Chapter 3: Key Messages

- Osteoporosis affects millions of Americans. Individuals with osteoporosis are at high risk of suffering one or more fractures, which are often physically debilitating and can potentially lead to a downward spiral in physical and mental health.
- The most common form of osteoporosis is known as "primary osteoporosis." It is the result of the cumulative impact of bone loss and deterioration of bone structure as people age. This bone loss can be minimized and osteoporosis prevented through adequate nutrition, physical activity, and, if necessary, appropriate treatment.
- There are a wide variety of diseases and certain medications and toxic agents that can cause or contribute to the development of osteoporosis. If recognized as a potential threat, this form of the disease—known as secondary osteoporosis—can often be prevented through proper nutrition and physical activity, along with appropriate therapy if needed.
- A number of childhood diseases cause rickets, a condition that results from a delay in depositing calcium phosphate mineral in growing bones. This delay leads to skeletal deformities, especially bowed legs. In adults, the equivalent disease is called osteomalacia. Both diseases can generally be prevented by ensuring adequate levels of vitamin D, but they can have devastating consequences for affected individuals.
- Patients with chronic renal disease are at risk for developing a complex bone disease known as renal osteodystrophy. While dialysis and transplantation have extended the life-expectancy of these patients, it may not prevent further progression of bone disease.
- Paget's disease of bone is a progressive, often crippling disorder of bone remodeling that commonly involves the spine, pelvis, legs, or skull (although any bone can be affected). If diagnosed early, its impact can be minimized.
- A large number of genetic and developmental disorders affect the skeleton. Among the more common of these is osteogenesis imperfecta (OI). Patients with this condition have bones that break easily.
- Some skeletal disorders tend to develop later in life. One of the most common of these acquired skeletal disorders is a malignancy of the bone. These malignancies can originate in the bone (primary tumors) or, much more commonly, result from the seeding of bone by tumors outside of the skeleton (metastatic tumors). Primary bone cancer also occurs in children. Both types of tumors can destroy bone.

Chapter 3

DISEASES OF BONE

The body systems that control the growth and maintenance of the skeleton, which are described in Chapter 2, can be disrupted in different ways that result in a variety of bone diseases and disorders. These include problems that can occur at or before birth, such as genetic abnormalities and developmental defects, as well as diseases such as osteoporosis and Paget's disease of bone that damage the skeleton later in life. In addition to conditions that affect bone directly, there are many other disorders that indirectly affect bone by interfering with mineral metabolism. This chapter reviews some of the more common diseases, disorders, and conditions that both directly and indirectly affect bone.

Osteoporosis

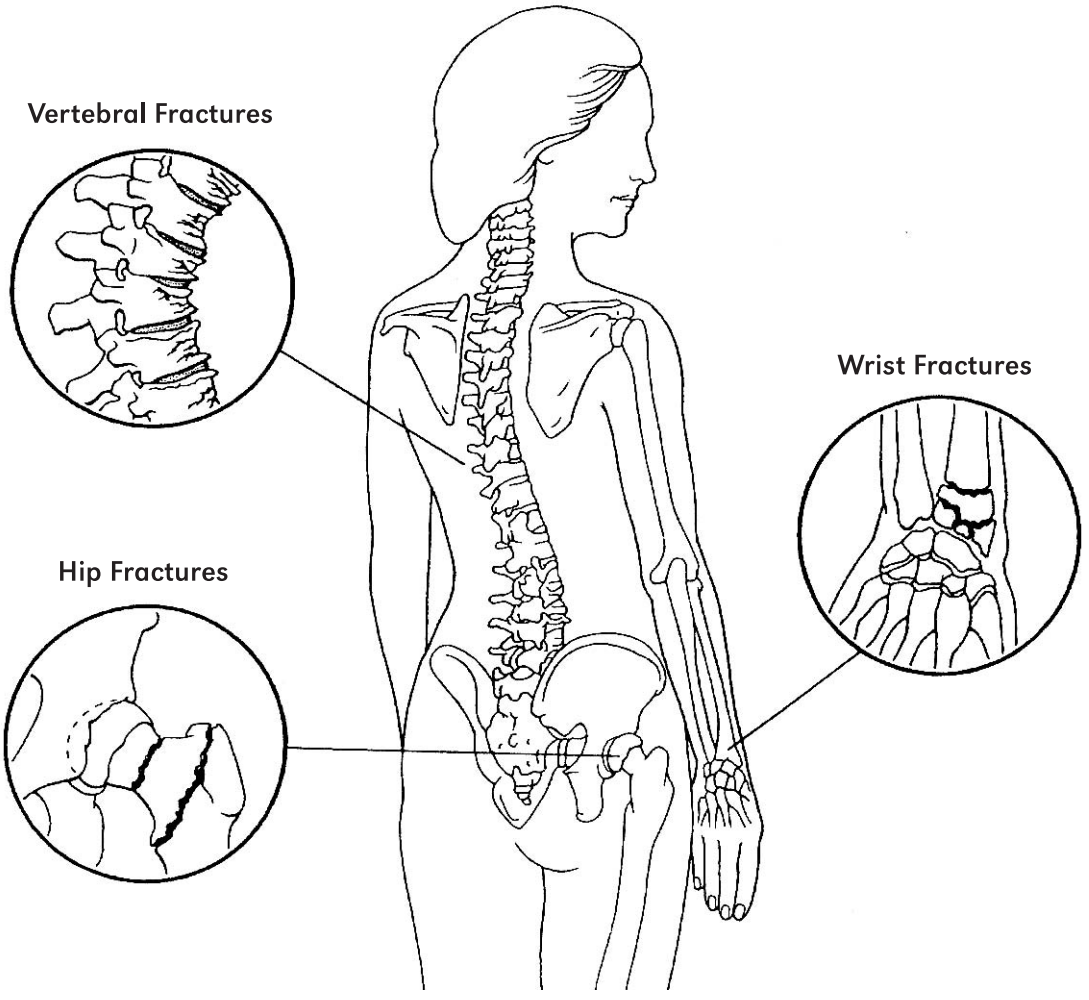
As pointed out in Chapter 2, osteoporosis is a disease characterized by low bone mass and deterioration of bone structure that causes bone fragility and increases the risk of fracture. For practical purposes, the World Health Organization has defined osteoporosis as a bone mineral density (BMD) value more than 2.5 standard deviations below the mean for normal young White women. Osteoporosis is a common disease affecting millions of Americans. As described in Chapters 4 and 5, it can have devastating consequences. Individuals with osteoporosis are at high risk of suffering one or more fractures, injuries that can often be

Classical Case

"A classical case of osteoporosis may start in a woman about 55 years of age with a wrist fracture. Ten years later she may present with back pain, with or without minor trauma, and thoracolumbar spine x-rays may show a vertebral fracture. She might have one of several risk factors: low body weight, premature menopause, a family history of fractures, smoking, heavy alcohol consumption, inactivity, calcium or vitamin D deficiency, or corticosteroid use. The back pain may remit and relapse with subsequent vertebral fractures. Approximately 10–15 years later, at the age of 75–80 years, the patient may fall and sustain a hip fracture, resulting in hospitalization, a 20 percent excess risk of death, considerable functional impairment and possibly a loss of independence if she survives. Although this scenario is instantly recognizable, osteoporosis may present with any of a wide range of fractures and at a variety of ages; it is also increasingly recognized among men" (WHO 2003). Recognition that the first fracture was a sentinel event may have triggered a detailed assessment that could potentially have prevented additional fractures. See Chapter 8 for more information on such assessments.

physically debilitating and potentially lead to a downward spiral in physical and mental health (Figure 3-1). Generalized osteoporosis is the most common form of the disease, affecting most of the skeleton. Osteoporosis can also occur in localized parts of the skeleton as a result of injury or conditions that reduce muscle forces on the bone, such as limb paralysis. There are a variety of different types of osteoporosis. The most common form of osteoporosis is known as "primary osteoporosis"—that is, osteoporosis that is not caused by some other specific disorder. Bone loss caused by specific diseases or medications (see below) is referred to as "secondary osteoporosis." Each of these major categories of osteoporosis is discussed in more detail on the following pages.

