

Tribute to Harold M. Frost M.D.

## Harold M. Frost, M.D.

### – His Contributions –

Harold M. Frost was a true iconoclast who may be best (or worst) remembered for the endless supply of acronyms he introduced to the language of bone biology. Frost is responsible for BMUs, BFR, MAR, SATMU, RAP and MES to name a few. Over the years, Frost boisterously announced his theories and opinions to everybody within earshot. Many times perhaps he pushed his ideas too forcefully and alienated colleagues. One has to look past Frost's sometimes acrimonious personality to see the true brilliance of his work. 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 everybody in the field of skeletal biology (according to the Science Citation Index, Frost is one of the most cited investigators in skeletal research). Of his many accomplishments, probably his greatest were the invention of quantitative bone histomorphometry and the discovery of the basic multicellular unit.

What follows is a summary of Frost's major contributions to the field of orthopaedic science.

**1) The development of the techniques to make quantitative measurements on non-decalcified bone sections and the invention of bone histomorphometry.** Dr. Frost was the first to utilize the calcium-binding and fluorescent properties of the antibiotic tetracycline in bone biology. Frost first developed sectioning and staining techniques for nondecalcified bone sections (1958), then utilized sequential dosing of tetracycline to demonstrate the movement of the mineralizing surface with time, thus providing a measurement of bone formation rate. Over the years, Frost perfected a series of stereological measurements of bone structure and formation dynamics that became the foundation for quantitative histomorphometry of compact (1969) and trabecular bone (1977).

Today, bone histomorphometry remains an important tool used by hundreds of laboratories worldwide for evaluating the effects of new drugs and genetic alterations in experimental animals. These measurements are considered a gold standard by the FDA for trials of drugs for metabolic bone diseases and osteoporosis.

**2) The use of the 11<sup>th</sup> rib biopsy for diagnosis of metabolic bone disease.** Frost first used tetracycline-labeling clinically in 1960. His approach involved giving the patient tetracycline pills at an interval of 1-2 weeks, after which a small section of the 11<sup>th</sup> rib was removed. This approach made histomorphometry clinically useful. In subsequent years, Frost studied the effects of cortisone, aging, and several metabolic bone diseases on bone formation dynamics. His early observations revolutionized the field of bone biology. He was the first to characterize osteomalacia, rickets, and osteoporosis in

terms of the functional activity of bone cells.

Although the 11<sup>th</sup> rib has fallen out of favor as a site for bone biopsies (the iliac crest is the preferred site), Frost's observations about bone diseases and hormone effects made using the rib biopsy, many of which were controversial in the '60s, have been confirmed and are widely accepted.

**3) The discovery of the basic multicellular unit as the key effector of bone metabolism.** Frost published *Bone Remodeling Dynamics* in 1963 and *Laws of Bone Structure* in 1964. These books put forward the new theory that osteoclasts and osteoblasts were somehow involved in a co-ordinated bone remodeling sequence. Frost called the cells involved in a remodeling packet the basic multicellular unit of BMU. He proposed that bone resorption preceded bone formation, and that the two events were coupled. Prior to this, bone cells were considered as individual units each working independently with little communication between. Frost's idea of a functional BMU, which forms the basis of modern bone biology, was slow to be accepted so Frost set out to prove it.

In collaboration with Robert Hattner and Bruce Epker, Frost published an article in *Nature* (1965) demonstrating that over 96% of bone formation in the adult skeleton occurs only after previous resorptive processes. This paper was recently chosen by the *Journal of NIH Research* as a landmark article (*J NIH Res* 1995; 7:54-57). To my knowledge, Frost and Marshall Urist are the only orthopaedic researchers who have received this recognition. Frost's discovery and his subsequent work provided a mechanistic model for bone biology, and like the sliding filament model for muscle, it provided new insights that spurred the advancement of the science.

**4) The experimental demonstration that estrogens reduce bone formation.** Frost showed in 1964 that estrogen decreased bone formation. This seemed paradoxical at the time because evidence was accumulating that showed bone loss in postmenopausal women, presumably due to the loss of circulating estrogens. Frost argued that decreased bone formation did not necessarily lead to bone loss, thus estrogen could preserve bone mass while decreasing bone formation. His argument was based upon his new concept of bone remodeling. He stated that maintenance of bone mass occurred through communication between osteoblasts and osteoclasts within the BMU. According to Frost, the absolute rates of bone formation or bone resorption were not as important as the "activation frequency", i.e., the rate at which new remodeling sites were created. He contended that estrogens reduced activation frequency but maintained equal amounts of bone formation and resorption thus maintaining the balance within the BMU so bone mass was main-

tained. Frost's explanation has been proven correct; estrogens effectively treat postmenopausal osteoporosis even though they reduce bone formation rates.

