REVIEW ARTICLE

MECHANISMS OF DISEASE

Bone Quality — The Material and Structural Basis of Bone Strength and Fragility

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N Engl J Med 2006;354:2250-61.

PROGRESS IN UNDERSTANDING THE PATHOGENESIS OF BONE FRAGILITY is hampered by the inaccessibility of bone for investigation. Bone densitometry is an effective, noninvasive, and quantitative method for the assessment of the risk of fracture, but structures such as the vertebral body are depicted as a two-dimensional image — the areal bone mineral density cast by the attenuation of photons by mineral during their passage through bone. Just as the shadow of the earth, cast on the moon, reveals nothing of the topology of the earth's mountain ranges, the densitometric image tells us little about the two properties that determine bone strength: its material composition and its structural design.[1,2]

In this review, we define how the composition and structure of bone determine its strength, describe bone modeling and remodeling — the cellular machinery responsible for constructing bone during growth and reconstructing it during adulthood, demonstrate how age-related abnormalities in these processes compromise the composition and structure of bone, and show how the mechanisms underlying the structural decay of bone offer rational approaches to the use of drugs that inhibit bone resorption and stimulate bone formation.

FABRIC AND STRUCTURE OF BONE — LEVERS AND SPRINGS

The strength of bone is determined by its material composition and structure.[2] Bone must be stiff and able to resist deformation, thereby making loading possible. Bone must also be flexible: it must be able to absorb energy by deforming, to shorten and widen when compressed, and to lengthen and narrow in tension without cracking. If bone is brittle (i.e., too stiff and unable to deform a little), the energy imposed during loading will be released by structural failure — initially by the development of microcracks and then by complete fracture. If bone is too flexible and deforms beyond its peak strain, it will also crack. Bone must also be light to facilitate movement. A unique feature of bone is that it can serve these contradictory needs of stiffness yet flexibility and lightness yet strength.[3]

COMPOSITION OF BONE

Bone is composed of type I collagen stiffened by crystals of calcium hydroxyapatite. An increase in tissue mineral density increases the stiffness of the fabric but sacrifices flexibility.[2,4] Variations in tissue mineral density affect function. Auditory ossicles are 90 percent mineral, conferring the stiffness essential for the fidelity of sound transmission (like tuning forks). Animal antlers are 40 percent mineral, conferring the flexibility needed to absorb energy during head butting to defeat suitors in mating season. Human bone is about 60 percent mineralized. The composition and degree of collagen cross-linking also influence function.[5-8] The triple

