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Perspective Article

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Coming changes in accepted wisdom about "Osteoporosis"

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Abstract

Here a voice from the past suggests 28 changes that will affect how people study, manage, classify and think about "osteoporoses" today. Those changes depend mainly on two things: (i) "Connecting the dots" between diverse evidence and ideas from many fields and sources in order to find larger "messages" hidden in mountains of often poorly-organized lesser details, (ii) and features of the still-evolving Utah paradigm of skeletal physiology. That paradigm sums contributions from many people who worked in many fields for over 100 years. In one view it is the most important development in skeletal physiology since Rudolf Virchow and others realized ≈ 150 years ago that cells provide the basis for human physiology and diseases. This article emphasizes the above messages instead of the details. The messages affect ideas about the nature, pathogenesis, diagnosis, classification, study and management of osteopenias and osteoporoses, as well as some roles of muscle, drugs, hormones, other agents and fatigue damage, in those disorders. Those larger messages also concern how to classify "osteoporosis fractures", how to define bone health, the choice of absorptiometric methods for noninvasive evaluations of bones, osteopenias and muscle strength, and new criteria for selecting patient cohorts for "risk-of-fracture" analyses and in searches for genetic roles in "osteoporoses". Finally, those larger messages identify many new targets for research that should prove unusually useful in clinical and pharmaceutical domains and work.

Keywords: Biomechanics, Absorptiometry, Physiology, Diagnosis, Pathogenesis, Utah Paradigm

Introduction

When offered predictions for the future, prudent readers could well ask "Who speaks?".

In answer, throughout a 55+ year career this octogenarian did and taught orthopaedic surgery and pursued seven professional hobbies (skeletal pathology, anatomy, histology, biomechanics and physiology; metabolic bone disease; and light microscopy). Before moving to Pueblo in 1973 research was done too, but afterwards connecting the dots" between multidisciplinary facts largely replaced the research. Those facts came in part from clinical experience, from experimental findings and from those seven hobbies (over 80 years ago, "connecting the dots" in varied physics data let a Swiss postal clerk realize that $E = mc^2$). With strong support from Dr. Jee and his uniquely-seminal Hard Tissue Workshops[1], that effort led to the Utah paradigm of skeletal physiology[2-9]. Experience acquired during that effort verified an old saying: "If failures are orphans, successes find many fathers." During those 55+ years professorships, a departmental chairman-ship, some honors, over 440 publications, some true friends and other things came along too.

That is "Who speaks?" here (although those things impressed others much more than me). So said, this article would share with readers 28 looming changes in some of today's "accepted wisdom" about "osteoporosis". References provide more details or tell where to find them. Table 1 collects and defines the abbreviations and symbols used below.

The 28 predictions

1) **The Utah paradigm of skeletal physiology.** *Ca* 1990 accumulated evidence and ideas, and increasing inadequacies of earlier ideas and terminology, made it necessary to update ideas about skeletal physiology. The Utah paradigm of skeletal physiology provides that update[2-4,9-22]. While devils can lie in the details, that paradigm concerns bone and bones; collagenous tissue, fascia, ligaments and tendons; cartilage, growth plates and synovial joints; mechanostats for bone, cartilage and collagenous tissues; related clinical prob-

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lems; and muscle and hormonal effects on skeletons.

However this article concerns things that relate to bones, osteopenias and osteoporoses. In essence load-bearing bones make the voluntary loads on them determine most of their strength after birth, and the Utah paradigm explains how bone's tissue-level biologic mechanisms do that.

Prediction #1: The Utah paradigm, by that or any other name, will become the preferred model of bone physiology in osteoporosis work. Michael Parfitt recently called bone's mechanostat "...the most important unsolved problem in bone biology..."[23].

2) **A definition of bone health.** Defining bone health had little discussion in the past. In one view "less bone than normal" means diseased bones[24,25]. But healthy load-bearing bones have enough strength to keep typical peak voluntary loads from breaking them. That observation could define a bone's health as a three-way *relationship* between *(i)* its strength, *(ii)* the kind and size of the voluntary loads on it, *(iii)* and any *nontraumatic* fractures (often called "spontaneous" ones) caused by such loads[2]. Signified by Proposition #1 elsewhere[15], that idea defines bone health as a function of the presumed chief purpose of load-bearing bones; it would also rank whole-bone strength above bone "mass" in physiologic importance. Example: Mouse ribs and horse femurs would be equally healthy if they satisfied Proposition #1 in the animals they came from, although their strengths and bone banks differ far more than 1000 times. Healthy mechanostats would make load-bearing bones satisfy Proposition #1, so presumably diseased mechanostats would explain failures to do that.