**5) The histological demonstration of microcracks in human bone biopsies.** In 1960, Frost developed a bulk staining technique to demonstrate microcracks in bone tissue. He proposed that a distinction between the disease osteoporosis and asymptomatic osteopenia could be made based upon the existence of microcracks and that bone remodeling might be directed to repair bone by removing microcracks. This result was met with considerable skepticism, in fact, many argued that microcracks in bone were merely artifacts of the specimen preparation techniques. However, due largely to Frost's persistence, others led by David Burr and Mitchell Schaffler have demonstrated that microcracks in bone are not artifact, but may be important in bone biology. Frost's initial hypothesis that microcracks contribute to the risk of osteoporotic fracture has not been confirmed, but his intuitive arguments about the role of microcracks in bone remodeling have led to several discoveries. Burr showed that bone resorption often targets and removes microcracks (J Biomech 1985; 18:189-200, Bone 1993; 14:103-109), and Schaffler demonstrated that osteocyte apoptosis plays a role in this process (JBMR 2000 15:60). These discoveries were inspired by Frost's early experimental work and his later theoretical musing.

**6) The basic theories for bone growth plate adaptation to mechanical loading.** From 1963-1973, Frost devised some of the basic theories for how bone and joints adapt to functional mechanical loading. He developed one of the first theories of how growth plates respond to mechanical loading. He also proposed that mechanical adaptation of bone was governed by a mechanical strain threshold which Frost called the minimum effective strain (MES). Charles Turner's lab later confirmed the existence of the MES in rat long bone (JBMR 1994; 9:87-97). Frost was one of the first to propose that bone adaptation is controlled by a negative feedback loop, subsequently demonstrated computationally by Bruce Martin. This proposal forms the basis for many mathematical and computational bioengineering models.

**7) The "mechanostat theory" of bone adaptation to mechanical effects.** In 1987, Frost extended his theories of bone adaptation to mechanical forces to include the concept of the "mechanostat". Frost proposed that bone structure is regulated by local mechanical effects but that these effects are adjusted by system hormones, just as you would adjust a thermostat.

Frost's theory describes a feedback control system where bone structure is maintained such that ordinary mechanical strains do not exceed a minimum effective strain (MES). If the local strains within the bone surpass the MES, bone will undergo modeling, or sculpting, and change its structure to reduce the local strains to below the MES. Frost further suggested that certain hormones and biochemical agents may fool the "mechanostat" of bone to alter the value of the MES. Therefore an agent could sensitize bone cells so that the MES is lowered so normal mechanical usage would increase bone mass and bone strength significantly.

This theory seemed highly speculative until the recent

work of Jade Chow provided experimental support. Chow has shown that mechanical adaptation of bone does not occur in the absence of parathyroid hormone, but the effect of mechanical loading on bone formation can be increased in proportion to dose of PTH given back to parathyroidectomized rats (AJP 1998; 274:E146). PTH thus has the ability to adjust the "mechanostat". This important finding has opened the door to a whole new outlook on bone physiology that was envisioned by Frost over 20 years ago.

**8) The Utah Paradigm of Bone Physiology.** In 1995, at the Sun Valley Hard Tissue Workshop, Dr. Frost put his 20 years of positive and negative thoughts on bone physiology into the Utah paradigm of bone physiology which involves the mechanostat. This paradigm included the mechanically-dedicated message traffic and feedback in the mechanostat. It suggests four things. **1)** The biologic mechanisms that determine skeletal health and disease need effector cells and non-mechanical agents in order to work, as cars need fuel, engines, and wheels in order to move. **2)** But mechanical factors guide those mechanisms in time and anatomical space, as drivers, steering, brakes, and accelerators do for cars. **3)** After birth, neuromotor physiology and anatomy dominate control of those biologic mechanisms. **4)** Most non-mechanical things can help or hinder but cannot replace or duplicate the mechanical control. Otherwise they could normalize skeletal architecture in congenitally or neonatally paralyzed limbs.

**9) Muscle-bone relationship.** More recently, Dr. Frost has proposed another concept that is fundamentally biomechanical: that bone mass is directly tied to lean muscle mass, and muscle force. Although not surprising to most in the engineering community, the idea has sparked controversy because it has been widely misunderstood to ignore the influences of hormonal and metabolic factors in bone physiology. In actuality, it doesn't ignore them; it provides a means to determine whether the primary abnormality in a given osteopenia is related chiefly to muscle pathology or bone pathology. From a diagnostic and therapeutic standpoint, this could be quite useful. Whether the idea ultimately turns out to be correct or incorrect is immaterial; the fact that it has initiated an active dialogue about the role that muscle force plays in the adaptation of bone is important. This is the basis of scientific inquiry.

There are few clinician scientists that have had such a profound impact on a scientific discipline as has Harold Frost. He has advanced the basic science of skeletal biology, but has used it to improve clinical diagnosis and treatment. It is impossible to overestimate his influence and contributions to the field of skeletal biology. He has molded the thoughts of a generation, in areas as widely divergent as orthopaedics, endocrinology, rheumatology, clinical medicine, anatomy, physiology, orthodontics, anthropology and bioengineering. It is not an overstatement to say that he has been the most influential theoretician in skeletal biology in the last century.

