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Between birth and maturity, the human skeleton increases in size and strength and adapts its parts to meet mechanical and other demands. It is now apparent that many defects in skeletal development, acquired skeletal diseases, and the effects of many agents on bone mass may all stem from changes in the way in which skeletal tissue perceives and adapts to typical mechanical usage[9, 10, 16, 19, 46] (Table 1). This concept is discussed here in relation to growth. Firstly, however, some basic terms and principal mechanisms are explained:

- *Osteopenia:* Less bone tissue than normal, not necessarily implying disease.
- *Osteoporosis:* A disease combining osteopenia with clinical evidence of increased bone fragility[42, 49].
- *Bone mass (or the bone bank):* The bone tissue contained by the skeleton and comprising cortical and trabecular fractions.
- *Mechanical usage:* All the forces applied to bone during usual activities, with emphasis on the magnitude rather than on the frequency of the forces (weight lifting has a greater effect on the bone bank than walking and marathon running do[1, 4, 42]).

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Principal mechanisms

Longitudinal bone growth and modeling drifts (macromodeling) control changes in bone length and shape during growth. Remodeling by the basic multicellular unit (BMU) controls bone losses throughout life. Setpoints establish the sensitivity level for skeletal adaptation to mechanical usage. Micromodeling determines what kind of bone forms, whereas microdamage and repair determine how bone endures ordinary activities. The stress that can break normal bone (the 'fracture' stress), which is about 130 MPa or 16000 psi, provides a yardstick against which other stresses may be compared[1, 3, 4, 46, 48].

Longitudinal bone growth

Cartilage growth at apophyseal and epiphyseal growth plates adds new length to growing bones. A complex process of endochondral ossification then replaces the deeper layers of new cartilage with trabecular bone. Most trabecular bone is created by this process, which also adds new length to the cortex and thus tends to increase the cortical part of the bone bank[3, 4, 32]. This process of trabecular bone creation begins with resorption of some of the mineralized cartilage at the base of growth plates and deposition of woven bone on the remainder. The resulting bars of mineralized cartilage covered with woven bone form the primary spongiosa. Then remodeling BMUs replace the primary spongiosa with new lamellar bone to form the trabeculae of the permanent or secondary spongiosa. As the

Osteoporosis	Aneurysm
adult acquired	Keloid
in children	Joint contracture
Osteopenia	Osteochondroma
in disuse	Retarded bone healing
in chronic disease	Retarded tendon healing
Osteogenesis imperfecta	Dwarfism
Arthrosis	Frozen shoulder
Spinal stenosis	Hallux rigidus
Increased bone fragility	Genu varum and valgum
Spontaneous tendon rupture	Congenital hip dysplasia
Spontaneous fracture	Club foot
Osteochondritis dissecans	Dentinogenesis imperfecta
Aseptic necrosis	Prognathism
Hernia	Ehlers-Danlos syndrome
Varices	Chondromalacia

Table 1: Some skeletal diseases in which altered perception of and adaptation to mechanical usage play major causative roles

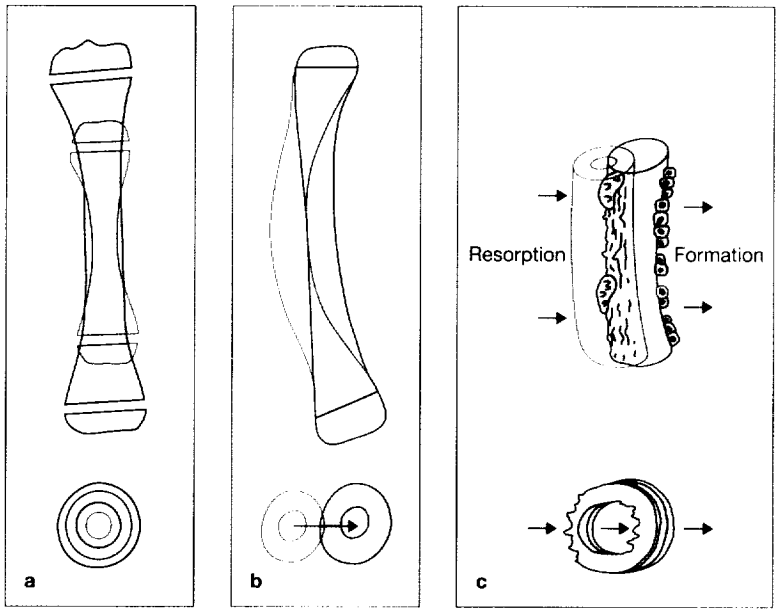

Fig. 1: Modeling drifts

a) A long bone during infancy (thin outlines represent initial size and shape). For the bone to maintain its shape as it grows in length and diameter, its surfaces must move in tissue space. Formation drifts build some surfaces up; resorption drifts remove bone from other surfaces.

b) A different drift pattern can correct the bowing due to a fracture malunion.

c) Movement of the whole segment by endocortical and periosteal drifts to the right in tissue space. The drifts are largely controlled by responses to mechanical usage (see text).

