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Perspective Article

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Why should many skeletal scientists and clinicians learn the Utah paradigm of skeletal physiology?

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Abstract

Adding later facts and ideas to a universally accepted "1960 paradigm" of skeletal physiology led to the still-evolving "Utah paradigm". The ASBMR's William Neuman award in 2001 to one of the latter paradigm's architects (HMF) suggested that physiologists began to view it as a valid supplement to its predecessor. Nevertheless it diffused poorly among most SSCs (Skeletal Scientists and Clinicians, plus all others who work in any way on skeletal matters), even though success in the quest for knowledge and recognition by many of them could depend on learning that paradigm's insights. Those insights can help to minimize serious errors in some experimental designs and in interpreting some kinds of data. To explain how success in that quest could depend on the Utah paradigm requires explaining the nature of the above errors, some features of both paradigms, some implications of the newer one, *and when that quest's success might not require knowing the Utah paradigm*. A three-part message distilled from the past for present and future SSCs concludes the article. It took decades to understand such things and find effective ways to explain them, and both matters probably need improvement (to paraphrase Pogo, "We met the enemy and perhaps it was us more than them"). During those decades the author changed from an active SSC hunter-player to a spectator, known to some as a feisty eccentric old dinosaur (FEOD) (Note A). So here a voice from the past would speak to present and future SSCs.

Keywords: Bone, Joint, Tendon, Ligament, Physiology, Biomechanics, Healing, Mechanostat

Introduction

Let a two-phase "thought experiment" set a stage for a message to present and future SSCs (i.e. Skeletal Scientists and Clinicians plus all others – nurses, techs, teachers, physical therapists etc.– who do or will work in any way on skeletal problems). The experiment: A hearing physiologist positioned healthy frogs at a starting line.

(A) A loud noise behind them made them jump.

(B) But after amputating both hind limbs the frogs did not jump.

Because $p<0.0001$ and $r^2>0.95$, he asked the prestigious Auditory Journal Of Key Evidence (AJOKE) to publish this discovery: *Frogs without hind limbs are deaf*.

Please! Do not reach for a tranquilizer or Martini, at least not yet. That thought experiment only helps to make the following two-part point, and out of respect for SHIP (seniority has its privileges) why not allow an old dinosaur enough wiggle room to make it?

i) "Selective ignorance" that jumping needs legs let the above scientist devise a false hypothesis about hearing in frogs from an association between hind legs and jumping.

ii) I contend that many respected SSCs who had not learned the Utah paradigm of skeletal physiology inadvertently made analogous *jumping frog errors* when designing experiments or evaluating evidence or hypotheses (I made my share of such errors in earlier times, so *mea culpa;* (see also Section #3 in Part III below). True: Most humans over four years of age learned that jumping takes legs. But also true: At present very few SSCs have learned the Utah paradigm (not the same thing as having heard about it).

While some readers might view the contention in "ii)" as evidence that my elevator does not reach the top, this article would like to share with them an explanation of that contention and some general predictions the explanation led to. Four things merit initial comments.

(i) The article's views and statements depend on over 50 years of work as an orthopaedic surgeon, investigator, teacher, histologist and amateur pathologist-biomechanician, as well as of learning from mistakes, (mine and those of others; Note B,a).

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(ii) The article concerns general issues, not small ones as defined later in Section #3, Part III; it leaves discussion of any devils in the details to other times and places (Note B,b).

(iii) Sometimes experience and hindsight can reveal things that youths do not perceive.

(iv) As PB deMenocal noted, the past helps to understand the present[1], so this article reviews some history and ideas, and it suggests how they "come together" in the present but why most SSCs still ignore that. Then it distills a message from such things.

I. Pertinent history and ideas

M Schermer noted that people tend to interpret facts "through the colored lenses" of their ideas[2]. Eric Hoffer said that thus: "*We usually see only the things we are looking for – so much so that we sometimes see them where they are not*". Some history and ideas that bear on this article's message follow.

1) *A common purpose of load-bearing skeletal organs*. Most contemporary SSCs would agree that a mammal's load-bearing bones, joints, ligaments, tendons and fascia should have only enough strength to keep voluntary loads from fracturing or rupturing them or wearing them out, or from making them hurt, whether those loads are persistently subnormal, normal or supranormal in size. That relationship between an organ's strength and its mechanical usage was called *Proposition #1* elsewhere[3].

2) During evolution few mammals that did not satisfy Proposition #1 would have reproduced. Why? Most prepubertal mammals handicapped by a fracture, tendon rupture or arthritic joint would have provided dinners for hungry predators, as handicapped zebras still do for hungry lions. Before the K-T extinction at the end of the Mesozoic era ≈ 65 million years ago, did carnivorous dinosaurs threaten early mammals in that way?

