Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians

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For over 200 years people have tried to understand mechanical influences on living bone.[10,11,16,27,70,81] For orthodontists, orthopaedic and maxillofacial surgeons and dentists this article summarizes some progress in that effort made by 1993. It combines knowledge and ideas from anatomy, biology, the clinic, engineering, materials science and pathology. The greatest progress lies in perceiving some unifying concepts in the abundant evidence and ideas, but through 1993 poor interdisciplinary communication left most clinicians unaware of many of them. To put that progress in context, look at Wolff's Law as stated in 1892:[81]

"Every change in the form and function of bone or of their function alone is followed by certain definite changes in their internal architecture, and equally definite alteration in their external conformation, in accordance with mathematical laws."

A true scientific law can predict a system's particular reactions to given stimuli, mathematics can express it and observation and experiment can test it. Yet as just stated, Wolff's Law cannot predict specific effects of specific mechanical challenges mathematically or verbally. It says mechanics can make bone's architecture change, but it doesn't say how, so it is a statement of relevance. Since Wolff's time others have tried to

Abstract

Basic Multicellular Unit-based bone remodeling can lead to the removal or conservation of bone, but cannot add to it. Decreased mechanical usage (MU) and acute disuse result in loss of bone next to marrow; normal and hypervigorous MU result in bone conservation. Bone modeling by resorption and formation drifts can add bone and reshape the trabeculae and cortex to strengthen them but collectively they do not remove bone. Hypervigorous MU turns this modeling on, and its architectural effects then lower typical peak bone strains caused by future loads of the same kind to a threshold range. Decreased and normal MU leave this modeling off.

Where typical peak bone strains stay below a 50 microstrain region (the MESr) the largest disuse effects on remodeling occur. Larger strains depress it and make it conserve existing bone. Strains above a 1500 microstrain region (the MESm) tend to turn lamellar bone modeling drifts on. By adding to, reshaping and strengthening bone, those drifts reduce future strains under the same mechanical loads towards that strain region. Strains above a 3000 microstrain region (the MESp) can turn woven bone drifts on to suppress local lamellar drifts but can strengthen bone faster than lamellar drifts can. Such strains also increase bone microdamage and the remodeling that normally repairs it.

Those values compare to bone's fracture strain of about 25,000 microstrain.

Key Words

Bone • Wolff's Law • Biomechanics • Remodeling • Modeling • Mechanical influences • Endoprostheses • Orthodontics • Orthopaedics

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Table 1
Abbreviations and Acronyms

BMU:	Basic Multicellular Unit of bone remodeling.
BSU:	Basic Structural Unit, referring to the packet of bone formed by a completed BMU. Example: The secondary osteon or haversian system.
F:	Bone formation by osteoblasts.
MESm:	The minimum effective strain range at and above which mechanically controlled lamellar modeling drifts turn ON (centered near 1500 με ?).
MESp:	The minimum effective strain range above which woven bone drifts turn ON and suppress local lamellar bone drifts (centered near 3000 με ?).
MESr:	The minimum effective strain range at and above which BMU creations begin decreasing towards normal, and a negative rho begins to become less so (centered near 50 με ?).
MU:	Mechanical usage in the sense of the size of the loads on bone, not their frequency. This acknowledges that weight lifting has larger effects on bone mass and strength than marathon running.
R:	Bone resorption by osteoclasts.
RAP:	The Regional Acceleratory Phenomenon.
SATMU:	Structural Adaptations to Mechanical Usage.
ρ:	rho, the amount of bone added or lost per typical completed BMU. It equals the formation fraction minus the resorption fraction.
με:	Microstrain, where 1500 με in compression equals a shortening of 0.15%, or from 100% to 99.85% of the original length. 25,000 με in tension — bone's fracture strain — equals a stretching of 2.5%, or from 100% to 102.5% of the original length.

find both verbal rules and mathematics that could predict such effects. This article summarizes some progress made in that regard by many people, but mostly after 1960.

Given that, then in health and disease the architecture of a whole bone, such as the mandible, depends on both cartilage and bone. In general and during growth, when cartilage and bone needs conflict the cartilage dominates and bone adapts.[29,47,51]

Some general cartilage roles.[19,51] a) In children, cartilage growth determines a bone's length and a joint's shape, size and alignment. b) During growth a cartilage layer at the bony attachments of fascia, ligaments and tendons controls the local growth, and migration during growth, of those attachments.[17,25] This includes the mandibular insertions of the masseter, pterygoids and temporalis. c) For both a) and b), chondral growth responds to mechanical influences in some known ways.[38]

Some general bone roles.[36,51,64] a) Bone provides rigid levers for muscles to act on, and support for joints and teeth. b) Lamellar and woven bone serve somewhat different purposes and can respond differently to mechanical and nonmechanical influences. c) Modeling drifts and remodeling BMUs can each shape, size and turn bone over. d) Yet each can also respond in its own way to aging, hormones, disease, drugs and mechanical influences.[29,36,37,52,53]

On stress and strain. A load (force) on a bone deforms or strains it. This stretches intermolecular bonds in the bone that resist with an elastic force called a *stress*.[17,64] As D'Arcy Thompson and the author suggested long ago,[24,25,76] living bone may depend more on strain than stress to generate the signals that control its biological reactions to mechanical loads.[5-7,33,55,61,67,72] Ergo, this article uses strain as an index of the effects of mechanical loads on bone.

On modeling and remodeling. Two bone-biologic activities can affect a bone's architecture.[5,19,29,51,61] *Modeling* by resorption and formation drifts, henceforth called modeling, can move a bone's surfaces in tissue space to shape and size it, much like modeling a statue in clay or plaster. *Remodeling* by BMUs (Basic Multicellular Units), henceforth called remodeling, can turn bone over in small packets. Each activity can respond in its own way to mechanical and other influences. The text ignores chondral and fibrous tissue responses to mechanical influences described elsewhere.[38,39] Some biologic and vital-biomechanical facts are reviewed first.

Table 1 lists abbreviations and symbols used below, where "architecture" means a bone's shape and size, and the amount and anatomical distribution of its bony tissue.

Bone modeling and its drifts

1) **Two kinds of drifts** (Figures 1 and 2): Osteoblasts in *formation drifts* can form (F) new bone on large regions of periosteal, cortical-endosteal and trabecular surfaces. Osteoclasts in *resorption drifts* can resorb (R) bone from other similar surfaces. Various stimuli, including mechanical ones, can make a drift and its resorption or formation begin. These two drifts are not coupled biologically.[25,29,51] During growth and by moving a bone's surfaces in tissue space, these drifts usually maintain a bone's shape while it increase in size. Other drift patterns can correct deformities from fracture malunions or other problems[25] (Figure 1B-C). Such drifts also move tooth sockets around in the mandible and maxilla in response to orthodontic forces.

