adult obesity, but most overweight children will not become obese. Because no method now exists to predict which children will develop obesity as adults, because research has not yet identified effective methods to prevent adult obesity, and because children require adequate energy and nutrients to develop and grow normally, low-calorie diets should not be generally recommended for this group. Instead, they should be reserved for children with elevated risk factors for chronic disease. For most overweight children and their families, qualified health professionals should provide counseling and assistance in developing diets that contain adequate, but not excessive, calories and social and physical activities in which the child enjoys participating.

Nutrition Programs and Services

Food Labels

Evidence related to the role of diet in obesity indicates that calorie information should be provided on most food product labels.

Food Services

Evidence related to the role of diet in obesity suggests that service programs should include a variety of foods low in calories in their menus.

Food Products

Evidence related to the role of diet in obesity suggests that the food industry should continue to develop food products low in calories and with adequate nutrient content.

Special Populations

Overweight patients should be provided with counseling and assistance in the development of diets low in calories and high in essential nutrients, as well as lifestyle modifications that include high levels of physical activity to achieve appropriate weight goals.

Research and Surveillance

Research and surveillance issues of special priority related to the role of nutrition and exercise in obesity and weight management should include investigations into:

- Determination of ideal or desirable body weights for individuals or for the population of various ages.

- Determination of the health risks associated with various degrees of overweight in children and adults.
- Identification of an effective means to measure total body fat and its regional distribution in individuals and in the population.
- Identification of the types of obesity most associated with increased chronic disease risk.
- The contribution of genetic and metabolic factors to obesity, including the molecular and genetic basis of energy metabolism and the nature of genetic aberrations in human obesity.
- The effects of diet, exercise, and weight loss on metabolism and thermogenesis.
- The effects of physical activity on maintenance of desirable body weight.
- The identification of dietary, behavioral, environmental, or genetic factors that predict development of obesity or the ability to lose weight successfully.
- Identification of the dietary, behavioral, environmental, social, or genetic factors that increase the risk of overweight in high-risk population groups.
- The health consequences of repeated cycles of weight gain and loss.
- The most effective individual, group, and community intervention strategies for weight management.
- The most effective intervention strategies for use with high-risk groups.
- The most effective means by which to educate individuals and the public about the factors predisposing to weight gain and loss.
- The most effective ways in which to promote increased physical activity in the population.
- The long-term effectiveness of existing weight control programs.

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Chapter 7

Skeletal Diseases

For the women of this city do not possess sufficient devotion to look after everything as the purely Greek women do. If nobody looks after the movements of the infants the limbs of the majority become distorted, as the whole body rests on the legs . . . [when] the bones have not yet become strong.
Childrearing advice to the women of
Rome, Soranus of Ephesus
in second century A.D. (Temkin 1956)

Introduction

Historical Perspective

Major skeletal diseases influenced by nutrition include rickets, osteomalacia, and osteoporosis. Among all the nutritionally related skeletal diseases, rickets, the "softening" of bones in children, is probably the most well known. Rickets and its adult form, osteomalacia, traditionally viewed as urban diseases, have been largely eradicated in the industrialized world by milk fortification, enrichment of infant foods with vitamin D, the use of vitamin D supplements by children, and improved environmental conditions that promote adequate exposure to sunlight. Rickets is still prevalent in the developing world and is occasionally found elsewhere, especially where rapid urbanization has created conditions similar to the Industrial Revolution when social conditions and air pollution prevented adequate exposure to sunlight.

Hippocrates was the first to describe rickets. In the fifth century B.C., he observed children whose ". . . legs and arms attain full size, but the body will not grow correspondingly at the spine." Not until 1645 was the first formal description of the condition published; the classic study *De Rachitide* by Glisson, who traced its origin to the Greek word rachitis, or spinal disease, followed soon after (Guggenheim 1981).

The incidence of rickets increased with the Industrial Revolution. Rickets became known as the "English Disease," although it was prevalent throughout Northern Europe, where overcrowding and substandard living

conditions had become the norm. The disease was astonishingly widespread. For example, in 1907, half of the children between ages 6 months and 3 years admitted to Paris hospitals were reported to suffer from rickets, and in 1921, perhaps three of every four infants in New York City were affected.