In that regard, by early middle age most mammals have produced and raised their young, and their load-bearing skeletal organs still satisfy Proposition #1. Yet increasing health problems can limit the survival of aged mammals. Could this mean that by the Mesozoic era evolution found how to let mammals *as a class* live long enough to multiply and endure, but it left finding how to let most aged mammals survive as healthy *individuals* to Cenozoic-era research by *homo sapiens*?

3) An elegant design stratagem would make its loads determine the strength of an organ intended to carry them without breaking, rupturing or wearing out. Achieving that could satisfy Proposition #1 <u>if</u> special criteria determined an appropriate *relationship* between such an organ's strength and the loads on it.

4) Historically, no matter how firm the belief in a science's *accepted wisdom*, in time other views modified or replaced it[4-6]. Most such changes met resistance and caused controversies. Examples: Copernicus' idea of a heliocentric instead of a geocentric solar system, and Semmelweiss' idea that the sepsis ("childbed fever") that killed too many just-delivered mothers in the 1600s came from the contaminated hands of doctors and nurses. His idea was viciously ridiculed while he lived, but proven correct after he died by bacteriologically-aware people. Also, Wegner's idea in 1912 of continental drift (plate tectonics). Other geologists ridiculed it but found it was correct after he died.

Such history lessons suggest great caution in viewing a science's accepted wisdom as a religion taught by some "high priests" to be defended, Taliban-like, from all challenge and change.

5) *Hidden assumptions* are not consciously made, realized or verbalized. All mortals make them but sometimes they can blind one to observations and/or ideas that are needed to understand a problem. When the resulting inadvertent errors became accepted wisdom, recognizing and verbalizing the assumptions that led to those errors usually caused controversies.

6) *Selective ignorance* affects all people; no mortal knows everything. But it caused problems when understanding some matter required knowing something one did not know, and if the matter was important the problems could be serious. While selective ignorance in the above frog experiment was an artifice, today most SSCs do not know the Utah paradigm. If some of them mentioned some of the jargon used to express it, their discussions often showed they did not understand (or perhaps accept?) what the jargon signified[4,6].

Ignorance, whether selective or not, is *not* stupidity. In some situations it can be quite naive, but *rejecting* knowledge or ideas needed to understand or resolve a problem could be stupid indeed.

7) *When hypotheses competed*, some people thought a long-favored older hypothesis invalidated a new one so they rejected the latter. Yet ancient Greeks knew no hypothesis can invalidate any other; only facts can do that. Facts can include associations that might suggest a cause-effect relationship between, say, "A" and "B". But sometimes selective ignorance can suggest a study thought to concern "A" and "B" concerned "C" and "D" instead, as in the above frog experiment (where "A,B" represented noise and hearing, and "C,D" represented hind legs and jumping).

In the past (and probably in the future),

A) validating hypotheses caused far more controversies than validating the facts that led to them,

B) more than one hypothesis could explain most collections of facts,

C) resolving controversies always improved an affected science or other field,

D) and good hypotheses proved much more useful than the facts that first suggested them (examples: The genetic code, and Einstein's $E = mc^2$).

8) *On a feature of biologic organization*. Biologic systems organize and combine numerous small things to make large things like skeletons. Like skeletons, cars combine many assemblies and thousands of parts, but the properties of any one assembly or part cannot reveal its role(s) in the car, nor how the car works nor its purpose(s). Equally, quarks in nuclear physics (a "microcosm") cannot predict the chemical properties of elements nor the physical properties and

function of steel, bone and cartilage ("macrocosms"). An analogous property applies to skeletons and later comments will concern it.

9) *On the "1960 paradigm" of skeletal physiology*. Before 1950 all physiologists recognized the existence, roles and importance of tissue-level mechanisms in the physiology and disorders of soft tissue organs. Examples include renal nephrons, hepatic lobules, pulmonary alveoli, the adrenal medulla, Peyer's patches in the gut, salivary gland acini, the optic chiasm, and sweat glands.

Yet before 1964 most of the skeleton's tissue-level "nephron-equivalent" functions[3] were not recognized. Before 1940 that made physiologists try to explain skeletal physiology and disorders mainly in terms of "effector cells" controlled by genetic and humoral factors. After 1940 that kind of reasoning added cell and molecular biology and biochemistry at work in those cells and, after 1980, in their precursor cells and in cell-cell and cell-intercellular matrix interactions. Through the "lens" of such ideas skeletal physiology could seem like a biochemical-genetic game played by humorally-modulated effector cells to pursue mainly genetically-predetermined biochemical goals[7-14].

Here "effector cells" mean those that make or resorb skeletal tissues, meaning short-lived osteoblasts and osteoclasts in bone, chondroblasts and chondroclasts in cartilage, and fibroblasts and multinucleated giant cells (could one call them "fibroclasts"?) in collagenous tissue.

