

The Utah paradigm on animal models of skeletal disorders: Quo vadis?

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Abstract

Skeletal disorders that need effective studies in suitable animal models include “osteoporosis”, arthroses and hard and soft tissue healing. For people doing or analyzing such studies this article provides a brief overview and some salient implications of the Utah paradigm of skeletal physiology. The article leaves discussing and resolving any disagreements and controversies about such things to other times, places and people.

Keywords: Skeletal Physiology, Biomechanics, Osteoporosis, Arthroses, Healing, Space Medicine

Introduction

Trauma excepted, the world’s most troublesome and commonest skeletal disorders probably include “osteoporosis”, osteoarthritis, and hard and soft tissue healing problems. This article concerns some problems in using animal models to study them and the relevant skeletal physiology. In brevity’s interest it must deal succinctly with salient features. In other articles Dr. WSS Jee and others discuss that matter from other perspectives.

After 1950 some people began to suggest that live animal work could stop because in vitro work could find what we needed to manage such disorders. But while in vitro work made impressive progress it has serious limitations that only live animal work can overcome. Explaining why requires summarizing the roots and nature of an old and new paradigm of skeletal physiology, and some of the implications of the new one.

The two paradigms

On extraskeletal physiology

Since 1940 all physiologists knew three general facts about extraskeletal physiology.

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1. Soft tissue organs (liver, lung, kidney, pancreas, etc) provide chiefly chemical functions, where “chemical” has the broadest meaning.
2. The physiology of those organs depends on tissue-level mechanisms that provide essential functions no single kind of cell can provide, and without them we can die¹. Examples of such mechanisms include the renal nephron, hepatic lobule, pulmonary alveolus and island of Langerhans.
3. Chemically-dedicated negative feedback systems use chemical factors to control those functions and any mechanical activities they depend on, such as peristalsis, breathing, circulation of the blood, ciliary action, pinocytosis, etc.

On skeletal physiology

No skeletal tissue-level or “nephron-equivalent functions” at all were known before 1964. Ergo, between 1900-1960 three hidden assumptions were made about skeletal physiology.

1. A skeleton’s effector cells would mainly determine its health and disorders, where effector cells are osteoblasts and osteoclasts in bone, chondroblasts in cartilage, and fibroblasts in collagenous tissues. Those are the cells that actually make or resorb tissues. They exclude the osteocytes, chondrocytes and fibrocytes that would participate in the associated signalling, maintenance and other activities.
2. Effector cells would do that under the control of chemical and genetic factors without important mechanical input.

3. Unlike soft tissue organs, skeletons did not have tissue-level nephron-equivalent mechanisms and functions.

Hence the basic 1960 paradigm of skeletal physiology, which was universally accepted in 1960²⁻⁴. With some modifications it still lingers⁵⁻⁹.

But in the 1960s Dr. WSS Jee and I began to find and study the skeleton's tissue-level nephron-equivalent functions. Aided by superb people in many disciplines and by the University of Utah's uniquely seminal Hard Tissue Workshops, that work revealed new general facts. Among them:

1. Skeletons exist mainly to provide mechanical functions.
2. Skeletons do have nephron-equivalent mechanisms and functions, and many of them.
3. Those mechanisms, of which effector cells are only parts, establish skeletal strength and health.
4. Mechanically-dedicated negative feedback systems use mechanical factors to control those mechanisms and their functions, and any biochemical activities they depend on, and thus to control skeletal strength and health too.
5. Most humoral and other chemical factors that are so important in controlling extraskeletal physiology, can only help or modulate the mechanical control of skeletal physiology.

By 1995-1996, supplementing the 1960 paradigm with those and other facts led to a new paradigm of skeletal physiology that accounts for formerly overlooked tissue-level phenomena that lie in the domain of the skeleton's Intermediary Organization.

