Chapter 9: Key Messages

- There have been important advances in the ability to prevent and treat fractures in the last 10 years, especially in those with skeletal fragility. Just as with the use of diagnostic measures, there has been a failure in the United States to apply appropriate preventive and treatment measures to many persons at risk for bone disease.
- Everyone should be informed of the basic elements of maintaining bone health and preventing bone disease. Paying attention to the basics—appropriate physical activity, nutrition, and smoking—is critical for everyone, especially those who have, or who are at risk of developing, osteoporosis.
- Any individual who is diagnosed with osteoporosis should be evaluated for potential secondary causes of the disease, including the presence of other disorders or the use of medications that can cause harm to bone. If secondary causes are present, actions should be taken to minimize their impact.
- For the most common bone diseases, drugs that prevent bone breakdown (antiresorptives) have been shown to be effective in reducing the risk of future fractures. These drugs not only slow any further deterioration of the skeleton, but also allow for some repair and restoration of bone mass and strength.
- When antiresorptive therapy is not enough, anabolic therapy is available to help build new bone and further reduce the risk of fracture. While this approach has been developed for the prevention and treatment of osteoporotic fractures, it can also be applied to other bone diseases.
- For individuals who remain at high risk of fracture, an extensive fall prevention program should be developed. This program should aim to minimize the risk of falls in the home and community; avoid the use of drugs that increase the risk of bone disease or falls; and protect those who do fall through the use of hip protectors.
- Specific, effective treatments exist for a number of bone diseases other than osteoporosis, including hyperparathyroidism, rickets, and osteomalacia. Treatment is also available for some congenital bone disorders and for bone disease associated with kidney failure. For all of these conditions, early detection and treatment are critical to avoiding crippling deformities and fractures.

Chapter 9

PREVENTION AND TREATMENT FOR THOSE WHO HAVE BONE DISEASES

Just as there have been great advances in the ability to identify individuals at risk of fracture (see Chapter 8), there have been equally important advances in the ability to prevent and treat fractures in these individuals, especially those with skeletal fragility. In particular the introduction of bisphosphonates and selective estrogen receptor modulators (SERMs) has given health care providers new approaches to therapy.

Just as for the use of diagnostic measures, numerous studies indicate that there has been a failure in the United States to apply preventive and treatment measures to many persons at risk for bone disease. As a result, most high-risk individuals (e.g., those who have suffered a fragility fracture) do not get the testing and treatment that they need. Use of bone mineral density (BMD) testing in this population ranges from 3–23 percent, while use of calcium and vitamin D supplementation ranges from 11–44 percent, and use of antiresorptive therapy ranges from 12–16 percent (Morris et al. 2004, Smith 2001 et al.). In fact, most physicians fail to discuss osteoporosis with their patients, even after a fracture (Pal 1999). In a large study of older adults, four out of five hip or wrist fracture patients did not receive any treatment after the fracture. The same study also found that certain groups of patients, including men, older persons, non-Whites, and those with comorbid conditions, were less likely than White women to receive treatments (Solomon et al. 2003). Even when physicians do suggest therapy, it often does not conform with recommended practice, as many patients with low BMD are not treated while others with high BMD are (Solomon et al. 2000). In other words, the gap between clinical knowledge and its application in the community remains large.

It is also important to recognize that the ideal drugs for the treatment of osteoporosis or other bone disorders have yet to be developed. Inexpensive, effective agents with few side effects are needed so that they can be used broadly to prevent fractures and deformities in the enormous number of individuals who will be at risk of bone disease as the population ages. (See Chapter 4 for more details on the large at-risk population.)

This chapter reviews the latest evidence on the prevention and treatment of fractures in individuals with or at high risk for bone disease. As the box below indicates, the use of the terms "prevention" and "treatment" can be confusing, since the goal of many treatments is the prevention of disease or fractures. At the same time, prevention is often considered a treatment for those with or at risk for bone disease. Nonetheless, it is important to recognize the critical role of prevention in all individuals, including (and perhaps especially) in those known to have bone disease and/or to be at high risk of fracture.

Treatment as Prevention, and Prevention as Treatment

The concept of prevention within the area of bone health is complex, and often encompasses measures that may be more commonly considered as treatments. In fact, in the field of bone health, the terms treatment and prevention are often used in an interchangeable manner, since the major goal of treatment is the prevention of fractures.

Within both bone health and general health care, prevention can be thought of as taking anticipatory actions designed to reduce the possibility that an event or condition will occur that could lead an individual to a state of dependency. Within this broad definition are three different types of preventive activities.

- *Primary* prevention refers to actions that prevent a disease or injury (e.g., osteoporosis) that could lead to a state of impairment.
- *Secondary* prevention refers to activities that block the progression of an existing impairment (e.g., bone disease) to a disability (e.g., fracture); interventions within this area are often also considered to be treatments.
- *Tertiary* prevention refers to actions that block or slow the progression of a disability (e.g., fracture) to a state of dependency. In some cases these actions may also be considered treatments.

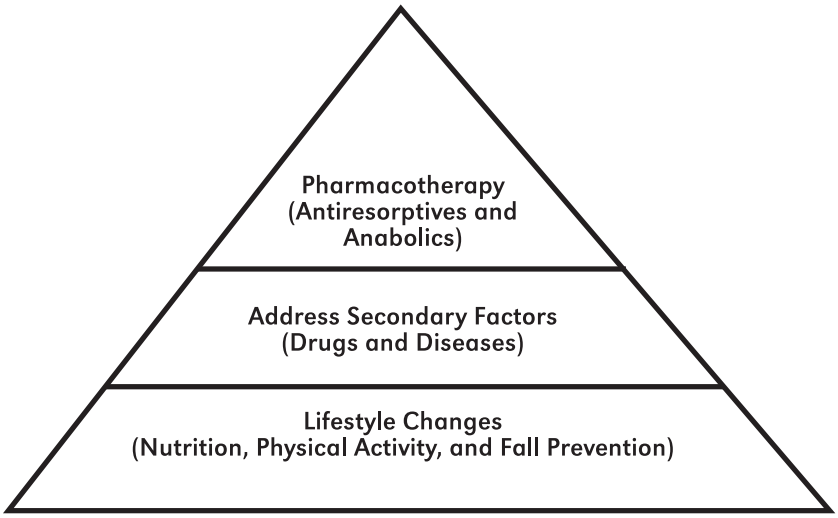
Preventive measures within the area of bone health span all three types. For example, certain measures to achieve optimal bone mass can be considered primary prevention, including encouraging adequate intake of calcium and vitamin D, appropriate physical activity, and other bone-healthy lifestyle behaviors. Other measures that are commonly considered treatments for osteoporosis, such as using antiresorptive and anabolic agents, should also be thought of as secondary prevention, since they are designed to retard the progression of the disease to prevent disability. Fall prevention in this population may also be seen as secondary prevention, since its purpose is to prevent disability in an individual who already has bone disease.

Appropriate and comprehensive treatment of a fracture is considered tertiary prevention, because such treatment attempts to prevent a person with a disability from becoming dependent. Drugs prescribed to individuals who have already sustained a fracture are also a part of this tertiary prevention effort. From a public health perspective, physical therapy and other forms of rehabilitation are considered methods of tertiary prevention in this population.

This paradigm also fits the management of other bone diseases. For example, early treatment of Paget's disease can prevent fractures and hence can be considered as either secondary or tertiary prevention, depending on the status of the patient when the treatment is given. The bottom line is that a spectrum of preventive activities exists within the area of bone disease, and treatment is a part of that spectrum. Assuring bone health requires that preventive measures be implemented in all its aspects: to optimize peak bone mass;, to block excessive resorption; to increase bone formation; to decrease skeletal fragility; to decrease the severity and frequency of falls; and to accelerate recovery from fracture. In fact, this entire spectrum of prevention is central to promoting bone health in all populations.

Treatment of Osteoporosis = Prevention of Fractures

Figure 9–1. The Osteoporosis Pyramid for Prevention and Treatment



Note:
The Base of the Pyramid: The first step in the prevention and treatment of osteoporosis and the prevention of fractures is to build a foundation of nutrition and lifestyle measures that maximize bone health. The diet should not only be adequate in calcium and vitamin D, but should have a healthy balance of other nutrients. A weight-bearing exercise program should be developed. Cigarette smoking and excessive alcohol use must be avoided. In the older individual, at high risk for fractures, the changes in lifestyle would include a plan not only to maximize physical activity, but also to minimize the risk of falls. The use of hip protectors can be considered in some high-risk patients. Diseases that increase the risk of falls by causing visual impairment, postural hypotension (a drop in blood pressure on standing, which leads to dizziness), or poor balance should be treated. Drugs that cause bone loss or increase the risk of falls should be avoided or given at the lowest effective dose.

The Second Level of the Pyramid: The next step is to identify and treat diseases that produce secondary osteoporosis or aggravate primary osteoporosis. These measures are the foundation upon which specific pharmacotherapy is built and should never be forgotten.

The Third Level of the Pyramid: If there is sufficiently high risk of fracture to warrant pharmacotherapy, the patient is usually started on antiresorptives. Anabolic agents are used in individuals in whom antiresorptive therapy is not adequate to prevent bone loss or fractures. Chapter 9 summarizes the indications for antiresorptive and anabolic therapy.

