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Perspective Article

Hylonome

# Perspective: Genetic and hormonal roles in bone disorders: Insights of an updated bone physiology

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**Abstract**

In 1997 Professor J. Gorski suggested endocrinology needed new paradigms (Endocrine News 1997; 22:4,12). "Connecting the dots" between diverse facts and ideas drawn from many lines of inquiry, plus accumulating evidence and increasing inadequacies of earlier ideas and terminology, led to an updated bone physiology called the "Utah paradigm" that reveals new genetic and hormonal potential roles in bone physiology and disorders. One way to find a bone disorder's cause(s) and treatment(s) could depend on understanding the underlying physiology well enough to design effective drugs for it. In early views cell-level effects on osteoblasts and osteoclasts could explain most endocrine and genetic roles in bone disorders. The updated bone physiology supplements those views with roles of bone's tissue-level "nephron-equivalent" mechanisms (NEMs) and their functions (NEFs), including some roles of biomechanics, whole-bone strength and muscle strength. That updated physiology reveals at least 42 nexuses above the cell level, some of them extraosseous, where genetic and/or hormonal effects might cause or help to treat varied bone problems. That multifactorial physiology also suggests that *in vivo* skeletal phenomena usually depend on many interlocking, laddered and nested feedback systems. Due to lack of study, how genes and hormones affect those nexuses and feedback systems still remains nearly unknown. Because studies of bone physiology in *in vitro* systems seldom if ever correctly predicted the *in vivo* effects, further live-animal research should seek the *in vivo* effects. This article suggests why more of that kind of research is needed, and some directions it could take

**Keywords:** Genes, Hormones, Biomechanics, Utah Paradigm, Modeling, Remodeling, Bone Strength

## I. Introduction

This article would share with readers the idea that exploiting an updated bone physiology could lead to better treatments of its disorders. But first the special usage of some terms in this text needs some comment.

Herein *disorders* signify all deviations from normal averages, and *diseases* mean the subgroups of such disorders that also impair an organ's health. Thus one blue and one brown eye in the same person is a disorder that is only a healthy departure from normal averages, but not a disease. Yet in mammals an inability to make bone is both a disorder and a disease, and a lethal disease[1]. Or, *All disorders = (healthy departures from normal means + departures that impair an organ's health and represent diseases)*. That distinction depends on how one defines an organ's health, and such a definition for bones follows shortly. Section #4 in Part IV below, and the Glossary, define what *osteopenia* and *osteoporosis* without quotes mean herein. In quotes they have other meanings also given in the Glossary. This article does not discuss longitudinal bone growth, infections and neoplasms[2,3].

Three ideas could introduce the updated bone physiology.

*Idea #1*: After birth load-bearing mammalian bones and trabeculae provide mainly mechanical functions[4,5]. Trabeculae mainly transfer loads back and forth between cortical bone, and joints, growth plates or tooth sockets. Other bone functions would be secondary to the mechanical one. Load-bearing bones include femurs, tibias, humeri, radii, mandibles, phalanges, etc., so they are not limited to weight-bearing bones.

*Idea #2*: Healthy such bones and trabeculae have enough *strength* to keep *voluntary* loads from causing *nontraumatic* fractures, (often called "spontaneous" fractures), whether those loads are tiny as on a mouse rib, or huge as on an ele-

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**DEFINITIONS OF ABBREVIATIONS**

| | |
|---|---|
| BMC: | bone mineral content as determined by X-ray absorptiometry |
| BMD: | bone mineral "density" as determined by X-ray absorptiometry |
| BMU: | basic multicellular unit of bone remodeling |
| BSI: | a Bone Strength Index that accounts for both the "mass" and architectural factors in whole-bone strength |
| DEXA: | dual energy X-ray absorptiometry (often written as DXA) |
| ES: | estrogen |
| GH: | growth hormone |
| MDx: | microscopic fatigue damage in bone |
| MESm: | the modeling threshold range (Minimum Effective Strain) |
| MESp: | bone's operational microdamage threshold range |
| MESr: | the remodeling threshold range that helps to control the switching between disuse-mode and conservation-mode remodeling |
| MS/WBSr: | muscle strength/whole bone strength ratio |
| NEF: | nephron-equivalent function, usually of an NEM |
| NEM: | nephron equivalent mechanism and/or function |
| pQCT: | peripheral quantitative computed tomography |
| PTH: | parathyroid hormone |
| TS: | testosterone |
| WHO: | World Health Organization of the United Nations |

**Table 1.**

phant femur. *A)* That observation could define a load-bearing bone's health as a three-way *relation-ship* between its strength, the loads on it, and any nontraumatic fractures. *B)* Called Proposition #1 elsewhere[6], that idea would define such a bone's health as a function of its presumed chief purpose in the body, *C)* and it would rank whole-bone strength above bone "mass", bone mineral "density", or the bone bank, in physiological importance.

"Voluntary" means intentional and not due to trauma or to jumping from a height. Some non-load-bearing bones include the cranial vault, ethmoids, turbinates, nasal and lachrymal bones, and inner ear ossicles. "Whole-bone" distinguishes bones as organs from bone as a tissue or structural material. Nontraumatic fractures occur during normal physical activities and are not caused by any known kind of 1trauma.

*Idea #3*: An elegant stratagem would make the voluntary loads on a load-bearing bone determine its strength in ways that let it endure them. Apparently our postnatal load-bearing bones do exactly that[7,8]. Cybernetic considerations[9] suggest that implementing such a stratagem should require at least four things: *(i)* Biologic mechanisms that could change a bone's strength, *(ii)* ways to monitor the relationship between the bone's strength and the loads on it, *(iii)* criteria for acceptable and unacceptable bone strength, *(iv)* and feedback between those things.

While devils and disagreements still lie in the details, some general features of that stratagem have become clarified. That clarification depended on "connecting the dots" between many kinds of evidence from many lines of inquiry, which also led to the Utah paradigm of skeletal physiology[8,10-34]. Below, numbers in braces {x} signify physiologic nexuses at which a bone disorder might arise and/or on which hormones, genes and other things including drugs might exert important effects.

"Idea #3" above raises three questions: What physical factors determine whole-bone strength, what biologic mechanisms determine it, and what are some implications of those things? Parts II-IV below concern those issues.

## II: Whole-bone strength: physical factors

Four such factors combine to determine the strength of bones and trabeculae[4,35-42] *(i)* When compared to the next three factors, the properties of bone as a tissue or material (stiffness, ultimate strength, fatigue properties, composition, etc. the *material properties* factor) {1}, vary relatively little in different bones and species and with aging, osteomalacia excepted. *(ii)* Fatigue damage or microdamage (MDx) in a bone reduces its strength without affecting its "mass" or architecture (the *MDx* factor) {2}[43]. *(iii)* The amount and kind of bone in a bone's cross section affects its strength (woven and lamellar bone, compacta and spongiosa; the "*mass*" factor) {3}. Usually the more bone in a cross section, the stronger it is. *(iv)* The cross-sectional and longitudinal shapes and size of a bone, and the distribution of its compacta and spongiosa in anatomical space, affect its strength (the *architectural* factor) {4}. Example: Doubling a hollow bone's diaphyseal diameter while keeping the same amount of bone in its cross section (which thins the cortex but does not change the "mass" factor) increases its bending strength about eight times.

Table 1 defines the abbreviations in this article.