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growth plates grow away from the newly-formed primary spongiosa an intricate series of changes begins in the number, composition, thickness, and stiffness of the trabeculae that are left behind. For a long time, these changes were thought to be controlled by systemic and local biochemical agents; however, they may instead be controlled by some vital biomechanical factors.

In sum, longitudinal bone growth increases bone length and creation of new spongiosa and compacta.

Effects of mechanical usage: hypervigorous mechanical usage tends to increase longitudinal bone growth slightly. Disuse, e.g. in congenitally paralyzed limbs, can retard longitudinal growth,

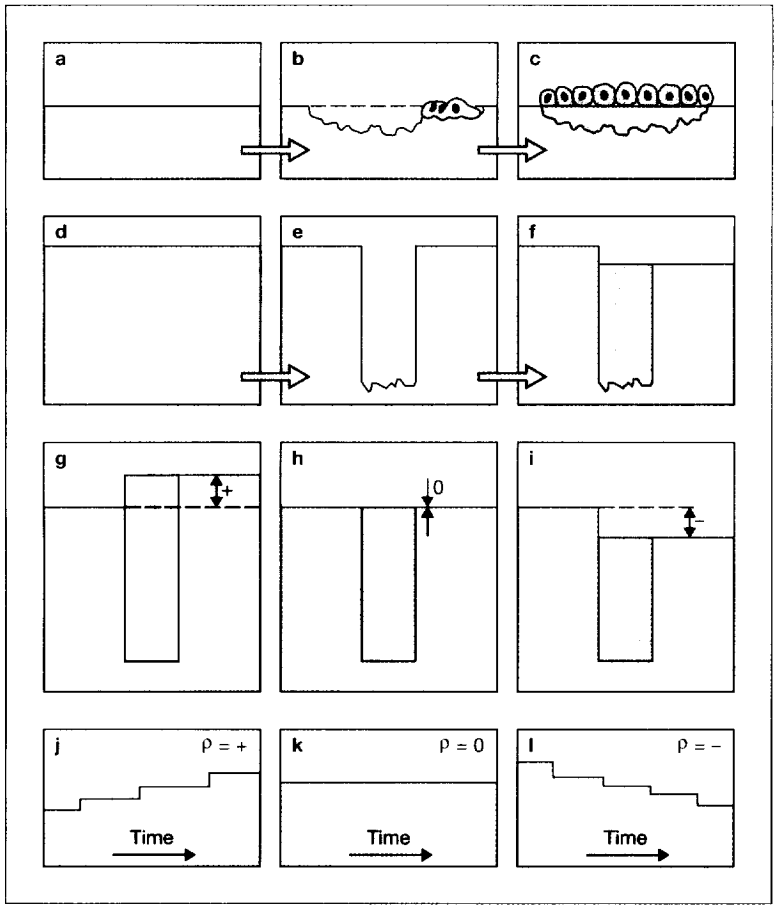


Fig. 2: Remodeling by the basic multicellular unit (BMU): an activation event on a bone surface (a) causes a bone resorption packet (b) and then replacement of the resorbed bone (c). Idealized diagrams (d–f) of these events can be used to show how much bone has been resorbed and formed in completed BMUs. 'BMU graphs' show a small excess of formation over resorption, as on periosteal surfaces (g); equalized resorption and formation, as on haversian surfaces (h); and a net deficit of formation, as on endocortical and trabecular surfaces (i). The 'stair graphs'[48] (j–l) show how a series of BMUs of the kind in g–i would affect the local bone balance and mass ($\triangle B$).
$\rho = \triangle B \cdot BMU$.

making bones shorter than normal[4, 18, 33]. A decrease in longitudinal growth correspondingly slows down the creation of new spongiosa and compacta.

Modeling drifts (modeling or macromodeling)

During growth, osteoblasts can form lamellar bone on bone surfaces without any coupling to osteoclasts. On other surfaces, osteoclasts can remove bone without any coupling to osteoblasts. These *formation and resorption drifts* can move whole bone surfaces in anatomical space and thus determine the bone's shape (hence the term 'modeling'), cortical thickness and outside diameter[3, 4, 32]. Figure 1 shows how these drifts maintain the shape of the bone as it grows to adult size. Modeling drifts can act on periosteal, endocortical, and trabecular surfaces. They tend to become less effective on cortical bone at skeletal maturity, but can continue to act on trabeculae throughout life. Thus, almost all cortical bone is created by formation drifts. Once formed, it can undergo piecemeal replacement by secondary haversian remodeling (see below)[20, 24, 32].

In sum, increased global (whole bone or skeleton combined) modeling (by drifts) tends to increase bone mass. Decreased modeling does not reduce bone mass, it simply retards further additions to it.

