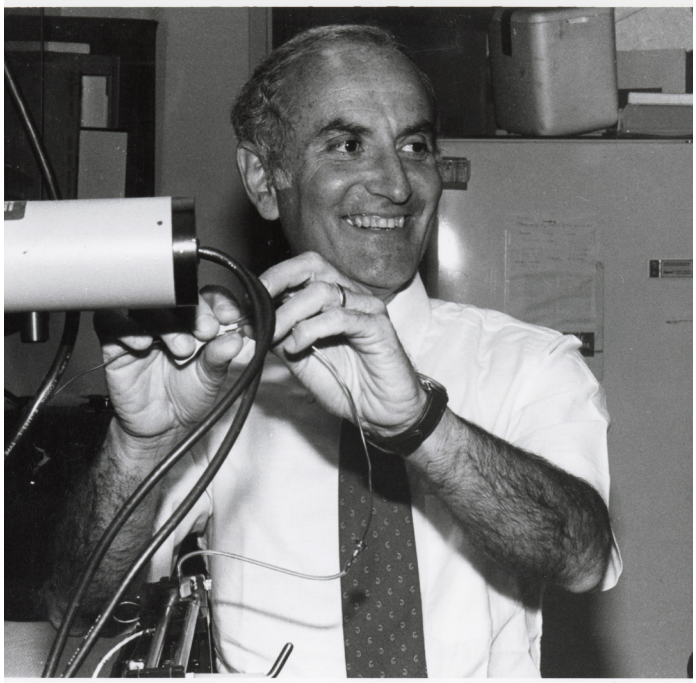
THE FACULTY OF MEDICINE
Harvard University

Irving H. Goldberg



Irving H. Goldberg, M.D., Ph.D., a far-sighted scientific leader, was born in Hartford, Connecticut, on September 2, 1926, to immigrant parents of little means. Irving's London-born father moved to France and then emigrated to America following the great Paris flood of 1910. His mother was originally from Eastern Europe. When Irving was a child, his father developed a parasitic liver infection and Irving had to take various jobs to help support the family. Despite those burdens, he excelled in school and received a scholarship to attend Trinity College in his native city. There (interrupted by a stint in the US Navy serving as a petty officer in electronics), he developed his interests in science and medicine and graduated as valedictorian with a B.S. in 1949. He then earned his M.D. at Yale University School of Medicine in 1953. While there he received a James Hudson Brown fellowship to work in the laboratory of John P. Peters, a leader in studying metabolism and a founder of modern clinical chemistry. Peters stressed the importance of physics and chemistry in treating human disease, which shaped much of Irving's career.

Irving went on to an internship and residency at Columbia-Presbyterian Medical Center, culminating in his appointment as chief resident and instructor in medicine. In 1957, his continuing interest in research led to his joining the laboratory of Fritz Lipmann, who had just moved to Rockefeller University from Massachusetts General Hospital and Harvard Medical School (HMS). Irving earned his Ph.D. in three years, with summer forays in 1958 to the Marine Biological Laboratory in Woods Hole and in 1959 to H. Gobind Khorana's laboratory in Vancouver to learn nucleic acid synthesis. Still, the biggest event of Irving's years in New York was meeting his wife Margaret (Peggy) while she was earning a degree in social work at Columbia. They were married for 63 years.

Though his thesis concerned enzymatic sulfurylation mechanisms, Irving's diverse interests led him to

delve into many of the other exciting areas in the Lipmann lab. Building on those studies, his scientific productivity skyrocketed in his first independent position as an assistant professor in Medicine and Biochemistry at the University of Chicago. Between 1961 and 1965, he published 22 papers, most with no more than two other authors. Seven of these appeared in Science, Nature, and PNAS, and they covered a remarkable variety of topics. One involved the synthesis and activities of pseudouridine nucleotides, an important component of tRNA. This work presaged recent studies of pseudouridine in mammalian mRNAs and its use to enhance the biological stability of mRNA vaccines and to suppress the innate immune response against them. A second was sequence-based DNA binding and inhibition of RNA polymerase in mammalian cells by the anticancer drug actinomycin D. These studies were the first steps towards what remains a holy grail – the development of sequence-specific DNA-binding therapeutics. A third was the biosynthesis of iodine-containing proteins and peptides, particularly thyroglobulin and thyroid hormones.

Based on these latter studies, in 1964, Irving was recruited as Chief of the Endocrinology-Metabolism unit at Beth Israel (BI) Hospital and as associate professor in Medicine and Biochemistry at HMS. Here his research interests expanded to include studies of the protein synthesis inhibitor sparsomycin (later revealed to contain pseudouracil), thus extending his attention to all three parts of the central dogma of molecular biology. In his new position, Irving attracted numerous predoctoral and postdoctoral trainees. He took a leadership role in scientific training in 1968 when, coincident with his promotion to Professor of Medicine, he became Chair of the Division of Medical Sciences (DMS) of the Faculty of Arts and Sciences of Harvard University, which oversees HMS graduate programs.

