H. M. Frost's Legacy: The Utah Paradigm of Skeletal Physiology

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The still-evolving Utah Paradigm of Skeletal Physiology with its key components, the mechanostat, inserts tissue-level realities into the knowledge gap between organ-level and cell-level realities. It concerns load-bearing bones in postnatal bony vertebrates and how bones adapt their strength to mechanical loads on them. The paradigm involves the neuromuscular system, the mechanostat and their interactions with local and systemic non-mechanical agents. The mechanostat contains the genetically determined minimum effective strain general biomechanical relationship ($MES_{remodeling} < E_{adaptation} < MES_{modeling} << MES_{pathologic} << FX_{fracture}$), set points, remodeling and modeling highways and feedback loops. Local and systemic non-mechanical agents can be permissive, mediate and modulate the strain-dependent signals or act directly on cellular parts of the mechanostat but cannot replace or duplicate the mechanical control. Altering the set points of the mechanostat along with the direct cellular action of anti-catabolic and anabolic drugs can be responsible for their mechanism of actions. Lastly, an understanding of the Utah paradigm by skeletal biologists can explain how bones adapt their strength to mechanical loads and help to avoid errors in experimental designs and interpreting data.

The ever-evolving Utah Paradigm of skeletal physiology for load-bearing bones is a legacy of 50 years of study by Harold M. Frost. (1-10) It replaces the 1960 paradigm of skeletal physiology in which effector cells (chondroblasts, fibroblasts, osteoblasts, osteoclasts, etc.) regulated by non-mechanical agents determined the architecture, strength and health of bones. Biomechanical and tissue level phenomena had no roles in that paradigm. Subsequent evidence slowly revealed the role of tissue-level and biomechanical mechanisms and their function in a new paradigm. The Utah paradigm consists of the neuromuscular system, the mechanosat with its mechanical loading system (mechanotransduction) to turn on or off tissue-level mechanisms with their feedback loops and local and systemic non-mechanical signals that mediate and modulate the signal and the cells of the mechanostat (relation 1). (4-10)

The basic element or heart of the Utah paradigm is the mechanostat. Frost first heard of the idea of a "mechanosat" applied to bone at a Gordon Conference aout 1957. There originators

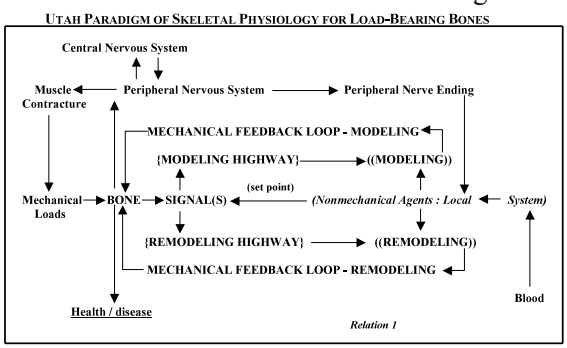

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Table 1.

COMPARISON OF MODELING & REMODELING		
	Remodeling	**Modeling**
Location	**Different surfaces**	**Spatially related**
Coupling	**A → R → F**	**A → F[c]; A → R[d]**
Timing	**Cyclical**	**Continuous**
Extent	**Small (<20%)[a]**	**Large (>90%)**
Apposition rate	**Slow (0.3-1.0μm/day)**	**Fast (2-10μm/day)**
Cement line	**Scalloped**	**Smooth**
Balance	**No change or net loss**	**Net gain**
Surfaces	**Adjacent to marrow**	**All surfaces**
Occurrence	**Throughout life span**	**Prominent during growth; ineffective in adults**
Function	**Maintenance and repair of microdamage**	**Skeletal adaptation to mechanical usage (shape & size)**
MES threshold[b]	**< 100 microstrain**	**> 1000 microstrain**

[a]Of available surface
[b]MES = minimum effective strain; A = activation ; R = resorption; F = formation
[c]Formation drift
[d]Resorption drift
Modified from Jee WSS (2001) In: Bone Mechanics Handbook, second edition, p. 1-25.(13)

were W. D. Armstrong, F. C. McLean, A. Reifenstein and I. Snapper, all long decreased, so the idea died and was buried. By 1987 Frost "dug up the 'mechanostat' coffin, exhumed and published its contents and admitted he undeservedly received most of the credit for it." (4)

The mechanostat deals mainly with load-bearing bones. Postnatally, there are 2 kinds of bones after birth - the load-bearing bones which implies muscles forces and the others with different needs like the cranial vault, cribiform plates of the ethmoid, nasal bones, turbinates, etc. Nevertheless, all are subject to gravity forces.