Lamellar or *woven bone* can each provide formation drifts on periosteal, cortical-endosteal and

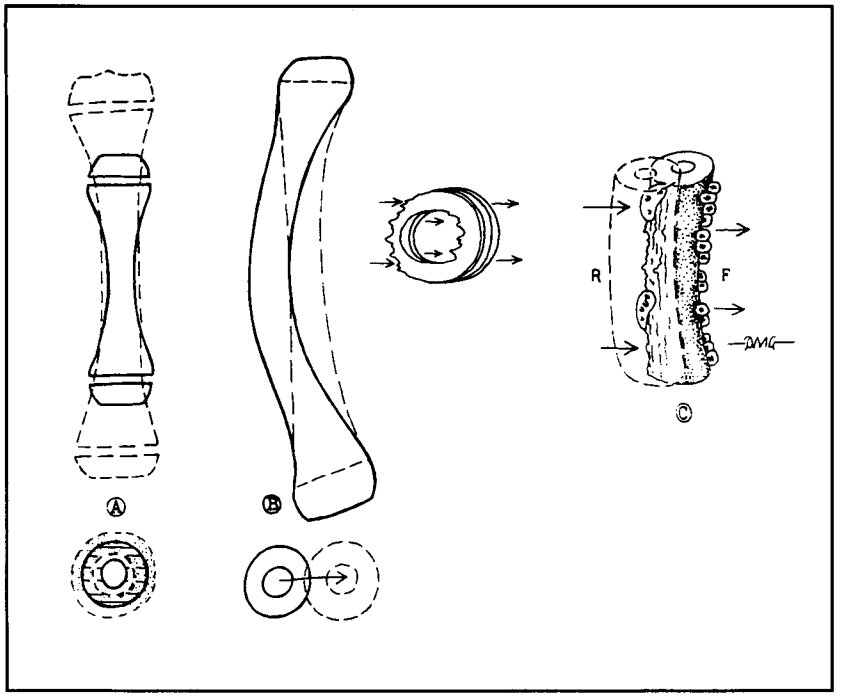


Figure 1

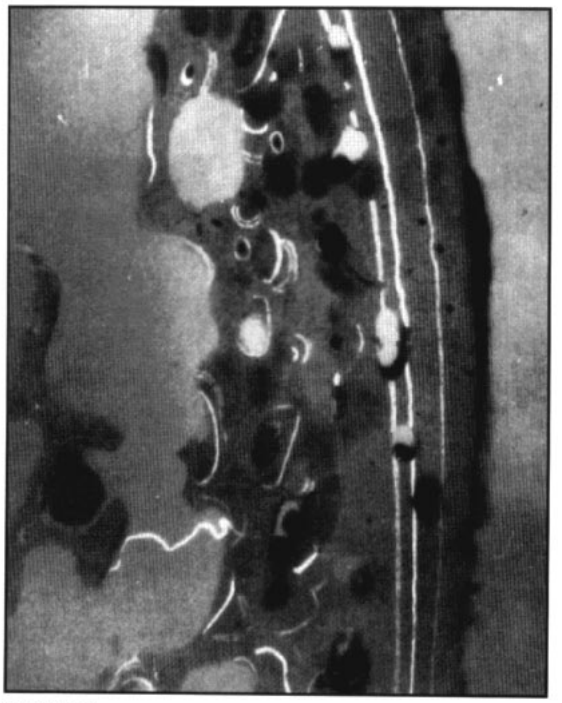


Figure 2

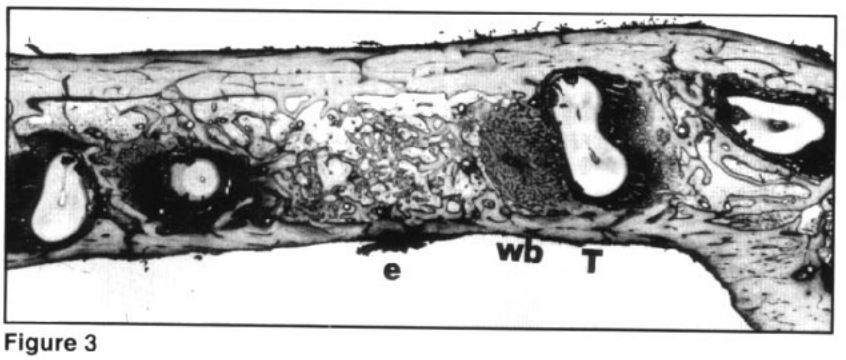


Figure 3

trabecular surfaces, but larger stimuli are needed to make woven bone form than lamellar bone.[19,25,29,42,51] b) Woven bone can appear in fracture healing, some neoplasms, infections, and in reaction to large mechanical loads.[7,29,35] It can arise in the marrow cavity ahead of a tooth socket containing a tooth subjected to excessive orthodontic forces (Figure 3). c) A drift either happens or does not, so it is either ON or OFF.[25,29] d) Once ON, a drift can act slowly or quickly but woven bone drifts can add bone much faster than lamellar drifts. e) Lamellar drifts can thicken or thin a cortex or trabecula no more than about 2 mm/year, a limit that may decrease with age.[36] f) Woven bone drifts always suppress and replace local lamellar drifts. g) Many properties of resorption drifts still need systematic study.

2) Macromodeling, minimodeling and micromodeling. Drifts control if, when, where and how much bone formation and resorption happen.[36,44] The naked eye can see their effects so

Figure 1
Some modeling drift patterns. A diagrams an infant's long bone, showing its original size and shape in solid line. To keep this shape as it grows in length and diameter, its surfaces must move in tissue space as the dashed lines suggest. Formation drifts build some surfaces up. Resorption drifts remove material from others. At B a different drift pattern can correct the fracture malunion in a child, shown in solid line. The cross section view to the right shows the cortical-endosteal as well as the periosteal drifts that achieve that. C shows how the drifts in B would move the whole segment to the right in tissue space (reproduced by permission: HM Frost, Osteogenesis imperfecta: The setpoint proposal. Clin Orthop Rel Res 216:280-297, 1987)

Figure 2
Modeling and remodeling. Undecalcified cross section of the cutaneous cortex, 6th rib, of an adolescent girl, removed at cardiac surgery. Blue-light fluorescence microscopy, about 10x. The bright bands are bone labels of tetracycline taken for infections at three times in the past. The long, vertical white bands on the right label periosteal lamellar bone formation drifts, which were faster near the top than the bottom of the figure. The short white arcs to the left of the drifts labelled secondary osteons during their formation. Newer osteons partly replaced most of them. Remodeling BMUs produced these osteons (reprinted by permission: HM Frost, Introduction to Biomechanics, Charles C Thomas, 1963).

Figure 3
Woven bone evoked by large orthodontic forces. Longitudinal undecalcified section through the ramus of a rat mandible. The tooth above "T" was being forced to the reader's left by large orthodontic forces in vivo. This overload made woven instead of lamellar bone began to form on the medullary left side of that tooth's socket (by permission, from Prof. B. Melsen, Royal Institute of Dentistry, Aarhus, Denmark).