Irving received a Guggenheim Fellowship for a sabbatical in Walter Bodmer's lab at Oxford during the 1970-71 academic year. Although he did not pursue genetic studies in his own lab, this experience exemplified Irving's intellectual breadth, which he demonstrated in his next leadership role as Gustavus Adolphus Pfeiffer Professor and Chair of the Department of Pharmacology at HMS in 1972. Both positions had been vacated by Otto Krayer, who had led, built, and broadened the department since the 1930's, only to see it demolished by neglect, leading to his resignation several years previously. Irving's challenge was to rebuild the department. Reflecting his interdisciplinary thinking, Irving explicitly sought to link activities in the department with other disciplines, stating, "Advances in molecular and cellular biology…render Pharmacology ideally suited for their translation to the therapy of diseased states. Further, analysis of…the interaction of drugs and biological macromolecules will hopefully provide…a rational basis for drug design (and) important information on the structure and function of… biological 'receptors' in health and disease." Irving went even further, asking to call the department "Chemical Biology," a name that did not come into widespread use until the next century. Irving subsequently became the Otto Krayer Professor.

Consistent with his philosophy, Irving recruited faculty with multidisciplinary interests and, often, without traditional pharmacology training. Notably, a number of faculty he brought into the department were subsequently recruited by other institutions to head not only departments of pharmacology,

but others such as neurobiology and microbiology. Irving also became program director of an NIGMS training grant in pharmacological sciences that, despite the untraditional nature of the HMS Pharmacology department and its successor department, still continues. Ironically, likely due to the demands of being chair, Irving narrowed his own research to focus on antibiotics that cause DNA damage, particularly a recently discovered antitumor protein, neocarzinostatin, essentially founding the field of enediyne cancer agents. His pioneering application of chemical principles led to the discovery of neocarzinostatin's antitumor activity: A small chromophore wedged into the much larger protein was the agent that bound to DNA and cleaved it to kill the cancer cell. He continued these studies into the late 2000's, with the additional irony that this narrowed focus led to the majority of his >170 papers. He took real joy from being in the lab, as can be seen in the attached photograph.

To his students, staff, and colleagues, Irving was a hard-core chemist with a clinician's perspective. His hands-off approach to mentoring nurtured his trainees' growth as independent scientists, with a willingness to let them run with new ideas, serendipitous findings, and controversial discoveries. Still, he aggressively engaged his full creative intellect at research meetings. Irving was simultaneously reserved yet warm, businesslike yet friendly, highly critical yet caring, always balancing the hard-driving Harvard professor phenotype with a clinician's humanity. He had the skill of pushing lab members hard but always with a smile and gentleness atypical of many successful professors. That said, Irving was intolerant of sloppy or thoughtless science and was intensely competitive with colleagues in the nucleic acid chemistry community. He believed strongly in scientific integrity and was especially dismayed when a Harvard colleague tried to scoop him after seeing Irving present at a Gordon Conference.

Irving's style as chair reflected his laboratory style and his science. He believed that faculty should be left alone, decide what they want to work on, and get on with it. He even tolerated three of his junior faculty forming a department rock band despite his finding the music too loud. Irving conducted departmental faculty meetings similarly, asking for everyone's opinion before voicing his own. When a one-time protegé of Irving's interviewed to be the next chair of Pharmacology and proposed to take a more top-down approach, telling faculty during interviews what they should work on, it went over poorly, especially with Irving. (He didn't get the job.) But Irving's reserve and seemingly passive approach belied a strong will and firm principles about what was best for the department, pharmacology education, and HMS. While he was not a fan of the nascent New Pathway medical curriculum in 1985, he neither encouraged nor forbade faculty participation in its case-study method. Those who did participate found many flaws, including that medical students were not learning the basic vocabulary of pharmacology. Regardless, this stance and other disagreements did not endear Irving to the Dean, who initiated a search for a new chair, culminating in the merger of Pharmacology with Biological Chemistry to form the Department of Biological Chemistry and Molecular Pharmacology under the leadership of Christopher Walsh in 1987.

Irving's greatest passion outside of work was his family. He cherished spending time with them and playing and watching sports, especially the Red Sox. His parenting style resembled his mentoring

approach. He loved travel, good food, photography, and the family's summer home in Sippewissett, just far enough away from all the scientists in Woods Hole. Irving had two children and his sister four. Of the six, two went on to perform research on parasites, possibly influenced by Irving's father's liver disease.

Irving died on November 14, 2022, survived by his children Nancy and Daniel and their spouses, and three grandchildren. He was a superb, creative scientist and as decent, honest, and humane a person as one would ever have the good fortune to meet. We were lucky to know such a great man.

Respectfully submitted,

Donald M. Coen, *Chairperson*
Peter C. Dedon
David E. Golan
Daniel E. Goldberg
Robert R. Rando