Effects of mechanical usage: when and where bone stresses rise to or above a threshold of about one-twelfth of the fracture stress, modeling drifts 'turn

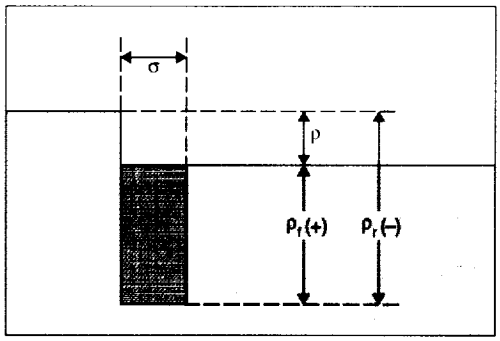


Fig. 3: For completed basic multicellular units ρ_r indicates the amount of bone resorbed, ρ_f the amount formed, and ρ the difference between them. This figure illustrates the negative ρ (meaning a net loss of local bone) usually found where bone touches marrow.
σ = remodeling period

on' and begin to change the bone in ways that strengthen it and tend to reduce subsequent stresses. When and where loads stay below this threshold, mechanically controlled modeling drifts tend to stay 'off'[4, 16, 32, 41, 42, 46]. Thus, global modeling drifts can adapt bone to overload, but apparently not to underload or disuse.

Micromodeling

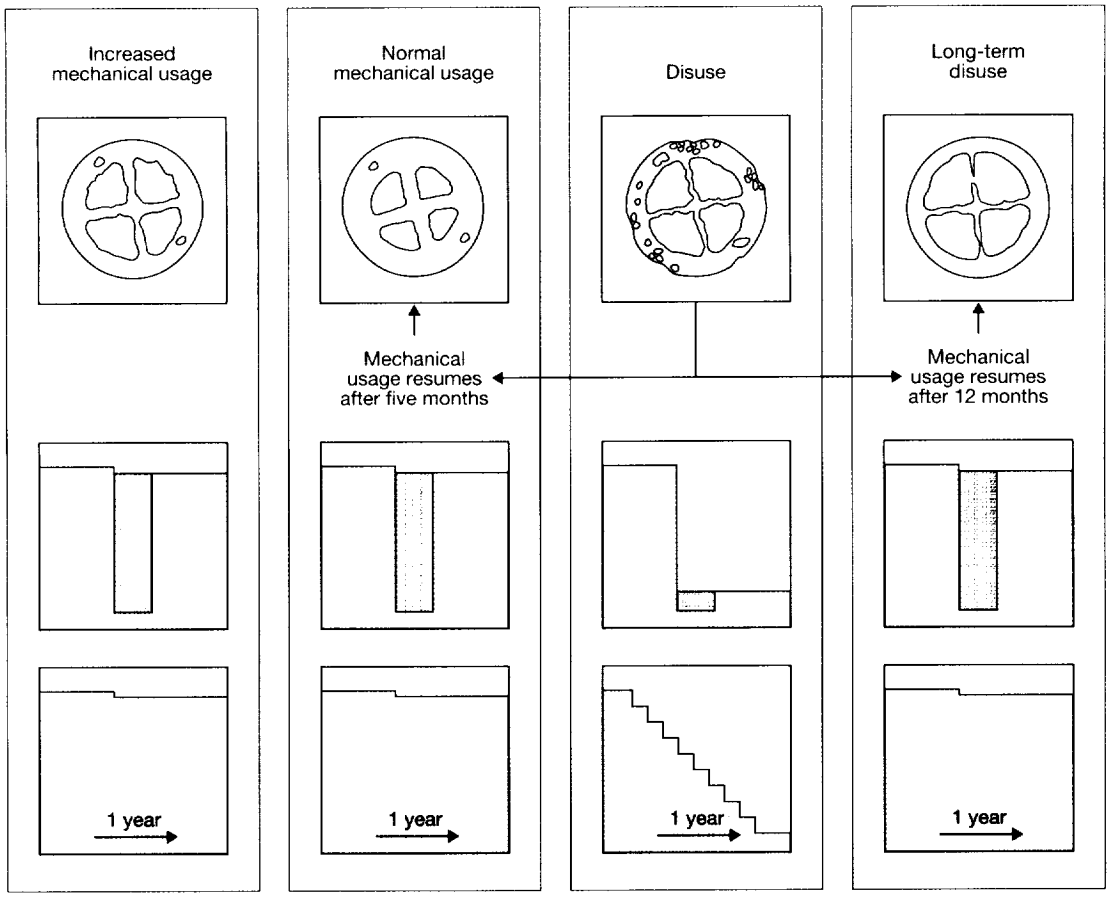
When bone is being formed, a different kind of cellular activity from normal determines the organization and grain of intercellular materials in the new tissue, the organization of the tissue's cells and blood vessels, and therefore the kind of tissue that forms. Micromodeling makes lamellar bone different from woven bone and fracture callus. It always makes the grain of lamellar bone parallel to the major loads on it during its formation[4, 24].

