proteins in intestinal mucosal cells increase in number, enhancing the capacity of these cells to transport calcium actively (see Chapter 27).

The small intestine is also a primary site for phosphate absorption. Uptake occurs by active transport and passive diffusion, but active transport is the primary mechanism. As indicated in Figure 36.2, phosphate is efficiently absorbed from the small intestine; typically, 80% or more of ingested phosphate is absorbed. However, phosphate absorption from the small intestine is regulated very little. To a minor extent, active transport of phosphate is coupled to calcium transport. Therefore, when active transport of calcium is low, as with vitamin D deficiency, phosphate absorption is also low.

### The Kidneys Play an Important Role in Regulating Plasma Concentrations of Calcium and Phosphate

As a result of regulating the urinary excretion of calcium and phosphate, the kidneys are in a key position to regulate the total body balance of these two ions. Hormones are an important signal to the kidneys to direct the excretion or retention of calcium and phosphate.

**Renal Handling of Calcium.** As discussed in Chapter 24, filterable calcium comprises about 60% of the total calcium in the plasma. It consists of free calcium ions and calcium

bound to small diffusible anions. The remaining 40% of the total calcium is bound to plasma proteins and is not filterable by the glomeruli. Ordinarily, 99% of the filtered calcium is reabsorbed by the kidney tubules and returned to the plasma. Reabsorption occurs both in the proximal and distal tubules and in the loop of Henle. Approximately 60% of filtered calcium is reabsorbed in the proximal tubule, 30% in the loop of Henle, and 9% in the distal tubule; the remaining 1% is excreted in the urine. Renal calcium excretion is controlled primarily in the late distal tubule; parathyroid hormone stimulates calcium reabsorption here, promoting calcium retention and lowering urinary calcium. Parathyroid hormone is an important regulator of plasma calcium concentration.

**Renal Handling of Phosphate.** Most ingested phosphate is absorbed from the GI tract, and the primary route of excretion of this phosphate is via the urine. Therefore, the kidneys play a key role in regulating phosphate homeostasis. Ordinarily about 85% of filtered phosphate is reabsorbed and 15% is excreted in the urine. Phosphate reabsorption occurs via active transport, mainly in the proximal tubule where 65 to 80% of filtered phosphate is reabsorbed. Parathyroid hormone inhibits phosphate reabsorption in the proximal tubule and has a major regulatory effect on phosphate homeostasis. It increases urinary phosphate excretion, leading to the condition of **phosphaturia**, with an accompanying decrease in the plasma phosphate concentration.

### Substantial Amounts of Calcium and Phosphate Enter and Leave Bone Each Day

Although bone may be considered as being a relatively inert material, it is active metabolically. Considerable amounts of calcium and phosphate both enter and exit bone each day, and these processes are hormonally controlled.

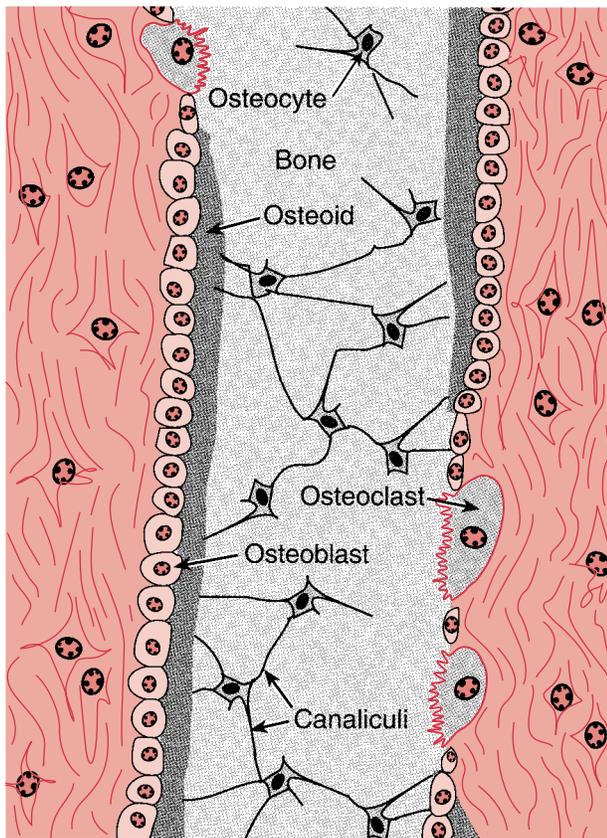
**Composition of Bone.** Mature bone can be simply described as inorganic mineral deposited on an organic framework. The mineral portion of bone is composed largely of calcium phosphate in the form of **hydroxyapatite crystals**, which have the general chemical formula  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ . The mineral portion of bone typically comprises about 25% of its volume, but because of its high density, the mineral fraction is responsible for approximately half the weight of bone. Bone contains considerable amounts of the body's content of carbonate, magnesium, and sodium in addition to calcium and phosphate (see Table 36.2).

The organic matrix of bone on which the bone mineral is deposited is called **osteoid**. **Type I collagen** is the primary constituent of osteoid, comprising 95% or more. Collagen in bone is similar to that of skin and tendons, but bone collagen exhibits some biochemical differences that impart increased mechanical strength. The remaining non-collagen portion (5%) of organic matter is referred to as **ground substance**. Ground substance consists of a mixture of various **proteoglycans**, high-molecular-weight compounds consisting of different types of polysaccharides linked to a polypeptide backbone. Typically, they are 95% or more carbohydrate.

Electron microscopic study of bone reveals needle-like hydroxyapatite crystals lying alongside collagen fibers. This orderly association of hydroxyapatite crystals with the collagen fibers is responsible for the strength and hardness characteristic of bone. A loss of either bone mineral or organic matrix greatly affects the mechanical properties of bone. Complete demineralization of bone leaves a flexible collagen framework, and the complete removal of organic matrix leaves a bone with its original shape, but extremely brittle.

**Cell Types Involved in Bone Formation and Bone Resorption.** The three principal cell types involved in bone formation and bone resorption are osteoblasts, osteocytes, and osteoclasts (Fig. 36.3).

**Osteoblasts** are located on the bone surface and are responsible for osteoid synthesis. Like many cells that actively synthesize proteins for export, osteoblasts have an abundant rough ER and Golgi apparatus. Cells actively engaged in osteoid synthesis are cuboidal, while those less active are more flattened. Numerous cytoplasmic processes connect adjacent osteoblasts on the bone surface and connect osteoblasts with osteocytes deeper in the bone. Osteoid produced by osteoblasts is secreted into the space adjacent to the bone. Eventually, new osteoid becomes mineralized, and in the process, osteoblasts become surrounded by mineralized bone.



**FIGURE 36.3** The location and relationship of the three primary cell types involved in bone metabolism.

As osteoblasts are progressively incorporated into mineralized bone, they lose much of their bone-forming ability and become quiescent. At this point they are called **osteocytes**. Many of the cytoplasmic connections in the osteoblast stage are maintained into the osteocyte stage. These connections become visible channels or **canaliculi** that provide direct contact for osteocytes deep in bone with other osteocytes and with the bone surface. It is generally believed that these canaliculi provide a mechanism for the transfer of nutrients, hormones, and waste products between the bone surface and its interior.

