Review Article

A 2003 Update of Bone Physiology and Wolff's Law for Clinicians

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Abstract: By 1892, Julius Wolff and others realized that mechanical loads can affect bone architecture in living beings, but the mechanisms responsible for this effect were unknown, and it had no known clinical applications. In 2003 we know how this effect occurs and some of its applications. Our load-bearing bones (LBBs) include tibias, femurs, humeri, vertebrae, radii, mandibles, maxillae, wrists, hips, etc (so LBBs are not limited to weight-bearing ones). The strength of such bones and their trabeculae would represent their most important physiologic feature but in the special sense of relative to the size of the typical peak voluntary loads on them. The biologic ''machinery'' that determines whole-bone strength forms a tissue-level negative feedback system called the mechanostat. Two thresholds make a bone's strains determine its strength by switching on and off the biologic mechanisms that increase or decrease its strength. Equally, two thermostats can determine a room's temperature by switching on and off the room's heating and cooling systems. General features show that the largest voluntary loads on LBBs determine most of their strength after birth. These loads come from muscle forces so muscle strength strongly influences the strength of our LBBs. This process affects, in part, the healing of fractures, bone grafts, osteotomies, and arthrodeses; the bone's ability to endure load-bearing joint and dental endoprostheses; why healthy bones are stronger than the minimum needed to keep voluntary loads from breaking them suddenly or from fatigue; some general functions and disorders of bone modeling and basic multicellular unit–based bone remodeling; some limitations of in vitro data and of pharmaceutical actions; and the fact that many bone-active humoral and local agents have permissive roles in a bone's adaptations and healing, instead of forcing them to occur. (*Angle Orthod* 2004;74:3–15.)

Key Words: Biomechanics; Mechanostat; Muscle; Healing; Bone strength; Utah paradigm

INTRODUCTION

Ten years after writing ''Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians,''[52] enough happened to justify summarizing the updated bone physiology for clinicians. This update depends on ''connecting the dots'' between mountains of facts and ideas from many sources to recognize parts of the ''big picture'' hiding in the details. These sources included, in part, orthopedics, medicine, pediatrics, and dentistry; anatomy, pathology, and basic science studies; and biomechanics, engineering, and cybernetics. More than 80 years ago, connecting the dots in physics data led a Swiss postal clerk to realize that $E = mc^2$.

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Some history that led to that updated physiology

On our soft tissue organs. By 1950, physiologists had learned five facts about such organs (kidneys, liver, adrenal glands, lungs, skin, gut, etc). (1) Organ-level functions make a healthy life possible; (2) tissue-level mechanisms provide the key players that support an organ's functions; (3) cell-level mechanisms directly support the tissue-level functions but support an organ's functions only indirectly; (4) cell-level realities could not reliably predict tissue-level or organ-level functions but could help to explain such functions after other means revealed them; (5) without both the tissue-level and organ-level functions a healthy life is impossible.

But for our bones. By 1900, physiologists knew that osteoblasts make bone and osteoclasts resorb it,[91] but no tissue-level bone functions were recognized as such before 1964 (later on they were called ''nephron-equivalent functions'').[61] Consequently, by 1964 physiologists had made some ''hidden assumptions'' about our bones. To wit (1) osteoblasts and osteoclasts were the key players in bone's physiology and disorders, and they worked and were con-

TABLE 1. Abbreviations and Symbols in the Text

BMU, basic multicellular unit of bone remodeling.
E, the typical peak strains caused by VMLs on an LBB.
Fx, a bone's fracture strength or ultimate strength.
GBR, the general biomechanical relation for healthy LBBs.
LBB, a load-bearing bone, one designed mainly to carry voluntary loads.
MDx, microscopic fatigue damage in bone and bones.
MESm, bone's genetically determined modeling threshold strain range, in and above which modeling usually turns on to strengthen a bone.
MESp, bone's genetically determined operational MDx threshold strain range, in and above which unrepaired MDx can begin to accumulate.
MESr, bone's genetically determined disuse-mode threshold strain range, below which the maximal disuse-mode activity occurs and above which it begins to decline or turn off.
MST, bone's tissue-level, genetically determined mechanostat, the collection of ''biologic machinery'' that can adapt LBBs to their typical peak VMLs.
SSF, a bone's strength-safety factor.
VML, a voluntary mechanical load on a bone, which implies muscle forces.
$\sim$, approximately, or approximately equals.
$<$, $\ll$, $<<<$: less than, much less than, or markedly less than, respectively.

trolled independently; (2) thus, increased osteoclastic activity caused bone losses; (3) increased osteoblastic activity caused bone gains; (4) chiefly biochemical-genetic factors made those key players determine bone architecture, bone healing, the size of the bone bank, and most bone disorders[1,19,36,37,83,103,145,158]; (5) and bones had no important tissue-level functions.

We make hidden assumptions without realizing it. When something or somebody challenges them, they become recognized.

Bone's tissue-level mechanisms were only recognized after 1963, mainly by me[40–44] and Prof Jee, and how those mechanisms support most organ-level bone functions became apparent to us by the mid-1990s.[61–65,89,101,141,147] Yet, after about 1930, many hundreds of textbooks, reviews, and articles for the lay press educated millions of people about the five hidden assumptions mentioned above. Thus, our efforts to tell those millions that the above five ideas apply to bones too and that those hidden assumptions were false met the same resistance that two very cold swimmers would have met by trying to push the Titanic away from the iceberg in 1912. Ergo, those five assumptions still linger.[9,37,95,118,126,131]

Resisting changes in long-accepted ''wisdom'' is human nature. Other examples include Aristarchus, who over 2000 years ago realized that this planet is round, not flat; Semmelweiss, who in the 1600s realized that the contaminated hands of doctors caused the ''child-bed fever'' that could kill new mothers, an idea for which his contemporaries ridiculed him savagely; and Wegner, who before AD 1920 realized that continental drift changes earth's geography. Those men died before others recognized the truth of their ideas. Also, when millions of people ''know'' beyond doubt that the solar system is geocentric, who would believe one man who said that it is heliocentric? Enter Copernicus, who had the heliocentric claim published after he died in 1543. Perhaps he did not want to be burned alive, because back then the Church and everyone else ''knew'' God made the solar system geocentric. In fact, the Inquisition did burn Giordano Bruno alive in 1600 for saying that stars might hold other planets and even life and that truth does not change because it is, or is not, believed by most people. In those times, one did not lightly challenge Church doctrines, so perhaps his stratagem did protect Copernicus from Bruno's terrible fate.

An interesting species, *Homo sapiens.* It could create Gounod's Ave Maria, the US constitution, and Lincoln's Gettysburg address, but it could also create the Holocaust in Germany, the killing fields in Cambodia, and the Taliban in Afghanistan.

The updated bone physiology and some of its clinical relevance are summarized below. Table 1 lists abbreviations and symbols the text uses in brevity's interest. The summary concerns mammalian including human bones but not longitudinal bone growth, infection, or neoplasia.

Ten features of the Utah paradigm of skeletal physiology

The still-evolving Utah paradigm inserts tissue-level realities into the former ''knowledge gap'' between organ-level and cell-level skeletal features.[61–66,75,79,147] Ten features of that paradigm can explain why the five ideas mentioned in the ''Introduction'' apply to bones too.

1. Their mechanical functions show we have two kinds of bones. (i) After birth, most of our bones carry voluntary mechanical loads (VMLs) (femurs, tibias, humeri, mandibles, maxillae, phalanges, hips, wrists, etc, so load-bearing bones [LBBs] are not limited to weight-bearing ones). ''Voluntary'' means intentional and not due to injuries, so it implies muscle forces. LBB design clearly keeps VMLs from causing nontraumatic fractures—often called ''spontaneous'' ones—suddenly or from fatigue.[57] (ii) Yet a few of our bones serve different needs (cranial vault, cribriform plate of the ethmoids, nasal bones, turbinates, etc).

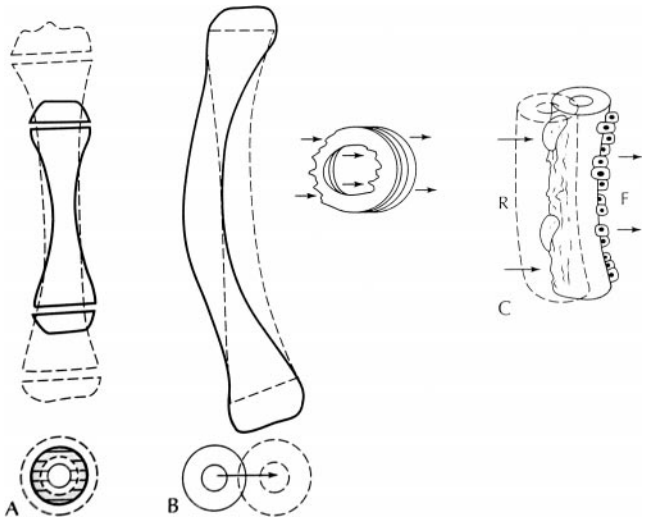

FIGURE 1. Bone modeling by drifts. (A) An infant's long bone with its original size and shape shown in solid line. To keep its shape as it grows in length and diameter, modeling drifts move its surfaces in tissue space as the dashed lines suggest. Formation drifts make and control new osteoblasts to build some surfaces. Resorption drifts make and control new osteoclasts to remove bone from other surfaces. (B) A different drift pattern can correct the fracture malunion in a child. The cross-sectional view to the right shows the endocortical as well as the periosteal drifts that do the correction. (C) How the drifts in B would move the whole segment to the reader's right. Changing the anatomy in that way reduces the bone's bending moments; it does not eliminate bending, but it does limit it. Drifts are created when and where they are needed, and they include capillaries, precursor and supporting cells, and some wandering cells. They are multicellular entities in the same sense as renal nephrons, and they usually act to minimize peak bone strains (reproduced with permission: Frost HM. Strain and other mechanical influences on bone strength and maintenance. *Curr Opin Orthop.* 1997;8:60–70).