Remodeling by the basic multicellular unit

As depicted in Figure 2, a BMU turns bone over in packets. An activation event make a BMU begin, resorption follows and formation replaces what was resorbed, thus completing the process (and the BMU), which takes about four months in man. The finished packet of new bone, the 'basic structural unit', contains about 0.05 mm^3 of bone. BMUs can act throughout life on all four bone 'envelopes': periosteal, haversian, endocortical, and trabecular surfaces. However, in children, most periosteal and endocortical activity comes from modeling drifts. On the haversian envelope inside the bone cortex, BMUs form secondary osteons or haversian systems.

BMU effects on bone mass, bone turnover, and bone gain or loss (ρ): newly formed BMUs normally resorb and form nearly equal amounts of bone on periosteal and haversian surfaces, so they rarely cause permanent bone gains or losses there. However, throughout life and where bone touches marrow, BMUs normally make slightly less bone than they resorb (about 0.003 mm^3 less per BMU). In acute disuse they may even make none at all. They do not make more than they resorb without pharmacological aid[5, 11, 17, 46]. This results in the loss of trabecular bone throughout life and the expansion of the marrow cavity diameter in adults (in children marrow cavity expansion is probably due to modeling drifts). Each completed BMU next to marrow removes a small 'bite' of bone, so ρ, the deficit or excess of bone in completed BMUs, is usually negative where bone touches marrow (Fig. 3). Thus, an increase in BMU creations (activation) would increase the number of bites taken out of trabecular and endocortical bone and increase their loss. If this is combined with larger deficits in completed BMUs (even greater negative ρ values) greatly increased bone loss next to marrow can happen. For example, remodeling normally removes about 0.75% of an adult's bone annually, yet in acute disuse combined with a fracture it can remove 40% of the trabecular bone in under two months, briefly increasing the local rate of loss to over 250 times normal. Only part of that loss, however, is 'irreversible'. The 'reversible' portion stems from the increased remodeling space caused by the increased numbers of partly resorbed and refilled resorption cavities or bays; when refilling finishes, this fraction of bone loss is restored[1, 4, 14, 15, 21, 23, 26, 27, 48].

In sum, global remodeling can conserve or remove but cannot add bone (without pharmacological aid). Increased BMU creations plus an even greater negative ρ value increase bone losses next to marrow. Decreased creations and a less negative ρ value tend to conserve bone. Generally, when and where global remodeling activity increases, so do losses of bone touching marrow. When and where it decreases, bone tends to be conserved.



Effects of mechanical usage (Fig. 4): in acute disuse, bone stresses fall and stay below a threshold at about 1/400th of the fracture stress. Then creation of BMUs can increase to over five times normal on all bone surfaces, while BMUs next to marrow begin making much less bone than they resorb. This can cause osteopenia. When normal mechanical usage resumes, bone stresses rise above the threshold and BMU creations begin to decrease towards normal. Resorption and formation in completed BMUs usually become equal and this tends to conserve existing bone and prevent osteopenia. This situation usually persists during hypervigorous mechanical usage[4, 6–8, 11, 33, 35, 40–42, 46, 47].

In sum, BMU-based global remodeling can adapt bone to disuse, but apparently not to overuse.

Fig. 4: Effects of mechanical usage on remodeling

Top row: cross-sectional diagrams of bone illustrating effects of normal and increased mechanical usage and effects of disuse.

Middle row: basic multicellular unit graphs showing the ρ values (see Fig. 3) for the mechanical usage in the cases above.

Bottom row: 'stair graphs' showing the changes in the creation of BMUs and in the ρ value associated with the mechanical usage in the cases above.

When disuse lasts only a short time, most of the losses can be restored. When it lasts for a long time, some permanent trabecular and cortical thinning and marrow cavity expansion result.

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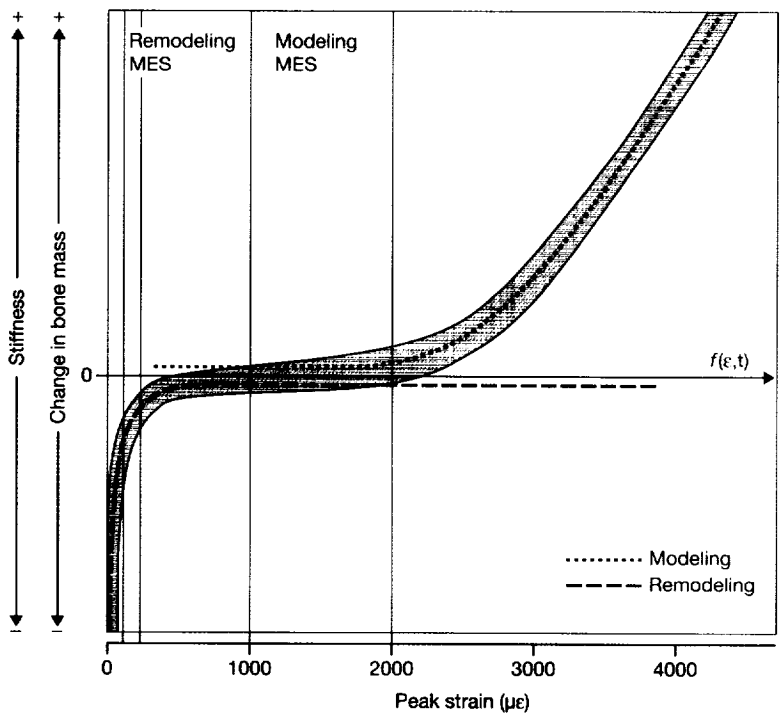