**Osteoclasts** are cells responsible for bone resorption. They are large, multinucleated cells located on bone surfaces. Osteoclasts promote bone resorption by secreting acid and proteolytic enzymes into the space adjacent to the bone surface. Surfaces of osteoclasts facing bone are ruffled to increase their surface area and promote bone resorption. Bone resorption is a two-step process. First, osteoclasts create a local acidic environment that increases the solubility of surface bone mineral. Second, proteolytic enzymes secreted by osteoclasts degrade the organic matrix of bone.

**Bone Formation and Bone Remodeling.** Early in fetal development, the skeleton consists of little more than a cartilaginous model of what will later form the bony skeleton. The process of replacing this cartilaginous model with mature, mineralized bone begins in the center of the cartilage and progresses toward the two ends of what will later form the bone. As mineralization progresses, the bone increases in thickness and in length.

The **epiphyseal plate** is a region of growing bone of particular interest because it is here that the elongation and growth of bones occurs after birth. Histologically, the epiphyseal plate shows considerable differences between its leading and trailing edges. The leading edge consists primarily of **chondrocytes**, which are actively engaged in the synthesis of cartilage of the epiphyseal plate. These cells gradually become engulfed in their own cartilage and are replaced by new cells on the cartilage surface, allowing the process to continue. The cartilage gradually becomes calcified, and the embedded chondrocytes die. The calcified cartilage begins to erode, and osteoblasts migrate into the area. Osteoblasts secrete osteoid, which eventually becomes mineralized, and new mature bone is formed. In the epiphyseal plate, therefore, the continuing processes of cartilage synthesis, calcification, erosion, and osteoblast invasion result in a zone of active bone formation that moves away from the middle or center of the bone toward its end.

Chondrocytes of epiphyseal plates are controlled by hormones. Insulin-like growth factor I (IGF-I), primarily produced by the liver in response to growth hormone, serves as a primary stimulator of chondrocyte activity and, ultimately, of bone growth. Insulin and thyroid hormones provide an additional stimulus for chondrocyte activity.

Beginning a few years after puberty, the epiphyseal plates in long bones (as in the legs and arms) gradually become less responsive to hormonal stimuli and, eventually, are totally unresponsive. This phenomenon is referred to as **closure of the epiphyses**. In most individuals, epiphyseal closure is complete by about age 20; adult

height is reached at this point, since further linear growth is impossible. Not all bones undergo closure. For example, those in the fingers, feet, skull, and jaw remain responsive, which accounts for the skeletal changes seen in acromegaly, the condition of growth hormone overproduction (see Chapter 32).

The flux of calcium and phosphate into and out of bone each day reflects a turnover of bone mineral and changes in bone structure generally referred to as **remodeling**. Bone remodeling occurs along most of the outer surface of the bone, making it either thinner or thicker, as required. In long bones, remodeling can also occur along the inner surface of the bone shaft, next to the marrow cavity. Remodeling is an adaptive process that allows bone to be reshaped to meet changing mechanical demands placed on the skeleton. It also allows the body to store or mobilize calcium rapidly.

### REGULATION OF PLASMA CALCIUM AND PHOSPHATE CONCENTRATIONS

Regulatory mechanisms for calcium include rapid nonhormonal mechanisms with limited capacity and somewhat slower hormonally regulated mechanisms with much greater capacity. There are also similar mechanisms involved in regulating plasma phosphate concentrations.

#### Nonhormonal Mechanisms Can Rapidly Buffer Small Changes in Plasma Concentrations of Free Calcium

The calcium bound to plasma proteins and a small fraction of that in bone mineral can help prevent a rapid decrease in the plasma calcium concentration.

**Protein-Bound Calcium.** The association of calcium with proteins is a simple, reversible, chemical equilibrium process. Protein-bound calcium, therefore, has the capacity to serve as a buffer of free plasma calcium concentrations. This effect is rapid and does not require complex signaling pathways; however, the capacity is limited, and the mechanism cannot serve a long-term role in calcium homeostasis.

**A Readily Exchangeable Pool of Calcium in Bones.** Recall that approximately 99% of total body calcium is present in bones, and a healthy adult body has about 1 to 2 kg of calcium. Most of the calcium in bones exists as mature, hardened bone mineral that is not readily exchangeable but can be moved into the plasma via hormonal mechanisms (described below). However, approximately 1% (or 10 g) of the calcium in bones is in a simple chemical equilibrium with plasma calcium. This readily exchangeable calcium source is primarily located on the surface of newly formed bones. Any change in free calcium in the plasma or extracellular fluid results in a shift of calcium either into or out of the bone mineral until a new equilibrium is reached. Although this mechanism, like that described above, provides for a rapid defense against changes in free calcium concentrations, it is limited in capacity and can provide for only short-term adjustments in calcium homeostasis.

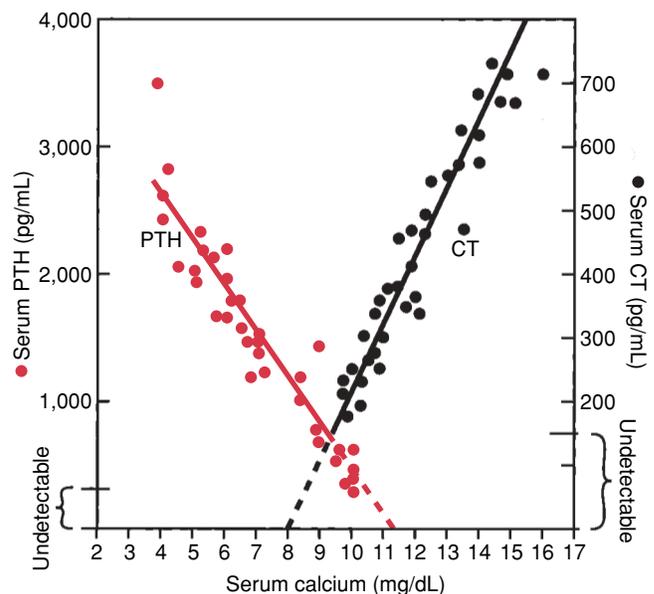
#### Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations

The hormonal mechanisms described here have a large capacity and the ability to make long-term adjustments in calcium and phosphate fluxes, but they do not respond instantaneously. It may take several minutes or hours for the response to occur and adjustments to be made. However, these are the principal mechanisms that regulate plasma calcium and phosphate concentrations.

**The Chemistry of Parathyroid Hormone, Calcitonin, and 1,25-Dihydroxycholecalciferol and the Regulation of Their Production.** One of the primary regulators of plasma calcium concentrations is **parathyroid hormone (PTH)**. PTH is an 84-amino acid polypeptide produced by the parathyroid glands. Synthetic peptides containing the first 34 amino terminal residues appear to be as active as the native hormone.

There are two pairs of parathyroid glands, located on the dorsal surface of the left and right lobes of the thyroid gland. Because of this close proximity, damage to the parathyroid glands or to their blood supply may occur during surgical removal of the thyroid gland.

