Perspective Article

New targets for fascial, ligament and tendon research:
A perspective from the Utah paradigm of skeletal physiology

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Abstract

Here an octogenarian voice from the past argues that the physiology of fascia, ligaments and tendons has strong and useful analogs in some general features of bone physiology, including the latter's tissue-level mechanostat. Such analogs could provide unusually important targets for future collagenous-tissue research. Even by 2002, this field's authorities seldom discussed those analogs so this text concerns them. How well the above research proceeds could depend partly on A) making collagenous-tissue physiologists aware of those analogs (hence this article), B) on following a four-step analytical strategy, C) on "connecting the dots" between evidence and ideas from many clinical and basic-science fields to find larger "messages" and patterns hidden in mountains of lesser things, D) and on combining (i), cell- and molecular-biologic work, expertise and insights, (ii) with live-animal research and expertise and insights of the Utah paradigm of skeletal physiology. Why the "*in vitro/in vivo* collaboration" in "D" above? Partly because few, if any, skeletal tissue-level mechanisms function normally in current cell, tissue and organ culture systems. Consequently and historically an agent's *in vitro* effects seldom predicted correctly its *in vivo* effects, although the former effects may help to explain the latter ones after other studies revealed the latter ones. Things summarized in this article provide a foundation on which to build in the future. Since aging and other things took me out of that "building game", younger people will do that building when and how, and if, they wish to. The directions for that building suggested in this article differ enough from currently accepted "wisdom" that it may take years for most physiologists to concede their merit and begin that building in earnest. If so, so be it.

Keywords: Biomechanics, Muscle, Mechanical Influences, Collagenous Tissue, Sports Medicine, Plastic Surgery

I: Introduction

Collagen helps to hold all tissues and organs in our bodies together, so it can contribute to extraskeletal disorders[1] as well as to the fascial, ligament and tendon problems that concern orthopaedic surgeons and sports medicine and rehabilitation specialists today. Table 1 lists some of those extraskeletal disorders and some medical specialties they could concern.

Herein I would like to share with others some lessons from an updated bone physiology that should help in the quest to improve an understanding of the physiology and dis-

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orders of mammalian collagenous tissues, and of fascia, ligaments and tendons made with them. Those lessons include a powerful four-step strategy that can help to teach a physiology or to improve our understanding of it. That strategy descends the ladder of biologic organization and it helped to create the Utah paradigm of skeletal physiology[2-4].

To explain, to teach renal physiology Step #1 would describe functions the organ (the kidney) provides to the body. Step #2 would describe how tissue-level mechanisms, functions and other features (here, of nephrons) contribute to the organ's functions. Step #3 would describe how cell and molecular-biologic realities (varied kinds of cells, intercellular materials, genes, receptors, cytokines, RNA, ultrastructure, etc.) directly support the tissue-level Step #2 functions, and only indirectly support organ-level Step #1 functions. Given all that information, Step #4 could A) describe the pathogenesis of known renal disorders, B) or predict still unrecognized disorders (see Section #9 in Comments).

By 1990-1995 it became necessary to update some earlier views about skeletal physiology. That update depended on

Some extraskeletal problems that involve collagenous tissue

Varices	Some aneurysms	Hernias
Some myopia	Some hyperopia	Varied duct stenoses
Pericardial stenosis	Dermatomyositis	Scar contractures
Delayed wound healing	Sagging breasts	Stretch marks
Intestinal adhesions	Pulmonary fibrosis	Emphysema
Hepatic cirrhosis	Ruptured chorda tendinae	Filum terminale syndrome
Scleroderma	Rheumatoid nodules	Peyronie's disease
Keloid	Urethral stenosis	

Medical specialties concerned with such problems

Belly surgery	Plastic surgery	Cardiology
Pediatrics	Gerontology	Pulmonary disorders
Gastroenterology	Ophthalmology	Dermatology
Vascular surgery	Neurosurgery	Pathology
Internal medicine	Physical medicine	Rheumatology
Urology	ENT surgery	Thoracic surgery

Table 1.

accumulating evidence, increasing inadequacies of early ideas and terminology, and "connecting the dots" between evidence and ideas from many fields to find larger "messages" hidden in mountains of often poorly-organized lesser things. If some reader feels "connecting the dots" represents an unworthy kind of scientific work, over 80 years ago connecting the dots between diverse physics data provided by others let a Swiss postal clerk realize that $E = mc^2$.