Figure 3–1. Bone Fracture Areas in Osteoporosis



Source: NOF 2004.

Primary Osteoporosis

Primary osteoporosis is mainly a disease of the elderly, the result of the cumulative impact of bone loss and deterioration of bone structure that occurs as people age (Seeman 2003). This form of osteoporosis is sometimes referred to as age-related osteoporosis. Since postmenopausal women are at greater risk, the term "postmenopausal" osteoporosis is also used. Younger individuals (including children and young adults) rarely get primary osteoporosis, although it can occur on occasion. This rare form of the disease is sometimes referred to as "idiopathic" osteoporosis, since in many cases the exact causes of the disease are not known, or idiopathic. Since the exact mechanisms by which aging produces bone loss are not all understood (that is, it is not always clear why some postmenopausal women develop osteoporosis while others do not), age-related osteoporosis is also partially idiopathic. A brief review of "idiopathic" primary osteoporosis and a more detailed review of the more common condition of age-related osteoporosis follows.

Idiopathic Primary Osteoporosis

There are several different forms of idiopathic osteoporosis that can affect both children and adolescents, although these conditions are quite rare (Norman 2003). Juvenile osteoporosis affects previously healthy children between the ages of 8 and 14. Over a period of several years, bone growth is impaired. The condition may be relatively mild, causing only one or two collapsed bones in the spine (vertebrae), or it may be severe, affecting virtually the entire spine. The disease almost always goes into remission (spontaneously) around the time of puberty with a resumption of normal bone growth at that time. Patients with mild or moderate forms of the disease may be left with a curvature of the spine (kyphosis) and short stature, but those with a more severe form of the disease may be incapacitated for life.

Primary osteoporosis is quite rare in young adults. In this age-group, the disease is usually caused by some other condition or factor, such as anorexia nervosa or glucocorticoid use (Khosla et al. 1994). When idiopathic forms of primary osteoporosis do occur in young adults, they appear in men as often as they do in women (this is in contrast to age-related primary osteoporosis, which occurs more often in women). The characteristics of the disease can vary broadly and may involve more than one disorder. Some young adults with idiopathic primary osteoporosis may have a primary defect in the regulation of bone cell function, resulting in depressed bone formation, increased bone resorption, or both (see Chapter 2). Others with a mild form of the disease may simply have failed to achieve an adequate amount of skeletal mass during growth. In some patients, the disease runs a mild course, even without treatment, and the clinical manifestations are limited to asymptomatic spinal compression fractures. More typically, however, multiple spine fractures occur over a 5–10 year period leading to a height loss of up to 6 inches.

Age-Related Osteoporosis

Age-related osteoporosis is by far the most common form of the disease (Figure 3-2). There are many different causes of the ailment, but the bone loss that leads to the disease typically begins relatively early in life, at a time when corrective action (such as changes in diet and physical activity) could potentially slow down its course. While it occurs in both sexes, the disease is two to three times more common in women (see Chapter 4). This is partly due to the fact that women have two phases of age-related bone loss—a rapid phase that begins at menopause and

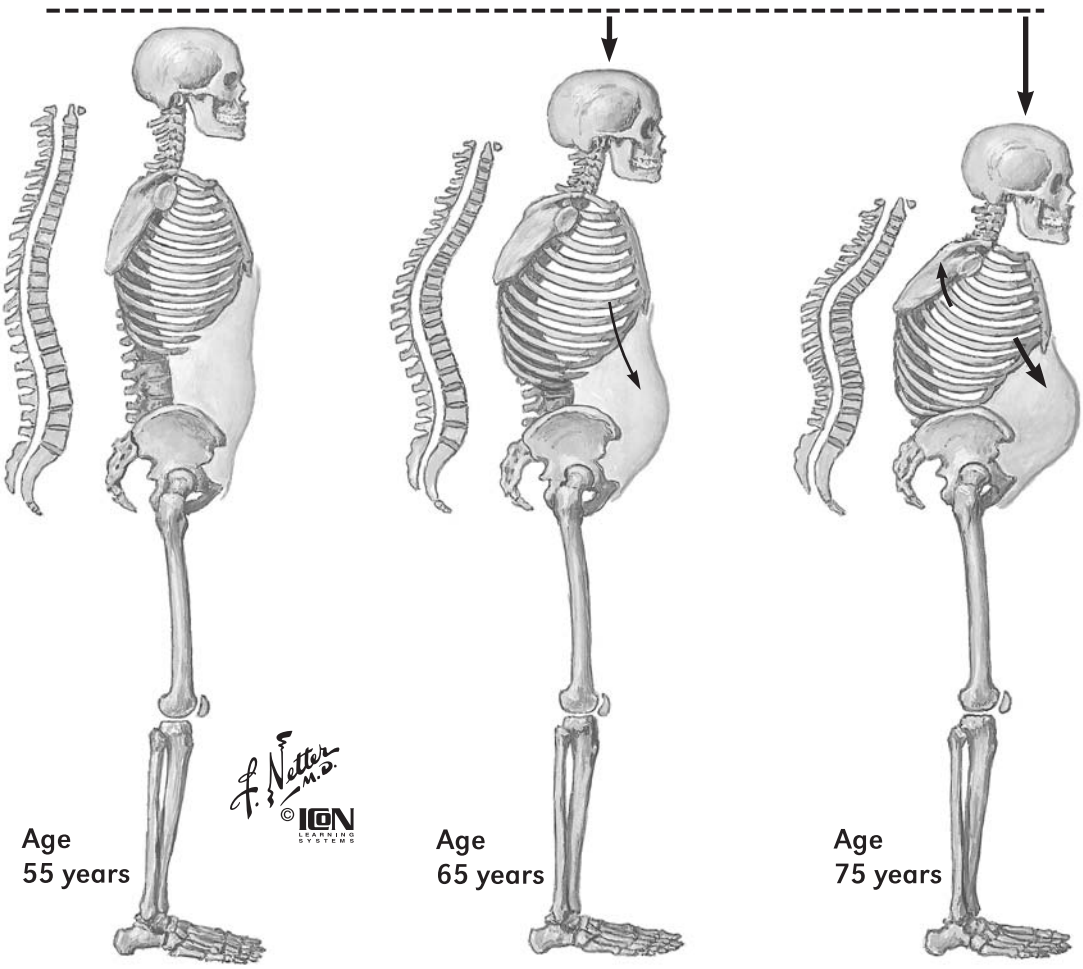
lasts 4–8 years, followed by a slower continuous phase that lasts throughout the rest of life (Riggs et al. 2002). By contrast, men go through only the slow, continuous phase. As a result, women typically lose more bone than do men. The rapid phase of bone loss alone in women results in losses of 5–10 percent of cortical bone (which makes up the hard outer shell of the skeleton) and 20–30 percent of trabecular bone (which fills the ends of the limb bones and the vertebral bodies in the spine, the sites of most osteoporotic fractures). The slow phase of bone loss results in losses of 20–25 percent of cortical and trabecular bone in both men and women, but over a longer period of time (Riggs et al. 2002).