The primary physiological stimulus for PTH secretion is a decrease in plasma calcium. Figure 36.4 shows the relationship between serum parathyroid hormone concentration and total plasma calcium concentration. It is actually a decrease in the **ionized calcium** concentration that triggers an increase in PTH secretion. The net effect of PTH is to in-



**FIGURE 36.4** Effect of changes in plasma calcium on parathyroid hormone (PTH) and calcitonin (CT) secretion. (Modified from Arnaud, CD, Littlelike T, Tsao HS. Simultaneous measurements of calcitonin and parathyroid hormone in the pig. In: Taylor S, Foster GV, eds. Proceedings of the Symposium on Calcitonin and C Cells. London: Heinemann, 1969, p. 99).

crease the flow of calcium into plasma, and return the plasma calcium concentration toward normal.

**Calcitonin (CT)** is a 32-amino acid polypeptide. Also known as thyrocalcitonin, CT is produced by **parafollicular cells** of the thyroid gland (see Fig. 33.1). Unlike PTH, for which only the initial amino terminal segment is required, the full polypeptide is required for CT activity. Salmon calcitonin differs from human calcitonin in 9 of 32 amino acid residues and is 10 times more potent than human CT in its hypocalcemic effect. The higher potency may be due to a greater affinity for receptors and slower degradation by peripheral tissues. CT is often used clinically as a synthetic peptide matching the sequence of salmon calcitonin.

In contrast to PTH, CT secretion is stimulated by an increase in plasma calcium (see Fig. 36.4). Hormones of the GI tract, especially gastrin, also promote CT secretion. Because the net effect of CT is to promote calcium deposition in bone, the stimulation of CT secretion by GI hormones provides an additional mechanism for facilitating the uptake of calcium into bone after the ingestion of a meal.

The third key hormone involved in regulating plasma calcium is **vitamin D<sub>3</sub>** (cholecalciferol). More precisely, a metabolite of vitamin D<sub>3</sub> serves as a hormone in calcium homeostasis. The D vitamins, a group of lipid-soluble compounds derived from cholesterol, have long been known to be effective in the prevention of rickets. Research during the past 30 years indicates that vitamin D exerts its effects through a hormonal mechanism.

Figure 36.5 shows the structure of vitamin D<sub>3</sub> and the related compound **vitamin D<sub>2</sub>** (ergocalciferol). Ergocalciferol is the form principally found in plants and yeasts and is commonly used to supplement human foods because of its relative availability and low cost. Although it is less potent on a mole-per-mole basis, vitamin D<sub>2</sub> undergoes the same metabolic conversion steps and, ultimately, produces the same biological effects as vitamin D<sub>3</sub>. The physiological actions of vitamin D<sub>3</sub> also apply to vitamin D<sub>2</sub>.

Vitamin D<sub>3</sub> can be provided by the diet or formed in the skin by the action of ultraviolet light on a precursor, **7-dehydrocholesterol**, derived from cholesterol (Fig. 36.6). In many countries where food is not systematically supplemented with vitamin D, this pathway provides the major source of vitamin D. Because of the number of variables in-

involved, it is difficult to specify a minimum exposure time. However, exposure to moderately bright sunlight for 30 to 120 min/day usually provides enough vitamin D to satisfy the body's needs without any dietary supplementation.

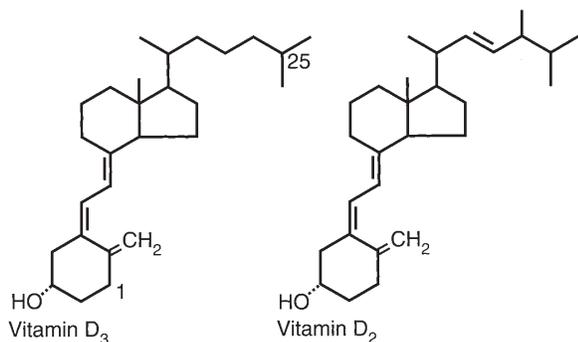
Vitamins D<sub>3</sub> and D<sub>2</sub> are by themselves relatively inactive. However, they undergo a series of transformations in the liver and kidneys that convert them into powerful calcium-regulatory hormones (see Fig. 36.6). The first step occurs in the liver and involves addition of a hydroxyl group to carbon 25, to form 25-hydroxycholecalciferol (25-OH D<sub>3</sub>). This reaction is largely unregulated, although certain drugs and liver diseases may affect this step. Next, 25-hydroxycholecalciferol is released into the blood, and it undergoes a second hydroxylation reaction on carbon 1 in the kidney. The product is **1,25-dihydroxycholecalciferol**, also known as **1,25-dihydroxyvitamin D<sub>3</sub>** or **calcitriol**, the principal hormonally active form of the vitamin. The biological activity of 1,25-dihydroxycholecalciferol is approximately 100 to 500 times greater than that of 25-hydroxycholecalciferol. The reaction in the kidney is catalyzed by the enzyme 1 $\alpha$ -hydroxylase, which is located in tubule cells.

The final step in 1,25-dihydroxycholecalciferol formation is highly regulated. The activity of 1 $\alpha$ -hydroxylase is regulated primarily by PTH, which stimulates its activity. Therefore, if plasma calcium levels fall, PTH secretion increases; in turn, PTH promotes the formation of 1,25-dihydroxycholecalciferol. In addition, enzyme activity increases in response to a decrease in plasma phosphate. This does not appear to involve any intermediate hormonal signals but apparently involves direct activation of either the enzyme or cells in which the enzyme is located. Both a decrease in plasma calcium, which triggers PTH secretion, and a decrease in circulating phosphate result in the activation of 1 $\alpha$ -hydroxylase and an increase in 1,25-dihydroxycholecalciferol synthesis.

