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Review article

The Utah paradigm of skeletal physiology: an overview of its insights for bone, cartilage and collagenous tissue organs

Harold M. Frost

Department of Orthopaedic Surgery, Southern Colorado Clinic, P.O. Box 9000, Pueblo, CO 81009-9000, USA

Abstract In a 1960 paradigm of skeletal physiology, effector cells (chondroblasts, fibroblasts, osteoblasts, osteoclasts, etc.) regulated by nonmechanical agents wholly determined the architecture, strength, and health of bones, joints, fascia, ligaments, and tendons. Biomechanical and tissue-level phenomena had no roles in that paradigm. Subsequent studies and evidence slowly revealed skeletal tissue-level mechanisms and their functions, including biomechanical ones, as well as "game rules" that seem to govern them. That slow discovery process found that effector cells are only parts of tissue-level mechanisms, as kidney cells are only parts of nephrons and wheels are only parts of cars. Normally all those things help to determine skeletal architecture, strength, and health, and adding them to the 1960 paradigm led to the still-evolving Utah paradigm of skeletal physiology that concerns, in part, how load-bearing skeletal organs adapt to the voluntary mechanical loads on them. That caused controversies this article does not try to resolve; instead, it describes some issues they concern. In that regard, controversy can depend on how one assesses the relevance of facts to a problem more than on their accuracy. If a paradigm added new facts to a former one and the new one's advocates viewed all those facts as relevant, but the former's advocates questioned the relevance of some of the new facts, their views about a problem could differ even though each view depended on accurate facts. Readers would make their own judgments about the bearing of those ideas on this article's content.

Key words Utah paradigm · Bone · Joint · Ligament · Biomechanics · Osteoporosis

Introduction

New insights have begun to affect our ideas about the pathogenesis, diagnosis, management, and research of many skeletal disorders. This article explains some history behind some of the resulting controversies and some salient features of the two paradigms that incited them.

Given that, before 1950 all mammalian physiologists knew that understanding renal function required understanding both the kidney's many kinds of cells and the functions of tissue-level nephrons made with those cells. The nephrons provide functions no single kind of cell can provide but ones that are essential for the organ's health. That would make it naive to try to explain renal function solely in terms of "kidney cells." The same idea applies to the lung, gut, liver, and heart, as examples.

However, ideas about skeletal physiology and disorders took a different path. To explain, for a moment let bone exemplify the skeleton's load-bearing structural tissues (which include cartilage and collagenous tissue too). By 1900, histologists knew osteoblasts make bone and osteoclasts resorb it. Although histological evidence of its tissue-level "nephron equivalents" was available then [1], its significance was not appreciated before 1964. Ergo, by 1930 it was generally assumed that osteoblasts and osteoclasts (bone's *effector* cells) determine most bone health and disease under the control of nonmechanical agents (Table 1), and that was done chiefly to meet homeostatic needs [2–4]. Because all the skeleton's tissue-level mechanisms and biomechanical influences remained unknown before 1964, by 1960 those ideas had become a "1960 paradigm" of bone physiology [3,4]. That paradigm was extended to collagenous tissue and cartilage, also [5,6], for which fibroblasts and chondroblasts, respectively, provide the effector cells. One could express the basic idea (that still lingers [7–10]) as it applies to bone thus:

Agents → *effector cells* → *bone health/disorders* (1)

By 1964, however, a few workers, Prof. W.S.S. Jee and myself among them, had begun to recognize and study

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Table 1. Some of the nonmechanical factors that can influence skeletal physiology

Calcium
Morphogens
Vitamin D
Hormones
Amino acids
Local pH
Thiazides
Genes
Age
Other minerals
Other cytokines
D metabolites
Blood P_{O_2}
Lipids
Bisphosphonates
Other drugs
Gene activation
Race
Mitogens
Apoptosis
Other vitamins
Blood CO_2
Local osmolality
Dilantin
Cell receptors
Gene repression
Sex

some of the skeleton's tissue-level nephron equivalents. Aided by Hard Tissue Workshops and numerous people from many nations and disciplines, gradually biomechanical and other functions of those tissue-level equivalents, and some rules that govern their activities, became apparent. That formerly hidden "dimension" of skeletal physiology led to the still-evolving Utah paradigm of skeletal physiology that supplements the 1960 paradigm (and Wolff's law for bone, too [11]). In the newer paradigm's view, trying to understand skeletal physiology and disorders solely as functions of effector cells could be like trying to understand this article by knowing the alphabet but no vocabulary or grammar. In the newer paradigm, tissue-level nephron equivalents could analogize a vocabulary, and their special functions and "game rules" could analogize a grammar [12–26].