Understanding developed slowly about the relationship between vitamin D deficiency and rickets. Cod liver oil was prescribed as treatment as early as 1807, but it was only in the late 1800's that rachitic lion and bear cubs at the London Zoo were cured when fed bone meal, milk, and cod liver oil (Todhunter 1973). The preventive powers of sunlight were observed in 1890.

It was not until this century that researchers untangled the complex interactions among vitamin D, sunlight, social conditions, and the disease. The isolation of vitamin D from fats and oils and the understanding of its activation in skin by ultraviolet radiation finally provided the keys to rational public health prevention of rickets and osteomalacia.

Today, osteoporosis—loss of bone mass—has become the most important bone disease in Western countries. The studies of early skeletons by Trotter and international comparisons by Nordin established that bone loss in aging persons occurs in every population. Such studies, coupled with population-based evidence suggesting a dietary contribution, stimulated current work on the role of diet in the prevention of age-related bone disease (Nordin 1984).

Significance for Public Health

Osteoporosis

The major skeletal disease in which nutrition may play a role is osteoporosis, characterized by a decrease in the amount of bone often so severe that it leads to fractures after even minimal trauma. Osteoporosis may be classified into primary and secondary forms. Primary osteoporosis, specifically involutional osteoporosis, may occur in two types: Type I (postmenopausal) osteoporosis (accelerated decrease in bone mass that occurs when estrogen levels decline after menopause), and Type II (age-related) osteoporosis, the inevitable loss of bone mass with age that occurs in both men and women (Riggs and Melton 1986). Secondary osteoporosis may develop at any age as a consequence of endocrinologic and gastrointestinal conditions or metabolic disorders, as well as prolonged bedrest and states of weightlessness, that result in bone demineralization.

Osteoporosis afflicts 15 to 20 million Americans, causing each year an estimated 1.3 million fractures of the vertebrae, hips, forearms, and other bones in those 45 years of age and older (Consensus Development Panel 1984). The risk of hip fractures is about twice as great in women as in men. Because women live longer than men, the absolute incidence is even higher. One-third of women 65 years and older have vertebral fractures, the most common break caused by osteoporosis. By age 90, one-third of women and one-sixth of men will have suffered hip fractures, leading to death in 12 to 20 percent of these cases and to long-term nursing home care for many of those who survive (Riggs and Melton 1986). Millions of other older Americans find their mobility restricted and the quality of their lives diminished by the consequences of osteoporosis. The total direct and indirect costs of osteoporosis to the U.S. economy were estimated to be between $7 and 10 billion in 1986 (Peck, Riggs, and Bell 1987).

Without effective measures to prevent the development of this disease, the costs of osteoporosis to the United States will increase because of the rapid increase in the number of older Americans. Prevention of osteoporosis is especially important, not only because of the costs of the disease, but also because treatment of osteoporosis, once fractures have occurred, is relatively ineffective and the functional limitations and deformities that develop are often irreversible. Precisely why certain individuals develop osteoporosis and others do not is incompletely understood. Aging itself, the loss of sex hormones at menopause, and genetics all play a role. To date, estrogen-replacement therapy is the best documented method of preventing osteoporosis in postmenopausal women. Although this treatment has been associated with increased risk of developing endometrial and other cancers, this association may not be significant especially at lower doses of estrogen (Ettinger, Genant, and Carn 1987). Table 7-1 lists factors that increase or decrease the risk for developing osteoporosis. Although much is yet to be learned about how diet can affect the development of this disease, sufficient scientific evidence now exists to make nutrition a focus of programs to prevent or to treat osteoporosis.

Rickets and Osteomalacia

Two other important diet-related bone diseases are rickets, which affects growing children, and osteomalacia, which affects adults. Both are characterized by an inadequate mineralization of bone. In osteoporosis, both the mineral and protein components of bone are lost; the remaining bone is thinner but normal in composition. In rickets and osteomalacia, the protein matrix is poorly mineralized, so the bone that remains is rubbery or soft.

Table 7-1
Scientific Validity of Risk Factors

Well Established	Moderate Evidence	Inconclusive or Inadequate Evidence
Obesity (−)	Alcohol (+)	Moderate physical activity
Black ethnicity (−)	Cigarette smoking (+)	Asian ethnicity
Age (+)	Heavy exercise (−)	Parity
Premenopausal oophorectomy (+)	Low dietary calcium (+)	Diabetes
Consumption of corticosteroids (+)		Thiazide diuretic use
Estrogen use (−)		Progestin use
Extreme immobility (+)		Drinking water fluoride
		Caffeine use

(+) = increased risk; (−) = decreased risk.