Hence the Utah paradigm of skeletal physiology, which keeps evolving to account for even newer facts and ideas¹⁰⁻¹⁴. Nevertheless, when it gelled many considered that "new kid on this block" just as suspect as geologists considered Wegner's idea of continental drift before 1930. While his originally disparaged idea had become a solidly proven fact 40 years later, the Utah paradigm only began that trek ca 1995. Must it too wait 40 years to achieve that status? Only time can tell; stay tuned....

Further skeletal features embodied in the Utah paradigm

1. Nephron-equivalent mechanisms called modeling can increase but not decrease the strength of load-bearing skeletal organs¹⁵⁻¹⁷.
2. Other nephron-equivalent mechanisms can adapt the strength of those organs to acute disuse¹⁸, they can repair limited amounts of their microscopic fatigue damage, they can correct creep in cartilage and collagenous tissues^{16,17}, they can provide longitudinal growth^{16,17,19}, and they can heal injured bone, cartilage and collagenous tissue.
3. As I inferred by 1964, special thresholds that one can express as strains or their equivalents help to control all those activities^{12,14}.

4. The existence and values of those thresholds should reside in some skeletal cells as genetically-determined internal or built-in standards.
5. Those and/or other cells would compare those standards to strain-dependent signals generated by an organ's voluntary mechanical usage.
6. When that comparison reveals an error, one or more other "error signals" would arise to make the appropriate nephron-equivalent mechanism(s) correct the error. Hence our skeleton's Structural Adaptations to its Mechanical Usage (SATMU)¹⁵⁻¹⁸.

People studying animal models of skeletal physiology or disorders should know six effects of those internal standards.

- i. They provide Nature's criteria for monitoring and determining the normal relationship between the strength of load-bearing skeletal organs and the size of the typical peak loads on them.
- ii. They make the largest strains, and thus the largest loads, control the above activities.
- iii. Because muscles cause the largest loads and strains, their strength and anatomy, plus neuromuscular physiology, strongly influence and may even dominate control of the strength and health of load-bearing skeletal organs.
- iv. That arrangement creates safety factors for the strength of such organs; they are stronger than needed for the typical peak loads they carry.
- v. Problems with those things could and do cause numerous skeletal disorders.
- vi. Failure to account for the above features when studying skeletal physiology and disorders in animal models can impair the value of such studies. Those features especially include muscle strength.

Parenthetically, failure to include basal controls can also impair the value of such studies²⁰.

Transient and steady states

As I noted between 1964-1973, due to features of the skeleton's nephron-equivalent mechanisms the initial effects of a treatment (or other stimulus) must be replaced by different and later effects that can continue as long as the treatment does^{21,22}. The initial responses or transients cannot continue indefinitely and cannot cure a skeletal disorder. But the final or steady state responses (not the same thing as equilibrium) do have the potential for curing skeletal disorders; hence one importance of the distinction. Extrapolating transient to steady-state effects always errs. Such mistakes caused many errors and much confusion and controversy in skeletal science and medicine; hence another importance of the distinction. Thus experimentalists and clinicians need to know the soonest time after starting some treatment when its steady-state effects can be studied (i.e, how long would the transients last?). For treatments that affect BMU-based bone remodeling that equals the remodeling period, sometimes called sigma by histomorphometrists²¹⁻²³.

The skeleton's mechanostats²⁴

All the above things combine to form more complex tissue-level negative feedback systems we call "mechanostats". Thus one kind of cell does not make a mechanostat, and effector cells are only small parts of one. Bone, cartilage and fibrous tissues would have their own mechanostats, which seem to dominate the control of all SATMU of load-bearing skeletal organs¹⁵⁻¹⁸. The above thresholds would help to tell a mechanostat if and where the strength, architecture, microdamage and/or creep of a skeletal organ needs corrective action. In live animals some humoral agents and other things may modulate the set points of those thresholds, to make a mechanostat change a skeletal organ's strength predictably. Genetic errors in those thresholds could cause many of the skeletal features in osteogenesis imperfecta, the chondrodystrophies, Ehler-Danlos syndrome and Marfan's syndrome, as examples only. The signalling mechanisms and cells that help to make all those things work became a separate field of study in skeletal science.