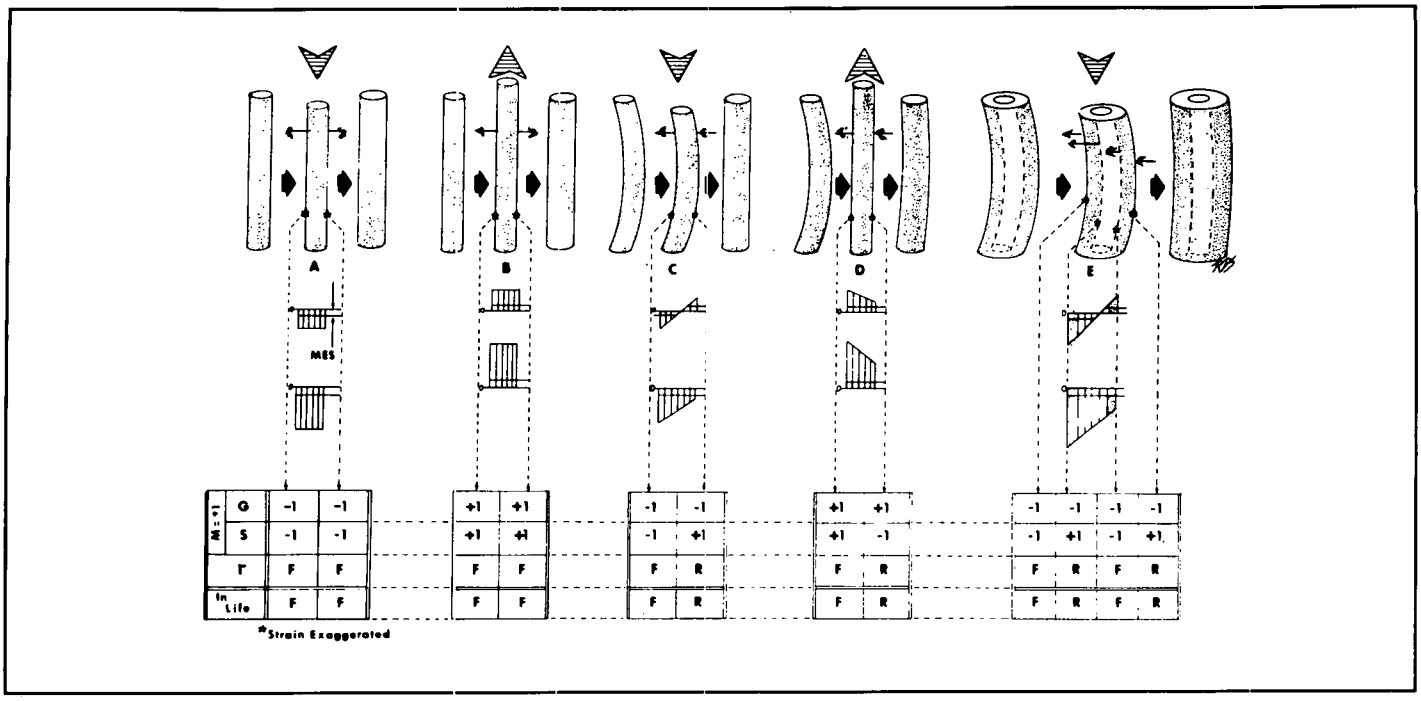


Figure 4

Five "principal structural adaptations". The left member of each trio shows a diaphysis or trabecula. The middle drawings show mild overloads in ways indicated by the arrows above. A: uniaxial compression. B: uniaxial tension. C: longitudinal compression plus flexure (dynamic bending). D: longitudinal tension plus flexure. E: a hollow bone loaded in longitudinal compression plus flexure. The strain graphs below show that the bone surface strains exceed the modeling MESm threshold. The right drawing of each trio shows how the modeling drifts evoked by the strain patterns in the middle drawings would change the bone diameter and shape. In A - E the diameter increases. In C - E the original bone curvature decreases. Each adaptation strengthens the structure and reduces its peak strains under the same loads towards the MESm threshold. In the Table below, the next to bottom row shows which modeling drifts the Three-Way Rule would predict as the response to the strain pattern shown in the drawings above (F = formation drift; R = resorption drift). The bottom row in the Table shows the real-life responses of bone to those strain patterns (adapted by permission from: HM Frost, An MGS derivation of Gamma in the Three-Way Rule for bone modeling. Bone and Min 22:117-127, 1993).

they provide macromodeling. On trabeculae these drifts provide minimodeling, since it takes magnification to see them.[36] Formation drifts create all cortical bone, which can then undergo progressive replacement by secondary osteons.

During any bone formation a different, cell-level activity determines the microscopic organization and "grain" of the new tissue. It organizes lamellar and woven bone differently. A similar activity organizes scar tissue differently from mature tendon or ligament, and meniscus differently from articular cartilage, as examples. This micromodeling only determines what *kind* of bone forms.[42-44,51] It always aligns lamellar bone's grain parallel to the major compression or tension loads on it while it was forming.[42] Therefore lamellar bone's grain in a mandible, tooth socket, maxilla or femur can show the orientation of the major mechanical loads on it during its formation.

3) **The age connection**. Lamellar drifts are most active during growth and become relatively ineffective on cortical bone in adults, but can happen throughout life on trabeculae.[36,51] Micromodeling can function throughout life in all animals wherever any kind of new tissue is being formed.[29]

4) **The loading history**. As inferred in 1963-1964,[24,25] bone's structural adaptations to mechanical usage (SATMU) respond to some average of many strains, not to single ones, and large strains influence modeling much more than small ones no matter how frequent.[14,15,25,27,61] How Nature ranks strain kind, number, size, range, frequency and gradients in controlling bone's biologic activities is under study. Below, "typical peak strains" signify such a loading history.

5) **Five "Principal" structural adaptations due to lamellar bone modeling** (Figure 4).[36] These adaptations show how lamellar drifts can respond to some defined mechanical challenges. Singly or in combinations these adaptations can explain most known adaptations of whole bones to specific mechanical challenges (but see Comments). They include mild overloads in uniaxial compres-

sion and tension, both alone and in combination with flexure (torque is ignored here), and in solid and hollow bones. Flexure means dynamic bending under a load, not the natural curves of unloaded bones. The adaptations in Figure 4 assume the bones begin unloaded with all drifts OFF. Their mechanical loads and corresponding strains and stresses then increase in size week by week until lamellar drifts just begin to change the architecture; this assigns them to the mild overload window described later. These adaptations happen slowly and can take months to years to finish.

6) **In sum**: By moving bone surfaces in tissue space, global modeling can increase but not decrease bone mass and strength. Decreased modeling simply slows down such increases. Here and below, "global" means summed up over a whole bone. Obviously a single resorption drift must remove bone locally.

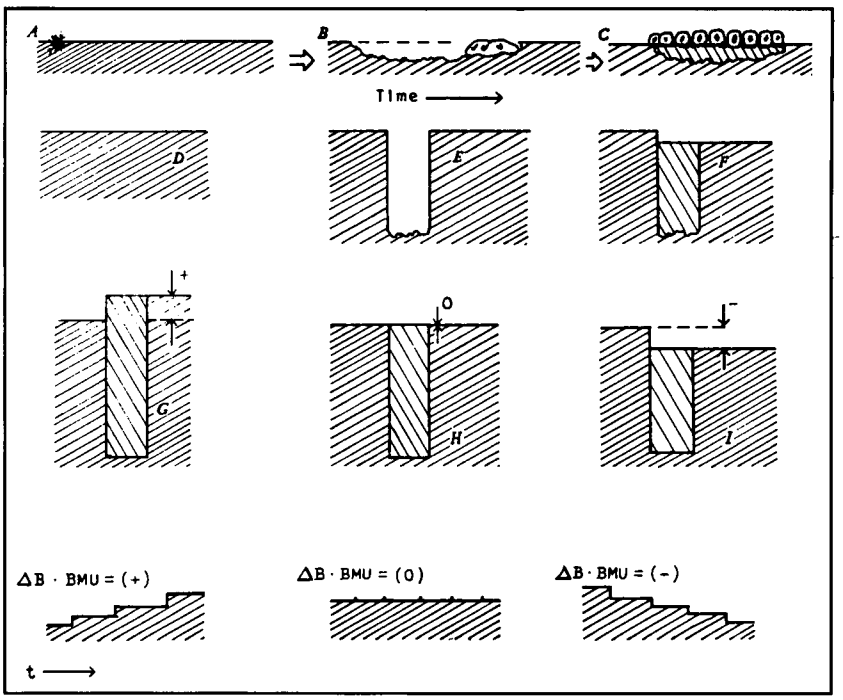
Bone remodeling and the BMU

Small "packets" called BMUs (Basic Multicellular Units) provide bone remodeling, as distinguished from the modeling described above.[21,26,51,68] In an Activation-Resorption-Formation (ARF) sequence a BMU replaces some old bone with new bone, to create a new bone packet or Basic Structural Unit (BSU).[29,50] The secondary haversian system is the best known example of a BSU. In man this ARF sequence replaces or turns over about .05 mm^3 of preexisting bone in about 4 months (Figure 5).[37] A BMU's osteoclastic activity does couple biologically to its subsequent osteoblastic activity.[26,51,66]

1) **The activation connection.** Continued remodeling for life requires continually creating ("activating") new BMUs to replace completed ones.[26] If these creations stop all resorption and formation by remodeling stop too. Human adults should create several million new BMUs annually.[37,47] BMU creations exert the primary control of bone turnover by remodeling. Modeling drifts also cause some bone turnover in children but little in adults.[5,19,51]

2) **The BMU "rho fractions".** A completed BMU can resorb more bone than it makes, or less, or equal amounts (Figure 5). Let rho equal any such deficit or excess of resorption over formation (Figure 6).[37] Then rho must equal the bone formed (the formation fraction) minus that resorbed (the resorption fraction) by a completed BMU.[25,37] On cortical-endosteal and trabecular surfaces rho apparently cannot go positive without pharmacologic help.[49,75] It may do that only on the periosteal envelope (see below).