Source: Peck, W.A.; Riggs, B.L.; Bell, N.H.; Wallace, R.B.; Johnston, C.C., Jr.; Gordon, S.L.; and Shulman, L.E. 1988. Research directions in osteoporosis. *American Journal of Medicine* 84:275–82. Copyright 1988, *American Journal of Medicine*, reprinted with permission.

Although clinical cases of rickets and osteomalacia are relatively uncommon in the United States today, they are important for public health consideration because they can be prevented or treated.

Scientific Background—Bone Physiology

Bone is a spongy protein matrix in which crystals of calcium and phosphorus salts are embedded. From birth until death, bone tissue is continually being formed, broken down, and reformed in a process called remodeling. The cells that break down bone are called osteoclasts, and those that build bone are called osteoblasts.

From infancy through young adulthood, the activity of the osteoblasts normally predominates over that of the osteoclasts, resulting in the steady accumulation of bone mass. By the fourth decade, this process levels off and the amount of bone mass achieved at this time is called peak bone mass. Men develop a peak bone mass 30 percent more dense than that of women, and blacks about 10 percent more dense than that of whites (Consensus Development Panel 1984). Hence, although all individuals lose bone as they get older, women are more susceptible to osteoporosis than men, and whites more than blacks. Men in general and blacks as a group can sustain a greater loss of bone before the onset of fracture because they have a greater bone mass at skeletal maturity. However, differences in

bone mass do not fully explain the differences in osteoporosis rates between the sexes and races. Differences in bone architecture and structure must also be important.

Usually between the ages of 30 and 40, the balance of bone remodeling activity then swings over to the osteoclasts and adults begin to slowly lose bone mass. Mineral is lost more readily from trabecular bones, found in the vertebrae and pelvis, than from the cortical bones that form the limbs. The decline in estrogen production after menopause is associated with the period of most rapid bone loss in women.

The nutritional controls of bone mineralization have yet to be identified fully. At present, the only established nutritional determinants of mineralization are calcium, phosphate, and vitamin D.

Several recent reviews summarize present knowledge of nutrition and bone metabolism (Aloia et al. 1985; Chan and Alon 1985; Chan, Alon, and Hirschman 1985; Favus 1985; Heaney 1986; Heaney et al. 1982; LSRO 1981; Marcus 1982; Parfitt et al. 1982; Peck, Riggs, and Bell 1987; Raisz 1982, 1988; Raisz and Kream 1983; Riggs and Melton 1986; Riggs, Seeman, et al. 1982; Riggs, Wahner, et al. 1982). The following sections cite only a few key articles and recent studies that are not included in these reviews.

Key Scientific Issues

- Role of Calcium in Skeletal Disease
- Role of Vitamin D in Skeletal Disease
- Role of Phosphate in Skeletal Disease
- Role of Calories and Protein in Skeletal Disease
- Role of Alcohol in Skeletal Disease
- Role of Other Minerals in Skeletal Disease
- Role of Other Vitamins in Skeletal Disease
- Role of Exercise in Skeletal Disease

Role of Calcium in Skeletal Disease

Ninety-nine percent of the body's calcium is found in the bones and teeth, where it is essential for their formation and maintenance; the remaining 1 percent in fluids and soft tissue is critical for proper functioning of every

nerve and muscle cell. Because of calcium's importance throughout the body, constant skeletal remodeling most likely evolved to provide a continuous supply of calcium.

Despite the evident physiologic importance of calcium, remarkably few studies have documented the effects of dietary calcium on peak bone mass reached by different populations, and none explains how different levels of dietary calcium affect age-related bone loss.

Such studies are complicated by the difficulties of studying large groups of people over long periods of time. In the United States, variations by age, sex, and season in calcium intake are thought to reflect the consumption of dairy products, which are also major sources of protein and phosphate, nutrients that may affect calcium metabolism. Moreover, the availability of calcium for building and maintaining the skeleton is determined not only by the amount of calcium in the diet but also by how much of that calcium is absorbed and how much is retained by the body.

