depress Ca^{2+} absorption by promoting the formation of nonabsorbable complexes. Disease states associated with steatorrhea, diarrhea, or chronic intestinal malabsorption also promote fecal loss of calcium.

Urinary excretion of Ca^{2+} is the net result of the quantity filtered at the glomerulus and the amount reabsorbed. About 9 g of Ca^{2+} is filtered each day. Tubular reabsorption is very efficient, more than 98% of filtered Ca^{2+} returning to the circulation. Reabsorption efficiency is highly regulated by parathyroid hormone (PTH) but also is influenced by filtered Na^+, the presence of non-reabsorbed anions, and diuretic agents. Diuretics acting on the ascending limb of the loop of Henle increase calciuresis. By contrast, thiazide diuretics uniquely uncouple the relationship between Na^+ and Ca^{2+} excretion, leading to reduced calciuria (Lemann *et al.*, 1985). It appears that minute-to-minute regulation of plasma Ca^{2+} is due to the effect of PTH on the renal tubule (Nordin and Peacock, 1969). Urinary Ca^{2+} is only slightly influenced by dietary calcium in normal people. Significant amounts of calcium are secreted in milk during lactation; sweat also makes a small contribution to daily losses.

Bone Remodeling. Growth and development of endochondral bone are driven by a process called *modeling*. Once new bone is laid down, it is subject to a continuous process of breakdown and renewal called *remodeling* that continues throughout life. After linear growth has ceased and peak bone mass has been approached, remodeling becomes the final common pathway by which bone mass is adjusted throughout adult life. Remodeling is carried out by myriad individual and independent "bone remodeling units" throughout the skeleton (Figure 61–2). It takes place on bone surfaces, about 90% of which are normally inactive, covered by a thin layer of lining cells. In response to physical or biochemical signals, recruitment of marrow precursor cells to a site at the bone surface results in their fusion into the characteristic multinucleated osteoclasts that resorb, or dig a cavity into the bone. Recent evidence identifies at least some of these signals as cytokines, particularly interleukins 1 and 6, that are released by osteoblasts (Boyce *et al.*, 1989; Lowik *et al.*, 1989; Feyen *et al.*, 1989; Ishimi *et al.*, 1990). In cortical bone, resorption creates tunnels within Haversian canals, whereas trabecular resorption creates scalloped areas of the bone surface called Howship's lacunae. On termination of the resorption phase, a cavity remains that is about 60 μm deep and which is bordered at its deepest extent by a cement line, a region of loosely organized collagen fibrils,

Completion of the resorption phase is followed by ingress of preosteoblasts derived from marrow stroma into the base of the resorption cavity. These cells develop the characteristic osteoblastic phenotype and begin to replace the resorbed bone by elaborating new bone matrix constituents, such as collagen, osteocalcin, and other proteins. Once the newly formed osteoid reaches a thickness of about 20 μm, mineralization begins. Completion of a remodeling cycle normally requires about 6 months.

If the replacement of resorbed bone matched the amount that was removed, remodeling would lead to no net change in bone mass. However, small bone deficits persist on completion of each cycle, reflecting an inefficiency in remodeling dynamics. Consequently, lifelong accumulation of remodeling deficits underlies the well-documented phenomenon of age-related bone loss, a process that begins shortly after growth stops. *Alterations in remodeling activity represent the final pathway through which diverse stimuli, such as dietary insufficiency, hormones, and drugs, affect bone balance.* A change in whole body remodeling rate can be brought about through distinct perturbations in remodeling dynamics. Changes in hormonal milieu often lead to an increase in the activation, or birthrate, of remodeling units. Examples include hyperthyroidism, hyperparathyroidism, and hypervitaminosis D. Other factors may impair osteoblastic functional adequacy, such as high doses of corticosteroids or ethanol. Finally, it appears that estrogen deficiency may augment osteoclastic resorptive capacity (*see* Marcus, 1987; Dempster, 1992).

At any given time, a transient deficit in bone exists called the remodeling space, representing sites of bone resorption that have not yet filled in. In response to any stimulus that alters the birthrate of new remodeling units, the remodeling space will either increase or

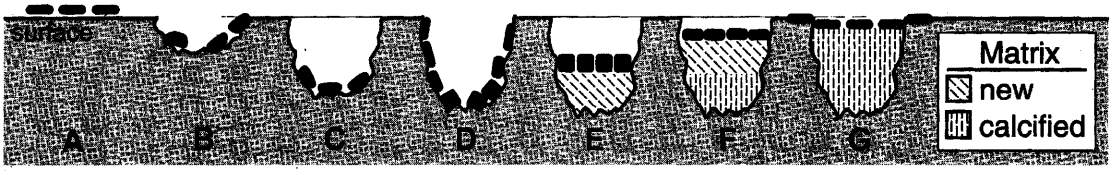

Figure 61–2. The bone remodeling cycle.