Although other factors such as genetics and nutrition contribute, both the rapid phase of bone loss in postmenopausal women and the slow phase of bone loss in aging women and men appear to be largely the result of estrogen deficiency. (This is demonstrated by the fact that correction of estrogen deficiency can prevent these changes.) For women, the rapid phase of bone loss is initiated by a dramatic decline in estrogen production by the ovaries at menopause. The loss of estrogen action on estrogen receptors in bone results in large increases in bone resorption (see Chapter 2), combined with reduced bone formation. The end result is thinning of the cortical outer shell of bone and damage to the trabecular bone structure (see Figure 2-5, Chapter 2). There may be some countervailing forces on this process, as the outside diameter of the bone can increase with age, thus helping to maintain bone strength (Ahlborg et al. 2003).

By contrast, the slower phase of bone loss is thought to be caused by a combination of factors including age-related impairment of bone formation, decreased calcium and vitamin D intake, decreased physical activity, and the loss of estrogen's positive effects on calcium balance in the intestine and kidney as well as its effects on bone (Riggs et al. 2002). This leads to further impairment of absorption of calcium by the intestine and reduced ability of the kidney to conserve calcium. If the amount of calcium absorbed from the diet is insufficient to make up for the obligatory calcium losses in the stool and urine, serum calcium begins to fall. Parathyroid hormone levels will then increase, removing calcium from bone to make up for the loss, as illustrated in Figure 3-3. The net result of this process is an increase in bone resorption. It is important to realize that these mineral losses need not be great to result in osteoporosis. A negative balance of only 50–100 mg of calcium per day (far less than the 300 mg of calcium in a single glass of milk) over a long period of time is sufficient to produce the disease.

For aging men, sex steroid deficiency also appears to be a major factor in age-related osteoporosis. Although testosterone is the major sex steroid in men, some of it is converted by the aromatase enzyme into estrogen. In men, however, the deficiency is mainly due to an increase in sex hormone binding globulin, a substance that holds both testosterone and estrogen in a form that is not available for use by the body. Between 30–50 percent of elderly men are deficient in biologically active sex steroids (Khosla et al. 1998). In fact, except for the lack of the early postmenopausal phase, the process of bone loss in older men is similar to that for older women. As with women, the loss of sex steroid activity in men has an effect on calcium absorption and conservation, leading to progressive secondary increases in parathyroid hormone levels. As in older women, the resulting imbalance between bone resorption and formation results in slow bone loss that continues over life. Since testosterone may stimulate bone formation more than estrogen does, however, decreased bone

Figure 3–2. Progressive Spinal Deformity in Osteoporosis



Note: Compression fractures of thoracic vertebrae lead to loss of height and progressive thoracic kyphosis (dowager's hump). Lower ribs eventually rest on ileac crests, and downward pressure on viscera causes abdominal distention.

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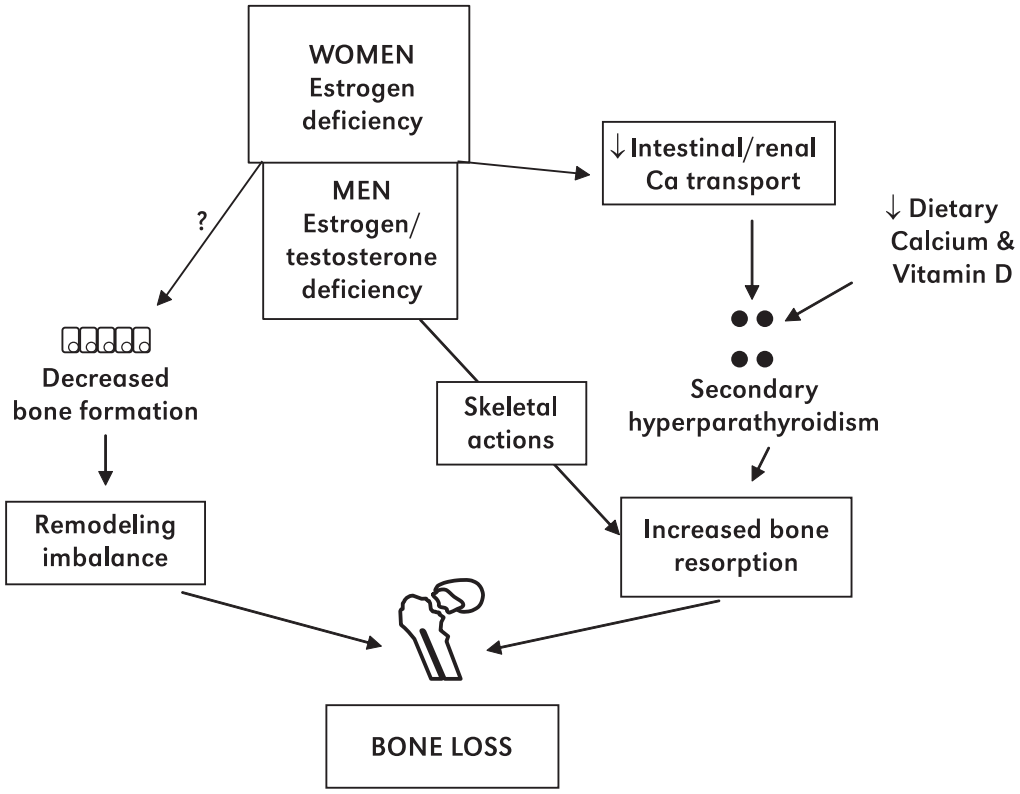
Figure 3–3. Schematic Representation of Model for Bone Loss in Postmenopausal Women and Aging Men



Source: Riggs et al. 1998.

formation plays a relatively greater role in the bone loss experienced by elderly men.

Secondary Osteoporosis

Young adults and even older individuals who get osteoporosis often do so as a byproduct of another condition or medication use. In fact, there are a wide variety of diseases (Table 3-1) along with certain medications and toxic agents (Table 3-2) that can cause or contribute to the development of osteoporosis (Stein and Shane 2003). Individuals who get the disease due to these "outside" causes are said to have "secondary" osteoporosis. They typically experience greater levels of bone loss than would be expected for a normal individual of the same age, gender, and race. Secondary causes of the disease are common in many premenopausal women and men with osteoporosis (Khosla et al. 1994); in fact, by some estimates the majority of men with osteoporosis exhibit secondary