*Collated from writings of  
Charles Turner, David Burr and Web Jee*

## Colleagues gather to say goodbye to dying doctor

Newspaper interview by Scott Smith, Pueblo Chieftain

His kidneys have shut down. He can't feel sensation in his bladder and bowels. He has no appetite and suffers from severe back pain and relentless fatigue. He's lost almost 80 pounds in the past two years, as the cancer that began in his prostate gland 16 years ago has inexorably spread throughout his body and into his bones and lungs.

"For one whose head is still working, this ain't no fun," said Dr. Harold Frost, pausing to take a thoughtful draw from his omnipresent pipe. "It ain't no fun."

Frost, an 82-year-old orthopaedic surgeon and world-renowned bone researcher, harbors no illusions. He's dying. And he knows it.

"I'm resigned," he said. "I know I'm approaching the time of death. I'm a little scared about what the hell I'll meet after I die . . . but I can't do anything about that."

What Frost can control is where he'll watch his final sunsets — and that's why he has chosen the comfort of his South Side home. No hospital bed for Frost, who is intent on exiting with dignity. He'd rather spend his final days or weeks seated in his living-room easy chair, voraciously reading novels and scientific magazines and chain-smoking his beloved pipes.

"Doris (his wife) wants me to stop that (smoking)," Frost said with a sly smile. "She says it'll kill me. Hah!"

Yeah, Frost's sense of humor remains just fine, thanks — and so are the rest of his brain functions. After all, this is a man who, until his recent kidney failure, was still practicing medicine 3 days a week.

"When he gave up his practice," said longtime friend Dr. Webster Jee, a professor of anatomy at the University of Utah, "I knew the end was pretty close."

Jee also knew what needed to be done. He quickly began making contact with Frost's far-flung peers and disciples — scientists and doctors and researchers and engineers, all bonded by the Pueblo surgeon's years of groundbreaking findings in the fields of bone structure and biodynamics. For the past four decades, the bone specialists have been gathering at sites around the world for annual hard-tissue workshops and conferences, all designed to further explore Frost's original ideas and the scientific dialogue they've spawned.

"He's like our father," said Jee, who has known Frost for almost 50 years.

The bone men, alerted by Jee and e-mails sent by Doris Frost that mentioned her husband's rapidly failing health, quickly decided to alter their scheduled meeting plans. They moved the workshop up to this weekend (from October), switched the location to Pueblo and have proclaimed the event a tribute to Dr. Harold Frost. Make that Dr. Harold Frost, FEOD — a self-proclaimed title that stands for Feisty, Eccentric, Old Dinosaur.

More than two dozen of Frost's friends and fellow researchers — some from as far away as Japan, Germany

and England — are expected to attend the celebratory dinners and workshop Friday and Saturday at the Holiday Inn. They'll toast their comrade, give him a few heartfelt hugs and wonder what the research community will be like without the gruff, outspoken workaholic who has made a lifelong commitment to figuring out how bones work.

"It's not easy for people to make this on such short notice, but it's something we wanted to do," Jee said.

Said Frost: "I'm planning to go, if I don't die first, OK?"

Then, with voice cracking and tears welling, he added, "It's nice to be taken into account. It's nice to be respected."

Respected? That would be a dramatic understatement. Here's a sampling of some written tributes from his peers about their founding father: They characterize Frost as "the one and only genuine theoretician in the field of hard-tissue biology and medicine," "a pioneer in the field of histomorphometry" and "an iconoclastic tinkerer who worked alone in his basement laboratory and used a technique of his own invention to make unprecedented observations of how human bones maintain their structure."

Said local physician Carl Bartecchi, "He's world-class."

He's also been happily at home in Pueblo for the past three decades. Frost moved here in 1973, after a 17-year tenure at Henry Ford Hospital in Detroit, where he chaired the orthopaedic surgery department. Before that, the Boston native and graduate of Northwestern University School of Medicine worked as an assistant professor at Yale University School of Medicine and began dabbling in bone research.

When Frost came to Pueblo (to the Southern Colorado Clinic) — drawn by the mountains, climate and laid-back lifestyle — he brought with him his international reputation as a dogged researcher, talented orthopaedist and prolific author.

He has written 442 published articles and 16 books/monographs; performed thousands of operations (his total was 10,000 in 1973, when he stopped counting); lectured in Brazil, Italy, Japan, Mexico, Austria, Spain, Switzerland and many other countries; and helped to revolutionize the fields of skeletal physiology, musculoskeletal biomechanics and bone histology and pathology.

His work ethic has been described as prodigious by his peers. Who else, they wonder, would list the following as a hobby? — "Correspondence and jawboning with clinical and research colleagues regarding skeletal science, medicine and surgery." Only Dr. Frost, of course.