The above ideas became the kernel of a universally-accepted 1960 paradigm of skeletal[3] physiology. Yet hindsight revealed hidden assumptions in it that still linger[7,11,12]. Among them,

A) the skeleton lacked tissue-level nephron-equivalent mechanisms and functions, so its effector cells were its key players (all false);

B) mechanical loads, muscle strength and neuromuscular physiology had little if any effects on the development and strength of load-bearing skeletal organs after birth (all false);

C) and genetics *predetermined* the development and most of the postnatal strength (and health) of such organs, which humoral agents could support and/or modulate (partly false).

Adherents of that 1960 paradigm still include most SSCs, so they keep trying to explain skeletal physiology and disorders in ways that fit the constraints of its hidden assumptions (see Section #2 in Part III).

10) *On the "Utah paradigm"*. Nevertheless, in healthy mammals strong muscles usually associate with strong load-bearing skeletal organs, and persistently weak muscles usually associate with correspondingly weak organs[3,15]. The still-envolving Utah paradigm that explains those associations began to gel by 1995[3,16-19], partly at the University of Utah's seminal Hard Tissue Workshops[20]. It explains how the strength of load-bearing skeletal organs adapts to the typical voluntary loads on them in ways that would satisfy Proposition #1.

That explanation depends on the skeleton's nephron-equivalent mechanisms and functions, of which Table 1 lists some that were recognized after 1963. The largest voluntary loads on load-bearing skeletal organs come from muscle forces[21], not body weight as formerly thought[22]. Strain-dependent signals created by those forces on such an organ[17,23,24] help to make its biologic machinery (see Part III below) adapt its strength to those forces according to genetically-determined *criteria* of "normal", but in a special way. The hundreds of such organs in the mammalian skeleton would not have hundreds of different criteria for their strength. Instead *general* criteria would control the *relationship* between the *strength* of any structural tissue and the *size* of the loads on it, and apparently similarly in the mouse, human and elephant, and in birds, reptiles and amphibians too. *Bone, cartilage and collagenous tissue would have their own criteria*. That would make a load-bearing organ's loads an independent variable, and its strength a dependent variable. Thus bigger loads could force the biologic machinery to make such organs stronger, but stronger such organs could not force the loads on them to increase in size.

Important such "criteria" would include the modeling and disuse threshold ranges for bone, cartilage and collagenous tissue[3]. The disuse thresholds for cartilage and collagenous tissues would analogize the threshold that seems to control the switching between conservation- and disuse-mode bone remodeling[3,25]. Corresponding strain ranges can express those thresholds, and the centers of their ranges can define their "set points".

II. A kernel of the Utah paradigm: the mechanostat hypothesis

Two analogies and eight comments can help to explain this mechanism[17,24,26-28]. It took years, mistakes and help to recognize its many parts and see how it works and its probable chief purpose. That involved a measure of "seeing what others saw, but thinking what they had not".

1) A car analogy (in six parts)

A) Let a load-bearing organ's voluntary mechanical usage analogize a car's driver.

B) Let tissue-level mechanisms and functions like those in Table 1 analogize the car's steering, brakes, accelerator and other assemblies.

C) Let skeletal effector cells analogize the car's wheels. Just as knowledge only about wheels could not explain why a car drove to Boston instead of Chicago, effector-cell knowledge alone should seldom explain why a skeletal organ developed a given disorder (a likely exception: the osteoclast defect(s) in osteopetrosis).

D) Let nonmechanical things like those in Table 2 be like the fuel, ignition, battery, engine, transmission and other such things in a car: Needed to drive it but not its driver, steering, accelerator or brakes. They would represent mainly "permissive" agents in tissue- and organ-level skeletal physiology[28], although in earlier views they dominated its control.

E) Combining "A-D" would form a complex negative feedback system called a "mechanostat". Bone, cartilage and collagenous tissue should have their own mechanostats to orchestrate their adaptations in time and anatomical space to

postnatal mechanical challenges.

F) Those three mechanostats would have the chief common purpose of making load-bearing skeletal organs satisfy Proposition #1. If so, stronger muscles should (and usually do) make mechanostats make correspondingly stronger organs, and persistently weak muscles should (and usually do) make correspondingly weak organs. In that process a skeleton's mechanical usage and loads would represent an independent variable while the mechanostats would join the dependent variables, as suggested in a seminal recent article[27].

Of the mechanostat hypothesis AM Parfitt said: "*... the mechanostat ... is the most important unsolved problem in bone biology...*"[6]. Other publications suggest how it would work in bone[15-17,24,29,30,32-34], cartilage[16,25,35-38], collagenous tissue[16,33,39-41], and organs made from them.