Briefly, the mechanostat consists of 4 major components: (1) the genetically determined baseline conditions; (2) loads generating signals (mechanotransducers) that that turn 'on' or 'off' tissue-level biologic mechanisms highways or pathways; (3) genetically determined minimum effective strain (MES) general biomechanical relations $MES_{remodeling} < E_{adaptation} < MES_{modeling} >> MES_{pathology} >> FX_{fracture}$; and feedback loops of above features. (3-14)

I. The genetically determined baseline conditions. Before birth, gene expression *in utero* created the baseline conditions of critical anatomy and relationships, basic neuromuscular anatomy and relationships, and tissue-level biologic machinery

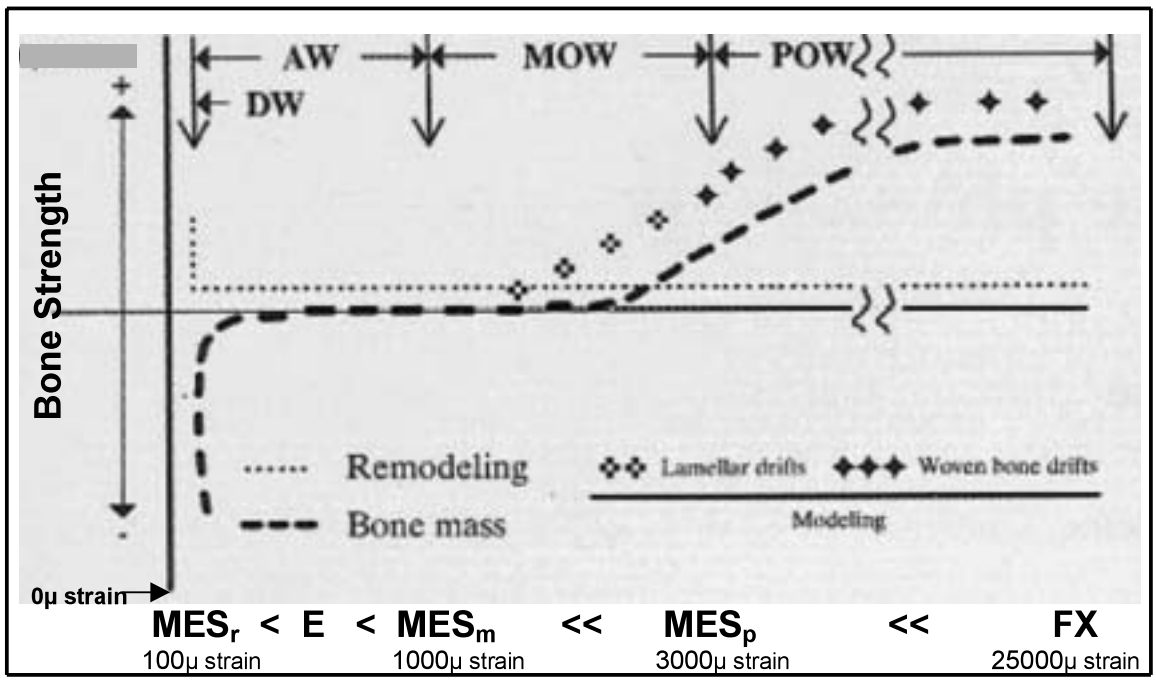


Figure 1. The Mechanostats General Biomechanical Relations on Load-bearing Bone Strength. The horizontal line at the bottom - the general biomechanical relations suggests peak bone strain from zero on the left to fracture strain of 25,000 microstrain on the right (FX). At the top, DW = disuse window or threshold range; AW = adapted window or threshold range; MOW = mild overload window or threshold range; POW = pathologic overload window or threshold range. The dotted downward line indicates disuse-mode remodeling removing bone next to marrow when strains are below the MES_r range (~ > 100 microstrain). At the adapted window range bone maintains existing mass and strength to voluntary mechanical loads. The upper dashed curved line indicates how modeling drifts increase bone strength when strains exceed the MES_m range (~ > 1000 microstrain). Beyond the MES_p range, woven bone formation and unrepaired microdamage are generated. *Adapted from Frost (7-9, 13) and Jee (14)*.