Table 3–1. Diseases That Cause or Contribute to Secondary Osteoporosis

Genetic Disorders		
Cystic Fibrosis	Homocystinuria	Osteogenesis Imperfecta
Ehlers-Danlos	Hypophosphatasia	Porphyria
Glycogen Storage Diseases	Idiopathic Hypercalciuria	Riley-Day Syndrome
Gaucher's Disease	Marfan Syndrome	
Hemochromatosis	Menkes Steely Hair Syndrome	
Hypogonadal States		
Androgen Insensitivity	Hyperprolactinemia	Turner's and Klinefelter's
Anorexia Nervosa	Panhypopituitarism	Syndrome
Athletic Amenorrhea	Premature ovarian failure	
Endocrine Disorders		
Acromegaly	Cushing's Syndrome	Hyperparathyroidism
Adrenal Insufficiency	Diabetes Mellitus (Type I)	Thyrotoxicosis
Gastrointestinal Diseases		
Gastrectomy	Malabsorption	Primary Biliary Cirrhosis
Inflammatory Bowel Disease	Celiac Disease	
Hematologic Disorders		
Hemophilia	Multiple Myeloma	Systemic Mastocytosis
Leukemias and Lymphomas	Sickle Cell Disease	Thalassemia
Rheumatic and Auto-Immune Diseases		
Ankylosing Spondylitis	Lupus	Rheumatoid Arthritis
Miscellaneous		
Alcoholism	Emphysema	Multiple Sclerosis
Amyloidosis	End Stage Renal Disease	Muscular Dystrophy
Chronic Metabolic Acidosis	Epilepsy	Post-transplant Bone
Congestive Heart Failure	Idiopathic Scoliosis	Disease
Depression	Immobilization	Sarcoidosis

causes of the disease (Orwoll 1998). In addition, up to a third of postmenopausal women with osteoporosis also have other conditions that may contribute to their bone loss (Tannenbaum et al. 2002). This section briefly describes some of the more common diseases, disorders, and medications that can cause or contribute to the development of osteoporosis.

Diseases and Disorders That Can Cause Osteoporosis

Several genetic diseases have been linked to secondary osteoporosis. Idiopathic hypercalciuria and cystic fibrosis are the most common. Patients with cystic fibrosis have markedly decreased bone density and increased fracture rates (Ott and Aitken 1998) due to a variety of factors, including calcium and vitamin D malabsorption, reduced sex steroid production and delayed puberty, and increased inflammatory cytokines (see Chapter 2). Some patients with idiopathic hypercalciuria have a renal defect in the ability of the kidney to conserve calcium. This condition may be aggravated if they are advised to lower their dietary calcium intake to prevent kidney stones. Several studies have documented low bone density in these individuals, and they may respond to drugs that decrease calcium excretion in the urine. Other genetic disorders (listed in Table 3-1), although rare, should be considered in patients with osteoporosis after more common causes have been excluded.

Estrogen or testosterone deficiency during adolescence (due to Turner's, Kallman's, or Klinefelter's syndrome, anorexia nervosa, athletic amenorrhea, cancer, or any chronic illness that interferes with the onset of puberty) leads to low peak bone mass (Riggs et al. 2002). Estrogen deficiency that develops after peak bone mass is achieved but before normal menopause (due to premature ovarian failure for example) is associated with rapid bone loss. Low sex steroid levels may also be responsible for reduced bone density in patients with androgen insensitivity or acromegaly. By contrast, excess thyroid hormone (thyrotoxicosis), whether spontaneous or caused by overtreatment with thyroid hormone, may be associated with substantial bone loss (Ross 1994); while bone turnover is increased in these patients, bone resorption is increased more than bone formation. Likewise, excess production of glucocorticoids caused by tumors of the pituitary or adrenal glands (Cushing's syndrome) can lead to rapidly progressive and severe osteoporosis, as can treatment with glucocorticoids (see below). The relationship between diabetes and osteoporosis is more controversial (Stein and Shane 2003). For example, hip fractures are increased in some studies of diabetic patients, but not in others. In general, patients with type 1 (insulin-dependent) diabetes, particularly those with poor control of their blood sugar (Heap et al. 2004), are at greater risk of osteoporosis than are those with type 2 (non-insulin dependent) diabetes (Piepkorn et al. 1997).

Primary hyperparathyroidism is a relatively common condition in older individuals, especially postmenopausal women, that is caused by excessive secretion of parathyroid hormone. Most often, the cause is a benign tumor (adenoma) in one or more parathyroid glands; very rarely (less than 0.5 percent of the time) the cause is parathyroid cancer (Wynne et al. 1992). Since most patients now come to clinical attention when they are unexpectedly found on routine examination to have an abnormally high calcium level in the blood (Wermers et al. 1997), the clinical presentation has changed over the past 30 years from an uncommon but highly symptomatic disorder involving renal stones and bone disease (osteitis fibrosa cystica) to a

common but relatively asymptomatic condition (Silverberg and Bilezikian 2001). Typically, cortical bone (for example, in the distal forearm) is affected to a greater extent than trabecular bone (for example, in the spine) in primary hyperparathyroidism (Silverberg et al. 1989). It is presumed that the reduction in bone mass is associated with the increased risk of fracture seen in these patients (Khosla and Melton 2002).

Diseases that reduce intestinal absorption of calcium and phosphorus, or impair the availability of vitamin D, can also cause bone disease. Moderate malabsorption results in osteoporosis, but severe malabsorption may cause osteomalacia (see below). Celiac disease, due to inflammation of the small intestine by ingestion of gluten, is an important and commonly overlooked cause of secondary osteoporosis (Bianchi and Bianchi 2002). Likewise, osteoporosis and fractures have been found in patients following surgery to remove part of the stomach (gastrectomy), especially in women. Bone loss is seen after gastric bypass surgery even in morbidly obese women who do not have low bone mass initially (Coates et al. 2004). Increased osteoporosis and fractures are also seen in patients with Crohn's disease and ulcerative colitis (Bernstein et al. 2000). Glucocorticoids, commonly used to treat both disorders, probably contribute to the bone loss. Similarly, diseases that impair liver function (primary biliary cirrhosis, chronic active hepatitis, cirrhosis due to hepatitis B and C, and alcoholic cirrhosis) may result in disturbances in vitamin D metabolism and may also cause bone loss by other mechanisms. Primary biliary cirrhosis is associated with particularly severe osteoporosis. Fractures are more frequent in patients with alcoholic cirrhosis than any other types of liver disease, although this may be related to the increased risk of falling among heavy drinkers (Crawford et al. 2003). Human immunodeficiency virus (HIV) infected patients also have a higher prevalence of osteopenia or osteoporosis (Brown et al. 2004). This may involve multiple endocrine, nutritional, and metabolic factors and may also be affected by the antiviral therapy that HIV patients receive (Thomas and Doherty 2003).

Autoimmune and allergic disorders are associated with bone loss and increased fracture risk. This is due not only to the effect of immobilization and the damage to bone by the products of inflammation from the disorders themselves, but also from the glucocorticoids that are used to treat these conditions (Lien et al. 2003, Orstavik et al. 2004). Rheumatic diseases like lupus and rheumatoid arthritis have both been associated with lower bone mass and an increased risk of fractures. A study found that 12 percent of women with systemic lupus erythematosus reported at least one fracture since the onset of disease, a 4.7-fold higher risk of fracture than for the typical woman. Fractures in these women were found to be associated with the following: older age at diagnosis, longer disease duration, longer duration of steroid use, and post-menopausal status (Ramsey-Goldman et al. 1999, Haugeberg et al. 2003).