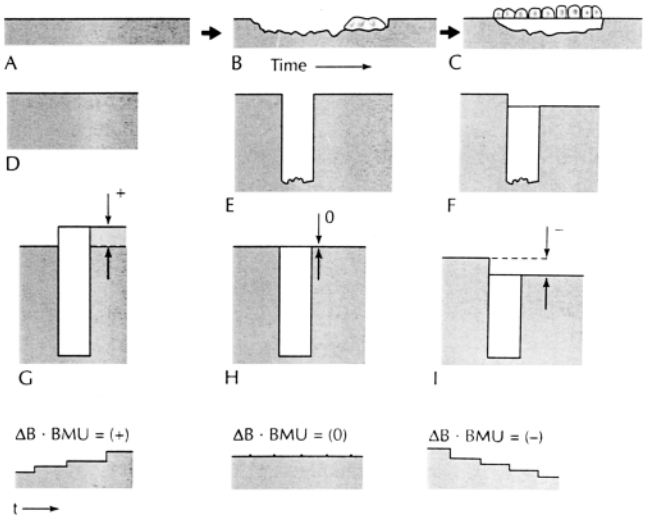

FIGURE 2. Bone remodeling BMUs. Top row: an activation event on a bone surface at (A) makes a packet of bone resorption begin (B), and then its osteoclasts are replaced by osteoblasts at (C). The BMU makes and controls the new osteoclasts and osteoblasts that do this. Second row: this emphasizes the amounts of bone resorbed (E) and formed (F) by completed BMUs. Third row: in these ''BMU graphs'' (G) shows a small excess of formation over resorption. (H) Equalized resorption and formation as on haversian surfaces and in ''conservation-mode'' remodeling. (I) A net deficit of formation, as in disuse-mode remodeling of endocortical and trabecular bone. Bottom row: these ''stair graphs'' show the effects of a series of BMUs of the kind immediately above on the local bone ''bank.'' BMUs are created when and where they are needed and include a capillary, precursor and supporting cells, and some wandering cells. They are multicellular entities in the same sense as renal nephrons (reproduced by permission: Frost HM. Strain and other mechanical influences on bone strength and maintenance. *Curr Opin Orthop.* 1997; 8:60–70).

2. Before birth, gene expression in utero creates some ''baseline conditions'' that include our initial bony anatomy and relationships, our basic neuromuscular anatomy and physiology, and the biologic ''machinery'' that can adapt bones after birth to mechanical and other challenges so that they can endure these challenges for life.[61]
3. This machinery includes two tissue-level mechanisms.[79] Modeling by formation and resorption drifts (Figure 1) can increase whole-bone strength.[61–65] ''Whole-bone'' distinguishes bones as organs from bone as a material or tissue. Remodeling by basic multicellular units (BMUs) turns bone over in small packets (Figure 2).[79] Its ''disuse-mode'' reduces a hollow bone's strength by removing some bone close to or next to the marrow.[58]
4. Loads on bones cause bone strains that generate signals that some cells can detect and to which they or other cells can respond.[89,98,99,119,143,148]
5. Genetically determined threshold ranges of these signals help to control modeling and remodeling. Where bone strains exceed bone's modeling threshold range (MESm), modeling can switch on to strengthen an LBB, whereas when bone strains stay below a lower threshold range (MESr), disuse-mode remodeling can turn on to reduce whole-bone strength by removing some trabecular and endocortical bone.[101] Equally, when a room is too cold, a thermostat can switch the furnace on to heat the room, and when the room is too hot, that thermostat turns the furnace off while another thermostat can switch the cooling system on to decrease the temperature. Thus if E signifies the typical peak strains of an LBB, then healthy small and large LBBs should satisfy this criterion: MESr $<$ E $<$ MESm.
6. Repeated bone strains cause microscopic fatigue damage in bone (microdamage, MDx).[26] This MDx has an operational threshold strain range (the MESp) that lies above the bone's MESm,[100] so MESr $<$ MESm $<$ MESp. Normally, LBBs can detect and repair the little MDx caused by strains that stay below the MDx threshold[65]; remodeling BMUs provide that repair[26,105] and osteocytes may provide this detection.[40,43]
7. Strains above the MESp threshold can cause enough

TABLE 2. Set Point Values for Bone's Thresholds and Ultimate Strength (in Microstrain, Stress and Unit-Load Terms)[a]

MESr, 50–100 microstrain; ~1–2 MPa, or ~0.1 kg/mm^2 (one can argue for a value of ~400 microstrain).[61]
MESm, 1000–1500 microstrain; ~20 MPa, or ~2 kg/mm^2.
MESp, ~3000 microstrain; ~60 MPa, or ~6 kg/mm^2. This also approximately equals bone's yield point.[32,64]
Fx, ~25,000 microstrain; ~120 MPa or ~12 kg/mm^2 in healthy young-adult mammals.

[a] MPa = megapascal = 10^6 Newtons/m^2. A one Newton force equals about 0.225 pounds/force. kg/mm^2 = ''unit loads''. The above values apply to cortical lamellar bone in healthy young-adult mammals, based on currently available information. One-thousand microstrain equals a 0.1% stretch or shortening, and the bone's fracture strain of 25,000 microstrain equals a 2.5% stretch or shortening. The above values show that bone strains and stresses do not always stay linearly proportional to each other.

MDx to escape repair and accumulate. Accumulated MDx in bones causes or helps to cause pathologic fractures, nontraumatic fractures in true osteoporoses and irradiated bone, and stress fractures in athletes, special forces trainees, and horses.[26,34] MDx accumulations would also cause or help to cause pseudofractures in osteomalacia,[145] collapse of subchondral bone in idiopathic aseptic necroses of the femoral head[46] osteochondritis dissecans, and nontraumatic fractures of some massive LBB allografts used in some tumor surgery and in some revisions of total joint replacements.[2,153] Such accumulations can also loosen some LBB, joint, and dental endoprostheses.[46] DR Carter's group found that a bone's MDx depends so sensitively on strain magnitude that doubling the bone loads that originally cause 2000 microstrain can increase MDx more than 400 times.[117]

8. The MESm and MESr threshold ranges of modeling and disuse-mode remodeling would make the typical largest loads on an LBB have far more influence on its strength than smaller loads. Trauma excepted, on earth lever-arm and gravitational effects make muscles put by far the largest loads on our LBBs, including on weight-bearing bones.[25,32,101] Thus, the dynamic loads on a soccer player's femur during a game can often, if briefly, exceed 5× the player's body weight,[31] and bone's biologic machinery would adapt postnatal LBB strength chiefly to muscle strength (and power?). Muscle forces cause the VMLs mentioned in this text.
9. Combining the above features would form bone's mechanostat (MST),[47,55,79,89,101] which Michael Parfitt recently called the most important unsolved problem in bone physiology.[156] Wherever this article mentions bone's biologic machinery, MST could substitute for it. MST functions presumably include (i) making LBBs strong enough after birth to keep VMLs from breaking them suddenly or from fatigue; (ii) adapting whole-bone strength to the strength (and power?) of the muscles that put VMLs on LBBs; (iii) and letting the MESr and MESm act as criteria for an LBB's ''acceptable'' strength relative to the size and kinds of VMLs on it. That helps to create the bone strength–safety factor (SSF) described under ''Some set point considerations and bone's SSF.'' (iv) MST functions would also include minimizing peak bone strains and stresses from bending, torsional and uniaxial compression loads, presumably to keep those strains (E) well below the MESp, so E $\ll$ MESp; (v) The MST would help to orchestrate the remodeling and modeling phases of bone healing described under ''Implications for healing fractures, bone grafts, osteotomies, and arthrodeses.'' The above material could help to explain why most wheelchair-bound children with complete and permanent lower-limb paralyses due to myelomeningoceles have stronger humeri than femurs, the opposite of the situation in normal children (this refers to an observation by the author. Many others probably noted the same, so it need not be an original observation; in the past, it did not seem important enough to deserve formal study and a formal report.)
10. The ''general biomechanical relation'' (GBR). Connecting some dots shows that in healthy MSTs, the magnitudes of some of the above features would ladder like this: MESr $<$ E $<$ MESm $\ll$ MESp $\ll$ FS.[62] In this GBR relation, MESr indicates the strain range below which the mechanically controlled disuse-mode remodeling function of decreasing a hollow LBB's strength would usually act maximally and above which that function begins to decrease and turn off; E, the typical peak strains caused by VMLs on an LBB; MESm, the strain range in and above which the mechanically controlled modeling function of increasing a bone's strength would usually turn on; MESp, bone's MDx strain threshold range in and above which unrepaired MDx can begin to accumulate; and Fx, an LBB's ultimate strength or fracture strength.

Each GBR entry constitutes a range, so its center could define its ''set point.'' Table 2 lists those set points as corresponding strains, stresses, and unit loads (ULs). A caveat: researchers still study how strain magnitudes, rates, frequencies, total numbers and kinds (including shear), modes of vibration, other kinds of stimuli, and aging might affect an LBB's MST and strength[87,89,112,121,124,132–135]; hence, some of the ''devils in the details'' that can lie below the generalities summarized in this article.

Figure 3 shows how the GBR's relationships would affect an LBB's strength.