The still-evolving Utah paradigm of skeletal physiology provides the above update[2-4]. It inserts tissue-level realities (Step #2 matters) into the former "knowledge gap" between organ-level realities (Step #1 matters) and cell-level and molecular-biologic realities (Step #3 matters), including some roles of biomechanics, muscle and mechanostats.

This article argues that some general features of bone physiology in that paradigm have analogs in collagenous tissue organs that offer important but little-studied targets for future research (but see Section #1C in Comments, Part III). Part II of this text summarizes those features and analogs.

Table 2 lists and defines abbreviations and symbols used in the text.

II: Some salient features of the Utah paradigm

While devils can lie in the details[5-16], some general features of bone physiology that clarified by 2002 comprise mostly tissue-level Step #2 matters that Step #3 matters must support. Nevertheless how Step #3 matters support the Step #2 ones remains nearly unstudied and unknown today; opinions may abound but proof does not. Future research must fill that "knowledge gap" in skeletal physiology. Below,

Section #1 summarizes bone-physiologic features, and Section #3 summarizes its putative analogs in collagenous tissue organs.

1) Fourteen salient features of bone physiology in 2002[2,3,8,9,17]. *1)* Healthy postnatal mammalian bones include many load-bearing bones (LBBs) intended mainly to carry voluntary mechanical loads (VMLs), and a few bones that presumably have other functions (nonLBBs). *2)* All LBBs presumably have the organ-level function of providing enough strength (not enough bone "mass") to keep VMLs from breaking them suddenly or in fatigue. *3)* By the time of birth gene expression patterns *in utero* have created a skeleton's "baseline conditions", including in part its basic bony anatomy and anatomical relationships, its basic neuromuscular anatomy and physiology, and the biologic "machinery" that will adapt LBBs to their postnatal VMLs.

That machinery includes several tissue-level features. *4)* In each LBB a multicellular "nephron-equivalent" mechanism (NEM) called *modeling* by formation and resorption drifts[18] can increase its strength. Increasing a bone's strength represents a Step #2 "nephron-equivalent" function (NEF) provided to the organ by that NEM (not by osteoblasts alone[18]). *5)* Each hollow LBB has another multicellular NEM called disuse-mode BMU-based *remodeling*, which can decrease the LBB's strength by removing bone next to or close to marrow[2,18]. Decreasing a bone's strength describes a NEF provided to the organ by that NEM (not by osteoclasts alone[18]). *6)* After birth strain-dependent bone signals can monitor the *relationship* between each LBB's strength and the size and kinds of the VMLs on it[9]. *7)* Genetically-determined threshold ranges of those signals, aided by dedicated signaling systems[2,16,19], help to turn those two bone-strength

Abbreviations and Symbols in the Text

"E": typical peak strains of load-bearing organs from their VMLs.

Fx: the ultimate strength of an LBB, an LBCO, or its tissue.

GBR: the "general biomechanical relation".

LBB: a load-bearing bone (femur, vertebra, tibia, phalanx, sesamoid, etc.).

nonLBB: a nonload-bearing bone (cranial vault, ethmoids, turbinates, etc.).

LBCO: a load-bearing collagenous-tissue organ (fascia, ligament or tendon).

nonLBCO: nonload-bearing collagenous-tissue organ (pleural and peritoneal fascia, broad ligament of the uterus, etc).

MDx: microdamage, microscopic fatigue damage.

MST: a mechanostat that adapts the strength of load-bearing organs to their VMLs (bone, cartilage and collagenous tissue would each have at least one MST).

NEF: a function provided by an NEM (see next).

NEM: a tissue-level nephron-equivalent skeletal mechanism.

NMI: a nonmechanical influence (genes, circulating hormones, vitamins, minerals and drugs, local cytokines, organelles, cell receptors, ligands, etc.

SSF: a load-bearing organ's strength-safety factor.

VML: voluntary mechanical load on a skeletal organ, so it implies muscle forces.

M: approximately, or approximately equals.

<,<<,<<<: less than, much less than, and very much less than, respectively.

Table 2.

functions on and off. *8)* Each LBB can develop microscopic fatigue damage (microdamage, MDx), which has its own operational threshold range in bone (MESp)[20]. Normally each LBB can detect and repair the limited amounts of MDx caused by strains that stay below the MDx threshold (MESp)[21]. DR Carter's group found that bone MDx depends very sensitively on strain and unit load magnitudes[11].