Nota bene: Excepting the pathologic "window" described later, what controls rho directly deter-



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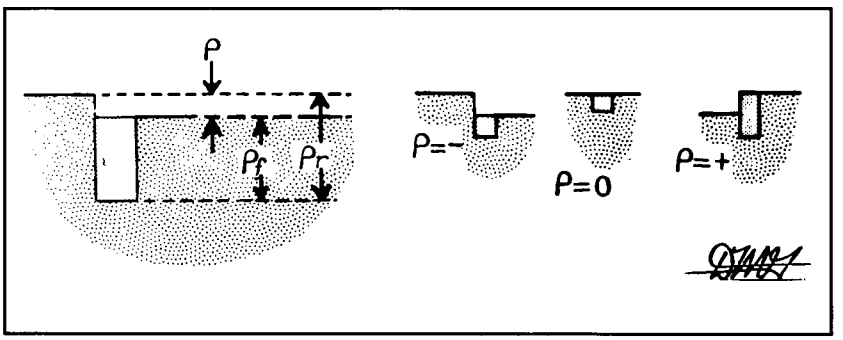
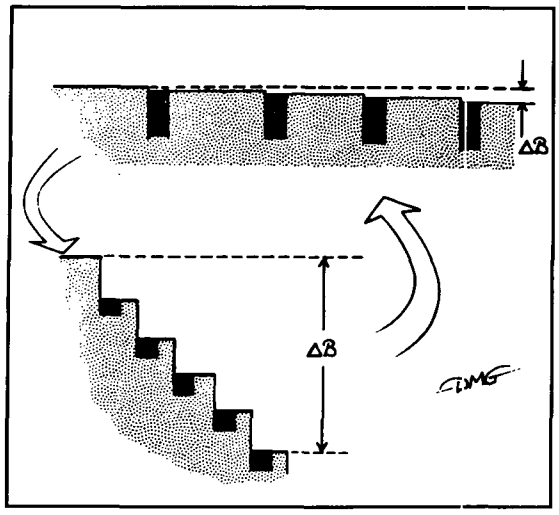


Figure 6

Figure 5
The major BMU functions. Top row. An activation event on a bone surface at (A) causes a packet of bone resorption at (B), and then replacement of the resorbed bone at (C). Second row. Idealize those events to emphasize the amounts of bone resorbed (E) and formed (F) by completed BMUs. Third row. In these "BMU graphs" (after the author) (G) shows a small excess of formation over resorption as on periosteal surfaces (rho is positive). (H) shows equalized resorption and formation as on haversian surfaces (rho is zero). (I) shows a net deficit of formation, as on cortical-endosteal and trabecular surfaces (rho is negative). Bottom row. These "stair graphs" (after PJ Meunier) show the effects on the local bone balance and mass of a series of BMUs of the kind immediately above. ΔB.BMU in this figure is the same as Greek lower case rho in this text (reprinted by permission: HM Frost, Osteogenesis imperfecta. The setpoint proposal. Clin Orthop Rel Res 216:280-297, 1987).

Figure 6
The rho fractions. These drawings show the meanings assigned to rho, the resorption fraction (rho-sub-r) and the formation fraction (rho-sub-f) in completed BMUs. A negative rho means completed BMUs resorbed more bone than they made. As an estimate, rho in humans could vary from zero to about -.05 mm^3 of bone lost per typical completed BMU.



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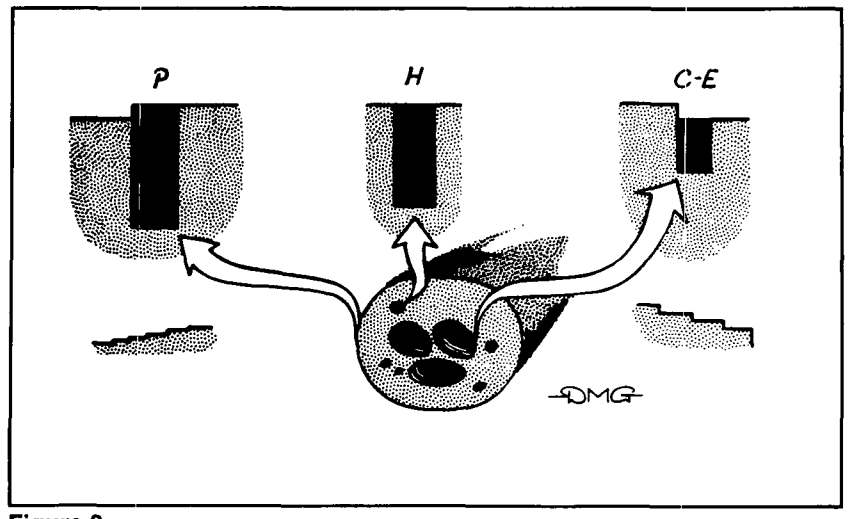

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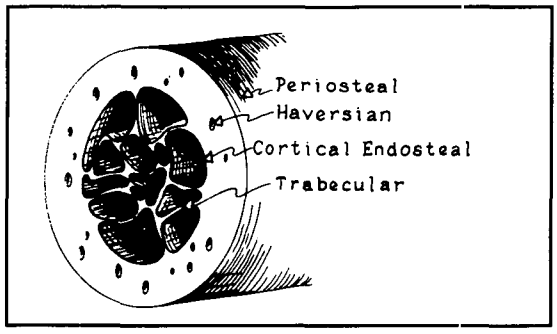

Figure 9

Figure 7
Bone balance, activation and rho. Top: Few BMU creations occur and rho nearly equals zero. Slow turnover of the local bone and very slow net losses result (i.e, conservation of existing bone). Bottom: Increasing BMU creations plus a more negative rho can markedly increase local bone loss. Disuse and a RAP can cause such effects. This efficient mechanism can increase bone loss over 200 times above the normal rate.

Figure 8
The rho-envelope features. These BMU graphs show typical normal signs of rho for the periosteal (P), haversian (H), and cortical-endosteal and trabecular (C-E) envelopes.

Figure 9
The bone envelopes. The anatomical surfaces or "envelopes" shown here differ in their responses to mechanical and nonmechanical agents. Throughout life the periosteal envelope accumulates bone, cortical-endosteal and trabecular surfaces lose it, and the haversian envelope changes little (reprinted by permission: HM Frost, Intermediary Organization of the Skeleton, CRC Press, Boca Raton, 1986).

mines if and where bone is conserved or removed by remodeling. BMU creations combined with the value of rho then directly and separately determine the rate of such losses Figure 7.[26,29,37]

3) **The envelope connection.** Remodeling happens on periosteal, haversian, cortical-endosteal and trabecular surfaces or "envelopes" Figure 8.[5,25,27,51] Normally rho may be positive only on the periosteal envelope, where completed BMUs may resorb a bit less bone than they make. Rho approaches zero on the haversian envelope, where net resorption and formation tend to equalize. Rho is usually negative on cortical-endosteal and trabecular surfaces where BMUs usually resorb a bit more bone than they make throughout life. On the latter two surfaces BMUs in adults may resorb about .003 mm^3 more bone than they make, so rho there could equal -.003 mm^3. The negative rho, where bone touches marrow, causes most of the marrow cavity expansion and loss of spongiosa in hollow bones that begin in the fetus and go on until death (Figure 9).[29,54]

4) **The age connection.** Bone remodeling goes on for life, but occurs faster in children and spongiosa than in adults and compacta. Small animals, such as mice and rats, show little haversian and periosteal remodeling but do show active trabecular remodeling.[29,45,51,68]

5) **In sum**: Global remodeling can remove or conserve bone but apparently cannot add to it (without pharmacologic assistance). Increased remodeling tends to remove bone next to marrow and make a bone weaker. Decreased remodeling tends to conserve bone and its strength.