Over the years, many of Frost's theories have been accepted by the scientific and medical communities, but along the way, he spent plenty of time and energy challenging — and failing to alter — accepted wisdom. One of his favorite quotations, by Daniel Boorstin, reflects his early frustrations: "The great obstacle to progress is not ignorance, but the illusion of knowledge."

Of course, Frost's tenacious approach and sometimes combative personality didn't help sway the established experts.

"Besides, how the hell can you expect an orthopaedic surgeon to come up with anything useful and scientific?" Frost said with a chuckle. "Everybody knows they're interested in the stock market and golf and Mercedes. It took a while for credibility to grow, but it's still building."

These days, Frost finds himself reflecting on a personal past he views as bittersweet. He's proud of his three children and their chosen careers — Patricia (surgeon), Bob (policeman) and Eric (commercial pilot) — and of his 16-year marriage to Doris, a nurse. He knows he's battled the cancer the best he could, with surgery, X-ray treatments and courage. And, of course, he's pleased that much of his research has been validated, accepted as fact and used to improve bone medicine and, more importantly, patients' lives.

But, with the clarity of hindsight, Frost claims he's lived an imperfect life — despite doing his best to follow some sim-

ple Confucian wisdom: "What you would hate if done to you, do not to others."

Said Frost, "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 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."

Spoken like a true, hard-working perfectionist and FEOD.

After taking another puff from his pipe, Frost added, "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."

"I guess the good part of it all was the journey, not the destination."

*Scott Smith*

*The Pueblo Chieftain*

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## Harold M. Frost, M.D. (1921-2004)

### Scientist, Surgeon, Clinician, Theoretician, Teacher

Harold M. Frost, M.D., lost his long battle to prostate cancer on June 19, 2004. Many of you may not have been fortunate enough to know him, but you should know about him anyway because we owe him so much. Harold called himself a "Feisty, Eccentric, Old Dinosaur (F.E.O.D.). He was old, except not in mind. He never lost his lust for science. A smart orthopaedic surgeon with two of his hobbies being "corresponding and jawboning with clinical and research scientists regarding skeletal science, medicine and surgery and teaching". At the time of his death, he was an orthopaedic surgeon at the Southern Colorado Clinic in Pueblo, Colorado and an active adjunct Professor of Anatomy at Purdue University and Radiobiology at the University of Utah School of Medicine.

Harold completed his M.D. from Dartmouth and Northwestern Medical Schools (1945), his surgical internship at Worcester in Massachusetts and residencies in orthopaedic surgery at Buffalo General and Children's Hospitals in New York (1948-1953). He spent several years in private practice (1953-1955), as well as serving our country as an officer in the Naval Medical Corps (1946-1948). His research career began when he became an Assistant Professor of Orthopaedic Surgery at Yale University School of Medicine (1955-1957). Hal moved on to Henry Ford Hospital in Detroit, Michigan to be the founder and Director of the Orthopaedic Research Laboratory (1957-1973) and later as Chairman of the department (1966-1972) as well as Clinical Research Professor of Surgery at University of Michigan School of Medicine (1968-1975). It

was his tenure at Henry Ford Hospital where Harold made many of his breakthroughs that changed the paradigm of bone biology (1957-1973).

What follows is a listing of Harold's major contributions in the field of skeletal science. (1) The development of the techniques to make quantitative measurements on non-decalcified bone sections and the invention of cortical and cancellous bone histomorphometry (1958, 1969 and 1977). (Today, bone histomorphometry remains an important tool used by hundreds of laboratories worldwide for evaluating the effects of new drugs and genetic alterations.). (2) The use of the 11<sup>th</sup> rib biopsy for diagnosis of metabolic bone disease in terms of functional activity of bone cells (1960). (3) The discovery of the basic multicellular unit as the key effector of bone remodeling dynamics (1963-1965). (4) The role of osteocytes in bone turnover (1960). (5) The experimental demonstration that estrogens reduce bone formation and activation frequency (bone turnover) (1964). (6) The histological demonstration of microcracks in human bone biopsies (1960). (7) The basic theories of bone growth plate adaptation to mechanical loading (1963-1973). (8) The "mechanostat hypothesis" of bone adaptation to mechanical usage with its mechanical loading negative feedback loops (1987). (8) The ever-evolving Utah Paradigm of Bone Physiology involving neuromotors and the muscle-bone relationship (1995-2004). The research during this period was way ahead of the times and his findings were not favorably received; but now much of his research has been validated. In addition, he helped to co-found and perpetuate

the Sun Valley Hard Tissue Workshops (1966).

In 1973 Hal moved on to join a former resident at the Southern Colorado Clinic in Pueblo, Colorado, partly because he tired of administration, loss of his NIH grant and being drawn to the mountains. While there he continued his active participation at the Sun Valley Workshops where he interacted with participants to develop cancellous bone histomorphometry (1977), generate and refine the mechanostat hypothesis (1987), and the ever-evolving Utah Paradigm of Bone Physiology (1997), and many, many more.

