THE FACULTY OF MEDICINE
Harvard University

Stephen M. Krane

Photo by Liza Green 2001

Stephen M Krane (1927 – 2015) was a widely admired and beloved physician, scientist, and intellectual and spiritual leader at the Massachusetts General Hospital and Harvard Medical School over a career that spanned 60 years of remarkable clinical and scientific achievement and institutional service. He was the initial incumbent of the Persis, Cyrus, and Marlow B. Harrison Distinguished Professor of Clinical Medicine Chair and the first master of the Walter Bradford Cannon Society at HMS, a post reflecting his commitment to medical student education. At Massachusetts General Hospital he served as Chief of the Arthritis Unit for four decades.

Born in New York City, Stephen served in the U.S. Navy at the end of World War II. He then attended Columbia University for undergraduate and medical school education, followed by three years of internal medicine residency at Massachusetts General Hospital where he began his lifelong research in the bone and connective tissue field. After a year as a research fellow in the MGH thyroid unit, he spent a year working with Robert Crane in the biochemistry department headed by Dr. Carl Cori at Washington University. He then returned to Massachusetts General Hospital to serve as Chief Resident in Medicine, a tribute to his excellence in clinical medicine and medical education, a commitment that he maintained throughout his career. After his appointment to the faculty of the Endocrine Unit he resumed his lifelong dedication to translational research studying the action of thyroid hormone on calcium and bone metabolism. In 1961, he was named chief of the Arthritis Unit and began his five decade-long, extraordinarily productive career in research on collagen biology and mechanisms of mineralization in bone, with an emphasis on the cellular and molecular pathophysiology of skeletal and connective tissue disorders. In his early studies he helped to identify the role of collagenases in physiological and pathological connective tissue turnover and bone remodeling and was the first to define their unique roles of collagenases in joint destruction in rheumatoid arthritis, a line of investigation that became the central focus of his research career.

In these studies, he showed that the rheumatoid synovial tissue was a rich source of collagenases. These

studies were the first to implicate the critical role of collagenase in the destruction of joint tissues in rheumatoid arthritis and related inflammatory disorders. In later studies, he worked with colleagues at Massachusetts Institute of Technology to employ genetic approaches in animal models to identify the molecular mechanisms by which collagenases degrade collagen molecules and to illustrate the role of collagenases and related molecules involved in collagen assembling and remodeling in the normal growth of long bones and physiology of connective tissue remodeling. These studies in turn led to the identification of specific defects in heritable human disorders of connective tissue remodeling.

His early studies were followed by a series of investigations, working with Jean-Michel Dayer, and Graham Russell, and later with Mary and Steven Goldring, in which they identified the essential role of cytokines produced by immune cells in the rheumatoid synovium in initiating and perpetuating the inflammatory process and pathological destruction of joint tissues and periarticular bone. This work laid the groundwork for the strategic targeting of proinflammatory cytokines in the treatment of rheumatoid arthritis and related forms of inflammatory arthritis.

His interest in bone was marked early in his career through his collaborations with Melvin Glimcher. Together they published a series of manuscripts describing the mechanisms of mineralization in bones and teeth and the central role played by the collagen matrix in initiating the mineralization process. Again the theme of fundamental work applied to clinical disorders was reflected in Stephen's life-long interest in the study of Paget's disease of bone and its treatment, providing classic descriptions of the disorder with Charles Nagant de Deuxchaisnes. Stephen, with Ted Harris, showed the increased levels of excretion of collagen fragments in the urine of patients with Paget's disease, illustrating the role of collagenase in the excessive bone remodeling in this disorder. With Steven Goldring he studied the actions of parathyroid hormone and calcitonin on bone cells, work that led to the ultimate cloning of the calcitonin receptor. With Fred Singer he established a role for calcitonin as a therapy for Paget's disease. His broad interest in bone disease was reflected in a scholarly collaboration with his close friend Louis Avioli, with whom Stephen co-edited the acclaimed two-volume textbook entitled, "Metabolic Bone Disease and Clinically Related Disorders".

The work summarized above exemplifies Stephen's scholarly approach to research in which he used the study of human pathological disorders to define fundamental mechanisms responsible for connective tissue remodeling in both pathological and physiological states. His career represents an exceptional model for clinician scientists, as well as basic scientists working in clinical settings. Over many years he provided mentorship, inspiration, and guidance to numerous trainees who later became successful scientists and leaders in their respective fields.

In the bone field, Stephen 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, as well as the Louis V. Avioli Memorial Lectureship. Stephen received many awards consistent with his remarkable accomplishments in science, medicine, and mentorship. Awards included honorary degrees from the University of Geneva and the University of Paris. He was awarded the Heberden medal, The Marion Ropes Arthritis Foundation Physician Achievement Award, and the Distinguished Investigator Award of the American College of Rheumatology. He also received the Carol Nachman Prize in Rheumatology and the Harold D. Copp Award of the International Bone and Mineral Society.

Stephen was warmly supported during 60 years of marriage by his lovely wife, Cynthia, whom he

met when she was a Head Nurse at the MGH and by their happy and mutually supportive family that included four sons and seven grandchildren. Many colleagues remember remarkable evenings at the Krane family homes in Waban and Woods Hole. Stephen's skills as a host included his superb talents as a chef and wine connoisseur. His sense of humor was famous bordering on the outrageous. He was an outstanding jazz pianist, a talent honed as a student playing piano in bars. Throughout his generous, spirited, and full life, Stephen remained committed to the highest standards of medicine and science, expecting from himself and others clear and creative thinking. As noted with affection in one of the many tributes written about him is the quote "His love of learning was exemplified by the stacks of journals, manuscripts, correspondence, and notebooks on his desk, chairs, tables, and sofa in his office with a sign above it all reading "**A NEAT DESK IS THE SIGN OF A SICK MIND**"

Respectfully submitted,

John Thomas Potts Jr., *Chairperson*
Jean-Michel Dayer
Mary Goldring
Steven Goldring
Henry Kronenberg
Andrew Luster
Dwight Robinson
Graham Russell
Frederick Singer