for adaptation. (7) The biologic machinery at the tissue-level involves modeling by formation and resorption drifts that increase bone mass and strength and remodeling by basic multicellular units (BMUs) that turn over bone. Table 1 compares the bone's biologic machinery characteristics of remodeling and modeling sites. Remodeling differs from modeling in location, coupling, timing, extent, appositional rate, cement line appearance, bone surface occurrence, bone balance, life span, function and genetically determined minimum effective strain windows, thresholds or ranges. Not well appreciated is that remodeling activity is mainly limited to adjacent to marrow. Although modeling is ineffective in adults, anabolic agents will stimulate modeling-dependent bone gain in the adult skeleton. Remodeling maintains bone tissue and repairs microdamage while modeling determines shape and size from adaptation to mechanical usage. (15)

II. Mechanical loads on bone cause bone strains (minimum effective strains, MES) that generate signals (mechanotransduction) so some cells (i.e., osteocytes, osteoblasts, osteoclasts, etc.) can

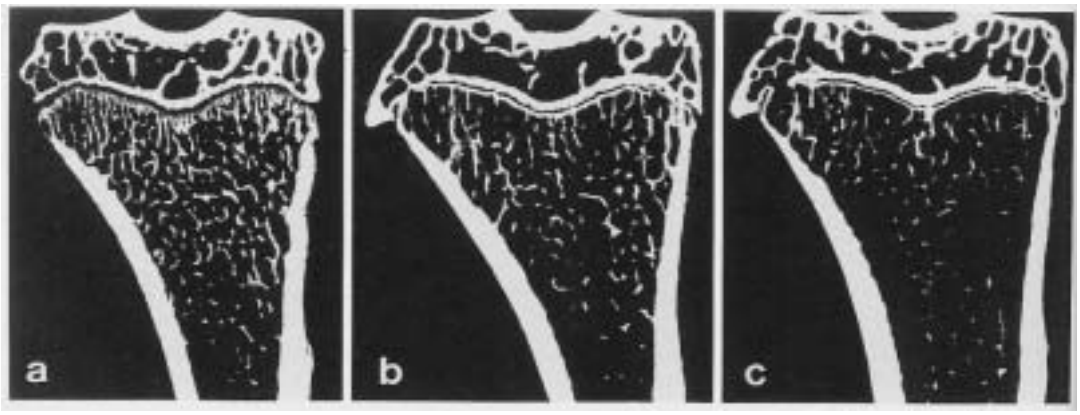


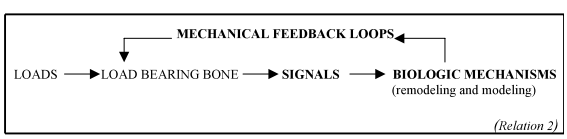
Figure 2. Microradiographs of rat proximal tibiae from a) 9 month-old basal control, b) 13.5 month-old aging control, and c) 13.5 month-old after 18 weeks of underloading from immobilization. The underloaded tibia contains less metaphyseal cancellous bone tissue of few and thinner trabeculation, a loss of 60% of trabecular bone mass (C). (22)

detect and respond. (4, 5, 8-13) The largest loads on bone come from muscles. (8-10, 16-20)

III. The signals can turn 'on' or 'off' the MES general biomechanical relations of $MES_{remodeling} < E_{adaptation} < MES_{modeling} << MES_{pathology} << FX_{fracture}$. The $MES_{remodeling}$ (MES_r) is bone's genetically determined disuse-mode threshold strain range below which remodeling is turned on to lose bone mass and strength. E is the threshold range caused by voluntary mechanical load. $MES_{modeling}$ (MES_m) is bone's genetically determined modeling threshold strain range in which modeling usually turns on to strengthen bone. $MES_{pathology}$ (MES_p) is bone's genetically determined microdamage threshold strain range in which unrepaired microdamage can accumulate. FX is bone's genetically determined strains above MES_p thresholds that can cause enough microdamage to escape repair and accumulate to cause pathologic fractures. (4, 5, 8-13)