For such reasons strong muscles make strong bones, tendons, ligaments and joints, and chronically weak muscles make weak ones.

Presumably mechanostats have the chief purpose of making load-bearing skeletal organs satisfy a health criterion called Proposition #1.

Proposition #1

The design and construction of healthy load-bearing skeletal organs provide only enough strength to keep postnatal voluntary loads from causing spontaneous fractures (of bones), ruptures (of tendons, ligaments and fascia) or arthroses, whether those loads are chronically subnormal, normal or supranormal²⁵. Achieving that "mechanical competence" would be the ultimate test of such an organ's health, and it would depend on the relationship between an organ's strength and the typical voluntary loads on it. As an example, the strength of the infrapatellar tendon in a mouse and horse differs more than 1000-fold, but the health of each depends on how well it satisfied Proposition #1 in the animal it came from. Implication: Like absorptiometry²⁶ and histomorphometry²³, bone strength alone cannot evaluate bone health. To do that one should compare reliable indicators of bone and muscle strength, and then compare the results to corresponding norms^{13,14,26}.

In humans and animal models, normal biologic mechanisms would make a skeleton satisfy that Proposition; hence, physiology at work. Failures to do that would usually stem from disorders of those mechanisms and would represent diseases. Such failures can be general (as in osteogenesis imperfecta or lathyrism), or localized to one structure and time (as in a spontaneous rupture of the Achilles tendon, or a medial compartment arthrosis due to genu varum). Any nonmechanical functions provided by skeletal organs would be secondary to their mechanical ones.

Some implications for animal models

In vitro vs. in vivo

Most experienced physiologists realize the skeleton's nephron-equivalent mechanisms and mechanostats do not function normally in any current in vitro system, so one must study them in suitable animal models and situations. In theory, in vitro studies could not predict how intact animals would respond to a given drug or other challenge, and in fact nearly all past extrapolations of in vitro to in vivo effects did err. Histomorphometry, tissue-time markers, fluorescence microscopy, standard histology and radiography provide valuable aids in live animal studies of skeletal physiology and disorders. Dr. WSS Jee pioneered their use in such work^{19,20}.

An analogy may help to clarify why these two paradigms can affect research strategies and methods so differently.

1. The 1960 paradigm would suggest that studying the skeleton's effector cells could explain why the three disorders mentioned in this article's first paragraph occur. That idea helped in vitro and other studies of those cells in such disorders to pepper the skeletal science literature. It also made many people attribute to effector cells and/or their disorders numerous things that really stem from nephron-equivalent functions and/or their disorders. As described elsewhere, those disorders include the three mentioned in this article's first paragraph.
2. But in the Utah paradigm's view, cars and skeletons seem alike in that each exists mainly to provide mechanical functions and to obey its driver. The car's steering, brakes and accelerator would analogize a skeleton's mechanostats; the car's driver would analogize a skeleton's voluntary mechanical usage; the car's wheels would analogize effector cells; and gas in the car's tank would analogize the skeletal roles of many things like calcium, vitamin D, thyroxine, growth factors, nitric oxide, dietary protein, etc. Then as studying only its wheels could not explain why a car drove to Denver instead of Boston, in the mechanostat's view studying only effector cells could seldom explain why the skeleton's biologic mechanisms cause the disorders mentioned in this article's first paragraph. Like a car's wheels relative to its steering, brakes and accelerator, effector cells pretty much do what mechanostats tell them to do, trauma and neoplasia excepted. Yet while a car's mechanical usage cannot make its strength or architecture change, a skeleton's postnatal mechanical usage can make its strength and/or architecture change.

As for animal models: Because mechanostats and their responses to mechanical and other influences neither exist nor function properly in present in vitro systems (cell, tissue and organ culture systems), one must study them in intact animals in suitable situations. In that regard, see next.