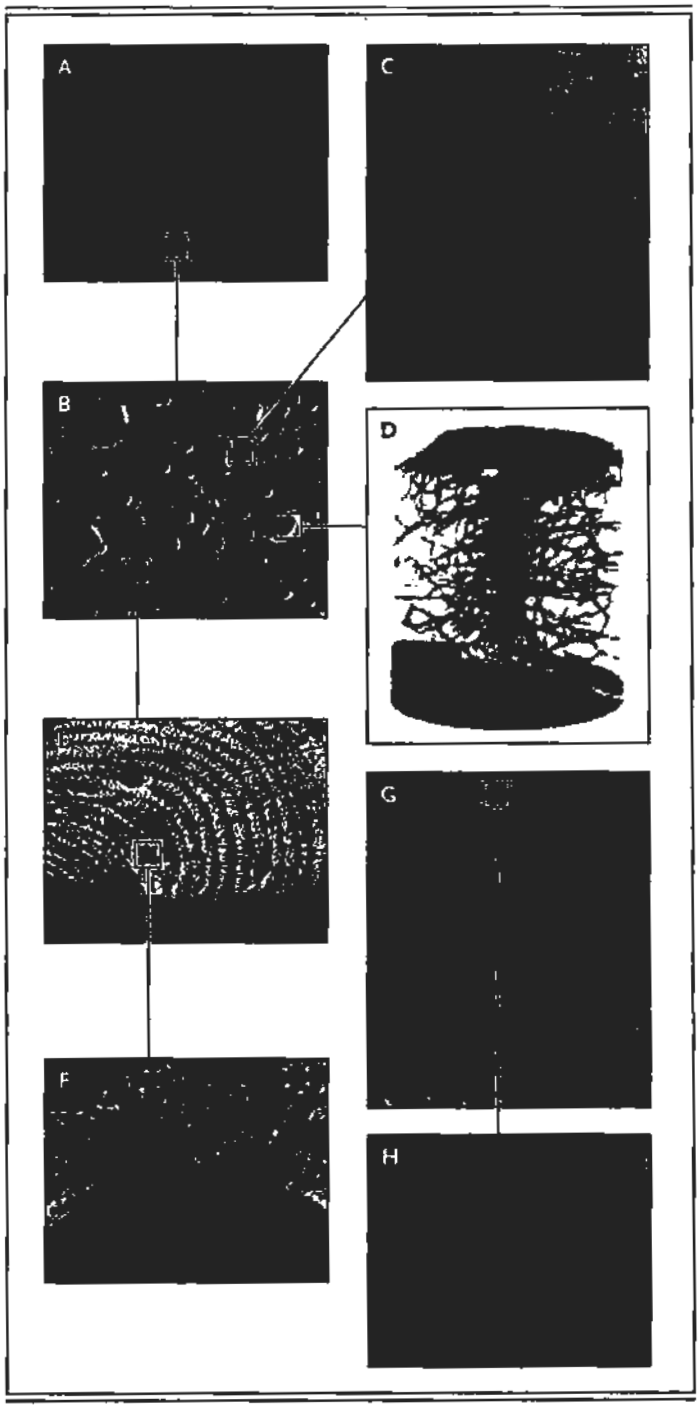

Figure 1. The Hierarchical Structure of Cortical Bone.
Within a cortical bone shaft, shown in cross-section (Panel A) are osteons surrounded by interstitial bone and many osteocytic lacunae distributed around the central haversian canal (Panel B). Panel C shows a microcrack that is largely confined to interstitial bone. Panel D shows the haversian canal system in cortical bone (microcomputed tomography courtesy of M.A. Knackstedt, Australian National University). In Panel E, alternating high-density and low-density concentric lamellae of an osteon produce a composite structure that is resistant to cracking, with an osteocytic lacuna at a higher resolution showing collagen fibers (Panel F) (scanning electron microscopy reprinted from Marotti[10] with the permission of the publisher). In Panel G, osteocytes connect with lining cells and with one another through a network of canaliculi (scanning electron microscopy of an acid-etched resin-embedded murine bone section, courtesy of Drs. Lynda F. Bonewald and Jian Q. Feng, University of Missouri–Kansas City). Panel H shows the detail of an osteoblast lining cell connected to an osteocyte (transmission electron microscopy reprinted from Marotti[10] with the permission of the publisher).

helix of type I collagen confers strength in tension. The cross-links in collagen keep its helixes fastened. If there are too few cross-links, the helixes may separate; if there are too many, the ability to absorb energy diminishes.

MICROSTRUCTURE AND MACROSTRUCTURE OF BONE

Bone fabric is woven at submicroscopic, microscopic, and macroscopic levels into an architectural masterpiece of biomechanical engineering — with an optimal mass adapted in size, shape, and architecture for structural strength (i.e., the ability to resist cracking).[9] Just as a wall is constructed with overlapping bricks, cortical bone consists of overlapping parallel osteons, the anatomical remnants of a completed remodeling event (Fig. 1).[10] A large number of osteons per unit of bone volume limits the propagation of cracking because they obstruct the passage of a crack as it navigates between the many osteons.[9] The entry of cracks into the osteon is blocked by the cement line delimiting each osteon and by concentric lamellae of mineralized collagen fibers that are packed in an alternating loose and dense pattern and are orientated in various directions. In addition, uncracked bone tissue within a crack forms a bridge that carries the load that otherwise would be used to drive the crack forward.[11] As a result, cracks are largely confined to the older, more densely mineralized interstitial bone between osteons.[12] Although small, confined cracks are undesirable, they are a final means of dissipating energy as a defense against the alternative means of energy release imposed by the stress on bone — fracture.[2]

LEVER ACTION OF LONG BONES

Cortical bone is used to build long bones. Long bones are levers needed for loading and movement, with rigidity favored over flexibility. Structural stiffness and lightness are achieved by the construction of a marrow cavity. Long bones grow in length by endochondral apposition on the inner, or endosteal, surface and in width by the deposition of bone on the outer, or periosteal, surface. Resorptive excavation of a marrow cavity during fetal and postnatal growth shifts the thickening cortex away from the neutral axis, thereby increasing resistance to bending.[13] Sex and racial differences in the extent of periosteal apposition and endocortical resorption during growth and aging establish variations in the diameter and cortical thickness of bone and in the distance of the cortical mass from the neutral axis — and thus differences in bone strength.[14-17]

Long bones are not like drinking straws, which have the same diameter and thickness throughout. The conical metaphyses are fashioned by the resorption and formation of bone on the periosteal surface, whereas endochondral bone forms the trabecular network. External and internal contours differ at each point along and around the shaft. For example, the femoral neck adjacent to the shaft is elliptical, with the longest diameter in the superior–inferior direction and greater cortical thickness inferiorly; these features minimize bending.[18] Near the femoral head, where stresses are mainly compressive, the femoral neck is more circular and largely trabecular, with a cortex of similar thickness around its perimeter. These structural adaptations to loading are not seen in quadrupedal primates.[19]

SPRING ACTION OF VERTEBRAL BODIES

Bone that will become vertebral bodies is assembled as an open-celled, porous structure that functions more like a spring than a lever in that the sponge-like structural design can absorb more energy by deforming more before cracking than can long bones. However, this structure sacrifices the ability to tolerate the peak loads that can be borne by long bones. The interconnecting trabecular plates achieve lightness and favor structural flexibility over stiffness.[20]

The greater loads that are better tolerated in men than in women and in some races better than in others are largely due to differences in bone dimensions.[14,15] Men and women generally have similar vertebral trabecular volumetric density (number plus thickness) and similar vertebral heights; the larger vertebral cross-sectional area in men contributes to sex-based differences in bone strength.[14] Black people tend to have wider but shorter vertebral bodies and higher measures of trabecular volumetric density than do white people owing to thicker trabeculae, a feature that may protect against the effects of age-related bone loss.[21-23]