Fig. 5: Combined effects of modeling and remodeling on bone mass plotted against dynamic mechanical strain history; f (ε, t) is a strain parameter combining elements of magnitude, rate, frequency, range and history – the horizontal axis here represents normal bone mass, strength, and stiffness. The contribution of remodeling to them lies below the horizontal, that of modeling above it. An increase in either activity drives its contribution further away from the horizontal and reduces or increases bone mass in the ways suggested. The shaded areas indicate suggested approximate ranges of minimum effective strain (MES) for remodeling and modeling. The value of 4000 would be about one-sixth of the strain that would fracture bone. This curve expands on one originally suggested by CARTER[2].

Combined effects on bone mass: the combined effects of modeling and remodeling on bone mass are plotted in Figure 5. Remodeling effects appear below the horizontal, which represents normal bone mass and therefore normal bone stiffness also, and the modeling effects appear above it. The figure also shows suggested locations of the threshold stress ranges for modeling and remodeling as corresponding typical peak strains.

Setpoint effects

The genome must partly determine the values or 'setpoints' of the two mechanical thresholds that determine how modeling and remodeling respond to mechanics. Increased setpoints should have the same effects on bone mass as disuse, and decreased setpoints the same effects as hypervigorous mechanical usage (Fig. 6). In principle, hormones, drugs, cytokines and other agents may change setpoints, and there is much circumstantial evidence to suggest that they do[4, 32, 36, 42, 46]. If so, elevated setpoints would make the biological systems perceive a spurious disuse and begin the previously described changes in bone mass and architecture observed in cases of true mechanical disuse, and in children. In most metabolic bone diseases, the bone mass changes show a strong tendency to copy the usual patterns of mechanical usage in children and adults[3, 5, 7, 9, 22, 41, 42].

Microdamage and its repair

Bone can develop mechanical damage from repeated cycles of loading and unloading. Called 'microdamage' in bone (and in other structural tissues), it increases with the number of loading cycles and the size of the loads. It makes bone more likely to fracture from injury than would appear to be the case from the existing amount of bone alone. The microdamage threshold of bone is approximately one-quarter of the fracture load based on the following: at one-sixth of the fracture stress, it would take a normally active adult about 40 years to accumulate enough microdamage to cause fatigue fracture. Yet at one-third of the fracture stress, fatigue

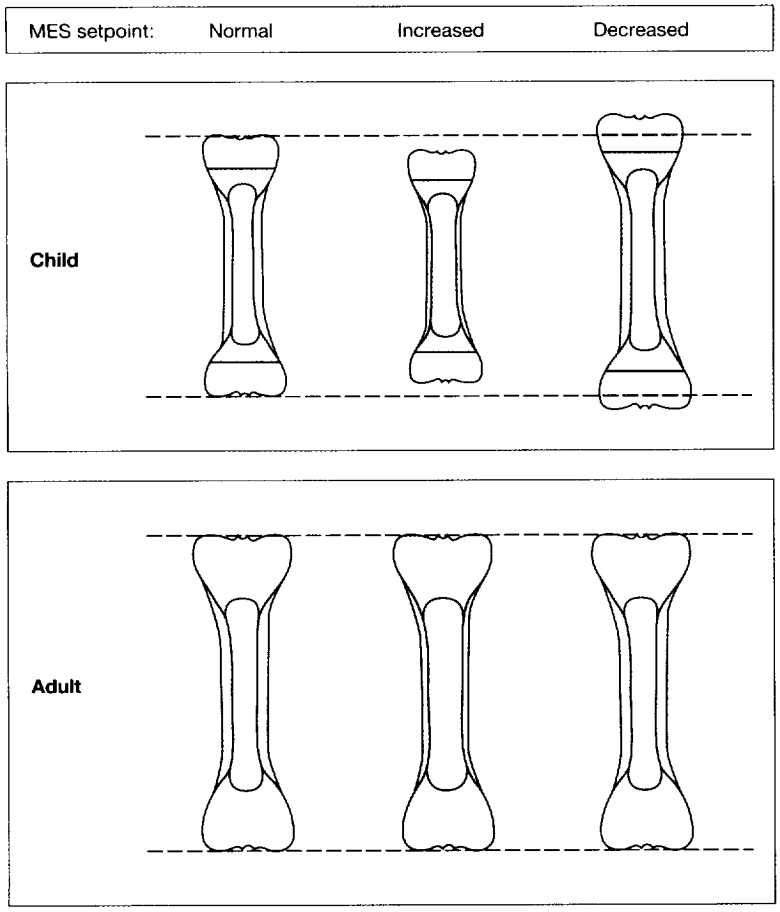

Fig. 6: Some effects due to changes in minimum effective strain (MES) setpoints.

