

Harold M. Frost**William F. Neuman Awardee 2001**

Today, the Journal pays tribute to Harold M. Frost, our honorary president of ISMNI, who received the William F. Neuman Award from the American Society of Bone and Mineral Research this October 2001. The Award is well deserved because Harold has been the most influential theoretician in skeletal biology. You will realize after reading the nominating letter and the excerpts from seconding letters, that in Harold we encounter one whose impact will live forever. In addition we are fortunate to be publishing two more articles of Harold's that emphasize his advances in basic science of skeletal biology that improve clinical treatment.



Harold M. Frost, M.D.
Honorary President of ISMNI

The nominating letter of Robert Recker, M.D.

April 12, 2001

Chairperson
Awards Nominating Committee
The American Society for Bone and Mineral Research
1200 19th Street, NW, Suite 300, Washington, DC 20036-2412

Dear Sir/Madam,

I am writing this letter to nominate Harold M. Frost, M.D. for the William F. Neuman Award of the ASBMR.

Harold Frost has been a friend and colleague for 24 years. Dr. Frost has made seminal contributions to bone research that have resulted in massive paradigm shifts in the field.

Dr. Frost first characterized *in vivo* bone remodeling through fluorochrome labeling. His work began with examination of cross sections of ribs from humans who had been given tetracycline for treatment of infections in their past. He described bone resorption and formation as occurring in physically and temporarily discreet units of cellular activity. Using light and fluorescence microscopy he described the sequence of activation, resorption, and formation, first in Haversian bone and later in trabecular bone. With light microscopy alone he reported in *Nature* in 1965 that 96.7% of the bone formation process in adult spongy bone occurs only after resorptive processes occurred beforehand on the same bone surface. He also suggested that bone formation occurring on surfaces that were not scalloped from prior resorption were due to bone formation after a pause at a previous formation site.

He is and has been an iconoclast. At the time of his characterization of remodeling and, for many years after their publication, bone investigators tended to regard bone cells as individual "atoms" that worked independently of one another. His major contribution in this area was noting that bone cells are organized to work together, in concert, in a stereotyped time sequence. He was the first to suggest that osteoclast and osteoblast activities are coupled, pointing out that if the function of one of these cells is perturbed, the other is virtually always perturbed as well.

He invented the idea of the basic multicellular unit of bone, the "BMU". By this he refers to the unit of cells and their activity that accomplish bone remodeling, starting with activation on a surface followed by resorption of bone on that surface followed finally by formation by osteoblasts on that same surface. These ideas have become a part of the basic canon of modern skeletal science.

In our world of modern, "high-tech", expensive, elaborate, team-based research, it is fascinating that Dr. Frost performed the majority of his laboratory work in a crude sink arrangement where he sawed cross sections of intact ribs and ground them under flowing water to sections less than 100 microns thick. The costliest and most technical instrument he used was a microscope with a fluorescence attachment. He recognized that demineralizing bone specimens for purposes of histologic examination resulted in loss of the most interesting information about bone biology. Thus, he was responsible for the turn toward studying non-demineralized bone specimens among scientists studying bone biology from the standpoint of morphology.

An important facet of Dr. Frost's brilliance is that he has generated most of his ideas and paradigms from observations made in living humans and in human biological specimens. He has developed great powers of observation during a long clinical

career of encountering patients with various skeletal diseases, injuries and handicaps. He observed, for example, that when one lower limb is paralyzed in a child, the bones tend to elongate at nearly the same pace in that limb as in the unparalyzed limb but the accumulation of bone mass is markedly reduced. Nevertheless, the general shape of the bone of the paralyzed limb remains intact. He was the first to recognize the significance of this fact, and to this day there have been few that grasp it or report on it. Frost formulated the concept of load driven modeling beginning with these observations. Since then he has developed and refined ideas about skeletal adaptation to loading and has introduced the concept of a mechanostat, a sensing mechanism that detects mechanical loads, their intensity and direction, and directs bone cellular machinery to respond to them. This paradigm has resulted in a flurry of research activity. Over the course of time, it has gradually become part of the conventional wisdom in the field. Subsequent expansion of these ideas has led to new paradigms regarding biomechanical factors involved in osteoarthritis, particularly of the knee, as well as factors involved in fracture healing.

Dr. Frost is a prolific writer who has showered his colleagues with manuscripts, letters and papers containing the gems of his thought and observation. They are treasured. Many of us venture to feedback on the ideas presented in them, and thus he has fostered a protracted, prolific and fascinating discourse on bone science over the years in these correspondences with his colleagues.

