

Review Article

# Harold M. Frost, M.D., D.Sc. (hon) – One man's association

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**Abstract**

The author described how and when he first met Harold M. Frost, M.D., that began a journey from the Henry Ford Hospital to the University of Utah and Sun Valley Hard Tissue Workshops that sequentially developed the technology of dynamic cancellous bone histomorphometry, the ever-evolving mechanostat hypothesis and the Utah Paradigm for Bone Physiology.

**Keywords:** Harold M. Frost, Histomorphometry, Mechanostat Hypothesis, Utah Paradigm for Bone Physiology

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## I. H.M.F.: The Encounter and the Beginning of a Wonderful Journey

It was in 1956, I met up with a fellow named Gaynor Evans, Ph.D., a Professor of Anatomy at Wayne State University, and later at the University of Michigan Medical School. He was invited to spend a sabbatical at the Atomic Energy Commission's Radiobiology Laboratory at the University of Utah College of Medicine, Salt Lake City, Utah, to initiate studies on changes in mechanical strength of bone with internally deposited radioelements. I was then the head of the Bone Group in this laboratory studying the toxicity of bone-seeking radionuclides. Gaynor was a pioneer in bone biomechanics and the father of American bone biomechanics<sup>1,2</sup>. His visit resulted in one study by a graduate student in physics entitled "Changes in mechanical strength of bone due to internally deposited radioelements"<sup>3</sup>.

### *The meet. It was "Serendipity"!*

It was not until 1960 when I visited Gaynor Evans in Detroit, Michigan, that as we met he said, "You may be interested in meeting someone who is doing some interesting studies". That morning we went to a house and he introduced me to Harold Frost, M.D., an orthopaedic surgeon at

Henry Ford Hospital. Harold promptly led me up to the attic where he showed me some magnificent fluorescent-labeled rib biopsy samples. I was amazed at the quality of the specimens and the wealth of basic and clinical information that could be garnered from this unique material. This is when the journey with Harold and I began.

### *Cementing the relationship*

Later contact occurred in 1963 when Harold had invited me to speak at the Henry Ford Hospital International Symposium on Bone Biodynamics (March 20-22, 1963) where I learned more about the Frostian approach to bone biology. Little Brown and Company published this symposium in 1964 with Harold as the editor<sup>4</sup>. The Program Committee consisted of Franklin C. McLean, Chairman, Paul Weiss, Robert A. Robinson, William F. Neuman, C. Leslie Mitchell, Boy Frame, Richmond Smith, and Harold M. Frost. It was an exciting, informative conference that made me aware of how little I knew about skeletal physiology and the need to expose others to Frostian bone biology. On my return from the meeting I applied to the Dental Institute (NIDR), National Institute of Health (NIH) for a grant, which was funded, to train summer dental students on Frostian bone physiology.

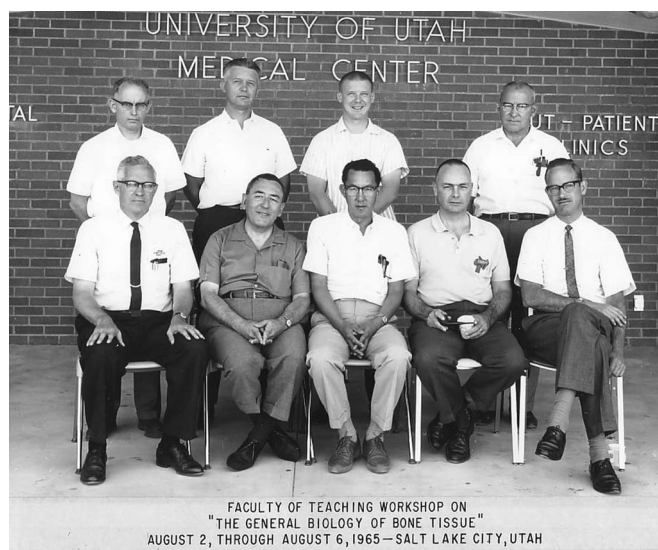
In August 1965 we had our first Workshop with support from the NIDR (Mineralized Tissues of Interest to Dentistry, 1964-1974), a summer Workshop for dental students interested in doing dental-related research. Each summer, several students would visit Salt Lake City to work in my laboratory to learn some of the newer techniques for studying bone. After a couple of months of work, a small cohort of experts in skeletal biology were invited as visiting faculty to