A, resting trabecular surface; B, *multinucleated osteoclasts* dig a cavity of approximately 20 μm; C, resorption to 60 μm is completed by *mononuclear phagocytes;* D, *osteoblast precursors* are recruited to the base of the resorption cavity; E, new matrix is secreted by *osteoblasts*; F, matrix continues to be secreted, with the initiation of calcification; and G, mineralization of the new matrix is completed. Bone has returned to a quiescent state, but a small deficit in bone mass persists. (*Adapted from Marcus, 1987, with permission.*)

CALCIUM

Ca^{2+} is the major extracellular divalent cation. The normal adult man and woman possess about 1300 and 1000 g of Ca^{2+}, respectively, of which more than 99% is in bone. Ca^{2+} is present in small amounts in extracellular fluids and to a minor extent within cells, where its ionized concentration under basal conditions is about 0.1 μM. In response to hormonal, electrical, or mechanical stimuli, a temporary increase in Ca^{2+} flux raises this concentration toward 1 μM, permitting interactions with specific Ca^{2+}-binding proteins that activate numerous processes. The major Ca^{2+}-binding protein in all organisms is calmodulin, a highly conserved protein that binds four moles of Ca^{2+} per mole of protein. Ca^{2+} is essential for many important processes, including neuronal excitability, neurotransmitter release, muscle contraction, membrane integrity, and blood coagulation. In addition, Ca^{2+} serves a second messenger function for the actions of many hormones.

To carry out these various roles, Ca^{2+} must be available in the proper concentration. In human plasma, calcium circulates at a concentration of about 8.5 to 10.4 mg/dl (2.1 to 2.6 mM). Of this, about 45% is bound to plasma proteins, primarily albumin, and about 10% is complexed with anionic buffers, such as citrate and phosphate. The remaining fraction, ionized Ca^{2+}, is the component that exerts physiological effects and, when reduced, produces hypocalcemic symptoms. Hence, interpretation of any given value for total plasma calcium is impossible without correction for the concentration of plasma proteins. As an approximation, a change in plasma albumin concentration of 1.0 mg/dl from a nominal value of 4.0 g/dl can be expected to change total calcium by 0.8 mg/dl.

Regulation of the extracellular Ca^{2+} concentration is under tight endocrine control that affects its entry at the intestine and its exit at the kidney, and which regulates a large skeletal reservoir for withdrawals at times of need.

Calcium Stores. The skeleton contains 99% of total body calcium in a crystalline form resembling the mineral hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], but other ions, including Na^+, K^+, Mg^{2+}, and F^- also are present in the crystal lattice. The steady-state content of calcium in bone reflects the net effect of bone resorption and bone formation, two coupled aspects of bone remodeling (*see* below). In addition, a labile pool of bone Ca^{2+} is readily exchangeable with interstitial fluid. The rates of exchange are modulated by drugs, hormones, vitamins, and other factors that directly alter bone turnover or that influence the level of Ca^{2+} in interstitial fluid.

Calcium Absorption and Excretion. In the United States, about 75% of dietary calcium is obtained from milk and dairy products. The recommended dietary allowance for adolescents and adults to age 24 years is 1200 mg/day and that for older adults is 800 mg/day. Although calcium intake by American men approximates the recommended dietary allowance at all ages, median intakes by girls and women fail to meet recommended levels by age 11 and never recover (Carroll *et al.*, 1983).

Figure 61–1 demonstrates the elements of whole body daily calcium turnover. Ca^{2+} enters the body only through the intestine. Two different mechanisms contribute to this relatively inefficient process. *Active* vitamin D–dependent transport occurs in the proximal duodenum. In addition, accounting for a large fraction of total Ca^{2+} uptake, *facilitated diffusion* takes place throughout the small intestine. There is also an obligatory daily intestinal calcium loss of about 150 mg/day, reflecting the mineral contained in mucosal and biliary secretions and in sloughed intestinal cells.

Intestinal Ca^{2+} absorption efficiency is inversely related to calcium intake, so that a diet low in calcium leads to a compensatory increase in fractional absorption, due in part to activation of vitamin D. The strength of this response decreases substantially with age. Drugs such as glucocorticoids and phenytoin depress intestinal Ca^{2+} transport. Some dietary constituents, *e.g.*, phytate and oxalate,

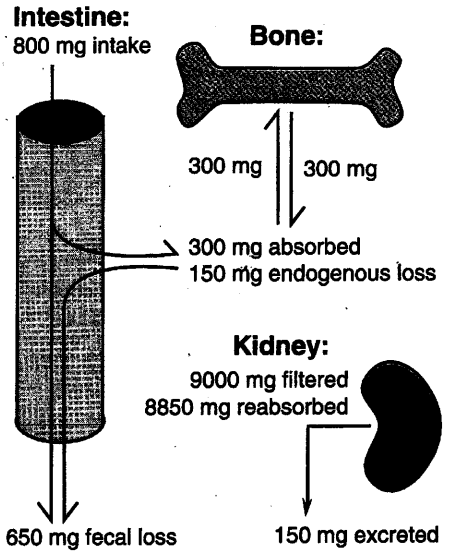

Figure 61–1. Schematic representation of the whole body daily turnover of calcium. *(Adapted from Yanagawa and Lee, 1992, with permission.)*