J Musculoskel Neuron Interact 2000; 1:5-9

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Perspective

Why the ISMNI and the Utah paradigm? Their role in skeletal and extraskeletal disorders

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Abstract

Besides bringing problems, aging can let the mind's eye see more clearly than before, and it can let us express ourselves better. As age, experience and common sense examine today's skeletal medicine and surgery two questions keep popping up: *A) How did we fail?; B) How to make it better?* The Utah paradigm of skeletal physiology and the seminal ISMNI offer some answers, but exploiting them faces problems. Problem #1: By 1960 all clinicians and physiologists "knew" (as the ancients "knew" this world is flat) that effector cells controlled solely by nonmechanical agents explain all skeletal physiology and disorders ("effector cells" include osteoblasts, osteoclasts, chondroblasts and fibro-blasts). Or, *nonmechanical agents → cell level → organ and intact subject*. Adding later-discovered information to that 1960 view led to the Utah paradigm, which reveals the formerly hidden tissue-level "dimension" of skeletal physiology. It builds on this idea: *(mechanical + nonmechanical agents) → (tissue level + cell level) → organ and intact subject*. The paradigm assigns great influence of neuromuscular physiology and physical activities on skeletal architecture, strength and mechanical competence. It also exposes flaws in many older views so controversies arise. Problem #2: The Utah paradigm and Wegner's concept of plate tectonics in geology seem alike in that each is valid but came before its time, so others fought it. They differ in this: The fight about Wegner's idea is over, but for the Utah paradigm and the ISMNI it just began. Hence more controversies. Nevertheless: A growing minority realizes that paradigm provides a far better base to build on than its antecedents, and since it keeps evolving as more evidence comes in it could endure for some decades. Yet very few realize this: *It and the ISMNI have important implications for fields besides biomechanics and orthopaedics*[18]. Examples include anatomy, cardiovascular disease, dentistry, endocrinology, family medicine, gastroenterology, general surgery, genetics, gerontology, gynecology, maxillofacial surgery, neurology, neurosurgery, nutrition, ophthalmology, pathology, pediatrics, physical medicine and rehabilitation, plastic surgery, radiology, rheumatology, space and sports medicine, and urology. Quite a list! For the italicized questions above this article offers answers, of which its conclusion distills an essence.

Keywords: Physiology, Bone, Joint, Tendon, Biomechanics, Skeleton, Utah Paradigm

Introduction

The multidisciplinary Utah paradigm and the ISMNI have implications for the future research and management of many clinical problems, and for the pharmaceutical industry. This article summarizes some of the Utah paradigm's features to provide some sense of it and of the scope of the ISMNI that provides its second forum. The first forum: The University of Utah's Hard Tissue Workshops[31].

As for that paradigm's origins, before 1950 physiologists realized renal function depends on the kidney's many kinds of cells and the functions of tissue-level nephrons made with those cells. Nephrons provide functions no single kind of cell can provide, but they are essential for our health. The same idea applies to the lung, gut, liver and endocrine organs, as examples only.

However ideas about skeletal physiology took a different path. Bone can illustrate it. By 1900 it was known that osteoblasts make bone and osteoclasts resorb it[35], but no skeletal "nephron equivalent" functions were recognized before 1964. Ergo, by 1960 everybody "knew" bone's effector cells (osteoblasts and osteoclasts) wholly determine bone health and disorders under the sole control of non-mechanical agents[1,39,47].

That idea was extrapolated to collagenous tissue and cartilaginous organs too[1,2,34], for which fibroblasts and chondroblasts respectively provide the effector cells[27].

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Accepted 15 February 2000

Or, *agents → effector cells → skeletal health/disorders*.

After 1960 Webster Jee and I began to recognize and study some of the skeleton's "nephron equivalents". Aided by the Hard Tissue Workshops[31] and many people and disciplines, that discovery process revealed some of those equivalents, their functions and the rules that govern them. Adding that and other information to 1960 views led to the still-evolving Utah paradigm[11-24,37,44-46]. It builds on this idea, where "agents" include mechanical and nonmechanical ones[37,45-47]:

(tissue level + cell level) → skeletal health/disorders
↑ ↑
..... agents .....

The following text summarizes some features of that paradigm. The text only mentions most things; references provide more information. The text concerns postnatal load-bearing skeletal organs in mammals (the dental system excepted). Below, a double asterisk (**) signifies this: "I realize some readers could find this point controversial and I respect their doubts. Nevertheless I am certain it is valid.".