## III: Whole-bone strength: biologic determinants

**1) Two biologic mechanisms that can change whole-bone strength**[7,34,41,44,45]. Two NEMs can change our postnatal whole-bone strength (and the bone bank). Global modeling by drifts (Figure 1) {5} has the function of increasing bone strength and, often, bone "mass" or the bone bank. Modeling does that by increasing cortical and trabecular thickness and

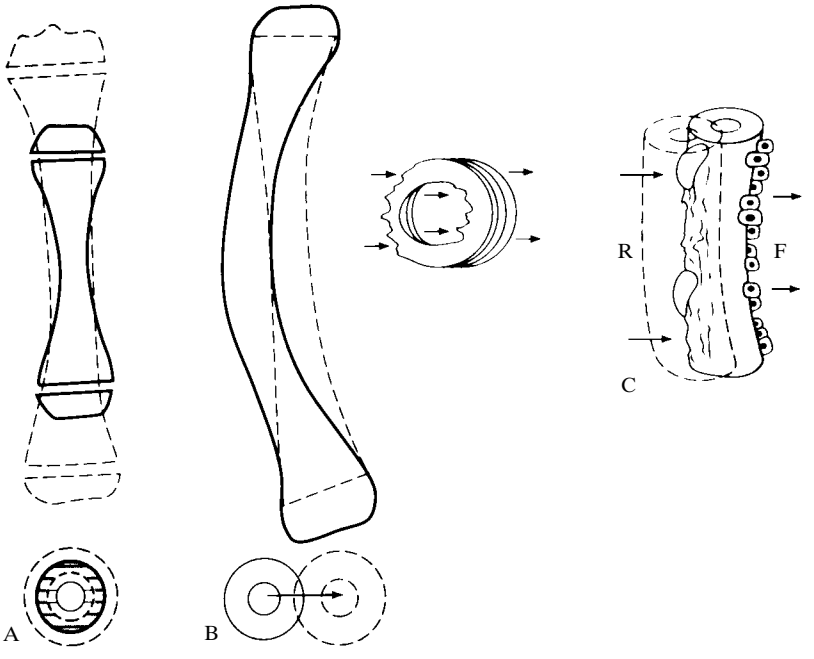



**Figure 1.** *Bone modeling by drifts.* A: diagrams an infant's long bone with its original size and shape in solid line. To keep its shape as it grows in length and diameter, formation and resorption drifts move its surfaces in tissue space as the dashed lines suggest. *Formation drifts* make and control new osteoblasts to build some surfaces up. *Resorption drifts* make and control new osteoclasts to remove bone from other surfaces. B: A different drift pattern can correct a child's fracture malunion shown in solid line. The cross section view to the right shows the endocortical as well as the periosteal drifts that do that. C: shows how the drifts in B would move the whole bone segment to the right. Changing bone architecture in that way reduces the bone's bending moments, strains and stresses. When orchestrated by the mechanostat those drifts provide the function of increasing whole-bone strength. Drifts are created when and where they are needed. They include capillaries, precursor and "supporting" cells {30} and some wandering cells as well as their relatively short-lived osteoblasts or osteoclasts. They are multicellular entities in the same sense as renal nephrons, and hormonal effects on them remain little studied (reproduced by permission: Frost H.M. Strain and other mechanical influences on bone strength and maintenance. Current Opinion in Orthopaedics 1997; 8:60-70).

outside bone diameter, and by changing the cross sectional and longitudinal shapes of bones and trabeculae. Or, *modeling turned on → increased bone strength (and bone "mass")*. "Global" means averaged over whole bones or skeletons.

Remodeling by BMUs {6} turns bone over in small packets in two modes. Its "conservation mode" {7} (Figure 2,H) does not cause significant gains or losses of bone. Its "disuse mode" {8} (Figure 2,I) has the function of removing bone *but only next to or close to marrow*, i.e., endocortical bone and trabecular bone[16]. That reduces a bone's strength and "mass". That and other evidence show that some NEM in marrow {9} can mediate the responses to mechanical and other influences of remodeling (and modeling) of bone next to or close to marrow[46,47]. Thus, *disuse-mode remodeling turned on → reduced whole-bone strength and bone "mass"*.

The early ideas that chiefly independently working and controlled osteoblasts increase bone strength and "mass", and chiefly independently working and controlled osteoclasts decrease them[48], proved too simplistic[10,44,49]. In adults disuse-mode remodeling causes "disuse-pattern osteopenias" by removing some trabecular and endocortical bone, expanding marrow cavities and reducing cortical thickness but not outside bone diameters. Such osteopenias depend on the past balance between a bone's modeling and disuse-mode remodeling functions. In children, failures of modeling to increase outside bone diameter and cortical and trabecular thickness can help disuse-mode remodeling to cause osteopenias in Turner's syndrome[34,50-53], in some types of osteogenesis imperfecta[46,54], and in juvenile rheumatoid arthritis.

During their work modeling and remodeling each needs and uses both osteoblasts {10} and osteoclasts {11} (bone's "effector cells"). They seem to be the same kinds of cells in both mechanisms[4]. Yet in the same bone at the same time, pioneering experiments in Dr. Jee's laboratory found the effector cells doing modeling can slow down or turn off while those doing remodeling increase their activities[55-63]. Such things emphasize that modeling and remodeling constitute independent mechanisms for affecting whole-bone strength and bone "mass". Bone's periosteal envelope may have an analogous mechanism {12} that mediates mechanical and nonmechanical influences on periosteal modeling and remodeling[7].

Hence (i) in Idea #3 in Part I.

**2) Monitoring the relationship between a bone's loads and its strength**[8,31,41,63-65]. Loads on bones cause strains that

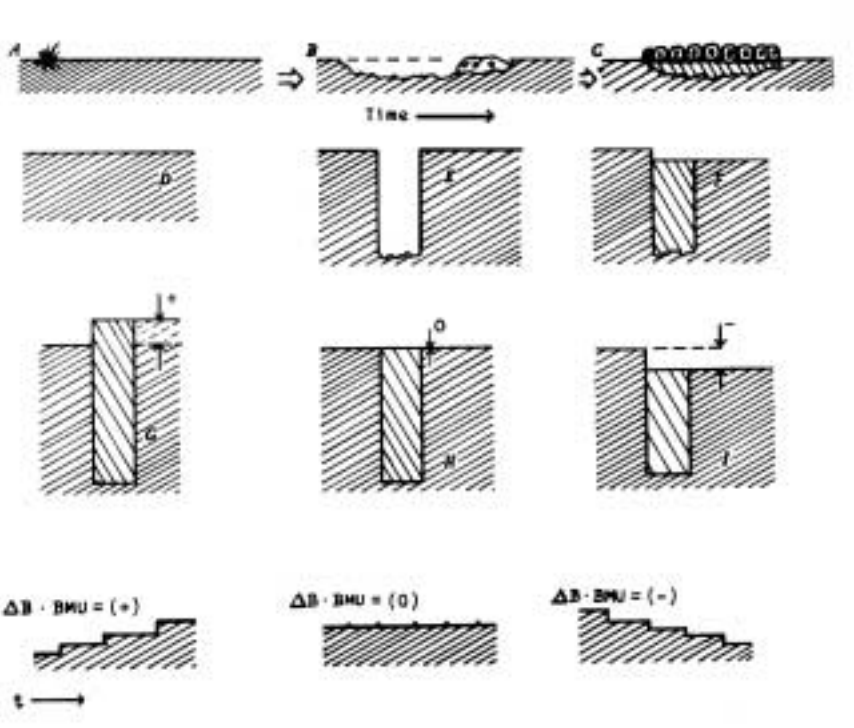



**Figure 2.** *Bone remodeling BMUs. Top row*: An activation event on a bone surface at (A) leads to packet of bone resorption (B); then new osteoblasts replace the resorbed bone (C on the right). The BMU makes and controls those osteoclasts and osteoblasts. *Second row:* This emphasizes the amounts of bone resorbed (E) and formed (F) by *completed* BMUs. *Third row:* In these "BMU graphs" (after the author), (G) shows a small excess of formation over resorption. (H) shows equalized resorption and formation as in "conservation-mode" remodeling. (I) shows a net deficit of formation, as in "disuse-mode" remodeling of endocortical and trabecular bone. *Bottom row:* These "stair graphs" (after P.J. Meunier[149]) show how a series of BMUs of the kind immediately above would affect the local bone "bank". When orchestrated by the mechanostat the "I" activity provides the function of reducing whole-bone strength. BMUs are created when and where they are needed. They include a capillary, precursor and "supporting" cells and some wandering cells, as well as their relatively short-lived osteoblasts and osteoclasts {30}. They are multicellular entities in the same sense as renal nephrons, and hormonal effects on them also remain little studied (reproduced by permission: Frost H.M. Strain and other mechanical influences on bone strength and maintenance. Current Opinion in Orthopaedics 1997; 8:60-70).

faithfully reflect the size, kind and other features of those loads. Those strains generate corresponding strain-dependent signals {13} that cells can detect and respond to, and which faithfully reflect those strains and loads. Ergo, those signals could monitor the relationship between a bone's strength and the loads on it. Or, *loads → bones → strains → signals → NEM responses*.

Hence (ii) in Idea #3 in Part I.

