The Utah paradigm: A brief 2003 perspective.

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Introduction

Here a voice from the past would like to share a few thoughts with present and future students of the physiology and disorders of mamalian load-bearing skeletal organs (LBSOs) (bones, joints, growth plates, fascia, ligaments and tendons). Those thoughts concern promising new directions for research that could considerably improve the diagnosis, management and study of skeletal disorders.

Table 1 collects and defines the abbreviations used below.

Pre-1964 ideas about skeletal physiology and disorders: A) In pre-1964 views effector cell (EC) responses to nonmechanical influences (NMI) explained most skeletal physiology and disorders. B) EC responses extrapolated directly to intact skeletons. c) Endochondral ossification excepted, no skeletal tissue-level "nephron-equivalent" mechanisms (NEMs) or "nephron-equivalent" functions (NEFs) were recognized as such, nor were influences of voluntary mechanical loads (VMLs) on skeletal organs, health and disorders. Hence the early emphasis on bone's role in calcium homeostasis [18,21].

Today's situation. Aided by prof. Jee's Hard Tissue workshops [13], by dynamic bone histomorphometry [6-8] , by studies of in vivo bone strains initiated by L Lanyon [15], by other developments in biomechanics [17], and by "connecting the dots" between varied evidence and ideas from many fields of study, many tissue-level skeletal NEMs-NEFs became known by 2002 [11, 12]. That supplemented early views with the still-evolving Utah paradigm of skeletal physiology [11, 12, 22], which inserts belatedly-recognized tissue-level physiology into the former "knowledge gap" between the skeleton's organ level realities and its cell-level and molecular-biologic realities.

That paradigm provides a foundation on which younger people than me could build in the future. Some of the paradigm's features follow.

Twelve general features of healthy postnatal

TABLE 1 Definition of abbreviations

CT:	calcitonin.
EC:	effector cells, the ones that make or resorb skeletal tissues. Not their precursor or other kinds of cells (hence osteoblasts and osteoclasts in bone, chondroblasts and chondroclasts in cartilage, fibroblasts and giant cells (?fibroclasts?) in collagenous tissues).
LBSO:	a load-bearing skeletal organ (bone, joint, growth plate, fascia, ligament, tendon). Some nonLBSOs include the cranial vault, ear and nasal cartilages, and pleural fascia.
MST:	a mechanostat that would orchestrate adaptations of an LBSO's architecture and strength to its VMLs.
NEM:	a nephron-equivalent skeletal mechanism.
NEF:	a function provided by a skeletal NEM.
NMI:	nonmechanical influences (genes, hormones, vitamins, minerals, drugs, cytokines, chemokines, ligands, cell receptors, etc).
VML:	a voluntary mechanical load, which implies muscle forces on LBSOs.

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mammalian load-bearing skeletal organs (LBSOs). 1) Mammalian skeletons have many LBSOs and some nonLBSOs. 2) LBSO functions include having enough strength to keep VMLs from breaking or rupturing LBSOs and, for joint surfaces, having the sizes, shapes and surface congruence that can prevent arthroses [12]. 3) By the time of birth gene expression patterns in utero have created a skeleton's "baseline conditions", including its basic anatomy and the biologic "machinery" that can adapt LBSOs to their postnatal VMLs.

That machinery includes the next seven tissue-level features. 4) After birth at least one NEM called modeling can increase the strength of each LBSO, 5) and at least one disuse-mode NEM can decrease its strength. 6) Strain-dependent signals can monitor the relationship between each LBSO's Strength and the VMLs on it, 7) and threshold ranges of those signals plus dedicated signalling mechanisms help to control the NEFs of those NEMs. 8) Each LBSO can detect and repair limited amounts of its microdanage, which would have its own threshold range in bone, cartilage and collagenous tissue. 9) Cartilage and collagenous tissues have cellular mechanisms that can detect, limit, and/or correct limited amounts of, plastic flow in tension (irreversible stretching) [12]. 10) Combining such things with feedback between them forms negative feedback systems called mechanostats (MSTs), and bone, cartilage and collagenous tissues should have their own MSTs. Michael parfitt called bone's MST the "....most important unsolved problem in bone physiology." [20].

11) After birth and on earth, MSTs adapt LBSO strength and architecture chiefly to muscle strength, because lever arm and gravitational effects make muscles put by far the largest VMLs on such organs [2]. 12) Bone's NEMs and NEFs do not function normally in current in vitro systems so live-animal research should study them [14]. Presumably that applies to the NEMs and NEFs for cartilage and collagenous tissues too [12].

COMMENTS

1) Bone people studied the above features more and longer than cartilage and collagenous tissue physiologists, so the bone-related features became better known and supported by firmer evidence [3-5,11,12,16,17].

2) The above 12 features identify some tissue-level NEMs and NEFs in all LBSOs that help to provide an organ's chief functions, just as nephrons provide most renal functions. Cell- and molecular-biologic mechanisms must support such NEMs and NEFs. Yet while skeletal cellular and molecular-biologic research advanced spectacularly [1], little of it studied how such things support the above tissue-level features. That would be like studying renal physiology by studying renal cells but ignoring nephrons. Hence an important "knowledge gap" (the NEMs and NEFs) arose between skeletal organ-level realities, and cell-level and molecular-biologic realities. Future research must fill that gap.

3) Three effects of that knowledge gap should concern future skeletal scientists and clinicians. (i) Finding how cell- and molecular-biologic phenomena support the skeleton's tissue-level features offers huge opportunities for unusually important future research. (ii) Each of the above 12 features needs more testing and study; hence more opportunities for such research. (iii) Future progress could depend strongly on combining cell and molecular-biologic expertise and work with live-animal expertise and research as well as with insights of the Utah paradigm [14].

4) Ignoring the connections between the skeleton's NEMs-NEFs and clinical evidence still causes "jumping frog errors" [9] (of which I made my share). Three examples follow. (i) After calcitonin (CT) was found to hinder osteoclasts in vitro, some

thought CT would cure "osteoporosis". Yet it did not, as mechanostat physiology would predict [11]. (ii) The 1940-1950 idea that supplemental dietary calcium would cure "osteoporosis" met the same fate [11]. (iii) Authors of a study of mechanical loading effects on growth plates concluded that "....compressive force suppresses growth rates, even at low.... loads" [19]. If so that must make growing bones in paralyzed limbs longer than in normal limbs, but clinicians know the opposite always occurs [10,12]. Also, in numerous in vivo studies partial deloading of limbs never increased longitudinal bone growth. These authors ignored such evidence (perhaps to promote a hidden agenda?).

5) In conclusion, the Utah paradigm provides a foundation for, and reveals many targets for, future skeletal research. Because reasonable people can devise different explanations for the facts that paradigm stands on, some people might question parts of it. If so more discussion, work and time should resolve such issues, and my crystal ball suggests the paradigm will survive such tests. I and numerous other people helped to create that foundation, but age took me out of that "game" so younger people must build on it when and however they wish to.

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