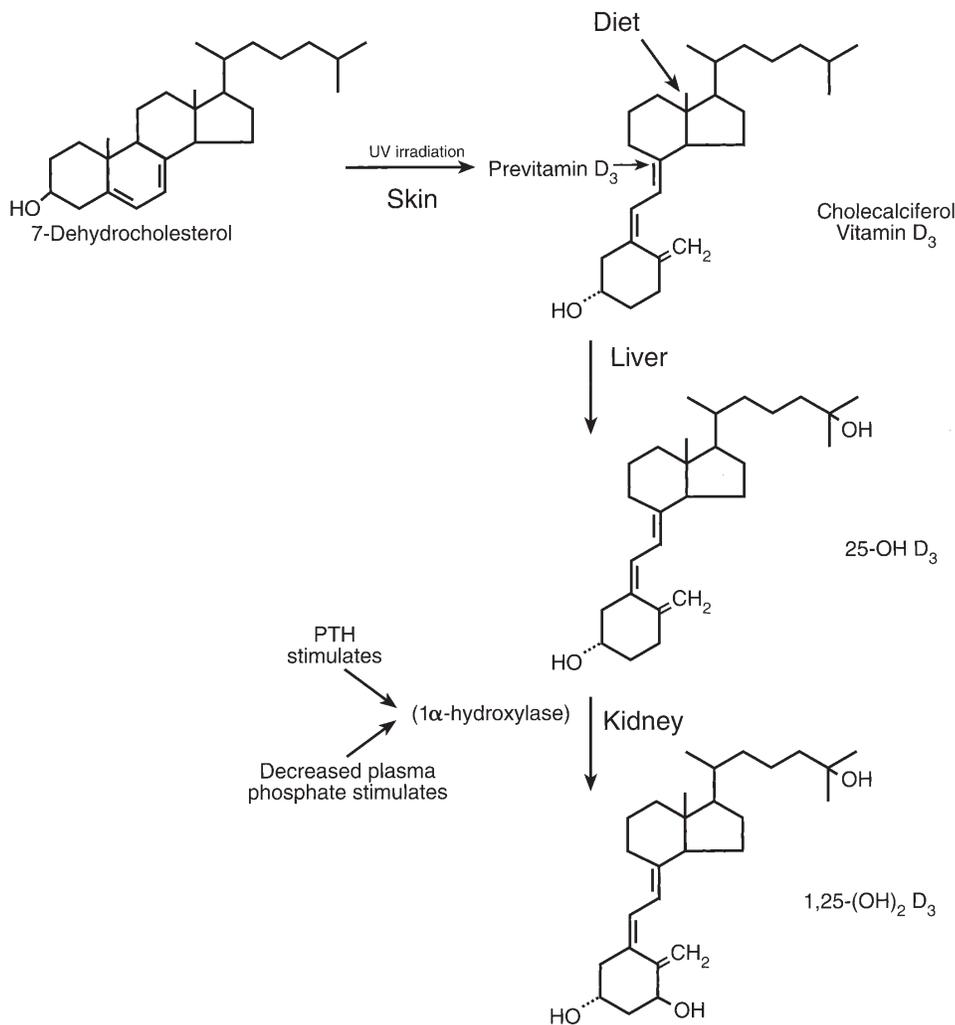
**The Actions of Parathyroid Hormone, Calcitonin, and 1,25-Dihydroxycholecalciferol.** Most hormones generally improve the quality of life and the chance for survival when an animal is placed in a physiologically challenging situation. However, PTH is essential for life. The complete absence of PTH causes death from hypocalcemic tetany within just a few days. The condition can be avoided with hormone replacement therapy.

The net effects of PTH on plasma calcium and phosphate and its sites of action are shown in Figure 36.7. PTH causes an increase in plasma calcium concentration while decreasing plasma phosphate. This decrease in phosphate concentration is important with regard to calcium homeostasis. At normal plasma concentrations, calcium and phosphate are at or near chemical saturation levels. If PTH were to increase *both* calcium and phosphate levels, they would simply crystallize in bone or soft tissues as calcium phosphate, and the necessary increase in plasma calcium concentration would not occur. Thus, the effect of PTH to lower plasma phosphate is an important aspect of its role in regulating plasma calcium.

Parathyroid hormone has several important actions in the kidneys (see Fig. 36.7). It stimulates calcium reabsorption in the thick ascending limb and late distal tubule, decreasing calcium loss in the urine and increasing plasma concentra-



**FIGURE 36.5** The structures of vitamin D<sub>3</sub> and vitamin D<sub>2</sub>. Note that they differ only by a double bond between carbons 22 and 23 and a methyl group at position 24.



**FIGURE 36.6** The conversion pathway of vitamin D<sub>3</sub> into 1,25-dihydroxycholecalciferol [1,25-(OH)<sub>2</sub> D<sub>3</sub>].

tions. It also inhibits phosphate reabsorption in the proximal tubule, leading to increased urinary phosphate excretion and a decrease in plasma phosphate. Another important effect of PTH is to increase the activity of kidney 1 $\alpha$ -hydroxylase, which is involved in forming active vitamin D.

In bone, PTH activates osteoclasts to increase bone resorption and the delivery of calcium from bone into plasma (see Fig. 36.7). In addition to stimulating active osteoclasts, PTH stimulates the maturation of immature osteoclasts into mature, active osteoclasts. PTH also inhibits collagen synthesis by osteoblasts, resulting in decreased bone matrix formation and decreased flow of calcium from plasma into bone mineral. The actions of PTH to promote bone resorption are augmented by 1,25-dihydroxycholecalciferol.

PTH does not appear to have any major direct effects on the GI tract. However, because it increases active vitamin D formation, it ultimately increases the absorption of both calcium and phosphate from the GI tract (see Fig. 36.7).

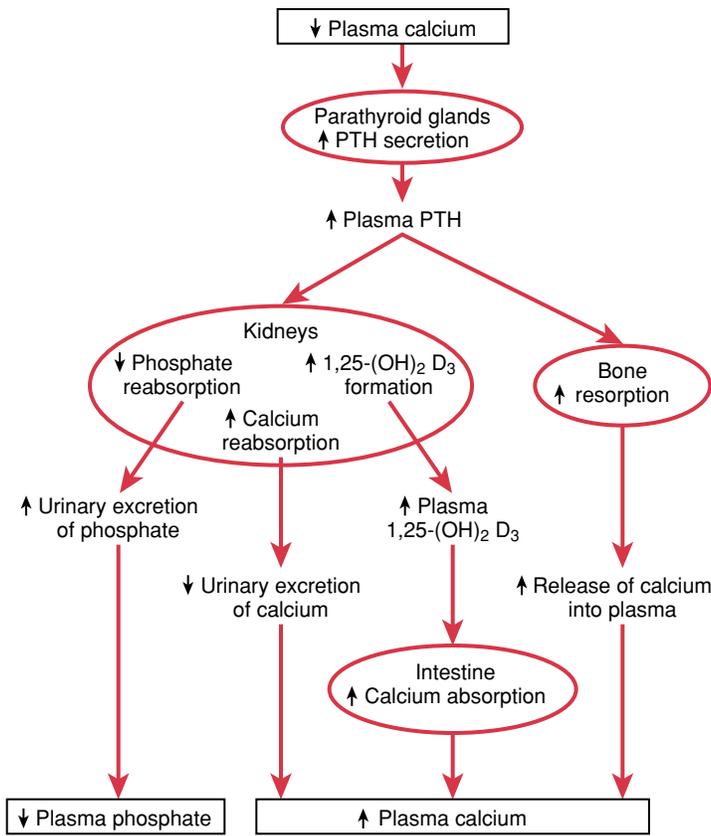
Calcitonin is important in several lower vertebrates, but despite its many demonstrated biological effects in humans, it appears to play only a minor role in calcium homeostasis. This conclusion mostly stems from two lines of evidence. First, CT loss following surgical removal of the thyroid gland (and, therefore, removal of CT-secreting parafollicu-

lar cells) does not lead to overt clinical abnormalities of calcium homeostasis. Second, CT hypersecretion, such as from thyroid tumors involving parafollicular cells, does not cause any overt problems. On a daily basis, calcitonin probably only fine-tunes the calcium regulatory system.