Because cartilage and collagenous tissues have their own tissue-level "nephron equivalents" [8,16–18], the newer paradigm builds on the following idea, where "agents" include both mechanical and nonmechanical ones and "skeletal" replaces "bone" in Eq. 1:

$$\begin{array}{l} \textit{tissue-level} \\ \textit{mechanisms} \end{array} \rightarrow \textit{effector cells} \rightarrow \begin{array}{c} \textit{skeletal health/} \\ \textit{disorders} \end{array} \qquad (2)$$
$$\uparrow \ldots . \textit{agents} \ldots . \uparrow$$

An overview follows of some of the new paradigm's features. The overview concerns postnatal life and does not discuss the dental system.

The Utah paradigm: some of its features

Proposition #1

In this paradigm, load-bearing skeletal organs (bones, joints, fascia, ligaments, tendons) would have the main purpose of satisfying "Proposition #1" [27,28]. To wit: *Healthy skeletal organs provide only enough strength to keep postnatal voluntary loads, whether chronically subnormal, normal or supranormal, from causing spontaneous fractures, ruptures, arthroses, or pain*. Achieving that state of "mechanical competence" would provide the ultimate test of a skeletal organ's health and be the main goal of its biological mechanisms. For example, bone functions such as homeostasis would be secondary to the mechanical one, and only disorders in bone's adaptive biological mechanisms would cause failures to achieve that competence.

That begs two questions: *What are those adaptive biological mechanisms? What do they do?* Answers follow.

The basic tissue-level biological mechanisms: growth, modeling, remodeling, and maintenance

Assuming steady-state effects [29] and excepting neoplasia, the immune response, and inflammation, four biological mechanisms determine most postnatal features of healthy skeletal organs [30].

Undirected growth increases the number of cells and amounts of intercellular materials to produce shapeless, disorganized masses of tissue. When external influences potentiate that growth in some places and retard it in others to produce biomechanically purposeful shapes, sizes, and organization, that defines tissue- and organ-level modeling [24,30]; it is analogous to making and shaping a statue with clay or plaster of Paris. Modeling of skeletal organs can increase but not decrease their strength and the amounts of structural tissue they contain. It also determines their shape and helps growth to determine their size (to repeat, those organs include bones, joints, fascia, ligaments, and tendons) [18,26].

Another tissue-level remodeling activity turns bone over in small packets called BMUs (basic multicellular units) [30]. In its "conservation mode" this does not cause gains or losses of bone, but "disuse-mode" remodeling removes more bone than it makes so bone losses occur, usually next to marrow, meaning of endocortical and trabecular bone [31,32]. Analogous tissue-level activities and effects occur in collagenous

tissues [17], and cell-level analogues of these presumably occur in cartilage [18,29,33,34].

After a structural organ's formation, some of its cells perform maintenance functions that maintain or help to maintain its physical and chemical properties and composition and the responsiveness of its biological mechanisms to varied stimuli. In part this involves osteocytes in bone, fibrocytes in collagenous tissues, chondrocytes in cartilage, and odontoblasts and cementocytes in the teeth [4,30]. An important maintenance function detects and repairs microdamage, as discussed later.

That begs another question: *What controls or helps to control these mechanisms and activities?* More answers follow.

Loads, strain, thresholds, and muscles

Mechanical loads on load-bearing skeletal organs deform them, even if slightly [24]. Directly or indirectly, after birth these changing deformations or dynamic strains help to control and guide these biological mechanisms in time and anatomical space while the mechanisms determine the architecture and strength of skeletal organs.

Where dynamic strains exceed a skeletal tissue's modeling threshold range (MESm), its mechanically controlled modeling turns on to increase the local strength and reduce later strains; that can involve adding more tissue or changing a structure's micro- and macroarchitecture [26,28,35]. Where strains stay below that range, mechanically controlled modeling stays turned off.

For load-bearing bones, when dynamic strains stay below a lower remodeling threshold range (MESr), disuse-mode remodeling removes bone next to marrow to decrease bone strength and "mass." When strains exceed that range, conservation-mode remodeling begins to conserve bone strength and "mass" [25,28]. Analogous tissue-level activities provide equivalent responses in load-bearing collagenous tissue organs [5,36], and analogous activities seem to do this in load-bearing cartilaginous structures [16,34,37,38].

The signaling mechanisms that help to control those activities have become a separate field of study in skeletal science [38–45]. Strain-dependent signals are thought to include fluid flow and electrical streaming potentials. As in squeezing a wet sponge, strains of these tissues make their interstitial water flow back and forth inside and out of them. The signals may also include piezoelectric and other effects. For bone and, at present, the cells that help to detect and process its strain-dependent signals are thought to include osteocytes, bone-lining cells, some cells in the marrow and periosteum, and possibly existing osteoblasts and osteoclasts [24,41–43]. Chondroblasts and chondrocytes presumably help in that regard in cartilage [38–40], as fibrocytes and perhaps other cells do in collagenous tissue organs. The possibilities that different kinds of signals detected by different kinds of cells may help to control the different modeling, remodeling, microdamage detection and repair, and any other activities and functions in each of those tissues still need systematic study.