Many neurologic disorders are associated with impaired bone health and an increased risk of fracture (Whooley, Kip et al. 1999; Lloyd, Spector et al. 2000). This may be due in part to the effects of these disorders on mobility and balance or to the effects of drugs used in treating these disorders on bone and mineral metabolism. Unfortunately, however, health care providers often fail to assess the bone health of patients who have these disorders or to provide appropriate preventive and therapeutic measures. For example, patients with stroke, spinal cord injury, or neurologic disorders show rapid bone loss

in the affected areas (Dauty, Perrouin Verbe et al. 2000; Poole, Reeve et al. 2002; Tuzun, Altintas et al. 2003). There are many disabling conditions that can lead to bone loss, and thus it is important to pay attention to bone health in patients with developmental disabilities, such as cerebral palsy, as well as diseases affecting nerve and muscle, such as poliomyelitis and multiple sclerosis. Children and adolescents with these disorders are unlikely to achieve optimal peak bone mass, due both to an increase in bone resorption and a decrease in bone formation. In some cases very rapid bone loss can produce a large enough increase in blood calcium levels to produce symptoms (Carey and Raisz 1985; Go 2001). Fractures are common in these individuals not only because of bone loss, but also because of muscular weakness and neurologic impairment that increases the likelihood of falls. Bone loss can be slowed—but not completely prevented—by antiresorptive therapy (Sato, Asoh et al. 2000). Epilepsy is another neurologic disorder that increases the risk of bone disease, primarily because of the adverse effects of anti-epileptic drugs. Many of the drugs used in epilepsy can impair vitamin D metabolism, probably by acting on the liver enzyme which converts vitamin D to 25 hydroxy vitamin D (Farhat, Yamout et al. 2000, Sheth 2002). In addition, there may be a direct effect of these agents on bone cells. Due to the negative bone-health effects of drugs, most epilepsy patients are at risk of developing osteoporosis. In those who have low vitamin D intakes, intestinal malabsorption, or low sun exposure, the additional effect of anti-epileptic drugs can lead to osteomalacia. Supplemental vitamin D may be effective in slowing bone loss, although patients who develop osteoporosis may require additional therapy such as bisphosphonates.

Psychiatric disorders can also have a negative impact on bone health. While anorexia nervosa is the psychiatric disorder that is most regularly associated with osteoporosis, major depression, a much more common disorder, is also associated with low bone mass and an increased risk of fracture (Coelho, Silva et al. 1999; Cizza, Ravn et al. 2001; Robbins, Hirsch et al. 2001). Many studies show lower BMD in depressed patients (Michelson et al. 1996). In addition, one large study found an increased incidence of falls and fractures among depressed women, even though there was no difference between their BMD and that of non-depressed women included in the study (Whooley, Kip et al. 1999). Higher scores for depressive symptoms have also been reported in women with osteoporosis. Yet what these studies do not make clear is whether major depression causes low BMD and increased fracture risk, or whether the depression is a consequence of the diminished quality of life and disability that occurs in many osteoporotic patients. One factor that may cause bone loss in severely depressed individuals is increased production of cortisol, the adrenal stress hormone. Whatever the cause of low BMD and increased fracture risk, measurement of BMD is appropriate in both men and women with major depression. While the response of individuals with major depression to calcium, vitamin D, or antiresorptive therapy has not been specifically documented, it would seem reasonable to provide these preventive measures to patients at high risk.

Finally, several diseases that are associated with osteoporosis are not easily categorized. Aseptic necrosis (also called osteonecrosis or avascular necrosis) is a well-known skeletal disorder that may be a complication of injury, treatment with glucocorticoids, or alcohol abuse (Pavelka 2000). This condition commonly affects the ends of the femur and the humerus. The precise cause is unknown, but at least two theories

have been suggested. One is that blood supply to the bone is blocked by collapsing bone. The other is that microscopic fat particles block blood flow and result in bone cell death. Chronic obstructive pulmonary disease (emphysema and chronic bronchitis) is also now recognized as being associated with osteoporosis and fractures even in the absence of glucocorticoid therapy. Immobilization is clearly associated with rapid bone loss; patients with spinal cord lesions are at particularly high risk for fragility fractures (Kiratli 2001). However, even modest reductions in physical activity can lead to bone loss (see Chapter 6). Hematological disorders, particularly malignancies, are commonly associated with osteoporosis and fractures as well. These are discussed in more detail later in the chapter.

Medications and Therapies That Can Cause Osteoporosis

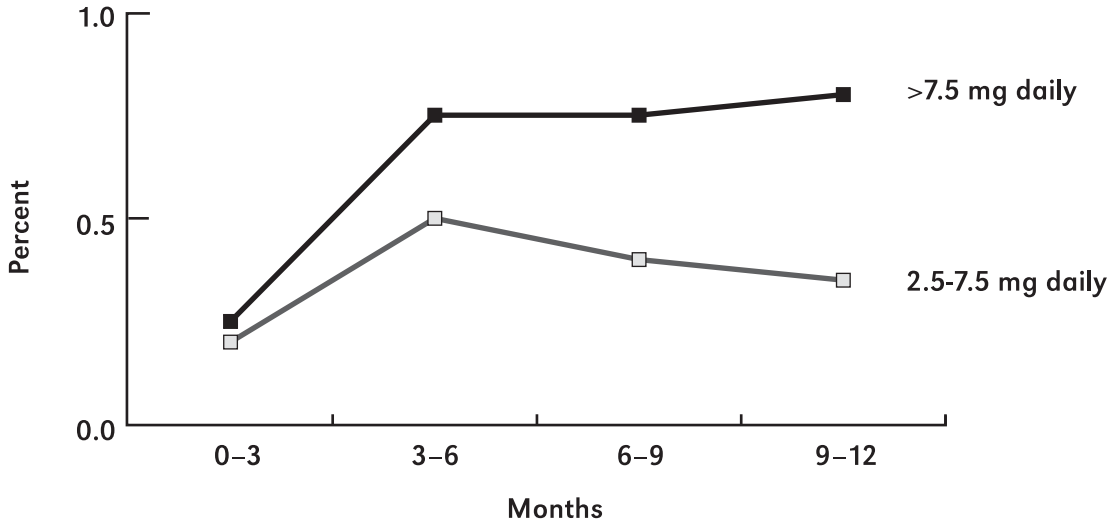
Osteoporosis can also be a side effect of particular medical therapies (Table 3-2).

Table 3–2. Medications Associated With Secondary Osteoporosis

Anticoagulants (heparin)
Anticonvulsants
Cyclosporine A and Tacrolimus
Cancer Chemotherapeutic Drugs
Glucocorticoids (and ACTH)
Gonadotropin-releasing Hormone Agonists
Lithium
Methotrexate
Parenteral Nutrition
Thyroxine

Glucocorticoid-Induced Osteoporosis (GIO). GIO is by far the most common form of osteoporosis produced by drug treatment. While it has been known for many years that excessive production of the adrenal hormone cortisol can cause thinning of the bone and fractures, this condition, a form of Cushing's syndrome, remains uncommon. With the increased use of prednisone and other drugs that act like cortisol for the treatment of many inflammatory and autoimmune diseases, this form of bone loss has become a major clinical concern. The concern is greatest for those diseases in which the inflammation itself and/or the immobilization caused by the illness also caused increased bone loss and fracture risk. Glucocorticoids, which are used to treat a wide variety of inflammatory conditions (e.g., rheumatoid arthritis, asthma, emphysema, chronic lung disease), can cause profound reductions in bone formation and may, to a lesser extent, increase bone resorption (Saag 2002), leading to loss of trabecular bone at the spine and hip, especially in postmenopausal women and older men. The most rapid bone loss occurs early in the course of treatment, and even small doses (equivalent to 2.5–7.5 mg prednisone per day) are associated with an increase in fractures (van Staa et al. 2002). As shown in Figure 3-4, the risk of fractures increases rapidly in patients treated with glucocortocoids, even before much bone has been lost. This rapid increase in fracture risk is attributed to damage to the bone cells, which results in less healthy bone tissue. To avoid this problem, health care providers are urged to use the lowest possible dose of glucocorticoids for as short a time as possible. For some diseases, providers should also consider giving glucocorticoids locally (e.g., asthma patients can inhale them), which results in much less damage to the bone.