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**Figure 1.** Faculty of the first teaching workshop on "The General Biology of Bone Tissue", August 2-6, 1965. University of Utah College of Medicine, Salt Lake City, Utah, USA. Seated (l-r): Roy Talmage, Leonard Bélanger, Web Jee, Harold Frost, Dick Greulich; standing (l-r): Lent Johnson, Ted Morstad, Murray Bartley, Norm Dockum.

lecture and critique the research performed by the students. The first Workshop included five invited faculty members (Harold Frost, Lent Johnson, Roy Talmage, Leonard Belanger and Richard Greulich), four local faculty members (Web Jee, Ted Morstad, Murray Bartley and Norm Dockum) and 9 students (5 summer dental students and 4 graduate students and bone researchers from neighboring Utah State University at Logan, Utah). One of the dental students was W. Eugene Roberts who is now an internationally recognized academic orthodontist; Don Kimmel and Tom Wronski were also graduates of the program (Figures 1 and 2). The following year, there were seven faculty members (Harold Frost, Jim Arnold, Robert Heaney, Roy Talmage, Harold Copp, Edgar Tonna and Howard Suzuki) with about 25 participants (Figure 3).

The success of these Workshops stimulated me to generate support from the pharmaceutical industry and the implant and medical device manufacturers once support from the NIH ended. The Workshops were moved to their current venue in Sun Valley, Idaho in 1969 and have become highly identified with that location.

Harold was the only one who helped organize and participate in every Workshop from 1965-2003. (Currently the Sun Valley Workshops are in the good hands of David Burr). These Workshops encouraged Hal to publish in peer-review journals. Before that, the bulk of his publications were in the Henry Ford Hospital Bulletin and several Charles C. Thomas volumes.

## II. H.M.F.: Productive Laboratory Investigation Era (1957-1973) – "The Golden Years"

It was a time when discoveries of completely unexpected kinds of things occurred. Tony Villanueva, a colleague during Hal's stay at Henry Ford, best described this era as follows:

*"Dr. Frost started his scientific investigation in his kitchen. As his work expanded, a small 10' x 12' Orthopaedic Research Laboratory was provided by Henry Ford Hospital in Detroit, Michigan. It was in this laboratory where many of his scientific achievements were created. A team of 16 undergraduate and graduate students were instrumental in producing several ground sections per day for his microscopic evaluation. He developed the staining of fresh, undecalcified ground sections of bone using a simple 1% alcoholic basic fuchsin. When all the observations had been collected, he found vast amounts of information of potentially great clinical and research values. Notable in his work was the quantitative and qualitative bone histomorphometry, and its application to the study of metabolic bone disease based on tetracycline markers. Dr. Frost used daring imagination formulating new hypothesis and in devising simple but conclusive experiments to test them. His painstaking and meticulous work gave the science of bone physiology a discipline and standard that contributed greatly to its orderly development. He has been highly critical in the interpretation of the results of his experiments while retaining great faith in the value of actual laboratory findings and hypothesis built upon them" (Figure 4).*

During this period he had difficulties in having his articles published in well-known journals. He still succeeded in publishing: 5 peer review articles; 8 Henry Ford Hospital Bulletin articles; 5 books and 4 chapters; edited one book; while chairing the Orthopaedic Surgery Department. (References to the articles can be found in his 2 volumes, Utah Paradigm for Skeletal Physiology, published in 2004)<sup>6,7</sup>.

## III. H.M.F.: The Transition – from Henry Ford Hospital, Detroit to Pueblo, CO

The move was caused by the following: (1) Tired of administration and fighting with the administration for equitable compensation for Orthopaedic Surgeon and a research budget; (2) Loss of NIH funding; and (3) To avoid a dangerous lifestyle in Detroit. He explored settling in the intermountain area with the mountains, climate and laid-back lifestyle he encountered in his numerous Sun Valley visits. He finally relocated in Pueblo to team up with one of his former Henry Ford Hospital fellows, Charlie Hanson.