Recapitulation. An ''elegant stratagem'' would make VMLs determine the postnatal strength of our LBBs and

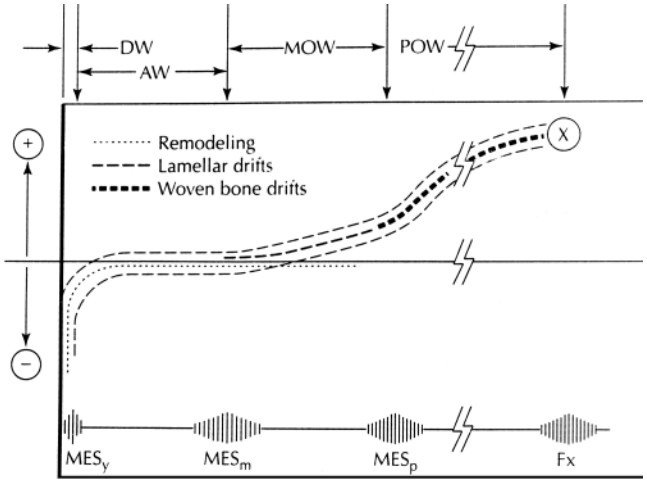

FIGURE 3. Combined modeling and remodeling effects on LBB strength. The horizontal line at the bottom suggests typical peak bone strains from zero on the left, to the fracture strain on the right (Fx), plus the locations of bone's three threshold ranges (the MESr, MESm, and MESp). The horizontal axis represents no net gains or losses of an LBB's strength. The lower dotted line curve suggests how disuse-mode remodeling would remove bone next to the marrow when an LBB's strains stay below the MESr range but otherwise would begin to keep the existing bone and its strength. The upper dashed line curve suggests how modeling drifts would begin to increase bone strength where strains enter or exceed the MESm range. The dashed outlines suggest the combined modeling and remodeling effects on an LBB's strength. Beyond the MESp range, woven bone formation usually replaces lamellar bone formation. At the top, DW indicates disuse window; AW, adapted window as in normally adapted young adults; MOW, mild overload window as in healthy growing mammals; and POW, pathologic overload window.[51] The span between MESr and MESm represents the span between those thresholds in bone's GBR. Carter[28] originally suggested such a curve (reproduced by permission: Frost HM. Strain and other mechanical influences on bone strength and maintenance. *Curr Opin Orthop.* 1997;8:60–70).

load-bearing trabeculae. Most trabeculae transfer loads between cortical bone on the one hand, and tooth sockets, joints, or growth plates, on the other hand. Cybernetic considerations[161] indicate that implementing this stratagem should require at least the following four factors: (1) biologic mechanisms that could change whole-bone strength after birth (which modeling and remodeling can do); (2) ways to monitor the relationship between an LBB's strength and the VMLs on it (which strain-dependent signals can do); (3) special criteria for acceptable and unacceptable whole-bone strength relative to the VMLs on an LBB (the MESm and MESr can provide these criteria); and (4) feedback between these features (which the MST provides).

In short, that ''elegant stratagem'' could indeed determine most of the postnatal strength of our LBBs. Although Nature seems concerned mainly about whole-bone strength, she lets a bone's stiffness determine its strength by making the relationship between its stiffness and the strains caused by the VMLs on it help to switch its modeling and disuse-mode remodeling functions on and off.

Applications and implications

The value of a better understanding of bone physiology would depend on its practical applications. The following sections concern a few of them that earlier physiologists and clinicians did not know about.[86,106,151,152,166,167]

Implications for healing fractures, bone grafts, osteotomies, and arthrodeses. In still-lingering views, bone healing comprised one indivisible process that depended on osteoblasts (its supposed key players), aided by angiogenesis, apoptosis, chondroblasts, stem cells, cytokines, Marshal Urist's BMPs, ligands, cell receptors, etc.[1,12,19,72,96,123,125,127,136,154]

Nephrons provide the key players in renal physiology; likewise, four tissue-level mechanisms provide the true key players in bone healing. They include the callus, remodeling and modeling phases, and a regional acceleratory phenomenon (RAP) that normally lasts throughout the healing process.[45,48,49,59,168] Each phase can malfunction independently, so many kinds of bone-healing problems can occur that do not stem from presently known treatment errors. Former histologists and pathologists described many light-microscopic features of these disorders,[1,96,123,158] but their roles in bone healing remained generally unrecognized and unstudied even in AD 2002. One reason for that may have been a reluctance of some authorities to agree that bone modeling by drifts and remodeling by BMUs constitute separate and independent mechanisms. Jee first tested this idea. In his experiments, in the same bone at the same time and in response to the same mechanical challenge, modeling turned off or decreased while remodeling increased.[76,77,92–94] Yet, both mechanisms seem to use the same kinds of osteoblasts and osteoclasts.[79] Later studies, too numerous to cite, found the same results, although their authors seldom remarked that fact (but see Chen et al[29] and Yeh et al[170] in which the same results followed a hormonal challenge to bones).

So said (1) at first a fracture, bone graft, osteotomy, or arthrodesis normally makes a local soft fracture callus form. It contains new vessels, supporting and precursor cells, osteoblasts making woven bone, and often chondroblasts making hyaline cartilage.[19] Normally, the callus embeds and ''welds'' to the fragments of the fracture or graft, and it lacks a long-range ''grain.'' Failure to form it in sufficient amounts causes one kind of ''biologic failure'' of bone healing.[48,49] (2) After the callus mineralizes, and usually only then (This refers to an observation by the author. Many others probably noted the same, so it need not be an original observation; in the past, it did not seem important enough to deserve formal study and a formal report.), remodeling BMUs normally begin to replace it or graft material with packets of new lamellar bone, the grain of which usually parallels the largest local compression or tension strains. Failure of the callus to mineralize could help to explain why pseudofractures can persist in osteomalacias.[37,145] This remodeling phase provides much of what

Schenk[136] called ''primary healing'' of bones. The osteoclast defect that causes osteopetrosis impairs replacement of fracture callus with lamellar bone, which would help to explain poor bone healing in that disease.[17,33,73] (3) Partly overlapping phase 2, modeling normally begins to reshape and resize the callus, presumably to make the healing bone strong enough to keep its strains below MESp, ie, to keep E $\ll$ MESp. Failures of phases 2 and 3 could cause late, rare failures of bone healing in which the bone heals well enough at first to let voluntary activities resume, but later on the healed region develops a stress fracture or begins to angulate.[171] In 55 years I only saw five such problems,[44] two of which led to successful malpractice suits (even today, few pathologists and orthopedists who might testify in such trials know about this problem). The relatively sluggish 1–3 phases last longer in adults, large bones and diaphyses than in children, small bones and metaphyses. (4) A fracture, arthrodesis, osteotomy, or bone grafting operation normally incites a RAP that lasts throughout the healing process. A RAP normally accelerates the other three phases by $\sim 2\times$ to $5\times$,[45,46] so an inadequate RAP can delay bony union. Besides impaired regional blood supply, sensory denervation in some peripheral neuropathies increases the probability of inadequate RAPs,[46] which, however, seldom affect children. The molecular-biologic mechanisms that support a RAP remained nearly unstudied in 2003. The idea that cigarette smoking might impair a RAP and bone healing deserves more study.[122]

In my experience, most bone-healing impairments not due to treatment errors stemmed from disorders of phases 1 and 4, and phase 4 disorders occurred more often than phase 1 disorders. As noted above, failures of phases 2 or 3 apparently can cause rare late failures of bone healing. Excessive or prolonged RAPs cause algodystrophies, also called ''migratory osteoporoses.''[35,88,138] RAPs usually accompany periodontal disease and most maxillofacial and other bone operations.

A role of strain—Production of the initial callus probably depends chiefly on biochemical agents released by the local injured cells. Still-enigmatic properties of a mineralized callus can initiate the remodeling phase, but small strains would help to guide the remodeling and modeling phases of bone healing in time and anatomical space after they have begun.[15,24,30,71,156,157,167,169] Without such strains, disuse-mode remodeling tends to remove a callus while modeling tends to stay off, so bone healing can retard or fail.[46] Of course, excessive strains (gross motion) can usually prevent bony union. The naturally ''permissible'' strains might lie in the 100–2000 microstrain region,[67,104] compared with bone's fracture strain in the 25,000 microstrain region (Table 2). The 100–2000 microstrain span would include the adapted and mild overload windows in Figure 3 (AW and MOW, respectively), or in GBR terms, MESr $<$ E $\ll$ MESp. Very small loads can cause harmfully large strains in the early phases of healing fractures, bone grafts, and arthrodeses, including spinal fusions.[90]

For strains to guide the bone remodeling and modeling healing phases in time and space would require living cells in large fracture fragments and large grafts. Why? Only such cells could detect and respond to these strains or to any accompanying MDx and help to create the local BMUs and modeling drifts needed for completion of bone healing. In devitalized fracture fragments and grafts, achieving this situation should depend on invasion by new vessels and cells from the surrounding host tissues. This invasion seems inadequate in many allografts and in most xenografts.

Bone healing (including in ''distraction osteogenesis'')[80] also depends on humoral and cell-biologic influences on bone cells. Known humoral influences include hormones, vitamins, minerals, drugs, etc.[10,108,144] Known cell-biologic influences include cytokines, growth factors, other ligands, angiogenesis, apoptosis, Marshall Urist's BMPs, stem cell hierarchies, ''supporting cell'' functions, cell proliferation and differentiation, various cellular pumps, gene expression patterns, etc.[27,68,154,159] To these, one could add electrical and ultrasound treatments.[21,70,134]

Because of lack of appropriate studies, how such things affect each bone-healing phase remains unknown at present, and many such things could have permissive roles in these phases instead of compelling them to occur (see section ''On shattered prospects'' below). Ultrasound treatment apparently can improve bone healing.[134] It causes tiny strains at very high frequencies and very high strain rates in bone-healing regions. Its effect(s) on each of the bone healing's four phases also remains unknown at present.