Because the largest loads on skeletons come from muscles, not body weight [24,46], muscles also cause the largest dynamic strains; that makes momentary muscle strength strongly influence the architecture and strength of growing and adult skeletal organs [22–24]. As Burr and others noted, like bone "mass" [47–51] muscle strength usually increases during growth, peaks in young adults, and declines slowly afterward [46,52–55].

An analogy may help to understand those features. Let heat = a skeletal organ's strength (let "=" mean "be like"), let its modeling = heating, let its remodeling = cooling, and let thermostats = the strain thresholds that help to control modeling and remodeling. Then, one thermostat can make a house furnace add heat when there is not enough, but it turns the furnace off when there is enough or too much heat. A different thermostat can make the cooling system remove heat when there is too much, but it turns the cooling off when there is enough or too little heat. In similar ways the modeling and remodeling thresholds would distinguish enough from too little or too much strength for a load-bearing organ, but in the special sense of relative to the voluntary loads on it. Of course this questions the idea that mainly genetic factors would predetermine such things.

Those thresholds would make the largest loads and strains strongly influence the strength and "mass" of load-bearing organs, and would cause smaller loads and strains, no matter how numerous, to have little effect, as seems to be true [24,53–55]. Figure 1 shows how those thresholds and responses to mechanical loading can affect bone strength and "mass." Similar ideas could apply to collagenous tissue organs.

Microdamage

Large enough strains as well as more frequent ones cause microscopic fatigue damage (MDx) in all skeletal organs [56,57]. Enough of it can cause spontaneous fractures of bones, spontaneous tendon and ligament ruptures, and, in articular cartilage, arthroses of joints (osteoarthritis) [55]. Because all "spontaneous" fractures and ruptures should stem from excessive accumulations of MDx, they would not really be spontaneous [56]. Bone, cartilage, and collagenous tissues have biological mechanisms that can detect and repair

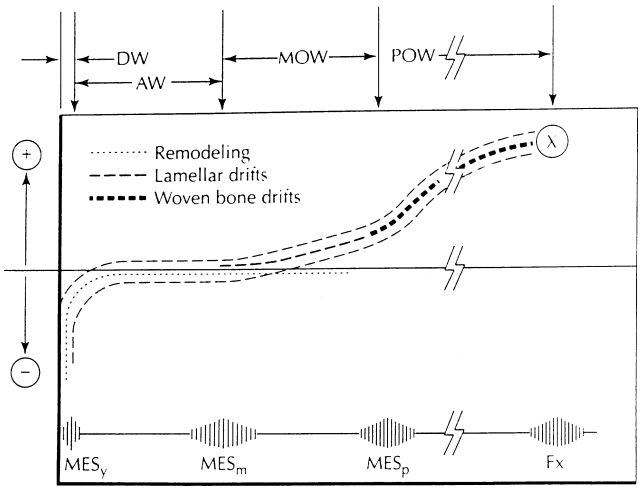

Fig. 1. Combined modeling and remodeling effects on bone strength and "mass." The *horizontal line at the bottom* suggests typical peak bone strains from zero on the *left*, to the fracture strain on the *right* (*Fx*), plus the locations of the remodeling, modeling, and microdamage strain thresholds (*MESr*, *MESm*, and *MESp*, respectively). The *horizontal axis* represents no gains or losses of bone strength or mass. The *lower dotted line curve* suggests how remodeling would remove bone when strains stay below the MESr range, but otherwise would begin to keep existing bone and its strength. The *upper dashed line curve* suggests how modeling would increase bone strength and "mass" where strains enter or exceed the MESm range. The *dashed outlines* suggest the combined modeling and remodeling effects (Carter first suggested such a curve in 1984 [117]). At the *top*: *DW*, the disuse window; *AW*, the adapted window as in normally adapted adults; *MOW*, the mild overload window as in healthy growing mammals; *POW*, the pathological overload window. The Utah paradigm suggests that a similar property would apply to growing joints, fascia, ligaments, and tendons (Reproduced from [95], with permission)

limited amounts of their MDx (remodeling BMUs repair it in bone) [24,56,58–60]. Normally modeling makes load-bearing organs strong enough to keep their MDx below those limiting amounts, which can define operational MDx thresholds (MESp). Those thresholds would lie above the modeling thresholds but well below the ultimate strengths of the skeleton's structural tissues. This arrangement clearly occurs in bone and collagenous tissues, and it probably also occurs in articular cartilage, where accumulated MDx can cause chondromalacia, fissuring, chondral debris, a synovitis, other changes, and, in time, an arthrosis [33,58,61].

