Some Causes of coming Improvements in Skeletal Physiology, its Research, and the Diagnosis, Study and Management of its Disorders.

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I: INTRODUCTION

After 1990, updating ideas about skeletal physiology with new evidence, new ideas and better terminology, led to the still-evolving Utah paradigm of skeletal physiology [11,12,14,58]. That paradigm's genesis depended strongly on six things: (i) Discoveries of completely unexpected kinds of things; (ii) connecting the dots between many ideas and evidence from numerous basic science and clinical fields; (iii) dynamic histomorphometry; (iv) biomechanics and some roles of muscle; (v) some unconventional thinking; (vi) and recognizing some big things hidden in mountains of lesser ones.

Younger people than us must build on the foundation provided by that paradigm. It begins to modify some long-accepted ideas about the nature, study and management of things like "osteoporosis" [8], osteoarthritis, hard- and soft-tissue healing problems, skeletal development and deformities, many other skeletal problems, and some extraskeletal disorders [10-12]. The paradigm shows important new targets for research about such things that should lead to improved understanding, diagnosis and management of skeletal disorders and of some extraskeletal ones.

One could say the paradigm developed in two broad phases. The first phase evoked general interest by discovering completely unexpected kinds of things that had largely-unknown functions at the time, and it met relatively little resistance. Yet some scientists and clinicians still resist some still-evolving second-phase features and implications. Part II of this article reviews those phases, and Part III discusses a few of their broader implications.

Table 1 collects and defines the abbreviations used below.

Table 1. Abbreviations in the Text

BMU:	basic multicellular unit of bone remodeling.
"E":	typical peak loads on, and/or strains of, an LBSO caused by its VMLs.
EC:	effector cells, the ones that make or resorb skeletal tissues (osteoblasts and osteoclasts in bone, chondroblasts and chondroclasts in cartilage, fibroblasts and giant cells -- ?fibroclasts? -- in collagenous tissues).
Fx:	an LBSO's ultimate strength.
LBSO:	a skeletal load-bearing organ (bone, joint, growth plate, fascia, ligament, tendon). nonLBSO: besides some bones -- cranial vault, turbinates, ethmoids, etc. -- this could include cartilage in the trachea, ear and nose, the pulmonary and peritoneal fascia, and basal laminae.
MDx:	microdamage, microscopic fatigue damage.
MESm:	the genetically-determined modeling threshold range above which a tissue's modeling can turn on. One can express it as a strain or stress.
MESp:	the genetically-determined MDx threshold range for any structural tissue in an LBSO. Bone, cartilage and collagenous tissue would have their own MDx thresholds. One can express it as strains or stresses.
MESr:	the genetically-determined threshold range below which an LBSO's maximal disuse-mode activities can turn on. One can express it as strains or stresses
MST:	a genetically-determined mechanostat for bone, cartilage or collagenous tissue.
NEM:	a nephron-equivalent mechanism.
NEF:	a function of a nephron-equivalent mechanism.
NMI:	a nonmechanical influence on skeletal physiology (a gene, hormone, mineral, vitamin, drug, other humoral agents, a cytokine, a receptor, etc).
VML:	a voluntary mechanical load on a skeleton, which implies muscle forces.

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II: TWO PHASES OF THE UTAH PARADIGM'S GENESIS

To repeat, in skeletal physiology the Utah paradigm inserts tissue-level realities into the former "knowledge gap" between organ-level realities on the one hand, and cell-level and molecular-biologic realities on the other hand.

1) Phase one (for bone and bones): 1964-1983.The development of dynamic bone histomorphometry (which one of us devised (HMF) and many others improved) initiated this phase and fuelled it for about 20 years. That method depended partly on undecalcified bone sections, bone-seeking tissue-time markers like the tetracycline antibiotics that could be used safely in humans, and studies of in vivo phenomena in laboratory animals and humans [7,13-15,41,45,51]. The method revealed the following unexpected kinds of things, among others.

A) It could locate active bone formation and resorption activities in all parts of the bony skeleton. It showed those activities occur in "packets" [25], and hollow bones have four functionally-independent surfaces or "envelopes" [41,56].