The structure of bone is contained in the genetic blueprint — fetal lower limb buds grown in vitro have the shape of the proximal femur.[24] Although structure determines the loads a bone will tolerate, the reverse also applies: loads determine structure. Bone can adapt its composition and structure to prevailing loads.[25] Adaptation in size and shape in the playing arm of tennis players is well documented.[2] The Mov13 mouse, a model of the mild form of osteogenesis imperfecta, compensates for defects in bone collagen by a structural adaptation that entails periosteal apposition; the Brittle IV mouse, another model of osteogenesis imperfecta, makes adaptations in the mineral:collagen ratio.[26,27] However, such adaptations may be unsuccessful. In the osteogenesis imperfecta (oim/oim) mouse, a compensatory increase in bone formation with defective collagen does not correct bone fragility.[28] Thus, bone fragility can be the result of failed material or structural adaptations or both, not just low bone mass.

MODELING AND REMODELING OF BONE

The cellular mechanisms responsible for the adaptation of bone are modeling (construction) and remodeling (reconstruction). Bone modeling produces a change in the size and shape of bone when new bone is deposited without previous bone resorption. During bone remodeling, resorption by osteoclasts precedes bone formation by osteoblasts. Osteoblasts and osteoclasts form the bone multicellular unit that reconstructs bone in distinct locations on the three components (endocortical, intracortical, and trabecular) of its endosteal envelope and, to a lesser extent, on the periosteal envelope.[29] Bone modeling and remodeling modify the external size and contours of bone and its internal architecture by the deposition or removal of bone from the surface of bone,

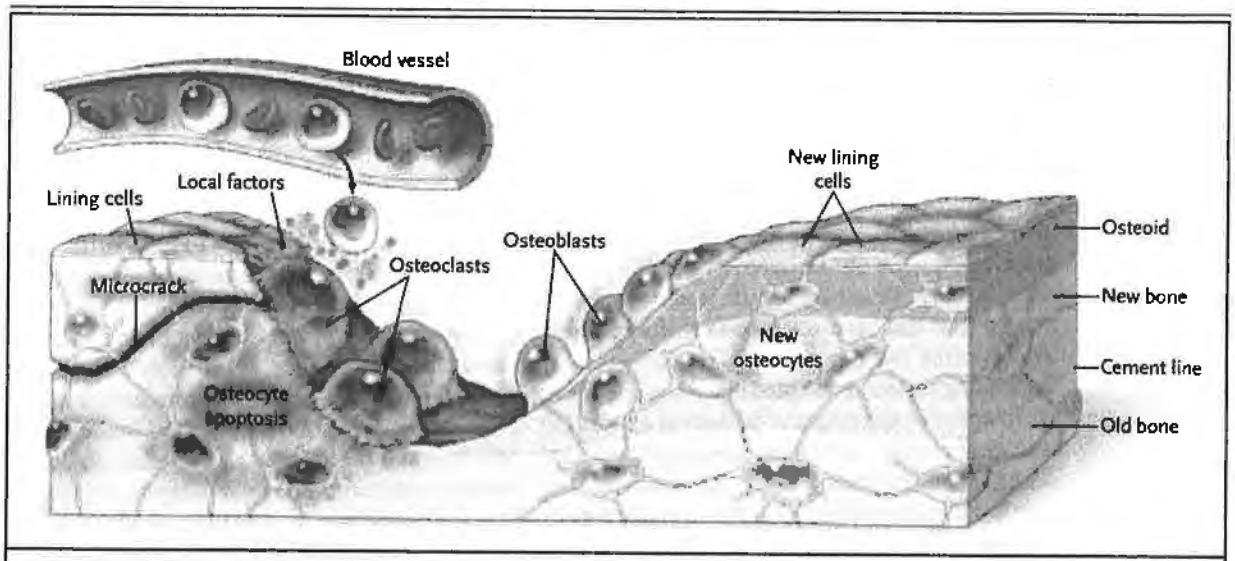

Figure 2. The Remodeling Cycle on a Trabecula.

A microcrack severs canaliculi, which causes osteocytic apoptosis, with the location and extent of the damage defined by signals to lining cells. Lining cells and osteocytes release local factors that attract cells from blood and marrow into the remodeling compartment in which osteoclastogenesis occurs. Osteoclasts resorb matrix and the microcrack, then successive teams of osteoblasts deposit new lamellar bone. Osteoblasts that are trapped in the matrix become osteocytes; others die or form new, flattened osteoblast lining cells.

causing cortical and trabecular thickening during growth and thinning during aging (Fig. 2).

The purpose of modeling and remodeling during growth is to establish the skeleton's peak bone strength; its purpose in adulthood is to maintain bone strength. In bone (as in roads, buildings, and bridges), damage due to fatigue develops during repeated loading, but only bone has the mechanism to detect the location and magnitude of the damage, remove it, replace it with new bone, and then reconstruct the material composition, microarchitecture, and macroarchitecture.[30,31] The role of remodeling in calcium homeostasis is outside the scope of this article.