9) Combining all such things with some others, and with feedback between them, would construct a tissue-level nega-tive-feedback system called bone's *mechanostat* (MST)[2,9], which AM Parfitt recently called the "....most important..... problem in bone physiology."[22]. It would constitute an important Step#2 feature of lamellar bone physiology in load-bearing bones (woven bone physiology might have a somewhat different MST). *10)* On earth bone's MST adapts a LBB's strength and architecture chiefly to postnatal *muscle strength* (and power?). Why not to body weight? On earth, lever arm and gravitational effects make muscles put by far

Set Point Values for Bone's Thresholds and Ultimate strength
(in microstrain, stress and unit load terms)*

MESr: 50-100 microstrain; ≈ 1-2 mpa, or ≈ 0.1 kg/mm² (one can argue for a value of ≈ 400 microstrain).

MESm: 1000-1500 microstrain; ≈ 20 mpa, or ≈ 2 kg/mm².

MESp: ≈ 3000 microstrain; ≈ 60 mpa, or ≈ 6 kg/mm².

Fx: ≈ 25,000 microstrain in healthy young adults (a bit more in children and less in aging adults); ≈ 120 mpa, or ≈ 12 kg/mm².

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*: values for analogous features for collagenous tissue organs are currently unknown. The values cited for bone apply to cortical lamellar bone in healthy young adults and depend on information available to me in 2002.

Table 3.

the largest VMLs on such bones[8,17,23]. In principle three organ-level things should follow. (i) Chronically strong muscles should usually associate with strong bones, and chronically weak muscles should usually associate with weaker bones. Both associations occur. (ii) Ignoring effects of general body growth, a postnatal LBB's strength should sum a baseline conditions part, plus any adaptations added after birth. If so, after total and permanent paralysis a LBB in a paralyzed limb should never disappear completely (which is true). Perhaps its baseline-conditions part persists. (iii) Since bones cannot foresee one-time loads from injuries, bones could not adapt to them.

11) Most nonmechanical influences (NMIs) previously thought to dominate control of bone physiology, and by implication of whole-bone strength too, would act as permissive agents the MST needs in order to work, but not ones that "guide" the MST in time and anatomical space (see Section #8 in Comments; "whole-bone" distinguishes bones as organs from bone as a tissue or material). *12)* For such reasons postnatal VMLs should strongly associate with the postnatal strength of LBBs, as they do. *13)* Bone's NEMs do not function normally in current cell, tissue and organ culture systems[2,10], so their properties in intact animals would need study in live animal research.

14) The "general biomechanical relation" (GBR) for healthy LBBs. Let MESr denote the threshold strain range below which bone's maximal disuse-mode remodeling function turns on, and above which it begins to turn off. Let "E" denote the typical peak strains of a normally-adapted LBB from its VMLs. Let MESm denote the threshold range in and above which bone's mechanically-controlled modeling function turns on. Let MESp denote the MDx threshold range in and above which unrepaired bone MDx begins to accumulate. Let Fx denote a bone's ultimate or fracture strength. Then the GBR for healthy postnatal young-adult mammalian LBBs made with lamellar bone could encode the laddered relationship of those things thus: $MESr < "E" < MESm << MESp <<< Fx^{2,3}$.

One could express those things in strain, stress or unit-load terms (kg/mm^2) as in Table 3. Instead of step functions, those things are ranges with unknown breadths so in a first approximation the centers of their ranges could define their "set points".

2) **Please note:** *(i)* "Connecting the dots" between experimental and clinical evidence and ideas, and cybernetics[24], strongly suggests that healthy load-bearing collagenous-tissue organs (LBCOs) have analogs of each of the above load-bearing bone features. *(ii)* If so one could restate the bone features as proposals for LBCOs after adding a feature to account for a slow plastic flow under tension (irreversible stretching) from VMLs. *(iii)* Things in Section #1 above show that in essence LBBs make VMLs determine most of their postnatal strength. Presumably the same stratagem could function in LBCOs, and presumably MSTs would orchestrate it.

(iv) In metaphor this text argues that analogs of the bone

physiology in the Utah paradigm could tell where gold lies in collagenous-tissue "country", so miners (skeletal researchers) could go directly there to get it instead of wasting time looking for it (see also Section #1C in Comments).

The above proposals follow.