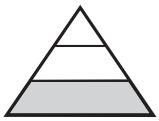
A Pyramid Approach

One of the primary goals in the treatment of osteoporosis and other bone diseases is to maintain bone health by preventing bone loss and perhaps even by building new bone. Another goal is to minimize the risk and/or impact of falls, since they are typically the precursor to the most devastating consequence of bone disease: fractures. The best way to realize these goals is to employ a combination of various prevention and treatment strategies. In fact, maintaining bone health and preventing fractures and deformities requires a "pyramid" approach (Figure 9-1).

The building blocks of physical activity and good nutrition (particularly with respect to adequate intake of calcium and vitamin D) represent

measures are not enough there are now additional treatments that can be given to build new bone (anabolics) and further reduce fracture risk. While this approach has been developed for the prevention and treatment of osteoporotic fractures, it can also be applied to other bone diseases.

For those individuals who remain at high risk of fracture even after treatment (e.g., the frail elderly), the base of the pyramid should include an extensive program to minimize the risk of falls in the home and community, to avoid the use of drugs that increase the risk, and to provide hip protectors that reduce the risk of fracture in those who do fall.



The Base of the Pyramid: Maintaining Bone Health and Preventing Fractures

Prevention is, by far, the most effective way to promote bone health, and thus represents the base of the pyramid (Figure 9-1a). Everyone should be informed of the basic elements of maintaining bone health. Everyone should strive for adequate levels of calcium and vitamin D intake. Everyone should engage in regular weight-bearing exercise and avoid behaviors that impair bone health such as smoking. Everyone should understand the basics about how to avoid falling. These elements serve as the foundation of prevention of bone disease and fractures. They may be all that are required in individuals at low risk of bone disease, but they are critically important for high-risk patients as well.

The remainder of this section provides a very brief overview of the key elements of prevention that every individual and provider should know. Much more detail about each of these areas is provided in Chapters 6 and 7.

Calcium: For postmenopausal women, the recommended total daily calcium intake is 1,200 mg per day in two or more doses. These levels of intake can be achieved through dietary sources of calcium, including both dairy and non-dairy products. A detailed list of these foods and beverages appears in Chapter 7, while another list ranked by calcium content can be found in Chapter 10. In addition, calcium supplements (e.g., calcium carbonate, calcium citrate, other calcium salts) are available in the form of pills, chewable tablets, and liquids, as discussed in Chapter 7. The total daily calcium intake should not exceed 2,500 mg (IOM 1997).

Vitamin D. Vitamin D is important for absorption of calcium and mineralization (hardening) of bone. As discussed in Chapter 6, vitamin D is synthesized in the skin through sunlight exposure, or it may be taken as a supplement. However, the skin of older individuals does not synthesize vitamin D as well as the skin of younger individuals, and in some parts of the country, the winter sun does not produce vitamin D in the skin of all individuals. In addition, vitamin D is not available in many foods other than fortified milk, which contains 100 IU (international units) per cup. Thus, many individuals will need to take a supplement, especially those who avoid sun exposure, use sun block, or do not drink milk. The recommended dose of vitamin D is 200 to 600 IU daily, with the dose dependent on age, as shown in Table 7-1 (IOM 1997). However, many experts are recommending more vitamin D for the frail elderly (Heaney and Weaver 2003). The total daily vitamin D intake of persons who are not vitamin D deficient should not exceed 2,000 IU (IOM 1997). Many calcium supplements contain vitamin D. Most multivitamins contain 400 IU of vitamin D. Vitamin D supplements can be taken on their own, or with calcium or food.

Patients who are vitamin D insufficient (low levels of vitamin D in the blood) or deficient

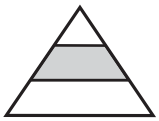
(very low levels of vitamin D in the blood) require treatment with higher doses of vitamin D. Vitamin D deficiency can lead to secondary hyperparathyroidism (see below) with normal levels of blood calcium. Severe cases lead to osteomalacia or rickets (see Chapter 3). It should be noted that the optimal range for 25-hydroxyvitamin D is higher than the "normal" ranges reported from clinical laboratories, since these ranges are obtained from a population that includes individuals with sub-optimal levels. Patients can be treated with vitamin D supplementation of 50,000 IU once a week for up to 3 months with follow-up blood tests of vitamin D, calcium, and PTH levels. Some patients may require longer courses of treatment (Pettifor 2003).

Physical Activity. Weight-bearing, strength, and balance-training exercises are also an important part of any osteoporosis prevention and treatment program, regardless of age. They can help increase or preserve bone mass and may also help reduce the risk of falling. As discussed in Chapter 6, all types of physical activity can contribute to bone health. Activities that are weight bearing or involve impact are most useful for increasing or maintaining bone mass. Activities that are not weight bearing or are low impact may help improve balance and coordination and maintain muscle mass, which can help prevent falls. To encourage increased levels of physical activity among all age groups, "Physical Activity and Health: A Surgeon General's Report" recommends a "minimum of 30 minutes of physical activity of moderate intensity (such as brisk walking) on most, if not all, days of the week" (USDHHS 1996). Since the skeleton responds preferentially to strength training and short bouts of high-load impact activity (such as skipping or jumping), the same report recommends that adults supplement their cardiorespiratory endurance activity with strength-developing exercise at least two times per week. Chapter 7 addresses specific ways to incorporate strength and loading activities into an overall habit of physical activity.

For those who cannot engage in regular physical activity due to disability, mechanical stimulation of the skeleton might prove beneficial. Recent, small studies found that use of vibrating platforms increased BMD and slowed bone loss (Rubin 2004 et al., Verschueren et al. 2004, Ward et al. 2004). This may provide another way to reduce fracture risk both in the elderly and in younger individuals with disabling conditions that limit their ability to exercise. However, the long-term safety and efficacy of such approaches remain to be determined, and therefore specific rehabilitation and exercise programs aimed at increasing activity and function remain critically important in the frail elderly and in younger individuals with neuromuscular disabilities.

Fall Prevention. Falls represent perhaps the biggest threat to the bone health and the functional independence of older individuals. Falls are common and frequently are the precipitating event that leads to a fracture or fractures in an individual. Thus, fall prevention offers another important opportunity to protect the bones throughout life, but particularly in those over age 60. Falls occur for a variety of reasons, with multiple factors often contributing to a single fall. These factors include problems with balance, mobility, vision, lower extremity weakness, and/or blood pressure or circulation. Often these problems are compounded by an acute illness (e.g., infection, fever, dehydration, arrhythmia), a new medication, or an environmental stress (e.g., standing or walking on an unsafe surface, poor lighting) that leads to the fall. To reduce the risk of falls, a variety of fall prevention mea-

sures should be encouraged for frail, elderly individuals. These include regular vision checks; elimination (where possible) of medications and/or dosages that may cause dizziness, low blood pressure, or confusion; and addressing environmental problems or obstacles that can lead to falls, including removing throw rugs, installing night lights, installing railings on stairs and grab bars in showers, encouraging use of rubber-soled shoes and slippers, and attaching phone cords and other wires to the baseboard of the wall. Hip protectors or hip pads might also be useful in reducing the impact of those falls that do occur. More information on fall prevention strategies can be found in Chapter 7.



The Second Level of the Pyramid: Assessing and Treating Secondary Causes

The first level of the pyramid applies to all individuals whether or not they have low bone mass or multiple risk factors for osteoporotic fractures. The second level (Figure 9-1b), which is important for patients at high risk for fractures, involves determining whether there are secondary causes or aggravating factors for the osteoporosis and addressing them therapeutically if they exist.

The vast majority of older postmenopausal women with osteoporosis will have the primary form of the disease, with secondary factors likely playing only a limited role. However, there can be considerable therapeutic benefit from uncovering such factors and dealing with them appropriately if they exist. In men and younger women with osteoporosis, secondary factors often play a major role, and the diagnosis and treatment of these factors may be the most important part of managing their bone disease. For a complete list of secondary factors that can cause or contribute to osteoporosis, see Chapter 3.

One important reason for dealing with secondary factors is that the therapeutic response to specific treatment can be substantial. For example, large increases in BMD have been observed after treatment of hyperparathyroidism (Silverberg 1995) and epidemiologic studies have shown that fracture rates decrease substantially when glucocorticoid therapy is discontinued (van Staa 2000).

A careful history can suggest possible secondary factors and guide the health care provider in carrying out appropriate tests. At a minimum, serum calcium concentration should be measured. In populations and geographic areas where vitamin D deficiency is common, measurement of 25-hydroxy vitamin D is another useful screening test. Measurement of calcium and creatinine in fasting, second-voided morning urines or 24-hour urines may be useful in detecting high or low calcium excretion. High calcium excretion may be associated with bone loss while low calcium excretion may be associated with malabsorption and vitamin D deficiency. Patients with gluten-sensitive enteropathy or sprue may present with osteoporosis yet have few gastrointestinal symptoms. Weight loss is often a key sign of this disorder or of other underlying diseases such as malignancy. Many physicians recommend screening for thyroid disease, which is relatively inexpensive. Because screening for Cushing's syndrome can be difficult and costly, it should be reserved for patients in whom the history and physical examination strongly suggest the possibility of this disorder.