The regional acceleratory phenomenon (RAP)

Infection, injury and some tumors can make all normally ongoing local tissue processes accelerate.[5,29,51,60,61,73,75] Normally this regional acceleration or RAP hastens healing and improves local resistance to infection and other challenges. In bone it can last for months. It explains much of the increased modeling and remodeling in the man-

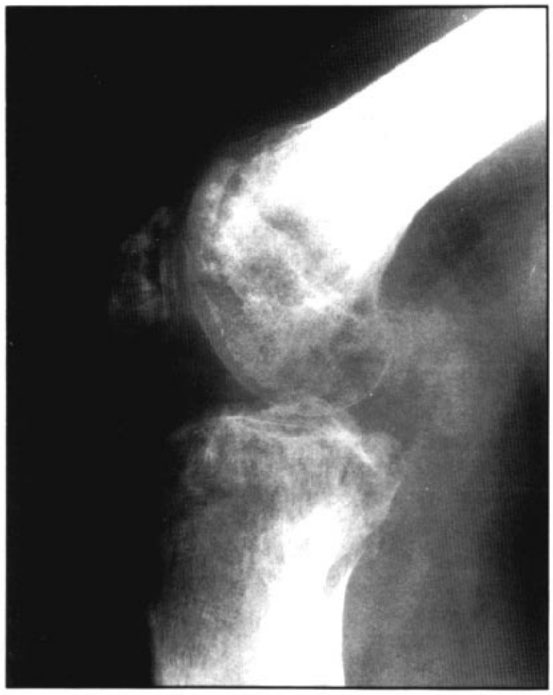

Figure 10

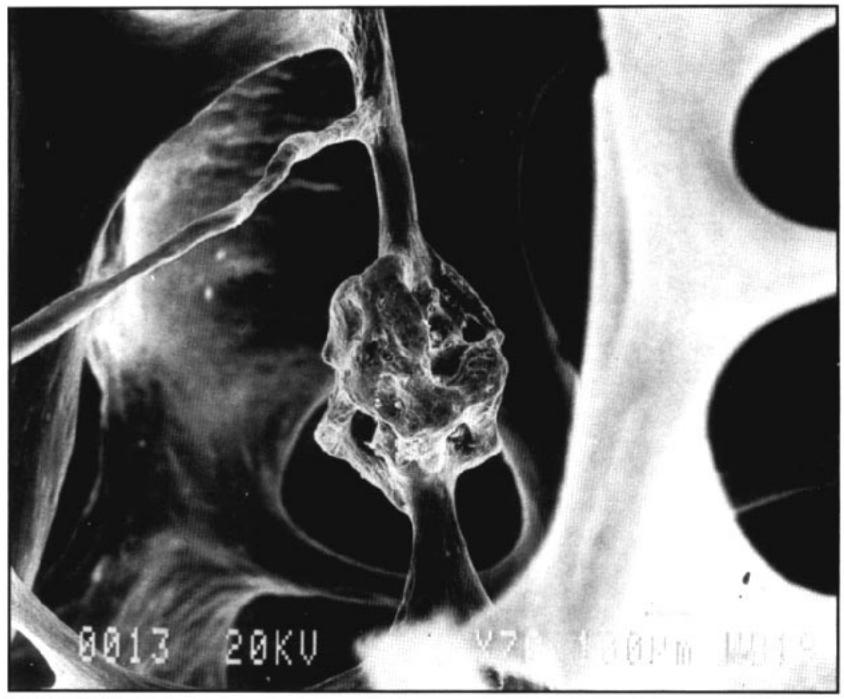

Figure 11

Figure 10
A RAP-induced osteopenia. Lateral X-ray of the knee of a man in his late 40s. He developed a "migratory osteoporosis", also known as algodystrophy. It is a pathologically intense and sustained RAP of unknown cause, which led within two months to the severe osteopenia shown here. That bone loss summarized two parts: A temporary or reversible loss due to the increased "remodeling space" always caused by the temporary holes accompanying increased BMU creations, and a permanent loss that summed up the negative rho of all completed BMUs next to marrow (Reproduced by permission: HM Frost, Bone Dynamics in Osteoporosis and Osteomalacia; Charles C Thomas, Springfield, 1966).

Figure 11
A fatigue fracture of a trabecula. This scanning electron micrograph shows the small ball of callus that is healing a complete fatigue fracture of a thin trabecula in an osteopenic human vertebra. The fracture itself should have happened several months before this stage of healing. Specimen collected at autopsy (reproduced by permission of Prof. Lis Mosekilde and the Department of Anatomy, University of Aarhus School of Medicine, Aarhus, Denmark).

dible and maxilla following fractures, surgical procedures, tooth extractions, after implantation of various devices in bone, and in periodontal disease. In the latter, as well as after tooth extraction, it can hasten alveolar ridge resorption. Because a RAP increases regional bone remodeling it usually also increases loss of bone next to marrow (Figure 10). When a RAP fails to develop, healing usually is slowed and infections can progress alarmingly.

Microdamage and its thresholds

Mechanical fatigue damage (microdamage) normally occurs in bone in life[4,8,13,22,28,34,41,61,65] and several methods can show it.[9,23,71] Remodeling BMUs usually repair the damage and keep it from accumulating, and probably independently of any depression by vigorous MU.[17,29] This is done by removing and replacing the damaged bone with new bone. Overloading the bone can increase microdamage and the BMU creations and remodeling that repair it. This can happen in pathologic fractures and in bone overloaded by endoprostheses and internal fixation implants.

The microdamage threshold. When loaded below about 2000 μE (microstrain), BMUs can easily repair what little microdamage occurs. Yet at and above 4000 μE enough microdamage can occur to overwhelm the repair mechanisms, resulting in accumulations of damage that can cause fatigue failures of trabeculae or whole bones. In this 2000-4000 μE range, merely doubling the size of the strains can increase microdamage hundreds of times.[34,46] This effect can loosen dental and orthopaedic bone implants. Since 3000 μE centers on this 2000-4000 μE range one could consider it the "set point" of the microdamage threshold originally inferred by Burr et al.[4] The largest normally allowed peak bone strains lie below it, in the 1500 μE region.[31]

Here modeling and remodeling seem to collaborate. Drifts would adjust bone architecture in ways that minimize microdamage by keeping peak strains below the 1500 μE range, while BMUs