2) A thermostat analogy (in four parts)

A) The skeleton's modeling and remodeling (or disuse) threshold ranges should act much like the thermostats that control a room's temperature. One thermostat controls the furnace that adds heat to raise that temperature. A second thermostat controls the cooling system that removes heat to lower that temperature. Let the two thermostat settings be like the modeling and disuse thresholds, respectively, for bone, cartilage and collagenous tissue. Let the room's heat content (expressed in kilogram-calories) be like a load-bearing organ's strength, and let the room's temperature be like the modeling and remodeling thresholds' set points.

B) When that temperature falls below the furnace thermostat's setting, the furnace turns on. At higher

For Bone
Mechanically-controlled modeling by drifts, and two longitudinal bone growth mechanisms. Disuse- and conservation-mode remodeling by BMUs.
Internal threshold ranges for modeling, BMU-based remodeling, and microdamage.
Detection and repair of limited amounts of microdamage.
A mediator mechanism in marrow that affects modeling and remodeling of bone next to or close to it.
A four-stage healing mechanism that includes a regional acceleratory phenomenon.
The baseline conditions and the basis of transients and steady states.
Combining the above things would form bone's mechanostat.
For Cartilage
Mechanically-controlled chondral modeling, and chondral-dependent longitudinal bone growth. Disuse-mode responses; and one or more "chondrons".
Internal threshold ranges for modeling, disuse-mode responses, and microdamage.
Detection and repair of limited amounts of microdamage.
Irreversible creep detection and compensation mechanisms (and thresholds?).
The endochondral ossification mechanism.
A four-stage healing mechanism that includes a regional acceleratory phenomenon.
The baseline conditions and the basis of transients and steady states.
Combining the above things would form the chondral mechanostat.
For Collagenous Tissue
Mechanically-controlled diametric modeling, and three longitudinal growth mechanisms. Disuse-mode responses, and a BMU analogous to bone's.
Internal threshold ranges for modeling, disuse-mode responses, and microdamage.
Detection and repair of limited amounts of microdamage.
Irreversible creep detection and compensation mechanisms (and thresholds?).
A four-stage healing mechanism that includes a regional acceleratory phenomenon.
The baseline conditions and the basis of transients and steady states.
Combining the above things would form the collagenous tissue mechanostat.

Table 1. Skeletal nephron-equivalent (IO-Biomechanical) mechanisms and functions.

temperatures it turns off. Similarly, excessive strains would indicate an organ is too weak for the loads on it, so its modeling threshold(s) would make modeling strengthen it. After that sufficiently reduced subsequent strains, mechanically-controlled modeling would turn off so the organ's strength would plateau at the new and higher level.

C) When the room temperature exceeds the cooling system's thermostat setting, that system turns on to remove heat. At lower temperatures it turns off. Similarly, persistently minimal strains would indicate an organ is far too strong for the loads on it, so its disuse threshold(s) would make disuse-mode activities reduce its strength. After that sufficiently increased subsequent strains, that mechanically-controlled activity would turn off so the organ's strength would plateau at the new and lower level (but see (iv) in Section #3 next).

D) This thermostat analogy fails in that lowering both thermostat settings would *reduce* a room's heat, but lowering both skeletal thresholds would make mechanostats *increase* a load-bearing organ's strength. The converses would hold true too.

3) Eight further features

(i) Mechanostats would make a skeleton's voluntary mechanical usage control in time and space the postnatal strength and health of its load-bearing organs. The modeling and disuse thresholds represent criteria that could define the upper and lower limits, respectively, of "normal" for such an organ's strength *relative to the size of the typical peak voluntary loads on it*. When and where the organ's strains exceeded its modeling threshold(s) it would need more strength, and modeling would provide it. When its strains stayed below its disuse threshold(s) it would have far too much strength for those loads, and its disuse responses would reduce its strength.

(ii) Changing those thresholds should make the mechanostats change a load-bearing organ's strength correspondingly. Also, the appositional rates of lamellar bone modeling formation drifts and the formation phase of BMU-based remodeling have natural limits that restrict how quickly they can respond to a challenge and correct some error[9,13]. Genetic factors and/or some humoral agents could change or modify those features[23,24,42].

(iii) Those mechanostats would include at least two groups of nephron-equivalent mechanisms. A *modeling* group uses different mechanisms in bone, cartilage and collagenous tissue to increase but seldom if ever decrease a load-bearing organ's strength[15]. A *disuse-mode* group (BMU-based disuse-mode remodeling in bone[3], and analogs of it in cartilage[3,43] and collagenous tissue[13,40,44]) reduces but does not increase such an organ's strength. Apparently neither mechanism provides the other's function so those three tissues would need their own modeling and disuse thresholds.