Bone resorption is not necessarily bad. During growth it is essential for the excavation of a marrow cavity and the fashioning of cortical and trabecular bone. In adults, the resorptive phase of the remodeling cycle removes damaged bone, and the formation phase restores the structure. The restitution of structure requires balanced remodeling; the volume of damaged bone removed must be replaced by the same volume of normal bone.

The most likely reason that a given point on a quiescent bone surface becomes a remodeling site is removal of damage.[32-36] But how does bone know the location of damage, as well as how much damage to remove and how much bone needs to be replaced? This process depends on the normal production, work, and life span of osteoclasts and osteoblasts, but another cell — the osteocyte — is also a likely participant.

Osteocytes are the most numerous, longest-lived, and least studied cells of bone. They are osteoblasts that have become entombed in lacunae in the bone matrix (osteoid) that they synthesize. These osteoblasts undergo a morphologic change and become osteocytes with cytoplasmic processes that connect them with other osteocytes and flattened lining cells (Fig. 1G and 1H).[33] The dense, lace-like communicating network of osteocytes ensures that no part of bone is more than several microns from a lacuna containing its osteocyte. This arrangement suggests that osteocytes are part of the machinery guarding the integrity of the material and structural strength of bone.[30-37]

Osteocytes probably sense bone deformation, thereby signaling the need for adaptive remodeling of bone size, shape, and distribution to accommodate prevailing loads.[33] The death of osteocytes by apoptosis — in estrogen deficiency, during corticosteroid therapy, in advancing age,

or after damage to bone — is associated with a loss of bone strength before any bone loss.[35-37] The death of these cells probably heralds (through biochemical and chemotactic signals) the presence of damage and its location and the initiation of targeted remodeling. Regions of microdamage contain apoptotic osteocytes, whereas quiescent zones do not.[37] The number of osteocytes that undergo apoptosis may provide the topographic information needed to target removal of damage by osteoclasts.

Hence, the first step in remodeling is unlikely to be bone resorption. Osteoclasts must first be formed and be told where to go and how much bone to resorb. These instructions are likely to arise from signals produced by the deformation or death of osteocytes, which define the location and amount of resorption needed. The signals are probably relayed, in part, by the cytoplasmic processes connected to flattened osteoblast lining cells.[31] These lining cells partly form the canopy of a bone-remodeling compartment.[38] Within this microenvironment, local factors, including vascular growth factors, provide the vascular supply, osteoclast precursors, macrophages, and activated T cells that participate with osteoblast precursors in osteoclastogenesis. Osteoblast precursors go on to become mature osteoid-forming osteoblasts. Bone formation may also be coupled with bone resorption by products from the resorbed matrix and from osteoclasts themselves.[39,40] Thus, the osteocyte is involved in initiating remodeling, and subsequent local regulation is bidirectional, with osteoblast precursors directing osteoclastogenesis and products of the osteoclast and of the resorbed matrix modulating bone formation.

NEGATIVE BALANCE IN THE BONE MULTICELLULAR UNIT

A negative balance in the bone multicellular unit — which causes bone loss, an increased remodeling rate, or both — compromises the strength of bone. During growth, the balance between the volume of bone that is resorbed and the volume that is formed in the bone multicellular unit is positive on a trabecular surface, so that each remodeling event adds a small moiety of bone. As skeletal size reaches its programmed dimensions, the need for rapid remodeling and a positive balance between the volume of bone removed and the volume of bone deposited in each bone multicellular unit lessens. The remodeling rate decreases as longitudinal growth ceases with epiphyseal closure.[41] The volume of bone formed in each bone multicellular unit may also decline, shifting the balance between the volume of bone that is removed and the volume that is formed in each bone multicellular unit from positive to equal (i.e., zero).

In adults, one of the first changes in the remodeling machinery that leads to bone loss is likely to be a decline in bone formation within the bone multicellular unit. There is evidence of a reduction in bone formation in midlife,[42,43] but this may begin in young adults when the need to build the skeleton (and thus the need for bone formation) declines.[44-46] When bone formation is less than prior bone resorption, each remodeling event removes a small moiety of bone from the skeleton, resulting in bone loss and structural damage.

The positive balance in the bone multicellular unit (net bone formation) during growth and the negative balance (net bone loss) during aging are small. For these reasons, the rate of gain in bone during growth and loss during aging is driven more by a high remodeling rate than by the magnitude of the positive or negative balance in the bone multicellular unit. This consideration is important, given the effect of antiresorptive agents such as the bisphosphonates on the rate of remodeling. Largely on the basis of cross-sectional data, bone loss appears to begin between the ages of 18 and 30 years, but the process is slow because remodeling is slow.[47]

Rapid remodeling (independent of an imbalance in the bone multicellular unit) is associated with an increased risk of fracture for several reasons. First, more densely mineralized bone is removed and replaced with younger, less densely mineralized bone, reducing material stiffness.[48-50] As a result, bone may become too flexible, bend excessively, and crack under usual loading conditions. Second, excavated resorption sites remain temporarily unfilled (because of the delay in the initiation and slower completion of bone formation that is coupled with resorption), creating stress concentrators that predispose bone to microdamage (as a small cut on the surface of a glass cylinder makes the tube easy to snap).[2] Third, increased remodeling impairs isomerization and maturation of collagen, which increases the fragility of bone,[5,6] probably by altering the cross-linking between adjacent collagen fibers.