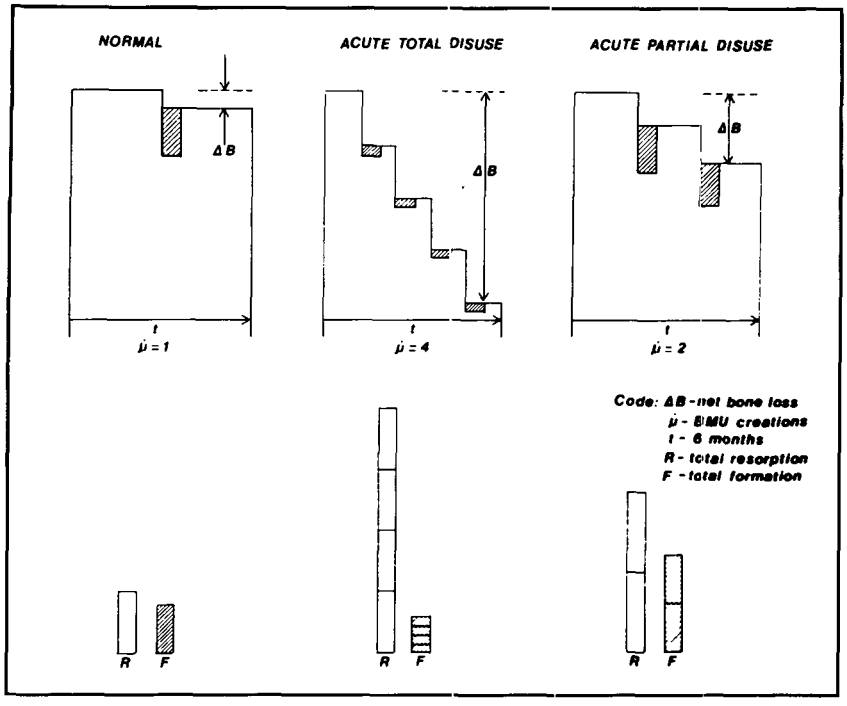

Figure 12

Remodeling responses to MU. Top: BMU graphs show a bone surface from the side. The depth of the resorption cavity suggests the rho resorption fraction, the amount of refill (shaded) the rho formation fraction, and the net deficit or local bone loss suggests rho itself. At left is normal MU of an adapted bone, acute disuse in the middle, and partial disuse on the right. Acute disuse increases BMU creations and decreases the formation fraction in completed BMUs. Bottom: Bar graphs add up the net or global bone resorption (R) and formation (F) in the situations above to show the effects on tissue-level and organ-level turnover as histomorphometry or bone seeking radioisotopes might reveal them. While global formation decreases in acute complete disuse, it increases in partial disuse, yet net bone loss increases in both situations.

would repair what microdamage does occur to prevent accumulations. Failure of either function can cause fatigue failures of bone (Figure 11.)

The parallel- and across-grain thresholds. The above two paragraphs concern tension and compression strains parallel to lamellar bone's grain, so they define a "parallel-grain" microdamage threshold. When loaded across its grain, lamellar bone has less resistance to fatigue. This "across-grain" microdamage threshold awaits systematic study but loosening of many load-bearing implants in bone probably stems from fatigue in across-grain loading of the supporting bone.[42]

Some qualitative mechanical usage (MU) responses

1) **In vivo strain evidence.**[2,3,6,7,48,56,57,63,65] While special gauges can measure bone strains in intact animals, stress cannot be measured directly. These strains provide useful indices of a bone's mechanical loads, stresses and MU history. Keep in mind below that normal bone fractures at about 25,000 με. This corresponds to a stress of about 130 megapascals or 16,000 Lbs/square inch.[12,61,64,69]

Then, by deliberate effort normal subjects cannot cause longitudinal bone strains above about 3000 με (12% of the fracture strain) during growth, and above about 1500 με (6% of the fracture strain) in adults. These values are approximate and the middles of small strain ranges. They may differ in different species, ages and bones and they need much more study.

For modeling, strains in the 3000-4000 με range (called the MESp) and above usually switch woven bone formation ON, and can also increase microdamage alarmingly.[44] Lesser strains in the 1500 με range (called the MESm) usually switch lamellar drifts ON.[44] Lower strains usually leave mechanically controlled modeling drifts OFF.[36]

For remodeling, in acute disuse strains should fall and stay below 50 με. Here BMU creations can increase over five times above normal and rho next to marrow goes markedly negative (Figure 12). This causes rapid loss of bone next to marrow.[37,40,43] Where strains rise above that range (called the MESr) towards 3000 με, BMU creations begin decreasing towards normal and rho tends to change towards zero (i.e, resorption and formation in completed BMUs tend to equalize).

2) **In sum**: For modeling: A threshold strain range, the MESm, can turn lamellar modeling drifts ON. Strains below it leave mechanically controlled modeling OFF. Strains above a larger range, the MESp, can suppress lamellar drifts and turn woven drifts ON instead.

For remodeling: Below a third, smaller threshold range, the MESr, BMU creations increase towards a maximum while next to marrow rho goes more negative. Strains above the MESr begin depressing BMU creations and equalizing resorption and formation by completed BMUs.

3) **Four MU "Windows":** The MU effects on modeling, remodeling, bone mass and bone strength can ladder into four "windows" according to increasing sizes of typical peak bone strains.[5,44,61] Excepting contributions of the longitudinal growth mechanism in children,[19,51] all mechanical and nonmechanical influences on bone modeling, remodeling, turnover and net gains and losses must act by controlling drifts, BMU creations, rho, microdamage, its repair and the RAP.[29] The old but persistent idea that mechanical and nonmechanical influences act only on existing osteoclasts or osteoblasts errs.[29]

The acute disuse window (Figure 12). In sudden, complete disuse typical peak bone strains should fall and stay below about 50 με [50]. Here BMU creations can increase over five times above nor-

mal and rho goes more negative as the formation fraction next to marrow decreases (it can even become zero there, meaning no significant formation happens). Mechanically controlled drifts stay OFF and no microdamage or RAP arise. Such effects increase cortical-endosteal and trabecular bone losses, tend to cause an osteopenia (e.g, less bone than normal), and weaken bone.[74,79]

Local disuse can arise after loss of teeth. The alveolar ridge can then begin resorbing due to increased numbers of BMUs acting in the disuse mode. The rate of this loss depends partly on BMU creations, so things that depress them (often called "activation depressors") can retard alveolar ridge recession, while things that increase them can accelerate it.

The adapted window. Bones already properly adapted to their MU would presumably apply to healthy adults. Here typical peak bone strains should range between about 50 to 1500 μE. Compared to acute disuse and as Figure 12 suggests, BMU creations fall to normal, completed BMUs tend to equalize their resorption and formation, modeling stays OFF and no RAP and little microdamage arise. Such effects conserve bone and its strength and prevent an osteopenia. In partial mechanical disuse, responses between those of acute disuse and normal MU usually happen (Figure 12). Responses to small MU changes can take long times to change bone architecture enough for existing methods to detect. Remodeling in disuse that lasts over 2 years still awaits systematic study.

The mild overload window. In healthy, growing, normally active mammals bones must keep trying to adapt to continually increasing muscle strength and body weight, and typical peak bone strains could range between 1500 to 3000 μE.[1,2,31,32,65,82,83] This may also apply to the strains caused by some dental and orthopaedic implants.[29,42] Where this happens BMU creations stay near normal, BMU resorption and formation tend to stay equalized and no RAP and little new microdamage arise. However lamellar drifts can now switch ON to begin adding to and strengthening the bone. On the 25,000 μE span of bone's fracture strain, the span of this window seems quite narrow.

The "pathologic overload window". Strains above 3000 μE usually increase bone microdamage, which can then increase BMU creations to repair it. A RAP can begin too, to further increase BMU creations and bone turnover.[65] This can increase the uptake of bone-seeking isotopes to make affected regions "hot" on scintigrams. Resorption and formation in completed BMUs still stay equalized, but now woven bone drifts can begin and mechanical crumbling, stress fractures and anarchic bone resorption (not coupled to formation) can result too. These things can happen in bone weakened by cysts and tumors, and in the bone embedding seriously overloaded dental and orthopaedic implants.