Salient features of the Utah paradigm

This paradigm has two important post-1960 insights. The first one follows. Proposition #1: *The design of postnatal load-bearing skeletal organs intends to provide only enough strength to keep voluntary physical loads from causing fractures, ruptures or arthroses, whether those loads are chronically subnormal, normal or supranormal*[22]**.

1) Some common features of skeletal organs.

Their strength depends on the properties of their tissues, on the amounts of structural tissues in them, on their architecture, and on how much fatigue damage they contain[7,37].

Pure growth increases the number of cells and the amounts of intercellular materials[27]. When external influences guide it to produce purposeful shapes, sizes, organization and strength, that represents modeling, as in modeling a statue with plaster of Paris[9,27,37]. Modeling can increase but seldom if ever decreases the strength of load-bearing organs**. Another mechanism can turn skeletal tissues over to maintain their properties and composition. Remodeling by BMUs[22,27] does that in bone and collagenous tissues, and presumably a cell-level equivalent does it in cartilage[13,23]. This remodeling can work in two modes**. In its "conservation mode" it turns tissue over without changing its amount. In its "disuse-mode" it reduces an organ's strength and/or the amount of tissue in it[20,23]. That is nature's chief way to reduce unneeded strength in skeletal organs**.

Three mechanical strain threshold ranges help to control those nephron-equivalent mechanisms. When strains stay below the lowest remodeling threshold the remodeling mechanism (or its chondral equivalent) reduces an organ's strength. Otherwise it conserves that strength. Where strains exceed the middle modeling threshold, modeling strengthens the affected organ[37]. Those two thresholds make the largest strains control those activities. Since muscle forces cause the largest strains, and trauma excepted, muscle strength strongly influences the postnatal architecture and strength (and "mass") of load-bearing skeletal organs[6,11-14,22,33]. By implication, so should muscle anatomy and neuromuscular function including coordination**.

Once growth, modeling and remodeling produce a skeletal organ, other activities provide essential maintenance functions. An important such function detects and repairs microdamage (MDx) (BMUs do it in bone and collagenous tissues), which repeated and large strains cause[5]. All skeletal organs can detect and repair limited amounts of their MDx**, but strains above the third and highest MDx threshold range can cause too much MDx to repair so it accumulates and weakens affected organs[24]. In bones such accumulations can cause spontaneous, stress and pseudofractures; in collagenous tissue organs they can cause spontaneous ruptures; and in joints they can cause arthroses (osteoarthritis)[23]**. MDx always involves breaking a tissue's collagen fibers and/or fibrils[37]. Since the modeling threshold seems to lie below the MDx threshold in all skeletal structural tissues, and since the former threshold makes organs strong enough to keep their strains below the MDx threshold, that arrangement would minimize MDx**.

At birth the skeleton has baseline conditions predetermined mainly by gene expression patterns in utero**. Those conditions include the skeleton's basic architecture and anatomy, and the biologic mechanisms that can adapt its organs to various challenges after birth. At any time after birth the differences in the size, architecture and strength of skeletal organs in paralyzed and contralateral normal limbs show the adaptations to postnatal loads in the normal limbs[9]. This may explain why a load-bearing organ's postnatal adaptations can disappear in permanent total disuse, but its predetermined baseline conditions should remain. Such organs never completely disappear during such disuse.

Trauma and other noxious stimuli cause a regional acceleratory phenomenon (RAP) in which all regional activities increase[9,37]. Normally that accelerates healing and improves resistance to infection. It accelerates any ongoing regional growth, remodeling, modeling and other activities too. Excessive, pathological RAPs also occur (algodystrophies or "migratory osteoporoses")[42].

The mechanostat hypothesis. This is another important insight of the Utah paradigm. In time and anatomical space mechanostats make voluntary loads control the adaptations of load-bearing skeletal organs to those loads[19,21,29,37]**. Bone, cartilage and collagenous tissues would have their own mechanostats, which would include the above three strain thresholds and the nephron-equivalent mechanisms that can change an organ's architecture and strength, repair its microdamage[5], and, in cartilage and collagenous tissues, which can prevent and correct limited amounts of creep[18]. As negative feedback systems, mechanostats make load-bearing

organs satisfy Proposition #1. Many nonmechanical agents could modulate but not replace that function, in part by changing the genetically-determined strain thresholds [21,28-30,37,43,46].