"Voluntary" means intentional and not due to any kind of trauma, so it implies muscle forces; "load-bearing" bones exclude in part the cranial vault, turbinates, ethmoids, ear ossicles and nasal and lachrymal bones; and "whole-bone" distinguishes bones as organs from bone as a tissue or material.

Predictions #2, #3: *#2)* Proposition #1, by that or any other name, will become the preferred criterion for evaluating a load-bearing bone's health in osteoporosis and some other matters (present criteria of bone health depend mainly on things like bone fragility, bone "mass", etc). *#3)* Neoplasms and infections excepted, diseased mechanostats will explain most failures of bones to satisfy Proposition #1, but not all of them[26].

3) **Noninvasive absorptiometry, whole-bone strength (WBS),** and bone strength indicies (BSIs). Whole-bone strength combines four physical factors: *(i)* Bone's material properties, *(ii)* a bone's microdamage (MDx) burden, *(iii)* the amount of bone in a cross section, a bone "mass" factor, *(iv)* and a bone's geometric or architectural features[27,28,29]. Breaking bones in a laboratory can reveal the combined effect of those four factors, but evaluating whole-bone strength in patients requires noninvasive methods. Unfortunately no current such method can evaluate the first two of those four factors.

Bone mineral content (BMC) and "density" (BMD) values obtained by dual-energy X-ray absorptiometry (DEXA) can evaluate the "mass" factor. Although currently popular[25], nevertheless BMD values provide extremely poor indicators of whole-bone strength and bone "mass"[27,28,30-33].

Yet peripheral quantitative computed tomography (pQCT) and suitable software can provide bone strength indices (BSIs) that evaluate whole-bone strength quite well, both *in vivo* and *ex vivo*. How? By accounting for both the "mass" and architectural factors in that strength[27,28,30, 31,33-36].

Predictions #4-#9: *#4)* BSIs, by that or any other name(s), will become preferred indicators of whole-bone strength in osteoporosis work and research, and in some other work. *#5)* BSIs will replace or at least supplement current DEXA and ultrasound ways to evaluate whole-bone strength. *#6)* BSIs will attract intensive studies. *#7)* Good BSIs should meet this "BSI criterion": When expressed in compatible units, multiplying BSIs for bones as different as mouse and horse femurs by the same constant (k) would predict their hugely different strengths (Fx). Or, Fx = (BSI)k. The BSIs devised by JL Ferretti in Argentina[31] and modified by H Schiessl in Germany[33,36] seem to approach that criterion. *#8)* Future "risk-of-fracture" analyses will replace BMD values with BSIs as indicators of bone strength (also see Predictions #12, #13 below). *#9)* Most authorities will agree that whole-bone strength ranks above BMD and/or BMC in physiologic importance.

4) Muscle and the "whole-bone-strength/muscle-strength ratio" (WBS/MSR). Dividing a whole bone's strength (WBS) by the strength of the muscles (MS) that load it would provide a ratio of those strengths, the whole bone strength/muscle-strength ratio (WBS/MSR) (see predictions #12-#14 below).

Loads on bones generate bone-strain-dependent signals that help bone's three threshold strain ranges (the bone's modeling threshold range (MESm), bone's operational microdamage threshold range (MESp) and bone remodeling threshold range (MESr) in Table 1) to control the mechanostat that determines most of our postnatal whole-bone strength37. One-time trauma excepted, the largest such loads come from voluntary muscle forces, not body weight29,38,39. Why? On earth lever-arm and gravitational effects require well over two kilograms of muscle force on bones to move each kilogram of body weight around2,29. For such reasons, (i) total loads on a soccer player's femur during a game can briefly but often exceed five times body weight; (ii) and muscle strength and anatomy, plus the neuromuscular physiology that controls muscles, should strongly affect our postnatal whole-bone strength and bone health. In that regard bones in paralyzed limbs lose considerable bone "mass" and strength while bones in normal limbs in the same subject do not. Electrical stimulation of the paralyzed muscles can lead to restoration of some of the lost bone7. Yet all bones in the same subject have the same kinds of cells with the same genome, and they receive the same chemical, hormonal and other messengers from the blood.