3) **Fifteen proposed features of collagenous-tissue organs in 2002**[3]. *1)* Postnatal healthy mammalian collagenous-tissue organs include (i) load-bearing collagenous-tissue organs (LBCOs), meaning fascia, ligaments and tendons that mainly carry VMLs; (ii) and some nonload-bearing structures, usually fascias, that presumably have other functions (nonLBCOs). *2)* Two of a LBCO's organ-level functions would include having enough strength *relative* to the size of the tension VMLs on it (i) to keep those VMLs from rupturing it suddenly or from fatigue, (ii) and to keep them from stretching it in irreversible plastic flow[3]. *3)* By the time of birth gene expression patterns *in utero* have created a skeleton's "baseline conditions", including in part its anatomy, its LBCOs, its basic neuromuscular anatomy and physiology, and the biologic "machinery" that will adapt LBCOs to their postnatal VMLs.

That machinery would include several tissue-level features. 4) In each LBCO a multicellular "diametric modeling" NEM[3,25] would have the NEF of increasing its tension strength and stiffness, and thickness, mainly by making this tissue's analogs of modeling formation drifts (which include fibroblasts in LBCOs) add more collagen to the organ's cross section, and partly by increasing the cross-linking between existing collagen fibrils and fibers[25]. 5) A different disuse-mode NEM and NEF analogous to disuse-mode BMU-based bone remodeling could decrease the tension strength and stiffness and, usually, the thickness of a LBCO, partly by removing some collagen and partly by reducing the cross-linking between existing collagen fibrils and fibers[3,26,27]. 6) Here too, postnatal strain-dependent signals[9,16,21] could monitor the relationship between each LBCO's strength and the VMLs on it. 7) Aided by dedicated signaling systems, genetically-determined threshold ranges of those signals would help to turn those two mechanically-controlled NEFs on and off, and thereby affect the relationship between a LBCO's strength and the postnatal VMLs on it. Let MESm denote the tissue's diametric modeling threshold range, and let MESr denote the tissue's lower disuse-mode threshold range. 8) MDx in collagenous tissues should have its own operational threshold range (MESp). Each LBCO could detect and repair limited amounts of its MDx. Diametric modeling would normally make such organs strong enough to keep strains from their VMLs below levels that would cause enough MDx to escape repair and begin to accumulate (i.e, $"E" < MESm << MESp$)[3]. Presumably strains in and above the MESp range could cause enough MDx to escape repair and begin to accumulate. 9) Clinical evidence cited in[3,28] shows that collagenous tissue organs can develop plastic flow in tension (irreversible stretching), and cellular mechanisms can detect and prevent it, and even correct limited amounts of it.

Examples of skeletal LBCO problems

Fascial healing	Tendon healing	Ligament healing
Tendinitis	Tennis elbow	Contracted joints
Patella baja	Patella alta	Frozen shoulder
Dupuytren's disease	Hallux varus	Trigger thumb
Hallux rigidus	Spontaneous ruptures	Arthrogryposis
Tendon adhesions	Filum terminale syndrome	Tendinitis
Intraarticular adhesions	Herniated or bulging intervertebral discs	"Charley Horse" problems in muscles
	Baseball-pitcher's shoulder	
	Ossification of the posterior longitudinal spinal ligament	

Table 4.

10) Combining all such things with feedback between them would construct a tissue-level negative feedback system called the *mechanostat* (MST) for collagenous tissue (ligaments, tendons, basal laminae, etc., might even have different MSTs). *11)* On earth that MST should adapt a LBCO's strength and architecture chiefly to postnatal muscle strength (and power?), partly for reasons given in Section #1 above. If so three organ-level features should follow: (i) Chronically strong muscles should usually associate with strong and thick LBCOs, and chronically weak muscles should usually associate with weak and, usually, thin LCBOs. Both associations occur[29]. (ii) The strength of every healthy tendon should match the strength of the muscle attached to it, whether something chronically weakened the muscle or if weight lifting chronically strengthened it. Those associations also occur[29]. (iii) An LBCO's postnatal strength could also sum a baseline conditions part plus any added postnatal adaptations. That might answer a seldom-discussed question: "After total and permanent paralysis, why does a LBCO (and a LBB too) never disappear completely?". Perhaps its baseline conditions part persists. That latter part could include added postnatal effects of general body growth and of some humoral agents, but not any adaptations to normal postnatal VMLs (total and permanent lower-limb paralyses in cases of myelomeningocele provide helpful "natural experiments" in trying to understand such things[29]).