Treatment of most secondary causes of bone loss and fractures is generally well established and is described later in this chapter. In patients with severe osteoporosis the treatment of secondary factors should be carried out together with pharmacotherapy for the bone itself, as this approach helps to improve bone strength and

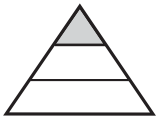
Study Design Issues Related to Treatment

Many studies have focused on the effectiveness and safety of treatments for bone disease, and consequently many issues must be considered in examining and comparing the results of these studies. First, therapeutic effectiveness is best examined with interventions that have been assessed in randomized (i.e., treatment is randomly given to patients), double-blinded (i.e., patients and physicians are not told what treatment the patients are on), placebo-controlled (i.e., some participants take an inactive pill to control for expectations) trials. Second, a study duration of at least 3 years is preferable in order to see meaningful results. In recent years, the FDA has required organizations that apply for FDA approval for drugs to treat osteoporosis to conduct randomized, double-blind, placebo-controlled trials of at least 3 years' duration to test the drug's effectiveness with respect to fracture reduction. Studies of fracture reduction can focus on clinical fractures (fractures that are painful), spine fractures assessed by standard x-rays (two-thirds of these fractures are *not* painful), non-spine fractures, and hip fractures. Although the most important study outcome is fracture risk reduction, changes in BMD or markers of bone turnover (see Chapter 8) can be used as supportive evidence of the effectiveness of treatment. Another study outcome relates to how quickly the medication will work in improving BMD or reducing risk of fractures. In addition, it is important to consider the duration of therapies (to help in determining the recommended length of treatment) and to know what happens when therapies are discontinued.

Despite the multitude of good studies, it is not possible to compare the effectiveness of different therapies by comparing the results from separate investigations. This is because the inclusion and exclusion factors for patient enrollment in the various studies are different; the duration, intensity of daily physical activity, outcome measures, and statistical analyses vary; and the amount or type of calcium/vitamin D supplements varies. Therapies can only be compared if they have been given to patients in the same trial. For this reason, the differences in effects on fracture reduction and BMD that are reported for medications from different studies may not represent true differences in the efficacy of the drug being used, but rather differences in the populations being tested. Because comparative studies require unrealistically high numbers of patients, it is unlikely they will be funded.

A meta-analysis is a summary of multiple studies evaluating the same type of treatment. Because it incorporates many studies, such analysis often provides the best available evidence on the effectiveness of a given treatment. Several meta-analyses have been conducted that help to better understand the value of treatments, including for calcium and vitamin D. The results of these studies are reported in Chapter 6.

minimize fracture risk as quickly as possible. BMD measurements, which are ordinarily done every 2 yearss during the treatment of primary osteoporosis, may be done more frequently for some individuals with secondary osteoporosis, including those with glucocorticoid-induced osteoporosis, which can cause relatively rapid changes in BMD.



The Third Level of the Pyramid: Treatment

Treatment represents the third level of the pyramid (Figure 9-1c). This section reviews treatment options for bone disease, with an emphasis on osteoporosis, the disease for which the most treatment options exist.

Drug Therapy for Osteoporosis

There are two primary types of drug therapy for osteoporosis. The first is use of antiresorptive agents, which are drugs that *reduce* bone loss, while the second involves use of anabolic agents, which are drugs that *build* bone. Antiresorptive therapies include use of bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), and calcitonin. Antiresorptive therapies reduce bone loss, stabilize the microarchitecture of the bone, and decrease bone turnover—all leading to fracture reduction. They increase BMD because the resorption spaces in bone get refilled with new bone and the amount of mineral in the bone increases. Antiresorptive therapies act by decreasing the activity of the osteoclasts, the cells responsible for bone resorption (breakdown). Antiresorptive therapy should be considered for all patients with the diagnosis of osteoporosis as well as for some other bone disorders. This therapy is effective in reducing the risk of future fractures, although, as discussed below, different forms of antiresorptive therapy vary in their safety and efficacy. At present, the Food and Drug Administration has approved two bisphosphonates, alendronate and risedronate, for prevention or treatment of osteoporosis for either daily or weekly oral administration. Another bisphosphonate, ibandronate, is being considered and additional agents (see below) are under investigation, including intravenous forms. Only one SERM, raloxifene, is FDA-approved. Many estrogen preparations are approved for prevention of bone loss. Nasal and injectable calcitonin are also approved for treatment of osteoporosis.

Anabolic therapy is now available for those individuals who continue to fracture or lose bone on an adequate program of general prevention and antiresorptive therapy. The only FDA-approved anabolic agent is a synthetic form of parathyroid hormone known as teriparatide. Teriparatide, which is given as a daily subcutaneous injection, costs substantially more than does antiresorptive therapy.

In some situations individuals with osteoporosis have been treated with a combination of two antiresorptive agents or with an antiresorptive and an anabolic agent. Sometimes the two agents are given simultaneously while other times they are given sequentially. The effectiveness of these types of combination therapies is currently being studied.

The remainder of this section reviews the evidence to date on the effectiveness of the different types of antiresorptive and anabolic agents that are available and of therapies that combine two antiresorptive agents or an antiresorptive agent with an anabolic agent.

Antiresorptive Therapy

Bisphosphonates. Bisphosphonates are phosphate-based, non-hormone compounds that have been shown to increase BMD and decrease fractures (Fleisch 2001). At present, there are two bisphosphonates that are FDA-approved and readily available for osteoporosis prevention and treatment: alendronate (Fosamax®) and risedronate (Actonel®). These medications bind to the bone surface and then are taken up by osteoclasts (cells that break down bone) as these cells attempt to resorb that bone. They block the pathway that leads to production of certain

essential lipid compounds inside the osteoclast, thus leading to earlier cell death and therefore a diminished ability for osteoclasts to cause bone loss.

The effectiveness of this approach has been well documented. For example, alendronate has been shown to increase BMD by 6–8 percent at the spine and by 3–6 percent at the hip over a three-year period in postmenopausal women with osteoporosis (Black et al. 1996, Liberman et al. 1995). These seemingly modest increases in BMD are associated with significant reductions in fracture risk—roughly 50 percent, in fact, for spine, hip, and wrist fractures (Black et al. 1996, Cranney et al. 2002a). These agents show benefits quickly, as evidence of a reduced risk of fracture can be seen as early as a year for spinal fractures and in 18 months for hip fractures (Black et al. 2000). In addition, approximately 95 percent of postmenopausal women who take alendronate maintained or increase their bone mass (Black et al. 2000, Liberman et al. 1995).

Alendronate has been shown to prevent bone loss in a diverse array of patients, includ ing younger postmenopausal women without osteoporosis and elderly, frail residents of long-term care facilities (Fleisch 2001). The drug has been studied in clinical trials and appears to be safe and effective for up to 10 years (Bone et al. 2004). Furthermore, the benefits of alendronate appear to continue after the therapy is stopped; for example, when older postmenopausal women discontinue therapy after several years of treatment, BMD appears to be maintained for 2 yearss (Tonino et al. 2000). Alendronate also appears to work for men, and it is therefore approved for the treatment of male osteoporosis. In one study, BMD of the spine increased approximately 5 percent at the end of 2 years in men with osteoporosis (Orwoll et al. 2000). In another 3-year study of men with primary osteoporosis, alendronate was compared to alfacalcidol, an active vitamin D analog, and found to reduce vertebral fractures by 57 percent and increase spine BMD by 11.5 percent, as compared to the alfacalcidol-treated group (Ringe et al. 2004). Alendronate and calcitriol were found to slow the rapid bone loss that occurs after heart transplantation, but calcitriol was found to cause an excessive increase in urine calcium excretion in many patients (Shane et al. 2004). Finally, alendronate is approved for the prevention of steroid-induced osteoporosis (Saag et al. 1998) and for the treatment of Paget's disease (Lyles et al. 2001) and has also been shown to be helpful for patients with osteoporosis imperfecta and bone loss due to hyperparathyroidism (Chow et al. 2003) (see below and Chapter 3).

Alendronate is currently approved for all women for *prevention* of postmenopausal osteoporosis at a dose of 5 mg daily or 35 mg if taken once a week. It is approved for the *treatment* of postmenopausal osteoporosis at a dose as compared to the alfacalcidol-treated group (Ringe et al. 2004). Alendronate and calcitriol were found to slow the rapid bone loss that occurs after heart transplantation, but calcitriol wasof 10 mg daily or 70 mg if taken once a week. Alendronate is well-tolerated (Liberman et al. 1995, Black et al. 1996, Cranney et al. 2002a); the most common side effects include pain in osteoporosis, alendronate was compared to alfacalcidol, an active vitamin D analog, and found to reduce vertebral fractures by 57 percent and increase spine BMD by 11.5 percent, the stomach or esophagus and swallowing difficulties. Esophageal ulcers have occurred in some patients on these types of daily bisphosphonates. Alendronate should not be used in patients with abnormalities of the esophagus that delay esophageal emptying, such as stricture (narrowing) or achalasia (muscle spasm).

Like alendronate, risedronate has also been shown to increase BMD and reduce fracture risk significantly. Studies have found that risedronate increases spine BMD by approximately 5 percent and hip BMD by 2–3 percent over 3 years in postmenopausal women with osteoporosis (Harris et al. 1999). Treatment with risedronate is associated with a 41 percent reduction in spine fractures (Harris et al. 1999), a 39 percent reduction in non-spine fractures (Harris et al. 1999), and a 30 percent reduction in hip fractures (McClung et al. 2001). Like alendronate, the benefits of risedronate can be seen relatively quickly. For example, reductions in spine fractures can occur after 1 year of therapy (Harris et al. 1999). Studies have examined the safety and effectiveness of risedronate for up to 5 years and have shown persistent reduction in fractures without adverse effects (Sorensen et al. 2003). Risedronate also has been shown to prevent bone loss at the hip and spine in postmenopausal women with low bone mass who do not have osteoporosis but have low bone mass (as indicated by BMD). Risedronate is approved for both the prevention *and* treatment of steroid-induced osteoporosis in men and pre- and postmenopausal women (Reid et al. 2000), and for the treatment of Paget's disease (Lyles et al. 2001) (see below and Chapter 3). Risedronate is approved at a dose of 5 mg per day or 35 mg once per week. The most common side effects include pain in the stomach or esophagus and difficulties in swallowing.