A laddered relationship between these thresholds seems to occur in load-bearing skeletal organs (weakly loaded exceptions include the ethmoids, turbinates, cranial vault, and nasal bones, the tracheal, ear, and nasal cartilages, and the collagenous capsules of soft tissue organs; see following) [28]). Let MESr, MESm, and MESp signify the remodeling, modeling, and microdamage thresholds, respectively, of such organs, let "E" signify typical peak strains caused by voluntary physical activities, and let Fx signify a tissue's ultimate strength or strain. Then:

$$MESr < \text{“}E\text{”} < MESm << MESp <<< Fx) \qquad (3)$$

Healthy load-bearing skeletal organs should satisfy Eq. 3 to attain mechanical competence and satisfy Proposition #1. According to the Utah paradigm, that would be the main goal of a load-bearing skeletal organ's adaptive biological mechanisms and the ultimate test of its health.

The mechanostat hypothesis

Let "mechanostat" signify the collection of things that makes load-bearing bones, joints, fascia, ligaments, and tendons seem to satisfy Proposition #1 in all healthy amphibians, birds, mammals, and reptiles of any kind, size, age, and sex [24,62]. Each skeletal structural tissue would have its own mechanostat and effector cells. View a mechanostat as resembling the combination of a car's steering, brakes, accelerator, wheels, and driver. Their skeletal analogues would include in part the modeling and remodeling mechanisms, their thresholds, the microdamage thresholds, the effector cells (analogues of the wheels), and, in cartilage and collagenous tissues, the creep and creep compensation mechanisms (which this text does not discuss) [16–18]. Voluntary mechanical usage would analogize the car's driver. As a combination, they would help to control the postnatal strength, architecture, and "mass" of each load-bearing skeletal organ. Hormones, drugs, and other agents might modulate the combination's functions and how skeletal organs satisfy Proposition #1 [13,22,23,31].

The mechanostat hypothesis suggests that, when agents only act on effector cells, after an initial change in the organ's strength such effects should tend to plateau [62]. Such plateaus usually signify negative feedback systems at work, as monographs on cybernetics by Regling and Wiener indicate [63,64]. For example, when low pressure in a tire pulls a car toward the right, the steering wheel can compensate to keep driving straight ahead. Equally, if an agent only depressed osteoclastic activity, the bone's mechanostat could make modeling and remodeling limit the effects of that depression on bone strength and "mass" so that they would tend to plateau.

A qualification: The mechanostat hypothesis applies to organs that adapt their strength and architecture to peak voluntary loads to satisfy Proposition #1. In some organs, however, such loads do not seem to control those features. As examples, the frontal and parietal bones do not carry large enough loads to explain their

considerable strength as adaptations to loads and strains. That observation would also apply to some other cranial bones such as the nasal bones, ethmoids, turbinates, and inner ear ossicles, and also to the nasal, ear, and tracheal cartilages. Such observations show that factors other than mechanical forces can control the architecture and strength of such organs [18,28]. The mechanostat hypothesis does not exclude or try to explain such effects (but see next).

The "baseline conditions" [18,29]

At birth, a skeleton's adaptive biological mechanisms and the ways they will respond to postnatal mechanical and nonmechanical influences already exist, as do the basic shapes and relative sizes of skeletal organs, their relationships to other structures, and neuromuscular anatomy. Those "baseline conditions" should chiefly reflect gene expression patterns in utero. At any time after birth the skeletal organs in neonatally paralyzed and normal limbs show typical differences in their strength, "mass," architecture, and tissue dynamics. Those differences should reveal the kinds and magnitudes of the adaptations to postnatal mechanical loads in the normal limbs. Structures in the totally paralyzed limbs should reveal the baseline conditions, affected by postnatal nonmechanical agents but not by normal postnatal loads.

Such factors suggest postnatal skeletal "mass" and strength have at least two components: one would meet postnatal mechanical needs, while the second could meet other if still speculative needs. Could that help to explain why, in total and permanent disuse, bones, fascia, ligaments, and tendons never disappear completely so that some structural tissue always remains?

The regional acceleratory phenomenon [24,29]

Injuries and other noxious stimuli usually increase all ongoing biological activities in the affected region of the body [65]. The increases include local perfusion, cell metabolism and turnover, and any ongoing growth, modeling, remodeling, healing, maintenance, or immunological activities. Those factors constitute the regional acceleratory phenomenon (RAP), which also causes long bone overgrowth after some fractures in children [66,67]. Failure to develop a RAP can retard skeletal tissue healing, as often occurs in the lower extremities of patients with diabetic neuropathy [21,24,68,69]. A RAP usually responds to great local need, and it causes three of the classical signs of inflammation: edema, erythema, and increased warmth. Pathological RAPs also occur and are known as algodystrophies or migratory osteoporoses [70,71].