Estrogen deficiency (e.g., after menopause) in-

creases the rate of remodeling and the volume of bone that is resorbed by prolonging the life span of osteoclasts. It also decreases the volume of bone that is formed by reducing the life span of osteoblasts, thereby aggravating the negative bone balance in the bone multicellular unit.[51] The combination of a rapid rate of remodeling and increased imbalance in the bone multicellular unit accelerates bone loss and structural decay after menopause.

TRABECULAR THINNING AND LOSS OF CONNECTIVITY

Remodeling occurs on bone surfaces. Trabecular bone is fashioned with more surface than cortical bone. Since there are more remodeling sites per unit volume in trabecular bone than in cortical bone, a greater proportion of trabecular bone is turned over and lost as each remodeling event removes more bone than it puts back.[52] The high remodeling rate and deep resorption cavities produce a loss of trabecular plates and of their connection (connectivity), which in turn produce a greater deficit in bone strength than does trabecular thinning.[53]

Bone fragility is more common in women than in men partly because the production of sex hormones in males does not decrease rapidly and there is no increase in the bone-remodeling rate in midlife. Although perforation and loss of connectivity between trabeculae occur in men, bone loss in men proceeds more by trabecular thinning (due to reduced bone formation within each bone multicellular unit) than by trabecular perforation (due to increased bone resorption within each bone multicellular unit).[54-57]

CORTICAL THINNING AND POROSITY

Rapid remodeling does not slow down with age; it continues because of persistent hypogonadism in women, emerging hypogonadism in some men, and secondary hyperparathyroidism in both sexes. With continued remodeling, trabeculae perforate and some disappear completely, and remodeling is more active on the endocortical surface than on remaining trabecular surfaces. Active endocortical and intracortical remodeling "trabecularizes" cortical bone (i.e., creates cortical bone with more surface area), so bone loss becomes mainly cortical in origin.[52,58,59]

Structural decay accelerates as each remodeling event removes bone from an ever-decreasing total volume of bone. Older, more densely mineralized interstitial bone, distant from surface remodeling, has a reduced number of osteocytes and accumulates microdamage.[12] Cortical thinning and porosity reduces the resistance of bone to the propagation of cracks. Pores coalesce, and the reduced bone mass cannot absorb the energy imparted by a fall.

PERIOSTEAL APPOSITION

Concurrent periosteal apposition, by depositing new bone on the external surface, partly offsets the loss of compressive and bending strength produced by cortical thinning and porosity, so that cortical thickness is better maintained than would occur without periosteal apposition.[54-62] However, details of the magnitude of changes in periosteal apposition during advancing age — as well as the effects of site, sex, and race — are difficult to evaluate prospectively, given the small changes in periosteal apposition (a few millimeters) throughout adult life. In addition, periosteal apposition is difficult to interpret in cross-sectional studies, given secular trends in bone mass and dimensions.[63] The findings in one study[62] that periosteal apposition occurs in the years after menopause to compensate for accelerated bone loss needs confirmation. Even the notion that periosteal apposition is greater in men than in women remains controversial[1,64,65]; recent studies suggest that sex-based differences occur at some, but not all, sites.[14,15] Moreover, these sex-based differences may vary according to race.

Albright and his colleagues suggested that osteoporosis is a disorder of reduced bone formation,[66] but they did not specify its morphologic basis. We now believe that in addition to the decreased volume of bone that is formed in each bone multicellular unit during aging,[42] the reduced formation of periosteal bone during growth, aging, or both partly explains the smaller size of the vertebral body and smaller bone mineral mass in women and men with vertebral fractures.[67,68]

BONE FRAGILITY IN PATIENTS WITH FRACTURES

Not all fractures have the same pathogenesis or structural abnormalities that cause bone fragility. Some fractures are associated with reduced tissue mineral density[69]; in others, there is a reduced density of osteocytes.[70] Women with fractures may have high, normal, or low rates of remodeling. Some women with fractures have a negative

balance in the bone multicellular unit owing to reduced bone formation, increased resorption, or both; other women with fractures have no negative balance in the bone multicellular unit balance[71-73] (Fig. 3). The heterogeneity of mechanisms suggests that all patients with fragility fractures should not be treated in the same way.

EFFECTS OF ANTIRESORPTIVE AND BONE-FORMING AGENTS

In most postmenopausal women, the remodeling rate is high — a large number of bone multicellular units excavate cavities while other units are at various stages involved in the completion of remodeling. When an antiresorptive agent is given, this steady state is perturbed.[74-76] The birth rate of new bone multicellular units decreases quickly when treatment is started, whereas the many bone multicellular units at various stages in the remodeling cycle complete the remodeling process by depositing a volume of new bone that reduces the depth of the excavated site (Fig. 4). The newly deposited bone undergoes primary mineralization and then slower secondary mineralization. (Primary mineralization is the rapid laying down of mineral during the deposition of osteoid in the formation period of the remodeling cycle. Secondary mineralization is the slow enlargement of the crystals occurring thereafter.) The deposition of bone reduces cortical porosity and focal stress, thereby preventing microdamage. These early material and structural changes partly reverse fragility by helping to restore bone strength, which may account for the early reduction in fracture risk during treatment.