**3) Criteria for unacceptable whole-bone strength**[11,12,30,31,66]. Where bone strains exceed a genetically-determined *modeling threshold* range (MESm) {14}, a bone would lack enough strength for the loads on it and modeling usually turns on to increase it. When strains stay below a lower genetically-determined *remodeling threshold* range MESr) {15}, a bone would have too much strength for the loads on it and disuse-mode remodeling usually turns on to reduce it. In both cases unacceptable whole-bone strength would exist *relative* to the typical peak voluntary loads on the bone. The span between those two thresholds in Figure 3 would define a "naturally" acceptable (i.e., safe) region (NAR) of whole-bone strength relative to the voluntary loads on the bone in question. Or, *MESr < NAR < MESm*, when (*f(MESr) + f(MESm)*) → NAR.

Hence (iii) in Idea #3 in Part I.

**4) The feedback**[8,9,14,31,63]. The above thresholds should reside in the genome of some cells {16}. Those and/or other cells {17} would compare {18} the thresholds to any strain-dependent signals. When that comparison revealed too little or too much bone strength an "error signal" {19} would arise to make modeling or disuse-mode remodeling, respectively, correct the bone-strength error. Then that error and its signal would vanish so mechanically-controlled whole-bone strength would tend to plateau at its new level. Or, *bone strength error → error signal → error correction → new bone-strength plateau*.

Hence (iv) in Idea #3 in Part I. The above "1-4" matters have become separate fields of study in skeletal physiology[8,31,37,41,63,64,67,68]. Note that modeling and remodeling have

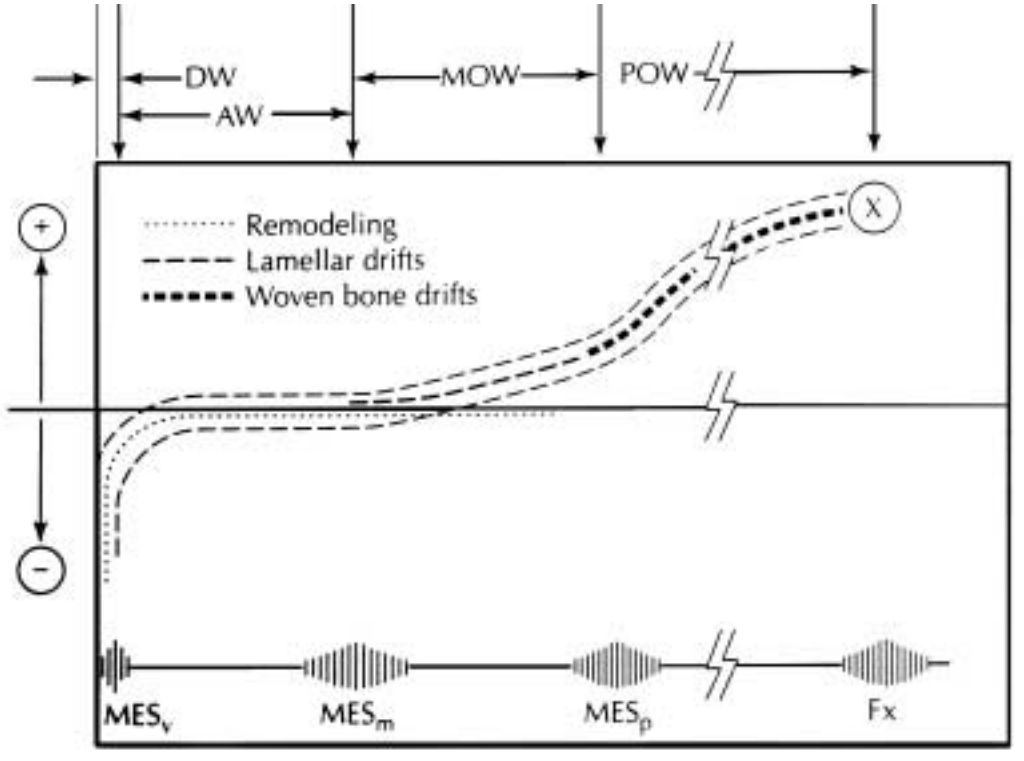



**Figure 3.** *Combined modeling and remodeling effects on bone strength and "mass"*. The horizontal line at the bottom suggests typical peak bone strains from zero on the left, to the fracture strain on the right (Fx), plus the locations of bone's three threshold ranges (MESr, MESm, MESp). The horizontal axis represents no net gains or losses of bone strength (and "mass"). *The lower dotted line* curve suggests how disuse-mode remodeling would remove bone when strains stay below the MESr range, but otherwise would tend to keep existing bone and its strength. *The upper dashed line* curve suggests how modeling would increase bone strength where strains enter or exceed the MESm range. The *dashed outlines* suggest the combined modeling and remodeling effects on a bone's strength and "mass". D.R. Carter originally suggested such a curve[150]. At and beyond the MESp range, woven bone formation usually replaces lamellar bone formation. Fx = the fracture strain range centered near 25,000 microstrain. At the top, DW = disuse window; AW = adapted window as in normally adapted young adults; MOW = mild overload window as in healthy growing mammals; POW = pathologic overload window[13]. *Nota bene:* The nearly flat part of this curve between the MESr and MESm, the above "AW", would define the region of naturally acceptable (safe) whole-bone strength mentioned in the main text (reproduced by permission: Frost H.M. Strain and other mechanical influences on bone strength and maintenance. Current Opinion in Orthopaedics 1997; 8:60-70).

further functions too[7].

**5) Three further features.** Muscle strength[34,45,53,65,69-71]. The above thresholds make the typical *largest* voluntary loads on bones control their postnatal strength (hence the "typical peak voluntary loads" in Section #3 above). Muscles instead of body weight cause those loads[66,72], so *muscle strength* {20} and neuromuscular physiology {21} should and do indirectly but strongly influence the postnatal strength of load-bearing bones, although better in children than in aging adults[73]. Our muscle strength (and power?) usually declines slowly after young-adult life, so most octogenarians have less than half their young-adult muscle strength (and power), and have a reduced muscle mass too, a "sarcopenia" {22}[6,74,75]. Corresponding losses of bone strength and bone "mass" usually accompany that loss of muscle strength, so relative to their young-adult bones most aged adults should and do have a disuse-pattern osteopenia {23}[76].

Microdamage (MDx. Repeated bone strains cause microscopic fatigue damage (MDx) in bones {24} that increases bone fragility[31,43]. Bone seems to have an operational, genetically-determined *MDx threshold* (MESp) {25}. Where strains stay below it remodeling BMUs can repair {26} any resulting MDx by removing and replacing the damaged bone with new bone[31,41,64]. However strains above the MESp can cause enough MDx to escape repair and accumulate, and cause nontraumatic fractures like those in the true osteoporoses described in Part IV below {27}. While not truly "spontaneous", trauma does not cause such fractures. Accumulated MDx also causes stress fractures in athletes, pseudofractures in osteomalacia, and it helps to cause pathologic fractures[10]. MDx has become another field of study in skeletal physiology[31,43].

The strain and stress equivalents suggested in the Glossary for the above three thresholds depend on currently available information.

The "baseline conditions". "Natural" experiments reveal

**NONMECHANICAL AGENTS THAT MIGHT AFFECT THE MECHANOSTAT'S WORKINGS**
**(and thereby affect whole-bone strength and bone "mass")**

| | | |
|---|---|---|
| Hormones | Vitamins | D metabolites |
| Dietary calcium | Nutrition | Other minerals |
| Cytokines | Paracrine effects | Autocrine effects |
| Cell-cell interactions | Amino acids | Lipids |
| The genome | Gene expression | Ethnic origin |
| Occupation | Gender | Some diseases |
| Age | Apoptosis | Ligands |
| Cell receptors | Medications and other artificial agents | |

*: Modified from[7].

**Table 2.**

**DEBILITATING CONDITIONS THAT CAN ACCOMPANY CHRONIC MUSCLE WEAKNESS IN HUMANS**
**(and disuse-pattern osteopenias)**

| | | |
|---|---|---|
| Asthma | Emphysema | Pulmonary fibrosis |
| Renal failure | Hepatic failure | Cardiac failure |
| Malnutrition | Anemia | Polyarthritis |
| Metastatic cancer | Depression | Stroke |
| Muscular dystrophy | Multiple sclerosis | Alzheimer's disease |
| Organic brain syndrome | Huntington's chorea | Myelomeningocele |
| Lou Gehrig disease | Paralyses | Leukemia |
| Cystic fibrosis | Still's disease | Alcoholism |
| Drug addiction | Nursing home residence | Turner's syndrome |
| Stroke | Aging | Wheel-chair bound |

*: Modified from[7]. In causing an osteopenia the relative importance of the mechanical disuse and muscle weakness, and of the biochemical-endocrinologic abnormalities accompanying some of these entries, remains uncertain. So far few studies tried to quantify and account for the muscle and mechanical usage effects.