Aging effects, and transient and steady states

On aging. The skeleton's responsiveness to some stimuli seems to decrease with aging. Some believe decreased numbers of the stem cells that create new effector cells could help to explain that decrease in responsiveness [72,73]. Aging also affects the ability of skeletal organs to change their strength to fit changes in their loads. Throughout life that ability works reasonably well in collagenous tissue organs. For bones, it works best during general growth; bones in adults have trouble increasing their strength in response to increased loading [53]. Throughout life joints cannot decrease in size in response to decreased loading, but in children (not in adults) they can increase modestly in size in response to increased loading [54,55]. Here, "increased loading" means larger loads, not more frequent ones.

Transient and steady states. Because of the composition, organization, and functions of the skeleton's multicellular nephron equivalents, a sudden competent stimulus must cause initial changes in their activities ("transients"), but later on other changes that can continue indefinitely ("steady states") must replace the initial changes [29]. Transients do not duplicate or suggest the later steady-state effects, and they seldom if ever cure skeletal disease. Only steady-state effects can cure most skeletal diseases. Those features, well known to histomorphomotrists who do live animal experiments [12,21,26,35,65], can help us to understand drug and treatment effects and design good experiments [21,24].

What "drives" the skeletal "car"?

In the Utah paradigm, mechanical factors would dominate the control in time and anatomical space of the postnatal strength, architecture, and "mass" of load-bearing skeletal organs. Most nonmechanical factors, like those in Table 1, could only help or hinder that process. For example, years after a paraplegia the lower-extremity bones can lose more than 40% of their strength and "mass" [74] while upper-extremity bones lose none, apparently no matter how much calcium, vitamin D, or calcitonin the patient might take meanwhile. Yet, the same blood carries the same nonmechanical agents to all extremities, the cells of which have the same genome. Even larger strength deficits occur in lower-limb bones, tendons, and joints in complete paraplegias caused by myelomeningocele. Such disorders question the idea that genetic factors predetermine most of our postnatal skeletal strength and "mass." Parenthetically, currently popular bone mineral "density" studies [51] do not provide reliable indicators of whole-bone strength [48–50].

Another analogy may clarify this paradigm's views on such matters. To discover why a car went to Paris instead of Berlin one would study its steering, accelerator, brakes, and driver instead of its wheels. Equally, in this paradigm's view (and in my view, too), one would more likely find an explanation for an osteoporosis, arthrosis, or spontaneous tendon rupture in the skeleton's nephron equivalents than in its effector cells. This idea also causes some controversy and it should take time, more work, and help from others to determine its validity.

Some applications of this physiology

The foregoing points raise one more question: *How might the newer physiology affect our approach to and views about some skeletal disorders?* Suggestions follow.

Two implications of that physiology

If neuromuscular physiology and anatomy and momentary muscle strength strongly influence skeletal adaptations to mechanical usage, and if the thresholds in Eq. 3 help to distinguish good from poor adaptations, at least two things should follow. (1) Future research should study the relationships between mechanical usage and muscle strength on the one hand and skeletal growth, development, and disorders on the other hand. (2) Numerous possible malfunctions of that arrangement should cause or help to cause many kinds of disorders. Many do occur, and some are mentioned next.

Bone and load-bearing bones

Relative to voluntary loads, the rules that govern bone modeling would make it provide the necessary whole-bone strength with the least amount of bone tissue, where "necessary" means making bones satisfy Proposition #1. Bone remodeling repairs microdamage by removing and replacing the damaged bone with new bone. Among other things, failure to do it should and does cause stress fractures in athletes and military inductees [56,75], spontaneous fractures in some osteoporoses [51], and pseudofractures in osteomalacia [76]. Conservation-mode remodeling should and does maintain bone strength and "mass" to prevent an osteopenia or progression of an existing one. Disuse-mode remodeling (not osteoclasts alone) seems to cause all adult-acquired osteopenias on earth and in orbit by removing bone next to marrow [28]. Therefore, depressing disuse-mode remodeling with antiremodeling agents should and does tend to prevent osteopenias [21,27,31,77]. While turning modeling formation drifts on (not osteoblasts alone) should and can cure an osteopenia, at least temporarily [21,78–82], it seems BMU-based remodeling cannot do that [28]. Chronic muscle weakness from any cause should and does make normal modeling and remodeling potentials cause a "physiological osteopenia" in which voluntary activities do not cause spontaneous fractures, so bones satisfy Proposition #1 [83]. Here only injuries would cause fractures, usually of extremity bones. Yet still-enigmatic modeling and remodeling disorders could cause "true osteoporoses" in which voluntary activities do cause spontaneous fractures, so Eq. 3 and Proposition #1 would not be satisfied and affected bones would be mechanically incompetent. Examples of such osteoporoses include juvenile idiopathic osteoporosis, hyperphosphatasia, and osteogenesis imperfecta, in which the spontaneous fractures can affect both extremity bones and the spine [84]. True osteoporoses also include a kind in women and some men in whom the spontaneous fractures mainly affect the thoracic and lumbar spine instead of extremity bones (the causes of increased extremity bone fractures in osteoporosis are discussed elsewhere [27,85]) [28,51]. BMU-based remodeling helps to replace mineralized cartilage at growth plates with a secondary spongiosa, and failure to do it causes osteopetrosis [86].