Calcium Absorption

Calcium absorption is determined by (1) the amount of dietary calcium that goes into solution, (2) the interaction of calcium with other dietary substances within the small intestine, and (3) the level of activity of active and passive transport systems that move calcium across the intestinal wall and into the body. The amount of calcium in solution in the intestinal tract is influenced by the physical and chemical form of calcium consumed (Recker 1985; Recker and Heaney 1985). Calcium salts in food or supplements are usually soluble in the stomach's acidic environment. Persons who cannot produce gastric acid may absorb calcium poorly (Recker 1985) and may require calcium supplements (e.g., calcium carbonate, calcium gluconate, calcium citrate), which should be ingested with meals.

Calcium is a cation, a positively charged molecule, that can react with negatively charged molecules, called anions, to form complexes. Some of these calcium complexes are insoluble and cannot be absorbed. For example, the anion oxalate, which is found in spinach, rhubarb, and other plant foods, reacts with calcium to form calcium oxalate, which is quite insoluble. Other food anions, particularly polyphosphates, can also impair absorption.

Calcium is transported across the intestine principally by calcium-binding proteins, whose concentration is regulated by the active hormonal form of vitamin D. Factors that diminish the availability and metabolism of vitamin

D also diminish the absorption of calcium from the small intestine. Many drugs can interfere with calcium absorption. Examples include tetracyclines, which bind with calcium to form insoluble complexes, and antiepileptic drugs that impair intestinal transport of calcium and inhibit activation of vitamin D.

Calcium Retention

Calcium is lost from the body primarily in the urine and in the feces. Renal excretion, an important determinant of calcium balance, is regulated by hormones and is influenced by dietary protein intake. Increasing the level of protein in the diet seems to increase the amount of calcium lost in the urine (Margen et al. 1974; Allen, Oddoye, and Margen 1979), and epidemiologic data show that hip fractures and protein intake are positively correlated (Hegsted 1986). Secretion of calcium into the intestine, on the other hand, is probably not regulated by hormones but reflects the rate of production of intestinal juice in the digestive process, all of which can be influenced by diet.

Calcium and Peak Bone Mass

Peak bone mass is determined by several factors. Calcium deficiency does not ordinarily cause selective impairment of mineralization. Instead, there is increased bone resorption or breakdown due to excessive parathyroid hormone (PTH) secretion (secondary hyperparathyroidism) and decreased bone formation. A rickets-like syndrome has been reported in infants on extremely low calcium intakes (Kooh et al. 1977), but it differs somewhat from the rickets produced by vitamin D and phosphate deficiency.

Genetic determinants of peak bone mass are important (Farmer et al. 1984). For example, the larger bone mass in blacks than in whites in the United States can be detected in the fetus and may be due to differences in the vitamin D endocrine system (Bell, Greene, et al. 1985). On the other hand, lactase deficiency, which is more common in blacks, has been associated with a decreased calcium intake and an increased likelihood of developing osteoporosis in whites (Newcomer et al. 1978). This inconsistency suggests a strong role for genetic factors in the incidence of osteoporosis, although current observations need to be evaluated with a closer assessment of the magnitude of individual variations within a given group.

The role of dietary calcium in determining peak bone mass is uncertain. Populations of similar ethnic backgrounds have been observed in which there are differences in calcium intake but no difference in bone mass. For

example, one study reported that Guatemalans and Panamanians have similar peak cortical bone mass, although calcium intake is thought to be considerably higher in Guatemalans (Garn et al. 1969).

Other population studies, however, suggest that calcium intake does affect peak bone mass. In two regions of Yugoslavia, where dairy product intakes differ, average bone mass was higher in the area with the higher calcium intake. Because dairy products also contain substantial amounts of phosphate and protein, calcium may not have been the only determinant of this difference. Nevertheless, the difference in peak bone mass seems to affect skeletal disease; the incidence of hip fractures was substantially lower in the group consuming more dairy products (Matkovic et al. 1979). One investigator in the United States has reported that women with a greater calcium intake because of a high calcium concentration in the water supply also had a greater bone mass, but only if they also had an adequate intake of vitamin D (Sowers, Wallace, and Lemke 1985).