Figure 1 illustrates the mechanostat's combined remodeling and modeling effects on load-bearing bone strength with its general biomechanical relations. The horizontal line represents no net gain or losses of bone strength. When the MES_r is the disuse window (DW) or threshold below 100 microstrain it loses bone mass and strength from disuse remodeling. In the E region or adapted window (AW) there are no net gain or losses, while loading exceeding 1000 microstrain would activate the mildly loaded window (MOW), MES_m, to increase bone mass and strength. Bone strain much greater than MES_m will generate woven bone and microdamage in the pathologic overload windows (POW) or threshold range. The MES greater MES_p will result in unrepaired microdamage and fractures (FX). (7-9, 13, 14)

IV. The mechanostat contains negative feedback loops of the remodeling and modeling highways (relation 2). (7-10)



Negative feedback loops are arrangements in which a system's activity or state can respond to external influences in ways that make the system change itself in some way or ways. Or the reaction of some results of a process serving to

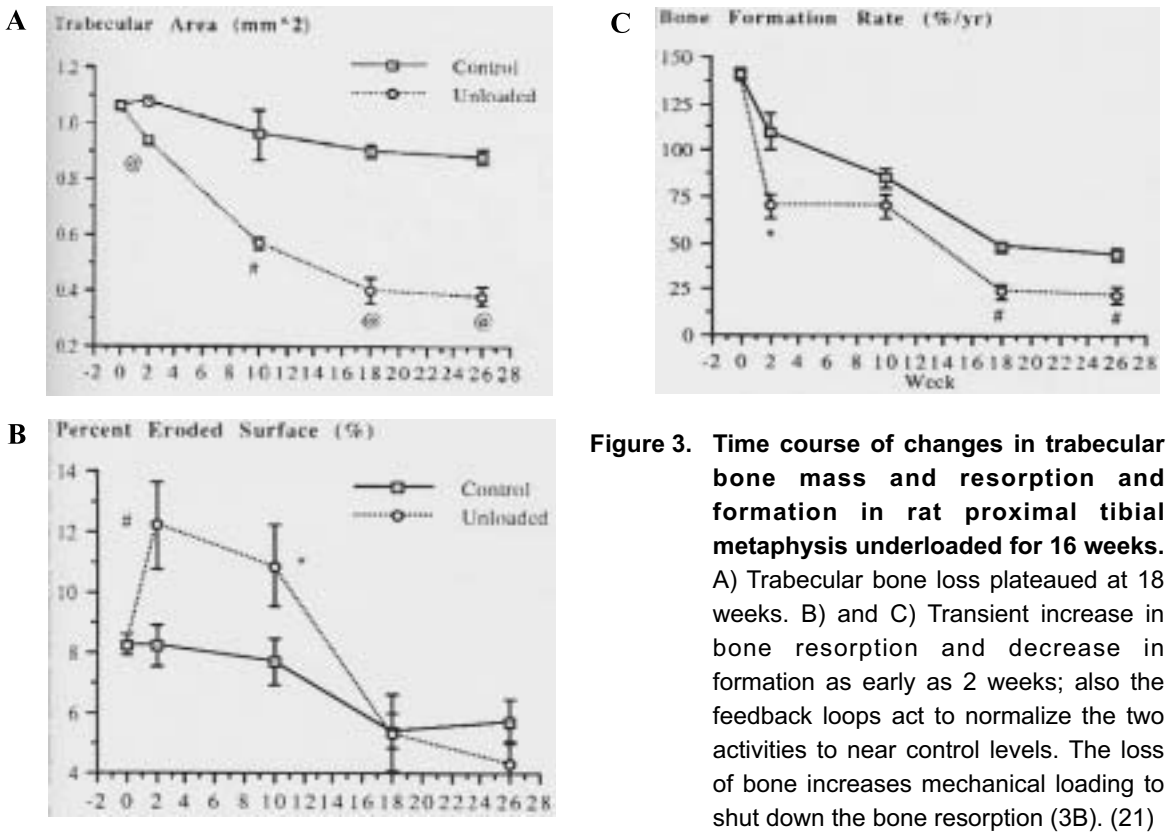


Figure 3. Time course of changes in trabecular bone mass and resorption and formation in rat proximal tibial metaphysis underloaded for 16 weeks. A) Trabecular bone loss plateaued at 18 weeks. B) and C) Transient increase in bone resorption and decrease in formation as early as 2 weeks; also the feedback loops act to normalize the two activities to near control levels. The loss of bone increases mechanical loading to shut down the bone resorption (3B). (21)