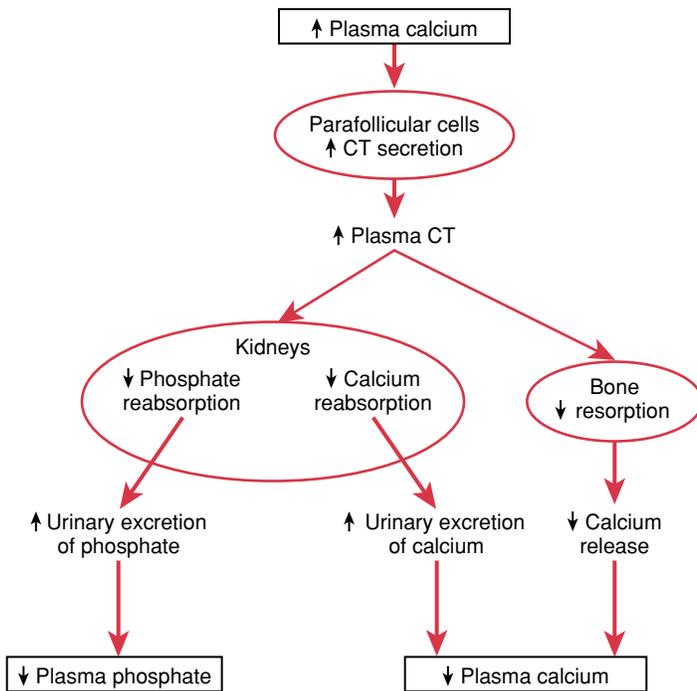
The overall action of calcitonin is to decrease *both* calcium and phosphate concentrations in plasma (Fig. 36.8). The primary target of CT is bone, although some lesser effects also occur in the kidneys. In the kidneys, CT decreases the tubular reabsorption of calcium and phosphate. This leads to an increase in urinary excretion of both calcium and phosphate and, ultimately, to decreased levels of both ions in the plasma. In bones, CT opposes the action of PTH on osteoclasts by inhibiting their activity. This leads to decreased bone resorption and an overall net transfer of calcium from plasma into bone. Calcitonin has little or no direct effect on the GI tract.

The net effect of 1,25-dihydroxycholecalciferol is to increase both calcium and phosphate concentrations in plasma (Fig. 36.9). The activated form of vitamin D primarily influences the GI tract, although it has actions in the kidneys and bones as well.

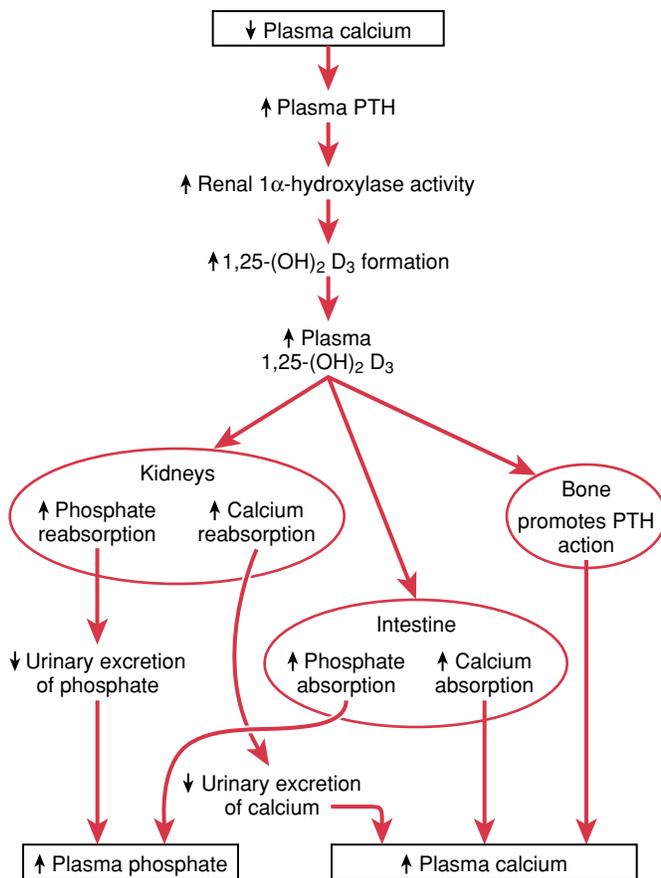
In the kidneys, 1,25-dihydroxycholecalciferol increases the tubular reabsorption of calcium and phosphate, pro-



**FIGURE 36.7** Effects of parathyroid hormone (PTH) on calcium and phosphate metabolism.



**FIGURE 36.8** Effects of calcitonin (CT) on calcium and phosphate metabolism.



**FIGURE 36.9** Effects of 1,25-dihydroxycholecalciferol [1,25-(OH)<sub>2</sub> D<sub>3</sub>] on calcium and phosphate metabolism.

moting the retention of both ions in the body. However, this is a weak and probably only minor effect of the hormone. In bones, the hormone promotes actions of PTH on osteoclasts, increasing bone resorption (see Fig. 36.9).

In the gastrointestinal tract, 1,25-dihydroxycholecalciferol stimulates calcium and phosphate absorption by the small intestine, increasing plasma concentrations of both ions. This effect is mediated by increased production of calcium transport proteins resulting from gene transcription events and usually requires several hours to appear.

### ABNORMALITIES OF BONE MINERAL METABOLISM

There are several metabolic bone diseases, all typified by ongoing disruption of the normal processes of either bone formation or bone resorption. The conditions most frequently encountered clinically are osteoporosis, osteomalacia, and Paget's disease.

#### Osteoporosis Is a Reduction in Bone Mass

Osteoporosis is a major health problem, particularly because older adults are more prone to this disorder and the average age of the population is increasing (see Clinical Fo-

cus Box 36.1). Osteoporosis involves a reduction in total bone mass with an equal loss of both bone mineral and organic matrix. Several factors are known to contribute directly to osteoporosis. Long-term dietary calcium deficiency can lead to osteoporosis because bone mineral is mobilized to maintain plasma calcium levels. Vitamin C deficiency also can result in a net loss of bone because vitamin C is required for normal collagen synthesis to occur. A defect in matrix production and the inability to produce new bone eventually result in a net loss of bones. For reasons that are not entirely understood, a reduction in the mechanical stress placed on bone can lead to bone loss. Immobilization or disuse of a limb, such as with a cast or paralysis, can result in localized osteoporosis of the affected limb. Space flight can produce a type of disuse osteoporosis resulting from the condition of weightlessness.

Most commonly, osteoporosis is associated with advancing age in both men and women, and it cannot be assigned to any specific definable cause. For several reasons, women are more prone to develop the disease than men. Figure 36.10 shows the average bone mineral content (as grams of calcium) for men and women versus age. Until about the time of puberty, males and females have similar bone mineral content. However, at puberty, males begin to acquire bone mineral at a greater rate; peak bone mass may be approximately 20% greater than that of

## CLINICAL FOCUS BOX 36.1

## The Toll of Osteoporosis

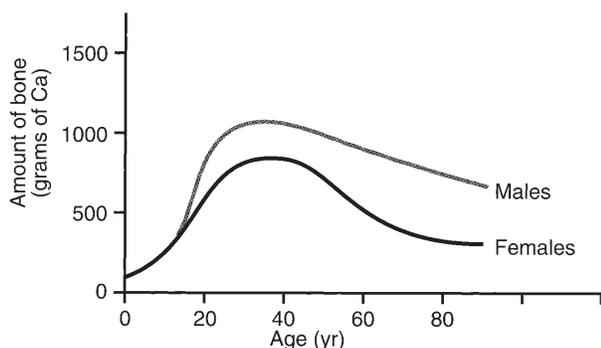
Osteoporosis is often called the “silent disease” because bone loss initially occurs without symptoms. People may not know that they have significant bone loss until their bones become so weak that a sudden strain, bump, or fall causes a fracture. Osteoporosis is a major public health threat in the United States because it affects some 28 million Americans. Some 10 million individuals have been diagnosed with the disease and another 18 million have low bone mass, placing them at increased risk for osteoporosis. Approximately 80% of those affected by osteoporosis are women. While osteoporosis is often thought of as an older person’s disease, it can strike at any age. The seeds of osteoporosis are sown in childhood, and it takes a lifetime of effort to prevent the disease. A frightening number of children do not get sufficient exercise, vitamin D, and calcium to ensure protection from developing the disease later in life.