Ibandronate is another bisphosphonate that is currently FDA-approved for the treatment and prevention of osteoporosis in postmenopausal women at a dose of 2.5 mg daily; however, it is not readily commercially available. Over a 3-year period, ibandronate has been shown to decrease the incidence of new spine fractures by 52 percent and to increase BMD at the spine by 5 percent (Delmas et al. 2002), with no abnormalities found on bone histology (Recker et al. 2004). Ibandronate has also been shown to prevent bone loss in early postmenopausal women who are not yet osteoporotic (McClung et al. 2004).

Etidronate is a bisphosphonate that is not FDA-approved for the prevention and treatment of osteoporosis in the United States, although it is approved in Canada and other countries. It is approved in the United States for the treatment of Paget's disease (see below). Several small studies in postmenopausal women with osteoporosis have shown that etidronate increases BMD by 4–5 percent at the spine over 2–3 years and decreases spine fractures by approximately 50 percent (Watts et al. 1990, Hanley et al. 2000). It also has been shown to prevent bone loss in patients who start or are on chronic steroid therapy. In contrast to the other bisphosphonates that are taken daily, etidronate is taken on an intermittent schedule of 400 mg per day for 2 weeks every 3 months which is repeated for 2 years or more. A generally well-tolerated drug (Hanley et al. 2000), etidronate acts differently than do other bisphosphonates. When it is removed from the bone surface by osteoclasts, it forms toxic products inside the cell, thus resulting in early death of osteoclasts. However, it is not as potent as the newer bisphosphonates and can also impair the laying down of mineral during new bone formation if given in high doses.

All bisphosphonates are poorly absorbed and therefore should be taken alone first thing in the morning on an empty stomach with a full glass of water. Food should not be eaten for at least 30 minutes after taking the drug. Patients should not lie down during this period, to

prevent irritation of the esophagus. Physicians should proceed cautiously when prescribing amino-bisphosphonates (alendronate or risedronate) to patients with a known history of narrowing or ulcers of the esophagus or long-term problems with stomach ulcers and heartburn that require medication. Bisphosphonates are incorporated into bone and, therefore, may continue to provide benefits for a long period of time after treatment is discontinued (unlike hormone therapy, as discussed earlier). Bisphosphonates should not be given to pregnant women or patients with poor kidney function, since good kidney function is required to clear this drug from the blood. Little information is available on the use of bisphosphonates in children. Bisphosphonates that need only be administered once a year on an intravenous basis are currently under investigation (see Future Agents). This approach would circumvent the problems of poor absorption and gastrointestinal irritation and might also improve compliance.

Hormone Therapy. As noted in earlier chapters, estrogen is a hormone that is important throughout life to bone development and maintenance in both men and women. Unlike the bisphosphonate drugs discussed earlier in this chapter, estrogen acts on many reproductive and non-reproductive tissues in the body. Therefore, the use of exogenous forms of estrogen as a drug for the prevention or treatment of osteoporosis necessarily involves consideration of how the form and dose of estrogen might affect other tissues. Of particular importance is whether there are any risks that might limit its use.

- *Background on Hormone Therapy.* Fuller Albright, a clinical researcher in the 1930s, observed that most of his patients with osteoporosis were postmenopausal women. Given this, Albright proposed that estrogen triggers a buildup of calcium reserves in bone during adolescence to provide for later reproductive needs (pregnancy and lactation), and that bone is lost after menopause when estrogen levels decrease (Riggs et al. 2002). Many subsequent observations have confirmed the theory that "replacing" estrogen in postmenopausal women prevents bone loss, and thus this approach naturally seemed to be an effective way to stave off the effects of menopause on bone.

The FDA approved estrogen in 1942 in the form of conjugated equine estrogens (CEE), derived from the urine of pregnant horses, for the relief of menopausal symptoms. The use of hormone therapy by postmenopausal women increased dramatically during the 1960s, and, in 1972, the FDA approval was extended to postmenopausal osteoporosis. This latter approval was based on evidence from trials that evaluated the impact of estrogen therapy on bone mass, not on fracture reduction. However, by the early 1970s it also became clear that estrogen alone (without progestin) was associated with an increased risk of endometrial (uterine) cancer. Since this time only women who have had their uterus removed by hysterectomy are prescribed estrogen alone; others receive estrogen combined with some form of progesterone, another hormone, to protect the uterus.

- *The Evidence on Estrogen and Combination Hormone Therapy.* Randomized, placebo-controlled studies have been conducted on the impact of hormone therapy on BMD, including the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (Writing Group 1996) and the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study (Lindsay et al. 2002). These trials and a recent meta-analysis

(Wells et al. 2002) show that postmenopausal hormone therapy has a consistent and favorable effect on BMD at all sites, including increases at the spine (3.5–7 percent), hip (2–4 percent), and forearm (3–4.5 percent). These studies also suggest that increases in BMD become apparent within the first year of hormone therapy. Both the PEPI trial and the meta-analysis, which included different forms of estrogen (CEE as well as estradiol, the natural form of estrogen in humans) and combination therapy, found no significant differences in the effects of different formulations of estrogen on bone density.

Research evaluating the impact of hormone therapy on fracture rates, however, is more limited. Studies comparing women who had taken postmenopausal hormones over a long period of time with women who had never taken hormones indicate that there are fewer fractures in the hormone users (Kiel et al. 1987, Cauley et al. 1995). These types of "observational" studies, which observe what people decide to do or take on their own, are subject to biases. For example, women who take hormones are also more likely to take other measures to enhance their health. In fact, up until the mid-1990s, there had been very few randomized clinical trials of estrogen focusing on fracture as an outcome, and these trials tended to be quite small.

Nevertheless, Torgerson and Bell-Syer attempted to fill this evidence gap by systematically reviewing those randomized trials of estrogen therapy that did include fractures as an outcome to be evaluated. Their meta-analyses suggest that estrogen reduces the risk of non-spine fractures by 27 percent (Torgerson and Bell-Syer 2001a) and spine fractures by 33 percent (Torgerson and Bell-Syer 2001b).

The WHI Hormone Trials, which were designed and initiated in the early 1990s to address the primary question of whether postmenopausal HT decreased the risk of heart disease, have provided answers on a range of chronic disease outcomes in older women, including fractures. Two separate trials were conducted. One enrolled women with an intact uterus and evaluated the effects of an estrogen-progestin combination or E+P (0.625 mg conjugated equine estrogen, CEE, and 2.5 mg medroxyprogesterone, MPA, daily) (Rossouw et al., 2002), while the second evaluated the effect of estrogen (0.625mg CEE) alone in women who have had hysterectomies (Anderson et al. 2004). The WHI trial of combined continuous hormone therapy confirmed for the first time the effects of these hormones on osteoporotic fracture reduction at several sites, including the hip (Cauley et al., 2003). Hip and spine fractures were reduced by at least one-third in both of the trials and total fractures fell by 24–30 percent. Thus, these two large trials, which included 16,608 women in the E+P study and 10,739 women in the estrogen-only study, confirmed the anti-fracture efficacy of postmenopausal HT, and they are consistent with observational studies of hormone users and the results of trials evaluating the effect of HT on BMD.

The clear benefits of postmenopausal HT to the skeleton must be tempered by the other results from the WHI trials, which were discontinued early because of the deleterious effects encountered. Both trials found an increased risk of stroke, cognitive impairment, and deep vein thrombosis in the women taking HT (Rossouw et al. 2002, Anderson et al. 2004, Shumaker et al. 2003; Shumaker et al. 2004). The trials also found no clear cardiovascular benefit to HT. Breast cancer risk was increased in women taking the combined continuous therapy (E+P) during the 5.2 years of the study, a

finding that is consistent with observational studies (Collaborative Group 1997, Lagro-Janssen 2003). This increase in breast cancer was not observed in the estrogen-only trial after 6.6 years of use. Extended follow-up of all WHI hormone trial participants is planned, and may provide further insight into this discrepancy.

- *The Future for Hormone Therapy and Bone Health.* Any decision to use hormone therapy must take into consideration its impact on the overall risk of negative health outcomes, including not only its potential to reduce the risk of fractures, but also its potential to increase the risk of other health problems. The Food and Drug Administration (FDA 2003) has advised that postmenopausal women who use or are considering using estrogen or estrogen with progestin discuss the therapy's benefits and risks with their physicians. These products are approved therapies for relief from moderate to severe hot flashes and symptoms of vulvar and vaginal atrophy. Although HT is effective for the prevention of postmenopausal osteoporosis, it should only be considered for women at significant risk of osteoporosis who cannot take non-estrogen medications. The FDA recommends that estrogens and progestins should be used at the lowest possible doses for the shortest amount of time needed to achieve treatment goals. It is not yet clear whether following this advice will lead to long term benefits for bone health. Lower doses of estrogen or combination hormones can help to preserve bone density in the short term in postmenopausal women. For example, the Women's HOPE study, a randomized, placebo-controlled study that investigated the efficacy of various lower doses of CEE and CEE/MPA found that doses as low as 0.3 mg per day of CEE or the combination significantly increased spine and hip BMD from baseline within 2 years of therapy (Lindsay et al. 2002). Prestwood et al. (2003) showed that low dose estradiol also preserves bone. Unfortunately, at this point, the long-term effects of different doses, formulations (including estrogens or progesterone), and modes of administration (e.g., transdermal administration) on bone and other tissues have simply not been studied.