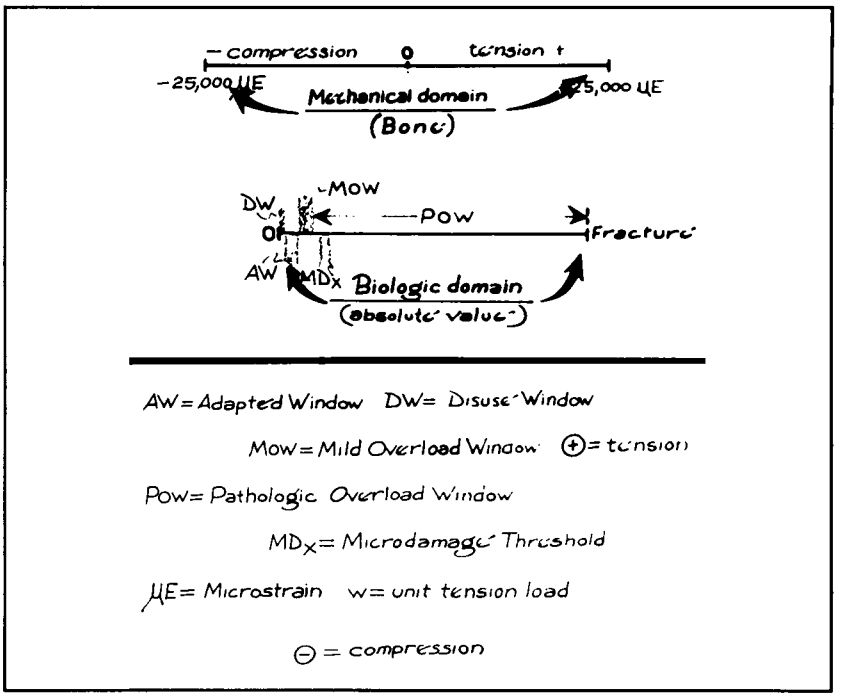

Figure 13

The fracture strain "yardstick". Top: In the mechanical domain, bone's strains (and corresponding stresses) can span the range from - 25,000 (compression) to + 25,000 μE (tension). Middle: Bone's biological activities seem to monitor strain magnitude more than its sign or polarity. Using this as a yardstick, this drawing suggests the location of the various threshold ranges and MU windows described in the text and their approximate boundaries.

Many bone implant loosenings may arise because implant design and usage load the supporting bone into this window.[42] Dental colleagues tell the author that orthodontic forces in this window can have harmful effects on teeth and their sockets.

4) **In sum**: Modeling drifts can adapt bone to overloads by changing bone architecture and adding bone, but apparently cannot adapt it to underloads or disuse. Normal bone can adapt to and endure mild overloads, given enough time, but may not endure under pathologic overloads.

Remodeling BMUs can adapt bone to underloads and disuse by removing bone next to marrow, they tend strongly to conserve normally used bone, but apparently they cannot add bone to adapt it to overloads.

Figure 13 suggests where these windows and their boundaries lie on the yardstick or span of bone's fracture strain. As an aside, the above

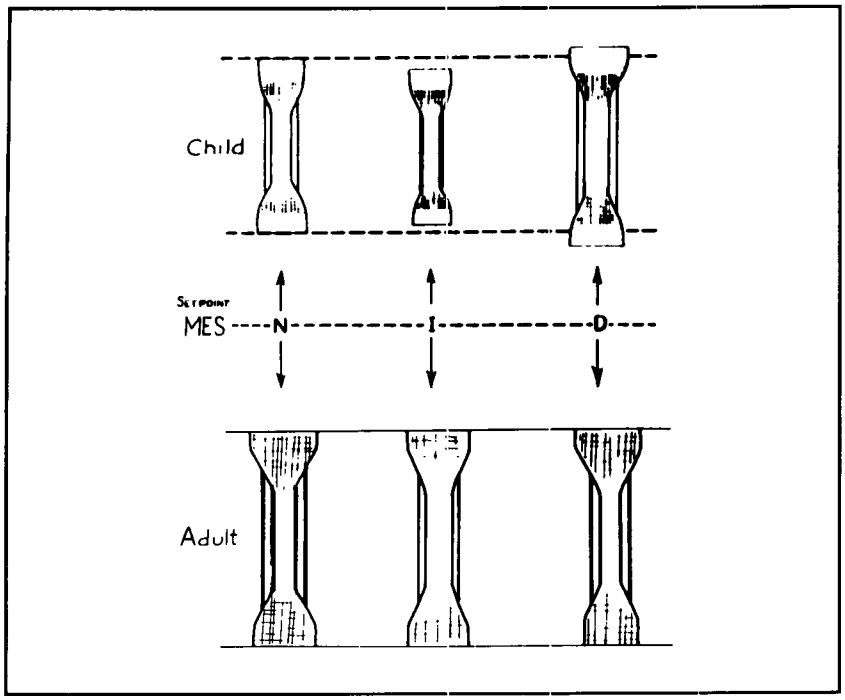

Figure 14

Some set point effects on whole bones. The middle row indicates normal (N), increased (I) and decreased (D) set points for longitudinal bone growth, bone modeling and remodeling. Top: In growing children and compared to normal, increased set points should lead to somewhat shorter bones, thinner cortex, less spongiosa and reduced outside diameter. Decreased set points should lead to somewhat longer bones, thicker cortex, increased outside diameter and retention of more spongiosa. Bottom: Adults lack longitudinal bone growth. If these set points changed in adult life, then after 20 years increased modeling and remodeling set points should lead to a thinner cortex due to marrow cavity expansion, and to less spongiosa, but retention of the previous outside diameter and bone length. Decreased set points should simply conserve the bone that existed before the set points decreased. Nota bene: The anatomical patterns caused by increased set points and by disuse both copy, and strongly so, the pattern observed in most if not all adult-acquired osteoporoses.

material suggests some "natural" definitions of bone overloads. "Normal" loads would be those causing strains between the MESr and MESm. Mild overloads would be those causing strains between the MESm and MESp. Severe overloads would be those causing strains equal to or greater than the MESp. Catastrophic overloads would cause strains equal to bone's fracture strain.

5) **Quantitative MU responses**. Four recent SATMU models can begin defining the responses of bone, cartilage and fibrous tissues to mechanics in provisional mathematical and quantitative formats.[36-39]

Comment

1) **The composition of drifts and BMUs**. Drifts and BMUs have a capillary, precursor and "supporting" cells, wandering and mast cells and other leukocytes. Many of these cells are created on demand where the mechanism will function. Their coordinated activities then marshall the osteoclasts that resorb bone, and/or make the osteoblasts that form bone, and control the subsequent activities of both. Many circulating agents, local cytokines, physicochemical influences and adjacent tissues could affect what drifts and BMUs do, where, when, how much and how quickly.[51,66,68] *Note: Mechanical and nonmechanical influences including hormones and drugs do not exert their major, steady state bone balance, architectural and bone mass effects by affecting only osteoclasts or only osteoblasts.*[29] *Instead they affect the whole drift or BMU such cells belong to, which then dictate what those cells do.*

2) **On intermittent and continuous loading**. Clinical, pathologic and experimental evidence suggests continuous bone loads (as in the tooth socket during orthodontic treatment, or in the human spine due to its erect posture) may have somewhat different effects on bone modeling and remodeling than the intermittent loads normally involved in use of the mandible and extremity bones.[44,47,48,63] This needs study and orthodontists should have good opportunities to do it.

