Osteoporosis—Extent and Cause of the Disease (42917)

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Osteoporosis is a common disorder producing an estimated 1.3 million fractures a year in the United States (1). It is characterized by low bone mass and fractures of the hip, spine, distal radius, pelvis, and proximal humerus (2). Fractures of the vertebrae are probably the most common of this group (3), but may be relatively asymptomatic in many cases. However, these vertebral fractures do produce deformity and cause pain for some individuals and in 1984 accounted for over 160,000 physician office visits and over 5 million days of restricted activity (4). Fractures of the hip are the most costly from a public health standpoint. It was estimated in 1984 that over 240,000 occurred in the United States (5). This number will increase as the population ages, doubling or tripling by the year 2050. The cost was estimated at 7.3 billion dollars in 1984 (6) and continues to rise. Hip fracture is associated with a 5–20% reduction in expected survival and half of the victims are unable to walk independently afterward (7). Much of this disability and the associated costs could be avoided if proper preventive measures were introduced earlier in life for those most at risk for future fractures.

It has previously been presumed that all osteoporotic fractures were of the same cause, but recently it has been suggested that some of these fractures may represent different syndromes (8, 9). Type 1 osteoporosis is associated with distal radial and vertebral fractures. It occurs primarily in women age 50–65 and is probably due to a decreased amount of cancellous bone at the fracture site. This deficit in cancellous bone may have resulted from an insufficient amount present at maturity or, alternatively, from an excessive loss after menopause. Which of these suggestions is correct is not known at present and different mechanisms may apply to different individuals.

Type 2 osteoporosis occurs in the older population, over 70, and is characterized by fractures of the hip, proximal humerus, and pelvis. There is loss of both cortical and trabecular bone. Considerable overlap exists between these two syndromes, but there separation is important since different mechanisms may play a role in the pathogenesis of each and thus effective clinical intervention may differ.

The increased fracture incidence associated with osteoporosis is generally attributed to low bone mass at the fracture site. However, other factors must also contribute, since all individuals lose bone with age and all elderly individuals have low bone mass, but all do not fracture. Some of the factors which contribute to skeletal fragility are intrinsic to the skeleton (Table I). Bone remodeling slows with age and, thus, microdamage can accumulate, leading to spontaneous fractures (10). Trabeculae are frequently lost rather than simply becoming thin, thus producing architectural abnormalities of the vertebrae and other cancellous bone which results in increased fragility (11). These defects cannot be reversed with current therapeutic agents, thus prevention of bone loss is critical if they are to be prevented. Osteomalacia occurs among the elderly (12) and may contribute to bone fragility and fracture as well. In addition to these intrinsic abnormalities, extra skeletal factors may be important. An increased incidence of falling leads to more frequent and, perhaps, more severe trauma (13). With the loss of muscle and soft tissue mass, which occur with aging, energy diffusion subsequent to a fall may be impaired, leading to greater strain within the bone and fracture.

Although other factors contribute to increased fracture frequency, low bone mass at the site of fracture is a necessary, if not, sufficient cause. The low bone mass which is present at the time of fracture may have resulted from an insufficient quantity which was present at skeletal maturity or from an excessive loss of bone later in life. It is not known which of these contributes the most and in an individual either may be important.

Both genetic and environmental factors contribute to the development of bone mass at maturity. Twin studies have shown a strong genetic component to the determination of radial bone mass (14). Other investigators have found less genetic effect for bone mass of the spine or hip (15) than for the radius, but subsequent studies done in our laboratory have found a strong genetic expression at these sites as well. Even though genetic effects are important, environmental effects also

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Table I. Intrinsic Abnormalities of the Skeleton Leading to Skeletal Fragility

Accumulation of microdamage
Architectural abnormalities
Osteomalacia

play a role in determination of peak bone mass. Such effects may even be at work *in utero*. In a small study of dichorionic and monochorionic monozygotic twins, the variance between twin pairs was greater for the dichorionic than the monochorionic twins, although the individuals are genetically identical, suggesting an environmental effect (16). It has also been postulated that nutritional factors, especially intake of milk (17) may be important during growth. It is not known whether this is due to calcium alone or to other nutrients in the milk. Other nutritional factors as well as exercise may be important in the determination of peak bone mass but these remain to be studied.

Some bone may be lost from the cancellous compartment before menopause (18), however there is an accelerated loss of all types of bone associated with menopause (19). This loss is stopped or attenuated by the administration of estrogen (20) or estrogen and a progestin (21). The rate of bone loss during the perimenopausal and early menopausal period is correlated with serum estrogen concentrations and with estrogen production rates, even when the estrogen levels have fallen to postmenopausal concentrations (19). Thus, it is apparent that estrogen deficiency is a cause of bone loss. When estrogen deficiency occurs, bone remodeling is increased (22). Since there is an imbalance between formation and resorption at bone remodeling sites, loss ensues. The cellular mechanism by which estrogen deficiency produces its effect is at present unclear. Recently estrogen receptors have been found in bone cells of the osteoblast lineage and presumably this explains, at least in part, the estrogen effect (23, 24). However, indirect effects through the vitamin D-parathyroid hormone endocrine system or on calcitonin secretion may also be important.

Bone loss continues beyond the menopause even though it slows later in life (25). Menopausal estrogen deficiency probably cannot account for this continued loss. Malabsorption of calcium occurs with aging (26) and could be responsible for the development of secondary hyperparathyroidism which would lead to increased bone loss. Parathyroid hormone concentrations do rise with age (27). The malabsorption of calcium may be due to abnormalities within the gut (28) or to failure to produce an adequate quantity of 1,25-dihydroxyvitamin D (29). A decrease in serum 1,25-dihydroxyvitamin D concentrations occurs with age. This decrease may be due to failure of the kidney to produce an adequate quantity of the active hormone or in some cases, inadequate substrate may be available because of an inadequate supply from the diet or failure of the skin to produce the precursor in the elderly.

Osteoporosis is a common disorder causing considerable morbidity and even death from fractures. The principle underlying cause of fracture is low bone mass, however other factors such as slowed remodeling, architectural abnormalities, osteomalacia, and increased frequency of falling play a role as well. Low bone mass at the time of fracture may be due to either low bone mass as maturity or to excess loss of bone later in life. Although genetic factors are quite important in determining peak bone mass, environmental factors such as calcium intake may also be important and could allow therapeutic intervention to increase peak bone mass and protect from subsequent fracture. Estrogen deficiency is probably the most important determinant of bone loss, especially just after menopause, but other factors such as calcium malabsorption may dominate later in life. Although we have learned much about osteoporosis and its attendant fractures, much remains to be learned to further reduce the impact of this disorder on health.

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