**Table 3.**

the following things[10]. At birth a bone's anatomy, anatomical relationships and the above biologic machinery already exist as genetically-predetermined "baseline conditions" {28}. At any time after birth the bones in neonatally totally and permanently paralyzed limbs, and in contralateral normal limbs, show typical *differences* in strength, architecture and bone "mass" that should reveal the kinds and magnitudes of the "functional adaptations"[8] to postnatal loads that were added to bones in the normal limbs. Bones in the paralyzed limbs should reveal how genes {29} and postnatal humoral agents {30}, but not normal loads, affect the baseline conditions. That means postnatal whole-bone strength in normal limbs should combine two parts: The baseline conditions, plus all added adaptations to postnatal mechanical demands. That might answer a seldom-pondered question: Why do bones in permanently and completely paralyzed limbs never disappear completely? Perhaps the baseline-conditions parts remain.

**6) The mechanostat hypothesis**[10,14,31,77]. Combining all features in Sections #1-#5 above including the feedback between them would form a negative feedback system called bone's *mechanostat* {31}. Presumably its chief purpose makes postnatal load-bearing mammalian bones satisfy Proposition #1. The marrow mediator, some hormones and some things like those in Table 2 might modulate the mechanostat's workings by affecting the biologic machinery's

responses to mechanical loads on bones and/or by affecting the above thresholds {32}[31,77,78]. All the biologic determinants of postnatal whole-bone strength mentioned above, including the feedback that "connects" and helps to coordinate them, would combine to form the *mechanostat*, so it is not one kind of cell. Its modeling and remodeling thresholds would act somewhat like the thermostats that determine a room's temperature by switching its heating and cooling systems on and off.

Hence again, (iv) in Idea #3 in Part I above. Professor A.M. Parfitt called the mechanostat hypothesis "...the most important unsolved problem in bone biology."[5].

## IV: Some implications

The realizations that one tissue-level mechanism (modeling, not osteoblasts alone) can increase a bone's strength and bone "mass", that another one (disuse-mode BMU-based bone remodeling, not osteoclasts alone) can reduce them, and that each mechanism has further functions[7,31], only dawned after 1964 although histologists described some of their structural features before 1900[3,48,79,80]. Connecting the dots between many kinds of evidence revealed those mechanisms and some of their functions and implications. It seems reasonable to assume that learning how to modify their functions could significantly enhance the study and management of many bone problems.

**1) The muscle-bone "functional unit"**[40,51-53]. In principle healthy mechanostats should make strong muscles associate with correspondingly strong bones, and make persistently weak muscles usually associate with correspondingly weak bones. Both associations occur, they are strong, and Figure 4 shows the results of an early study of that association[76,81]. Healthy mechanostats should also make age-related losses of muscle strength usually cause corresponding disuse-pattern osteopenias. If those things are true several things should follow. *A)* When compared to their young-adult bones, loss of muscle strength in most aged people should lead to a disuse-pattern osteopenia. *B)* Aging adults who keep their young-adult muscle strength better than other adults should keep their young-adult bone strength better too. *C)* In edentulous states loss of tooth and masticatory forces should cause recession of the alveolar ridge and osteopenias of the mandible and pterygoid, zygomatic and maxillary bones. *D)* Increased muscle strength (and power?) should make healthy mechanostats increase whole-bone strength and the bone bank, although better during growth than in aging adults. *E)* Because marathon running puts smaller loads on bones than weight-lifting, healthy mechanostats should make weight-lifters have the stronger bones.

Again, those "A-E" features do occur[8,15,32,73,76,82-84]. Long ago D'Arcy Thompson wrote, "...between muscle and bone there can be no change in the one but it is correlated with changes in the other..."[85]. Subsequent evidence supporting that idea revealed the responsible NEMs, NEFs and related things, which were all unknown in 1917 and to Wolff of Wolff's Law in 1892[86]. Such things support E. Schönau's suggestion that one could view the muscle-bone relationship as a "functional unit"[34].

*Implications: (i)* In principle encouraging strenuous exercise during adolescence should help one to enter adult life with extra whole-bone strength and bone "mass"[53]. *(ii)* Also in principle, keeping that extra strength and bone "mass" in adult life should require continuing such exercise, and/or using drugs or other things that depress disuse-mode remodeling without harmful side effects[87,88]. Why? In vigorous youths who subsequently become sedentary adults, healthy mechanostats could make disuse-mode remodeling begin to remove the no-longer-needed extra young-adult bone strength, so a disuse-pattern osteopenia would develop. *(iii)* Hormonal, genetic and other effects on muscle strength and the "muscle-strength/whole bone-strength relationship" need more study.

**2) To evaluate whole-bone <u>strength</u>.** If whole-bone strength ranks above bone "mass" in physiological importance, how could one evaluate the former? While breaking bones in the laboratory would reveal the combined effects of all four physical factors described in Part II[4,39,40,42,] studying patients demands noninvasive methods.

Unfortunately no current noninvasive absorptiometric method can reliably evaluate the material properties or MDx factors in a bone's strength. Dual energy X-ray absorptiometry (DEXA) can evaluate the "mass" factor as bone mineral content (BMC) values[35,36-40,89,90], but unfortunately the currently popular bone mineral "density" (BMD) values (which are further "mass" factors) evaluate whole-bone strength *very* poorly[71,91,92]. That could weaken many arguments based on BMD data. For example, healthy mouse and horse femurs would have similar volumetric BMD values (speed-of-sound values too) but huge differences in their strengths.

By accounting for both the "mass" and architectural factors, bone strength indices (BSIs) obtained by peripheral quantitative computed tomography (pQCT) and appropriate software can evaluate whole-bone strength quite well[40,69,91,93]. A good BSI should satisfy the BSI *criterion*: Multiplying the BSIs of such different bones as mouse and elephant femurs by the same constant (k) would correctly predict their hugely different breaking strengths (Fx). Or, $BSI\ X\ k = Fx$. The BSIs devised by J.L. Ferretti[39] in Argentina and modified by H. Schiessl[93-95] in Germany approach that "BSI criterion".

*Implications: (i)* BSIs need further development and should see more use in the future, and BMD values less use. *(ii)* Hormonal, genetic and other effects on whole-bone strength, on BSIs, and on the physical and biologic determinants of that strength, need systematic study.

**3) To evaluate bone <u>health</u> as Proposition #1 defines it**[27]. According to Proposition #1 and excepting stress and pathologic fractures, nontraumatic fractures should stem from diseased mechanostats and impaired bone health. Clinical features can reveal such fractures in extremity bones, and later-