Implications for the design and use of load-bearing implants.[50] This section concerns only one of the many problems of such implants. The updated bone physiology suggests that the design of load-bearing endoprostheses should (1) keep typical peak strains in the bone supporting the implants below the bone's MDx threshold, (2) but let those strains exceed bone's MESr, and perhaps exceed its MESm too. Why? Strains in MOW in Figure 3 might make modeling strengthen the supporting bone but should help to keep disuse-mode remodeling from removing it. In GBR terms, this means strains in the bone supporting load-bearing implants should satisfy this criterion: MESr $<$ E $\ll$ MESp. This criterion should apply to load-bearing artificial joints, partial bone-replacement endoprostheses, dental implants, and some spinal instrumentation. When something makes E approach or exceed MESp, then bone MDx accumulations would usually occur and lead to nontraumatic and stress fractures.

Yet, even in AD 2002, no marketed load-bearing skeletal implant intentionally tried to satisfy the above criterion. It seems that Branemark's dental implant system did it unintentionally,[20] so it can be done.

Load-bearing implants used for internal and external fixation of osteopenic bones with thin cortices and reduced

amounts of spongiosa would need more or larger screws, pins, and other devices to provide larger LBB-implant interfaces. Why? The larger the interfaces, the smaller the loads on each square millimeter of the supporting bone, and prudence suggests one should try to keep those unit loads (ULs) below the bone's MESp, or UL $\ll$ MESp. Combined with suitable postoperative management, this arrangement could help to keep the ULs on these interfaces below the bone's MESp range, which in stress terms should center near ~6 kg/mm^2 (Table 2). Otherwise, accumulating MDx in the bone supporting the implants could eventually help to loosen them.

Again, such implants have many other problems, including the role of a ''shear lock'' that is discussed elsewhere.[46,50]

Some set point considerations and bone's SSF. Healthy LBBs have more strength than needed to keep VMLs from breaking them suddenly or from fatigue damage, so they have an SSF. Why? The MESm's set point would determine the largest strain or stress that VLMs should cause in healthy bones, so an MESm set point that lies below the bone's ultimate strength (MESm $<$ Fx) must create an SSF. In such cases, the SSF could equal a bone's ultimate strength divided by its modeling threshold, or SSF = Fx $\div$ MESm. By expressing the latter two terms as stresses, healthy young-adult LBBs should have about six times more than the minimum strength needed to keep typical peak VMLs from breaking them (from Table 2, 120 MPa ~20 MPa = 6). An often-cited value of two used bone's yield point of ~60 MPa (Table 2) instead of its MESm to calculate its SSF.[13]

Those observations suggest two possibilities. (1) A modestly increased MESm set point ($\uparrow$MESm) might lower an LBB's SSF from six to, perhaps, four. Affected bones should become a bit weaker and more prone to traumatic and stress fractures.[101] (2) A modestly decreased MESm set point ($\downarrow$MESm) might increase a bone's SSF from six to perhaps eight. Affected bones should become a bit stronger and more resistant to traumatic and stress fractures.

Experienced clinicians, coaches, and trainers know that both these situations occur in a few individuals who seem either unusually prone to or unusually resistant to stress and traumatic fractures.[26,82] Thus, learning to lower the MESm's set point with some medication might (1) let children accumulate more bone and enter adult life with larger bone banks,[142] (2) minimize nontraumatic fractures in true osteoporoses and stress fractures in athletes and special forces trainees,[26,57] and (3) help to prolong the service lives of some joint replacement and dental endoprostheses, as described in section ''Implications for the design and use of load-bearing implants.''

Why decrease the MESm's set point? That would let smaller strains and VMLs than before make modeling strengthen bones.[101] Most nontraumatic, stress, and pathologic fractures should occur in situations where, for whatever reason(s), E ~MESp or E $>$ MESp. Sections ''Some bone modeling functions and disorders (or, what should modeling do, and what happens when it fails to?)'' and ''Some BMU-based remodeling functions and disorders (or, what should remodeling do, and what happens when it fails to?)'' below suggest a few such situations.

How aging might affect the SSF is uncertain, but the MST hypothesis predicts that the ''error-driven'' and sluggish mechanically controlled bone modeling could let the SSF of our bone diaphyses lag behind mechanical needs and decrease during growth[53,54] and decrease further during our adolescent growth spurt.[56] Yet, in young adults, when body weight and muscle strength have usually plateaued, the diaphyseal SSF could recover from these ''adaptational lags'' and peak in value. This should decrease metaphyseal and diaphyseal forearm fractures from falls in young adults. Our age-related fracture patterns correlate quite well with these ideas,[16,128,129,162] which may not validate but does support them.

In the updated bone physiology whole-bone strength would be more important than the physical parameters that contribute to it (bone ''mass,'' bone mineral content, absorptiometric bone mineral ''density,'' outside bone diameter, trabecular connectivity and thickness, a bone's shape, bone's material properties, etc). If so, whole-bone strength should become an important datum in future studies that concern stress fractures, bone healing, the design and use of load-bearing endoprostheses, and ''osteoporosis'' (''osteoporosis'' in quotes signifies current conventional definitions).[84] Noninvasive methods can evaluate whole-bone strength in patients.[6,11,38,81,139,140,142,163] Such methods have virtues and limitations.[38,81] For example, neither bone mineral density nor speed-of-sound studies can reliably evaluate bone mass or whole-bone strength,[38,109,110] even though such studies became popular.[97]

Some bone modeling functions and disorders (or, what should modeling do, and what happens when it fails?). (1) Modeling formation drifts create our initial supplies of cortical bone.[79] Excessive periosteal formation drifts cause some bone deformities associated with Paget's disease and congenital lues (''saber shin'').[73,96] Bone-anabolic agents, such as prostaglandin E-2[78] and parathyroid hormone,[146,147] add bone and strengthen a bone mainly by inciting new modeling formation drifts on compacta and spongiosa. (2) Modeling (not osteoblasts alone) can slowly increase whole-bone strength, partly by increasing the bone bank and partly by reshaping a bone as in Figure 1B. This could tend to keep typical peak VMLs from causing bone strains that approach or exceed a bone's MESp. Failure to do this could help to increase bone fragility in true osteoporoses and osteogenesis imperfecta.[57] How? In GBR terms, by letting or helping E ~MESp or E $>$ MESp. (3) Section ''Implications for healing fractures, bone grafts, osteotomies, and arthrodeses'' above describes modeling's role in bone healing and some of its malfunctions. (4) Section ''Impli-

cations for the design and use of load-bearing implants'' above suggested a modeling role in the bone supporting load-bearing implants. (5) Most laminar periosteal new bone formation layers often called ''periostitis'' by radiologists represent new bone formation drifts evoked by a local stress fracture, infection, tumor, or other process. Sometimes humoral agents can cause them too, as in pulmonary hypertrophic osteoarthropathy and scurvy.[7,73,96]

Some BMU-based remodeling functions and disorders (or, what should remodeling do, and what happens when it fails?). (1) Remodeling ultimately replaces primary spongiosa beneath growth plates with a secondary spongiosa made of lamellar bone.[79] Failure to do this causes one kind of osteopetrosis.[73] Remodeling ultimately replaces mineralized cartilage in osteochondromas, and in the basal layer of articular cartilage, with a secondary spongiosa made of lamellar bone. It slowly replaces cortical bone formed by formation drifts (called circumferential lamellae) with secondary osteons.[3,79] Section ''Implications for healing fractures, bone grafts, osteotomies, and arthrodeses'' above described its role in bone healing. (2) Section ''Ten features of the Utah paradigm of skeletal physiology'', point (7), summarized remodeling's roles in MDx physiology and some of its malfunctions when, for whatever reason(s), E approaches or exceeds the MESp. (3) Disuse-mode remodeling (not osteoclasts alone) removes mechanically unneeded bone close to or next to marrow (trabecular and endocortical bone), which may explain why our postnatal diaphyseal marrow cavities contain little or no spongiosa. This mode also causes bone loss during treatment with medications like Prednisone, it helps to cause subchondral cysts in osteoarthritis, and it should help to cause lytic bone lesions associated with tumors like sarcoid, multiple myeloma, some metastases, unicameral bone cysts, Brodie's abscesses, and nonossifying fibromas. Disuse-mode remodeling (not osteoclasts alone)[58,79] should cause the bone losses next to marrow associated with postpubertal losses of estrogen and androgen in women and aging men, respectively.[58,97] Combined with modeling malfunctions, excessive disuse-mode remodeling would help to cause true osteoporoses and osteogenesis imperfecta.[57] In these situations and in GBR terms an MST disorder could let E ~Fx. Presumably disuse-mode remodeling causes all adult-acquired osteopenias on earth and osteopenias in astronauts in space. (4) Where woven bone carries loads, remodeling usually replaces it with lesser amounts of lamellar bone (this refers to an observation by the author. Many others probably noted the same, so it need not be an original observation; in the past, it did not seem important enough to deserve formal study and a formal report.) This occurs in fibrous dysplasia, in myositis ossificans, and in heterotopic bone formation about injured hips, elbows, and other joints. (5) Remodeling and osteoclasts have minor roles in calcium homeostasis.[5,115,150]

Please note four points—(1) Modeling and remodeling may have still-unrecognized functions or disorders. (2) A special bone resorption mechanism that remained unstudied after its original description may participate in some bone-loss disorders.[74] (3) Woven bone can form de novo, meaning where no bone of any kind existed before, but lamellar bone only forms on pre-existing bone of any kind (this refers to an observation by the author. Many others probably noted the same, so it need not be an original observation; in the past, it did not seem important enough to deserve formal study and a formal report.) (4) The MST controls modeling and remodeling in ways that let a minimum of bone tissue provide optimum whole-bone strength.