Osteoporosis is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, 700,000 vertebral fractures, 250,000 wrist fractures, and 300,000 fractures at other sites. It is estimated that osteoporosis costs some 10 to 15 billion dollars a year for hospitalization and nursing home care. Additional losses in wages and productivity send these numbers far higher. Nearly one third of people who have hip fractures end up in nursing homes within a year; nearly 20% die within a year.

What causes osteoporosis, and what can be done to prevent or treat the disease? While it is known that a diet low in calcium or vitamin D, certain medications such as glucocorticoids and anticonvulsants, and excessive ingestion of aluminum-containing antacids can cause osteoporosis, in most cases, the exact cause is unknown. However, several identified risk factors associated with the disease are being a woman (especially a postmenopausal woman); being Caucasian or Asian; being of advanced age; having a family history of the disease; having low testosterone levels (in men); having an inactive lifestyle; cigarette smoking; and an excessive use of alcohol.

A comprehensive program to help prevent osteoporosis includes a balanced diet rich in calcium and vitamin D, regular weight-bearing exercise, a healthy lifestyle with no smoking or excessive alcohol use, and bone density testing and medication when appropriate. Although at present there is no cure for osteoporosis, there are five FDA-approved medications to either prevent or treat the disease in women: estrogens; alendronate and risedronate (both bisphosphonates); calcitonin; and raloxifene, a selective estrogen receptor modulator. Although 20% of all osteoporosis cases occur in men, only alendronate and risedronate are currently FDA approved for use in men and only for cases of corticosteroid-induced osteoporosis. Testosterone replacement therapy is often helpful in a man with a low testosterone level.

women. Maximum bone mass is attained between 30 and 40 years of age and then tends to decrease in both sexes. Initially this occurs at an approximately equivalent rate, but women begin to experience a more rapid bone mineral loss at the time of menopause (about age 45 to 50). This loss appears to result from the decline in estrogen secretion that occurs at menopause. Low-dose estrogen supplementation of postmenopausal women is usually effective in retarding bone loss without causing adverse effects. This condition of increased bone loss in women after menopause is called **postmenopausal osteoporosis** (see Clinical Focus Box 36.2).



**FIGURE 36.10** Changes in bone calcium content as a function of age in males and females. These changes can be roughly extrapolated into changes in bone mass and bone strength

## Osteomalacia and Rickets Result From Inadequate Bone Mineralization

Osteomalacia and rickets are characterized by the inadequate mineralization of new bone matrix, such that the ratio of bone mineral to matrix is reduced. As a result, bones may have reduced strength and are subject to distortion in response to mechanical loads. When the disease occurs in adults, it is called osteomalacia; when it occurs in children, it is called rickets. In children, the condition often produces a bowing of the long bones in the legs. In adults, it is often associated with severe bone pain.

**TABLE 36.3** Causes of Osteomalacia and Rickets

Inadequate availability of vitamin D	Dietary deficiency or lack of exposure to sunlight
Defects in metabolic activation of vitamin D	Fat-soluble vitamin malabsorption
	25-Hydroxylation (liver)
	Liver disease
	Certain anticonvulsants, such as phenobarbital
	1-Hydroxylation (kidney)
	Renal failure
	Hypoparathyroidism
Impaired action of 1,25-dihydroxycholecalciferol on target tissues	Certain anticonvulsants
	1,25-Dihydroxycholecalciferol receptor defects
	Uremia

## CLINICAL FOCUS BOX 36.2

**Cytokines, Estrogens, and Osteoporosis**

It is well established that a decline in circulating levels of  $17\beta$ -estradiol is a major contributing factor in the development of osteoporosis in postmenopausal women. Until recently, specific mechanisms by which estradiol might influence bone metabolism were largely unknown. Recent studies suggest that estradiol influences the production and/or modulates the activity of several cytokines involved in regulating bone remodeling.

Normal bone remodeling involves a regulated balance between the processes of bone formation and bone resorption. Osteoclast-mediated bone resorption involves two processes: the activation of mature, functional osteoclasts and the recruitment and differentiation of osteoclast precursors. In addition to PTH, the cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF) are involved in the activation of mature osteoclasts to cause bone resorption. For maturation of osteoclast precursors, the cytokines macrophage-colony stimulating factor (M-CSF) and interleukin-6 (IL-6) appear to be involved. Estradiol plays a role

in bone remodeling by suppressing the formation of these cytokines. As a result of its ability to interact with bone cells and their precursors to regulate local paracrine signaling mechanisms, estradiol produces anti-osteoporotic effects in bone.

When estradiol is present, as in a premenopausal state, it acts as a governor to reduce cytokine production and limit osteoclast activity. When estradiol levels are reduced, the governor is lost, secretion of these cytokines increases, and osteoclast formation and activity increase, resulting in increased bone resorption.

Current research efforts attempt to define more clearly the specific source(s) and roles of the cytokines involved. The elucidation of these factors might allow the development of diagnostic tools, such as the assessment of cytokine levels, to monitor osteoporosis. In addition, such knowledge should facilitate the development of drugs that might interfere with cytokine action and potentially be of value in the treatment of osteoporosis.

The primary cause of osteomalacia and rickets is a deficiency in vitamin D *activity*. Vitamin D may be deficient in the diet; it may not be adequately absorbed by the small intestine; it may not be converted into its hormonally active form; or target tissues may not adequately respond to the active hormone (Table 36.3). Dietary deficiency is generally not a problem in the United States, where vitamin D is added to many foods; however it is a major health problem in other parts of the world. Because the liver and kidneys are involved in converting vitamin D<sub>3</sub> into its hormonally active form, primary disease of either of these organs may result in vitamin D deficiency. Impaired vitamin D actions are somewhat rare but can be produced by certain drugs. In particular, some anticonvulsants used in the treatment of epilepsy may produce osteomalacia or rickets with prolonged treatment.

**Paget's Disease Leads to Disordered Bone Formation**

Paget's disease affects about 3% of people older than 40. It is typified by disordered bone formation and resorption (remodeling) and may occur at a single local site or at multiple sites in the body. Radiographs of affected bone often exhibit increased density, but the abnormal structure makes the bone weaker than normal. Often those with Paget's disease experience considerable pain, and in severe cases, crippling deformities may lead to serious neurological complications.

The cause of the disease is not well understood. Both genetic and environmental factors (probably viral) appear to be important. Several therapies are available for treating the disease, including treatment with CT, but these typically offer only temporary relief from pain and complications.