alter or reinforce the character of the process. An excellent example of the feedback loop phenomenon is the study of immobilization-induced bone loss. (21, 22) It illustrates the transient, steady (plateau) and feedback loop responses. Figure 2 shows the effect of immobilizing (underloading) the rat proximal tibia for 26 weeks. The unloaded tibia contains less cancellous bone (Figure 2C). The unloading -induced trabecular bone loss reached steady state or plateaued by 18 weeks (Figure 3A). Figure 3B and C showed early transient responses at 2 weeks of increased resorption (% eroded surface) and decreased formation that more or less reverted back to control level at 18 weeks from the feedback response. The loss of bone triggered the feedback loops response - the loss of bone mass increased mechanical loading to drive resorption and formation to approach control values (Figure 3B and C).

In summary, the Frost's mechanostat entitles mechanical loads to determine the postnatal strength of load-bearing bone by (1) employing biologic mechanisms of tissue-level modeling and remodeling that change whole-bone strength after birth; (2) providing strain-dependent signals to monitor the relationship between a load-bearing bone's strength and the mechanical loads on it; (3) providing the MES_m and MES_r to contain special criteria for acceptable whole-bone strength relative to mechanical load and load-bearing bones; and (4) providing feedback between these features. (8-10)

The Utah Paradigm of Skeletal Physiology

Besides the mechanostat, the Utah Paradigm of Skeletal Physiology added the (1) The neuromuscular involvement where except in

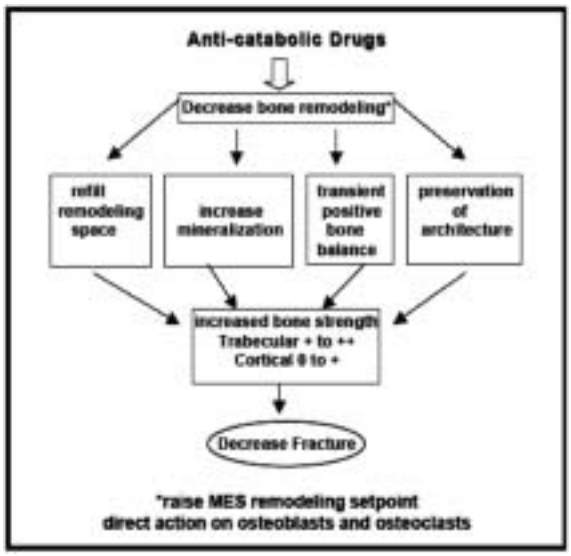


Figure 4. Possible role of the Utah paradigm in the mechanisms of action of anti-catabolic drugs. Anti-catabolic drugs increase bone strength by decreasing bone remodeling. It reduces resorption, increases mineralization, preserves microarchitecture, and fills remodeling spaces to increase bone mass. (23) Anti-catabolic drug may accomplish this by mainly raising the minimum effective strain threshold set point to diminish bone remodeling-dependent bone loss. In addition, the direct depressive effect on osteoclasts would foster increased mineralization and preserve bone mass and architecture.

cases of trauma, lever arm and gravitational effects causes muscles to put the largest load on load-bearing bones, (relation 1) (8-10, 16-20) even on weight-bearing bones to provide loading signals for the mechanostat; (2) the role of local non-mechanical agents like genes, cytokines, ligands, antibodies, receptors, paracrine and autocrine effects, apoptosis, etc.; and (3) the role of systemic non-mechanical agents like hormones, minerals, vitamins, drugs, nutrients, etc. These non-mechanical agents can be permissive, mediate, and modulate the strain-dependent signals or act directly on cells of parts of the modeling and remodeling highways. (7, 8-10)

In summary, the Utah paradigm of skeletal physiology suggests four conditions: (1) The biologic mechanisms that determine skeletal health and disease need effector cells and nonmechanical agents in order to work; (2) Mechanical factors guide those mechanisms in time and space; (3) After birth, neuromotor physiology and anatomy dominate control of those biologic mechanisms; and (4) Most nonmechanical factors can help or hinder but cannot replace or duplicate the mechanical control.