On shattered prospects. Pharmaceutical and molecular-biologic researchers often suggest that new findings do or could hold a final answer to some vexing clinical problem(s). Yet, such shattered prospects hugely outnumbered successes like penicillin, blood typing before transfusions, aseptic surgery, and insulin for diabetes. Knowing three reasons for exaggerated prospects might help clinicians to assess their merits.

On permissive agents—(1) In some views, genes and humoral agents like hormones, calcium, vitamins C and D, and some drugs, dominated control of postnatal bone health; by implication they would dominate determining a postnatal LBB's strength too.[14,22,37,68,95,103,107,111,118,126,130,160]

(2) Yet, the MST hypothesis (it is a hypothesis, but perhaps in the same sense that $E = mc^2$ technically still constitutes a hypothesis) plus the accumulating data suggest that most—not all—such agents would act as ''permissive'' ones that the MST needs to achieve a normal ''bone load–bone strength'' relationship in LBBs and to satisfy the GBR. Equally, cars need fuel, motors, wheels, etc, to be driven, but they do not drive cars or choose their destinations; for these purposes, such things would represent permissive agents. No known bone-active humoral agents can replace mechanical-loading effects in time and space on a bone's ''functional adaptations'' to changes in its mechanical usage.[85,89] In proof, such agents cannot normalize whole-bone strength in paralyzed limbs (this refers to an observation by the author. Many others probably noted the same, so it need not be an original observation; in the past, it did not seem important enough to deserve formal study and a formal report.)

(3) The bone literature seldom discussed permissive agents after 1900, but they have a revealing property. Their deficiencies can cause serious problems, but in healthy subjects, their excesses have no or only small effects or different kinds of effects such as toxicity.[66] Examples follow. (i) Vitamin C deficiency causes scurvy, but its excesses have little effect in healthy bodies. (ii,iii) Vitamin D and thyroxine deficiencies cause short stature[8,155,164]; yet their excesses do not cause gigantism but can cause toxicity. (iv) Growth hormone (GH) might chiefly permit, instead of compel, whole-bone strength to increase when the VMLs on an LBB become larger.[60] Without increased bone loads,

GH did not significantly increase whole-bone strength[39]; so GH could indeed have a permissive role in this matter. Yet, in current views GH would compel whole-bone strength to increase regardless of the VMLs on a bone.[4,7,18,97,114,130,164]

This permissive role may help to explain some disappointing results of treating osteoporosis with GH.[130,165] How so? When such patients did not exercise to increase their muscle strength, GH's permissive role could manifest itself as a failure to increase whole-bone strength enough to decrease ''osteoporosis fractures.''

Similar permissive roles may characterize some effects on LBB strength of agents like testosterone, calcium, and vitamin D (and perhaps of many cytokines, chemokines, cell receptors, ligands, etc). Experiments like Mark Forwood's[39] could help to reveal and study the permissive roles of many agents in the physiology and disorders of bones and of bone's MST.[40]

On skeletal microcosms and macrocosms—In physics and astronomy, ''microcosms cannot predict macrocosms.''[137] Or, trying to predict galaxies and cars solely from knowledge about atoms has a nearly zero chance of success, although atoms can help explain already-known features of such concepts.

Trying to predict a skeleton's organ-level functions only from its cell-biologic realities would try to predict a skeletal macrocosm from a skeletal microcosm, ie, it would try to predict (1) or (2) from (3) or (4) in the ''Introduction.'' That would be like trying to understand renal physiology without accounting for nephrons.

Historically most such efforts failed and caused ''jumping frog errors.''[64] Examples follow. (i) Recognition in the early 1960s that calcitonin hindered osteoclastic but not osteoblastic activities in vitro suggested it could increase the bone bank and cure osteoporosis when given in vivo. Yet, it did not. This idea tried to predict skeletal macrocosms from microcosms, and it tried to bypass a bone's tissue-level functions too. Both of these represent jumping frog errors. (ii,iii) Between 1935 and 1955, some people thought that supplements of estrogen or dietary calcium should also increase bone mass and cure osteoporosis (because their deficiencies usually caused osteopenias). Yet, they did not. In retrospect, these ideas mistook an agent's permissive role in MST physiology for a compelling determinant of whole-bone strength. (iv) Authors of a study of mechanical loading on mammalian long-bone growth plates decided that even small loads reduced their growth.[113] If so, bones in paralyzed limbs would grow longer than corresponding bones in normal limbs. Yet, for more than 2000 years physicians knew the opposite usually occurs, and numerous studies never found bones in deloaded limbs growing longer than corresponding bones in control limbs. (v) Other authors[69] decided that deloading bones made their cells resistant to GH's presumed ability to compel whole-bone strength to increase regardless of a bone's VMLs. Yet that study really supported GH's permissive role in that situation, as in the study of Forwood et al.

Such errors seldom stemmed from faulty data. They stemmed from varied combinations of faulty interpretations of data, from not ''connecting the dots'' in other relevant evidence, from trying to predict biologic macrocosms from microcosms, from confusing transient with steady-state effects,[46] and from not thinking ''outside the box'' of long-accepted wisdom. In the past, I made such errors, so mea culpa. We live and learn. Hopefully.

On cell-biologic and molecular-biologic research, and understanding bone physiology—Skeletal cell-biologic and molecular-biologic research have become very valuable, challenging, active, productive, and popular fields of study that will probably continue. Each of the tissue-level ''targets'' under ''Ten features of the Utah paradigm of skeletal physiology'' needs understanding at those levels. Yet, how cell- and molecular-biologic features support those targets remains little-studied and largely unknown in 2003 (if opinions abound, proof does not). Most bone analogs of the kidney's nephrons still wait for understanding at those levels, and lack of it explains why this article says so little about it. Others commented about such problems.[23,102,120] This lack left a serious knowledge gap in skeletal physiology, a situation that would resemble trying to understand renal physiology without accounting for nephrons. Filling that gap should provide opportunities for unusually useful research that could lead to better diagnosis and management of many bone disorders. For example, that osteoblasts or osteocytes can respond to bone loads and strains[89] need not mean and does not prove that they contain bone's MESm and MESr thresholds too.

Not discussed in this article. This article does not discuss other applications of the updated bone physiology. They include, in part only, new classifications of osteopenias, osteoporoses, and osteoporosis fractures; some uses and limitations of absorptiometric methods, scintigrams, and magnetic resonance imaging; some roles of genes, hormones, vitamins, minerals, drugs, and aging in that physiology; bone's role in calcium homeostasis; some roles of properly timed intermittent-sequential treatment with two or more agents; the existence and roles of mediator mechanisms in marrow and perhaps on bone's periosteal envelope; other problems in the design and use of load-bearing orthopedic and dental endoprostheses; and uses and limitations of biochemical ''markers'' of bone turnover, growth, and healing. This article also does not discuss some naive ideas that have taken root in today's skeletal physiology and skeletal biomechanics.

Although the updated bone physiology can challenge some long-accepted wisdom (and one could expect that wisdom to defend itself), today the challengers need not risk suffering Giordano Bruno's horrible fate.

CONCLUSIONS

The above material is certainly not the ''whole thing'' (''no matter how much we know now, there is always more''), but it provides a good foundation on which to build. The prospect seems so exciting that I wish I could begin my career anew and help that building. But age and other factors indicate that this cannot be. As the Rubaiyat said,

The Moving Finger writes; and having writ,
Moves on: nor all thy Piety nor Wit,
Shall lure it back to cancel half a Line,
Nor all thy Tears wash out a Word of it.

So people younger than this octogenarian will do that building, and when, how, and if they choose to.

So be it.