Figure 3–4. Rapid Increase in Vertebral Fracture Rates in Patients Treated With Glucocorticoids



Note: Before glucocorticoid treatment was started, the rate of fractures was less than 0.2% per year. On the higher doses (more than 7.5 mg of prednisone or equivalent per day) the rate increased at least four fold by 6 months, and there was a significant increase even on doses of 2.5 to 5 mg/day. Non-vertebral fractures also showed an increase which began in the first 3 months of treatment.

Source: van Staa et al. 2002.

Other Medications That Can Cause Osteoporosis. Cyclosporine A and tacrolimus are widely used in conjunction with glucocorticoids to prevent rejection after organ transplantation, and high doses of these drugs are associated with a particularly severe form of osteoporosis (Cohen and Shane 2003). Bone disease has also been reported with several frequently prescribed anticonvulsants, including diphenylhydantoin, phenobarbital, sodium valproate, and carbamazepine (Stein and Shane 2003). Patients who are most at risk of developing this type of bone disease include those on long-term therapy, high medication doses, multiple anticonvulsants, and/or simultaneous therapy with medications that raise liver enzyme levels. Low vitamin D intake, restricted sun exposure, and the presence of other chronic illnesses increase the risk, particularly among elderly and institutionalized individuals. In contrast, high intakes of vitamin A (retinal) may increase fracture risk (Michaelsson et al 2003). Methotrexate, a folate antagonist used to treat malignancies and (in lower doses) inflammatory diseases such as

rheumatoid arthritis, may also cause bone loss, although research findings are not consistent. In addition, gonadotropin-releasing hormone (GnRH) agonists, which are used to treat endometriosis in women and prostate cancer in men, reduce both estrogen and testosterone levels, which may cause significant bone loss and fragility fractures (Smith 2003).

Rickets and Osteomalacia

Rickets (which affects children) and osteomalacia (which affects adults) are relatively uncommon diseases in the United States, since they can generally be prevented by ensuring adequate levels of vitamin D. These diseases can have devastating consequences to those who get them (Chesney 2001, Pettifor 2002 and 2003).

A number of childhood diseases cause rickets, a condition that results from a delay in depositing calcium phosphate mineral in growing bones, thus leading to skeletal deformities, especially bowed legs. In adults, the equivalent disease is called osteomalacia. Since longitudinal growth has stopped in adults, deficient bone mineralization does not cause skeletal deformity but can lead to fractures, particularly of weight-bearing bones such as the pelvis, hip, and feet. Even when there is no fracture, many patients with rickets and osteomalacia suffer from bone pain and can experience severe muscle weakness.

Rickets and osteomalacia are typically caused by any of a variety of environmental abnormalities. While rare, the disorder can also be inherited (Drezner 2003) as a result of mutations in the gene producing the enzyme that converts 25-hydroxy vitamin D to the active form, 1,25-dihydroxy vitamin D, or in the gene responsible for the vitamin D receptor. Osteomalacia can also be caused by disorders that cause marked loss of phosphorus from the body. This can concur as a congenital disorder or can be acquired in patients who have tumors that produce a protein that affects phosphorus transport in the kidney.

Since vitamin D is formed in the skin by sunlight, the most common cause is reduced sun exposure. This is particularly important in northern latitudes where the winter sun does not have the power to form vitamin D in the skin. Thus the disease is often seen in individuals living at northern latitudes, particularly immigrants who have pigmented skin that decreases the formation of vitamin D or who habitually cover themselves. This problem can also occur in children who are confined indoors and in individuals who are house-bound (e.g., due to chronic ill health or frailty). Patients with diseases of the gastrointestinal tract, such as gastrectomy, malabsorption syndromes, and small bowel resection, are also at higher risk, since these conditions reduce vitamin D absorption from the diet.

There is also a second form of rickets and osteomalacia that is caused by phosphate deficiency. This condition can be inherited (this is known as X-linked hypophosphatemic rickets), but it is more commonly the result of other factors. Individuals with diseases affecting the kidney's ability to retain phosphate rapidly are at risk of this condition, as are those with diseases of the renal tubule that affect the site of phosphate reabsorption. While most foods are rich in phosphate, phosphate deficiency may also result from consumption of very large amounts of antacids containing aluminum hydroxide, which prevents the absorption of dietary phosphate. Finally, rickets due to phosphate deficiency may occur in individuals with acquired or inherited defects in acid secretion by the kidney tubule and those who take certain

drugs (Table 3-3) that interfere with phosphate absorption or the bone mineralization process.

There are also patients who develop tumors that secrete a factor that causes loss of phosphate from the body. This condition is called tumor-induced or oncogenic osteomalacia.

Table 3–3. Causes of Drug-Induced Rickets/ Osteomalacia

Drugs resulting in hypocalcemia
Inhibitors of vitamin D formation or intestinal absorption
Sunscreens Cholestyramine
Increased catabolism of vitamin D or its metabolites
Anticonvulsants
Drugs resulting in hypophosphatemia
Inhibitors of intestinal phosphate absorption • Aluminum-containing antacids Impaired renal phosphate reabsorption • Cadmium • Ifosfamide • Saccharated ferric oxide
Direct impairment of mineralization
Parenteral aluminum Fluoride Etidronate

Source: Pettifor 2003. Reproduced from J Bone Miner Res 1998: May; 13(5): 763-73 with permission of the American Society for Bone and Mineral Research.

Renal Osteodystrophy

Patients with chronic renal disease are not only at risk of developing rickets and osteomalacia (Elder 2002), but they are also at risk of a complex bone disease known as renal osteodystrophy (Cunningham et al. 2004). This condition is characterized by a stimulation of bone metabolism caused by an increase in parathyroid hormone and by a delay in bone mineralization that is caused by decreased kidney production of 1,25-dihydroxyvitamin D. In addition, some patients show a failure of bone formation, called adynamic bone disease. As a result of this complexity, bone biopsies are often needed to make a correct diagnosis (Martin et al. 2004). By the time the patient progresses to end-stage renal failure, clinical manifestations of the disease appear, including bone cysts that result from stimulation of osteoclasts by the excess parathyroid hormone. While dialysis can significantly extend the life-expectancy of patients with chronic renal failure, it does nothing to prevent further progression of the osteodystrophy. In fact, the managing of the patient through dialysis may lead to further bone abnormalities that become superimposed on the underlying osteodystrophy, thus increasing the risk of fractures (Alem et al. 2000). While a renal transplant (offered to a growing number of patients on dialysis) may reverse many features of renal osteodystrophy, the use of antirejection medication in transplant patients may cause bone loss and fractures.

Paget's Disease of Bone

Paget's disease of bone (Siris and Roodman 2003) is a progressive, often crippling disorder of bone remodeling (see Chapter 2) that commonly involves the spine, pelvis, legs, or skull (although any bone can be affected). If diagnosed early, its impact can be minimized.