In the mechanostat hypothesis the skeleton's nephron equivalents would be like a car's steering, brakes and accelerator, and effector cells would be like its wheels. Voluntary mechanical usage would be like its driver. Implication: As studying only the wheels could not explain why a car drove to Milan instead of Rome, in the paradigm's view studying only effector cells would seldom explain why an osteoporosis, arthrosis, some healing problem or a spontaneous tendon rupture occurred**.

The post-1950 studies of effector-cell roles in repair processes [3,4] overlooked the four essential tissue-level stages of healing in all skeletal tissues ("essential" because if any stage fails so does healing)[10,32,48]**. A) At first some kind of soft callus forms. B) Then a remodeling mechanism replaces it with the mature kind of tissue, C) while modeling reshapes and sizes it to provide normal strength. D) A concurrent RAP accelerates "A-C". Strains, presumably in the adapted and mild overload windows[15], help to guide and potentiate "A-C" in time and space. The whole healing process would make injured organs satisfy Proposition #1 again. Impairments of those four stages cause several kinds of "biologic failures" of healing (ones not due to treatment errors)[32].

Nota bene: In 2000 AD many physiologists and clinicians might find some of the above information and ideas strange, even radical. Nevertheless I am certain they are valid.

Discussion

1) On the roles of hormones, other humoral and non-mechanical agents, genetics and cytokines.

Past basic research focused so much on how such factors affect the skeleton's effector cells (the skeleton's "wheels")[2-4,7,34] that proven knowledge (as opposed to opinions) about their effects on the skeleton's nephron-equivalent functions remains very sketchy. Yet those functions help to determine the phenotypes of bones, joints, tendons and ligaments, as well as our body height and limb lengths and alignments**. In my view explaining such things solely in terms of efector cell effects would be like trying to explain why a car drove to Milan instead of Rome by only studying its wheels. How agents affect the skeleton's effector cells in current cell, tissue and organ-culture systems seldom predict correctly how such agents affect skeletons in vivo. Why? As Michael Parfitt also noted[40], bone's nephron equivalents do not function and respond normally in present in vitro systems[9,19]. That means one should study them in vivo. WSS Jee led the way in showing how[28-31].

A few implications. The above physiology has too many implications for future research and clinical management to list here. A few examples: The cell and molecular biology on which all the skeleton's nephron-equivalent functions depend need systematic study; we need normal standards for the muscle/skeletal-organ/strength relationships[8]; we need more reliable noninvasive indicators of whole-organ strength[8]; neurophysiologic effects on skeletal modeling, remodeling and maintenance need extensive study; space and sports medicine, pathology, rheumatology and hard and soft tissue healing studies[32,48] need to account for the Utah paradigm's insights; current schemes for diagnosing and classifying osteoporoses, arthroses, healing problems and developmental disorders need revision and/or supplementation[25]; the signalling mechanisms that help to control nephron-equivalent functions need more study[26,36]; and the roles of collagenous tissue physiology and different collagen Types in problems in the medical specialties mentioned in the Abstract need systematic study[18].

2) Some special features of bone and bones[9,11,12].

Separate formation and resorption drifts provide bone modeling[27]. They determine the cross sectional size and shape and the longitudinal shape of bones and trabeculae, and thus their strength. Mechanically-controlled bone modeling works best during growth[37]. It becomes inefficient in adult cortical bone but it can affect trabeculae throughout life. A mediator mechanism in bone marrow helps to control modeling and remodeling of bone next to it[20]**. It can cause disuse-mode remodeling of bone next to marrow, and it causes all adult-acquired osteopenias on earth and in orbit**. Chronic muscle weakness for any reason usually causes a "physiologic osteopenia" in which bones satisfy Proposition #1, since only injuries would cause fractures[22]**. Yet some modeling and remodeling disorders can cause a "true osteoporosis" in which voluntary activities cause fractures, so Proposition #1 is not satisfied[22]**. Growing cartilage layers at the ends of most bones (growth plates and articular cartilage) determine their length[9,28]. Partly under biomechanical control, another nephron-equivalent mechanism called endochondral ossification replaces the added cartilage with spongiosa[16,17,27].

3) Some special features of fascia, ligament, tendon and collagenous tissue[9,24].