The minimum effective strain threshold set point and bone anti-catabolic and anabolic drugs

The center of a minimum effective strain threshold range or window that in effects turns its biologic activity on to provide function is known as a set point. One can postulate the alteration in bone mass and strength by anti-catabolic and anabolic drugs may be due to raising or lowering the set points. Anti-catabolic drugs may raise the MES remodeling set point to inhibit disuse remodeling bone loss as well as act directly on osteoblasts and osteoclasts in inhibiting resorption (Figure 4).

Anabolic drugs may lower both the set points for minimum effective strain for remodeling and modeling to turn on disuse remodeling-dependent bone loss, periosteal and trabecular modeling-dependent bone gain as well as directly stimulate osteoblastic lineage cells resulting in a positive remodeling and modeling bone balance (Figure 5).

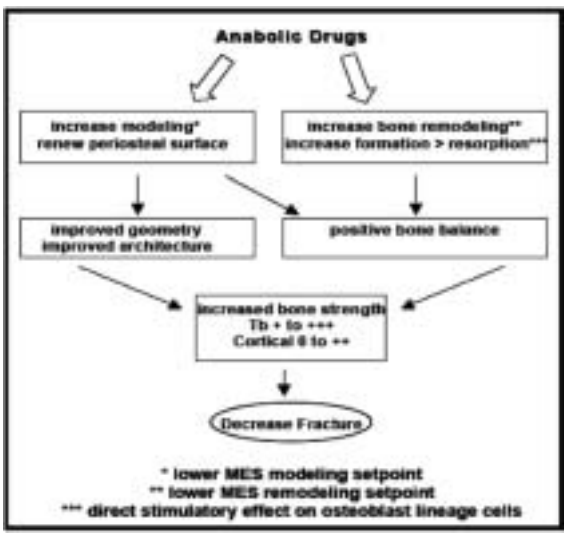


Figure 5. Possible role of the Utah paradigm in the mechanism of action of anabolic drugs. Anabolic drugs increase bone strength by increasing bone mass as a result of increased bone remodeling (BMUs), positive BMU balance and renewed periosteal and trabecular modeling that improves geometry and architecture. (23) The lowering of the MES remodeling and modeling set points would increase positive bone remodeling balance and turn on modeling-dependent bone gain. The direct stimulatory effect on osteoblastic lineage cells would further enhance bone strength.

Why should skeletal scientists and clinicians learn the Utah paradigm of skeletal physiology?

An understanding of the insights of the Utah paradigm of skeletal physiology is a prerequisite for all *in vivo* skeletal research. These insights can help to minimize serious errors in experimental designs and in interpreting data. (8,9)

Summary

The still-evolving Utah Paradigm of Skeletal Physiology with its key components, the mechanostat, inserts tissue-level realities into the knowledge gap between organ-level and cell-level realities. It concerns load-bearing bones in postnatal bony vertebrates and how bones adapt their strength to mechanical loads on them. The paradigm involves the neuromuscular system, the mechanostat and their interactions with local and systemic non-mechanical agents. The mechanostat contains the genetically determined minimum effective strain general biomechanical relationship ($MES_r < E < MES_m << MES_p << FX$), set points, remodeling and modeling highways and feedback loops. Local and systemic non-mechanical agents can be permissive, mediate and modulate the strain-dependent signals or act directly on cellular parts of the mechanostat but cannot replace or duplicate the mechanical control. Raising the MES remodeling set point coupled with the direct effect on osteoblasts and osteoclasts can be responsible for the mechanism of action of a typical anti-catabolic agent. Lowering the MES modeling and remodeling set points along with direct stimulation of osteoblastic lineage cells can be responsible for the mechanism of action of a typical anabolic agents. All students of in vivo skeletal biology should have an understanding of the Utah paradigm of skeletal physiology. Insights into the paradigm can help to minimize serious errors in experimental designs and in interpreting data.

Lastly, please remember it took decades for Harold M. Frost to develop, understand and find effective ways to explain the Utah paradigm of skeletal physiology. It is still evolving and needs improvement.

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