Harold published nearly 500 peer-reviewed scientific and clinical articles, 2 textbooks and 11 monographs, and currently has 2 volumes entitled "The Utah Paradigm of Skeletal Physiology" (in press). According to the Science Citation Index, Harold is one of the most cited investigators in skeletal research. He was Associate Editor and on Editorial Boards of numerous scientific journals.

Besides the Hektoen Gold Medal by the AMA (1963), respect came late. Most notable were the Special Senior Investigator Award from the American Society of Biomechanics (1987); the first recipient of the Sun Valley Hard Tissue Workshop Remodeling in Bone (RIB) award (1991); Honorary Doctor of Science degree bestowed by Purdue University (1994); Honorary Professor of Surgery at Guangdong Medical College, Zhanjiang, China (1994); and the William F. Neuman Award from the American Society of Bone and Mineral Research (2001); the Harold M. Frost Professorship at Henry Ford Hospital (1991). The ASBMR/Harold Frost Young Investigator and the Harold Frost Asian Pacific Bone Morphometry Awards (2004) were

named after him. He was the first and only Honorary President of the International Society of Musculoskeletal & Neuronal Interactions (ISMNI) and the first Honorary Member of the International Chinese Hard Tissue Society (ICHTS).

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 Group, ICHTS, ISMNI and the Black Forest Workshops.

There are few clinician scientists that have had such a profound impact on a scientific discipline as has Harold Frost. He has advanced the basic science of skeletal biology and used it to improve clinical diagnosis and treatment. It is impossible to overestimate his influence and contributions to the field of skeletal biology. He has molded the thoughts of a generation, in areas as widely divergent as orthopaedics, endocrinology, rheumatology, clinical medicine, anatomy, physiology, orthodontics, anthropology and bioengineering. It is not an overstatement to say that he has been the most influential theoretician in skeletal biology in this century.

We will miss his ideas, manuscripts, letters, faxes and debates and the many acronyms he introduced into the vocabulary of bone biology, the BMUs, BFR, MAR, SATMU, RAP and MES to name a few.

Many thanks to F.E.O.D., that brilliant, feisty, eccentric, old dinosaur.

*Webster S.S. Jee, Ph.D.*

## In Memorium

### Harold M. Frost, M.D.

#### Orthopaedist

The Journal pays tribute to Harold Frost, M.D., who died on June 19, 2004 after a protracted bout with cancer. Harold leaves a truly awesome legacy of paradigm generation in bone physiology and pathophysiology. We mourn his passing, and we celebrate his seminal contributions to the bone field.

Dr. Frost first characterized *in vivo* cortical and trabecular bone remodeling as we now know it using fluorochrome (tetracycline) labeling. Tetracycline labeling was also the basis for his landmark description of the three elements of "Intermediary Organization" of bone – growth, modeling and remodeling. From 1958, when he first described methods for sectioning undecalcified bone specimens, his contributions include: analysis of tetracycline labeling, 1960; demonstration of microcracks in bone, 1960; demonstration that estrogen *reduces* bone formation, 1964; development of cortical histomorphometry, 1969; and trabecular histomor-

phometry, 1977; generation of the mechanostat theory, 1987; and many more. Although it was many years before his ideas were widely accepted, most have now become part of the canon of bone physiology. He was far ahead of his time.

Harold was an iconoclast and tinkerer. Most of his ideas were tested by using simple tools in a cluttered basement laboratory, where he sawed cross-sections of ribs, grinding them to thin sections by hand under running water, and mounting them on slides. His most sophisticated tool was a microscope equipped with a fluorescent light source.

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.

He was an ASBMR Neuman award winner in 2001. This

award highlighted the fact that his ideas had become widely accepted in the field. Harold greatly appreciated the award, and many scientists in the field were most pleased by this recognition of his brilliance and his achievements.

We will miss the ideas, manuscripts, letters, debates that we have enjoyed with our friend, the "Feisty Eccentric Old Dinosaur". A colleague once said, "I cannot think of any other scientist that has had more influence than Harold. As

Thomas Kuhn would say, 'Frost changed the paradigm for bone biology'". I believe he would be pleased to be remembered that way. May he rest in peace.

**Robert R. Recker,  
M.D., M.A.C.P., F.A.C.E.**

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## For Hal

Harold Frost died last week. Many of you may not know who he was. That was fine with him. But I think you should know anyway.

Hal was an orthopaedic surgeon, a very smart orthopaedic surgeon, who conceptualized bone as a living tissue, responsive to influences. He thereby conceived of bone as changing shape in response to stresses and strains by two distinct processes: modeling and remodeling. The idea of changing shape was not new. All medical students know Wolff's law. But to attach physical influences to distinct alterations and sites of bone removal and replacement was indeed new, as was the concept of the "mechanostat", a hypothetical mechanism by which bone detected and acted on external influences. He conceived the "bone remodeling unit", or BMU, and went on to help us understand why bone does what it does, and how it could be modulated in disease. And he helped put together the first practical manual on doing bone histomorphometry. He was on his way to explaining the alterations of cartilage modeling in OA when cancer caught up with him.