12) Most NMIs formerly thought to dominate control of the physiology of LBCOs, and by implication control of their strength too, would act chiefly as permissive agents (see Section #8 in Part III) which a MST needs in order to work properly but which would not guide it in time and anatomical space. *13)* Postnatal VMLs on healthy collagenous-tissue LBCOs should strongly affect their strength, and presumably their MST determines how that is done. Three examples follow, the first two taken from "natural experiments" in times when surgical reconstruction of post-polio residuals was common. (i) After permanent paralysis of a muscle its tendon usually becomes weak and, often, tenuous[29]. (ii) Yet after transplanting a strong muscle to such a tendon the latter always strengthens, stiffens and thickens again, and well enough to provide the two functions noted in *2)* above for the remainder of life[29]. (iii) A tenuous and weak tendon would usually attach to a correspondingly weak muscle (example: the human plantaris tendon and muscle), while a thick and strong tendon would attach to a correspondingly strong muscle (example: the gluteus medius tendon and muscle). *14)* Like the case for bone, collagenous-tissue NEMs do not seem to function normally in current cell, tissue and organ culture systems[29]. If so live animal research should study them.

15) The GBR for healthy LBCOs. The following things deserve the emphasis of repetition. Let MESr denote the threshold strain range below which a LBCO's maximal mechanically-controlled disuse-mode function turns on, and above which it begins to turn off. Let "E" denote the typical peak strains caused by VMLs on a normally-adapted LBCO. Let MESm denote the threshold strain range in and above which the LBCO's mechanically-controlled modeling turns on. Let MESp denote the MDx threshold range in and above which unrepaired MDx can begin to accumulate in a LBCO. Let Fx denote a LBCO's ultimate strength. Then bone's GBR could encode the laddered relationship of those Step #2 features for healthy postnatal LBCOs too. Thus, *MESr < "E" < MESm << MESp <<< Fx.*

Those things are ranges with unknown breadths, so in a first approximation the centers of those ranges could define their "set points". One could express them in strain, stress or unit-load terms, but lack of appropriate studies makes their values for LBCOs uncertain at present. Finding those values poses an important task for future fascial, ligament and tendon research that would help to fill the earlier-mentioned knowledge gap.

III: Comments

1) **Where's the evidence?** *A)* Bone people studied the features described in Section #1, Part II, longer and more intensively than people who study collagenous tissues, so evidence supporting the bone features became firmer and better accepted in 2002. Nevertheless, in my view, clinical-pathologic evidence cited in[2,3,25,28,30] strongly suggests the features summarized in Section #3, Part II above do exist.

B) In that regard, the physiology of LBBs and LBCOs shows many general similarities. Both begin at birth with baseline conditions, and both exist mainly to carry VMLs without breaking or rupturing suddenly or in fatigue. Both use monitoring by strain-dependent signals, plus modeling, disuse-mode and MDx thresholds, plus MDx detection and repair mechanisms, to help to control the NEMs that establish and maintain a healthy relationship (as in the GBR) between the strength of such organs and the VMLs on them. By far the largest loads to which LBBs and LBCOs would adapt come from VMLs, so both LBBs and LBCOs seem to let muscle strength determine most of their postnatal strength. For both, MSTs would orchestrate their adaptations, and many agents formerly thought to dominate or control their health and strength would act instead as permissive agents. For both the GBR seems to encode how those things ladder in relation to each other. Long ago DR Carter suggested bone design might intend to minimize fatigue failures more than to provide great momentary strength[31]. The GBR's laddered relationships could achieve that goal for both LBCOs and LBBs, both of which also depend on the same four-phase healing process described in[3].

C) Collagenous tissue structures and the MSTs that govern their physiology and strength presumably had evolved by Cambrian times, and thus before bone, bones and presumptive evidence of bone's MST appeared in the fossil record (in the Silurian-Devonian time span?). If so nature may have used analogs of collagenous tissue physiology to design the physiology of LBBs. If so this article would reverse that arrangement by extrapolating from known features of bone physiology to collagenous tissue physiology.

2) **Two LBCO areas need systematic study.** *First area*: All 15 proposals in Section #3, Part II would need systematic study. Directing future collagenous-tissue research to those proposals could prove unusually productive, partly because their problems should cause or help to cause many clinical skeletal problems. Table 4 lists examples of such LBCO problems to complement the extraskeletal examples in Table 1. Understanding the Step #2 causes of the problems in those two tables could lead to considerably improved clinical diagnosis and management.