## REVIEW QUESTIONS

**DIRECTIONS:** Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

- As part of a routine physical exam, a patient's serum electrolyte levels were measured. Among the measurements, it was determined that total plasma calcium concentration was 10.2 mg/dL. What percentage of total plasma calcium is normally present as the free  $\text{Ca}^{2+}$  ion?
  - 1%
  - 50%
  - 60%
  - 100%
- A healthy individual consumed 1,000 g of calcium during a 24-hour period. What is the major route of calcium excretion from the body?
  - Urine
  - Sweat
  - Feces
  - Bile
- The major route by which ingested phosphate leaves the body is via the
  - Urine
  - Sweat
  - Feces
  - Bile
- 1,25-Dihydroxycholecalciferol can be formed in the body by metabolism of cholesterol. Which of the following is *not* either directly or indirectly involved in formation of 1,25-dihydroxycholecalciferol?
  - Bone
  - Skin
  - Kidney
  - Liver
- A 42-year-old woman develops an autoimmune disease that damages her kidneys. Of the following conversions, which is most likely to be impaired in this person?

(continued)

- (A) Cholecalciferol to 7-dehydrocholesterol  
 (B) Vitamin D<sub>3</sub> to vitamin D<sub>2</sub>  
 (C) 25-Hydroxycholecalciferol to 1,25-dihydroxycholecalciferol  
 (D) Calcium to hydroxyapatite
6. A 62-year-old woman stumbles on a crack in the sidewalk, falls, and breaks her right hip. She suffers from a form of metabolic bone disease in which there is an equivalent loss of bone mineral and organic matrix. What is this disease?  
 (A) Paget's disease  
 (B) Rickets  
 (C) Osteoporosis  
 (D) Osteomalacia
7. Parathyroid hormone has effects on

bone, kidney, and indirectly the GI tract. The net result of PTH actions is that it tends to  
 Raise plasma calcium and phosphate  
 (A) Lower plasma calcium and phosphate  
 (B) Lower plasma calcium and raise plasma phosphate  
 (C) Raise plasma calcium and lower plasma phosphate

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## CASE STUDIES FOR PART IX

### CASE STUDY FOR CHAPTER 31

#### Diabetes Mellitus

Charlie was diagnosed with type 1 diabetes mellitus during the summer of his eighth year. Charlie's mother suspected he was drinking excessive amounts of fluids that summer; however, he was in and out of the house and visiting friends, and she couldn't be certain. During an afternoon at a friend's birthday party, Charlie drank nearly 3 quarts of fruit juice; his mother became alerted to a possible problem and took him to their family doctor.

Charlie's tests are normal, except that he tests positive for glucose in the urine (dipstick test) and his fasting blood sugar is elevated (620 mg/dL). Plasma insulin (5  $\mu$ U/mL) and C-peptide (0.6 ng/mL) are reduced. Charlie is placed on a regimen of daily insulin injections, along with monitoring of blood and urine glucose concentrations. His mother is instructed about changes in Charlie's diet. During the next year, Charlie returns to the doctor for several follow-up visits and to adjust his insulin dosage. Data from his 1-year visit are as follows: fasting blood glucose, 120 mg/dL; C-peptide, 0.1 ng/mL.

#### Questions

1. What might be the reason for the decrease in Charlie's C-peptide after one year?
2. Why weren't plasma insulin values measured after one year?

#### Answers to Case Study Questions for Chapter 31

1. The decrease in C-peptide reflects further destruction of Charlie's insulin-producing pancreatic beta cells and indicates a further impairment in his own insulin production capacity.
2. Because Charlie is taking insulin injections, measurement of circulating insulin levels would not have provided any information about insulin secretion. This information is inferred from the C-peptide data.

### CASE STUDY FOR CHAPTER 32

#### Growth Hormone

A 6-year-old boy was brought to the clinic to be evaluated for GH deficiency. The boy's height is between 2 and 3 standard deviations below the average height for his age. Initial physical examination rules out head trauma, chronic illness, and malnutrition. The patient's family history does not suggest similar short stature in immediate relatives. Thyroid hormones are normal.

#### Questions

1. Why would the doctor order a blood test for levels of IGFBP3 and IGF-I?
2. The levels of IGFBP3 and IGF-I are below the normal range in this patient. What does this finding suggest?
3. What is GH resistance, and what measurements would support the presence of this problem?
4. Why is it important to treat GH deficiency and short stature prior to the onset of puberty?
5. Why is resistance to insulin action a potential adverse effect of giving extremely high pharmacological doses of GH for a long time?

#### Answers to Case Study Questions for Chapter 32

1. GH is released in a pulsatile manner; between pulses of GH secretion the blood concentration may be undetectable in normal individuals. GH induces the synthesis and secretion of IGF-I and IGFBP3, both of which are easily detectable in the serum. Low IGF-I and IGFBP3 levels would indicate insufficient GH secretion.
2. In most cases, low levels of IGF-I and IGFBP3 in the blood would indicate insufficient GH release. However, low levels of IGF-I and IGFBP3 could also be due to a defect in the GH receptor, resulting in GH resistance.
3. GH resistance is characterized by impaired growth as a result of low levels of IGF-I and IGFBP3 in the blood. However, the blood concentration of GH is high. Defects in the GH receptor, which prevent GH from stimulating the production of IGF-I and IGFBP3, are a common cause of GH resistance.

Measurement of a GH in the blood should detect the extremely high levels of the hormone to confirm diagnosis.

4. GH and IGF-I stimulate the epiphyseal growth plate of the long bones to grow. The epiphyseal plate fuses several years after puberty, at which time GH and IGF-I can no longer stimulate the growth of the bone. Therefore, the earlier GH therapy is initiated, the greater will be the chance of achieving normal adult height before long bone growth stops.
5. GH has diabetogenic actions, which oppose the actions of insulin. Thus, chronic, high doses of GH can impair the actions of insulin. Insulin resistance is a condition in which tissues in the body do not respond very well to insulin (see Chapter 35).

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## CASE STUDY FOR CHAPTER 33

### Thyroiditis

A 35-year-old woman is seen in the Endocrine Clinic for evaluation of thyroid disease. The patient complains of weight loss, irritability, and restlessness. Physical examination reveals enlargement of the thyroid gland, weakness in maintaining the leg in an extended position, warm moist skin, and tachycardia. Family history indicates that the patient's mother had hypothyroidism after the birth of the patient's brother and an aunt had Hashimoto's disease.

#### Questions

1. Based on the history and physical examination, what would be a reasonable initial diagnosis?
2. From a blood sample, what hormone concentrations should the laboratory measure, and what would be the likely results?
3. What antibody titers should the laboratory determine? Which antibody titer is the most useful in the diagnosis of Hashimoto's disease?
4. Which antibody titer would be most useful in the diagnosis of Graves' disease?
5. The antibody titers indicate that the patient has Graves' disease. What treatment would be appropriate for this patient?