He was obstreperous, cranky, unreasonable, and possessed. He taught hundreds of us, maybe thousands. He and Web Jee initiated the Sun Valley bone conference, a "brains-on", full contact seminar series that was part learning conference and part "survivor." He was intolerant of technique for technique's sake, and that included molecular biology. But if you look now at who is leading the field in understanding why

and how bone does what it does, they are all children of Hal.

Hal would never have survived in a pharma company. He didn't survive academia. But he was driven to understand and teach, even those he thought slow (and that was most of us), and he invented a new field, new ways of understanding, and paved the way for us to come behind, fill in the blanks, and invent therapies for the afflicted.

I miss Hal. I miss who he was and what he contributed. And I miss his kind, those self-identified "dinosaurs" that stay on scientific point, even when the way is unclear, when the methods are unknown, and the field is not with them. They make breakthroughs.

I miss Hal. And if you didn't know him, I'm sorry. But there are other Hals out there, though they be unappreciated or even reviled. But it is their lonely lot to make the breakthroughs that serve us all. And because of that, I adjure you to find them, sit at their feet, put up with their insults and intolerance, and learn.

Millions of patients now and forever owe their health to Hal Frost, that lone, irksome, smart dinosaur. We all owe him and his kind so much.

RIP, sir. And thanks.

**D.W. Axelrod,  
M.D., Ph.D.**

## Harold M. Frost, M.D. (1921-2004)

Harold Frost died on June 19, 2004. We really miss him.

Harold was certainly an excellent teacher throughout his life. In 1960 when I met him the first time in Detroit and thereafter, I knew Harold was a hard working orthopaedic surgeon, in the operating room and on emergency calls. He was primarily interested in the treatment of acute trauma; nevertheless, he had a wide interest in bone and joint diseases. He was responsible to an outpatient clinic as well as a cerebral palsy clinic. He was interested in metabolic bone diseases and bone tumors.

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 was an exceptionally deep thinking researcher. His unique, original concepts always came from his clinical experiences, sharp observation on various cases, and undecalcified ground sections made in his small orthopaedic laboratory and sometimes in the basement of his house. Observations

of tetracycline deposits in a piece of bone removed from an osteomyelitis case was a starting point of bone histomorphometry and a shape of a cement line of the Haversian system was a hint of his classic theory of Activation, Resorption and Formation and Basic Multicellular Units.

His influence has spread worldwide, not only North and South America and Europe, but also Asia, including Japan, China, Korea, Thailand and others. Many fliers from him,

including reprints, copies of manuscripts and letters signed by FEOD, the Feisty, Eccentric, Old Dinosaur always encouraged and told us how important to think and interpret based on the clinical materials.

As one of his disciples, I am very proud of him and certainly miss him. He made a great shift in my thinking with his paradigm of bone physiology. Salute, Big Chief and thank you.

*Hideaki E. Takahashi, M.D.*

## Harold M. Frost, M.D.

### (A Tribute)

Mankind owes an immeasurable debt to many scientific workers who laid down the groundwork for the dramatic expansion of medical knowledge in the eternal battle against diseases. One of these expanding areas is that of metabolic bone disease. Dr. Harold M. Frost has been a leader in the search for better understanding of these diseases through the use of histologic techniques and cybernetic analysis. One of the most important concepts contributed by Dr. Frost was the *quantum concept of bone remodeling*. His ingenuous methods for studying skeletal physiology have led to the exploration of bone biomechanics, and the skeleton's tissue-level features and functions.

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 was the first one who developed the staining of fresh, undecalcified ground sections of bone using 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 conclu-

sive 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.

Dr. Frost also had a long and distinguished career as a lecturer, professor and prolific writer on many scientific topics, having been editor of books and journals, and author of 17 books and over 440 scientific publications. He has been a consultant to many scientific institutions. In 1963, he was awarded the highest award (Hektoen Gold Medal) in recognition of the most original research and scientific excellence during the American Medical Association Meeting in Atlantic City and the Wolverines Frontiersman Award for his distinguished research in Orthopaedic Surgery in 1967. In 1991, Henry Ford Hospital created a Harold M. Frost, M.D. professorship, an honor given only to distinguished individuals or alumni in the field of medicine.

The science of bone physiology and technology clearly reflected and demonstrated the work of one man – Harold M. Frost, M.D., surgeon, researcher, scientist, writer, biologist, theorist, biomechanician, teacher, and the Father of Bone Histomorphometry.