On “osteoporosis”

Future studies, articles and texts should use the osteopenia and osteoporosis terms more selectively than was customary in the past²⁵. Why? Consider:

1. Any cause of chronic muscle weakness causes the commonest kind of so-called “osteoporosis” in the world²⁷. Called “physiologic osteopenias” elsewhere²⁵, here normal biologic mechanisms reduce whole-bone strength to adapt it to reduced momentary muscle strength, and in ways that prevent “spontaneous” fractures. Accordingly, here bones would remain healthy by the Proposition #1 criterion^{28,29}. Thus the many past searches for causative bone effector cell disorders in such osteopenias were futile, because muscle causes them. These osteopenias affect most aged human adults. They also occur regularly in chronic debilitating disorders, such as chronic cardiac, renal, hepatic and respiratory failure, malnutrition, alcoholism, terminal AIDS, rheumatoid polyarthritis, and stroke.

As for animal models: ovariectomized and/or orchietomized³⁰ mammalian animals are not good models of this osteopenia, although the contrary but mistaken idea seems common today. Tail suspension methods could provide good models, and could also provide useful models of muscle force effects on bone’s mechanostat, modeling, remodeling and strength. So could live animal studies in so-called microgravity conditions in space²⁵.

2. Healthy women lose about 15% of their bone “mass” during and after menopause²⁹. That loss comes from disuse-mode remodeling of bone next to marrow, and here too normal biologic mechanisms do it²⁵. Since most such women never have spontaneous fractures, their osteopenic bones would be healthy by Proposition #1. A minor fraction of such women have traumatic fractures, but falls cause nearly all of them so they affect extremity bones like hips and wrists.

As for animal models: many (but not all, such as the dog) ovariectomized mammalian animals show the same anatomical pattern of bone loss and do not develop spontaneous fractures either²⁰, so they should provide good models of this osteopenia. Such conditions should represent further physiologic osteopenias, and physiology at work instead of diseases²⁹.

3. The same observations could apply to bone loss in orchietomized men and mammalian animal models³⁰.
4. But in some postmenopausal women bone’s mechanostat fails to make some bones strong enough to satisfy Proposition #1, so “spontaneous” fractures affect those bones (an osteopenia usually coexists). Called a “true osteoporosis” elsewhere²⁵, the spontaneous fractures in this osteoporosis localize to thoracic and lumbar vertebral bodies and do not affect the pelvis or extremity bones²⁷ (spontaneous fractures usually depend on excessive bone micro-damage^{12,25}). That means past searches in biopsies of pelvic or extremity bones for causative

effector-cell disorders in this osteoporosis were futile, because its spontaneous fractures only affect the spine. Other but less common true osteoporoses occur in which spontaneous fractures affect both extremity bones and the spine (exs: osteogenesis imperfecta, juvenile idiopathic osteoporosis).

Abnormally functioning biologic mechanisms cause true osteoporoses.

As for animal models: no currently accepted one for such osteoporoses is known. However osteogenesis imperfecta in lower animals might provide such a model, although it was overlooked in that regard (hence a potential value of trying to collaborate with a veterinary college of medicine). Ovariectomized and/or orchietomized³⁰ mammalian animals, and tail suspension and microgravity situations, could not provide good models of these osteoporoses, which by Proposition #1 would be true diseases.

5. Clinical, pathologic and other evidence shows the above disorders do occur and have different pathogeneses. At present upper-echelon osteoporosis authorities begin to wrestle with the many implications of that realization. In principle, a given drug need not similarly affect all such disorders, just as a given drug would not similarly affect iron-deficiency, sickle-cell and pernicious anemias. Hence good reasons to use the terms “osteopenia” and “osteoporosis” more appropriately in the future than in the past. Just because most scientists and clinicians still call human postmenopausal bone loss, or an ovariectomized animal’s bone loss, an “osteoporosis” instead of an osteopenia, and consider it a disease instead of physiologic, does not make those things correct.
6. According to the 1960 paradigm a drug that only depressed existing osteoclasts, or only stimulated existing osteoblasts, should normalize bone strength and “mass” in osteopenic or osteoporotic subjects. Intensive research sought such agents, but the mechanostat hypothesis would predict that any contingent increases in bone “mass” would soon plateau at a new steady state, and in spite of longer treatment and/or larger doses of the agent. Time after time that has been true, and for over 50 years. As AM Parfitt suggested at a former Hard Tissue Workshop, permanently increasing bone strength in such people could require making bone’s mechanostat, especially its built-in thresholds, evaluate the existing bone strength as inadequate and initiate a correction.