## IV. H.M.F.: The Continuing Intellectual Journey – Another Intellectual Surge with the Utah and Sun Valley Connections (1975-2003)

It was a new environment for Harold. He no longer had a large laboratory and a medical library available but was con-



**Figure 2.** Participants of the first Workshop on "The General Biology of Bone Tissue". Harold is seated in the second row, the fourth person from the right.

fined to an active orthopaedic practice. Nevertheless, he had his continual interaction with Sun Valley Workshop participants, his hobby of "corresponding and jawboning" with clinical and research colleagues regarding skeletal science, medicine and surgery, became a consultant to an Upjohn Company 25(OH)<sub>2</sub>D<sub>3</sub> clinical trial involving fluorescent labeled iliac bone biopsies, and a consultant to Procter and Gamble, and encouragement for him to publish in the *Anatomical Record* where I was an Associate Editor. This setting allowed him to what he called, "connect the dots", and to publish his research on tissue level mechanisms of intermediary organization, biomechanics, dynamic cancellous bone histomorphometry, the mechanostat, the Utah Paradigm for Bone Physiology and many others.

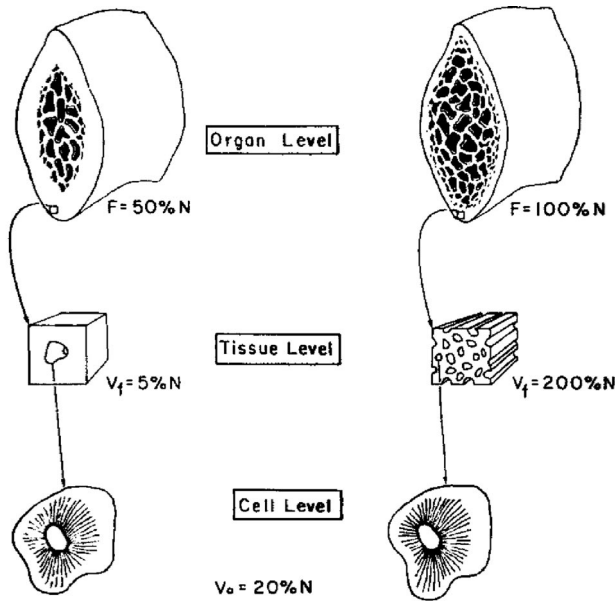
*Generation of dynamic cancellous bone histomorphometry*

Even though Harold developed the important tool for static and dynamic cortical bone histomorphometry<sup>8</sup>, the technology of dynamic bone histomorphometry did not blossom until Harold extended it to dynamic cancellous bone histomorphometry. It was the combination of a Frenchman named Phillipe Bordier who popularized obtaining human transilial bone biopsies<sup>9,10</sup>, plus a development in the late 1940s by a radiobiologist named James Arnold for producing reliable thin plastic-embedded undecalcified cancellous bone sections<sup>11,12</sup>, that made it possible to readily analyze tetracycline labeled cancellous bone. James Arnold and co-workers used his plastic-embedded undecalcified thin bone sections to perform autoradiographs for the study of bone-



Faculty of Teaching Workshop on  
"The General Biology of Bone Tissue"  
August 8, through August 12, 1966 – Salt Lake City, Utah

**Figure 3.** Faculty of the second workshop at the University of Utah College of Medicine, August 8-12, 1966. Harold is seated on the top row, the third person from the left. Front row (l-r): Gaynor Evans, Edgar Tonna, Web Jee, Norm Dockum, Howard Suzuki; back row (l-r): Jim Arnold, Bob Heaney, Harold Frost, Hal Copp, Roy Talmage, Murray Bartley.