In most people muscle strength peaks in young adults and then slowly declines, so an octogenarian can retain less than half of his or her young-adult muscle strength (and power?)[38].

Usually corresponding losses of whole-bone-strength accompany such muscle-strength losses (hence an explanation for at least part of our age-related bone loss). Muscle strength can be measured in cooperative humans[38,40], and determining muscle weight or volume as well as some absorptiometric methods[8,36,40-45] can provide useful indicators of it.

Such things made Dr. George Lyritis in Athens create the International Society for Musculoskeletal and Neuronal Interactions (ISMNI).

Predictions #10-#14: *#10)* Many more norms will appear for human WBS/MSRs that should prove very useful. JL Ferretti, H Schiessl, E Schönau, their coworkers, and others, show various ways to obtain them[8,30,31,34-36,40,42-45]. *#11)* Those ratios will largely replace the absorptiometric BMD and BMC bone "mass" norms recommended in 1994 by the World Health Organization (WHO)[24,25] (see Section #5 below). *#12)* In future risk-of-fracture analyses, *#13)* as well as in searches for genetic causes of "osteoporo-sis", WBS/MSRs will supplement or replace BSIs. *#14)* When expressed in suitable units, reliable indicators of the strength of whole bones (WBS), say of mouse and horse femurs, when divided by reliable indicators of the strength of the muscles (MS) that load those bones, will yield approximately constant ratios (k), or $\kappa \approx WBS \div MS$. That could help to explain why chronically strong muscles usually associate with strong bones, and why chronically weak muscles usually associate with weak bones.

5) **On defining osteopenias and osteoporoses.** The WHO absorptiometric criteria suggest that "less bone than normal" is a bone disease[24]. They define BMD values 2.5 or more standard deviations below applicable norms ("Z" scores) as "osteoporosis", and lesser deficits as "osteopenias"[25]. Those criteria fostered three ideas: *(i)* Subnormal BMD values constitute a bone disease; *(ii)* the genome makes bones have a predetermined and ideal bone "mass"; *(iii)* and "osteoporosis" and "osteopenia" are different severities of the same disease, like severe and mild pernicious anemias.

The WHO criteria do not account for the causes and clinical features of those disorders (when in quotes "osteoporosis" and "osteopenia" signify the WHO definitions, but without quotes they have the meanings given below).

Yet in the Utah paradigm three major groups of osteopenias (meaning less whole-bone strength than applicable norms) depend on their causes and clinical and other features including Proposition #1, but not on the size of their bone "mass" or strength deficits[15].

Group 1: In physiologic osteopenias healthy mechanostats cause osteopenias in which nontraumatic fractures caused by voluntary activities do not occur, so affected bones would satisfy Proposition #1 no matter how severe the osteopenia. Only falls or other trauma cause fractures in these osteopenias, usually of extremity bones like the hip and wrist[25,45]. Most (not all) such osteopenias occur in response to losses of muscle strength, to losses of some bone effects of estrogen, androgens and perhaps growth hormone, and perhaps to losses of some androgen and growth hormone effects on muscles. "Transient osteopenias" are regional, temporary, and follow regional trauma and other noxious stimuli[15]. They provide a "natural experiment" in which the initial loss of muscle forces on bones leads to a regional osteopenia, and resumption of muscle forces after the injury heals corrects that loss of whole-bone strength. In my view, whether aging independently causes bone loss remains uncertain because few if any past studies of age-related bone loss accounted for the accompanying age-related muscle and hormonal effects on bone.

Group 2: In *true osteoporoses* still-enigmatic mechanostat diseases would cause osteopenias in which voluntary activities, not trauma, do cause nontraumatic ("spontaneous") fractures. Affected bones would not satisfy Proposition #1. In uncommon examples like osteogenesis imperfecta and idiopathic juvenile osteoporosis the nontraumatic fractures can affect both extremity bones and the spine[25]. A commoner and widely-discussed true osteoporosis affects some pre- and postmenopausal women and some aging men[25]. Curiously, its nontraumatic "fractures" only affect the thoracic and lumbar vertebral bodies, not the cervical spine or extremity bones (except for rare nontraumatic pelvic, sacral and hip fractures).