The upper row suggests what configuration the bones would have if a child grew with the indicated changes in setpoints for longitudinal growth, bone modeling, and basic multicellular unit based bone remodeling.

The lower row shows what an adult's bone would be like if the setpoints changed in adult life. Increased setpoints would cause osteopenia, but decreased setpoints would lead to better conservation of the original bone rather than to real additions, since cortical modeling becomes less effective in adults and longitudinal growth stops.

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fracture can occur in less than two months of normal activity. Normal bone can detect microdamage as it happens. BMUs then repair the damaged bone by removing and replacing it with new bone. If the repair processes become impaired, microdamage can accumulate and weaken the bone.

Possible biomechanical explanations for the architecture of growing long bones

A typical growing bone consists of two wide ends (the epiphyses), two flared, inwaisted (funnel-shaped) metaphyseal growth-plate complexes, and a slender hollow column (the mid-shaft). The epiphyses are filled with moderately thick low-turnover trabeculae, while the metaphyses contain primary and secondary spongiosa. The primary spongiosa consists of trabeculae made of a fine latticework of calcified cartilage cores and woven bone. The secondary spongiosa has fewer but thicker high-turnover trabeculae. The slender hollow column of cortical bone (the shaft or diaphysis) that unites the metaphyses is usually free of trabeculation[4, 29, 32, 37, 44].

There are a number of biomechanical explanations for this design (Fig. 7):

- Wide ends are needed to accommodate the large areas of articular cartilage — it takes about four times more cross-sectional area of articular cartilage area than of bone to carry the same load.

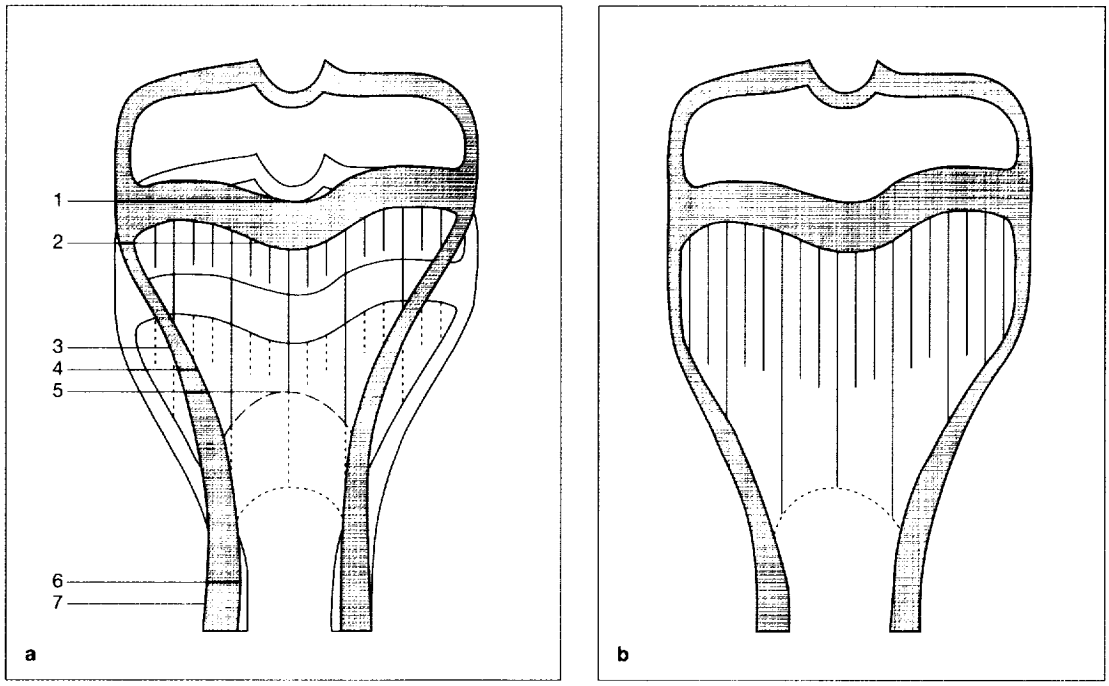

Fig. 7: Diagrams of modeling during growth of the proximal end of the tibia (see text for biomechanical explanation)

a) The status of the proximal tibia after 14 days' growth (dark brown) is shown superimposed on the initial status (light brown).