REFERENCES

1. Aegerter E, Kirkpatrick JA. *Orthopaedic Diseases.* Philadelphia, Pa: WB Saunders Co; 1958.
2. Aho AJ, Ekfors T, Dean PB, Aro HT, Ahonen A, Nikkanen V. Incorporation and clinical results of large allografts of the extremities and pelvis. *Clin Orthop Rel Res.* 1994;307:200–213.
3. Anderson WAD, Kissane JM, eds. *Pathology.* 7th ed. St Louis, Mo: CV Mosby Co; 1977.
4. Andreassen TT, Jorgensen PH, Flyvberg A, Orskov H, Oxlund H. Growth hormone stimulates bone formation and strength of cortical bone in aged rats. *J Bone Miner Res.* 1995;10:1057–1067.
5. Arnold JS, Frost HM, Buss RO. The osteocyte as a bone pump. *Clin Orthop.* 1971;78:47–55.
6. Augat P, Reeb H, Claes L. Prediction of fracture load at different skeletal sites by geometrical properties of the cortical shell. *J Bone Miner Res.* 1996;11:1356–1363.
7. Aurbach GB, Marx SJ, Spiegel AM. Metabolic bone disease. In: Wilson JD, Foster DW, eds. *William's Textbook of Endocrinology*. 8th ed. Philadelphia, Pa: WB Saunders Co; 1992:1477–1517.
8. Avery ME, First LR, eds. *Pediatric Medicine.* 2nd ed. Baltimore, Md: Williams and Wilkins; 1993.
9. Babbitt AM. Osteoporosis. *Orthopedics.* 1994;17:935–941.
10. Bak B, Jorgensen PH, Andreassen TT. The stimulating effect of growth hormone on fracture healing is dependent on onset and duration of administration. *Clin Orthop Rel Res.* 1991;264:295.
11. Banu MJ, Orhii PB, Mejia W, McCarter RJM, Mosekilde L, Thomsen JS, Kalu DN. Analysis of the effects of growth hormone, voluntary exercise, and food restriction on diaphyseal bone in female F344 rats. *Bone.* 1999;25:479–480.
12. Barnes GL, Kostenuik PJ, Gerstenfeld LC, Einhorn TA. Growth factor regulation of fracture repair. *J Bone Miner Res.* 1999;14:1805–1815.
13. Biewener AA. Safety factors in bone strength. *Calcif Tissue Int.* 1993;53(suppl):68–74.
14. Bilezikian JP, Raisz LG, Rodan GA. *Principles of Bone Biology*. Orlando, Fla: Academic Press; 1996.
15. Blenman PR, Carter DR, Beaupre GS. Role of mechanical loading in the progressive ossification of a fracture callus. *J Orthop Res.* 1989;7:398–407.
16. Blount WP. *Fractures in Children.* Baltimore, Md: Williams and Wilkins; 1955.
17. Bollerslev J. Autosomal dominant osteopetrosis: bone metabolism and epidemiological, clinical and hormonal aspects. *Endocr Rev.* 1989;10:45–67.
18. Bouillon R. Growth hormone and bone. *Horm Res.* 1991;36(suppl):49–55.
19. Brand RA, Rubin CT. Fracture healing. In: Albright JA, Brand RA, eds. *The Scientific Basis of Orthopaedics.* 2nd ed. Norwalk, Conn: Appleton and Lange; 1987:325–346.
20. Branemark PI. Tooth replacement by oral endoprostheses: clinical aspects. *J Dent Educ.* 1988;52:821–823.
21. Brighton CT, Shaman P, Heppenstall RB, Esterhai JL, Pollack SR, Friedenberg ZB. Tibial nonunion treated with direct current, capacitive coupling, or bone graft. *Clin Orthop Rel Res.* 1995;321:223–234.
22. Bronner F. Calcium and osteoporosis. *Am J Clin Nutr.* 1994;60:831–836.
23. Brown W, Haglund K. Landmarks. *J Natl Inst Health Res.* 1995;7:54–59.
24. Buckwalter JA, Grodzinshy AJ. Loading of healing bone, fibrous tissue and muscle: implications for orthopaedic practice. *J Am Acad Orthop Surg.* 1999;7:291–299.
25. Burr DB. Muscle strength, bone mass, and age-related bone loss. *J Bone Miner Res.* 1997;12:1547–1551.
26. Burr DB, Milgrom C, eds. *Musculoskeletal Fatigue and Stress Fractures.* Boca Raton, Fla: CRC Press; 2000.
27. Cao Y, Mori S, Mashiba T, et al. Raloxifene, estrogen and alendronate affect the process of fracture repair differently in ovariectomized rats. *J Bone Miner Res.* 2002;17:2237–2246.
28. Carter DR. Mechanical loading histories and cortical bone remodeling. *Calcif Tissue Int.* 1984;36(suppl):19–24.
29. Chen M-M, Yeh JK, Aloia JF. Skeletal alterations in hypophysectomized rats: II. A histomorphometric study on tibial cortical bone. *Anat Rec.* 1995;241:513–518.
30. Claes L, Wilke H-J, Augat P, Suger G, Fleischman W. The influence of fracture gap size and stability on bone healing. *Orthop Res Soc Abstr.* 1994;19:203.
31. Crowninshield RD, Johnston RC, Andrews JG, Brand RA. A biomechanical investigation of the human hip. *J Biomech.* 1978;11:75–85.
32. Currey JD. *The Mechanical Adaptations of Bones.* Princeton, NJ: Princeton University Press; 1984.
33. de Palma L, Tulli A, Macccauro G, Sabetta SP, del Torto M. Fracture callus in osteopetrosis. *Clin Orthop Rel Res.* 1994;308:85–89.
34. Devas M. *Stress Fractures.* London: Churchill-Livingston; 1975.
35. Duncan H, Frame B, Arnstein AR, Frost HM. Migratory osteolysis of the lower extremities. *Ann Intern Med.* 1973;66:1165–1173.
36. Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* New York, NY: ASBMR, Raven Press; 1993.
37. Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* Philadelphia, Pa: Lippincott-Raven; 1996.
38. Ferretti LJ, Cointry GR, Capozza RF. Noninvasive analysis of bone mass, structure and strength. In: H An Yuehuei ed. *Orthopaedic Issues in Osteoporosis.* Boca Raton, Fla: CRC Press; 2002:145–161.
39. Forwood MR, Li L, Kelly WL, Bennett MB. Growth hormone is permissive for skeletal adaptation to mechanical loading. *J Bone Miner Res.* 2001;16:2284–2290.
40. Frost HM. *Introduction to Biomechanics.* Springfield, Ill: Charles C Thomas; 1963.
41. Frost HM. *Laws of Bone Structure.* Springfield, Ill: Charles C Thomas; 1964.
42. Frost HM. *Mathematical Elements of Lamellar Bone Remodelling.* Springfield, Ill: Charles C Thomas; 1964.

43. Frost HM. *Bone Dynamics in Osteoporosis and Osteomalacia.* Springfield, Ill: Charles C Thomas; 1966.
44. Frost HM. *Orthopaedic Biomechanics.* Springfield, Ill: Charles C Thomas; 1973.
45. Frost HM. The regional acceleratory phenomenon. A review. *Henry Ford Hosp Med J.* 1983;31:3–9.
46. Frost HM. *Intermediary Organization of the Skeleton.* Vols I, II. Boca Raton, Fla: CRC Press; 1986.
47. Frost HM. The mechanostat: a proposed pathogenetic mechanism of osteoporoses and the bone mass effects of mechanical and nonmechanical agents. *Bone Miner.* 1987;2:73–85.
48. Frost HM. The biology of fracture healing, Part I. *Clin Orthop Rel Res.* 1989;248:283–293.
49. Frost HM. The biology of fracture healing, Part II. *Clin Orthop Rel Res.* 1989;248:294–309.
50. Frost HM. Perspectives: on artificial joint design. *J Long Term Eff Med Implants.* 1992;2:9–35.
51. Frost HM. Perspectives: bone's mechanical usage windows. *Bone Miner.* 1992;19:257–271.
52. Frost HM. Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians. *Angle Orthod.* 1994; 64:187–212.
53. Frost HM, Jee WSS. Perspectives: a vital biomechanical model of the endochondral ossification mechanism. *Anat Rec.* 1994; 240:435–446.
54. Frost HM, Jee WSS. Perspectives: applications of a biomechanical model of the endochondral ossification mechanism. *Anat Rec.* 1994;240:447–455.
55. Frost HM. Perspectives: a proposed general model of the mechanostat (suggestions from a new paradigm). *Anat Rec.* 1996; 244:139–147.
56. Frost HM. Perspectives: on increased fractures during the human adolescent growth spurt. Summary of a new vital-biomechanical explanation. *J Bone Miner Metab.* 1997;15:115–121.
57. Frost HM. Osteoporoses: new concepts and some implications for future diagnosis, treatment and research (based on insights from the Utah paradigm). *Ernst Schering Res Found AG*. 1998; 7–57.
58. Frost HM. On rho, a marrow mediator and estrogen: their roles in bone strength and ''mass'' in human females, osteopenias and osteoporoses (insights from a new paradigm). *J Bone Miner Metab.* 1998;16:113–123.
59. Frost HM. Some vital biomechanics of bone grafting and load-bearing implants in dental and maxillofacial surgery: a brief tutorial. In: Jensen OT, ed. *The Sinus Bone Graft.* Ill: Quintessence Publishing Co, Inc; 1998:17–29.
60. Frost HM. Could some biomechanical effects of growth hormone help to explain its effects on bone formation and resorption? *Bone.* 1998;23:395–398.
61. Frost HM. The Utah paradigm of skeletal physiology: an overview of its insights for bone, cartilage and collagenous tissue organs. *J Bone Miner Metab.* 2000;18:305–316.
62. Frost HM. Does bone design intend to minimize fatigue failures? A case for the affirmative. *J Bone Miner Metab.* 2000;18:278–262.
63. Frost HM. The Utah paradigm of skeletal physiology: what is it? *Vet Comp Orthop Traumatol.* 2001;14:179–184.
64. Frost HM. Why should many skeletal scientists and clinicians learn the Utah paradigm of skeletal physiology? *J Musculoskeletal Neuronal Interact.* 2001;2:121–130.
65. Frost HM. From Wolff's Law to the Utah paradigm: insights about bone physiology and its clinical applications. *Anat Rec.* 2001;262:398–419.
66. Frost HM, Schönau E. On longitudinal bone growth, short stature, and related maters: insights about cartilage physiology from the Utah paradigm. *J Pediatr Endocrinol Metab.* 2001;14:481–496.
67. Frost HM, Meyer U, Joos U, Jensen OT. Dental alveolar distraction osteogenesis and the Utah paradigm. In: Jensen OT, ed. *Alveolar Distraction Osteogenesis.* Carol Stream, Ill: Quintessence Publ Co; 2002:1–16.
68. Goldring SR, Goldring MB. Cytokines and skeletal physiology. *Clin Orthop Rel Res.* 1996;324:13–23.
69. Halloran BP, Bickle DD, Harris J, Autry CO, Currier PA, Tanner S, Patterson-Buckendahl P, Morey-Holton E. Skeletal unloading induces selective resistance to the anabolic actions of growth hormone on bone. *J Bone Miner Res.* 1995;10:1168–1176.
70. Hamanishi C, Kawabata T, Yoshii T, Tanaka S. Bone mineral density changes in distracted callus stimulated by pulsed direct electrical current. *Clin Orthop Rel Res.* 1995;312:247–252.
71. Hanafusa S, Matsusue Y, Yasunaga T, Yamamuro T, Oka M, Shikinami Y, Ikada Y. Biodegradable plate fixation of rabbit femoral shaft osteotomies. *Clin Orthop Rel Res.* 1995;315:262–271.
72. Inoue N, Chao EYS, Larsson S, Kim W, Hirasawa Y. Dynamic loading effects on fracture healing at microscopic and ultrastructural level [abstract]. *2nd World Congress on Biomechanics.* II, 1994;68.
73. Jaffe H. *Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints.* Philadelphia, Pa: Lea and Febiger; 1972.
74. Jaworski ZFG, Meunier PJ, Frost HM. Observations on two types of resorption cavities in human lamellar cortical bone. *Clin Orthop.* 1972;83:279–285.
75. Jee WSS. The skeletal tissues. In: Weiss L, ed. *Cell and Tissue Biology. A Textbook of Histology.* Baltimore, Md: Urban and Schwartzenberg; 1989:211–259.
76. Jee WSS, Li XJ. Adaptation of cancellous bone to overloading in the adult rat: a single photon absorptiometry and histomorphometry study. *Anat Rec.* 1990;227:418–426.
77. Jee WSS, Li XJ, Schaffler MB. Adaptation of diaphyseal structure with aging and increased mechanical loading in the adult rat. A densitometric, histomorphometric and biomechanical study. *Anat Rec.* 1991;230:332–338.
78. Jee WSS. Proceedings of the International Conference on Animal Models in the Prevention and Treatment of Osteopenia (Ed). *Bone.* 1995;17(suppl):1–466.
79. Jee WSS. Integrated bone tissue physiology: anatomy and physiology. In: Cowin SC, ed. *Bone Mechanics Handbook.* 2nd ed. Boca Raton, Fla: CRC Press; 2001:1–68.
80. Jensen OT, ed. *Alveolar Distraction Osteogenesis.* Carol Stream, Ill: Quintessence Publ Co; 2002.
81. Jiang Y, Zhao J, Rosen C, Gensens P, Genant H. Perspectives on bone mechanical properties and adaptive response to mechanical loading. *J Clin Densitom.* 1999;2:422–433.
82. Johnson ML, Picconi JL, Recker RR. The gene for high bone mass. *The Endocrinologist.* 2002;12:445–453.
83. Jowsey J, Offord KP. Osteoporosis: juvenile, idiopathic and postmenopausal. In: Horton JE, Tarpley TM, Davis, WF (eds). *Mechanisms of Localized Bone Loss. Calcif Tissue Int.* 1978; 22(suppl):345–364.
84. Kanis JA, Melton LJ III, Christiansen C, Joyhnston CC Jr, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res.* 1994; 9:1137–1141.
85. Kannus P, Sievanen H, Vuori L. Physical loading, exercise and bone. *Bone.* 1996;18(suppl 1):1–3.
86. Koch JC. The laws of bone architecture. *Am J Anat.* 1917;21: 177–298.
87. Kotani H, Kawaguchi H, Shimoaka T, Iwasaka M, Ueno S, Ozawa H, Nakamura K, Hoshi K. Strong static magnetic field stimulates bone formation in a definite orientation in vitro and in vivo. *J Bone Miner Res.* 2002;17:1814–1821.