Second area: Much cell-biologic and molecular-biologic collagenous-tissue research has been done. It includes studies of the tissue's genes, composition, chemistry, cellular biology, material properties, ultrastructure, cytokines, ligands, organelles, etc., which would all constitute Step #3 matters[6,14,26,32-36]. That research was unquestionably valuable, necessary and popular, and it made enormous progress. *Yet today how Step #3 matters support Step #2 matters in collagenous tissue physiology and its disorders remain nearly unstudied and thus unknown*. Like trying to understand renal physiology and disorders without accounting for nephrons, that would represent an analytical "no-no" (see Section #3 next). Because all Step #2 features in LCBOs must have Step #3 support, seeking and studying that support poses another task for collagenous-tissue research that could prove unusually productive and useful. It would help to fill the earlier-mentioned "knowledge gap" between Step #2 and Step #3 skeletal matters.

3) **On microcosms and macrocosms.** The above matters relate to a phenomenon noted by M Schermer[37,38]. To wit: In astronomy and physics "microcosms cannot predict macrocosms", although the former may help to explain the latter after other studies revealed the latter. Or, one cannot predict galaxies, stars or cars from atoms, but atoms can help to explain already-known properties of such things.

That idea applies to LBCOs (to LBBs too). Step #3 matters cannot predict Step #1 or #2 matters (that analytical "no-no" caused many "jumping frog errors" in the past[30]), even though the former matters can help to explain the latter ones after other studies reveal the latter ones. 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 tried to predict two organ-level effects (a macrocosm) of effects on skeletal cells *in vitro* (a microcosm). (ii, iii) The 1940-1955 ideas that estrogen or supplemental dietary calcium should increase bone "mass" enough to cure "osteoporosis" met the same fate and for similar reasons. (iv) Authors of a study of mechanical loads on mammalian long-bone growth plates concluded that even small loads retard the growth of such plates[39]. If so, bones in normal growing limbs would become shorter than corresponding bones in paralyzed or partly deloaded growing limbs. Yet for over 2000 years physicians knew the opposite occurs: bones in paralyzed growing human limbs become shorter than corresponding bones in normal limbs. Furthermore, in partly deloaded limbs in experimental animals, bones never grew longer than in control limbs. Ignoring such evidence helped to cause that naive error. Please note that the data in that study are not questioned here, but the conclusion drawn from those data was naive.

4) Modifying Michael Parfitt's statement about bone's MST might apply it to collagenous-tissue physiology too (as well as to cartilage and organs made from it): "Understanding the skeleton's MSTs belongs among the most important problems facing skeletal physiology today.".

5) Many collagen types, kinds of proteoglycans, elastic and reticular fibers and other proteins occur in collagenous tissues[6,26,35,36]. Abnormalities in some of those Step #3 matters (which might involve some cell-intercellular matrix interactions) associate so regularly with some diseases as to

suggest causal relationships[14].

Nevertheless, and to repeat, how such things might help to control the NEFs summarized in Section #3, Part II, remains virtually unstudied and unknown. Future "targeted" research must fill that knowledge gap.

6) **On the relative roles of genes, biomechanics and biochemistry.** In one view genetic predetermination would explain most of the architectural, physical and other features of postnatal LBCOs (of LBBs too).

But in the Utah paradigm *(i)*, genetic expression patterns *in utero* would create a LBCO's baseline conditions including its MST. Ligaments, tendons, basal laminae and some fascias might even have their own MSTs as well as their already-known different mixes of collagen Types, kinds of proteo-glycans, reticular and elastic fibers, and other proteins. *(ii)* After birth VMLs on a LBCO would presumably incite Step #2 adaptations that added to its baseline conditions. *(iii)* After birth some NMIs might modulate both the adaptations and the baseline conditions (both things do occur in bones[17]). *(iv)* Meanwhile many other things would act as "permissive" agents which the system needed in order to work properly, but which did not control the system in time and anatomical space (again, see Section #8 below).

Ergo, the physiologic "music" played by LBCOs after birth should represent a trio, not a genetic, biomechanical or biochemical solo.