These data are not entirely consistent, but they suggest the importance of peak bone mass in skeletal health and the need for further research on the nutritional determinants that affect the skeleton up to age 35. Presumably, persons with greater bone mass in early adulthood are able to resist the effects of age-related bone loss.

One reason for uncertainty about the influence of dietary calcium intake on bone mass is that young individuals can adjust to a decreasing calcium intake by an increased efficiency of calcium absorption. This compensation is mediated by calcitriol (1,25-dihydroxyvitamin D), the active hormonal form of vitamin D. However, this compensatory response is blunted with age.

Nevertheless, a low calcium intake could interfere with the adolescent growth spurt and could compromise the subsequent consolidation of skeletal mass that occurs up to the age of 35. From 1976 to 1980, the median calcium intake for boys ages 12 to 14 was 1,024 mg, which is close to the Recommended Dietary Allowance (RDA) of 1,200 mg for that age group. In contrast, median calcium intake of 793 mg for girls in that age group was below the RDA (Carroll, Abraham, and Dresser 1983). More recent data on the calcium intakes of men and women 19 to 50 years of age indicate that while calcium intakes have increased slightly from 1977 to 1985 and are above the RDA of 800 mg for men, they fall below the RDA of 800 mg for women (Marston and Raper 1987). Thus, the influence of this level of intake on peak bone mass in women is of great interest.

Calcium and Age-Related Bone Loss

At present, studies of the effect of calcium supplementation on age-related bone loss are inconclusive. Some reports indicate that a sufficiently high calcium intake can reverse a negative calcium balance and thereby suppress bone loss (Horsman et al. 1977; Recker, Saville, and Heaney 1977). Other studies have found that daily calcium supplementation as high as 2,000 mg/day is of little or no help in preventing bone loss in postmenopausal women (Nilas et al. 1985; Riis, Thomsen, and Christiansen 1987). However, it should be noted that the Danish women in this study were consuming an average of 950 mg/day before entry into the study (Riis, Thomsen, and Christiansen 1987). This intake is well above the RDA for calcium of 800 mg/day, making it difficult to extrapolate these results to American women, many of whom consume less than 500 mg/day in their diet.

Understanding the influence of calcium intake on age-related bone loss is complicated in that age itself may influence both the intestinal absorption of calcium and the skeleton's subsequent utilization of calcium. It is not clear when age-related decreases in calcium absorption first begin. Decreases in absorptive ability may begin as early as age 30 or as late as age 60 (Heaney et al. 1982). Decreased absorption may result from the kidney's decreased ability to synthesize calcitriol (the active form of vitamin D) and decreased intrinsic absorptive capacity. Treatment of older individuals with calcitriol regularly increases calcium absorption (Gallagher et al. 1982), but whether this means that osteoporosis could be caused by an inadequate supply of vitamin D is debatable. Osteoporotic persons have somewhat lower calcitriol levels in their blood. Although older people may have a reduced ability to synthesize calcitriol in response to PTH, one study has found no difference between postmenopausal women with osteoporosis and age-matched healthy postmenopausal women in response to PTH (Riggs, Hamstra, and DeLuca 1981). Differences in calcitriol synthetic ability in response to PTH stimulation may explain differences in the underlying pathologies of Type I and Type II osteoporosis. A recent study reported impaired calcitriol synthesis in aging women with age-related osteoporosis (Tsai et al. 1984), while others (Riggs, Hamstra, and DeLuca 1981) reported no differences in postmenopausal osteoporotics relative to their age-matched controls. Trials with calcitriol have failed to demonstrate its safety and efficacy for treatment of osteoporosis (Ott and Chesnut 1987; Falch et al. 1987; Aloia et al. 1988).

At least two possible mechanisms might explain why calcitriol synthesis and intestinal absorption both decrease with age. One mechanism may be

important to the pathogenesis of Type I (postmenopausal) osteoporosis, while the other may be more important in the pathogenesis of Type II (age-related) osteoporosis (Riggs and Melton 1986). In the first, the reduced inhibition of estrogen on bone resorption at menopause increases the supply of calcium released from bone into the blood and reduces PTH secretion, which in turn reduces calcitriol synthesis in the kidney, and, as a result, decreases calcium absorption in the intestine. The failure to respond to decreased calcium intake could then be attributed to an unregulated increase in bone resorption and loss.