(iv) By the time of birth genetics has created a skeleton's initial anatomy, relationships and mechanostats. Those *baseline conditions*[3] would be like an equation's initial conditions.

To those baseline conditions, the mechanostat would add the adaptations of load-bearing skeletal organs to any *postnatal* challenges. Then, at any time after birth the *differences* between the architecture and strength of such organs in limbs paralyzed at or near birth, and in contralateral normal limbs, should reveal the postnatal adaptations to mechanical demands in the normal limbs. The paralyzed limbs would reveal the baseline conditions, influenced by genes and humoral agents but not by normal mechanical loads. That might answer a seldom-pondered question: Why do skeletal organs never disappear completely in total and permanent disuse? Perhaps it is the baseline-conditions parts that persist.

(v) Because *muscle strength* should dominate mechanical control of the mechanostat's postnatal workings, muscle anatomy and strength and neuromuscular physiology should, and do, strongly influence the architecture, physiology, development and strength of the skeleton's load-bearing organs after birth. In 1999 that realization led Dr. GP Lyritis in Greece to form the International Society for Musculo-skeletal and Neuronal Interactions (ISMNI), and its own journal. Earlier, similar realizations made Prof. WSS Jee study those relationships[44] and organize the University of Utah's famous Hard Tissue Workshops[20].

(vi) Varied evidence suggests some little-studied mediator mechanism in marrow, and another in periosteum, helps to control modeling and remodeling next to or close to those bone surfaces or "envelopes"[46,47].

(vii) The mechanostat hypothesis can answer a question posed years ago by Ker et al.[19]: In healthy mammals, why does the strength of every tendon exactly fit the strength of its muscle? Analogous questions could apply to bones, joints, ligaments and fascia.

In answer, the mechanostats would make voluntary mechanical loads determine most of the strength of load-bearing organs after birth, and the modeling and disuse thresholds would determine what constitutes normal strength *relative to those loads* (recall Section #3 in Part I?).

(**mainly as "permissive" agents**)		
Hormones	Vitamins	D metabolites
Dietary calcium	Other minerals	Cytokines
Paracrine effects	Autocrine effects	Cell-cell interactions
Dietary protein	Dietary lipids	The genome
Gene expression	Ethnic origin	Occupation
Gender	Some diseases	Malnutrition
Age	Apoptosis	Ligands and receptors
Medications	Toxins	Other Artificial Agents
Cell-intercellular matrix interactions		

Table 2. Nonmechanical factors that could help to modulate skeletal adaptations.

Three examples follow.

A) Attaching strong muscles to the tenuous tendons of long-paralyzed muscles, a common surgical procedure before polio vaccines, led in a year or more to corresponding increases in the thickness and strength of those tendons in ways that satisfied Proposition #1[16].

B) After a paralysis when significant muscle forces no longer act on load-bearing organs in the paralyzed limbs, they usually lose strength correspondingly but similar organs do not lose strength in contralateral normal limbs. Yet all such organs in the same individual would have the same kinds of tissues, cells and genes, and would receive the same humoral agents from the blood.

C) Electrical stimulation of paralyzed muscles can partially restore the lost bone in chronically paralyzed limbs[48].

Thus in subjects that act as their own controls, removing muscle forces can make an organ weaker and restoring those forces can strengthen it.

(viii) The above features added a tissue-level "dimension" to classical biomechanics and skeletal physiology. One might call it the biomechanics of the skeleton's Intermediary Organization[49], or "IO-biomechanics".

III. Comments and predictions

1) Which is the better hypothesis?

In essence, the 1960 paradigm extrapolated properties of its smallest constituents to the physiology and disorders of the whole skeleton, and the Utah paradigm explains why that would err (a matter mentioned again below). While those paradigms are incompatible, both are still hypotheses so more facts – and help – must reveal the better one. While growing numbers of people believe the Utah paradigm is the better one and that is my own bias, why not "stay tuned"?

2) What delayed acceptance of the Utah paradigm?

Hindsight suggests at least five reasons for that delay.

A) By example instead of with explicit sentences, beginning ca 1900 the world's million or more SSCs taught the 1960 paradigm's hidden assumptions to their students, who taught them to their students, etc. They "knew" that was correct, just as in Ptolemy's time everyone "knew" the cosmos was geocentric. Thus adherents of the 1960 paradigm's hidden assumptions could keep thinking effector cells (the "wheels") drive the skeletal "car" by obeying mainly genetic and humoral instructions[8,9,13], and that genetic factors, perhaps in effector cells, predetermine at least most of the strength of most skeletal organs.