3) **Modeling and remodeling as final common pathways**. The nonmechanical things that can influence modeling and remodeling include hormones, vitamins, drugs, disease, inflammation (including infection), genetics (including race and species), nutrition, climate and occupation.[5,29,51,75] Study of such matters produced a vast literature that assumed the major purposes of modeling and remodeling involve, not mechanics, but things related to metabolic bone disease: Homeostasis and providing calcium and buffer sink-reservoir functions to the blood. Yet the nonmechanical functions of modeling and remodeling probably rank second to controlling bone architecture, strength, conservation and losses, and preventing and repairing microdamage. Some nonmechanical influences may even modify how bone perceives its typical MU, and maintaining mechanical competence of bone and bones apparently can dictate where bone can and cannot be spared to meet nonmechanical needs (see Section #6 below).[29,31,40]

4) **The baseline conditions**. Some modeling and remodeling go on in congenitally paralyzed limbs where normal MU influences should not exist.[19,29] Likely predetermined in the uterus, such "baseline conditions" (and activities) can continue after birth. The postnatal differences between a congenitally paralyzed and the contralateral normal limb should show the postnatal MU effects, direct and indirect, on bone architecture and tissue dynamics that add to the baseline conditions shown

in the paralyzed limb. Such differences need systematic study.

5) **The chondral "modeling barrier".** Cartilage on a bone surface prevents lamellar modeling drifts from arising there.[25,27] During growth that includes the bony attachments of most tendons, ligaments and fascia, excepting the periodontal ligament. It would include the mandibular insertions of the masseter, pterygoid and temporalis. In such locations growth and its responses to MU follow chondral SATMU rules, not the bone rules.[38] As one result, growth of the mandibular angle caudally and posteriorly depends more on growth of the cartilage layer at the masseter's insertion than on formation drifts that obey the original Epker-Frost "flexure drift rule".[20] Failure to account for this feature compromised the design and interpretation of some vital biomechanical experiments; effects of a chondral barrier were sometimes attributed to bone modeling drifts instead.

6) **On set point effects** Figure 14.[5,29,36,37,43-47,61] Let the centers of the MESm, MESr and MESp ranges define their "set points". They suggest where the corresponding biologic activities change from OFF to ON. Then age, genetics, drugs, hormones, disease and other things might change those set points. If so the changes should affect bone architecture predictably.

Increased set points. For modeling this should make bones underadapt to their MU, and thus more likely to fracture from an injury. They should also develop fatigue fractures more readily, since the increased strains caused by normal MU of underadapted bone would lie closer than normal to its microdamage threshold. An increased remodeling set point would give bone a spurious "disuse message" and cause net bone loss next to marrow. As examples, increased set points may exist in osteogenesis imperfecta [30] and postmenopausal osteoporosis.[46]

Decreased set points. For modeling this should make bones stronger than really needed, because smaller than normal strains would make modeling drifts strengthen and stiffen them. A decreased remodeling set point would conserve existing bone better than normally. As examples, the better bone in blacks than whites, and in active (but not in treated or "burned out") acromegaly than in normal people, may reflect such decreased set points.[46] The better acceptance of load bearing bone implants in some patients might also reflect subnormal set points. This could make their biologic activities strengthen bone overloaded (inadvertently of course) by the implants better than in people with normal set points.

Table 2
Some New Fundamental Concepts in Bone Physiology

1) The basic activities of growth, modeling and remodeling determine the architecture and strength of bones.
2) Define the mechanically adapted state as that fit of bone architecture to mechanical usage that keeps typical peak bone strains everywhere within the region spanned by its modeling and remodeling threshold strain ranges (the MESm and MESr).
3) Let the centers of the MESm and MESr ranges define their set points, which can then define "mechanical adaptation" quantitatively. Disease, drugs, genetics and other things can change these set points.
4) Bone modeling and remodeling should have the major function of producing mechanically adapted bones.
5) The threshold strain range that controls lamellar bone modeling responses to mechanics (the MESm) normally lies below bone's microdamage threshold.
6) During growth the SATMU tend to keep each bone's typical peak strains everywhere equal to or less than its MESm, and therefore below its microdamage threshold too. This would define one purpose of the SATMU, but not their only one.
7) Microdamage repair by remodeling BMUs should keep what microdamage normally happens from accumulating. This would define one purpose of remodeling, but not its only one.
8) Errors in these functions can and do cause skeletal disease and problems encountered in orthopaedic and maxillofacial surgery, orthodontics and dentistry.

7) **On implant design.** Because the MESm strain normally lies below bone's microdamage threshold, normal bone architecture could have the major purpose of minimizing microdamage production.[42] This would be achieved by making architecture keep typical peak strains below the microdamage threshold. In strain terms this would make a bone about eight times stronger than needed to carry its typical peak loads (in stress terms smaller numbers apply but the basic idea is the same[61]).

In short: The great momentary strength of bone could come from adjusting its architecture to keep typical strains below its microdamage threshold.

That arrangement has a corollary message: The design and use of all load-bearing bone implants should keep the strains of the supporting bone below its microdamage threshold(s). Some basic scientists knew this by 1984[4,14,15] but even in 1993 no implant design marketed in the world specifically tried to achieve it. As dental people know

(few orthopaedic surgeons know it), the Branemark implants either succeed in this regard or come closer to it than any other implant known to the author.

8) **Some meanings for research.** Four comments seem appropriate here.

First, the things summarized above emerged from fogs of controversy and confusion so recently that experimentalists have not had much time to study how drugs, hormones, cytokines, electrical and mechanical influences and other things affect them, nor have clinicians had much opportunity to exploit them. Yet the ability to potentiate or depress them at will could probably improve the management of many dental and orthopaedic problems.

Second, in the future experimentalists and clinicians might study how such agents specifically affect: Lamellar and woven bone drifts, BMU creations and rho, the RAP, microdamage and its repair, how each responds to MU, what mechanically generated signals control their responses, and how. Those seem to be the major "handles" Nature uses to control bone health or to cause bone disease and failures to adapt to mechanical and nonmechanical challenges, whether naturally occurring or iatrogenic.

Third, without exception for over 60 years, diverse experimental and clinical-pathologic evidence supports this statement: Never do the effects any agent has on intact, living bones stem from the responses of only osteoclasts or only osteoblasts.[29,45] Ergo, research studies solely of osteoclast or osteoblast responses to an agent cannot see the "whole picture" of its effects in intact subjects. Many molecular and cell biologists working with bone now acknowledge this.

Fourth, hopefully the designers of implants will begin to exploit the message in the above relationship between bone's microdamage thresholds and its MESm. That may happen more quickly when informed surgeons begin quizzing implant salespeople on how the designs manufactured by their companies try to satisfy that message.

Conclusion

Table 2 lists some fundamental concepts of the new vital biomechanics of bone that clinicians (including but not limited to orthodontists and orthopaedic surgeons) might try to exploit in coming years. While some of those concepts may seem new to some readers, they were probably already ancient in Nature when dinosaurs began roaming the earth in the Jurassic. We certainly do not "know it all" yet, but some of the progress made since 1960 seems ready to inject into the clinical domain.

The special format of the Hard Tissue Workshops organized by Prof. W.S.S. Jee since 1965 seems ideally suited to fostering such efforts.[84] Perhaps others could organize similar workshops for the benefits they could bring to both skeletal science and patients.

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84. The Hard Tissue Workshops organized annually since 1965 by Prof. WSS Jee provide seminal, multidisciplinary forums for presenting and critiquing new methods, evidence and ideas, including vital biomechnical ones, that concern human skeletal disease. Sponsored by the University of Utah, they probably had more effect on how people think about and study skeletal physiology and disease today than any other regularly held meetings in this century. Most material in this article had its first hearing at those Workshops, many authorities contributed to it and it benefits from the resulting discussions. Dr. Jee is Professor of Anatomy at the University of Utah School of Medicine in Salt Lake City, Utah, and director of its Radiation Biology Laboratory too.