These results raise the question as to whether there might be some benefit to using hormone therapy for a short period of time and then terminating its use (so as to reduce the likelihood of negative health outcomes). Two randomized clinical trials shed some light on this issue, as they followed women who stopped hormone use at the end of a clinical trial. These studies indicate that bone loss begins again when hormones are withdrawn (Greendale et al. 2002, Greenspan et al. 2002b). Moreover, the long-term observational studies (Kiel et al. 1987, Cauley et al. 1995) suggest that even long-term hormone therapy users (including those on therapy for more than 10 years) who terminate therapy do not enjoy a lower risk of hip fractures many years later. In fact, a recent study (Yates et al. 2004) found that there was a higher rate of hip fracture in those who discontinued hormone therapy than in those who never used it. Another study, a large prospective trial of 5,200 fractures among 140,000 postmenopausal women in the United Kingdom, found that while there was a decrease in fracture risk at all sites in patients currently on estrogen, there was no decrease in risk in past users of hormone therapy, even those who had discontinued use within the past year (Banks et al. 2004). Thus, the bottom line is that taking hormone therapy during early menopause is unlikely to have a long-term effect on the risk of fractures.

Despite all the negatives that have been raised recently about HT, it is important to remember that natural estrogen (i.e., that which is produced by the body) is still critical to bone health, even for postmenopausal women (and older men). The evidence suggests that postmenopausal women with extremely low endogenous estrogen levels face an increased risk of both spine and hip fractures when compared with postmenopausal women with average levels of estrogen (Cummings et al. 1998). Very low doses of hormone therapy for these individuals may be a promising treatment (Prestwood et al. 2003).

The goal of this type of an approach is to capture the positive effects of estrogen on bone without incurring any of the deleterious effects on other tissues. In fact, this is the principle that has driven research into the selective estrogen receptor modulators or SERMS that are discussed in the next section; these agents selectively act on the estrogen receptors in bone, breast, and other tissues.

> *"In the final analysis very little is known about anything, and much that seems true today turns out to be only partly true tomorrow."*
>
> —Fuller Albright, reflecting on the state of affairs of medicine in general and of endocrinology in particular in 1948 (Albright and Reifenstein 1948).

Selective Estrogen Receptor Modulators. Selective estrogen receptor modulators (SERMs) interact with estrogen receptors located throughout the body (McDonnell 2003). Estrogen receptors are the "switches" that turn cell activity on and off (see Chapter 2 for more details). SERMs bind to the estrogen receptors, altering the way they interact with other proteins and DNA. Different SERM medications may have different actions on cholesterol, breast and uterine tissue, clotting, BMD, and hot flashes. They have been shown to provide some of the benefits of estrogen (improvement of BMD and cholesterol) without some of the negative side effects (such as breast tenderness and menstrual bleeding or spotting) (Ettinger et al. 1999). In fact, in large-scale clinical trials of postmenopausal women with osteoporosis, raloxifene (Evista®), the only FDA-approved SERM, has been shown to increase spine BMD by 2–3 percent and hip BMD by approximately 2.5 percent after 3 years (Ettinger et al. 1999). Spine fractures were reduced by approximately 50 percent, but there was no effect on hip or other non-spine fractures (Ettinger et al. 1999, Cranney et al. 2002b). Spine fracture reduction is evident at 1 year (Maricic et al. 2002) and is sustained for up to at least 4 years if patients remain on therapy (Delmas et al. 2002). When therapy is discontinued, bone turnover (breakdown) can return to its previous state, resulting in bone loss. Other potential benefits include a decrease in total cholesterol and low density cholesterol; there is no change in high density cholesterol. Although studies have not been specifically designed to examine prevention of breast cancer with raloxifene, investigators from the study mentioned above found that there was a decreased incidence of breast cancer in the women who took raloxifene for 3 years (Cummings et al. 1999). There are now studies ongoing to examine raloxifene's effect on breast cancer and cardiovascular disease prevention.

Raloxifene is FDA-approved for the prevention *and* treatment of postmenopausal osteoporosis at a dose of 60 mg daily. There are some side effects, including the potential for a return of hot flashes, blood clots in the legs, or blood clots in the lungs. Therapy with SERMs

must be discontinued for patients who are immobilized or inactive for long periods of time (e.g., during hospitalizations).

Another SERM, tamoxifen, is used for the prevention of breast cancer, but it is not approved for the prevention and treatment of osteoporosis. Small clinical trials in premenopausal and postmenopausal women participating in a breast cancer prevention study demonstrated that tamoxifen maintains or improves BMD in postmenopausal women but causes bone loss in premenopausal women (Powles et al. 1996). Information on fracture reduction from clinical trials is not available.

Newer SERMs under development may be more beneficial to the bones, heart, and breast tissue. They may also decrease hot flashes and improve cholesterol. There are no data to suggest that SERMs would be beneficial in the treatment of male osteoporosis, Paget's disease, or childhood osteoporosis.

Calcitonin. Calcitonin is a hormone secreted by the parafollicular (non-thyroid) cells found within the thyroid gland (Silverman 2003). Its effect on bone is to inhibit bone resorption by acting directly on the osteoclasts. Its ability to inhibit osteoclast activity has been known for more than four decades. At one time in the 1970s, calcitonin was the only drug available to treat hypercalcemia of malignancy and Paget's disease of the bone. Calcitonin was also one of the first drugs available for the treatment of osteoporosis.

In the 1970s and 1980s, calcitonin was administered as a subcutaneous (under the skin) injection. More recently, nasal calcitonin replaced the injection form of this hormone. Although originally very popular as an alternative for postmenopausal women who could not tolerate bisphosphonates, estrogen, or raloxifene, its use has declined with the advent of newer treatments for postmenopausal osteoporosis. Oral and inhaled forms of calcitonin are currently under development.

There are only a few randomized controlled trials for nasal calcitonin. The Prevent Recurrence of Osteoporotic Fractures (PROOF) trial, the largest RPCT of nasal calcitonin, reported that spine fractures declined by 33 percent for those individuals taking a 200 IU dose per day, but there was no significant decline for those receiving 100 or 400 IU per day. Furthermore, there were no significant differences in non-spine fracture rates after 5 years (Chesnut et al. 2000).

The PROOF trial has come under scrutiny for a number of reasons, including the somewhat surprising finding that those individuals taking a higher dose did not see a reduction in fractures. In addition, a large number of the subjects did not complete the study. Hence flaws in the study methods used do not allow a firm conclusion about calcitonin's impact on spine and non-spine spine fractures (Chesnut et al. 2000). Calcitonin may have a somewhat unique benefit in providing pain relief, particularly for women who have just sustained a spine fracture (Mehta et al. 2003). Studies looking at this potential benefit also do not provide a clear-cut answer. Nasal calcitonin has very few side effects, namely, nasal stuffiness, nausea, and dry mouth. It is currently approved at 200 IU per daily spray for the treatment (not prevention) of osteoporosis in women who underwent menopause five or more years ago.

Combination Antiresorptive Therapy. Although bisphosphonates, hormone therapy, and SERMs are all antiresorptive drugs, they work through different mechanisms of action, implying that they could have an additive effect if used in combination (i.e., using both would be more beneficial than would either used alone).

Therefore, antiresorptive drugs have been studied in combination. One study compared 2-year use of two antiresorptive therapies together to similar use of estrogen and alendronate alone in postmenopausal women with a hysterectomy (Bone et al. 2000). BMD increased approximately 8 percent at the spine in those on combination therapy, compared to 6 percent in women taking alendronate or estrogen. Similar trends were noted in BMD at the hip, where combination therapy resulted in a 1–2 percent greater increase in BMD than either therapy alone. Importantly, participants in the combination therapy group did not have additional unexpected side effects. A recent 3-year study in women age 65 and older found that using hormone therapy and alendronate together resulted in greater increases in bone mass at the spine and hip than did therapy with either agent alone (Greenspan et al. 2003).

Hormone therapy has also been used in combination with risedronate in a short-term study. At the end of a year, the hip BMD (but not the spine BMD) of participants on combination therapy was greater than that of participants receiving hormone therapy or risedronate alone (Harris et al. 2001). In another 1-year study, hip BMD was greater in participants taking a combination therapy of alendronate and raloxifene than in those taking either agent alone (Johnell et al. 2002). The study also found that BMD of the spine and hip in participants taking alendronate alone was significantly higher than in participants taking raloxifene alone; however, the study was not large enough to determine whether there was any difference in fracture reduction.

Studies have also examined another important issue—whether combination therapy is better than single-agent therapy at maintaining BMD after discontinuation of the treatment. Investigators who examined BMD in women on combination therapy (alendronate and estrogen replacement) and single therapy (alendronate or hormone therapy) followed them for an additional year after therapy was discontinued. Those who had taken combination therapy or alendronate alone during the first 2 years maintained BMD of the spine and hip following discontinuation of therapy. However, women who gained bone during 2 years on hormone replacement lost their BMD gains at the spine and hip during the year after therapy was discontinued (Greenspan et al. 2002).