B) Osteoblasts and osteoclasts combine with other cells to form independent tissue-level mechanisms called modeling by formation and resorption drifts, and remodeling by basic multicellular units (BMUs) [16,25,58]. Both mechanisms seem to use the same kinds of osteoblasts and osteoclasts to do their work [25]. As one of us (HMF) recognized ca 1964, many later experiments showed those mechanisms are independent entities. How so? In the same bone at the same time the osteoblasts and osteoclasts involved in modeling could decrease their activities or turn off, while those involved in BMU-based remodeling increased their activities. Four citations [17,18,35,36] concern the first in vivo experiments designed by one of us (WSSJ) to test that idea intentionally.

C) The method could measure bone formation and resorption amounts and rates at the cell, tissue and organ levels with useful accuracy.

D) The method began to reveal bone's tissue-level domain [25], and its tissue-level mechanisms too which were unknown as such before 1964, even though histologists described many of their features before 1900 [24,49]. Consequently pre-1964 explanations of bone physiology and disorders emphasized bone's role in calcium homeostasis and its effector-cell (EC) responses to nonmechanical influences (NMI), especially to humoral ones [40,61] (see Section #7 on "permissive agents" in Part III). Things revealed by histomorphometry as well as growing understanding also improved the design of in vivo studies of skeletal physiology in laboratory animals [21,24,28,29,42].

E) During Phase #1 it became clear that studies of NMI effects on ECs in present cell-, tissue- and organ- culture systems seldom predict or reveal NMI effects on bones in vivo [11,21,46]. Histomorphometry revealed that an essential but missing factor for success in such efforts constituted knowledge about the skeleton's special tissue-level mechanisms and functions.

Please note: Before ca 1985 things revealed by that histomorphometry met little resistance, yet still lingering exceptions include tendencies for many cell and molecular biologists, and most pharmacologists, to ignore "E" above, and/or to pay mere lip service in their thinking to bone's tissue-level mechanisms and functions [2]. That caused many "jumping frog errors" [10] (see Part III, Section #2).

Phase #2 (for bone and bones, cartilage and collagenous tissue, joints, growth plates, fascia, ligaments and tendons): 1990-??. Chiefly three things characterized this phase. To wit:(i) More research accumulated, including in biomechanics [1-9,15-39,42,43,48,50,52,55-60,63,64].(ii) More dots were connected, partly between experimental evidence and clinical medicine, orthopaedics, dentistry and pathology, anatomy, mechanical en-

gineering, and cybernetics [62]. If some scientists might view "connecting the dots" as an unworthy kind of serious scientific work, over 80 years ago connecting the dots in varied physics data provided by other people let an inquisitive Swiss postal clerk realize that E = mc2. (iii) By 2002 some important basic functions of the skeleton's organ-level and tissue-level features had clarified. In our view they stand on strong evidence [4-6,33,59] despite devils in some details [33,50,52, 53]. Recognizing them became an exercise in perceiving the big things hidden in mountains of lesser things.

This still-evolving phase should provide a foundation on which much future important skeletal research would stand. As Phase #2 bone features came to light it seemed obvious that analogs of them might occur in nonosseous load-bearing skeletal organs (LBSOs) too (i.e, in synovial joints and growth plates made from cartilage, and in fascia, ligaments and tendons made from collagenous tissue). Indeed, connecting the dots between diverse evidence and cybernetics [62] did and still does suggest those analogs exist in nonosseous LBSOs.

Accordingly and in metaphor, we argue here that lessons from bone could tell where gold lies in collagenous-tissue and cartilage-tissue "countries", so "prospectors" (skeletal researchers) could go directly there to mine it instead of wasting time looking for it.

So said, the general Phase #2 bone features could apply to all LBSOs [11,12], given extra entries to account for plastic flow in tension (irreversible stretching) of collagenous tissue and cartilage (the latter can also develop plastic flow in shear [12]), and to account for some essential properties of joint size, shape and surface congruence.

The following Phase #2 features come from [11,12].

Twelve proposed salient features of all LBSOs. 1) Mammalian skeletons have mostly LBSOs (load-bearing bones, joints, growth plates, fascia, ligaments, tendons) and some nonLBSOs (see Table 1). 2) LBSO organ-level functions include three things: (i) Having enough strength to keep VMLs from breaking or rupturing an LBSO suddenly or in fatigue [11]; (ii) preventing irreversible stretching in tension in collagenous-tissue LBSOs; (iii) and having the joint surface size, shape and congruence relative to the VMLs on, and relative to the neuromuscularly-imposed motions of, a growing joint that would minimize arthroses [12]. 3) By the time of birth gene expression patterns in utero have created the "baseline conditions" of all LBSOs, including their basic anatomy and relationships, their basic neuromuscular anatomy and physiology, and the biologic "machinery" that will adapt LBSOs to postnatal VMLs.