The increased tissue mineral density and reduced porosity slightly improve bone strength. During treatment, the slow remodeling rate and the reduced depth of a decreased number of excavated sites produce bone loss and structural decay but more slowly than before, and bone fragility reemerges. Fractures continue but are less frequent than in untreated controls in whom rapid remodeling and a negative balance in bone multicellular units exponentially increase bone fragility. Thus, early in treatment, antiresorptive agents partly restore bone strength by reducing the rate of bone remodeling and by promoting the completion of remodeling by bone formation in the many excavated sites that were present before treatment. The drugs then slow the progression of fragility by suppressing the rate of remodeling and reducing the depth of resorption in each of the reduced number of bone multicellular units engaged in remodeling bone.

Given that the purpose of remodeling is to maintain bone strength by repairing microdamage, could such suppression of remodeling be harmful? Heterogeneity in the distribution of tissue mineral density — with younger, less densely mineralized regions adjacent to older, more densely mineralized regions — obstructs the progres-

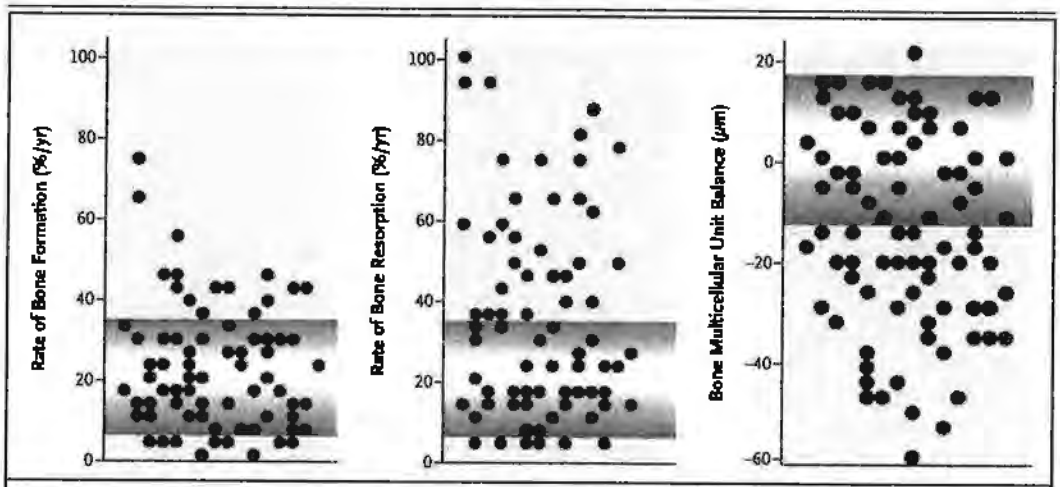

Figure 3. Heterogeneity in the Pathogenesis of Bone Fragility in Women with Fractures.
Women with fractures may have rates of bone formation and resorption that are high, normal, or low and a normal or negative bone multicellular unit balance. The shaded area in each graph depicts the normal range (the 10th to 90th percentile). Data are adapted from Eriksen et al.[71]

