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

Harold M. Frost, BA, MD, DrSc

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,” 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 \( E = mc^2 \).

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, but no tissue-level bone functions were recognized as such before 1964 (later on they were called “nephron-equivalent functions”). 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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BMU</td>
<td>basic multicellular unit of bone remodeling.</td>
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<td>E</td>
<td>the typical peak strains caused by VMLs on an LBB.</td>
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<td>Fx</td>
<td>a bone’s fracture strength or ultimate strength.</td>
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<td>GBR</td>
<td>the general biomechanical relation for healthy LBBs.</td>
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<td>LBB</td>
<td>a load-bearing bone, one designed mainly to carry voluntary loads.</td>
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<td>MDx</td>
<td>microscopic fatigue damage in bone and bones.</td>
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<td>MESp</td>
<td>bone’s genetically determined operational MDx threshold strain range, in and above which modeling usually turns on to strengthen a bone.</td>
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<tr>
<td>MESr</td>
<td>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.</td>
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<tr>
<td>MST</td>
<td>bone’s tissue-level, genetically determined mechanostat, the collection of “biologic machinery” that can adapt LBBs to their typical peak VMLs.</td>
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<td>SSF</td>
<td>a bone’s strength-safety factor.</td>
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<tr>
<td>VML</td>
<td>a voluntary mechanical load on a bone, which implies muscle forces.</td>
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- , approximately, or approximately equals.
- less than, much less than, or markedly less than, respectively.

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 non-traumatic fractures—often called “spontaneous” ones—suddenly or from fatigue. Yet a few of our bones serve different needs (cranial vault, cribiform plate of the ethmoids, nasal bones, turbinates, etc).
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.89,99,119,143,148

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 threshold65; remodeling BMUs provide that repair26,105 and osteocytes may provide this detection.40,43

7. Strains above the MESp threshold can cause enough
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 $5 \times$ 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 myelomeningocelees 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: $MESr < E < MESm \ll MESp \ll FS$. 52 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

### TABLE 2. Set Point Values for Bone’s Thresholds and Ultimate Strength (in Microstrain, Stress and Unit-Load Terms)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>MESr</td>
<td>50–100 microstrain; $\sim$1–2 MPa, or $\sim$0.1 kg/mm² (one can argue for a value of $\sim$400 microstrain). 61</td>
</tr>
<tr>
<td>MESm, 1000–1500 microstrain; $\sim$20 MPa, or $\sim$2 kg/mm².</td>
<td></td>
</tr>
<tr>
<td>MESp, 3000 microstrain; $\sim$60 MPa, or $\sim$6 kg/mm². This also approximately equals bone’s yield point. 32,64</td>
<td></td>
</tr>
<tr>
<td>$F_x$, 25,000 microstrain; $\sim$120 MPa or $\sim$12 kg/mm² in healthy young-adult mammals.</td>
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* MPa = megapascal = $10^6$ Newtons/m². A one Newton force equals about 0.225 pounds/force. kg/mm² = “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.
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 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.

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 MESm). 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. The span between MESr and MESm represents the span between those thresholds in bone’s GBR. Carter 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).

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.

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. Neophrons 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.

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, 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. Yet, both mechanisms seem to use the same kinds of osteoblasts and osteoclasts. Later studies, too numerous to cite, found the same results, although their authors seldom remarked that fact (but see Chen et al and Yeh et al 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. 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. 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 osteomalacia. This remodeling phase provides much of what
Schenk\textsuperscript{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.\textsuperscript{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 $E \ll \text{MESp}$. 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.\textsuperscript{171} In 55 years I only saw five such problems,\textsuperscript{14} 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 $5 \times$.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.”\textsuperscript{135,138} 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.\textsuperscript{15,33,30,71,156,157,167,169} Without such strains, disuse-mode remodeling tends to remove a callus while modeling tends to stay off, so bone healing can retard or fail.\textsuperscript{46} Of course, excessive strains (gross motion) can usually prevent bony union. The naturally “permissible” strains might lie in the 100–2000 microstrain region,\textsuperscript{13,104} 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, $\text{MESr} < E \ll \text{MESp}$. Very small loads can cause harmfully large strains in the early phases of healing fractures, bone grafts, and arthrodeses, including spinal fusions.\textsuperscript{80}

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”)\textsuperscript{80} also depends on humoral and cell-biologic influences on bone cells. Known humoral influences include hormones, vitamins, minerals, drugs, etc.\textsuperscript{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.\textsuperscript{27,68,154,159} To these, one could add electrical and ultrasound treatments.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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: $\text{MESr} < E \ll \text{MESp}$. 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,\textsuperscript{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 ∝ 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/mm² (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.6,50

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 ÷ 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 (↑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 (↓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.6,50 Thus, learning to lower the MESm’s set point would let an LBB’s SSF 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 ÷ 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

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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 ~ MESm or E > MESp. Sections “Some bone modeling functions and disorders (or, what should modeling do, and what happens when it fails?)” and “Some BMU-based remodeling functions and disorders (or, what should remodeling do, and what happens when it fails?)” 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 growth54 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 endoprosthesis, and “osteoporosis” (“osteoporosis” in quotes signifies current conventional definitions). Noninvasive methods can evaluate whole-bone strength in patients.6,11,38,81,139,140,142,163 Such methods have virtues and limitations. 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?)

Some bone modeling functions and disorders (or, what should modeling do, and what happens when it fails?)

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 “Implications for the design and use of load-bearing implants” above describes modeling’s role in bone healing and some of its malfunctions. (4) Section “Implications for the design and use of load-bearing implants” above describes modeling’s role in bone healing and some of its malfunctions. (4)
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.71 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 daphysal 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 sarcom, multiple myeloma, some metastases, unicameral bone cysts, Brodie’s abscesses, and non ossifying fibromas. Disuse-mode remodeling (not osteoclasts alone)68,79 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.5,115,130

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.4,14,22,37,68,95,103,107,111,118,126,130,160

(2) Yet, the MST hypothesis (it is a hypothesis, but perhaps in the same sense that E = mc² technically still constitutes a hypothesis) plus the accumulating data suggest that most—not all—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 stature89,131,164; 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 theVMLs on an LBB become larger.60 Without increased bone loads,
GH did not significantly increase whole-bone strength; 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.

This permissive role may help to explain some disappointing results of treating osteoporosis with GH. 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 could help to reveal and study the permissive roles of many agents in the physiology and disorders of bones and of bone’s MST.

On skeletal microcosms and macrocosms—In physics and astronomy, “microcosms cannot predict macrocosms.” 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.” 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. 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 de-loaded limbs growing longer than corresponding bones in control limbs. (v) Other authors decided that de-loading 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, 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. 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 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 be it.

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