This sequence does not explain the age-related bone loss associated with an increasing PTH level that occurs in both men and women. Although the increasing level of immunoreactive PTH might be due to impaired renal excretion of inactive metabolites of this hormone, measures of PTH biologic activity also show an age-related increase. These findings were confirmed in several recent studies that reported an increase in the biologically active form of the hormone with age (Forero et al. 1987; Young et al. 1987). Hence, a second hypothesis explains age-related bone loss in both sexes in terms of the kidney's decreased ability to synthesize calcitriol (Tsai et al. 1984) and (probably) the intestine's decreased intrinsic ability to transport calcium (Francis et al. 1984). These two conditions would result in secondary hyperparathyroidism, but because of the renal abnormality, there would be blunted or minimal increase in calcitriol synthesis, persistent impairment of calcium absorption, and negative calcium balance.

Both hypotheses may be true in different individuals or in the same individual under different circumstances, but whichever mechanism holds, calcium supplementation could theoretically decrease bone loss. If bone resorption increases because of decreased estrogen, the effect of increased calcium should be inhibition of bone resorption, but only to the extent that calcium supplementation either decreases PTH secretion or increases calcitonin secretion. If the primary event is decreased calcitriol synthesis, then calcium loading should be effective only to the extent that it increases passive absorption.

Whatever the role of calcium in achieving and maintaining skeletal mass, calcium intake is superimposed on genetic and age-related changes in bone cell function. Calcium may also affect bone formation directly by increasing either the replication or differentiation of bone cells. Even when calcium supplies are adequate, an age-related decrease in osteoblastic bone formation may occur. This change is demonstrated by the fact that the packets of new bone formed on remodeling surfaces are thinner or smaller in older individuals (Courpron 1981).

Calcium Toxicity

Excessive calcium intake can cause inappropriate mineralization, particularly in the soft tissues. Many years ago, large amounts of calcium carbonate were regularly prescribed for patients with peptic ulcer. A small proportion of them developed milk-alkali syndrome, characterized by hypercalcemia, deposits of calcium in the kidneys, and progressive impairment of renal function. This disorder is now rare (Carroll and Clark 1983). Moreover, the prescribed doses were much larger than the 1 to 2 g of calcium per day that have been suggested for women in the general population.

Nevertheless, some people who have a defective intestinal barrier to calcium absorption may absorb too much calcium and develop soft tissue calcifications or renal stones (see chapter on kidney diseases). Therefore, when calcium supplements are recommended to pre-or postmenopausal women who are at high risk for development of renal stones, they should be screened for excessive urinary concentrations of calcium to determine the appropriate dose. A high fluid intake (i.e., at least 2 liters of water per day) should be encouraged when calcium supplements are used. High calcium intakes may also cause constipation in some individuals.

Role of Vitamin D in Skeletal Disease

The role of vitamin D in preventing rickets and osteomalacia is well established (Jacobs 1979). Subtle abnormalities in vitamin D metabolism can affect the development and maintenance of bone mass in the absence of these two diseases.

Vitamin D is synthesized in the skin in response to sunlight. In the body, the vitamin is transformed first by the liver to 25-hydroxyvitamin D and then by the kidneys into its active hormonal form, called 1,25-dihydroxyvitamin D or calcitriol. This active form helps to increase the absorption of calcium by stimulating intestinal formation of the calcium-binding proteins that transport calcium across the intestinal wall into the body. Vitamin D also acts directly on bone: in low doses it stimulates deposition of new bone, but at high doses it stimulates resorption of bone.

The supply of vitamin D can easily be limited or its activation to calcitriol impaired. Although only a few minutes of exposure to sunlight produces the daily requirement of vitamin D in the skin, many people do not receive this exposure, particularly in the winter. This deficiency can be overcome by consuming foods fortified with vitamin D; however, some individuals

who are on vegetarian diets that limit dairy products and who have limited intake of these foods may not obtain enough vitamin D from their diets (Hellebostad, Markestad, and Halvorsen 1985).