Combination therapies (multiple drugs) are more expensive and, in principle, could cause more side effects than therapy with single drugs. Moreover, because these trials did not examine fracture reduction, it is unclear if combination therapy is a cost-effective strategy for reducing risk of fracture. Therefore, in clinical practice today, combination therapy is generally reserved for patients who have experienced a fracture while on therapy with a single drug, those who start out with a very low BMD and a history of multiple fractures, and those with very low BMD who lose more bone mass on therapy with a single drug. The combination of anabolic and antiresorptive agents is discussed below.

Anabolic Therapy. Over the last half century, antiresorptive therapy has been the primary treatment for osteoporosis. Recent research has discovered the potential of intermittent parathyroid hormone (PTH) as a therapeutic option for patients with severe osteoporosis. Unlike other available agents, bone-building therapy with PTH features stimulation of new bone formation (Rosen and Rackoff 2001). Eighteen months of PTH therapy causes thickening of the outer shell of bones, large increases in connections between bony islands within the skeleton, and an overall net increase in bone strength.

Every normal person has PTH. It is typically secreted at a low level, but secretion increases in response to reduced levels of serum calcium, a process that appears to contribute to bone breakdown. In fact, primary hyperparathyroidism, that is, uncontrolled overactivity of the parathyroid glands, has been known to contribute to bone loss, particularly of the cortical (outer shell) of bone (see Chapter 3). Intermittent injections of PTH as a therapy actually hold promise as a means of building up bone. Animal studies have demonstrated that PTH given intermittently as a daily subcutaneous injection leads to significant increases in BMD, restoration of the inner structure of bone, and increases in bone size (Lotinun et al. 2002). This paradox—the fact that PTH secreted continuously can break down bone while intermittent injections of the same hormone may actually build bone—has never been fully explained. It may be related to the intermittent nature of the exposure to the hormone that occurs during treatment, as opposed to the exposure to continuous, excessive levels of PTH that occur in individuals with hyperparathyroidism.

Human recombinant PTH (1-34), known as teriparatide, was developed in the 1980s, with the hope that it could promote bone building in humans. Clinical trials designed to test the impact on fracture rates in humans, which were originally designed to last 3 years, were stopped early because of animal data showing osteosarcoma (bone tumor) formation. Despite early discontinuation the studies demonstrated significant increases in BMD and reduction in fractures. For example, in a study with over 1,600 postmenopausal, osteoporotic women, spine BMD increased by 9.7 percent and hip BMD increased by 2.6 percent (Neer et al. 2001) after approximately 21 months on teriparitide. Spine fractures decreased by 65 percent and non-spine fractures by 53 percent (Neer et al. 2001). Teriparatide also increases BMD in men; in an approximately 10-month study, spine BMD increased by 5.9 percent and hip BMD by 1.2 percent (Orwoll 1998). The effects on fracture risk have not been studied in men.

Because of these significant potential benefits, the FDA approved teriparatide for the treatment of osteoporosis in postmenopausal women and in men who are at high risk for fracture. The approved dose (20Fg daily by subcutaneous injection) and duration of treatment have not been found to be associated with an increased risk of osteosarcoma in humans.

While the PTH administered daily to postmenopausal women and men with osteoporosis may benefit some patients (particularly those with very severe disease), there are some limitations to use of the drug. First, it should not be prescribed to pediatric patients or adult patients with hypercalcemia (high levels of calcium in the blood), Paget's disease (see below), kidney disease, kidney stones, bone metastases (cancers that have traveled from another part of the body to bone), or bone cancer. Second, a small subset of patients may develop high blood calcium as well as leg cramps and dizziness. Third, it may increase serum uric acid, which could potentially lead to gout, although there is no evidence of an increase in clinical gout. Fourth, there may be issues related to compliance since a daily injection is required. Finally, it is much more expensive than antiresorptive therapy.

Additional forms of PTH therapy may be on the horizon. For example, PTH(1-84) has shown early promise as a treatment for osteoporosis in preliminary bone density studies (Hodsman et al. 2003).

Combination Antiresorptive/Anabolic Therapy. The idea of combining an anabolic agent with an anti-resorptive therapy has been around

for more than a decade. With the advent of PTH, combination studies have been proposed to evaluate the impact of PTH therapy with antiresorptive therapies such as estrogen and alendronate. PTH plus estrogen has been shown to have a greater effect on spine and hip BMD than estrogen alone, but there are no trials comparing that combination to PTH alone, nor are there any studies that evaluate differences in the impact on fracture rates (Cosman et al. 2001). Two studies examining the effects of simultaneous PTH and alendronate treatment suggest that there may actually be smaller BMD increases with combination therapy than with PTH alone (Black et al. 2003, Finkelstein et al. 2003). Another recent study evaluated the impact of sequential treatment with PTH for a year followed by alendronate for a year in 66 women with postmenopausal osteoporosis year. This sequential treatment method resulted in substantial increases in spinal BMD (Rittmaster et al. 2000). The response to PTH treatment may be affected by prior treatment with different antiresorptive agents. Like those patients on estrogen therapy (Lindsay et al 1997), patients previously treated with raloxifene showed a rapid and complete response to PTH, while those previously treated with alendronate had a reduced response in terms of biochemical markers of bone formation and BMD (although they did show increases eventually) (Ettinger et al. 2004). No data on the relative impact of PTH treatment on fractures are available for these different groups.

Future Agents. There are several new antiresorptive and anabolic drugs on the horizon for the treatment of osteoporosis. Among antiresorptive agents, progress has been made both in developing new treatments and in improving the means of administering bisphosphonates. For example, intravenous pamidronate has been available for the treatment of Paget's disease and hypercalcemia of malignancy (high blood calcium due to cancer) for nearly a decade. Smaller studies have also demonstrated that it is effective in increasing bone mass when administered every 3 months to postmenopausal women with osteoporosis (Coleman et al. 2000). A newer drug, zoledronic acid, was recently approved for the treatment of metastatic breast cancer, myeloma (see below) and hypercalcemia (Coleman et al. 2000). It is administered intravenously is extremely effective in treating these conditions. A recent trial of this agent, given as a single intravenous dose once per year, was shown to increase spine BMD in women with osteoporosis (Reid et al. 2002). A large phase III trial is in progress to assess its effectiveness at reducing fractures.

Along with finding new uses for existing antiresorptive agents, researchers have also uncovered several potential new types of treatments during the drug discovery process. A newer class of antiresorptive drugs (known as integrin inhibitors) prevent osteoclasts from anchoring to bone surfaces and thereby absorbing the underlying bone (Hutchinson et al 2003). Early studies with this therapy are encouraging with respect to both safety and effectiveness. Agents that mimic the action of osteoprotegerin can also inhibit bone resorption and could become useful drugs (Onyia et al. 2004). Statins, the cholesterol-lowering drugs, have been found to stimulate bone formation and may also decrease bone resorption in animals. Some observational studies in humans suggest that statin users have fewer fractures, while other studies do not. Controlled cardiovascular trials did not confirm a reduction in fractures (Bauer et al. 2004). Finally, strontium ranelate is an element that has some antiresorptive as well as anabolic qualities, but the method of action is unclear. In initial studies, strontium has been shown to improve

Osteoporosis Drug Therapy

- Antiresorptive agents (reduce bone loss)
  - ~ Bisphosphonates (alendronate, risedronate)
  - ~ Hormone or estrogen replacement
  - ~ Selective estrogen receptor modulators (SERMs) (raloxifene)
  - ~ Calcitonin
- Anabolic agents (build bone)
  - ~ Parathyroid hormone (teriparatide)

spine bone density and reduce spine fractures (Meunier et al. 2002, 2004).

Other new anabolic agents are also being developed and tested. PTH-related peptide (PTHrP), a naturally occurring relative of PTH that is normally made in the breast, uterus, and pancreas, is undergoing clinical trials for the treatment of osteoporosis. PTHrP is best known as a secretion of certain cancers that produces severe hypercalcemia (high calcium levels in the blood) and bone resorption. However, when administered as a single dose intermittently, it has been shown to markedly increase BMD without causing hypercalcemia (Horwitz et al. 2003).

Treatment of Osteoporotic Fractures

For all osteoporotic fractures, the consistent goal is for patients to regain their pre-fracture level of function. All patients with low-trauma fractures should be evaluated for other bone diseases (see below) and secondary causes of bone loss (see Chapter 3). They should also be evaluated with respect to the need for additional preventive measures (calcium, vitamin D, exercise, fall prevention) and for drug therapy, as described earlier in this chapter. What follows is a review of the various available treatments for specific types of osteoporotic-related fractures, including fractures of the hip, spine, and wrist.

Hip Fractures. Surgery is the most common treatment for individuals who suffer a hip fracture. Virtually all intertrochanteric fractures (those in the major part of the hip) and most femoral neck fractures (those in the neck section of the hip) are surgically stabilized with the use of internal metal devices. A large percentage of displaced (unconnected) femoral neck fractures are treated with partial or total replacement of the hip because of the significant risk of healing complications (Zuckerman 1996).

Proper management of hip fracture patients begins before surgery, at the time of admission. Evaluation and management of pre-existing medical conditions is necessary before proceeding to surgery. When possible, management of pre-existing conditions and surgical repair within 24–48 hours of admission has been shown to decrease the incidence of post-surgery complications and the possibility of death within a year of surgery by more than 40 percent (Zuckerman et al. 1995). The procedure should be performed by a surgeon who has expertise in hip fracture stabilization, which will allow the initiation of mobilization immediately after surgery. The vast majority of hip fracture patients should be encouraged to become mobile by the first or second post-operative day. Mobility can help to avoid the medical problems associated with prolonged bed rest, such as muscle atrophy, blood clots in the legs or lungs, pressure sores, skin breakdown, and overall deconditioning.