That machinery would include seven tissue-level features. 4) In each LBSO at least one "nephron-equivalent mechanism" (NEM) called modeling can increase its strength, while in acute and thereafter persistent disuse at least one different NEM, a disuse-mode mechanism, can reduce its strength. 5) After birth strain-dependent signals can monitor the relationship between each LBSO's strength and its VMLs, 6) and threshold ranges of those signals plus dedicated signaling systems [26,27,33,39] should help to turn the "nephron-equivalent functions" (NEFs) of those NEMs on and off. 7) Each LBSO can detect and repair limited amounts of its microscopic fatigue damage (microdamage, MDx), and MDx would have its own operational threshold range in each tissue of an LBSO [5,11, 12]. Failures of that arrangement can cause nontraumatic and stress fractures in bones, nontraumatic ruptures of tendons, ligaments and fascia, and arthroses in joints [12]. 8) Cartilage and collagenous tissues have mechanisms that can detect and limit, and correct limited amounts of, plastic flow in tension (irreversible stretching), and in shear too for cartilage [12]. 9) A chondral MST can make joint size and

shape, and articular-surface congruence, fit the VMLs on, and the typical voluntary motions of, growing joints [12]. 10) Combining all such things plus feedback between them would construct tissue-level negative feedback systems called mechanostats (MSTs) [11,25,39]. Michael Parfitt called bone's mechanostat the "....most important unsolved problem in bone physiology." [47]. Bone, cartilage and collagenous tissues should each have at least one MST [11,12], and different kinds of cartilage might even have their own MSTs. Likewise for different kinds of collagenous tissue.

11) After birth and on earth, MSTs would adapt LBSO strength and architecture chiefly to muscle strength instead of to body weight. Why? Trauma excepted, on earth lever-arm and gravitational effects make muscles put by far the largest loads on LBSOs [4,6]. For such reasons, and because LBSOs cannot foresee and adapt to one-time loads from injuries, strong muscles should usually associate with strong LBSOs, weak muscles should usually associate with weak LBSOs, and muscle strength should strongly if indirectly affect the postnatal strength and architecture of all LBSOs. Those things do occur, and presumably MSTs orchestrate them. In growing joints the articular cartilage MST would also help to adapt joint-surface size, shape and congruence to the joint's VMLs and neuromuscularly-imposed motions [12] (we realize that some authorities think mainly genetic mechanisms predetermine such features, but we respectfully disagree).

12) It seems probable at present that a laddered "general biomechanical relation" would apply to all healthy postnatal LBSOs. If so, MESr < "E" < MESm << MESp <<< Fx [12]. In that relation let the MESr threshold denote an LBSO's disuse-mode mechanism and response, below which its maximal response turns on and above which it begins to turn off; let "E" denote the typical peak strains caused by its VMLs on a healthy, normally-adapted LBSO; let the MESm threshold denote the LBSO's modeling mechanism and response; let the MESp denote the LBSO's operational MDx threshold(s); and let Fx denote an LBSO's ultimate strength. One could express those things as strains or corresponding stresses. Since each thing would constitute a range instead of a true step function [62], in a first approximation the center of each range could define its "set point".

Please note:(i) Bone people studied the above things more intensively than people working with cartilage, collagenous tissues and organs made with them, so in 2002 evidence supporting the bone features was more abundant, firmer and better accepted. Hence numerous opportunities for targeted and important chondral and collagenous tissue future research. (ii) Like the situation for bone [11,46], the above features of nonosseous LBSOs probably do not function normally in current in vitro systems [11,12]. If so, studying their in vivo responses to various things would depend strongly on further live-animal research [12,13,21]. That could invalidate the proposal by some animal rights activists that in vitro research eliminates the need for continued in vivo research. (iii) The above bone features [11,25,33,39] have many implications for things like the nature of "osteoporosis" and how to diagnose, study and treat it [8,11]. Those bone features also concern the healing of fractures, arthrodeses, bone grafts and osteotomies [12], and the service lives of load-bearing endoprostheses [11]. (iv) One nephron-equivalent function (NEF) of bone modeling increases whole-bone strength where the above strain-dependent signals exceed bone's modeling threshold range (the MESm). A disuse-mode bone remodeling function (another NEF) reduces whole-bone strength by removing bone only next to or close to marrow when strain-dependent signals stay below a bone's disuse-mode remodeling threshold (the MESr) [11,58]. (v) Bone modeling and remodeling have further functions not discussed in this

text.