88. Langloh ND, Hunder GG, Riggs BL, Kelley PJ. Transient painful osteoporoses of the lower extremities. *J Bone Joint Surg.* 1973;55A:1188–1196.
89. Lanyon L, Skerry T. Postmenopausal osteoporosis as a failure of bone's adaptation to functional loading: a hypothesis. *J Bone Miner Res.* 2001;16:1937–1947.
90. Larsson S, Kim W, Caja VL, Egger EL, Chao EYS. The effect of dynamization on long bone fracture union under external fixation. [abstract]. *2nd World Congress on Biomechanics.* II, 1994;68.
91. Lewis FT, ed. *Stohr's Histology*. 6th U.S. ed. Philadelphia, Pa: P Blakiston's Son and Co; 1906.
92. Li XJ, Jee WSS, Chow S-Y, Woodbury DM. Adaptation of cancellous bone to aging and immobilization in the rat. A single photon absorptiometry and histomorphometry study. *Anat Rec.* 1990;227:12–24.
93. Li XJ, Jee WSS. Adaptation of diaphyseal structure to aging and decreased mechanical loading in the adult rat. A densitometric and histomorphometric study. *Anat Rec.* 1991;229:291–297.
94. Li XJ, Jee WSS, Ke HZ, Mori S, Akamine T. Age-related changes of cancellous and cortical bone histomorphometry in female Sprague-Dawley rats. *Cells Mater.* 1992;(suppl 1):25–36.
95. Liegibel UM, Sommer U, Tomakidi P, et al. Concerted action of androgens and mechanical strain shifts bone metabolism from high turnover into an osteoanabolic mode. *J Exp Med.* 2002; 196:1387–1392.
96. Luck JV. *Bone and Joint Diseases.* Springfield, Ill: Charles C Thomas; 1950.
97. Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis.* Orlando, Fla: Academic Press; 1996.
98. Marotti G, Palazzini S, Palumbo C, Ferretti M. Ultrastructural evidence of the existence of a dendritic network throughout the cells of the osteogenic lineage: the novel concept of wiring, and volume transmission in bone. *Bone.* 1996;19(suppl 3):151.
99. Marotti G. The osteocyte as a wiring transmission system. *J Musculoskeletal Neuronal Interact.* 2001;1:133–136.
100. Martin RB. Mathematical model for repair of fatigue damage and stress fracture in osteonal bone. *J Orthop Res.* 1995;13:309–316.
101. Martin RB, Burr DB, Sharkey NA. *Skeletal Tissue Mechanics.* New York, NY: Springer-Verlag; 1998.
102. Mayr E. Cause and effect in biology. *Science.* 1961;134:1501–1506.
103. McLean FC, Urist MR. *Bone.* 2nd ed. Chicago, Ill: University of Chicago Press; 1961.
104. Meyer U, Meyer T, Wiesmann HP. The effect of magnitude and frequency of interfragmental strain on the tissue response to distraction osteogenesis. *J Oral Maxillofac Surg.* 1999;37:1331–1339.
105. Mori S, Burr DB. Increased intracortical remodeling following fatigue damage. *Bone.* 1993;14:103–109.
106. Muller W. Bone physiology. *Z Orthop Chir.* 1926;47(suppl): 1–5.
107. Mundy GR. Regulation of bone formation by bone morphogenetic proteins and other growth factors. *Clin Orthop Rel Res.* 1996;324:24–28.
108. Nakajima A, Shimoji M, Shiomi K, Shimizu S, Moriya H, Einhorn TA, Yamazaki M. Mechanisms for the enhancement of fracture healing in rats treated with intermittent low-dose human parathyroid hormone (1–34). *J Bone Miner Res.* 2002;17:2038–2047.
109. Neu CV, Rauch F, Manz F, Schoenau E. Modeling of cross-sectional bone size, mass and geometry at the proximal radius: a study of normal bone development by peripheral quantitative computed tomography. *Osteoporos Int.* 2001;12:538–547.
110. Nielsen SP. The fallacy of BMD: a critical review of the diagnostic use of dual X-ray absorptiometry. *Clin Rheumatol.* 2000; 19:174–183.
111. Nordin BEC. The definition and diagnosis of osteoporosis. *Calcif Tissue Int.* 1987;40:57–58.
112. O'Connor JA, Lanyon LE, MacFie H. The influence of strain rate on adaptive bone remodeling. *J Biomech.* 1982;15:767–781.
113. Ohashi N, Robling AG, Burr DB, Turner CH. The effects of dynamic axial loading on the rat growth plate. *J Bone Miner Res.* 2002;17:284–292.
114. Ohlsson C, Bergtsson B-A, Andreasson TT, Slootweg MC. Growth hormone and bone. *Endocr Rev.* 1998;19:55–79.
115. Parfitt AM. Calcium homeostasis. In: Mundy GR, Martin TJ, eds. *Handbook of Experimental Pharmacology.* Vol 107. Berlin: Springer-Verlag; 1993:1–65.
116. Parfitt AM. Osteoporosis: 50 years of change, mostly in the right direction. In: Compston J, Ralston S, eds. *Osteoporosis and Bone Biology.* International Medical Press; 2000:1–13.
117. Pattin CA, Caler WE, Carter DR. Cyclic mechanical property degradation during fatigue loading of cortical bone. *J Biomech.* 1996;29:69–79.
118. Pietschmann P, Resch H, Peterlik M. Etiology and pathogenesis of osteoporosis. In: An YH, ed. *Orthopaedic Issues in Osteoporosis.* Boca Raton, Fla: CRC Press; 2002:3–18.
119. Pienkowski D, Pollacks SR. The origin of stress generated potentials in fluid saturated bone. *J Orthop Res.* 1983;1:30–41.
120. Polanyi M. Life's irreducible structure. *Science.* 1968;160:1308–1312.
121. Pollacks SR, Salastein R, Pienkowski D. The electric double layer in bone and its influence on stress-generated potentials. *Calcif Tissue Int.* 1984;36(suppl):77–81.
122. Porter MD, Hanley EN Jr. The musculoskeletal effects of smoking. *J Am Acad Orthop Surg.* 2001;9:9–17.
123. Putschar WGJ. General pathology of the musculoskeletal system. In: Buchner F, Letterer E, Roulet F, eds. *Handbuch der Allgemeinen Pathologie.* Berlin: Springer-Verlag; 1960:361–488.
124. Raab-Cullen DM, Kimmel DB, Akhter MP, Recker RR. External loading of the aged and young rat tibia at similar strains causes a similar bone response. *Orthop Res Soc Abstr.* 1996;129.
125. Rahn BA. Bone healing: histologic and physiologic concepts. In: Sumner-Smith G, ed. *Bone in Clinical Orthopaedics.* Philadelphia, Pa: WB Saunders; 1982:335–386.
126. Raisz LG, Seeman E. Causes of age-related bone loss and bone fragility: an alternative view. *J Bone Miner Res.* 2001;16:1948–1952.
127. Rhinelander FW, Wilson JW. Blood supply to developing, mature and healing bone. In: Sumner-Smith G, ed. *Bone in Clinical Orthopaedics.* Philadelphia, Pa: WB Saunders Co; 1982:81–158.
128. Rockwood CA Jr, Green DP, eds. *Fractures in Adults.* 4th ed. Vols I, II. Hagerstown, Md: Lippincott-Raven; 1997.
129. Rockwood CA Jr, Green DP. *Fractures in Children.* 4th ed. Vol III. Hagerstown, Md: Lippincott-Raven; 1997.
130. Rosen CJ, Wüster C. Growth hormone rising: did we quit too quickly? *J Bone Miner Res.* 2003;18:410–412.
131. Rosen CJ. Restoring aging bones. *Sci Am.* 2003;288:70–77.
132. Rubin C, McLeod K. Endogenous control of bone morphology via frequency specific, low magnitude functional strain. In: Odgaard A, Weinans H, eds. *Bone Structure and Remodeling.* London: World Scientific; 1995:79–89.
133. Rubin C, Li C, Sun Y, Fritton C, McLeod K. Non-invasive stimulation of trabecular bone formation via low magnitude high frequency strain. *Trans Orthop Res Soc.* 1995;20:548.
134. Rubin C, Bolander M, Ryaby JP, Hadjiaegyu M. Current concepts review: the use of low-intensity ultrasound to accentuate the healing of fractures. *J Bone Joint Surg.* 2002;83A:259–270.
135. Rubin C, Turner AS, Muller R, Mittra E, McLeod K, Lin W,