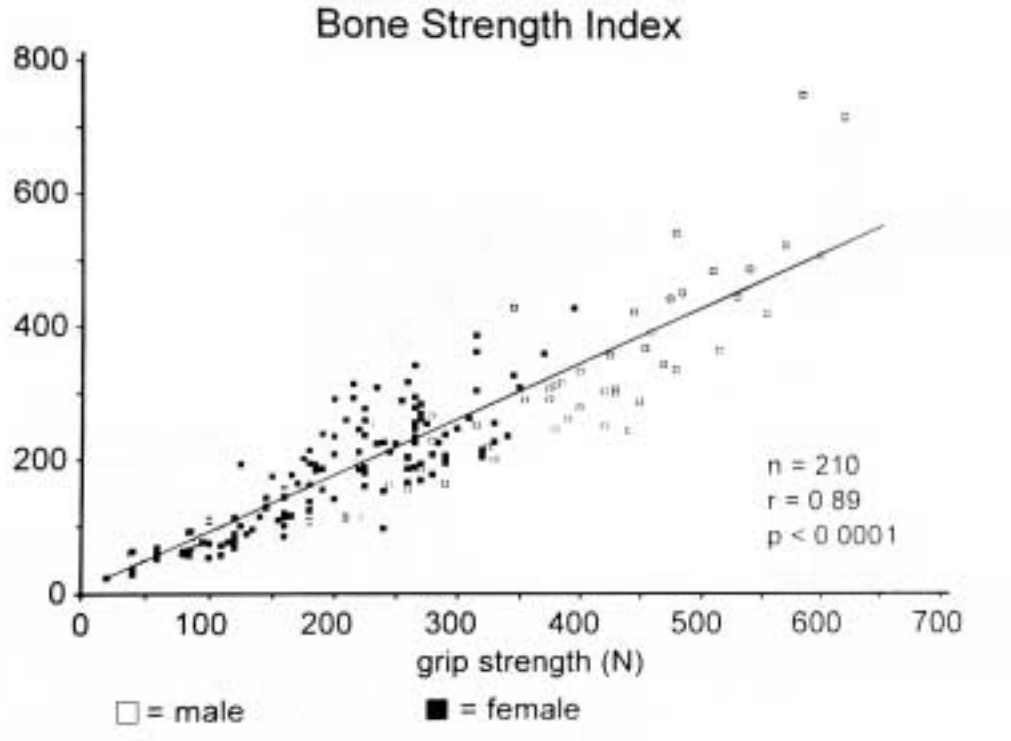



**Figure 4.** *A muscle strength-whole-bone strength comparison.* This graph compares the measured grip strength in Newtons (N) to a pQCT-derived bone strength index (BSI) in the forearm bones of the nondominant side in 210 healthy German children and young adults. Their strong association persisted in subjects of both sexes in spite of large differences in ages, heights and body weights (reprinted by permission: 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: Paediatric Osteology. Prevention of Osteoporosis – a Paediatric Task? E Schönau, V Matkovic (eds). Excerpta Medica, Amsterdam, 1998; 191-202.

al spine X-rays can reveal them in vertebral bodies.

This text does not discuss the slow and usually asymptomatic changes in vertebral body morphology that many authorities currently call vertebral "fractures"[76,81], beyond noting that unlike traumatic fractures, those vertebral phenomena usually seem to occur slowly and without symptoms while they occur[82]. However the postural changes they can cause such as the "dowager's hump" can lead to symptoms later on.

Finding a *muscle-strength/whole-bone strength ratio (MS/WBSr)* above applicable norms, but before nontraumatic fractures occurred, could suggest too little bone strength for a patient's muscle strength[53,69,95]. If so, affected bones and the mechanostat could be unhealthy by the Proposition #1 criterion.

*Implications: (i)* This field's authorities need to decide how to define bone health. *(ii)* The field needs more MS/WBSr norms[40,51-53]. *(iii)* In intact subjects no current blood, urine or other biochemical test[34,96] and no current ultrasound technique[82], could evaluate whole-bone strength or bone health as Proposition #1 defines the latter.

**4) On defining osteopenias and osteoporoses.** The World Health Organization (WHO) criteria evaluate bone health in terms of DEXA-based BMD and/or BMC values. In effect they say "less bone than normal" is a bone disease, "osteopenias" are mild diseases with BMD values less than 2.5 standard deviations (Z scores) below applicable norms, while "osteoporoses" are more severe diseases of the same kind to but with BMD values 2.5 or more standard deviations (Z scores) below such norms[5,71,96]. Those definitions ignore the causes and clinical features of those disorders. That would be like calling all anemias with the same hemoglobin values the same disease regardless of their different causes and other features.

But the updated bone physiology in the Utah paradigm distinguishes three groups of disuse-pattern osteopenias in ways that depend on their causes, and on their clinical and other features including Proposition #1, but not on their severity[6,19-28].

In Group 1 osteopenias (*physiologic osteopenias*[6], no matter how severe the osteopenia nontraumatic fractures do not occur, so affected bones satisfy Proposition #1. Only trauma, typically falls, causes fractures in these osteopenias, usually of extremity bones like the hip and wrist. Alone or in combinations, losses of muscle strength (Table 3), losses of some bone effects of estrogen, androgens and perhaps growth hormone, and losses of some muscle effects of androgen and growth hormone, should cause most (not all) such osteopenias[52,76,81,97]. Whether aging can independently cause bone loss remains uncertain because few if any past studies of age-related bone

loss accounted for the accompanying muscle and hormonal effects on bone loss. Healthy mechanostats would cause these osteopenias. Over two-thirds of postmenopausal women and aging men never develop nontraumatic fractures[81], so their bones would satisfy Proposition #1 regardless of the severity of any accompanying osteopenias and bone-"mass" deficits. These osteopenias can affect children and aged adults of both sexes. Only injuries such as falls {33} cause fractures in these osteopenias, usually of extremity bones like the hip and wrist[44,71,98,99]. Impairments of coordination {34}, balance {35}, vision {36} and muscle strength (and power?) help to increase falls and related fractures in most aging adults[100-105]. Those impairments provide important extraosseous causes of many so-called "osteoporotic fractures". We still know little about hormonal and other effects on those causes.

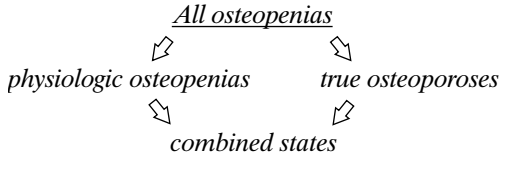
"Transient osteopenias" are regional, inherently temporary, and follow regional trauma and other noxious stimuli[72]. Nontraumatic fractures do not affect them so they should represent physiologic osteopenias instead of true diseases. Healthy mechanostats would cause them.

In Group 2 osteopenias (true osteoporoses)[6] nontraumatic fractures do occur so affected bones do not satisfy Proposition #1. Still-enigmatic mechanostat disorders {37} should cause these osteoporoses. Uncommon examples include osteogenesis imperfecta[46,54] and idiopathic juvenile osteoporosis[92,106], in which the nontraumatic fractures can affect the spine and extremity bones. A commoner example affects some pre- and postmenopausal women and some aging men[76,97,107]. Its nontraumatic "fractures" affect thoracic and lumbar vertebral bodies but, curiously, not the cervical spine, wrist or cranial bones, and rarely the pelvis, sacrum and hip[76,81]. Presumably excessive MDx helps to cause the nontraumatic fractures in these osteoporoses, perhaps partly due to impaired MDx detection and/or repair[6,43,108].

In Group 3 osteopenias *(combined states)*, in principle features of the physiologic osteopenias and true osteoporoses could combine variably.

Because all those osteopenias and osteoporoses can have equally mild or severe whole-bone strength and bone "mass" deficits, X-ray absorptiometry, present ultrasound methods and the WHO criteria cannot distinguish them from each other. It takes other evidence to do that. Traumatic fractures can occur in all of them so that could not distinguish them from each other either.

In essence the Utah paradigm would classify osteopenias thus:




*Implications. (i)* To repeat, the above osteopenias and osteoporoses can have equally mild or severe bone strength and bone "mass" deficits, so absorptiometry, current ultrasound methods and the WHO criteria cannot distinguish them from each other. *(ii)* Regardless of their cause(s), all osteopenias (and/or excessive MDx) facilitate fractures from falls or low-energy trauma[31,109-110]. *(iii)* In principle increased muscle strength and physical activities could benefit physiologic osteopenias because their mechanostats had responded properly to mechanical challenges by the Proposition #1 criterion. Besides increasing whole-bone strength, things that improve balance, muscle strength, neuromuscular coordination and/or vision in aging adults should reduce both their falls and extremity-bone fractures[98,101,102]. Yet in principle increased muscle strength and increased physical activities might make true osteoporoses worse[17,18], since their mechanostats had not responded normally to previous mechanical challenges. Anecdotal observations support those ideas[82]. *(iv)* The updated bone physiology predicted that treating "osteoporoses" diagnosed by the WHO criteria with growth hormone could have troublesome side effects[18]. Endocrinologists at the KGIS/KMIS Workshop in Sicily in 2000 had observed those side effects but found them puzzling. That emphasizes the needs for more "drug targeting" research[6,19,111], and to distinguish physiologic osteopenias from true osteoporoses before prescribing treatment. *(v)* Because the effects on the above matters of hormones, genes, drugs and other things remain uncertain, future work must find them. *(vi)* Calling the bone loss in postmenopausal women (or in otherwise healthy postpubertal ovariectomized or orchidectomized mice, primates or rats) an "osteoporosis" may have outlived its usefulness.