Various diseases may impair the conversion of vitamin D to calcitriol. Hepatic disease, for example, may lead to decreased synthesis of the intermediate 25-hydroxyvitamin D. Impairment of intestinal mucosal function decreases absorption of vitamin D and calcium. Too rapid intestinal transit and impaired fat absorption also decrease calcium and vitamin D absorption. Loss of vitamin D metabolites through enterohepatic circulation may be less important because there is no clear evidence that conjugated vitamin D metabolites excreted in the bile are conserved by reabsorption (Arnaud 1982). Although gastrointestinal disorders might be expected to lead to impaired bone mineralization, most persons with gastrointestinal disease and decreased bone mass have osteoporosis rather than osteomalacia. Moreover, diminished bone mass in persons with gastrointestinal disease often fails to respond to treatment with vitamin D in any form (Arnaud 1982). Other nutritional elements such as protein, and other factors from the liver and intestine such as somatomedin or insulin-like growth factors and enteroglucagon, may be as important as, or more important than, vitamin D in the bone loss that accompanies gastrointestinal disease.

Osteoporosis

Perhaps the most important question concerning vitamin D supplementation is its use in the prevention and treatment of postmenopausal and age-related osteoporosis. Ten to fifteen years ago, patients with osteoporosis were given vitamin D supplements in doses of 50,000 to 150,000 IU a week in addition to other forms of therapy such as calcium, estrogen, and fluoride supplements. Retrospective analysis of these studies indicates that large doses of vitamin D have no significant effect on the incidence of vertebral compression fractures (Riggs, Seeman, et al. 1982). Thus, current recommendations are that vitamin D intake be adequate—400 to 1,000 IU/day—but not increased.

The possibility that impaired activation of vitamin D into 1,25-dihydroxyvitamin D or calcitriol, rather than vitamin D supply, is the limiting factor in older persons and in people with osteoporosis has inspired several experiments with calcitriol supplementation. Calcitriol supplements can increase calcium absorption and may increase the body's stores of calcium, but effects on bone mass and the incidence of bone fractures are as yet unknown. Some studies argue that calcitriol supplementation actually decreases bone mass (Jensen et al. 1985), a finding that is consistent with

previous observations that excessive 1,25-dihydroxyvitamin D has a direct catabolic effect on bone. On the other hand, those studies were done in embryonic bone cultures and may have limited *in vivo* application. Because most of these studies do not show an increase in bone mass, yet some suggest that the incidence of fractures decreases (Gallagher et al. 1982), calcitriol supplementation may improve the quality rather than the quantity of bone.

Some data suggest that a decreased availability of 25-hydroxyvitamin D also could be important in osteoporosis, particularly in the older population. Before vitamin D is converted to calcitriol in the kidneys, it is transformed to 25-hydroxyvitamin D in the liver. An inadequate amount of the liver precursor could lead to an insufficient amount of calcitriol formed in the kidneys. Blood levels of 25-hydroxyvitamin D are reduced in older subjects, particularly in those who have limited exposure to the sun (Lamberg-Allardt 1984). These individuals are at especially high risk for developing hip fractures. Many patients with hip fractures also have low levels of 25-hydroxyvitamin D.

Maintaining an adequate supply of vitamin D, either through exposure to sunlight or from dietary sources, may help to reduce the incidence of hip fractures in older persons, but it is difficult to judge how great that effect might be.

Rickets and Osteomalacia

Vitamin D deficiency rarely causes rickets and osteomalacia in the United States because most Americans get enough sunlight and ingest sufficient amounts of vitamin D available in fortified foods and dietary supplements. Nevertheless, rickets and osteomalacia due to vitamin D deficiency do occur and need to be prevented.

Rickets occurs most often in children who stay indoors and who are breastfed and not given vitamin D supplements (Edidin et al. 1980). The incidence may be somewhat higher in black children, who make less vitamin D for a given amount of sun exposure than do white children. Socioeconomic factors may also be important. Children with vitamin D-deficiency rickets often do not have adequate health care, or they are affected by unusual practices that limit sun exposure or vitamin D intake.

The most common cause of osteomalacia in the United States is an inherited or acquired defect in the metabolism of vitamin D (Jacobs 1979). Formation of 25-hydroxyvitamin D in the liver is usually not the problem,

because only a relatively small amount of hepatic tissue is required to supply adequate amounts. A failure to form 1,25-dihydroxyvitamin D in the kidney is a much more serious problem. As indicated above, this problem may occur in a subtle form with aging.