Qin Y-X. Quantity and quality of trabecular bone in the femur are enhanced by a strongly anabolic, nonvasive mechanical intervention. *J Bone Miner Res.* 2002;17:349–357.
136. Schenk RK. Biology of fracture repair. In: Browner BD, Jupiter JB, Levine AM, Trafton AG, eds. *Skeletal Trauma*. Philadelphia, Pa: WB Saunders Co; 1992.
137. Schermer M. Starbucks in the forbidden city. *Sci Am.* 2002;285: 34–35.
138. Schiano A, Elsinger J, Acquaviva PC. *Les Algodystrophies*. Paris: Armour-Montagu; 1976.
139. Schiessl H, Frost HM, Jee WSS. Perspectives: estrogen and bone-muscle strength and ''mass'' relationships. *Bone.* 1998;22: 1–6.
140. Schiessl H, Ferreti JL, Tysarczyk-Niemeyer G, Willnecker J, Wilhelm G. The role of muscles to the mechanical adaptation of bone. In: Lyritis GP, ed. *Advances in Osteoporosis.* Vol 1. Athens: Hylonome Editions; 1998:53–62.
141. Schönau E, ed. *Pediatric Osteology. New Trends and Diagnostic Possibilities.* Amsterdam: Elsevier Science; 1996.
142. Schönau E, Westermann F, Mokow E, Scheidhauer K, Werhahn E, Stabrey A, Müller-Berghaus J. The functional muscle-bone-unit in health and disease. In: Schönau E, Matkovic V, eds. *Paediatric Osteology. Prevention of Osteoporosis—A Paediatric Task?* Amsterdam: Excerpta Medica; 1998:191–202.
143. Skerry T. Neurotransmitters in bone. *J Musculoskeletal Neuronal Interact.* 2002;2:401–403.
144. Skoglund B, Forslund C, Aspenberg P. Simvastin improves fracture healing in mice. *J Bone Miner Res.* 2002;17:2004–2008.
145. Snapper I. *Bone Disease in Medical Practice.* New York, NY: Grune and Stratton; 1957.
146. Takahashi HE, Tanizawa T, Hori M, Uzawa T. Effect of intermittent administration of human parathyroid hormone (1–34) on experimental osteopenia of rats induced by ovariectomy. In: Jee WSS, ed. The Rat Model for Bone Biology Studies. *Cells Mater.* 1991;(suppl 1):113–118.
147. Takahashi HE, ed. *Spinal Disorders and Growth and Aging.* Tokyo, Japan: Springer-Verlag; 1995.
148. Tami AE, Nasser P, Verbogt O, Schaffler MB, Tate MLK. The role of interstitial fluid flow in the remodeling response to fatigue damage. *J Bone Miner Res.* 2002;17:2021–2029.
149. Tashjian AH Jr, Hjabner BA. Commentary on clinical safety of recombinant human parathyroid hormone 1–34 in the treatment of osteoporosis in men and postmenopausal women. *J Bone Miner Res.* 2002;17:1151–1161.
150. Tate MLK, Niederer P, Knothe U. In vivo tracer transport through the lacunocanalicular system of rat bone in an environment devoid of mechanical loading. *Bone.* 1998;22:107–117.
151. Thompson D'Arcy W. *On Growth and Form.* Cambridge, UK: University of Cambridge Press (reprint and revision of a monograph published in 1917); 1943.
152. Treharne RW. Review of Wolff's Law and its proposed means of operation. *Orthop Rev.* 1981;10:35–47.
153. Tsahakis PJ, Beaver WB, Brick GW. Technique and results of allograft reconstruction in revision total knee arthroplasty. *Clin Orthop Rel Res.* 1994;303:86–94.
154. Urist MR. The first three decades of bone morphogenetic protein research. *Osteologie.* 1995;4:207–223.
155. Vaughn VC, KcKay RJ, Nelson WE. *Nelson Textbook of Pediatrics.* 10th ed. Philadelphia, Pa: WB Saunders Co; 1975.
156. Wallace AL, Draper ERC, Strachan RK, McCarthy ID, Hughes SPF. The vascular response to fracture micromovement. *Clin Orthop Rel Res.* 1994;301:281–290.
157. Wang GJ, Dunstan JC, Reger SI. Experimental femoral fracture immobilized by rigid and flexible rods (a rabbit model). *Clin Orthop.* 1981;154:286–290.
158. Weinmann JP, Sicher H. *Bone and Bones.* 2nd ed. St Louis, Mo: CV Mosby Co; 1955.
159. Weiss S, Baumgart R, Jochum M, Strasburger CJ, Bidlingmaier M. Systemic regulation of distraction osteogenesis: a cascade of biochemical factors. *J Bone Miner Res.* 2002;17:1280–1289.
160. Whedon GD. Disuse osteoporosis: physiological aspects. *Calcif Tissue Int.* 1984;36(suppl):146–150.
161. Wiener N. *Cybernetics.* Cambridge, Mass: MIT Press; 1964.
162. Wiley JJ, McIntyre MW. Fracture patterns in pediatric patients. In: Uhthoff HK, ed. *Current Concepts of Bone Fragility.* Berlin: Springer-Verlag; 1980:159–165.
163. Wilhelm G, Felsenberg D, Bogusch G, Willnecker J, Thaten I, Gummert P. Biomechanical examinations for validation of the Bone Strength Strain Index SSI, calculated by peripheral quantitative computed tomography. In: Lyritis GP, ed. *Musculoskeletal Interactions.* Vol II. Athens: Holonome Edtions; 1999:105–110.
164. Wilson JD, Foster DW, eds. *William's Textbook of Endocrinology.* 8th ed. Philadelphia, Pa: WB Saunders Co; 1992.
165. Wilton P. Demographic and safety data: a report from the KIMS database. *KIMS Annual Report.* #1. London: Pharmacia and Upjohn, OCC Ltd; 1999:1–18.
166. Wolff J. *Das Gesetz der Transformation der Knochen.* Berlin: A Hirschwald (Springer-Verlag published an excellent English translation of this monograph in 1986); 1892.
167. Wolff JW, White AA, Panjabi MM, Southwick WO. Comparison of cyclic loading versus constant compression in the treatment of long-bone fractures. *J Bone Joint Surg.* 1981;63A:805–810.
168. Woodard JC. Morphology of fracture nonunion and osteomyelitis. *Vet Clin North Am.* 1991;21:813–844.
169. Yeadon A, Foux A, Uhthoff HK. An optimal axial flexibility for internal fracture fixation plates—a biomechanical study in canine femora. *Abstr, 2nd World Congress on Biomechanics.* II, 1994;63.
170. Yeh JK, Chen MM, Aloia JF. Skeletal alterations in hypophysectomized rats: I. A histomorphometric study in tibial cancellous bone. *Anat Rec.* 1995;241:505–512.
171. Yin Y, Rotman MB, Gilula AL. A 9-year-old girl with a bowed right forearm 6 months after a fracture. *Am J Orthop.* 1995;24: 717–722.