**5) On some endocrine effects on bone.** Illustrative comparisons follow of former and recent views about some bone effects of four hormones[112]. Further work must clarify the relative merits of those views as well as comparable features for genes and other things. All bone-active hormones and other humoral agents would constitute extraosseous nexuses in the complex web of things that, collectively, comprise and explain bone physiology.

Growth hormone (GH) {38} *A)* In gigantism outside bone diameter and bone "mass" increase. Some attributed that to direct stimulation of osteoblasts by GH and/or somatomedins[112-117].

However, *B)* GH also increases chondral-dependent longitudinal bone growth[2,112]. By making bones longer {39} that increases bending strains from the same loads. *C)* GH increases muscle strength too {40}[17,112], particularly during exercise against maximum resistance[82]. *D)* By increasing periosteal bone strains, those "B,C" effects should make normal mechanostats increase outside bone diameter, whole-bone strength, and bone "mass".

*E)* GH and/or some somatomedins (and other hormones?) may also affect the mechanostat's responsiveness {41} to mechanical and other influences[78], another matter that deserves more study.

Estrogen (ES) {42}. *A)* ES reduces BMU-based bone turnover on all bone envelopes, which reduces bone loss and led to its use as an "osteoporosis" preventive[76,118,119]. *B)* At puberty girls begin to store extra bone next to marrow[32,40,117,118] (Figure 5), and menopause leads to loss of that

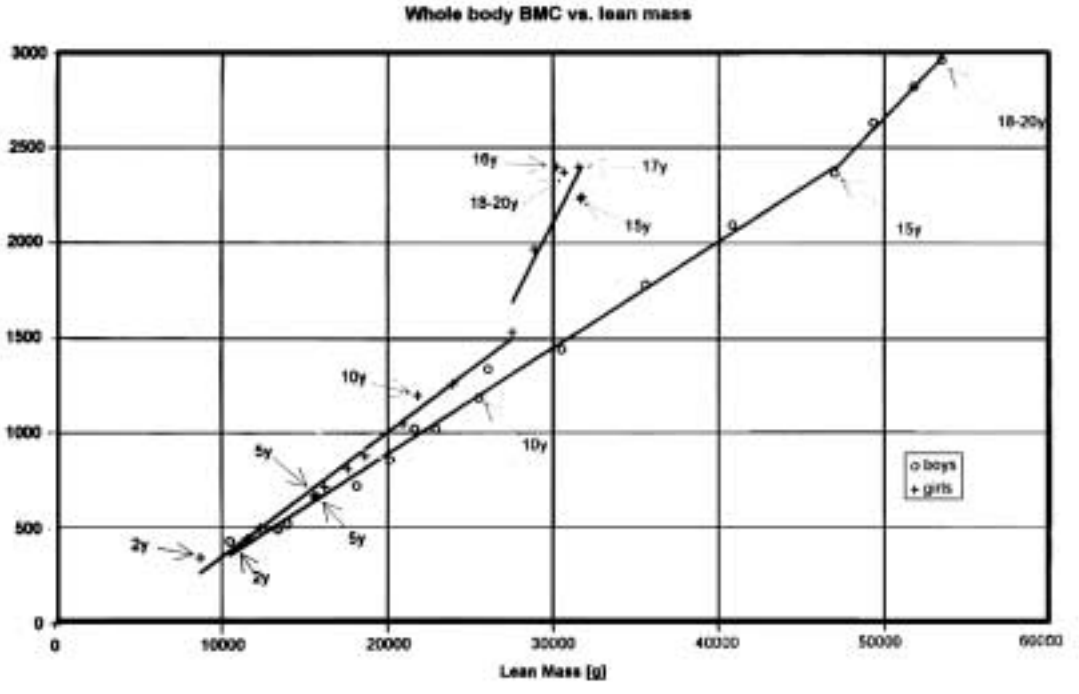



**Figure 5.** *A bone-muscle mass association.* H. Schiessl constructed this graph from an Argentine study of healthy 345 boys and 443 girls between 2 and 20 years of age[151]. The grams of total body bone mineral content (TBMC, whole-bone strength indicator) plotted on the vertical axis corresponded to the grams of lean body mass (LBM, a muscle strength indicator) plotted on the horizontal axis, as determined by DEXA. Crosses: girls. Open circles: boys. Each data point stands for an age one year older than the data point on its left, and it shows the means for all subjects in that one-year age group. Around 11 years of age TBMC began increasing faster than before in girls, but by M 15 years of age their TBMC and LBM both plateaued. Since both indicators kept increasing in the boys they ended up with more muscle and bone than the 20-year-old girls. These data support the relationship between muscle, bone, estrogen and androgens mentioned in the main text. The extra bone stored next to marrow during a woman's fertile years might serve the needs of lactation more than to increase whole-bone strength (reproduced by permission)[152].

bone and to a disuse-pattern osteopenia[76,97]. *C)* Such facts suggested ES could directly depress osteoclasts and/or stimulate osteoblasts[112].

However, *D)* ES also limits longitudinal bone growth in girls[2], so postpubertal girls usually have shorter bones than postpubertal boys. Shorter bones would tend to reduce periosteal bending strains and periosteal formation drifts. *E)* Most women and adolescent girls have weaker muscles than most comparable males. *F)* Those "D,E" effects should make normal mechanostats in women and adolescent girls cause smaller outside bone diameters and weaker bones than in otherwise comparable males. *G)* The marrow mediator mechanism could help to explain why only bone next to or close to marrow is lost when ES effects decline.

How do other hormones as well as genes and other agents affect those things? Such questions wait for answers based on hard evidence instead of opinions (including mine).

Testosterone (TS) {43}. *A)* In adolescent males TS can increase outside bone diameter and bone "mass"[107,120,121], *B)* while loss of TS in adult males usually leads to a disuse-pattern osteopenia[76]. *C)* Such facts suggested TS directly stimulates osteoblasts[121,122].

However, D) TS also increases muscle mass and strength (and power?)[123], particularly during exercise against resistance [82]. *E)* TS does not depress longitudinal bone growth[2,122]. *F)* The increased periosteal bone strains from those "D,E" effects should make normal mechanostats increase postpubertal periosteal formation drifts, outside bone diameter, whole-bone strength and bone "mass" more in males than in females. An age-related decline of TS effects on muscle could help to explain the disuse-pattern osteopenia that affects most aged human males.

*G)* An aromatase that can convert some TS into estrogen in males[124] complicates interpretation of some of the above matters.

Does TS still increase muscle strength in hypophysectomized and/or ovariectomized mammals? Does anyone know?

Parathyroid hormone (PTH) {44}. *A)* Before 1970 many thought continuously elevated PTH secretion in hyperparathyroidism due to an adenoma caused "osteoporosis"[48]. *B)* Over long times such PTH elevations can increase BMU-based remodeling on all four bone envelopes and cause clinically harmful marrow fibrosis, hypercalcemia and nephro-

calcinosis[122,125]. *C)* Nevertheless better clinical diagnosis showed that true osteoporoses in hyperparathyroidism are not common, as suggested long ago[126].

*D)* Furthermore, when given intermittently – say three times/week – PTH evokes modeling formation drifts (which some authors refer to as "formation without prior resorption")[127]. Those drifts can considerably increase trabecular and cortical bone "masses" and whole-bone strength during growth and in adults[88,127-130]. *E)* The relatively small bone-anabolic doses used in intermittent PTH administration seem to cause too little hypercalcemia, marrow fibrosis and nephrocalcinosis to pose serious clinical problems[130]. *F)* When that intermittent treatment stops, increased disuse-mode remodeling begins to remove the added bone (a mechanostat effect?), and a bisphosphonate can depress that removal[131-132]. *G)* That exemplifies the "LRM" treatment (Lose, Restore, Maintain) suggested by W.S.S. Jee at a 1980s Hard Tissue Workshop[133], and subsequently validated by him[67,88] and others. This has become an FDA-accepted treatment in the USA for human "osteoporosis".

*Implications:* It could take years to resolve the above issues, to understand the cellular and molecular biology on which they must depend, and to determine how hormones, genes and other things influence them.

**5) On traumatic fracture patterns in children and adults**[7,38]. In children radius fractures from falls can affect both the diaphysis and the metaphysis, but in aged adults falls usually only fracture the metaphysis (the wrist)[134,135]. Could that change have a biomechanical basis?