(vi) Intermittent doses of parathyroid hormone as well of some prostaglandins can incite modeling formation drifts that strengthen compacta and spongiosa [21,36,43,57,59,64]. That could cure the whole-bone strength deficits in most osteopenias and osteoporoses [21,59], and in the USA it led to an approved treatment for such disorders in humans. Some bisphosphonates can depress BMU-based remodeling and help to prevent osteopenias [3,21,42], while estrogen can make extra bone accumulate next to marrow, which minimizes its contribution to whole-bone-strength [11,21,55].

III: COMMENTS

1) A four-step analytical strategy. A powerful but simple strategy that descends the ladder of biologic organization helped to understand the things in Phase #2 [11]. To explain, teaching already-known renal physiology can begin with Step #1: describing organ-level functions provided to the body (here, by kidneys). Step #2 describes how tissue-level mechanisms, functions, structures and other features help to provide the organ's functions (which nephrons do in kidneys). Step #3 would describe how cell-level and molecular-biologic features (varied cells, intercellular materials, genes, cytokines, related mechanisms, ultrastructure, etc.) support tissue-level (nephron) functions directly, and only indirectly support the organ's (kidney's) functions. All that information would let Step #4 describe the pathogenesis of known renal disorders, or even predict not yet recognized ones.

Nota bene: Following that four-step strategy could also help to improve our understanding of skeletal physiology, which most contemporary physiologists would agree needs it. Sections #2, #3 below concern an application of that strategy.

2) On microcosms and macrocosms. As M Schermer noted [54], in physics and astronomy "microcosms cannot predict macrocosms", even though the former can help to explain the latter after other things revealed the latter's features. Thus one cannot predict galaxies, stars and cars solely from knowledge about atoms. Yet atoms can help to explain already-known features of galaxies, stars and cars.

Trying to predict a skeleton's Step #1 features (its organ-level functions) only from its Step #3 features (which comprise cell-biologic and molecular-biologic ones) would try to predict a skeleton's macrocosm from its microcosm. Historically most if not all such efforts failed, and they usually caused "jumping frog errors" too (of which one of us (HMF) made his share in the past) [10]. Four examples of such errors follow. (i) Recognition in the early 1960s that calcitonin hindered osteoclastic but not osteoblastic activities in vitro suggested it would increase bone "mass" and cure "osteoporosis". Yet when given in vivo it did neither. That constituted predictions of two organ-level effects (a macrocosm) from effects on skeletal cells in vitro (a microcosm). (ii, iii) The 1945-1960 ideas that estrogen or supplemental dietary calcium should increase bone "mass" and cure "osteoporosis" met the same fate. (iv) Authors of a study of mechanical loading effects on the growth rate of mammalian long-bone growth plates concluded that even low loading rates depressed that growth [44]. If so bones in normal limbs would become shorter than corresponding bones in paralyzed or partly deloaded growing limbs. Yet physicians know the opposite occurs; growing bones in normal limbs always become longer than corresponding bones in paralyzed limbs, while numerous researchers found that growing bones in partly deloaded limbs in experimental animals never grew longer than in control limbs [12,19-21,35,37]. Ignoring the dots between other evidence helped to cause this error (see also Section #9 below).

3) On cell and molecular-biologic research and knowledge. Skeletal cellular and molecular-biologic research created very rich, valuable, chal-

Table 2. Examples of clinical problems for which the Utah paradigm should lead to the kinds of improvements suggested in the text (as discussed in [11,12]).