In disuse, paralysis, menopause, malnutrition, aging, after ovariectomy, and during microgravity, permanent (i.e, steady-state) bone losses only occur next to or close to marrow [31], even though osteoclasts and BMUs can arise and work in intracortical and on subperiosteal bone, too [32]. Long ago that suggested that some mediator mechanism in marrow helps to control gains and losses of bone next to it [87]. Apparently it can sense some mechanical and nonmechanical influences, some of which can make conservation-mode remodeling prevent an osteopenia or progression of an existing one [31], while others can make disuse-mode remodeling cause a disuse-pattern osteopenia [28].

Table 2 lists some bone features the Utah paradigm can explain plausibly.

Collagenous tissue and load-bearing fascia, ligament, and tendon

Where tension strains exceed a "modeling threshold" range, a nephron-equivalent activity and function analogous to formation drifts in bone adds new collagen to thicken and strengthen these organs. Throughout life, that sluggish "diametric modeling" can increase but not decrease the thickness and strength of such organs [14,26]. When strains stay below that threshold, this mechanically controlled modeling should and does turn off. When strains stay below a lower threshold, as in acute total disuse, another nephron-equivalent activity

Table 2. Some load-bearing bone features the Utah paradigm can explain plausibly[a]

Why only bone next to marrow is lost in osteopenias and osteoporoses
Why most people with an osteopenia do not develop spontaneous fractures or bone pain during voluntary activities
Why muscle strength strongly influences whole-bone strength and "mass"
Why standards for the muscle strength–bone strength relationship are needed
Why postmenopausal bone loss only comes from bone next to marrow
Why most aging adults lose bone strength and "mass"
Why weight lifters have greater bone strength and "mass" than marathon runners
Why men have greater bone strength and "mass" than women
Why stimulating only osteoblasts would not cure an osteopenia
Why depressing only osteoclasts would not prevent an osteopenia
Why drug effects on osteoblasts or osteoclasts in cell or tissue culture systems cannot predict correctly how intact skeletons respond to a drug
Why the 1994 WHO consensus classification of "osteoporoses" needs revision
Why true osteoporoses and disuse osteopenias only affect hollow bones
Why normal bones have a safety factor for their strength, and why its value for cortical bone approximately equals six
Why bones seldom fail in fatigue although bone is a very fatigue-prone material

[a] That an explanation is plausible does not prove it is correct, too. However, a paradigm's usefulness increases as the things it can explain increase. The 1960 paradigm could neither predict nor explain the features listed here and in Table 3

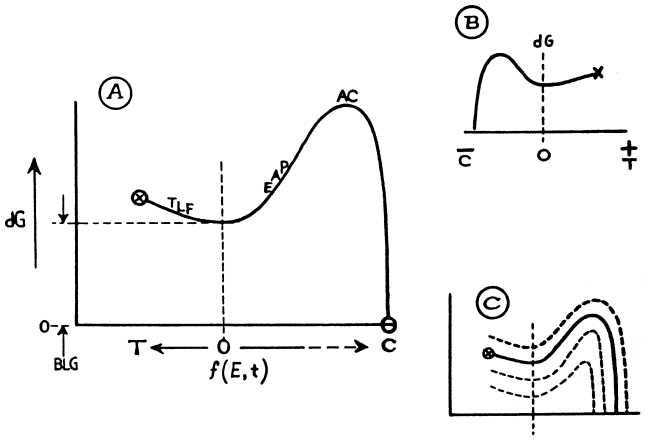

Fig. 2. The chondral growth force response curve (CGFRC). **A** CGFRC: *TLF*, cartilage layers at the bony attachments of tendon, ligament, and fascia; *EAP*, epiphyseal and apophyseal growth plates; *AC*, articular cartilage. The *horizontal axis* plots mechanical loads on or strains of a cartilage layer such as a growth plate or an articular cartilage. Maximum tension lies on the *left* (*T*), compression on the *right* (*C*), and zero load in the *middle* (*0*). The *vertical axis* plots the speed of growth, e.g., in millimeters per year. Under no load, some "baseline growth" (*BLG*) occurs in children. **B** Tension is plotted on the *right* and compression on the *left*, as engineers usually give the former negative values and the latter positive ones. Because different cartilage layers probably have different responsiveness to a given load or strain, the family of *curves* in **C** suggests how such different growth speed potentials might cause different amounts of modeling in response to the same loads or strains, but without necessarily changing the pattern of their responses to changes in loads or strains; this might help to explain why chondral layers grow slower in fingers and mice than in knees and giraffes (Reproduced from [30], with permission)

