

NEWS

In Memoriam: Stephen M Krane

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Stephen M Krane (1927–2015) made outstanding and wide-ranging contributions to the bone and mineral field, to rheumatology and to clinical medicine. He was influential in the establishment of the American Society for Bone and Mineral Research, served as its fourth President and won the Society's highest honor, the William F. Neuman Award.

Steve grew up in New York City and served in the US Navy at the end of World War II. He graduated from Columbia University and then received his medical degree from Columbia University College of Physicians and Surgeons. After 3 years of internal medicine residency at the Massachusetts General Hospital, he spent a year as a Research Fellow in the MGH Thyroid Unit, followed by a year in Carl Cori's Biochemistry Department at Washington University, where he studied sugar transport with Robert Crane. He then returned to the MGH to serve as Chief Resident in Medicine, followed by his appointment to the Faculty of the Endocrine Unit where he studied the effects of thyroid disease on calcium homeostasis.

In 1961, Steve became Chief of the Arthritis Unit at the MGH, a post that he held until 2000. After his appointment, he initiated collaborations with Melvin Glimcher at the Children's Hospital, laying the foundations for his longstanding interests in collagen biology and the mechanisms of deregulated connective tissue remodeling in genetic diseases and inflammatory arthritis. Together with Mel Glimcher, he published a series of manuscripts describing the mechanisms of mineralization in bones and teeth and in 1972, published the first description of a heritable disorder of connective tissue attributable to hydroxylysine deficiency. In studies spanning his entire career, he contributed to the description of several additional genetic disorders associated with abnormal collagen structure and remodeling.

In the mid 1960s, he began a series of studies investigating the role of collagenases in the tissue damage and deregulated bone remodeling in Paget's disease of bone and inflammatory arthritis, a line of investigation that became the central focus of



his research career. In 1967, he published two landmark papers in *Science*. Both studies were performed with Ted Harris, one of his first rheumatology fellows. Ted went on to a highly successful career in rheumatology, including serving as the President of the American College of Rheumatology and as the Chief of Medicine at Stanford University School of Medicine.

Steve's career provides an exceptional role model for any aspiring clinician-scientist. Over many years, he provided mentorship, inspiration and guidance to numerous trainees who later became successful scientists and leaders in their respective fields. In his first publication in *Science*, he showed that patients with Paget's disease of bone excreted fragments

of collagen in their urine providing evidence of a role for collagenases in bone remodeling in Paget's disease. In the other study, he was the first to identify a human collagenase involved in connective tissue breakdown using synovial organ cultures from patients with rheumatoid arthritis. These early studies formed the basis for his major contributions to the understanding of the role of collagenases in deregulated connective tissue remodeling and joint tissue destruction in inflammatory arthritis. These papers exemplify his approach to research in which he used the study of human pathological disorders to define fundamental pathophysiological mechanisms responsible for connective tissue remodeling in both pathological and physiological states.

For the next five decades, Steve and his group continued to make major advances in the understanding of cellular and molecular mechanisms involved in the breakdown of joint tissues in rheumatoid arthritis and in defining the central role of collagenases in health and disease. In his early work in the 1970s with Jean-Michel Dayer, who later became Head of the Division of Immunology and Allergy at the University of Geneva School of Medicine, and Graham Russell, then a visiting scientist from Oxford and the University of Sheffield, they were the first to identify the essential role of inflammatory cytokines produced by immune cells in synovial tissues in the pathogenesis of synovial inflammation and joint destruction in rheumatoid arthritis. These discoveries laid the foundation for the later clinical use of anticytokine therapies. These studies were continued in collaboration with Steve and Mary Goldring and Ed Amento over the next several decades. Later, in a collaboration with Rudolph Jaenisch at M.I.T., he established the importance of collagenase action in collagen degradation, employing a mouse with a collagen $\alpha 1$ molecule mutated to resist collagenase digestion. Subsequently, Steve's group established a mouse model missing the MMP13 gene and demonstrated the crucial role for collagenase in normal growth of long bones and in physiological connective tissue remodeling. Throughout these many years, Steve benefited from a close collaboration with Mike Byrne, a skilled scientist whose close interactions with Steve allowed Steve always to be just one step from the bench.

In the field of metabolic bone disease, Steve had a life-long interest in the study of Paget's disease of bone and its treatment. He provided classic descriptions of the disorder with Charles Nagant De Deuxchaisnes, establishing a role for calcitonin as a therapy with Fred Singer and studying calcitonin action with Steve Goldring, work that culminated with the cloning of the calcitonin receptor. Altogether with his close friend Lou Avioli, a founder of the ASBMR, Steve coedited the much acclaimed two-volume

treatise entitled, 'Metabolic Bone Disease and Clinically Related Disorders'.

Steve was a master clinician educator in various roles at the MGH and Harvard Medical School. His most important teaching role was probably as the first Master of the Walter B Cannon Society of HMS from 1987 to 2001, a position from which he mentored large numbers of medical students about their future careers.

Stephen Krane was the Persis, Cyrus and Marlow B Harrison Professor of Medicine, Harvard Medical School, and won many national and international awards for his research. These included the Heberden Medal (London), the Carol-Nachman Prize in Rheumatology, the Distinguished Investigator Award of the American College of Rheumatology, the Harold D Copp Award of the International Bone and Mineral Society and the Louis V. Avioli Memorial Lectureship of the ASBMR.

Steve met his wife, Cynthia, when she was a nurse at the MGH. They had a wonderful married life of 60 years together. Cynthia encouraged Steve in what he sometimes said was his second career, as a superb and inventive cook, conducted in great style in an exceptionally well-equipped kitchen in their family home in Newton. Another little-known skill of Steve's was as a jazz pianist, which he used to advantage as a student in playing piano in bars. In the early 1970s, he and his family had spent a sabbatical year in Oxford in the William Dunn School of Pathology. During this time, Steve further indulged his musical talents by supervising the construction of a harpsichord, which was proudly shipped back to his Boston home.

Steve and Cynthia brought up a close-knit family, whose great devotion was evident in the care their children gave to their parents in their last few years and particularly to Steve after Cynthia died in 2012. Steve was deeply attached to his four sons (David, Peter, Ian and Adam) and seven grandchildren, of whose accomplishments he was immensely proud. He often recalled with great affection those many summers spent with the family at their second home in Woods Hole, MA, USA. It was the focus of great times with the family but also where he often retreated for thinking and writing. Steve and Cynthia both loved a party and were great hosts. Steve's 70th and 80th birthday parties, both held in Woods Hole, were memorable events.

Steve was not only a brilliant scientist but also a warm friend to many in the field. His sense of humor was famous and outrageous; most of his jokes would not be printable in this fine journal. At the same time, he was a rigorous scholar, expecting from himself and others the clearest and most creative thinking. His deep and very serious commitment to science, combined with his warmth and humor, made Steve Krane truly unique. He will be sorely missed and remembered with great affection.