Osteopenias	Osteoporoses	Osteomalacias
Bone healing	Tendon healing	Ligament healing
Cartilage healing	Chondrodystrophies	Osteogenesis imperfecta
Scoliosis	Dwarfism	Limb torsions
Club foot	Pes planus	Inguinal hernia
Some aneurysms	Varices	Chorda tendinae ruptures
Osteoarthritis	Stress fractures	Spontaneous tendon ruptures
Scleroderma	Genu varus/valgus	Hip dysplasia
Spastic deformities	Osteopetrosis	Aseptic necroses
Myopia	Hyperopia	Tennis elbow
Carpal tunnel syndrome	Cubitus valgus	Frozen shoulder syndrome
Joint contractures	Neuromas	Esophageal strictures
Erb's palsy	Arthrogryphosis	Slipped epiphysis
Dupuytren's disease	Keloid	Osteochondritis dissecans
Blue sclerae	Scleroderma	Myositis ossificans
Patella alta	Patella baja	Patellar malalignment
Congenital hip dysplasia and dislocation		Pericardial stenosis
The regional acceleratory phenomenon (RAP)		Neurotrophic joints
Patent ductus arteriosus		

lenging, active and popular fields of study. In that regard, while each "target" for all LBSOs in Phase #2 would need testing and more study, each Step #2 target in that phase also identifies something that cell and molecular-biologic features and research must explain. Yet how Step #3 features (cellular and molecular-biologic ones) support Step #2 skeletal targets (tissue-level ones) remained nearly unstudied and unknown in 2002 (if opinions abound, proof does not). That oversight created an important "knowledge gap" in skeletal physiology (again, all Step #2 targets constitute tissue-level ones). Filling that "knowledge gap" provides numerous opportunities for especially useful future skeletal research (see also Section #6,(iv) below). In our view such work would lead to improved diagnosis and management of many skeletal and some extraskeletal disorders, of which Table 2 lists examples.

4) On the skeleton's multiple MSTs. Rephrasing Prof. Parfitt's statement about bone's MST might apply his observation to all LBSOs. To wit: "Understanding the skeleton's several MSTs poses one of the most important problems in skeletal biology today.". In American slang, MSTs should sit in the skeleton's "cat-bird seat", and the still-unknown cells and genetic mechanisms that determine the nature and values of the three thresholds in the "general biomechanical relation" mentioned earlier would help to construct that seat.

5) On questions and disagreement. Reasonable people can explain the same facts differently, and can even disagree about which facts are germane to a problem. Consequently some such people could question some things in this article. Presumably only more work, evidence and time could resolve such issues to the satisfaction of the general skeletal science and clinical communities. Because the issues concern important world health-care concerns, and because they concern a foundation on which others could build in the future, such issues deserve open discussion and resolution. After all, in the past resolving controversies always fuelled progress in all science. Fostering conferences like the Univer-

sity of Utah's Hard Tissue Workshops might hasten the above resolution [14]. How so? One of us (WSSJ) made parts of many of those Workshop programs consider challenges to some then-accepted "wisdom", so reasonable people could discuss them rationally in friendly and informal circumstances. Indeed, that helped the Utah paradigm to hatch.

6) What about resistance to the Utah paradigm? That resistance might cause confusion and controversy about this paradigm for years to come. At least four things could reduce that resistance. (i) Time. (ii) More pertinent evidence, which however accumulates so slowly that holding one's breath until the resistance stopped could invoke the suicide exemption in one's life insurance policy. (iii) A quip attributed to Planck, the physicist, might apply here: "Resistance to many good scientific ideas only ceased when their strongest opponents died.". That brings to mind Copernicus, Semmelweiss and Wegner, who died before their ideas found general acceptance [11].

(iv) How rapidly the above areas progress could depend strongly on making cell- and molecular-biologic expertise and work collaborate with live-animal work and expertise and with the Utah paradigm's insights. An ingenious example of that "in vitro/in vivo collaboration" -- and of "drug targeting" by "designer drugs" too -- appeared recently in Science [31]. Partly for reasons given earlier (see Phase #1,E in Part II, and Section #3 in Part III), many future skeletal scientists and clinicians should learn to collaborate in that way [11,12,21,31]. Parenthetically and perhaps not coincidentally, a coauthor of that report in Science, Prof. Parfitt, had suggested that "in vitro/in vivo collaboration" during a Hard Tissue Workshop discussion in the late 1980s (at the time he called it "molecular histomorphometry").

7) On permissive agents. (i) In former views things like genes, and humoral agents like hormones, calcium, vitamins C and D and some drugs, dominated skeletal health, and by implication the strength of skeletal organs. Such ideas still linger [2].

(ii) Yet in LBSOs most such agents, especially humoral ones, really act as "permissive" ones the organs and their NEFs need in order to function properly (as cars need fuel, motors, wheels, etc), but most such agents do not "drive" skeletal health and strength in time and anatomical space. They cannot duplicate or replace the mechanical-loading and muscle-strength effects on Lanyon's "functional adaptations" of LBSOs to their mechanical usage [33].