On arthroses (osteoarthritis, degenerative joint disease)³¹.

Joints with these disorders do not satisfy Proposition #1, but current rheumatologic literature does not make it clear that their mechanical incompetence usually has two sequential “first” and “final” causes or stages.

Excessive microdamage (MDx) in articular cartilage, especially in its Type II collagen, seems to constitute the “final cause” of most arthroses, and the main common denominator in their pathology too. Many “first causes” can

lead to or help to cause that final cause. While in principle the final cause would be irreversible, many first causes could be correctable, which could prevent a final arthrosis from developing.

Eight of those first causes include:

1. Biochemical and other abnormalities in a joint's tissues that let normal loads and strains cause excessive MDx.
2. Retarded joint adaptations to mechanical usage that let excessive unit loads and strains cause too much MDx.
3. Structural maladaptations (SATMU errors) that leave a joint too small and/or improperly shaped for normal loads, so MDx increases.
4. Impaired maintenance activities that let MDx accumulate in joint tissues.
5. Excessive total or unit loads, and their gradients and associated strains, on normal joints that increase their MDx.
6. Genetic factors, some drugs, toxins, diseases and other things, that cause or help to cause the above things.
7. Combinations of the above.
8. And "X", meaning what we should know but don't - yet.

Arthritis texts show that rheumatologists knew examples of all such first causes for a long time⁸.

In the past most joint physiologists and rheumatologists tried to view arthroses through the lens of the 1960 paradigm of skeletal physiology, so ideas about their pathogenesis emphasized biochemical features and causes (where biochemical has the broad meaning), often in the aggrecans or proteoglycans in articular cartilage^{8,9}. But in the Utah paradigm, the accumulated MDx in the tissue's collagen that ultimately causes arthroses is a chiefly mechanical phenomenon. Since articular cartilage collagen does not show in sections viewed with the light microscope¹, it was hard to study. That should help to explain the delayed recognition of the importance of its strain-dependent MDx (is that an example of "out of sight, out of mind"?). While most animal models of arthroses used mechanical factors to cause an arthrosis, the results were usually explained in biochemical instead of biomechanical terms. Thus, intensive *in vitro* studies of articular cartilage, its cells and of synovial fluid, peppered the rheumatologic literature after 1950.

While recent literature shows a slow awakening among some joint physiologists about the role of MDx in articular cartilage in arthroses¹⁸, it also shows continuing reluctance to credit the SATMU roles in their pathogenesis.

On animal models: Hence opportunities to do many useful, even pioneering, live animal studies of those roles.

On hard and soft tissue healing^{32,33,19}

1. Healing of bones, collagenous tissue structures and articular cartilage involves four essential but long overlooked nephron-equivalent phases. Fracture healing can provide an illustrative example.
 - a. An initial soft, isotropic and fragile callus is produced, here one made chiefly of woven bone.
 - b. Then a remodeling mechanism begins to replace it with the

anisotropic mature tissue, which is lamellar bone here.

- c. Overlapping that, modeling begins to reshape the callus, here a fracture callus.
- d. Meanwhile a regional acceleratory phenomenon (RAP) speeds up those three processes. They take longer to occur in adults and large animals than during growth and in small animals.

Again, those four phases occur routinely during bone, tendon, ligament and articular cartilage healing. They would have the goal of making an injured structure satisfy Proposition #1 again. Failure of any of those four phases can prevent successful healing, and lesser impairments of them can retard it. By 1930 histologists and pathologists had already described microscopic features of those nephron-equivalent activities, but their nature, meanings and roles remained enigmatic until the Utah paradigm gelled.