**Figure 4.** Figure 1 from Harold's 1969 classical paper on tetracycline-based analysis of cortical bone remodeling in the human rib<sup>8</sup>.

seeking radionuclides<sup>11-13</sup>. This methodology produced excellent histology sections, exceeding decalcified paraffin-embedded and ground undecalcified bone sections in quality as well as retaining the mineral in which radionuclides and fluorescent antibiotics localized. By 1964, Frost had perfected his analysis of cortical bone histomorphometry<sup>8</sup>. There was no wide acceptance of Harold's unique development for static and dynamic cortical bone histomorphometry because not many investigators harvested human rib bone biopsy, dominated by cortical bone while there was a need to quantify the static and dynamic histomorphometric parameters for the cancellous bone-dominated human transiliac biopsy. The stimulus for accelerating the modification came about with his participation in the study by the Upjohn Company's need to evaluate the effect of 25-dihydroxyvitamin D3 in the treatment of renal dialysis patients<sup>14</sup>. The experimental design called for the analysis of cancellous bone histomorphometry in sequential transiliac biopsies. Frost accomplished this task in record time<sup>14-17</sup>. He first reported his development at the Second International Workshop on Bone Morphometry in 1976 in Lyon, France<sup>15</sup> (Figure 5). The technology gained wide acceptance by all as a research and clinical tool to assess the tissue-level organization of bone, the dynamic aspects of osteoblastic and osteoclastic functions, the pathophysiology of osteopenias and osteoporoses, the efficiency of treatment, and the safety and mechanisms of action of new therapeutic agents, etc.<sup>16-20</sup>. Furthermore, the technology improved our understanding of basic multicellular unit (BMU) of remodeling, skeletal adaptation to mechanical usage and led to the "mechanostat hypothesis" and the Utah Paradigm of Skeletal Physiology.



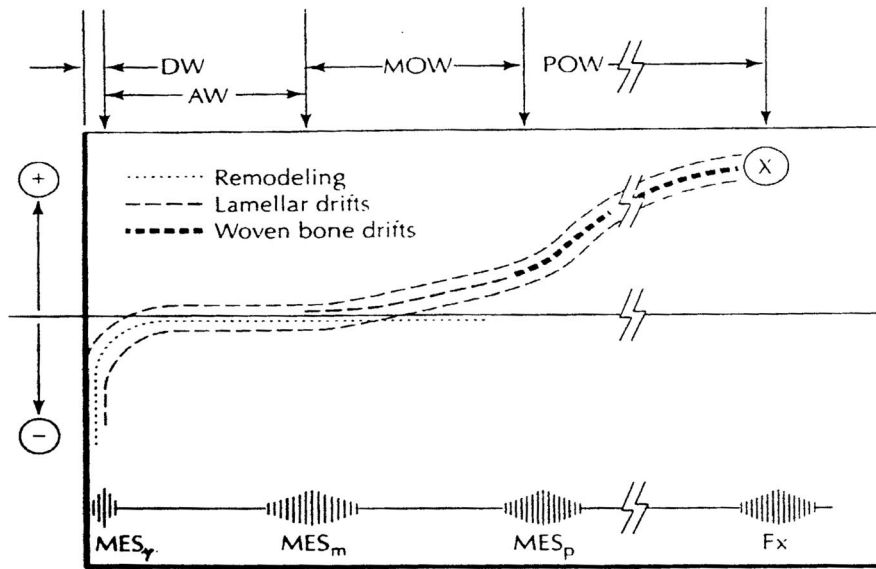
**Figure 5.** Harold with an "ARF ribbon" at the Second International Bone Morphometry meeting, Lyon, France, 1975, where he first describes the method of analysis of dynamic trabecular bone histomorphometry.

*Publications in the Anatomical Record (1972-2001), an excellent example of "Publish or Perish"*

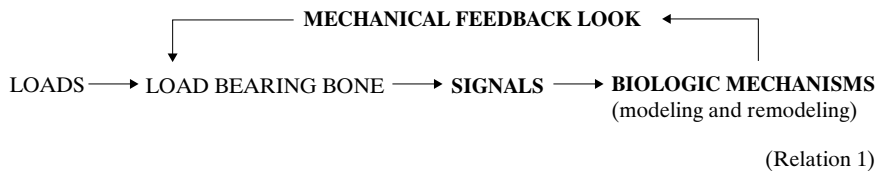
I encouraged him to publish some 10 articles in that journal when I was an Associate Editor<sup>21-30</sup>. One of them was the first publication of the mechanostat in 1987<sup>22</sup>.