#### Answers to Case Study Questions for Chapter 33

1. The physical findings, including the presence of goiter, suggest that the patient may be hyperthyroid. However, goiter can also occur in hypothyroidism. Since autoimmune thyroid disease runs in families, the family history suggests that the thyroiditis might be due to an autoimmune response.
2. The laboratory should determine the blood levels of thyroid hormones ( $T_4$  and  $T_3$ ) and TSH. Thyroid hormones should be increased. TSH may be increased if it is early in the progression of Hashimoto's disease or decreased if the patient has Graves' disease.
3. The laboratory should measure antibodies to TSH receptor, thyroid peroxidase, and thyroglobulin. Antibodies to thyroid peroxidase are elevated to the greatest extent in Hashimoto's disease.
4. Antibodies to TSH receptor, thyroid peroxidase, and thyroglobulin can all be elevated in Graves' disease. However, the presence of TSH receptor antibodies is diagnostic.

5. A thionamide compound should first be used to inhibit thyroid hormone synthesis. This treatment will relieve the symptoms of hyperthyroidism and may result in a reduction in immune response. The drug may be withdrawn after several months of treatment to determine whether the disease is in remission. If thyroid hormone levels increase with cessation of the drug, ablation of the thyroid gland with  $^{131}\text{I}$  (or less commonly with surgery) would be indicated.

## CASE STUDY FOR CHAPTER 34

### Congenital Adrenal Hyperplasia

The pediatric endocrinologist is called in to consult on the case of a 1-week-old girl. The baby was born at home and is now in the emergency department because she appeared listless and has not nursed during the past 24 hours. On physical examination, the baby exhibits signs of virilization (growth of pubic hair) and volume depletion, and laboratory results indicate hyponatremia and hyperkalemia.

1. Based on the history, physical examination, and laboratory findings, what would be a reasonable initial hypothesis?
2. What are the two most likely congenital defects in adrenal steroidogenic enzymes that could explain the findings in this child?
3. From a blood sample, what hormones/metabolites should the laboratory measure, and what would be the likely results?
4. From the hormone/metabolite analysis, how would the two most likely causes for this case of congenital adrenal hyperplasia be distinguished?
5. A genetic screen utilizing DNA from the baby's white cells identifies an inactivating mutation in the gene (*CYP21A2*) for 21-hydroxylase. What would be appropriate hormone replacement for this patient?

#### Answers to Case Study Questions for Chapter 34

1. A reasonable initial hypothesis is that the baby has a form of congenital adrenal hyperplasia. The virilization (appearance of pubic hair) suggests the presence of excess androgen production by the adrenal gland. The hyponatremia, hyperkalemia, and volume depletion suggest a "salt wasting" syndrome.
2. Mutations in *CYP21A2*, which encodes 21-hydroxylase, account for more than 90% of all cases of adrenal hyperplasia associated with excess androgen production. Mutations in *CYP11B1*, which encodes 11 $\beta$ -hydroxylase, would also result in excess adrenal androgen production.
3. Adrenal androgens would be significantly elevated in patients with virilizing forms of congenital adrenal hyperplasia. Adrenal hyperplasia is usually due to defects in cortisol production. Therefore, the serum concentrations of precursors of cortisol biosynthesis such as progesterone, 17 $\alpha$ -hydroxyprogesterone, and 11-deoxycortisol could be elevated. In addition, serum ACTH would be elevated as a result of the lack of negative feedback from the absent cortisol.
4. Genetic defects in the gene for 11 $\beta$ -hydroxylase, resulting in a reduction in the activity of this enzyme, would result in increased 11-deoxycortisol. Defects in the gene for 21-hydroxylase, which impair the activity of the enzyme, would not lead to the production of 11-deoxycortisol. Since 11-deoxycortisol has significant mineralocorticoid activity, excess production of this steroid is usually associated with hypertension, rather than the volume depletion and hypotension observed in this patient.
5. Treatment would be directed toward replacement of gluco-

corticoids and mineralocorticoids. Glucocorticoids would replace the missing cortisol and also suppress ACTH secretion. With less ACTH stimulation of steroid production from the adrenal gland, the hyperandrogenemia should subside. Mineralocorticoids are given to treat the “salt wasting” that occurs in the absence of aldosterone.

## CASE STUDY FOR CHAPTER 35

### Type 2 Diabetes

A 65-year-old semi-retired college professor was diagnosed with type 2 diabetes about 4 years ago during a routine physical examination at his family doctor’s office. Treatment for the diabetes initially consisted of one tablet daily of an oral antidiabetic drug of the sulfonylurea class and two daily injections of insulin. The patient’s doctor also recommended modest weight loss and a regular exercise program. With diligence to the treatment program, the patient was able to control his blood sugar levels adequately.

About 2 years ago, the patient developed gallstones, which required surgery to remove the gallbladder. For about one week after the surgery, the patient had to increase his insulin dosage to maintain normal blood glucose levels. He gradually returned to his presurgery insulin dose.

Because of the surgery, the patient vows to take better care of himself. He increases his physical activity and begins a diet that results in loss of 7 kg in 3 months. The weight loss and exercise result in the cessation of the patient’s need for insulin injections, although he still takes his daily oral medication.

### Questions

1. Why might the gallbladder disease and resulting surgery have increased the patient’s need for insulin?
2. What might be the consequences if the patient were to regain the weight he lost after surgery?
3. Why is exercise an important part of the treatment regimen for type 2 diabetes?

### Answers to Case Study Questions for Chapter 35

1. Stress, such as surgery, results in increased production of epinephrine and norepinephrine, both of which inhibit insulin secretion. The patient’s pancreas will produce less insulin, and thus, more exogenous insulin will need to be provided.
2. If the patient were to regain weight, he would most likely have to go back to taking insulin injections.

3. Exercise not only helps to control weight, it stimulates glucose uptake in skeletal muscle, lessening the requirements for injected insulin.

## CASE STUDY FOR CHAPTER 36

### Bone Fractures

A 38-year-old Caucasian man recently came to the attention of his physician when he suffered the second of two bone fractures in the past year and a half. He previously was in relatively good health, was not a smoker, and used alcohol only moderately. However, his only form of exercise was cutting the lawn on weekends during the summer months. He has not required any major surgeries during his lifetime, and had only minor bouts of the typical childhood illnesses. However, at age eight he was diagnosed with asthma after he suffered severe respiratory problems during a baseball game on a hot summer day. He has been treated ever since with a daily tablet of a synthetic glucocorticoid and the occasional use of an inhaler when needed to relieve acute symptoms of the disease.

The fractures that the patient experienced were to the left wrist and the right forearm. In both cases, the trauma that caused the fracture was relatively minor. Suspecting that there may be an underlying problem, his physician orders a series of bone density scans. Results of these studies show that the patient has a considerable reduction in bone mass compared with other men of the same age.

### Questions

1. What is the most probable diagnosis?
2. What is the most probable underlying cause for the patient’s problem?
3. What risk factors are present (or absent) in this case?

### Answers to Case Study Questions for Chapter 36

1. Osteoporosis and, perhaps, glucocorticoid-induced osteoporosis.
2. Because the patient is young and has a relatively healthy lifestyle, the most probable cause of his osteoporosis is his 30-year history of treatment with glucocorticoids for asthma. Glucocorticoids increase bone loss by inhibiting osteoblasts, stimulating bone resorption, impairing intestinal calcium absorption, increasing urinary calcium loss, inhibiting secretion of sex hormones, and other effects.
3. The patient lacks the risk factors of smoking, excessive alcohol intake, and being female. He does appear, however, to have the risk factor of a somewhat sedentary lifestyle.