Individuals with this condition experience an increase in bone loss at the affected site due to excess numbers of overactive osteoclasts. While bone formation increases to compensate for the loss, the rapid production of new bone leads to a disorganized structure. The resulting bone is expanded in size and associated with increased formation of blood vessels and connective tissue in the bone marrow. Such bone becomes more susceptible to deformity or fracture (Figure 3-5). Depending on the location, the condition may produce no clinical signs or symptoms, or it may be associated with bone pain, deformity, fracture, or osteoarthritis of the joints adjacent to the abnormal bone. Paget's disease of bone can also cause a variety of neurological complications as a result of compression of nerve tissue by pagetic bone. In very rare cases (probably less than 1 percent of the time) the disease is complicated by the development of an osteosarcoma.

Although Paget's disease is the second most common bone disease after osteoporosis (see Chapter 4), many questions remain regarding its pathogenesis. There is a strong familial predisposition for Paget's disease, but no single genetic abnormality has been identified that can explain all cases. Paget's disease can be transmitted (or inherited) across generations in an affected family; 15–40 percent of patients have a relative with the disorder (Morales-Piga et al. 1995). Studies in the United States (Siris et al. 1991) suggest that a close relative of a pagetic patient is seven times more likely to develop Paget's disease than is someone who does not have an affected relative. However, environmental factors are likely play a role in the majority of cases. For example, some studies have suggested that Paget's disease may result from a "slow virus" infection with measles (Friedrichs et al. 2002).

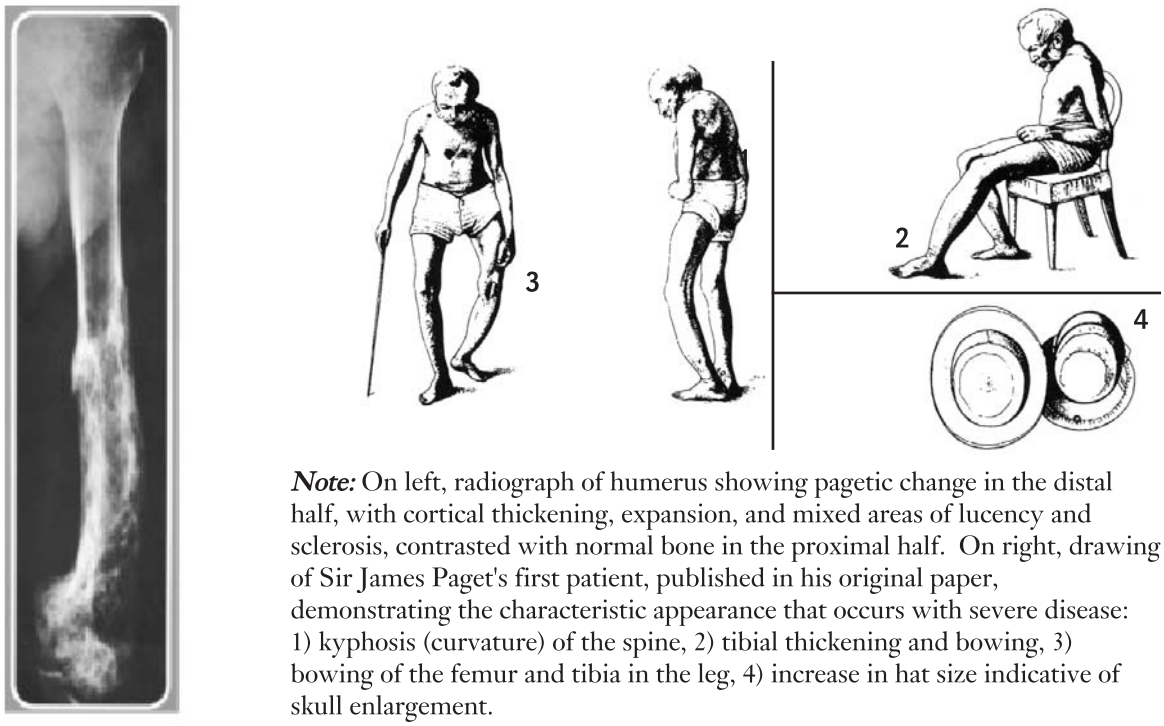
Paget's Disease of Bone

Paget's disease may present in many different ways since it can affect bones throughout the body. A typical case might be a man in his 60s who complains to his doctor of pain in the hip. The doctor might tell him he has arthritis and suggest that he take ibuprofen or acetaminophen (Tylenol). Then, several years later, a routine screening may show a high alkaline phosphatase level. This test would then prompt use of a bone scan and radiographs, which would finally show Paget's disease of his femur and pelvic bone. Unfortunately, by this time the man likely has developed some bowing of the leg and suffered damage to the joints, neither of which can be reversed by treatment. However, treatment with a bisphosphonate can stop the progression of the disease. As a result, the man lives the rest of his life with some pain and he walks with a limp. Not surprisingly, the man, his family, and his doctor all wish that the diagnosis had been made earlier. Since Paget's disease runs in families, they decide to test the man's relatives. These tests show that the man's younger brother has a similar problem. He is treated immediately and no deformities ever develop.

Developmental Skeletal Disorders

A large number of genetic and developmental disorders affect the skeleton. Among the more common and more important of these is a group of inherited disorders referred to as osteogenesis imperfecta or OI (Whyte 2003, Rauch and Glorieux 2004). Patients with this condition have bones that break easily (therefore, the condition is also known as brittle bone disease). There are

Figure 3–5. Paget's Disease of Bone



Note: On left, radiograph of humerus showing pagetic change in the distal half, with cortical thickening, expansion, and mixed areas of lucency and sclerosis, contrasted with normal bone in the proximal half. On right, drawing of Sir James Paget's first patient, published in his original paper, demonstrating the characteristic appearance that occurs with severe disease: 1) kyphosis (curvature) of the spine, 2) tibial thickening and bowing, 3) bowing of the femur and tibia in the leg, 4) increase in hat size indicative of skull enlargement.

Sources: Favus 2003, Reproduced from Primer on the metabolic bone diseases and disorders of mineral metabolism, 5th ed., Washington, D.C.: 2003, with permission of the American Society for Bone and Mineral Research. Paget 1877.

a number of forms of OI (see Table 3-4) that result from different types of genetic defects or mutations. These defects interfere with the body's production of type I collagen, the underlying protein structure of bone. As illustrated in Table 3-4, most, but not all, forms of OI are inherited. The disease manifests through a variety of clinical signs and symptoms, ranging from severe manifestations that are incompatible with life (that is, causing a stillbirth) to a relatively asymptomatic disease. However, most OI patients have low bone mass (osteopenia) and as a result suffer from recurrent fractures and resulting skeletal deformities. There are four main types of OI, which vary according to the severity and duration of the symptoms. The most common form (Type I) is also the mildest version; and patients may have relatively few fractures. The second mildest form of the disease (which is called Type IV, because it was the fourth type of OI to be discovered) results in mild to moderate bone deformity, and sometimes in dental problems and hearing loss. These patients also sometimes have a blue,

purple, or gray discoloration in the whites of their eyes, a condition known as blue sclera. A more severe form of the disease (Type III) results in relatively frequent fractures, and often in short stature, hearing loss, and dental problems. Finally, patients with the most severe form of the disease (Type II) typically suffer numerous fractures and severe bone deformity, generally leading to early death.