When this tissue's strains exceed its modeling threshold it adds collagen to thicken and strengthen the affected organ without changing its length. In collagenous tissues this mechanically-controlled diametric modeling ability lasts for life[14]**. It makes the strength of tendons exactly match the muscle forces on them**. When strains stay below this tissue's "remodeling threshold" cellular mechanisms reduce its collagen content and the affected structure becomes thinner and weaker. Unlike healthy bone, under constant tension loads collagenous tissue also can stretch or "creep" irreversibly (not the same thing as viscoelastic deformation)**. A "creep compensation" mechanism can prevent or correct limited amounts of it[14]**. Excessive creep compensation causes joint contractures, and contractures in

Dupuytren's and Peyronie's diseases**. Failure of that mechanism can cause lax joints, for example in rheumatoid arthritis and Ehler-Danlos syndrome**. Collagenous tissues can repair limited amounts of microdamage in their collagen, and failure to do it causes, among other things, spontaneous tendon ruptures and, in the vertebral annulus, many spinal disc problems**.

Normally this tissue's modeling, creep compensation and microdamage repair mechanisms make collagenous organs satisfy Proposition #1**. Problems with those mechanisms cause or help to cause all spontaneous ruptures of tendons, ligaments and muscles. A growing layer of cartilage at the bony attachments of ligament, tendon and fascia helps to lengthen them in childhood, when ligaments and fascia can also increase in length ("grow") by the creep mechanism**.

Nota bene: Interstitial collagen, and/or collagenous sheaths, membranes, capsules, adventitia and fascia hold all soft tissue organs together. Accordingly collagen problems can cause or help to cause many extraskeletal disorders. A few examples include some varices, aneurysms, hernias, strictures and stenoses; myopia and hyperopia; hepatic cirrhosis; pericardial stenosis and intestinal obstructions from adhesions; arthrogryposis; scleroderma; and sagging skin and breasts with aging. Hence the implications of this paradigm for many medical specialties listed in this article's Abstract.

4) Some special features of joints and cartilage[13,23].

During growth mechanically-controlled chondral modeling affects the size and shape of joints, the thickness of articular cartilage, and the congruence or "fit" of opposed joint surfaces. It makes growing joints large enough and strong enough to satisfy Proposition #1**. Cartilage strains above a threshold range can turn this mechanically-controlled modeling on; otherwise it stays off**. Normal chondral modeling nearly stops at and after skeletal maturity, so adult joints must depend largely on maintenance functions to endure their mechanical usage [9]. Hyaline and fibrocartilage can repair limited amounts of microdamage in their collagen, and inadequate repair of it in articular cartilage is the "final cause" of most arthroses and of degenerated menisci in the knee and temporomandibular joints[23]**. These tissues too can creep irreversibly and very slowly (also called "plastic flow", and not the same thing as viscoelastic deformation)**. Presumably they too have mechanisms that can prevent or correct limited amounts of creep[23]. In combination, Chondral Modeling, Maintenance and Creep Compensation (CMMCC) make normal joints satisfy Proposition #1**; otherwise an arthrosis develops. Disorders of those mechanisms also cause or help to cause skeletal disorders like Marfan's syndrome, Morquio's disease, Blount's disease, achondroplasia, Madelung's deformity and congenital hip dysplasia**, which are also some "first causes" of arthroses**. Examples of other first causes include chondrocalcinosis, rheumatoid disease, pyarthroses and overloads due to joint malalignments and trauma[34].

Nota bene: CMMCC disorders can also cause or help to cause extraskeletal disorders of the ear and nasal cartilages, larynx, trachea and bronchia**.

5) Some recent history.

By 1990 the Utah paradigm suggested this: Neuromuscular function and physiology strongly influence, and may even dominate, control of the biologic mechanisms that determine the postnatal architecture and strength of load-bearing bones, joints, fascia, ligaments and tendons. In 1990 most people thought that idea was too radical to deserve testing, yet by 1999 both live-animal and human studies strongly supported it[25,28-30,43,44]. I and some colleagues (JL Ferretti, WSS Jee, H Schiessl, E Schönau) are now certain that idea is valid. We understand and respect the doubts of others, but those studies clearly show the idea needs serious consideration. Only help from many people and disciplines can test it further, and we invite and welcome that.

The above material helps to explain the Utah paradigm's status in skeletal science, medicine and surgery today, when most people still view it as a "new kid on the block" and wait for proof they could accept of its worth. The ISMNI aims to explore and find how to exploit the above physiology. Neoplasia excepted, the broad domain of the Utah paradigm and the ISMNI includes most skeletal disorders as well as many disorders of soft tissue organs[18].

Conclusion

As for the Abstract's two italicized questions: A) We overlooked the tissue-level skeleton's rich, golden Dorado; B) So, mine it!

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