B) However in the 1960s WSS Jee and I began to recognize the skeleton's nephron-equivalent mechanisms and functions as well as the 1960 paradigm's flawed hidden assumptions. Formerly unrecognized "connections" between facts and ideas in many disciplines, plus discussions at the Hard Tissue Workshops[20] helped to do that, but erratically and over many years. Some of the basic science disciplines included anatomy, anthropology, biochemistry, biomechanics, cell biology, cybernetics, embryology, engineering, genetics, histology, mathematics, paleontology and pharmacology. Some of the clinical disciplines included human and veterinary dentistry, internal medicine, neurology, orthopaedics, pathology, pediatrics, physical medicine, radiology and rheumatology.

C) The skeletal-physiologic puzzle's numerous "pieces" (facts and ideas) scatter willy-nilly in those disciplines, so *extremely* poor interdisciplinary communication hid and still hides many important pieces from people who needed and still need to know them. It took a long time to recognize the "connections" between those pieces, how the resulting assemblies work, and their purposes.

D) "A,B,C" above had at least five effects.

(i) They put the few original challengers of the 1960 paradigm's hidden assumptions in the very suspect position of claiming that in those matters, the world's million or so other SSCs were the ones who were out of step in the skeletal science parade(!).

(ii) In the minds of those SSCs that cast shadows on the credibility of those politically-incorrect challengers[50].

(iii) Those shadows discouraged other SSCs from testing this field's accepted wisdom. After all, what young and/or insecure SSC would want to become the statue spattered with "gifts" from pigeons, when flying with those pigeons (by staying politically correct) could help to get jobs, grants, promotions, program time and respect?

(iv) That can let even respected SSCs fall into the kind of analytical trap in the above frog experiment (but see Section #3 below). Some of my early publications contained such jumping frog errors[51], which could illustrate an old truism: "We grow too soon old and too late smart".

(v) So many people trusted the above hidden assumptions for so long that the resulting huge "conceptual inertia" made trying to expose and correct them like a lone swimmer trying to push the Titanic away from the iceberg by hand.

E) Phenomena mentioned below in Part IV, Section #1 C, and in Note C, also helped to delay acceptance of the Utah paradigm.

3) An important exception

At present that paradigm concerns long-overlooked tissue- and higher-level things in skeletal physiology, instead of small things that usually lie below the tissue level. *Thus people working on small things could suffer little if at all from not knowing the Utah paradigm* ("small" does not mean unimportant!). Small things could include things like the mechanisms of gene expression, micro-tubule turnover, formation of gap junctions, methylation of DNA, apoptosis, nitric oxide, proteoglycan synthesis, glycosolation, pinocytosis, seeking cell receptors and their ligands, how to separate different collagen types and other proteins or RNA species, and how best to measure and express trabecular connectivity, articular cartilage strength, irreversible creep (plastic flow) in

tendons, accumulating fatigue damage, etc.

However: For decades people who suggested their pet small thing caused some skeletal disorder usually ended up with egg on their faces (again, *mea culpa*). Why? Probably because so many nephron-equivalent mechanisms and other things intervene between a given gene, macromolecule, receptor or kind of cell on the one hand, and the disorders of intact skeletons on the other hand. Important such disorders include arthroses, "osteoporosis" and impaired healing. Hindsight shows such suggestions usually stood on inadequate information and/or ideas (as in the above frog experiment). In that regard, SSCs may benefit by recognizing the biologic relevance of a well-known phenomenon in physics. As M Shermer noted, "*Quantum effects wash out at large scales. Microcosms do not correspond to macrocosms*."[52]. Or, knowledge solely of its smallest constituents cannot reveal or predict the properties *and functions* of the whole system. Equally, in IO-biomechanics knowledge solely of an agent's effects on one kind of effector cell cannot reliably reveal or predict how it affects intact skeletons[49].

Long, troubled experience with such jumping frog errors taught the American FDA not to approve a drug for human use until it proved safe – as well as effective – for long times in other intact mammals. Such ideas are not new. Among others, Brown and Haglund[4], RA Evans[53], J Gorski[54], E Mayer[55], AM Parfitt[6,56], M Polanyi[57] and M Shermer[2,52] voiced analogous ones.

How could one recognize a jumping frog error? One clue occurs when an author suggests some subtissue-level thing could cause a skeletal disorder without first explaining its effects on the kinds of IO-biomechanical mechanisms and functions in Table 1. That kind of reasoning still prevails among most SSCs, but it assumes the skeleton lacks important nephron-equivalent functions so one could reliably extrapolate to an intact skeleton (the macrocosm,) the response to an agent of something in the skeleton's microcosm. If that might become possible in the future, now is not that time.