analogous to disuse-mode bone remodeling reduces the strength, stiffness, thickness, and collagen content of these organs [5,18]. Ergo, normally its mechanical usage should make the architecture and strength of a fascia, tendon, or ligament satisfy Eq. 3 and Proposition #1; that should and apparently does make a normal tendon's strength always match the strength of the muscle that loads it, and in both paralyzed and normal limbs. Normally these organs should and apparently do detect and repair limited amounts of their microdamage, and their diametric modeling seems to make them strong enough to keep the amounts of microdamage within that limit. Failure for any reason to do that could cause events such as spontaneous ruptures of tendons and chordae tendinae and many inguinal hernias, aneurysms, and varices [18].

Cartilage and joints

A chondral growth–force response curve suggests how mechanical loads can affect how quickly growing articular cartilage layers grow (Fig. 2) [16,88]. That mechanically controlled chondral modeling would determine or help to determine a growing joint's alignment [54], size, shape, surface curvatures and smoothness, and surface congruence [55]. Presumably this tissue's nephron equivalents (which Poole called "chondrons" [89]) provide and control those activities in ways that reduce strains and minimize microdamage in articular cartilage, which can also detect and repair limited amounts of its microdamage. Thus, during growth a joint's mechanical usage should make its chondral modeling produce an architecture, strength, and size that satisfied Eq. 3 and Proposition #1. Numerous possible disorders in that arrangement ("first causes") could let enough articular cartilage microdamage accumulate (the "final common cause") to cause an arthrosis, i.e, osteoarthritis or degenerative joint disease [55]. Many examples of such "first-cause" disorders are known [33].

At the 1986 Hard Tissue Workshop, I suggested joint design minimizes arthroses by minimizing micro-

Table 3. Synovial joint features the Utah paradigm can explain plausibly

Why joint surfaces are smooth and reasonably congruent in the directions of the relative motions of their surfaces
Why a small amount of joint surface incongruence normally exists and persists
Why, during growth, joint surface curvatures of a given joint like the knee decrease more in normal than in paralyzed limbs
Why larger voluntary loads on a growing joint increase its size
Why most joints have longer fatigue lives than a person's life span, although articular cartilage is a very fatigue-prone material
Why joint surfaces usually align perpendicularly to the line of action of the usual loads on them
Why most arthroses affect adults and seldom occur in children
How an inflammatory arthritis can cause a later arthrosis
The role of menisci in the knee, temporomandibular joint, and other joints, and why some kinds of meniscal derangements can cause arthroses
Why increased subchondral bone "mass" or "density" can cause an arthrosis
Why normal joints have a safety factor for their strength relative to the usual voluntary loads they carry
Why an arthrosis could have numerous "first causes" (biochemical, biomechanical, cell-biological, genetic, traumatic)
What causes the ball-and-socket ankle joint, genu varum and valgum, Madelung's deformity, coxa valgum, idiopathic scoliosis, and cubitus valgum
What causes congenital hip dysplasia, and hip dislocations in spastic children
Why a painful but secondary synovitis accompanies some arthroses

Adapted from [55], with permission

damage. While that idea caused some controversy it has growing support [61] (to quote D.R. Eyre, "Damage to the collagen framework of articular cartilage is a critical event in the pathogenesis of osteoarthritis." [58]), but the matter is not yet resolved. Chondral modeling disorders, not bone disorders, cause such conditions as genu valgum, Blount's disease (tibia vara [89]), idiopathic scoliosis, Madelung's deformity, and congenital hip dysplasias and dislocations [88–91]. The normal chondral modeling capability decreases profoundly after skeletal maturity, so adult joints should depend mainly on their maintenance activities to endure their mechanical usage. That may explain why joint overloads that develop after skeletal maturity, as in adult-acquired obesity, for example, became a known cause of some arthroses [33]. Table 3 lists some joint features the Utah paradigm can explain plausibly.

Skeletal tissue healing

A role of strain [69,92]. Many nonmechanical agents participate in hard and soft tissue healing, but strain seems to have important roles in it, too. When strains stay near zero, this healing usually retards, whereas excessive strains (excessive motion) can prevent healing [93,94]. In a middle ground, presumably in the adapted and mild overload "windows" in Fig. 1, strains seem to potentiate healing, provided an adequate regional acceleratory phenomenon occurs [94].