*Mechanostat Hypothesis (1987-2003), a product of the Gordon Conference (1957), the Sun Valley Workshops and interaction with colleagues*

Frost first heard the idea of a "mechanostat" applied on bone at a Gordon Conference in about 1957. The originators were W.D. Armstrong, F.C. McLean, A. Reifenshtein and I. Snapper, all long deceased, 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"<sup>22</sup>. The mechanostat hypothesis is based on the idea that minimum effective strains must be exceeded to excite a positive adaptive response via bones' biologic mechanisms of modeling and remodeling to mechanical overloading. He suggested there are strain thresholds or windows that will evoke no response, "E"; strains above this E



**Figure 6.** Combined modeling and remodeling effect on load-bearing bone (LLB). 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 thresholds (MESr, MESm and MESp, respectively). The horizontal axis represents no net gains or losses of an LBB’s strength. The lower dotted line curve suggests how disuse-mode remodeling would remove bone next to marrow when strains stay below the MESr range, but otherwise would tend to maintain existing bone and its strength. The upper dashed line curve suggests how modeling drifts would begin to increase bone strength when strains enter or exceed the MESm range. The dashed outlines suggest the combined modeling and remodeling effects on a bone’s strength. Such a curve was originally suggested by Carter<sup>48</sup>. Beyond the MESp range, woven bone formation usually replaces lamellar bone formation (by Frost)<sup>31</sup>. At the top, DW = disuse window; AW = adapted window, as in normally adapted young adults; MOW = mild overload window, as in healthy growing mammals; and POW = pathologic overload window (by Frost)<sup>50</sup>. The strain span between the MESr and MESm represents the span between those features in bone’s general biomechanical relation. This scheme omits possible non-mechanical effects on muscle and the nervous system (from Frost; reproduced by permission)<sup>49</sup>.



threshold will evoke a positive adaptive response (i.e., modeling-dependent bone gain) and strains below the no-response threshold will cause a negative adaptive response (i.e., disuse mode remodeling-dependent bone loss) (Figure 6)<sup>21-34</sup>. This combined modeling and remodeling effect on load-bearing bone strength is an integral part of the mechanostat hypothesis and the Utah Paradigm of Bone Physiology (Relation 1).

*The mechanostat hypothesis and the ever-evolving Utah Paradigm of Bone Physiology, a new paradigm of skeletal physiology*

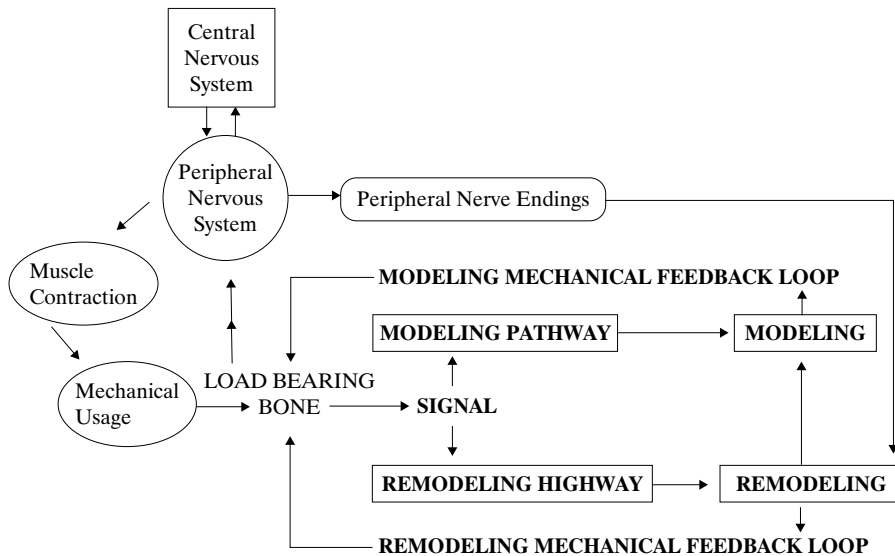
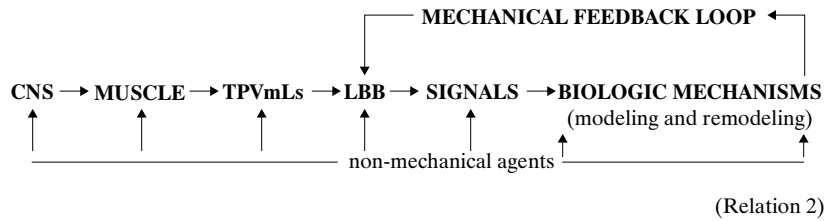
The paradigm is based on Hal’s proposition #1:

*"The design of healthy, mammalian load-bearing bones would provide only enough strength to keep postnatal voluntary*

*loads from causing spontaneous fractures, whether those loads are chronically small, normal or huge in size*<sup>6,7,31,38</sup>.

The paradigm stated that the primary function of bone is mechanical load-bearing with subsidiary function to participate in plasma calcium homeostasis and to support hematopoiesis. The new paradigm emerged from his earlier studies on the morphology and dynamics of bone cells and tissue in growth, modeling and remodeling, the osteocyte as mechanoreceptor, fatigue and microdamage repair, biomechanical influence on bone adaptation, maintenance and turnover, transient and steady-state conditions, muscle-marrow-bone relations, osteonal bone remodeling and tissue changes in aging and select bone diseases.

It is unclear when Harold started to "connect the dots" to



come up with the Utah Paradigm of Bone Physiology. It may have begun during the numerous discussions on the skeletal adaptation of mechanical loading with Hans Schiessl at Pforzheim, Germany, in the early '90s that stimulated him to put together the ever-evolving Utah Paradigm of Bone Physiology. Those many discussions involved the role of the nervous system in co-ordinating the involvement of muscles that put the largest loads on load-bearing bone (Relation 2).

In the simplified relationship of the Utah Paradigm CNS is for central nervous system, TPVmls is for typical peak voluntary mechanical loads, and LBB is for load-bearing bone. In relation 2, the boldface letters are the mechanostat. The ever-evolving Utah Paradigm is missing the detailed involvement of the vascular and lymphatic systems which can be currently included under the effects of non-mechanical agents.

The Utah Paradigm of Skeletal Physiology was featured in many of his publications<sup>6,7,30,35-38</sup> with the heart of it, its mechanically dedicated message traffic system, the mechanostat hypothesis found in bold letters in the Utah Paradigm of Skeletal Physiology Relation 3<sup>21-38</sup>.

There is some confusion as to what Harold called the Utah Paradigm. In his last two peer-reviewed publication he

called these relationships (Relation 3) the "mechanostat hypothesis"<sup>31-38</sup>. However, in the two volumes he heroically generated during his fatal illness the relationships were named the Utah Paradigm of Physiology<sup>6,7</sup>.

### V. H.M.F.: As Defined by a Few

- "Best remembered for his endless supply of acronyms (ARF, BMU, BSU, MES, FX, IO, MTA, MU, RAP, rho, SATMU, Sigma, VMU, etc.)." – Turner, Burr<sup>39</sup>
- "Self made skilled researcher, provocative." – High<sup>40</sup>
- "Obstreperous, cranky, unreasonable and possessed." – Axelrod<sup>41</sup>
- "Prodigious work ethic." – High<sup>40</sup>
- "Gruff, outspoken, workaholic." – Smith<sup>42</sup>
- "World class." – Bartecchi<sup>42</sup>
- "An iconoclast and thinker." – Recker<sup>43</sup>
- "Frost changed the paradigm for bone biology." – Recker<sup>43</sup>
- "Exceptionally deep thinking researcher with unique original concepts from his clinical experience, sharp observations in various cases." – Takahashi<sup>44</sup>
- "We are still exploiting the rib material that Hal had accumulated almost 50 years ago." – Parfit<sup>45</sup>