In a March 1996 volume of the *Journal of NIH Research* I quote the following which characterizes Dr. Frost rather well. "Harold Frost fits almost perfectly a Hollywood image of a brilliant but controversial scientist. The iconoclastic tinkerer working alone in his cluttered basement laboratory, uses a technique of his own invention to make unprecedented observations of how human bones maintain their structure. He proposes a revolutionary theory that bone remodeling is a dynamic but specific interaction of bone resorption with bone formation—the latter almost never going on without the former. But the renegade scientist's ideas contradict those of the academic establishment and he suffers professional rejection for them. He loses government funding for his work and later resigns his position of chairman of a department of a major metropolitan hospital. Thirty years later our scientist, successful but relatively isolated in a small desert town, recounts his story. The years have proven him right and modern scientists who study bones respect him. His once ridiculed ideas have become a modern paradigm of bone resorption and formation."

I believe it is altogether fitting that the ASBMR recognize this renegade scientist who has had such a major impact on the field. I heartily support his nomination for the William F. Neuman Award of the ASBMR for 2001.

Sincerely,

Robert R. Recker, M.A.C.P., F.A.C.E
Professor of Medicine
Section of Endocrinology and Metabolism

Excerpts from seconding letters

"He is the one and only genuine theoretician in the field of skeletal tissue biology and medicine. The late Dr. Marshall Urist, past editor of *Clinical Orthopaedics* and discoverer of BMP, calls him 'Orthopaedic surgery's idea man or theorist'. Dr. William Peck at Washington University in St. Louis called him a genius."

"Harold Frost will go down in time as one of the most important names in the field of bone health and disease. According to Science Citation Index he is one of the most cited investigators in skeletal research."

"Harold Frost's view of bone biology was once controversial but is now well accepted. Many of the acronyms Frost constructed to describe bone cellular processes are now part of the bone lexicon and are commonplace in bone biology."

"I cannot think of any other scientist that has had more influence than Harold Frost's worldview. In the words of the late Thomas Kuhn, Frost changed the paradigm of bone biology. The most fundamental change came with his explanation for the intermediary organization of bone. To this day, bone is the only connective tissue for which structural remodeling can be quantitated and it is no coincidence that there is currently a revolution in drug development for treatment of metabolic bone diseases and osteoporosis."

Webster S.S. Jee, Ph.D.
Professor of Anatomy and Neurobiology
Research Professor of Radiobiology
Organizer of Sun Valley Hard Tissue Workshops

“Besides specific accomplishments, he has exemplified the fine qualities of a teacher by acting as a mentor to many young scientists who have yet to reach their full potential. In this way, the full impact of Dr. Frost’s accomplishments has not yet been felt.”

“Over the past 35 years, Dr. Frost has transformed our basic and clinical understanding of biological processes in the skeleton through the publication of more than 400 articles, 16 books, and contributions to more than 20 symposia. No other individual has so completely transformed the face of a scientific discipline as has Harold Frost in skeletal biology and orthopaedic science. It is not an overstatement to say that he has been the most influential theoretician in skeletal biology in this century.”

“Dr. Frost is responsible for most widely accepted concepts about how the skeleton adapts to metabolic, hormonal and mechanical influences. These concepts transcend any single discipline, extending to the entire field of skeletal health and disease. Collectively, these ideas led to the formation of the quantum concept of bone turnover, and the development of dynamic histomorphometry, which is the standard used today both for experimental measurements of bone change over time and for all quantitative clinical assessment of bone diseases from iliac crest biopsies.”

“He has had a profound effect on thinking in the biomechanics community as regards to the adaptation of bone to mechanical stimuli. He was the first to describe flexural strain as the major mechanical determinant of bone architecture (1964).”

“. . . .The concept of a mechanical feedback system that affects modeling and remodeling differentially began with Frost in the 1960’s. These ideas culminated in the theory of the mechanostat in the mid 1980’s. The idea of a mechanostat is now used routinely by bioengineers. It has become an established concept in the biomechanical and bone adaptive lexicon.”

“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. the idea has sparked controversy. . . . 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.”

“It is impossible to overestimate his influence and contributions in 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. In the past 15 years he has had a particularly profound effect on the biomechanics community.”

David B. Burr, Ph.D.

Professor and Chairman of Anatomy & Cell Biology

Professor of Orthopaedic Surgery

“The conceptual framework elucidated in his research and seminal works have transformed our understanding of skeletal biology, and formed the basis of clinical practice across a range of disciplines.”

“Dr. Frost is undoubtedly one of the monumental figures in the field of bone and mineral research. His contribution to the basic and clinical science performed by members with the Society is impossible to estimate.”

Mark R. Forwood, Ph.D.

Associate Professor

Department of Anatomical Sciences

University of Queensland

“He worked for almost twenty years with little or no recognition from his peers. Finally, when recognition came and his concepts were studied, his descriptions of bone growth, renewal and health were accepted. His work affected the research emphasis of the entire field of bone. As the result of his work, a completely new subdiscipline of bone function has developed. Every area of the health and wellbeing of human bone was influenced by his studies.”

“He is long overdue for honor and recognition for his contributions to our knowledge of bone and to the problems of health and disease in all areas related to human bone.”

Roy V. Talmage, Ph.D.

Professor of Orthopaedics, Retired

University of NC,

School of Medicine, North Carolina

William F. Neuman Awardee 1984