Resorption occurs at four different sites:
- *resorption of calcified cartilage septa (2)(only about one in three of the original septa remain),*
- *resorption drift along the periosteal surface of the metaphysis (3),*
- *elongation of the marrow cavity by resorption of metaphyseal cancellous bone (5), and*
- *radial expansion of the cavity by resorption of subendocortical bone (6).*

Formation occurs at three different sites:
- *formation of new hyaline cartilage (1),*
- *formation of endocortical bone (4) (endocortical formation drift), and*
- *expansion of outer diameter of shaft by periosteal bone formation (7) (periosteal formation drift).*

The combination of these activities increases bone length, adds new spongiosa and compacta, redistributes the number of trabeculae in the metaphysis, and maintains the inwaisting of the metaphysis.

b) The configuration of a metaphysis when resorption is inhibited; as can be seen, the proximal metaphysis is bulging.

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- A slender but massive shaft of cortical bone is needed to resist buckling caused by compression and bending loads on hollow bones.
- The flared metaphyses expedite the transition from an enlarged metaphysis to a slender diaphysis. An endocortical formation drift and a periosteal resorption drift model the new metaphyseal cortex created at the growth plate in the direction of the marrow cavity during longitudinal growth. These centripetal drifts reduce outside diameter and maintain inwaisting while the bone's size and length increase during growth. If inwaisting is not maintained, a 'trumpet' shape results (convex instead of concaved[32, 37]; Fig. 7b).
- Thick, low-turnover, epiphyseal trabeculae are created because the epiphyses bear the highest

end-loading and compression-loading from the joints and because overloads tend to enhance modeling-dependent bone gain and depress remodeling-dependent bone loss[44].

- The wide growth cartilage is needed to accommodate the epiphysis and for longitudinal growth (endochondral ossification) to generate new cancellous and cortical bone. The end-product of wide growth cartilage, called the growth plate, is primary spongiosa[37]. The trabeculae of the primary spongiosa are of inferior quality and presumably unable to bear local loads, so they are remodeled into secondary (lamellar) trabeculae. The conversion of primary into secondary trabeculae may be partly driven by microdamage that triggers remodeling and local formation drifts.
- The end-product of the conversion from primary to secondary trabeculae is the secondary spongiosa of fewer, thicker, high-turnover secondary trabeculae[44]. The reason for this configuration of trabeculae is the progressive reduction in loads as they are transferred from the epiphysis to the metaphyseal cortex. Thus, the further the trabeculae are from the growth plate, the smaller the loads they carry (i.e. they become deloaded).
- Towards mid-shaft, the marrow cavities are free of trabeculae because the thick compacta bears all the mechanical load and unloaded trabeculae are either removed or thinned.
- As longitudinal growth takes place, the long bone shaft increases in diameter. This maintains the shaft's strength during growth while making its wall proportionally thinner. If 100 units of area are removed from the endocortical (inner) cortex of the bone to accommodate the marrow cavity, the bending strength can be maintained by adding only 30 units of area onto the periosteal (outer) surface. These modeling activities feature net bone formation on the periosteal surface and net resorption on the endocortical surfaces[42].

Some clinical problems involving the principal *biological mechanisms*

Osteopenia

Osteopenia develops in children when additions by growth and modeling slow down, when losses by remodeling increase, or both. A combination usually happens in true disuse situations, which can include chronic debilitating medical diseases (e.g. cardiac and pulmonary insufficiency, cirrhosis, starvation, cystic fibrosis, and juvenile rheumatoid arthritis), paralyses, and muscular dystrophies.

Hormones, cytokines, drugs, other agents, and setpoints

In the past it was thought that such agents acted directly on osteoclasts or osteoblasts[43, 45]. Modern biology of bone shows that these agents can change the modeling and remodeling setpoints, or act directly on the above cells, or both (Table 2). In any case, the skeleton then protects itself from further adverse effects on bone mass and 'mechanical competence' by causing the effects to plateau instead of allowing them to progress continuously with continued treatment. The probable mechanism of this protective and frequently manifested plateauing was described recently[23, 36].

Many believe that estrogen normally lowers the setpoints, so a lack of estrogen would raise them. This could explain the osteopenia in growing females with Turner's syndrome. Adrenocortical hormones may raise the setpoints, which would explain the

Table 2: Some agents/conditions that probably exert effects on bone either by changing the modeling and remodeling setpoints alone or combined with direct actions on osteoclasts, osteoblasts, and other cells