OI is not the only group of developmental skeletal disorders. An even larger group of rare diseases (sclerosing bone disorders) causes an increase in bone mass (Whyte 2003). One of these, osteopetrosis (marble bone disease), is more or less the opposite of osteoporosis. Instead of overactive osteoclasts, osteopetrosis results from a variety of genetic defects that impair the ability of osteoclasts to resorb bone. This interferes with the normal development of the skeleton and leads to excessive bone accumulation. Although such bone is very dense, it is also brittle and thus fractures often result. In addition, by compressing various nerves, the excess bone in patients with osteopetrosis may cause neurological symptoms, such as deafness or blindness. These patients may also suffer anemia, as blood-forming cells in the bone marrow are "crowded out" by the excess bone. Similar symptoms can result from overactivity of these bone cells, as in fibrous dysplasia where bone-forming cells produce too much connective tissue.

Malignancy and the Skeleton

Some other skeletal disorders are not inherited but rather develop only later in life. One of the most common of these acquired skeletal disorders is a tumor of the bone. Bone tumors can originate in the bone (these are known as primary tumors) or, much more commonly, result from the seeding of bone by tumors outside of the skeleton (these are known as metastatic tu-

Osteogenesis Imperfecta (OI)

There is an enormous range of severity in OI cases, from children who are stillborn due to multiple fractures in the womb and the inability to breathe, to children who suffer a few fractures, to mild cases where fractures do not occur until later in life, much like in patients with osteoporosis.

One scenario that causes tremendous hardship for the patient and the family is the occurrence of multiple fractures in the first few years of life in a child without the telltale sign of OI—a blue color in the "whites" of their eyes. Often the parents of these children are accused of child abuse. While it may be possible to make a diagnosis by analyzing the child's tissues, this expensive, difficult-to-perform test is not widely available. Typically, the frequency of fractures decreases over time and may even stop entirely at puberty. As an adult, an OI patient may be left with considerable deformity and short stature, but he or she can generally function well with the right environment and support. When females with OI reach menopause they sometimes start to fracture again. Since treatment is now available, it is important to identify OI patients at all stages of life, and to alert family members of the possibility that they may also be affected. Pediatricians, orthopedists, emergency room physicians, and others who see children with fractures need to consider OI as a possible cause, particularly in cases involving multiple fractures or a family history of fractures. These points are covered in detail in a recent book (Chiasson et al. 2004).

Table 3–4. Clinical Heterogeneity and Biochemical Defects in Osteogenesis Imperfecta (OI)

OI type	Clinical features	Inheritance	Biochemical defects
I	Normal stature, little or no deformity, blue sclerae, hearing loss in about 50% of individuals. Dentinogenesis imperfecta is rare and may distinguish a subset	AD	Decreased production of type I procollagen. Substitution for residue other than glycine in triple-helix of α_1(I)
II	Lethal in the perinatal period, minimal calvarial mineralization, beaded ribs, compressed femurs, marked long bone deformity, platyspondyly	AD (new mutation) AR (rare)	Rearrangements in the COLA1 and COLA2 genes. Substitutions for glycyl residues in the triple-helical domain of the α_1(I) α_2(I) chain. Small deletion in α_2(I) on the background of a null allele
III	Progressively deforming bones, usually with moderate deformity at birth. Sclerae variable in hue, often lighten with age. Dentinogenesis imperfecta is common, hearing loss is common. Stature very short	AD AR	Point mutations in the α_1(I) or α_2(I) chain Frameshift mutation that prevents incorporation of pro α_2(I) into molecules (noncollagenous defects)
IV	Normal sclerae, mild to moderate bone deformity, and variable short stature. Dentinogenesis imperfecta is common, and hearing loss occurs in some	AD	Point mutations in the α_1(I) chain. Rarely point mutations in the α_1(I) chain. Small deletions in the α_1(I) chain

AD, autosomal dominant; AR, autosomal recessive.

Source: Byers 2001.

mors, since they have spread from elsewhere). Both types of tumors can destroy bone, although some metastatic tumors can actually increase bone formation. Primary bone tumors can be either benign (noncancerous) or malignant (cancerous). The most common benign bone tumor is osteochondroma, while the most common malignant ones are osteosarcoma and Ewing's sarcoma. Metastatic tumors are often the result of breast or prostate cancer that has spread to the bone (Coleman 2001). These may destroy bone (osteolytic lesion) or cause new bone formation (osteoblastic lesion). Breast cancer metastases are usually osteolytic, while most prostate cancer metastases are osteoblastic, though they still destroy bone structure (Berruti et al. 2001). Many tumor cells produce parathyroid hormone related peptide, which increases bone resorption (Bryden et al. 2002). This process of tumor-induced bone resorption leads to the release of growth factors stored in bone, which in turn increases tumor growth still further.

Bone destruction also occurs in the vast majority (over 80 percent) of patients with another type of cancer, multiple myeloma, which is a malignancy of the plasma cells that produce antibodies (Berenson 2002). The myeloma cells secrete cytokines (see Chapter 2), substances that may stimulate osteoclasts and inhibit osteoblasts (Roodman 2001, Tian et al. 2003). The bone destruction can cause severe bone pain, pathologic fractures, spinal cord compression, and life-threatening increases in blood calcium levels (Callander and Roodman 2001). A benign form of overproduction of antibodies, called monoclonal gammopathy, may also be associated with increased fracture risk (Melton et al. 2004).

Bone-resorbing cytokines are also produced in acute and chronic leukemia, Burkitt's lymphoma, and non-Hodgkins's lymphoma; patients with these chronic lymphoproliferative disorders often have associated osteoporosis. Both osteoporosis and osteosclerosis (thickening of trabecular bone) have been reported in association with systemic mastocytosis, a condition of abnormal mast cell proliferation (Schneider and Shane 2001). In addition, there are other infiltrative processes that affect bone, including infections and marrow fibrosis (myelofibrosis).

Oral Health and Bone Disease

Oral bone, like the rest of the skeleton, comprises both trabecular and cortical bone and undergoes formation and resorption throughout the life span. When oral bone loss exceeds gain, it can cause a loss of tooth-anchoring support or it can diminish the remaining ridge in those areas where partial or complete tooth loss has occurred.

The prevalence of oral bone loss is significant among adult populations worldwide, and it increases with age for both sexes. Oral bone loss and attendant tooth loss are associated with estrogen deficiency and osteoporosis. As a consequence, osteoporosis or osteopenia in postmenopausal women may have an impact on the need for, and the outcomes from, a variety of periodontal and prosthetic procedures, including guided tissue regeneration and tooth implantation. Furthermore, it is possible that oral examination and radiographic findings may be useful signs of extra-oral bone loss (Jeffcoat et al. 2000, Geurs et al. 2000).

Key Questions for Future Research

The major diseases of bone have been broadly characterized, but many questions remain unanswered, as outlined below:

- Within the spectrum of clinical disorders that represent "primary osteoporosis," are there differences in the mechanisms that lead to bone loss and bone fragility? What implications do these differences have for diagnosis and treatment?
- How do the environmental and genetic determinants of bone mass and strength interact in individuals with certain diseases? For example, are there genetic differences in the response to estrogen or calcium deficiency that affect their relative importance in the pathogenesis of osteoporosis?
- Are the animal studies on the role of cytokines relevant to human disease?
- What are the implications of research on the pathogenetic mechanisms for diseases other than osteoporosis? For example, further research on Paget's disease could uncover more about the ways in which excessive osteoclastic bone resorption can occur.
- What is the role of phosphate in bone mineralization?
- How is bone affected in patients who have cancer? What implications do these changes have with respect to both the spread of the cancer and to other skeletal disorders?

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