4) On the "so what?" test

Any physiologic paradigm's value should depend on its practical uses and what it can predict, the "so what?" test. A few such applications of the Utah paradigm follow. Some of them have begun, and controversies already embroil others. Given that, the paradigm's value should depend on how it affects ideas about the pathogenesis, pathology, diagnosis, classification, management, study and research of, in part:

A) Arthroses, osteoporoses, osteopenias, hard and soft tissue healing problems, spontaneous fractures of bones and ruptures of collagenous tissue organs, chondrodystrophies, short stature, limb malalignments, joint contractures and malalignments, and congenital hip dysplasia and dislocation. Also hernias, strictures, varices, hyperopia and myopia, sagging breasts, intestinal adhesions, cardiac stenosis, pulmonary fibrosis, chorda tendinae ruptures in the heart, and Peyronie's disease.

Why include extraskeletal organs in that list? They all depend partly on the collagen that forms tendons and ligaments, granted the still-enigmatic roles of different collagen types, proteoglycans and other things in the physiology and disorders of such organs.

B) The Utah paradigm should also affect design criteria for load-carrying endoprostheses and other implants, and the kinds and uses of devices employed in noninvasive absorptiometry.

C) It should affect ideas about the roles of genetics and whole-organ strength in skeletal health and disorders, and how to define the health of skeletal organs. It would rank a skeletal organ's strength above its "mass", absorptiometric "density", speed of sound or dimensions.

In brevity's interest this article does not mention other features of that paradigm. A few examples include the basis for transients and steady states, microdamage physiology in all skeletal tissues, the regional acceleratory phenomenon, four nephron-equivalent phases of hard and soft tissue healing, modeling and irreversible creep physiology in cartilage collagenous tissues, aging effects, and a mediator mechanism in marrow that helps to control modeling and remodeling of bone next to marrow and a possible (probable?) analogous mechanism in periosteum.

5) On an open mind

Some history can suggest why SSC high priests (please see Note D!) who still doubt the Utah paradigm's merits might find it prudent to keep an open mind on the matter.

A) In 1895 Lord Kelvin, a famous high priest of physics then and later, said heavier-than-air flying machines were impossible (it seems the Wright brothers did not listen).

B) Simple ideas from Semmelweiss and Wegner eventually improved obstetrics and geology, although most experts of their times ridiculed their ideas.

C) Copernicus had his heliocentric challenge to the Church dogma of a geocentric solar system published after his death in 1543. Presumably he did that to avoid the Inquisition's tendency to broil such challengers alive. Recall Galileo's later brush with that dogma? And Giordano Bruno, burned alive at the stake in 1600 for saying that instead of a geocentric cosmos, the universe might have other worlds? And because most people believed something need not make it true? While people handle such challenges differently in these "enlightened" times, one hesitates to use the term when genocide still occurs while talking heads bewail it on CNN.

D) Ernst Mach, another high priest of physics, ranked producing data well above hypotheses, and he even disparaged the $E=mc^2$ idea. Einstein admired him but ignored that advice[58] – fortunately. Note that Einstein was not an experimental physicist. Instead he sought the "connections" between physical phenomena studied by others. The Utah paradigm would do the same thing for skeletal physiology and disorders, and its IO-biomechanics seems just as testable as $E=mc^2$ has been.

E) Hindsight (which some wag called the "retrospectroscope"

and our most reliable diagnostic instrument) can perceive things that escape notice in the hurly-burly of fast-moving research, jostling for turf, grants and program time, and of shifting controversies about scientific and political matters.

F) Historically, far more young than senior people embraced, improved and/or exploited new ideas in all science.

G) Santayana noted that who ignores history could repeat it (or help to).

H) As for the merits of politically-correct opinion, 20 centuries ago it freed Barabbas.

IV. Conclusion; Quo vadis?

1) On the role of this field's "high priests"
again, please see Note D

A) Most SSCs learn their basic skeletal physiology from teachings of the field's basic science and clinical high priests. Probably over 98% of today's SSCs lack the personal knowledge needed to make informed judgements about things like the merits of these two paradigms, or the modeling rules for bones, joints and ligaments, or which absorptiometric method excels for studying "osteoporosis", or how to classify arthroses, "osteoporoses" and healing problems, etc., etc. As a result most such SSCs believe and trust two things:

(i) Their high priests present the truth,

(ii) and when those priests do not even mention something that means it does not deserve mention.

B) For such reasons most such SSCs reject challenges to their high priests' teachings, just as most Spaniards rejected challenges to the Inquisition's high priests 400 years ago.

C) *Ergo, wide acceptance of the Utah paradigm may only begin when most of this field's high priests begin to sing its "song" in classrooms, texts and lectures* (and in their editorial duties) (Note E). Until then most SSCs could keep thinking the 1960 paradigm provides the basic skeletal physiology they need to know. Daniel Boorstin probably had such things in mind in saying, "*The great obstacle to progress is not ignorance but the illusion of knowledge*".

2) A three-part "message"

(i) Present and future SSCs might heed Santayana by trying harder than their predecessors to supplement former facts, ideas and assumptions with better ones to build better things with their sum.