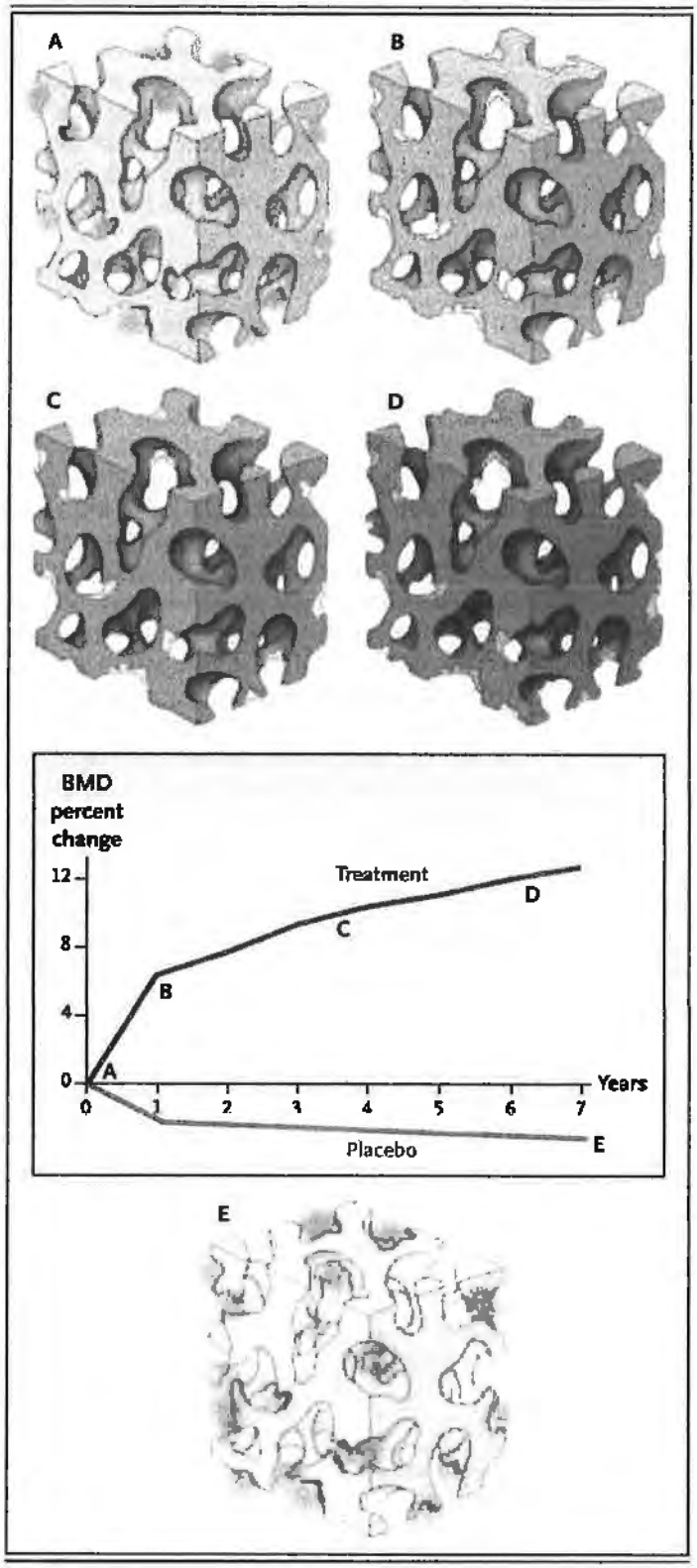

Figure 4. Effects of Antiresorptive Treatment on Bone Remodeling.

Before treatment, rapid remodeling and resorption in each remodeling unit produce numerous deep cavities on trabecular surfaces (colored pink) (Panel A and point A in graph). Treatment with antiresorptive agents suppresses the birth of new remodeling units, and remodeling continues with the deposition of new bone (colored yellow) (Panel B and points A to B in the graph). The newly deposited bone partly maintains bone structure. Slow remodeling during treatment permits more complete secondary mineralization of the newly deposited bone and the rest of the bone (darker color) (Panels C and D), which slowly increases bone mineral density (BMD) for years (points B to D in the graph). Remodeling continues, but fewer and more shallow resorption cavities (colored yellow) remove less bone (Panel D). In the placebo group, rapid remodeling reduces tissue mineral density (colored light gray), and deep resorption in each cavity produces trabecular thinning, perforation, and a loss of connectivity (colored pink), with a decrease in BMD (Panel E and points A to E in the graph).

sion of microcracking. Since remodeling is slow during treatment with antiresorptive agents, more time is available for secondary mineralization of the new bone deposited in the many sites of resorption that were present before treatment and in bone that has not undergone remodeling because it is distant from the endosteal surface. The slower remodeling allows tissue mineral density to increase so that there is a loss of heterogeneity in the distribution of tissue mineral density between adjacent regions. The former increases tissue stiffness, thereby predisposing the bone to microdamage. The greater homogeneity in tissue density offers less resistance to the propagation of cracking.[2] Reduced remodeling may also reduce removal of microdamage in bone.[49,50,76-81]

Microdamage and increased brittleness of bone occur in animals given high doses of bisphosphonates. Although convincing evidence in humans is lacking, case reports suggest that research is needed to determine whether prolonged suppression of remodeling is deleterious[82,83] and whether drugs that greatly suppress remodeling are more appropriate in persons with high remodeling rates and low tissue mineral density but less appropriate in persons with lower remodeling rates and normal tissue mineral density, in whom further suppression may predispose bone to microdamage.