(iii) Permissive humoral and local agents have a special behavioral property. To wit, their deficiencies 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 already healthy bodies; vitamin D and thyroxine deficiencies cause short stature, yet their excesses do not cause giantism (but can cause toxicity); as one of us suggested several years ago (HMF), growth hormone permits whole-bone strength to increase during adaptations to larger bone loads, but a clever Australian study showed that lacking such loads the hormone does not increase that strength [9]. Etc., etc.

8. Aging and genetic effects. How aging and genes affect all the above things, especially the mechanostats and their thresholds and dedicated signaling systems, remained nearly unstudied and thus unknown in 2002 AD.

9) On communication between skeletal basic scientists and clinicians. Most skeletal basic scientists (mostly M.As. and Ph.Ds.) and most skeletal clinicians (mostly M.Ds.) have very different training, experience and work. For over 70 years that caused communication problems between skeletal basic scientists and clinical specialists, problems that could trouble and frustrate, and even harm the careers of, young people caught

up in them in the future. How so?

(i) Clinicians tend to assume basic scientists already know what they need to know about clinical disorders and their pathology. (ii) Basic scientists tend to assume that very competent skeletal clinicians are also masters of skeletal physiology.

In our experience both those assumptions usually err. In fact few competent clinicians who work with skeletal problems constitute masters (sensei) of skeletal physiology, while few basic scientists who work on skeletal problems really know much about skeletal clinical and pathologic features.

(iii) That neither the scientists nor the clinicians know enough about each other's "business" to know which findings, experience and questions in one domain bear on the other's concerns, only accentuates that communication problem. The situation in Section #6,(iv) above exemplifies this problem. Its authors were not experienced clinicians and probably did not discuss their conclusion with orthopaedic surgeons in their own medical school, who could have told them their conclusion erred. Talking with such clinicians could have prevented that error.

Hence another virtue of the University of Utah's Hard Tissue Workshops: One of us (WSSJ) repeatedly made basic scientists and clinicians get together and talk to each other about disorders and other problems of mutual interest.

IV: CONCLUSION

In our crystal ball skeletal scientists and clinicians approach such an exciting future that we wish we could set the calendar back, begin our careers anew, and participate in that future's unfolding. But: Only if we could still know that the seed of the Utah paradigm is a road leading to that future as well as a foundation on which to build better things. It took each of us over 55 years to learn and understand enough to write this article and say such things, and neither of us would like to repeat what he went through during that process.

But of course one cannot set the calendar back. To quote from the Rubiayat:

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

Ergo, younger people than us will walk the above road and do that building. To every one of them we both say here: Have at it! Good fortune! During your life's work try to follow this Confucian rule (it can be tough at times but it pays off in the long run): What you would hate if done to you, do not to others.

And, vaya con Dios

Summary

Long ago the Roman emperor Marcus Aurelius Antoninus said in effect, "All present things are seeds for the future.". Here two senior citizens would like to share such a seed and some of its future effects with younger people. The seed provides a foundation on which other people can build better things in the future. The seed comprises updated knowledge and ideas about skeletal physiology, and we believe nurturing it will lead to considerable improvements in a), understanding that physiology, b) in the classification, diagnosis and management of its many disorders, c) and in research devoted to such things.

That updated knowledge led to the Utah paradigm of skeletal physiology, which injects tissue-level realities into the former "knowledge gap" between organ-level realities and cell-level and molecular-biologic knowledge. The paradigm concerns bones, joints, growth plates, fascia, ligaments and tendons, as well as the tissues that construct them. Belatedly-recognized features of organs made with those tissues include tissue-level functions and insights, some biomechanical realities, roles of muscle strength, and mechanostats. The paradigm identifies targets for

unusually productive future skeletal research that should lead to the above improvements. To expedite progress much such research might depend on the "in vitro/in vivo collaboration" explained in Section #6,(iv) of this article's Comments. A powerful analytical strategy helped to reveal such things.

Omens suggest the resulting advances could take so long to mature that we would not live to see them. But people like us have had our day, so this field's future and the above matters belong to younger people. If people like us helped to create a foundation on which to build better things in the future, younger people than us will do that building when and how they wish, while they walk their own roads and follow their own dreams and ambitions in coming years.

So be it.

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