2. Because most people studying this healing assumed, and still assume, the 1960 paradigm's assumptions are valid, mistakenly in my view they think of that healing as a single indivisible process in which the chief players are osteoblasts, fibroblasts or chondroblasts, depending on which tissue is injured. Most such people also remain unaware of the existence and roles of the RAP, which I described formally in 1983³⁴. Because none of those four phases exists or functions normally in present cell, tissue or organ culture systems, here too one must do effective studies of them in intact animals, and take care not to mistake transients for steady states.
3. Since the roles of those four phases presently lack systematic study, the roles of ligands, receptors, cytokines, growth factors, etc, in those phases still remain nearly unknown.

On animal models: Hence opportunities to do many useful, even pioneering, live-animal studies of such things.

Should one analyze upward or downward on the ladder of biologic organization?

Both theory and experience show that to understand a skeletal disorder efficiently one must first find its features in intact animals at the organ level, and then at the tissue level. Then *in vitro* biochemical, cell and molecular biologic studies can help to understand the tissue-level features. But one cannot predict reliably the *in vivo* features of a skeletal disorder solely from information acquired by *in vitro* studies. Equally, studies of bricks alone, no matter how exhaustive, could not reveal the design, functions, properties and purposes of structures made from them, nor the disorders that might affect those structures.

Since most experienced physiologists would agree with those ideas, why is there a problem? In my view, and with full respect to people who would disagree, mainly two things cause it.

1. Too many scientists and clinicians think they already know the important organ and tissue-level features of the three disorders mentioned in this article's first para-

- graph, yet, and as the above Sections indicate, they do not.
2. Too many of them still think the features of the 1960 paradigm remain valid, but they do not.

In that regard Daniel Boorstin, a former librarian of Congress, quipped, "*The great obstacle to progress is not ignorance but the illusion of knowledge*". Something to think about?

Conclusion

Resolving disagreements about such matters - there were, are and will likely be many of them - will take time. Lots of it. Likely more than this old dinosaur has left. I accept that, but paraphrasing something said elsewhere seems appropriate in that regard. To wit:

Different current majority views about the above matters depend on what we knew and thought in the past. That was a necessary step in trying to understand skeletal physiology and its disorders, and in no way do I, nor should anyone else, disparage that step or the people who contributed to it (indeed, in earlier times I was one of them).

"But, is it not time to supplement former facts and views with new ones, and build better things with their sum?"

Could readers accept that as at least one answer to the "Quo vadis?" in this article's title?