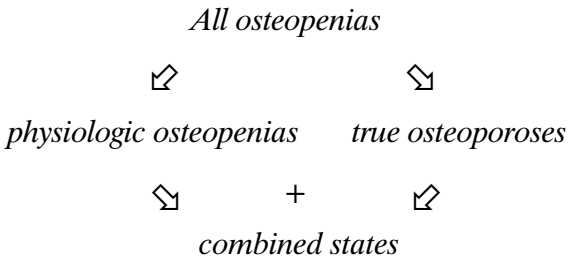
Group 3: In *combined states* features of the Group #1 and #2 disorders would combine variably.

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. Neither can traumatic fractures, because they can occur in all those osteopenias and osteoporoses. Yet clinical features can help to distinguish physiologic osteopenias from true osteoporoses.

Predictions #15-#21: *#15)* The Group #1-#3 terms, or others with the same meanings, will become preferred ways to classify all osteopenias (an idea that some question today; see Prediction #21 below). *#16)* Managing (preventing or curing) physiologic osteopenias and true osteoporoses will depend on different things[15]. *#17)* As in humans, osteopenias normally follow losses of estrogen and androgens in otherwise healthy postpubertal female and male mice, rats and primates. Yet physiologists will stop viewing them as models of "osteoporosis" because they do not develop nontraumatic fractures. Thus their bones satisfy Proposition #1. By that criterion those disorders would constitute physiologic osteopenias. *#18)* The physiologic hormonal effects of estrogen and androgens on bone strength and the bone bank will modestly modify the above MS/BSR norms. *#19)* Most authorities will concede that healthy mechanostats cause physiologic osteopenias, and diseased mechanostats cause true osteoporoses. *#20)* The current classification of nontraumatic changes in vertebral body morphology (wedging, end-plate cod-fishing) as "fractures"[25] will be revised[15]. *#21)* The Utah paradigm's classification of all osteopenias will become an accepted standard (where osteopenia means less whole-bone strength than in applicable norms, and physiologic osteopenias represent healthy departures from such

norms, like one brown and one blue eye in a person who has normal vision).

Thus:



6) **On two kinds and causes of "osteoporosis fractures".** These include *traumatic and nontraumatic* fractures.

As for traumatic fractures and no matter how severe the osteopenia, only trauma -- usually a fall -- causes them. They preferentially affect extremity bones (hence hip, wrist, humoral surgical neck, and ankle fractures). Impairments of muscle strength (and power?), balance, vision and neuromuscular coordination increase falls and the related extremity-bone traumatic fractures in most aging humans[45-47].

But in some people voluntary muscle forces instead of trauma cause nontraumatic fractures. Presumably diseased mechanostats and excessive amounts of microdamage (MDx) cause them. The 40-year-old idea that excessive MDx causes at least most such fractures meets growing acceptance[26,48].

Thus traumatic and nontraumatic fractures have different causes, like anemias due to hemorrhage and to aplastic bone marrows. Please note three things: *(i)* "Osteoporosis fractures" only affect load-bearing bones, *(ii)* all osteopenias as well as MDx, regardless of their causes, facilitate traumatic fractures from low-energy trauma and falls, *(iii)* and the occurrence of nontraumatic fractures would reveal an established true osteoporosis (exceptions include pathologic fractures, and stress fractures in athletes and special-forces trainees).

Predictions #22-#25: *#22)* Future risk-of-fracture analyses, *#23)* like studies of drug effects on "osteoporosis fractures", *#24)* and like searches for genetic causes of "osteoporosis", will avoid studying patient groups that mix those two kinds of fractures.

Why? In analogy one would not seek the cause of, or a cure for, "anemia" by studying patient groups that randomly mixed anemias due to hemorrhage with anemias due to, say, sickle cell disease, falciparum malaria, aplastic bone marrows, iron deficiency, and renal failure.

#25) As suggested in 1999[45], studies of drug effects on fracture rates will also study drug effects on falls. Why? A drug that decreased falls by, say, 15%, should similarly decrease extremity bone "osteoporosis fractures", but to tell if a drug has that effect one must seek it. Such an effect might depend on improving balance, muscle strength (and power?), neuromuscular coordination and vision, alone or in combinations.

7) **On permissive agents.** In former views things like genes, humoral agents like hormones, calcium, vitamins C and D and some drugs, and some local cytokines, chemokines, ligands, etc, dominated control of the health and strength of load-bearing bones. Such ideas still linger[15,34,49].