*A)* In children the whole radius would adapt its strength to growing voluntary muscle forces. Its diaphysis would adapt to combined muscular uniaxial compression, bending and torque forces, but the very low friction of the radiocarpal joint would make the metaphysis adapt mainly to uniaxial compression muscle forces. *B)* Both parts of a healthy adult radius should have adapted to those differing loads. *C)* Falls on the outstretched hand can put large one-time combined bending, torque and compression loads on the *whole radius*. Because its metaphysis would have adapted mainly to uniaxial compression loads, the large bending forces on it from a fall would more likely break it than the diaphysis. Hence the common Colle's fracture in aging adults.

That could help to explain why falls and related mishaps in aging adults usually fracture the metaphyseal but not the diaphyseal regions of other long bones (hip, humeral surgical neck, supracondylar femur, ankle malleoli)[38].

*Implication:* Opinions aside, how hormones, genes and drugs might affect the above things remains uncertain; more work must find the answers.

**6) Roles of nonmechanical factors.** Knowledge about the physiology of bone's effector cells ({10}, {11}), and about genetic and hormonal effects on them, grew impressively after 1960[32,136-139], yet this article hardly mentions them.

Why?

Most of that work overlooked how bone's other nexuses respond to postnatal genetic and hormonal challenges, so the cell and molecular biology on which those responses must depend remain enigmatic. Opinions and ideas abound but proof does not. That "knowledge gap" in bone physiology needs filling, but people who could fill it and agencies that could fund such work must first know the need exists, and its nature.

That is "Why?".

Many agents formerly thought to affect bone strength by acting directly on bone's effector cells, seem to act instead (or also?) as *permissive* agents that the mechanostat needs in order to work properly, but they do not control it in time and anatomical space[14]. Table 2 lists examples of such agents. Equally, a car needs a motor, transmission, wheels, fuel, etc., in order to be driven, so they comprise permissive things for that activity. But they do not decide if the car drives to Berlin or into some ditch, and adding more fuel to its tank or giving it a bigger engine does not keep it out of a ditch.

Behaviorally speaking, permissive-agent deficiencies can cause large deficits in whole-bone strength, but excesses of such agents have small effects on already-normal bone strength[2,21]. That behavior suggests permissive bone agents include calcium, phosphate, vitamin D and its metabolites, and dietary protein[140].

Some nonmechanical agents long thought to affect whole-bone strength (and bone "mass") by acting directly on bone's effector cells, affect muscle strength too, so via the mechanostat they could affect whole-bone strength indirectly. Such agents include calcium, vitamin D, growth hormone and somatomedins[112], and androgens[112].

As for receptors in bone's effector cells[141], many of the other cells that help to form bone's NEMs (see the last two sentences in the legends for Figures 1, 2, and nexuses {5-9} and {12-19} in Table 4) could have the same receptors but could be the true chief determinants of a ligand's long term *in vivo* effects on whole-bone strength and bone "mass".

*Implications" (i)* It seems that to predict reliably how an effector-cell response to some agent would affect bones *in vivo*, one should first know how the agent affects the other nexuses in Table 4 in order to minimize the "jumping frog" errors described elsewhere[26].

*(ii)* Do genes or mechanics dominate the determination of postnatal bone health? At present that issue incites strong opinions. In the updated bone physiology *the bone-strength "music" played by genes and postnatal mechanical adaptations is at least a duet,* not a solo. It will take more work to tell if-when-where which partner in that duet plays the major role. That work might benefit from studying the natural experiment mentioned in describing the baseline conditions.

## V: Conclusion

**1) On the "law of unintended consequences", accepted wisdom and controversy.** Who could foresee that the apparently simple matter of defining bone health obeys the law of unintended consequences? Material in Part IV above shows the bone-health definition in Part I has potentially important

implications for many other matters, and some of those implications could question some long-standing wisdom and cause controversies.

**2) Which nexuses need study as possible targets for hormonal and/or genetic treatments of bone disorders?** Each nexus in Table 4 needs such studies, but except for {10,11}[136] few were studied so far[3,112]. Each nexus represents a place where one or more genes, hormones or drugs could affect bone physiology and its problems[25]. We must also learn how to make an agent selectively affect one target and avoid others[111]. Because that "targeting" of an agent's effects occurs in nature[6], better "drug targeting" for treating bone problems should be possible.

**3) How could one study endocrine and/or genetic effects on bone's NEMs?** Unfortunately bone's NEMs and NEFs do not work normally in current cell, tissue or organ culture systems[10,49], and effector cell responses in such systems seldom if ever correctly predict the *in vivo* responses[26]. *Nota bene: A)* Attributing an *in vivo* response to some cellular, molecular, humoral or genetic feature after observing the *in vivo* response, *B)* differs from predicting an *in vivo* response from *in vitro* data before observing the former[10,49]! "B" usually causes "jumping frog" errors[26], and abundant unhappy experience with them helps to explain why live-animal studies must precede approvals for using new drugs in humans.

For such reasons many future studies of hormonal, genetic and other effects on bone strength and bone "mass" should involve live-animal research, dynamic histomorphometry[142], and reliable evaluations of whole-bone strength, often combined with other methods[143]. Proven ways to do such studies and to evaluate an agent's effects on specific bone NEMs and their functions already exist[40,45,60,67,75,78,118,127,144,145]. W.S.S. Jee led the way in learning how to do them[68,133], and F. Manz, E. Schönau and their co-workers in Germany currently pursue them with very productive clinical studies[146].

Finding how hormones, genes, drugs and other things affect bone's nexuses and disorders poses a daunting problem, noting that each nexus could depend on many interlocking and nested feedback systems, some of which could affect more than one nexus. Resolving that problem should take much work, thought and time. Developing effective and safe "designer drugs"[111] for many bone problems could depend strongly on the success of such work, and I suspect it will.

## Glossary

**BMU:** the Basic Multicellular Unit of bone remodeling[44]. In 3 or more months and in an Activation → Resorption → Formation or ARF sequence, a typical completed human BMU turns over ≈ 0.05 $mm^3$ of bone (Figure 2). When a *completed* BMU makes less bone than it resorbs that "disuse mode" tends to remove bone permanently, but only next to or close to marrow. When it resorbs and makes equal amounts of bone, that "conservation mode" turns bone over without causing significant gains or losses. Normally, completed BMUs do not seem to increase bone "mass". Healthy adult humans may create and complete about 3 million BMUs annually, but in disease and other circumstances that can change more than five times[7].

**Bone bank:** see bone "mass" next.

**Bone "mass":** the amount of bone tissue in a bone or skeleton, preferably viewed as a volume minus the soft tissues in the marrow cavity. In absorptiometry it does not mean mass as that term is used in physics. In quotes herein it has the absorptiometric meaning. The "bone bank" term would have the same meaning and might be more apt.

**Bone mineral "density":** since the true physical density of bone as a material varies relatively little with age, sex, bone and species (osteomalacia excepted), bone "density" as absorptiometrists use the term only provides an indicator of the amount of bone in the path of one or more X-ray beams as a bone-mineral equivalent. Here one can assume gamma rays and X-rays are the same. While many still think otherwise, true bone density is relatively normal in most osteoporoses and osteopenias[147]. In quotes in this article "density" has its absorptiometric meaning.

**Effector cells:** herein, bone's osteoblasts and osteoclasts, the cells that actually make and resorb bone. The term excludes all precursor and other cells.

**Microdamage threshold (MESp):** in bone this corresponds to a range centered near ≈ 3000 microstrain or ≈ 60 megapascals. Besides greatly increasing the amount of new MDx, strains above it tend to evoke the formation of woven bone instead of lamellar bone.

**Modeling:** of bone, the formation and resorption drifts that produce functionally purposeful sizes and shapes to bones and trabeculae (Figure 1), and that can increase but seldom if ever decrease their strength.

**Modeling threshold (MESm):** the genetically-determined Minimum Effective Strain range (or equivalent Signal), at and above which mechanically-controlled bone modeling turns on to increase bone strength (Figure 3). Where strains stay below it mechanically-controlled modeling turns off. Its threshold range seems to center near 1000-1500 microstrain in most young adults, which corresponds to a stress of ≈ 20-30 Newtons/$mm^2$ (one Newton/$mm^2$ = one megapascal).