*Antonio R. Villanueva,  
M.A., Ph.D., MCS, ASCP*

## A Commemorative Tribute to Harold M. Frost, M.D.

Harold M. Frost, M.D., died June 19, 2004. Dr. Frost was an orthopaedic surgeon, teacher/mentor, accomplished self-made research skeletal scientist and author of a vast number of medical, surgical and scientific articles, chapters and

books. His work activities, over 50+ years, led to his profound discoveries and inventions that in turn provided major and fundamental insights (breakthroughs) that greatly enhanced our knowledge and understanding of the fun-

damental factors and mechanisms responsible for the musculoskeletal system in health and in disease states. From these contributions, Dr. Frost has left a profound and seminal legacy on a new paradigm of the musculoskeletal system that is and was provocative in the making. His works have revolutionized not only our understanding, but our approaches in the study and in the treatment of musculoskeletal disorders.

Some of his major contributions include: (1) development of the techniques and methods to prepare undecalcified microscopic bone sections, and to obtain dynamic bone formation (rate) data using *in vivo* fluorochrome (tetracycline) bone labeling; (2) development of the techniques and methodologies for quantitative cortical and trabecular bone histomorphometry; (3) discovery and characterization of Bone Multicellular Units (BMUs) – the bone tissue-level, which structurally and functionally links the bone organ-level with the bone cell-level; (4) discovery and characterization of the Bone Intermediary Organization – with the depiction and distinction between growth, modeling and remodeling processes; (5) conceptual insights into the adaptation of bone to mechanical forces; (6) conceptual insights into the structure-function of endochondral bone formation; and (7) conceptual insights into bone and cartilaginous factors that can and do lead to osteoarthritis among others.

Dr. Frost, who has referred to himself over the years as "Feisty, Eccentric, Old, Dinosaur [F.E.O.D]," was perhaps somewhat eccentric. He was definitely different from most medical and scientific professionals in his uncanny ability to appreciate and perceive important biologic phenomena in both medical and scientific research settings that most missed. Perhaps it was also this difference, at least in part, which enabled him to effectively wear both the medical and research scientist HATS (and never mixing the two). Harold worked tirelessly, and enthusiastically on medical, surgical and scientific skeletal matters, and as such was labeled by some colleagues as a driven, possessed, workaholic. Likely (reading between the lines), the F.E.O.D may have been on a self-imposed mission/journey – with the objective(s) of pursuing the unknown, fundamental missing pieces of knowledge and understanding of the musculoskeletal system in health and disease in order that he could better treat and care for his patients. It is also likely that he found that the tenet of skeletal knowledge and information taught during his formal training – that changes in bone cell activity and/or numbers were the fundamental basis for disease – limited him as an effective orthopaedist and orthopaedic surgeon.

Elated and enthusiastic with the evolution of his discoveries and new found insights into the biologic mechanisms underlying a number of observed diseases and disease processes he was always eager to communicate, share and exchange them with others in the medical and scientific communities. For many years, however, he met only with

rejection. Understandably, he understood that some of his new findings, insights and theoretical concepts contradicted many of those of established dogma and thus were difficult to accept. He obviously found these rejections without any consideration or discourse most frustrating. Thus, one of his favorite quotations, by Daniel Boorstin, reflects his early and ongoing frustrations: "The great obstacle to progress is not ignorance, but the illusion of knowledge."

Nevertheless, he continued his pursuit for skeletal knowledge and understanding and explored avenues to facilitate better communication between and amongst skeletal/dental doctors and scientists. Thus, a number of his colleagues thought of him as an iconoclast. Approximately 40 years ago, he then worked with a colleague, Professor Webster Jee, who founded and established a unique annual forum designed for effective communication whereby sharing, exchanging and discussing of biologic skeletal findings, ideas, concepts, etc., between the medical and scientific communities could occur: The Sun Valley Hard Tissue Workshop.

Slowly over the years and particularly in recent years, the goals of his self-imposed mission/journey were accomplished, and within his life time: at last, the medical and scientific communities recognized and embraced his landmark contributions, including the new skeletal paradigm, and gave him the long overdue recognition and respect for his profound contributions. Many of his concepts and methodologies are now widely accepted and are an integral part of our understanding, knowledge, teaching and study of the skeletal sciences. He received the ASBMR William F. Neuman Award in 2001; ASBMR and the Sun Valley Workshop organizers agreed to collaborate in honoring him by supporting, developing and establishing the ASBMR Harold M. Frost Young Investigator Award; and the 2004 Sun Valley Hard Tissue Workshop was dedicated to paying tribute to Dr. Frost for his many contributions to skeletal science.

I miss the F.E.O.D. (Feisty, Eccentric, Old, Dinosaur): I miss his provocative ideas, concepts, manuscripts and discussions.

At last, however, with his self-imposed mission/journey accomplished – and within his life time, I understand he was pleased, as reflected in his April 2004 statements: "It's nice to be taken into account. It's nice to be respected," and "I guess the good part of it all was the journey, not the destination." As such, he leaves us knowing that we will not remember him only as F.E.O.D., but that much of his life's work and contributions, and his seminal legacy on the new skeletal paradigm are now widely accepted into the medical and scientific communities and thus are in potential and real use for the benefit of patients with orthopedic disorders. I thank you and I salute you F.E.O.D.