Anabolic agents such as parathyroid hormone

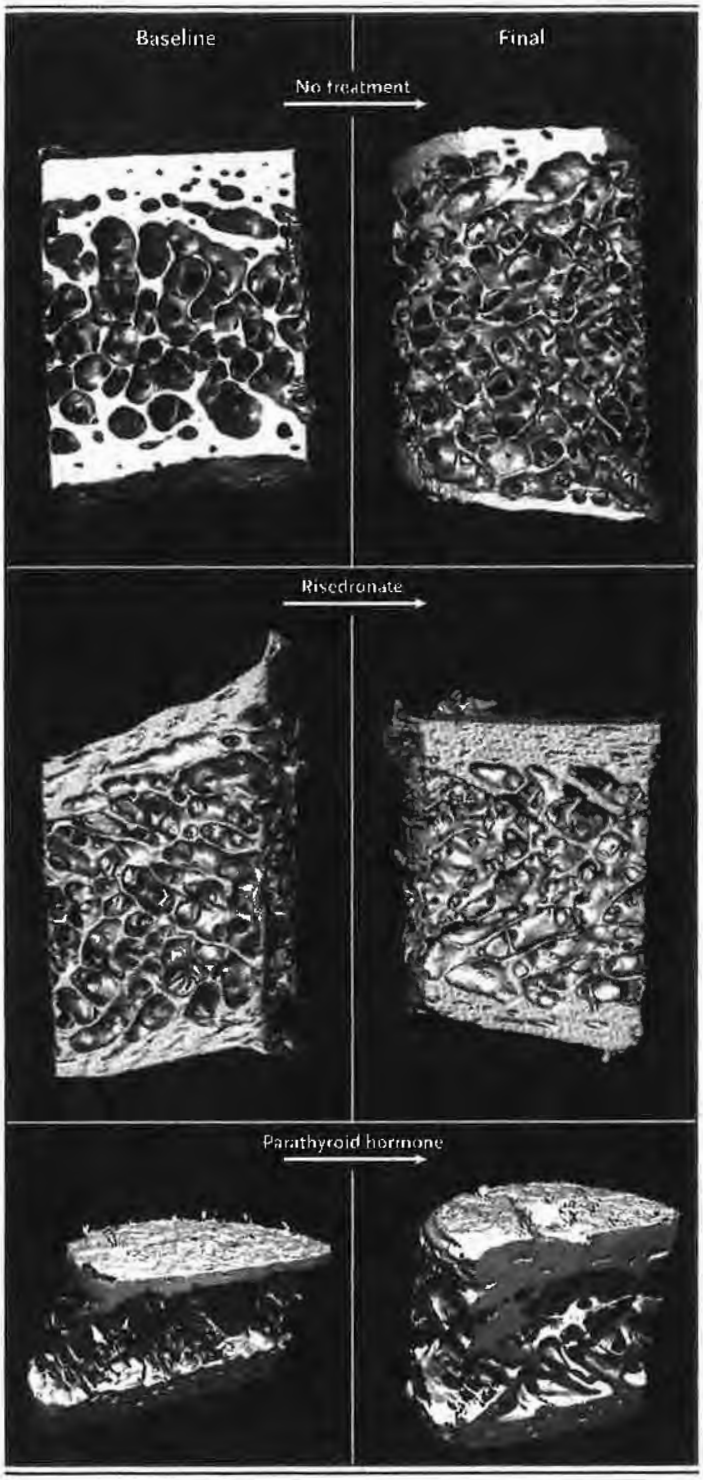

Figure 5. Effects of Treatment with Anabolic or Antiresorptive Agents.

Microcomputed tomography of biopsy specimens of the iliac crest at baseline and after three years in an untreated control subject shows cortical and trabecular thinning and a loss of connectivity (Panel A). In Panel B, treatment with the antiresorptive agent risedronate maintains structure. (microcomputed tomography in Panels A and B courtesy of B. Borah, Procter & Gamble Pharmaceuticals.) In Panel C, treatment with parathyroid hormone, an anabolic agent, promotes the deposition of bone and cortical and trabecular thickening, as shown on microcomputed tomography of biopsy specimens of the iliac crest at baseline and after 18 months of treatment. (Reprinted from Jiang et al.[84] with the permission of the publisher.)

stimulate periosteal apposition in growing animals (Fig. 5). Evidence in adult subjects is limited.[84] Most of the increase in cortical and trabecular thickness, as well as the improved trabecular structure induced by parathyroid hormone, is caused by bone formation on the inner surfaces adjacent to marrow. Although seemingly more appropriate in patients with a reduced rate of remodeling and bone formation, the anabolic action may require bone resorption[85]; efficacy in the prevention of fracture appears to be similar in persons with low rates and those with high rates of remodeling.[86] There is no evidence that fracture rates are reduced more by combined therapy with antiresorptive agents and parathyroid hormone than by either therapy alone. Previous use of antiresorptive agents does not seem to influence the eventual response to the hormone.

Advances in noninvasive techniques are likely to provide insights into the effects of these therapeutic agents on bone structure and increasingly accurate information concerning the structural heterogeneity of bone fragility from patient to patient and so may improve the sensitivity of the prediction of fracture risk.[87] Evidence of this is suggested by the finding that patients with low bone mass, high remodeling rates, and a prevalent fracture have an increased fracture risk. When the absolute risk of fracture is high, more patients who are exposed to treatment actually benefit from it because a greater proportion of these high-risk patients have fractures.[88,89]

CONCLUSIONS

The purpose of bone modeling and remodeling throughout life is to adapt the material composition and structure of bone to prevailing loads. During growth, these processes fashion a structure able to accommodate Herculean loads and

maintain its strength by adapting one trait to compensate for a defect in another. Advancing age is accompanied by accumulating abnormalities in this cellular machinery, hormonal deficiency and excess, deficiency and excess of local growth factors, declining muscle mass and mobility, nutritional deficiencies, and other factors that overwhelm the declining ability of the remodeling machinery to adapt bone to prevailing loads. Abnormalities in the balance and rate of remodeling and limits to periosteal apposition compromise the material composition and structural design of bone so that it is no longer "just right" for the loads it must endure. Bone fragility is the consequence of failed adaptation. Why bones become fragile is a problem of cell biology. How and when bones fail is a problem of biomechanical engineering. The solution to the problem of structural failure requires a study of the qualities of bone and the cellular mechanisms maintaining these qualities from region to region in the body.

No potential conflict of interest relevant to this article was reported.

We are indebted to T.J. Martin of the University of Melbourne for his advice and critical comments.

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