References

1. Weiss L. Cell and Tissue Biology. A Textbook of Histology. Urban and Schwarzenberg, Baltimore; 1989.
2. Luck JV. Bone and Joint Diseases. Charles C Thomas, Springfield; 1950.
3. McLean FC, Urist MR. Bone (2nd ed). University of Chicago Press, Chicago; 1961.
4. Weinmann JP, Sicher H. Bone and Bones (2nd ed). CV Mosby Co, St Louis; 1955.
5. Albright JA, Brand RA. The Scientific Basis of Orthopaedics (2nd ed). Appleton and Lange, Norwalk; 1987.
6. Favus MJ. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (ed) (3rd ed). Lippincott-Raven Press, New York; 1996.
7. Favus MJ. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (4th ed). Lippincott-Williams and Wilkins, Philadelphia, PA; 1999.
8. Kippel JH, Dieppe PA. Rheumatology. Mosby-Year Book, Inc, 1994.
9. Kuettner KE, Goldberg VM. Osteoarthritic Disorders. Amer Acad Orthop Surg, Rosemont, IL; 1995.
10. Frost HM. Why the ISMNI and the Utah paradigm? Their role in skeletal and extraskelatal disorders. J Musculoskel Neuron Interact 2000; 1:5-9.
11. Jee WS. Principles in bone physiology. J Musculoskel Neuron Interactions 2000; 1:11-13.
12. Martin RB, Burr DB, Sharkey NA. Skeletal Tissue Mechanics. Springer-Verlag, New York; 1998.
13. Schönau E. Paediatric Osteology. New Trends and Diagnostic Possibilities. Elsevier Science, Amsterdam; 1996.
14. Takahashi HE. Spinal Disorders in Growth and Aging. Springer-Verlag, Tokyo; 1995.
15. Frost HM. Structural adaptations to mechanical usage (SATMU):1. Redefining Wolff's Law: The bone modeling problem. Anat Rec 1990; 226:403-413.
16. Frost HM. Structural adaptations to mechanical usage (SATMU):3. The hyaline cartilage modeling problem. Anat Rec 1990; 226:423-432.
17. Frost HM. Structural adaptations to mechanical usage (SATMU):4. Mechanical influences on fibrous tissues. Anat Rec 1990; 226:433-439.
18. Frost HM. Structural adaptations to mechanical usage (SATMU):2. Redefining Wolff's Law: The bone remodeling problem. Anat Rec 1990; 226:414-422.
19. Jee WSS. The skeletal tissues. In: L Weiss (ed) Cell and Tissue Biology. A Textbook of Histology. Urban and Schwarzenberg, Baltimore; 1989:211-259.
20. Jee WSS. Proceedings of the International Conference on Animal Models in the Prevention and Treatment of Osteopenia. Bone 1995; 17(Suppl):1-466.
21. Frost HM. Mathematical Elements of Lamellar Bone Remodelling. Charles C Thomas, Springfield; 1964.
22. Frost HM. The origin and nature of transients in human bone remodeling dynamics. In: H Duncan, B Frame and AM Parfitt (eds) Clinical Aspects of Metabolic Bone Disease. Excerpta Medica, Amsterdam; 1973:124-137.
23. Recker RR. Bone Histomorphometry. Techniques and Interpretation. CRC Press, Boca Raton; 1983.
24. Frost HM. Perspectives: A proposed general model of the mechanostat (suggestions from a new paradigm). Anat Rec 1996; 244:139-147.
25. Frost HM. Osteoporoses: New Concepts and Some Implications for Future Diagnosis, Treatment and Research (based on insights from the Utah paradigm). Ernst Schering Research Foundation AG 1998; 7-57.
26. Ferretti JL, Frost HM, Schiessl H. On new opportunities for absorptiometry. J Clin Densitom 1998; 1:41-53.
27. Riggs BL, Melton LJ III. Osteoporosis. Etiology, Diagnosis and Treatment (2nd ed). Lippincott-Raven Publishers, Hagerstown, MD; 1995.
28. Helminen HJ, Hyttinen MM, Lammi MJ, Arokoski JPA, Lapvetelaubeb T, Jurvelin J, Kiviranta I, Tammi MI. Regular joint loading in youth assists in the establishment and strengthening of the collagen network of articular cartilage and contributes to the prevention of osteoarthrosis later in life: a hypothesis. J Bone Miner Metab 2000; 18:245-257.
29. Schiessl H, Frost HM, Jee WSS. Estrogen-bone-muscle relationships. Menopause Digest 1998; 5:10-11.
30. Yao W, Jee WSS, Chen J, Liu H, Tam CS, Cui L, Zhou H, Setterberg RB, Frost HM. Making rats rise to erect bipedal stance for feeding partially prevented orchidectomy-induced bone loss and added bone to intact rats. J Bone Min Res 2000; 15:1158-1168.

31. Frost HM. Joint Anatomy, Design and Arthroses: Insights of the Utah Paradigm. *Anat Rec* 1999; 255:162-174.
32. Frost HM. The biology of fracture healing. *Clin Orthop Rel Res* 1989; Part I:248:283-293, Part II:248:294-309.
33. Frost HM. Some vital biomechanics of bone grafting and load-bearing implants in dental and maxillofacial surgery: A brief tutorial. In: OT Jensen (ed) *The Sinus Bone Graft*. Quintessence Publishing Co. Inc, 1998:17-29.
34. Frost HM. The regional acceleratory phenomenon. A review. *Henry Ford Hosp Med J* 1983; 31:3-9.