- "Uncanny ability to appreciate and perceive important biologic phenomena in both medical and scientific research settings that most missed." – *High*<sup>40</sup>
- "I can think of no one whose work has influenced my own work more than his, and I would venture to say that this is true of a majority of orthopaedic researchers whether they realize it or not." – *Martin*<sup>46</sup>
- "Frost is, in my opinion, the most influential theoretician in skeletal biology of the last century. Beginning with his early work in 1958. Frost's ideas have influenced virtually everyone in the field of skeletal biology (according to the Science Citation Index, Frost is one of the most cited investigators in skeletal research)." – *Turner, Burr*<sup>39</sup>
- "He was admired for his ability to learn from broad experience in clinical orthopaedics. He saw things in patients that others did not. His most brilliant insights came from careful, thoughtful interpretation of what he saw, "on the hoof" as he referred to it, in the clinic and operating room." – *Recker*<sup>43</sup>

## VI. H.M.F.: The Teacher (Figures 6 and 7)

*"I think that teaching is the highest level of intellectual activity, more than discovery in the lab. To be able to tailor the story to reach the people. . . . .that's the greatest challenge" – Ira Herskowitz*

- "Above all, Harold loved to teach. He taught thousands, young and old, friend and foe. He always made time to help revise drafts of manuscripts and debate about disagreements. He fostered numerous efforts to facilitate better communication among skeletal scientists by helping to form the ASBMR *In Vivo* Working Groups, International Chinese Hard Tissue Society (ICHTS), International Society of Musculoskeletal and Neuronal Interactions (ISMNI) and the Black Forest Forums." – *Jee*<sup>39</sup>
- "He was an excellent teacher. When he was at Henry Ford Hospital making rounds in wards and clinics, he always asked residents and interns how they interpreted what they saw, why it occurred and how it was to be treated. He always encouraged and told us how important it is to think and interpret based on the clinical materials." – *Takahashi*<sup>44</sup>
- "He taught hundreds of us, maybe thousands." – *Axelrod*<sup>41</sup>

## VII. H.M.F.: Self Evaluation – Quotes from Harold<sup>42</sup>

- "The great obstacle to progress is not ignorance, but the illusion of knowledge." – *Daniel Boorstein*
- "What you would hate if done to you, do not to others." – *Confucius*
- His Hobby: "correspondence and jawboning with clinical and research colleagues regarding skeletal science, medicine and surgery." – *Hal*
- "I've made a lot of mistakes. When I was 40, 50, 60 years younger, I really didn't know a damn thing, and I thought



**Figure 7.** The dedicated teacher, Harold with Jörn Rittweger at the microscope at the Sun Valley Workshop.



**Figure 8.** The perpetual teacher. Trying to straighten out Mas Sato, April 23, 2004, a few months before his death.



**Figure 9.** The hurried gathering to give our respect to Harold, April 23, 2004. Front row, seated (l-r): Hideaki Takahashi, Doris Frost, Harold Frost, Web Jee, Dave Van Sickle; 2<sup>nd</sup> row (l-r): Satoshi Mori, Jörn Rittweger, Howard Winet, Linda Ma, Becky Setterberg, Mas Sato, Bob Norrdin; 3<sup>rd</sup> row (l-r): Hans Schiessl, Rick Sumner, Dieter Felsenberg, Chris Jerome, Scott Miller, Mei-Shu Shih, Charlie Bleau.

I knew everything, OK? I'm glad for one thing, that after I conk, I won't be the one who has to judge me." – *Hal*

- "Actually, I've been very fortunate, I had a lot of breaks, and my dad (also a surgeon) was very understanding and supportive. And, unlike most of my colleagues, I was never interested in getting rich." – *Hal*
- "It's nice to be taken into account. It's nice to be respected." – *Hal*

(These remarks were reported by Scott Smith in the Pueblo Chieftain a week before the gathering of friends in Pueblo prior to his passing.) (Figure 8)

### **VIII. Thanks, Feisty, Old, Eccentric, Very Smart Dinosaur (F.O.E.D). It was a great trip and I will miss you dearly. (Figure 9)**

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