Yet most such agents act chiefly as "permissive" ones which bone's mechanostat needs in order to function properly, as cars need fuel, motors, wheels, oil, etc, in order to be driven. Most such agents cannot duplicate or replace the mechanical-loading and muscle-strength effects on the "functional adaptations" of load-bearing bones to their voluntary mechanical usage[37].

Permissive humoral and local agents have a distinctive behavioral property. Deficiencies of such agents can cause big problems in skeletal health, architecture and strength, but their excesses in healthy subjects have small or no effects, or different kinds of effects including toxicity. Thus vitamin C deficiency causes scurvy but its excesses have little effect on healthy bodies. Vitamin D and thyroxine deficiencies cause short stature, yet their excesses do not cause giantism but can cause toxicity. As suggested several years ago[16], growth hormone might mainly permit whole-bone strength to increase during adaptations to larger bone loads. A clever Australian study showed that lacking such loads the hormone does not increase that strength[50], so the hormone does have a permissive role in that activity.

8) **On jumping frog errors.** Historically, extrapolating from bone's effector cell responses to varied agents to intact bones while ignoring the functions and responses of bone's tissue-level mechanisms including its mechanostat, erred as regularly as doing the same thing would for renal physiology while ignoring the roles of nephrons[14]. "Effector cells" are the osteoblasts and osteoclasts that make and resorb bone respectively, but not their precursor or other cells.

Called "jumping frog errors" elsewhere[21], extrapolating from cell-level and molecular-biologic data to bone's organ-level functions while ignoring bone's tissue-level mechanisms continues in this field. In the past such errors suggested that effector cell responses could cause and/or cure most "osteoporoses". Past examples involved some bone effects of dietary and serum calcium; apoptosis, leptin and other receptors in bone's effector cells; parathyroid hormone and calcitonin; zinc, copper and certain amino acid deficiencies; osteocyte death; nitric oxide, cyclic AMP, and glutamate signalling; vitamins A and D; mechanical bone stress; bioelectric potentials; fluoride and strontium; various genes; varied cytokines and chemokines; etc.

Prediction #26: In time most authorities will recognize and discourage such errors.

9) **On treatment.** *(i)* Most past efforts to treat "osteoporosis" emphasized preventing bone loss or restoring a normal bone "mass". Hence estrogen, bisphosphonates, low-dose intermittent parathyroid hormone treatment, fluoride, etc.[25]. *(ii)* Later efforts try to reduce falls, and/or minimize their effects with things like hip pads. Prediction #27: The "(ii)" efforts will find growing successes, and "balance training" and, probably, some drugs, can help to reduce the falls that

Abbreviation	Definition
BMC:	absorptiometric bone mineral content.
BMD:	absorptiometric bone mineral "density".
BSI:	bone strength indicator or index.
DEXA:	dual energy X-ray absorptiometry (often written as DXA).
"E":	a bone's typical peak strains from voluntary muscle forces.
Fx:	a bone's ultimate strength.
k:	any constant, whether scalar or vectorial.
MDx:	microscopic fatigue damage in bone.
MESm:	bone's modeling threshold range.
MESp:	bone's operational microdamage threshold range.
MESr:	bone's remodeling threshold range that controls the switching between conservation-mode and disuse-mode remodeling.
WBS/MSR:	the whole-bone-strength/muscle-strength ratio.
pQCT:	peripheral quantitative computed tomography.
SSF:	bone's strength-safety factor.
WBS:	whole-bone strength.
WHO:	World Health Organization of the United Nations.
<, <<, <<<:	less than, much less than, markedly less than, respectively.
≈:	approximately, or approximately equals.

Table 1. Definitions of abbreviations

cause so many traumatic "osteoporosis fractures".

10) **On future research.** This Conference concerns research as well as "osteoporosis". In that regard the cellular and molecular biology on which the above things and those in Table 2 must depend remain mostly unknown today, and likewise how hormones, vitamins, minerals, drugs, other humoral agents, nutrition, genes and some other things, affect them. Why? So far such effects lacked systematic study. Prediction #28: "Targeted" studies of those effects should prove exceptionally useful and productive[15]. A good example of such targeted research and of the development of "designer drugs" too[51] appeared recently in Science[52]. Other examples have been done by WSS Jee and his fellows[53].