The use of antibiotics for the first 24–48 hours after surgery is also advisable, as this practice has been shown to be effective in decreasing post-surgery infections. Use of techniques to thin

the blood after surgery has also been shown to be effective in decreasing the incidence of blood clots, particularly in patients who are slow to mobilize (Todd et al. 1995). Adequate pre- and post-surgery pain control is also important, not only for patient comfort, but also to promote active participation in rehabilitation.

Since hip fractures generally occur in elderly patients with other, associated medical and psychosocial problems, the health care team should include professionals from many disciplines, including the orthopaedic surgeon, medical specialists (geriatricians, physiatrists [rehabilitation specialists], primary care physicians, and medical sub-specialists as necessary), nurses, physical and occupational therapists, nutritionists, and social workers. The in-hospital care of hip fracture patients should be guided, whenever possible, by the use of evidence-based clinical care pathways (clinical care based on medical studies) that make use of standardized evaluation and management approaches. This approach should also extend to the entire continuum of care, from the acute care hospital into the post-discharge setting, whether that setting is an acute or sub-acute rehabilitation facility, a skilled nursing facility, or a return home. Effective communication across health settings by health care providers is also important to effective care management (Morris and Zuckerman 2002). Discharge from acute care hospitals and independent rehabilitation facilities should be based on patient progress.

Spine Fractures. Spine fractures usually occur in the middle or lower section of the back as a result of minor strain, such as lifting a grocery bag. Some patients develop fractures without any identifiable trauma. Spine fractures due to osteoporosis result in the progressive collapse of bones in these areas, which typically cause increasing levels of spinal deformity and pain. However, about two-thirds of spine fractures go undiagnosed because there is little or no pain, or the pain is attributed to one of the many other causes of back pain (Johnell et al. 2002). Similarly, other signs of a spine fracture, including deformities and height loss, are often accepted as a normal part of aging and thus not investigated further.

It is not unusual for patients to have prolonged pain and disability following spine fractures. Treatment of spine fractures typically focuses on pain control and progressive increases in levels of mobilization. Back braces are of limited benefit. More recently, procedures have been developed to treat patients who have prolonged pain. Vertebroplasty is a technique in which acrylic cement (or orthopedic cement mixture) is injected into the spine bone for the purpose of stabilizing the fracture (Evans et al. 2003). Kyphoplasty involves using a balloon to re-expand the collapsed bone and then filling the cavity with bone cement. This procedure has the potential to stabilize the fracture, prevent further collapse, and restore some degree of height to the bone (Lieberman et al. 2001). Both vertebroplasty and kyphoplasty have been shown to provide effective pain relief and stabilization of the fracture (Evans et al. 2003, Lieberman et al. 2001). Although complications from these procedures have been infrequent, they can be significant if the bone cement leaks out into the blood stream or into the spinal canal, causing nerve damage. Unfortunately, the potential benefit of these two procedures has not yet been accurately assessed in RPCTs, where they might be compared to each other and to nonsurgical management.

Wrist Fractures. Wrist fractures commonly occur as a result of osteoporosis. They include fractures of the radius and/or ulna (the two long bones in the forearm), as well as of the small

bones of the wrist. The term Colles' fractures refers to fractures of the end of the radius, which has a large amount of trabecular bone. Wrist fractures are usually treated by either surgical repositioning and casting or placement of an external fixation device to prevent further fracture. Depending on the type of fracture, one of the following will be used to immobilize the wrist until an x-ray shows evidence of healing (usually in 4–8 weeks): a brace or splint, cast, external fixation, internal fixation, or combined external and internal fixation. Although most patients return to an adequate level of functioning, many do experience some loss of range of motion of the wrist.

Other Fractures. Osteoporotic fractures occur in other areas of the body, including the upper arm, thigh, shin, collar bone, and ribs. These fractures are treated by a variety of surgical and non-surgical measures.

Rehabilitation of Osteoporotic Fractures

Hip Fractures. As noted previously, hip fracture patients typically undergo surgery to reposition the hip through internal fixation (e.g., insertion of a metal pin or plate) or to replace the hip through joint replacement. Immediately following either type of surgery, in-hospital rehabilitation focuses on training the patient to safely move in bed, to get out of bed, and to begin walking with partial weight-bearing on the surgical side using either a walker or crutches. A physician specializing in rehabilitation medicine or a physical therapist evaluates the patient, administers or supervises the treatment sessions, and makes discharge recommendations. An occupational therapist also may evaluate the patient and provide training in performing activities of daily living (e.g., bathing, dressing) during recovery from the fracture. The occupational therapist may also provide the patient with assistive devices, such as long-handled shoe horns and devices that help the patients put on his or her socks.

Since the inpatient hospital stay typically is limited to 2–3 days after surgery, most patients require additional rehabilitation. Transfer to a rehabilitation facility (a specialty hospital or a skilled nursing home) is common, with length of stay in this setting ranging from several days to several weeks. Following discharge to home, rehabilitation is continued through in-home therapy with a physical therapist or visits to an outpatient facility. This phase of the rehabilitation focuses on general conditioning, strengthening of muscle, and walking longer distances on different terrains and with less assistance. The degree to which a patient progresses from relying on the support of assistive devices during walking to more complete weight-bearing on the fractured limb will depend on the type of surgery and implanted metal as well as the physical condition of the patient. The "typical" patient progresses from a walker to a four-footed cane to a single-point cane to no assistive device for walking. However, 85 percent of patients still use an assistive device for walking 6 months after the fracture (Marotolli et al. 1992).

Nutrition has been shown to be important during recovery from hip fracture. Supplementation with calcium, vitamin D, and protein (20 grams per day) have been reported to improve hospital and rehabilitation courses and to increase BMD a year after the fracture (Schurch et al. 1998).

6 months after hospital discharge, an evaluation should be performed to determine the patient's functional status and to set goals for the future. Many patients require further therapy to reach these goals, whereas others may have reached their potential.

Spine Fractures. As noted above, only about one-third of spine fractures come to clinical attention, but those that do usually are painful. Therefore, pain control is a high priority after the initial spine fractures and after multiple fractures, when chronic pain often becomes a problem. Bedrest should be partial (resting in bed interspersed with 30- to 60-minute periods of erect sitting, standing, and walking) and limited to 4 days or less. Individuals should be taught to position themselves (e.g., while sitting, standing, or lying down) and to move (e.g., when lifting, dressing, doing housework) while maintaining good posture, which reduces loads on the fracture and minimizes pain. To minimize pain and decrease risk of a new spine fracture, family members should be taught to assist patients in performing tasks without increasing the loads on the patient's spine (Bonner et al. 2003).

Walking should be encouraged even in frail individuals. A gradual progression starting at only 2–3 minutes and working up to twenty or more minutes can be achieved by adding a minute or two to walking sessions each week. Short-term use of a back brace is recommended when trunk weakness prevents a patient from maintaining an upright posture. An occupational therapist can fit the proper device. Weaning from the device, as muscle strength and endurance improve, will maximize recovery. However, in some patients with chronic pain and deformity, continued use of a flexible support device that helps maintain back strength and posture may be helpful in reducing pain and improving function (Pfeifer et al. 2004). If walking is limited due to pain, use of a rolling walker with four wheels and hand brakes may help the patient stay active during recovery, thus preventing loss of muscle strength and bone mass. This type of walker allows the use of the arms to keep the trunk erect, thereby shifting the weight of the upper body away from the newly fractured bone. Individuals with a new spine fracture should avoid use of a standard walker, since each time the walker is lifted the loads on the vertebral bodies are increased.

Exercising in a way that safely challenges balance is also important for rehabilitation of spinal fracture patients, although this exercise must be accompanied by an assessment of the risk of falling and the addressing of modifiable risk factors for falling, such as vision problems, medications that cause dizziness, and hazards in the home. Active range of motion exercises should be continued during recovery, but resistance/strengthening exercises should not be initiated or resumed until the fracture has healed (in approximately 8 to 12 weeks). Since the risk of another spine fracture is high in patients who have had fractures, patients should be instructed to avoid exercises and activities that put high loads on the bones of the spine, such as flexing or rotating the spine (sit ups, toe touches). Exercises and activities done with good spine alignment and low to moderate amounts of weight should be gradually increased, with the goals of regaining muscle strength and promoting maintenance of bone mass. Abdominal strengthening (by tightening the muscles in the abdomen or belly without moving the back) is safe and important to reducing loads on the low back. Spinal extension exercise (i.e., stretching backwards) within a moderate range is safe and can improve hyperkyphosis (a spine that is bent excessively forward) and may help prevent new spine fractures (Sinaki et al. 2002).

Wrist Fractures. Rehabilitation of the wrist after the cast, brace, or surgical metal is removed requires about 3 months, but reaching maximum

levels of recovery can take up to 24 months, and some problems may persist for years. During healing of a wrist fracture, all of the following are important: arm elevation; early mobilization of the hand, elbow, and shoulder; and control of swelling. Progressive exercises, taught by either a physical or occupational therapist, typically include active and passive range of motion and resistance and grip strengthening, such as squeezing a ball (Bonner et al. 2003). A small number of patients suffer from sympathetic dystrophy (complex regional pain syndrome) after a wrist fracture, resulting in swelling, weakness, and chronic pain in the wrist.