7) **On "*in vitro/in vivo* collaboration".** Because collagenous-tissue NEMs and NEFs do not seem to function normally in current cell, tissue and organ culture systems[29], much productive research on those NEFs in the future could depend on *collaboration* of, *(i)* cell and molecular-biologic expertise and *in vitro* work, *(ii)* with *in vivo* research and the Utah paradigm's insights. An example of that "*in vitro/in vivo* collaboration" – and of "drug targeting" and devising "designer drugs" too[40,41] – appeared recently in Science[42]. Other examples appear in many studies done by Professor WSS Jee and his fellows and students[43]. That paradigm injects Step #2 features into earlier views about skeletal physiology. Also, collagen-associated problems contribute to many extraskeletal disorders (Table 1 listed some examples) so students of such disorders could benefit by studying the targets for collagenous-tissue research that the Utah paradigm and this article suggest.

8) **On permissive agents.** *(i)* 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 the health and strength of LBCOs. Such ideas still linger[5,14,33-36,40].

(ii) Yet most such agents, especially humoral ones, act chiefly as "permissive" ones the MSTs of LBCOs need 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"[9] of LBCOs to their mechanical usage.

(iii) Permissive humoral and local agents have a long-known but seldom-discussed behavioral property that constitutes another larger "message" hidden in mountains of lesser details. To wit: Deficiencies of permissive 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 I suggested several years ago[44], 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[45], so the hormone would have a permissive role in that activity. Analogous effects may apply to androgen effects on whole-bone strength and on muscle strength. Etc., etc.

9) **On strength-safety factors (SSFs) in LBCOs.** Healthy mammalian LBCOs (LBBs too) have more strength than needed to keep VMLs from rupturing them suddenly or in fatigue, so they have SSFs.

The "E" $< MESm << MESp <<< Fx$ relationship in the GBR <u>must</u> create a SSF, and as noted elsewhere this expression can calculate it: $SSF = Fx \div MESm^2$. By expressing the latter two terms as stresses (Table 3), the SSF for healthy young-adult mammalian bones $\approx$ six. Its value for LBCOs remains unknown at present. Two variations of that arrangement for LBCOs may help to explain some clinical observations.

(i) A modest increase in collagenous tissue'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 LBCO. That would make the LBCO weaker than before, decrease its SSF, make it more likely for VMLs to rupture it, and/or make it more prone to excessive MDx. Some years ago before these ideas gelled, I received a pathetic request for help from a man who had numerous puzzling nontraumatic (spontaneous) tendon ruptures. Whether this explanation accounts for his problem remains unknown, but it seems interesting that it could predict such a previously unrecognized problem (an example of Step #4,B?).

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

Clinical experience, plus experience with special forces trainees, athletes and equine training, reveals that some individuals do seem unusually prone to ruptures and MDx-related problems with their LBCOs, 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 (more Step #4 examples?).

Interestingly, in both those *(i)*, *(ii)* cases the involved tissues and organs need not show associated abnormalities in

histology, composition or metabolism, or in their material properties.

10) **Another useful but hidden "message".** "Connecting some dots" showed that both LBBs and LBCOs can adapt to most mechanical challenges throughout mammalian life *provided they are given enough time* (which can sometimes exceed two years in adult humans[25]). Furthermore, muscle strength can usually change more rapidly than the strengths of LBBs and LBCOs can change to adapt to such VML changes. Synovial joints differ in that respect, because after general body growth stops they lose most of their ability to adapt to large increases in their VMLs[3].

11) **Other LBCO features.** Discussed in[2,3] but not mentioned in this article, those features include in part three longitudinal growth mechanisms; multicellular LBCO analogs of bone's modeling drifts and remodeling BMUs; the four-phase healing process of LBCOs; the roles of cartilage layers and Sharpey's fibers at the bony attachments of most fascias, ligaments and tendons; the roles of LBCO innervation, including affecting the VMLs on a LBCO; the nature and some effects of transients and steady states in LBCOs; the regional acceleratory phenomenon; the idea that skeletal design intends to minimize fatigue failures more than to provide great momentary strength of load-bearing organs; and how aging, genes, hormones, drugs, etc., affect such things.

12) **In conclusion:** *A)* Reasonable people can usually devise more than one explanation for a given collection of facts. Partly for such reasons some such people might question some statements and ideas in this article. With full respect to them and their views, I believe most physiologists will eventually concede the merits of the views expressed in this article. That could take discussion, more data and perhaps more time than I have left.

B) I foresee such exciting times unfolding in the above areas that I wish I could begin my career anew to participate in those times. But that cannot be, so that future will belong to younger people than me. Again, so be it.

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