11) **On strength safety factors (SSFs) in bones.** Healthy mammalian bones have more strength than needed to keep voluntary loads from rupturing them suddenly or in fatigue, so they have SSFs.

As noted elsewhere strength safety factor = a bone's ultimate strength divided by bone's modeling threshold *(SSF = Fx ÷ MESm)* can calulate bone's SSF[3]. When expressing the latter two terms as stresses the SSF for healthy young adult mammalian bones ≈ six[2]. Two variations of that arrangement may help to explain some clinical observations.

(i) A modest increase in bone's modeling threshold (MESm), due perhaps to genetic, humoral agent or drug effects, would require larger loads and strains than before to make modeling strengthen a bone. That would make the bone weaker than before, decrease its SSF, make low-energy trauma more likely to to break it, and/or make it more prone to excessive MDx.

(ii) A modest decrease in the MESm would let smaller strains and loads than before make modeling strengthen a bone, so its SSF would become larger than normal. That would make the bone more resistant to traumatic fractures and to MDx.

Clinical experience, plus experience with special forces trainees, athletes and equine training, reveals that some individuals do seem unusually prone to fractures and MDx-related problems with their bones, while some other people seem unusually resistant to such problems. Such things would not prove the above ideas are correct but they do support the ideas.

Interestingly, in both the *(i)*, *(ii)* cases the involved tissues and organs need not show associated abnormalities in histology, composition or metabolism, or in their material properties.

Feature Introduced	Year
Four functionally different bone envelopes	1963**
The distinctions between modeling drifts, BMU-based remodeling, and woven bone physi-ology	1963-**
Dynamic bone histomorphometry	1964 compacta, 1977 spongiosa*
Thresholds for mechanically-controlled modeling and disuse-mode remodeling	1964*
An operational threshold for MDx	≈1990*
Some roles of those three thresholds in clinical disorders	1985-2002**
The mechanostat	1987*
The marrow mediator mechanism	1966**
A similar mechanism for the periosteal envelope	2001-**
Bone microdamage (MDx)	1960*
Functions and clinical roles of modeling and remodeling	1985+**
Proposition #1 as a criterion of bone health	≈1998**
The distinction between physiologic osteopenias and true osteoporoses	≈1966**
Traumatic and nontraumatic (spontaneous) fractures have different causes	≈1990*
The Utah paradigm of skeletal physiology	1995**
Distinguishing nonload-bearing bones from load-bearing ones	≈1990*
Defining "jumping frog" errors	1986**
Bone's "strength safety factor" as $SSF = Fx \div MESm$	2001
Adding bone's tissue-level mechanisms and functions to its cell-level ones	1964**
Bone's BSI criterion, as $Fx = (BSI)k$	2002**
Some clinical effects of altered set points of bone's three thresholds - the MESm, MESp and MESr -	1985, 1990**
Roles of MDx in true osteoporoses	1966**
Some drugs might alter the incidence of falls	1999**
A general biomechanical relation for normally-adapted load-bearing bones, as $MESr < "E" < MESm << MESp <<< Fx$	1998**
The regional acceleratory phenomenon (RAP)**.	
Conservation-mode and disuse-mode bone remodeling	1966, 1998**

*: Caused past controversy. **: Still causes controversy. BSI, "E", Fx, k, MDx, MESm, MESr, MESp, SSF: See Table 1.

Table 2. Features of the Utah Paradigm that Concern Osteopenias and Osteoporoses.

Conclusion

1) Table 2 lists some features of the Utah paradigm that concern "osteoporoses". Many more than the above 28 changes should occur, including some that depend on unpredictable chance. But it would be foolish to wait for chance to resolve such matters. Why? As Voltaire said, "Dame Chance gives shoes to a man without feet, and gloves to a man without hands.".

2) The above predictions do challenge some "accepted wisdom" in this field. Historically accepted wisdom in science and physiology welcomed challenges with the same enthusiasm as the Taliban and the Spanish Inquisition did. So while in my view those changes will happen (indeed, some have begun), today many people could question some of them. I respect such people and questions, and quite agree that trying to see the future in some crystal ball risks making errors. Time and more work should resolve such questions, but age and other things make me unable to help to resolve them. That means younger people must resolve them when and how -- and if -- they wish to.

So be it.

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