(ii) At present that could require learning the Utah paradigm, of which others recently said *"all musculoskeletal biologists should be aware of the Utah paradigm of skeletal physiology"* (granting the exceptions in Section #3 of Part III above[18]).

(iii) When asked why he robbed banks Willie Sutton reportedly said "That's where the money is". Let *die Zukunft* signify that future time when we could prevent or cure all mammalian skeletal disorders. Then, "That's where *die Zukunft* is" could explain why many present and future SSCs should learn the Utah paradigm.

3) In conclusion

Readers who read this far graciously let this voice from the past have its say, so the above matters lie in the hands of present and future SSC hunter-players. They will find *die Zukunft* and answers to "Quo vadis?" in their own ways and times. Here this octogenarian ex-player would bid each of them *very* good hunting, and *vaya con Dios*!

And, with regret, *adieu*....

Notes

Note A.

(i) In brevity's interest this article does not defend the Utah paradigm. Instead it describes some features of it and the 1960 paradigm and leaves discussions about their relative merits to other times, places and people.

(ii) As proof of age I still think grass is to be mowed, coke is a bottled soft drink, pigs provide bacon, somebody stretched the mile and made stairs higher, and made nose and ears replace the scalp in growing hair.

Note B.

(a) Two ways to avoid making mistakes in science include: (i) Never lead, only follow; (ii) Never do, only criticize what others did (HMF).

(b) Many SSCs might want articles cited that contained the inadvertent errors mentioned in the text. Although hundreds of such errors were published after 1995 (that is not an exaggeration), many readers could interpret citing them as disparaging their authors. But I am not wise enough to do that, while trying to set one's self up by putting others down is pretty shabby. Also I learned – the hard way – to try to live by some advice from Confucius over 2000 years ago (*"What you would hate if done to you, do not to others."*).Thus, no such authors are cited here. Instead five general problems follow that many authors discussed.

1) Most people still attribute adult-acquired "osteoporoses" to excessive bone resorption by osteoclasts. Yet osteoclasts exist on all four bone envelopes but the bone loss that causes those disorders only comes from bone next to or close to marrow[46]. Thus, the chief *target* of most causative agents (estrogen or androgen loss, adrenalcortical steroids, malnutrition, chronic muscle weakness, etc.) should be something in marrow, not osteoclasts (or osteoblasts) or their precursor cells. It remained unsought in 2001 AD.

2) Falls of people with an osteopenia cause nearly all so-called osteoporotic fractures of extremity bones. Without falls such fractures rarely if ever occur. Yet most past studies of "osteoporosis" treatments and risk-of-fracture analyses only studied the osteopenias.

3) Things like vitamin D, growth hormone, androgens, calcium and genes affect muscle strength, which strongly influences the development, strength, maintenance and health of bones, joints, tendons and ligaments. Yet even after 1995 most hypotheses of how those and related things affect such organs ignored muscle and assumed the agents only affected

skeletal-organ effector cells.

4) Clinically-irreversible arthroses only exist when the type II collagen that keeps articular cartilage intact disrupted mechanically. Yet ideas about the causes of arthroses emphasized things like synovium, proteoglycans, chemokines and cytokines, and ignored how joints adapt to their mechanical usage during growth and, until recently, ignored that collagen's roles too.

5) Hard and soft tissue healing depends on four essential nephron-equivalent stages (callus, remodeling, modeling and a regional acceleratory phenomenon). Failure of any stage can abort healing[3,15,16], yet most people studying that healing assumed it was one indivisible process conducted mainly by effector cells (i.e., its "wheels" drove the healing "car").

Note C.

A quote from Niccolo Machiavelli may help to explain the resistance to the Utah paradigm. The quote concerned political matters but it could apply to scientific ones too. To wit: "There is no more delicate matter to take in hand, nor more dangerous to conduct, nor more doubtful in its success, than to set up as a leader in the introduction of changes. For he who innovates will have for enemies all those who are well off under the existing order of things..."

Interesting? Appropriate? You decide...

Note D.

"High priests" *implies no disrespect whatsoever*. It only signifies experts properly recognized as the most reliable ones in some field of contemporary skeletal science, medicine and/or surgery. They are usually invited to write review articles and book chapters, and to advise pharmaceutical companies, granting agencies like the NIH, and journal editors. In my experience they are honest, learned and usually correct. Only special IO-biomechanical circumstances in contemporary *skeletal* science, surgery and medicine made some of them doubt or err about some things mentioned in this text.

Note E.

Some SSC high priests have begun to sing the Utah paradigm's "song", so the former resistance to it begins to decline. The 2001 Neuman award to me probably signaled a change in attitude among skeletal physiologists from one of prompt resistance to, "OK, show me!". At least in my view, that represents real progress.

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