Deficient absorption of vitamin D also causes rickets and osteomalacia in the United States. Gastrointestinal disease impairs absorption, but it is more likely to cause osteoporosis than osteomalacia, probably because general nutritional deficits decrease bone formation, increase bone resorption, and deplete the protein matrix. Causes of deficient absorption include pancreatic insufficiency, nontropical sprue, or intestinal bypass surgery (Passmore and Eastwood 1986). In patients with these conditions, vitamin D as well as calcium and other nutrients may be poorly absorbed. Vitamin D metabolism may also be abnormal after gastrectomy (Nilas, Christiansen, and Christiansen 1985). Clear-cut osteomalacia due to vitamin D deficiency is also rare, but it occurs occasionally in older individuals who remain indoors and eat inadequate diets.

In renal failure, impaired vitamin D hydroxylation to the biologically active form may lead to marked impairment of mineralization (see chapter on kidney diseases). Most patients in the United States with renal failure do not develop typical osteomalacia, but instead develop osteitis fibrosis cystica, a condition characterized by resorption of bone due to marked secondary hyperparathyroidism (Dunstan et al. 1985), failure to form 1,25-dihydroxyvitamin D, and impaired intestinal absorption of calcium. In chronic renal failure, however, sufficient calcium may be obtained through dialysis or from increased resorption of bone to maintain mineralization even though dietary sources are reduced.

In renal osteodystrophy, some observations suggest that 1,25-dihydroxyvitamin D is not always sufficient to produce mineralization in patients with osteomalacia. Although it has been suggested that the lack of 24,25-dihydroxyvitamin D, another renal metabolite, causes this condition, administration of this metabolite does not consistently cure osteomalacia. The role of other substances such as aluminum and magnesium is also uncertain.

Osteomalacia can also result from prolonged ingestion of anticonvulsant medication, particularly phenytoin, perhaps due to impaired formation of 25-hydroxyvitamin D in the liver or to a direct effect on intestinal calcium transport. This problem is usually associated with marginal intakes of vitamin D or limited sun exposure and can be overcome by moderate vitamin supplementation (Mosekilde et al. 1977).

Finally, osteomalacia can occur in renal tubular acidosis associated with such disorders as the Fanconi syndrome (Chan and Alon 1985). Other defects, including impaired vitamin D hydroxylation to the biologically active form and low tubular reabsorption of phosphate, may be present as well. It is not clear that acidosis by itself impairs mineralization, although it certainly decreases skeletal mass and impairs bone growth.

Inherited or acquired defects in vitamin D metabolism produce some forms of rickets. In vitamin D-dependent rickets, for example, 1,25-dihydroxyvitamin D does not form in the kidney. This defect can be treated effectively by replacement doses of calcitriol. Other kinds of rickets resist treatment with large doses of vitamin D because of defects in the function of cellular receptors for 1,25-dihydroxyvitamin D.

Other vitamin D metabolites may play a role in mineralization. In several experiments, 25-hydroxyvitamin D or 24,25-dihydroxyvitamin D has been used successfully to treat certain patients who failed to respond to calcitriol. These compounds are bound more tightly to vitamin D-binding protein than is calcitriol and retain activity for longer time periods. In animal studies and *in vitro*, some evidence indicates that 24,25-dihydroxyvitamin D can stimulate cartilage growth. On the other hand, none of the vitamin D metabolites is essential to rats for normal growth and mineralization of the skeleton when adequate calcium and phosphate are supplied by dietary manipulations or by continuous subcutaneous infusion (Underwood and DeLuca 1984). At present, it is uncertain whether 25-hydroxyvitamin D or 24,25-dihydroxyvitamin D has a specific role in maintaining skeletal mineralization (Brommage and DeLuca 1985). Thus, the major role of vitamin D in mineralization appears to be its effect on the intestine and, perhaps, on renal tubular reabsorption of phosphate in the kidney.

Vitamin D Toxicity

Excessive amounts of vitamin D are potentially toxic and can cause bone loss by increasing resorption or breakdown and by impairing bone growth and mineralization (Coburn and Brautbar 1980; Holmes and Kummerow 1983), although the moderate increases in intake that occur through dietary supplementation seem unlikely to have such adverse effects.

Role of Phosphorus in Skeletal Disease

Phosphorus is the second most abundant mineral in the body, exceeded only by calcium. About 85 percent of the body's phosphorus is in bone as bone mineral, principally hydroxyapatite crystals containing about two