Treatment of Other Diseases of the Bone

There are specific, effective (and often curative) treatments for a number of bone diseases other than osteoporosis, including hyperparathyroidism, rickets, and osteomalacia. There is also treatment available for some congenital bone disorders and for bone disease associated with kidney failure. Early recognition and treatment of all of these conditions is the key to avoiding crippling deformities and fractures. What follows is a brief review of treatment options for the most common of these diseases.

Primary Hyperparathyroidism. Primary hyperparathyroidism is caused by an excessive release of PTH from one or more of the parathyroid glands. (See Chapter 3 for more a more detailed description.) Surgical removal of the parathyroid adenoma (benign tumor) or of three-and-a-half glands (if all four glands are enlarged) often cures the disease. In 2002, an NIH-sponsored workshop on the management of non-symptomatic primary hyperparathyroidism concluded that patients who are clearly symptomatic with bone disease or kidney stones should be advised to have surgery (Bilezikian et al. 2002, Bilezikian and Silverberg 2004). There is considerable controversy concerning the need for intervention in patients who have no clear signs or symptoms of the disease. Treatment guidelines for non-symptomatic patients relate to the degree of hypercalcemia (greater than 1 mg/dL serum calcium above the upper limits of normal), hypercalciuria (greater than 400 mg per day urine calcium), and age (under age 50). An independent panel of experts that convened after the end of the NIH workshop suggested that new guidelines for surgery for non-symptomatic patients with primary hyperparathyroidism should be based on levels of bone density that are in line with modern definitions of osteoporosis. If T-score measurements are below –2.5 at any site, surgery is now being recommended. The evidence suggests, moreover, that parathyroid surgery is effective; patients who undergo such surgery have increased their bone mass by 10 percent or more over the 3- to 4-year period following surgery, with the largest gains occurring in the spine (Silverberg et al. 1999). Parathyroid surgery patients have also experienced a decreased incidence of fractures (Vestergaard and Mosekilde 2004). Optimal parathyroid surgery requires exceptional expertise in being able to localize and identify abnormal parathyroid glands and remove them with minimal injury to other tissues. Recent advances have led to newer approaches such as minimally invasive parathyroidectomy for removal of a single parathyroid adenoma with a small incision and minimal trauma to other tissues (Udelsman 2002). This approach requires successful pre-surgery location of the abnormal parathyroid gland, usually by technetium-99m-sestamibi scanning and/or ultrasound imaging (Alexander et al. 2002). Many patients who are not

candidates for surgery for parathyroidectomy appear to do very well when they are managed conservatively with appropriate measures to avoid dehydration and further bone loss (Silverberg et al. 1999).

Currently, there are no FDA-approved medications for primary hyperparathyroidism. However, medical therapy may be available in the future. Specifically, calcimimetic (calcium-mimicking) agents, which can inhibit parathyroid hormone secretion, offer a direct approach to the medical therapy of primary hyperparathyroidism (Silverberg et al. 1997). Antiresorptive therapy can be used in patients with primary hyperparathyroidism and low bone mass who refuse surgery or for whom surgery is contraindicated (Rubin et al. 2003, Parker et al. 2002, Chow et al. 2003).

Renal Osteodystrophy. Renal osteodystrophy is a complex bone disease that occurs because of chronic renal (kidney) failure; a more detailed description of the disease and its causes can be found in Chapter 3. Treatment of renal osteodystrophy depends on the type of abnormality in the bone and on the stage of the renal disease. An important aspect of prevention of renal osteodystrophy is the early implementation of dietary phosphate and protein restriction, oral 1,25-dihydroxy vitamin D (calcitriol) treatment, and adequate oral intake of calcium and vitamin D. A recent analysis of hemodialysis patients suggested that treatment with a vitamin D analog, paricalcitol, resulted in lower mortality than did treatment with calcitriol (Teng et al. 2003). All patients progressing to end-stage renal disease are offered treatment to control uremia (high levels of blood urea nitrogen) with dialysis. An increasing number of patients on dialysis are offered the option of kidney transplantation. The incidence of osteoporosis after transplantation (when bone loss can be aggravated by the drugs that are used to suppress the immune response and prevent rejection of the transplant) can be reduced by keeping the dose of corticosteroids and anti-transplant drugs to a minimum (Cohen and Shane 2003). However, osteoporosis in post-transplant patients may also be treated in its own right by anti-osteoporotic therapies such as bisphosphonates.

Paget's Disease of Bone. Paget's disease of bone is localized, excessive bone remodeling that leads to increased bone resorption and formation (see Chapter 3 for more details). The primary therapy involves use of bisphosphonates, which decrease bone resorption and slow bone turnover (Lyles et al. 2001). Alendronate, risedronate, tiludronate, and etidronate are bisphosphonates that are approved for the treatment of Paget's disease. The doses used for treatment of Paget's disease are generally higher than those used for osteoporosis treatment. Bisphosphonates lead to a decrease in alkaline phosphatase and often decrease the skeletal pain associated with the excessive bone turnover. Calcitonin (as an under-the-skin injection or nasal spray) has also been used to treat Paget's disease, but is less effective than bisphosphonates (Deal 2004). PTH should not be given to patients with Paget's disease.

Bone Metastases of Cancer. Bone metastases are common in a number of cancers, and they contribute heavily to morbidity and mortality, most prominently in prostate, breast, and multiple myeloma. Bone metastases are often associated with severe and frequently intractable pain (Mundy 2002). The relationship between prostate cancer and the bone is unique among cancers. Approximately 90 percent of advanced prostate cancer patients develop clinically significant bone metastasis,

Treatment of Other Bone Diseases

- Primary hyperparathyroidism
  - ~ Removal of parathyroid adenoma(s) by surgery if signs or symptoms meet guidelines
  - ~ Hormone therapy or bisphosphonates may be helpful
- Renal osteodystrophy (bone disease from kidney failure)
  - ~ Treatment of kidney problem (dialysis, transplantation)
  - ~ Special diets
  - ~ Calcitriol
- Paget's disease of bone
  - ~ Bisphosphonates (alendronate, risedronate, tiludronate, etidronate)
- Multiple myeloma
  - ~ Chemotherapy
  - ~ Stem cell transplantation
  - ~ Bisphosphonates
- Osteogenesis imperfecta
  - ~ Rehabilitation
  - ~ Physical therapy
  - ~ Bisphosphonates

causing osteoblastic remodeling of the bone that contributes to the morbidity and mortality of patients. Bone metastases are also frequent in breast cancer, often leading to both osteoblastic and osteoclastic lesions. Multiple myeloma can cause rapid bone loss with pain, fractures, and increased blood calcium (see Chapter 3 for more details). The major source of morbidity and mortality associated with MM are osteolytic lesions that form throughout the axial skeleton, resulting from increased osteoclastic bone resorption that occurs adjacent to the myeloma cells. New bone formation that normally occurs at the sites of bone destruction is also absent, as local factors produced by myeloma cells appear to induce extensive bone destruction and block new bone formation.

There are some treatments available to treat bone metastases caused by cancers. Bisphosphonates, which are potent inhibitors of bone resorption, significantly reduce skeletal morbidity in patients with advanced breast cancer and can reduce metastasis to bone by human breast cancer cells in an experimental model (Cancer Supplement 2003). Pamidronate, a second generation bisphosphonate, has recently been approved by the FDA for treatment of breast cancer osteolysis. Zoledronic acid, a third-generation bisphosphonate, has also been approved for treatment of cancer patients. Another inhibitor of bone resorption, the protein osteoprotegerin, has also been shown to be effective in reducing bone metastases in animal models of breast and prostate cancer and in reducing bone pain in patients (Cancer Supplement 2003). Although bisphosphonates significantly reduce skeletal morbidity associated with solid tumor metastases to bone, most studies indicate no improvement in survival (Cancer Supplement 2003). Thus, in order to improve therapy and ultimately prevent bone metastases, a more precise understanding of the pathophysiology of bone metastases is necessary, as the level of current understanding is very limited (Cancer Supplement 2003).

Osteogenesis Imperfecta. Osteogenesis imperfecta (OI) is an inherited skeletal disorder that results from several different genetic defects (see Chapter 3 for more details). Patients with OI have low bone mass and brittle bones that fracture easily. Treatment of patients is mainly oriented at preventing and treating fractures in these patients. It involves a team of health professionals that typically includes orthopedists, rehabilitation physicians, and physical therapists. Encouraging results have been reported with bisphosphonate therapy (Glorieux et al. 1998).

Key Questions for Future Research

There is good evidence that proper nutrition and lifestyle can promote bone health and that pharmacotherapy can slow bone loss or even build new bone. However, there is still no "cure" for osteoporosis or for most other bone disorders. Those drugs that do exist, moreover, are still not ideal in terms of their expense, ease of administration, and/or side effects. Answers to the following research questions would help to move the field closer to the development of "ideal" therapies that can prevent and/or cure bone disease:

- What are the relative risks and benefits of different types of drug therapies in different populations? When is it best to use bisphosphonates, SERMS, or anabolic agents?
- What is the effectiveness of pharmacotherapy in treating persons who have already sustained hip fractures?
- Are combination therapies more effective than single therapies? Is there any time when it is best to use a combination of anti-resorptive and anabolic therapy?
- What doses, schedules, and methods of administration are most effective in encouraging compliance and preventing fractures in the community (not just within the confines of a clinical trial)? Can lower doses, shorter courses, or wider spacing of treatment help?
- What is the efficacy and utility of vertebroplasty and kyphoplasty?
- How can we improve the therapy of other bone diseases, particularly osteogenesis imperfecta, hyperparathyroidism, and renal osteodystrophy?

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