

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

– Note –

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The still-evolving Utah paradigm of skeletal physiology inserts tissue-level constructs into the former knowledge gap between bones' organ-level and cell-level features. It concerns load-bearing bones in postnatal bony vertebrates, physiologic bone loading, neuromuscular involvement, local and systemic non-mechanical agents that can mediate and/or modulate the strain-dependent signals or act directly on parts of the modeling and remodeling highways. The mechanostat forms the basis of the Utah paradigm. Seven features make up the mechanostat: (1) After birth most bones carry voluntary mechanical loads (implies muscle forces) besides weight-bearing ones; (2) After birth, gene expression *in utero* creates baseline conditions - initial bone anatomy and relationships, neuromuscular relationships and the "biologic machinery"; (3) The biologic machinery includes modeling to increase whole bone strength and disuse remodeling to remove bone next to marrow; (4) Loads on bone cause bone strain (minimum effective strains, MES) that generate signals that cells detect and respond; (5) Genetically determined threshold range of these signals helps to control modeling and remodeling; (6) The healthy mechanostat consists of a general biomechanical relation of: $MES_{remodeling} < E_{adaptation} \ll MES_{modeling} \ll MES_{pathology} \ll FS_{fractures}$; (7) The center of its MES threshold range is defined as the "set point". The combination of signal system, set points, modeling and remodeling highways and negative feedback loops form the mechanostat. The addition of local and systemic non-mechanical

agents that can be permissive, mediate and modulate the strain-dependent signals or act directly on parts of the modeling and remodeling highways makes up the Utah paradigm of skeletal physiology. Lastly, how the Utah paradigm impact on the mechanism of action of anti-catabolic and anabolic drugs will be proposed.



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