The four essential tissue-level healing phases. Normal hard and soft tissue healing involves four different but absolutely essential tissue-level and nephron-equivalent phases [68,94]. Initially a very soft and compliant callus of some kind welds the fractured, ruptured, or incised parts together. Then, a remodeling mechanism begins to replace the callus with the mature kind of tissue. Overlapping this, modeling activities also begin to shape, size, and organize the transforming callus in ways that should tend to keep its strains from exceeding the mature tissue's modeling threshold. A concurrent local regional acceleratory phenomenon accelerates the other three phases [29]. In humans, the whole healing process takes months to finish, and longer in adults and large subjects and organs than in growing and small subjects and organs.

Malfunctions of any one of those phases can cause healing problems and failures, even when the other phases proceed normally [94]. Such "biological failures" differ from "technical failures" caused by treatment errors [68]. As those phases progress, several mechanisms also make the healing region slowly increase in strength and stiffness from nil to optimal. As a result, and as long known by orthopaedic surgeons, early in the healing process very small loads can cause large enough strains to disrupt and stop subsequent healing. This effect could cause a still underappreciated problem in efforts to cause human articular cartilage injuries and defects to heal [95].

So far, studies of the cell and molecular biology involved in hard and soft tissue healing, as well as studies of agents hoped to enhance it, concentrated on effector cells and overlooked the roles of the nephron equivalents. Also, and in my view erroneously, people doing such studies usually viewed that healing as a single indivisible process that depended wholly or chiefly on cell-level effector cell activities.

Conclusion

This article omits some features of the Utah paradigm that are described elsewhere [18,26,96], but four things deserve concluding comments.

Quo vadis?

Past efforts to understand skeletal physiology focused heavily on effector cells and recently on their creations

[5,7–10,33,34,97,98]. The Utah paradigm's insights suggest that could be like trying to understand renal physiology by studying kidney cells but not nephrons [29,99]. If so, research also needs to study the cell- and molecular biological roots and organization of the skeleton's nephron equivalents. In other words, besides studying the in vitro effects of genes, cytokines, telomerase, ligands, or apoptosis as examples on "osteoblast-like cells," one should also study their in vivo effects on the nephron-equivalent functions summarized earlier [29]. Among others, Parfitt echoed that idea [99–103], and for nearly five decades Dr. Jee's laboratory pioneered ways to obtain such information in live animal experiments [19–22,104–108]. The foregoing studies should depend heavily on them. Why? It seems few if any of the skeleton's nephron equivalents function normally in current cell, tissue, and organ culture systems [29,99].

On collagen–cell mechanical interactions

Some such interactions may help to control skeletal modeling and remodeling responses to mechanical loads and strains. Besides type I collagen in bone, tendon, ligament, and fascia, and type II in hyaline cartilage [30,33], each tissue has lesser amounts of other types, but their possible roles in the foregoing physiology remain unstudied. Yet the regular association of some skeletal modeling and remodeling disorders with abnormal collagens suggests collagen–cell mechanical interactions could have important roles in their pathogenesis. Such disorders include in part arthrogryphosis, Marfan's syndrome, Ehler–Danlos syndrome, and osteogenesis imperfecta [76,86,109–112]. The molecular biology that should support any roles of such interactions on the modeling and remodeling disorders in such conditions also remains unstudied.

Threshold possibilities

Many think some nonmechanical agents including hormones and genes can "modulate" the thresholds that help to control the skeleton's nephron-equivalent functions [12,13,22,28,79,102]. Such agents could modify mechanical effects on skeletal architecture, strength, and health in helpful or harmful ways [13,24,25]. In discussion at the 1997 Hard Tissue Workshop, Michael Parfitt echoed the idea that permanent control of bone "mass" in osteoporoses may depend on controlling bone's modeling and remodeling thresholds and thus its mechanostat [62]. Genetically based changes in bone's modeling and remodeling thresholds could explain plausibly most clinical and radiographic bone features in osteogenesis imperfecta [84,109,113,114].

At present, most interest in this idea focuses on bone, estrogen, parathyroid hormone, and osteoporosis [13,20,78]. Nevertheless, in my view the idea should also apply to joints and collagenous tissue organs. Recently, Ferretti, Schiessl, Schönau, and their colleagues found that a way I suggested to compare muscle strength to bone strength in vivo and noninvasively can help to evaluate such thresholds in humans and laboratory animals [49,110,115,116]. That procedure could provide valuable information about the thresholds in bone, joints, tendon, and ligament that no other presently known noninvasive method can provide, at least in humans.

Interdisciplinary communication and controversies

Although growing evidence supports the Utah paradigm, poor interdisciplinary communication retarded its diffusion in (or acceptance by?) the general skeletal basic science, medical, surgical, and pathology communities, even though these two paradigms probably describe different sides of the same coin. It will take time and help from others to resolve any resulting controversies. As two of the Utah paradigm's architects, Professor Jee and I invite and would welcome their help.

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