*Wanda B. High, D.V.M., Ph.D.*



## About Harold M. Frost

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. (I say this because orthopaedic science now utilizes many of the concepts introduced by Dr. Frost through the years and, ironically, even the more controversial of these ideas are now often taken for granted.) In a textbook that David Burr, Neil Sharkey and I authored, we tried to convey the significance of Harold Frost's contributions as follows:

"Coincidentally with the advent of more quantitative studies of bone's remodeling dynamics, much more became known about the mechanical properties of bone in the second half of the [20<sup>th</sup>] century. The "old" bone biology, dominated by interest in mineral metabolism, began to be replaced by a "new" bone biology based on broader perspectives. The lamp of this new bone biology has been fueled by contributions from many individuals, but the flame was kindled by an orthopaedic surgeon named Harold M. Frost. Using simple laboratory techniques, he began in the 1960s to make histologic sections of bone and look at them with an independent mind. He deduced that osteoclasts and osteoblasts usually do not work independently, but are coupled together in teams, with osteoblasts automatically following osteoclasts and replacing the bone which they removed. Frost called these teams of bone cells *Basic Multicellular Units*, or *BMUs*. He went on to make many other observations and deductions about bone biology. Initially, his ideas were poorly understood and often rejected, but through the years many of his concepts have been accepted in one form or another. Central to these ideas is the concept that the skeleton is primarily a mechanical organ, rather than a calcium reservoir. While bone plays an important role in calcium homeostasis, the main job of osteoclasts and osteoblasts is now seen as maintenance of the mechanical integrity of the skeleton. How this is done by teams of cells communicating by chemical messengers and other means,

while still fulfilling the metabolic roles of the skeleton, is the principal focus of current orthopaedic research."

To more completely describe Dr. Frost's many contributions to our field would be far too much for a letter of this kind, but I would like to name just three that I consider to be the most important. First is the concept of bone remodeling mentioned above, its distinction from modeling, and the fundamental roles that they each play in virtually all bone diseases. The second is the concept of mathematically analyzing bone remodeling dynamics, based on histomorphometric measurements of sections bearing fluorochrome labels. This was the essential foundation for all quantitative bone biopsy work. Closely related to this concept is that of mathematically formulating various aspects of Wolff's law. A very few other early workers pursued such ideas contemporaneously with Dr. Frost, but his understanding of modeling and remodeling gave his work a unique clinical and biological perspective. He not only introduced such ideas as "minimum effective strain" and basic control theory to bone biologists, but also emphasized to the engineers that mechanical adaptive responses had to be explained in terms of modeling and remodeling processes. Finally, the third important concept I would mention is what Dr. Frost calls bone's "intermediary organization", referring to bone's organization at the level of cells and groups of cells, which enables modeling and remodeling to be effected. In this time of fascination with molecular biology on the one hand, and "mechanobiology" on the other, I believe it is especially important to remember that both the signaling of mechanical events, and the biological responses to these signals, require the intermediate levels of organization that Harold Frost has always stressed in this work.

In summary, I believe that Harold Frost has uniquely contributed to bone biology in the last 40 years to the point that our current concepts are largely supported on foundations that he built.

*R. Bruce Martin, Ph.D.*

## - A Personal Note -

I first became aware of Hal Frost in 1967 when I read his book, *Bone Dynamics in Osteoporosis and Osteomalacia*. I did not understand it all, but recognized it as a completely new way of thinking about bone. I first met Hal in 1969, an encounter that persuaded me that I should accept Boy Frames's offer to move from the University of Queensland to Henry Ford Hospital. When I arrived two years later, looking down the microscope with the help of Tony Villanueva was a revelation. At that time I had written virtually nothing about bone, but I convinced Hal that I was determined to understand it. I read everything that he had written – I still have the books and papers I used. Hal persuaded Web Jee to invite me to Sun Valley, where I first met many of the people who became important to me. When Hal left Henry Ford Hospital, I was honored to assume responsibility for his former laboratory. I have tried to make his ideas more intelligible to a wider

audience and to build on his foundation, work which is still in progress. I was able to pay him a brief tribute by selecting a seminal paper for the Landmarks series in the Journal of NIH Research, and I strongly supported Bob Recker's nomination of Hal for the Neuman Award. I have continued to collaborate with Dan Rao and Shijing Qiu, who took over the lab when I moved to Arkansas. We are still exploiting the normal rib material that Hal had accumulated almost 50 years ago.

I often disagreed with Hal and think that he was wrong about many small things (which of us was not?), but he was right about the big things and his work continues to inspire me to greater understanding, and wider dissemination of his fundamental ideas, still not fully grasped by many in our field.

*A. Michael Parfitt, M.D.*

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