**Muscle strength:** a muscle's maximum *momentary* contractile force can be expressed in Newtons, or as the peak torque in Newton-meters produced by muscles across joints like the hip, elbow, knee and fingers. It differs from *endurance*, which concerns how long and often submaximal muscle forces can be exerted, as in marathon running. It differs from mechanical work or *energy*, which can be expressed in Newton-meters (a different physical unit than Newton-meters of torque), Joules or kilowatt-hours. It differs from *power*, which concerns how rapidly muscles perform mechanical work and is usually expressed in Newton-meters/sec, Joules/sec, or watts. Since load-bearing bones seem to adapt their strength and stiffness to the typical peak momentary voluntary loads they carry, accounting for these distinctions can minimize errors in interpreting mechanical usage effects on bones.

**NEXUSES THAT AFFECT BONE PHYSIOLOGY AND GENETIC/HORMONAL EFFECTS***

| | |
|---|---|
| {1} | material properties factor |
| {2} | microdamage factor |
| {3} | bone "mass" factor |
| {4} | bone architectural factor |
| {5} | modeling by drifts |
| {6} | remodeling by BMUs |
| {7} | conservation-mode remodeling |
| {8} | disuse-mode remodeling |
| {9} | the mediator mechanism in marrow |
| {10} | osteoblasts (one kind of bone's effector cells) and their precursors |
| {11] | osteoclasts (the second kind of bone's effector cells) and their precursors |
| {12} | a periosteal mediator mechanism? |
| {13} | strain-dependent signals |
| {14} | bone's modeling threshold range |
| {15} | bone's remodeling threshold range |
| {16} | the cells containing the modeling and remodeling thresholds |
| {17} | cells that compare strain-dependent signals to those thresholds |
| {18} | comparing the thresholds to strain-dependent signals |
| {19} | error signals that could turn modeling or disuse-mode remodeling on |
| {20} | momentary muscle strength |
| {21} | neuromuscular physiology |
| {22} | sarcopenia |
| {23} | disuse-pattern osteopenia |
| {24} | microdamage (MDx) |
| {25} | the microdamage threshold |
| {26} | repair of MDx by BMUs |
| {27} | nontraumatic fractures |
| {28} | the baseline conditions |
| {29} | genes in bone cells and NEs |
| {30} | humoral agents that can affect bone physiology |
| {31} | the mechanostat |
| {32} | modulators of the mechanostat's workings |
| {33} | falls and their causes |
| {34} | neuromuscular coordination |
| {35} | balance |
| {36} | vision |
| {37} | mechanostat malfunction(s) in true osteoporoses |
| {38} | growth hormone, somatomedins and any modulation of their effects by other factors |
| {39} | longitudinal bone growth |
| {40} | growth hormone effect on muscle strength and any modulation by other factors |
| {41} | growth hormone effect on mechanostat responsiveness and any modulation by other factors |
| {42} | estrogen effects on bone and any modulation by other factors |
| {43} | testosterone effects on bone and muscle and any modulation by other factors |
| {44} | parathyroid hormone effects on bone and any modulation by other factors |

*: Listed in the order mentioned in the text. The number of these nexuses seems conservative, since each one could depend on many lower-level mechanisms and on many genes. The only cell-level nexuses in this Table are {10}, {11}. Comparable nexuses should exist for chondral and collagenous tissue physiology[20], and hormones could affect many of them too.

**Table 4.**

**Nephron equivalent mechanisms (NEMs):** renal health and disorders depend on the special functions of nephrons composed of many different kinds of cells. Bones have tissue-level, multicellular "nephron equivalent mechanisms" or NEMs (modeling drifts, remodeling BMUs, thresholds, and other things), and their functions (NEFs) have the same relationship to their many kinds of cells and bone health and disorders as nephron functions do to the many kinds of cells in nephrons and to renal health and disorders. No bone NEMs were recognized as such before W.S.S. Jee and I began to recognize and study them in the 1960s.

**Osteopenia:** herein and when not in quotes this signifies less bone and/or less whole-bone strength than usual for most healthy people of the same age, height, weight, sex and race (a negative Z score), or than before in the same person (a negative T score). Affected bones would usually be weaker than normal ones and more likely to fracture from falls and low-energy trauma. Herein an osteopenia would always be a disorder, but need not always be a disease.

"**Osteopenia":** herein, and when in quotes and by the WHO diagnostic criteria[148], this is a BMD deficit less than 2.5 standard deviations below applicable norms (i.e., a negative Z or T score between zero and –2.5).

**Osteoporosis:** herein and when not in quotes this means an osteopenia in which voluntary physical activities cause nontraumatic (spontaneous) fractures, so affected bones would not satisfy Proposition #1. This would be a true bone disease with impaired bone health. To repeat, osteopenias and osteoporoses as defined here can have similarly small and large negative T and Z scores, and similarly mild and severe deficits of whole-bone strength and bone "mass". Ergo, absorptiometry alone could not distinguish them from each other.

"**Osteoporosis":** herein and when in quotes and by the WHO diagnostic standards[148], this exists when a BMD deficit exceeds 2.5 standard deviations below applicable norms (i.e., a negative Z score of ≥ 2.5). that could suggest "osteopenias" and "osteoporoses" were different severities of the same disorder, like the hemoglobin in mild and severe pernicious anemias. Those criteria ignore the disorder's cause(s), on which effective treatment could depend. Many authors find the "Type I, Type II" terms confusing[81]. The pathogenetically-based definitions suggested at Hard Tissue Workshops[133] should supplement others.

**Remodeling:** here, turnover of bone in small packets by BMUs. Pre-1964 literature did not distinguish it from modeling and lumped them together as "remodeling". The distinctions between growth, modeling, remodeling, maintenance and healing have become accepted by most anatomists, histomorphometrists and bone physiologists.

**Remodeling threshold (MESr):** the Minimum Effective Strain range (or equivalent Signal) for controlling the switching between mechanically-controlled conservation-mode and disuse-mode remodeling. When strains exceed it *completed* BMUs begin to make and resorb equal amounts of bone (conservation-mode remodeling). When strains stay below it completed BMUs next to marrow make less bone than they resorb (that disuse-mode remodeling removes bone next to or close to marrow). By one definition (there are others) this threshold would correspond to bone strains that stay below ≈ 50-100 microstrain, or to stresses that stay below ≈ 2 Newtons/mm$^2$.

**Resorption:** some authors use this term to mean net bone loss, and in that sense discuss "antiresorption agents". While often called antiresorption agents, estrogen and bisphosphonates mainly depress BMU creations[87,88]. At first that decreases global resorption, but due to the ARF sequence in the BMU, an equal decrease in global bone formation eventually follows (Figure 2), so these are really "antiremodeling agents". In this text resorption means bone resorption by osteoclasts. It refers to net losses of bone as such and separately.

**Strain:** the deformation or change in dimensions and/or shape caused by a load on a bone (stretching, shortening, twisting bending, alone or in combinations). Loads *always* cause strains, even if very small ones. Biomechanicians often express strain in microstrain units, where 1000 microstrain in compression would shorten a bone by 0.1% of its original length, 10,000 microstrain would shorten it by 1% of that length, and 100,000 microstrain would shorten it by 10% of that length (and break it). *Note:* Current studies concern the roles of strain kinds, rates, frequencies and number, and of other mechanically-generated signals, in controlling bone's adaptive mechanisms. Thus where this text mentions strain as a control of a biologic activity the qualifier, "or equivalent factor", should always be understood.

**Strength:** bone's ultimate strength expressed as a strain is a range centered near ≈ 25,000 microstrain in young adults, and a bit less in aged bone and a bit more in children[4,42]. That would correspond to a stress of ≈ 120 megapascals, and to a unit load of ≈ 12 kg/mm$^2$ of a bone's cross section. Bone's three thresholds normally ladder thus, from the smallest to the largest and relative to its ultimate strength (Fx): MESr < MESm < MESp << Fx.

**T score:** an absorptiometric BMC or BMD compared to an earlier one in the same subject, expressed in standard deviations. A negative T score by the WHO criteria[148] means less bone than before in the same subject.

**Z score:** an absorptiometric BMC or BMD compared to normal subjects of the same age, sex, height and race, expressed in standard deviations. A negative Z score by the WHO criteria[148] means less bone than in healthy subjects of the same age, sex, height and race, which reveals nothing about the disorder's pathogenesis.

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