Adrenocortical steroids	Estrogens
Progestins	Parathyroid hormone
Growth hormone	Somatomedins
Testosterone	Calcitonin
Low serum calcium	Elevated serum calcium
Dietary calcium	Dietary phosphate
Thyroxine	Fluoride
Starvation	Vitamin D (+metabolites)
Bisphosphonates	Prostaglandins
Some cytokines	Genetic factors
Metabolic acidosis	Metabolic alkalosis
Nonsteroidal anti-inflammatory drugs	

pattern of bone loss in *iatrogenic* Cushing's disease. Congenitally elevated setpoints could explain the bone problems in osteogenesis imperfecta[5]. Smaller elevations might explain the bone deficit in juvenile idiopathic osteoporosis. On the other hand, growth hormone, low- and intermittent-dose parathyroid hormone, and some somatomedins may lower these setpoints, which could partly explain the improvement in bone mass they can cause during growth. The increased bone mass in gigantism stems from increased additions by longitudinal growth and modeling that may involve a lowering of setpoints by growth hormone or by a somatomedin. Increased bone density in osteopetrosis stems from reduced losses due to remodeling being greatly depressed in this disease. Increased bone density in familial vitamin-D-refractory rickets also stems from depressed remodeling, which tends to conserve previously made bone.

It seems that dietary protein, calcium, and vitamin D, rather than increasing bone mass directly, only enable bone to adjust its mass optimally to its typical mechanical usage, and that usage and the associated setpoints determine the optimal response. Dietary deficiencies would simply tend to limit the gains needed for mechanical usage, the limitation being greater in those parts of a bone that are subjected to greater levels of stress (see 'Homeostasis and calcium' below). Probably because of this, dietary supplements of such agents given to children who, for whatever reason, are chronically inactive do not usually lead to an accumulation of normal bone masses. This is something that pediatricians need to know.

Osteoporoses and bone fragility

Osteopenia in all osteoporoses certainly makes bones weaker than normal. However, bone fragility usually increases beyond the level expected on the basis of reduced bone mass alone. It is becoming increasingly clear that bone microdamage also increases in most osteoporoses and may account for a major rather than minor proportion of the increased fragility in many of them[3].

Stress fractures

When microdamage increases to such an extent that it cannot be repaired by remodeling, or when repair is impaired, 'spontaneous' fractures can occur during normal mechanical usage. These fractures, usually called 'stress' fractures, can happen in athletes, in special forces trainees, and occasionally in apparently healthy children and adults. Such fractures usually heal well. They can also happen when and where a tumor or cyst destroys bone. Destruction of this kind tends to increase the loads on the remaining bone, often so much that the microdamage threshold is crossed and a pathologic fracture results. Such fractures can happen in osteomalacia (pseudo-fractures or Looser's zones) and aseptic necrosis of bone (Perthes', Kienböck's, and Osgood-Schlatter diseases)[42, 46, 48].

Homeostasis and calcium

When bone has to supply large amounts of calcium to the blood in times of dire need, there are net losses of bone tissue. However, known effects of such challenges on osteoclasts in vitro cannot explain the special way in which this occurs. The bone removed for this purpose does not come equally from all bone surfaces or parts of the skeleton. Instead, it tends to come from the least stressed parts of the bone, which, for mechanical reasons, are trabecular and endocortical bone. The part of bone that is of greatest mechanical importance is on the periosteal and adjacent haversian surfaces and is usually preserved during times of loss caused by homeostasis. This suggests that the responses of bone to mechanical usage can control some of its responses to homeostatic challenge. This should also apply to challenges associated with chronic renal disease, chronic primary hyperparathyroidism, nutritional deprivation, osteomalacias, vitamin-D deficiency, and chronic metabolic acidosis[4].

Fracture healing

Normally fracture healing proceeds as follows: fracture, granulation tissue, formation of callus, replacement of callus with lamellar bone, recontouring of callus towards normal local bone shape. The last two steps are performed by BMU-based remodeling and modeling drifts respectively. Disorders in these processes can occur and cause biological failures of bone healing (so termed to distinguish them from failures due to treatment problems)[4, 12, 13, 50]. These failures can also affect the healing of surgical osteotomies and bone grafts for established nonunions and of spine fusions and arthrodeses of other joints.

Conclusion

Informed readers will have noted the lack of discussion of how a variety of agents can affect osteoclasts or osteoblasts in vitro. Many such agents could affect bone mass more by changing the way in which the skeleton perceives typical mechanical usage than by acting directly on osteoclasts or osteoblasts. This relatively recent perception partly explains why the effects of such agents in vitro usually cannot predict their effects in vivo (the complex biological systems responsible do not exist intact or function normally in vitro). The skeleton tries to adapt to that altered perception, which can include spurious disuse or spurious hypervigorous usage. While little research addresses this recent perception, such work as has been done supports it[1, 26, 28, 30, 31, 33–35, 38–42, 46].

The material in this article neither questions nor replaces previous views of bone physiology. It simply adds to them a belatedly perceived but real dimension of bone physiology, most of which was probably already ancient when dinosaurs began roaming the earth in the Jurassic. The authors and many of their colleagues believe that the time has come to begin publicizing this new dimension to clinicians who deal with skeletal problems.

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